STATISTICAL ANALYSIS PLAN

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL-GROUP, PHASE II TRIAL OF JKB-121 FOR THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS (NASH)

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Protocol: A Randomized, Double-Blind, Placebo Controlled, Parallel-Group, Phase II trial of JKB-121 for the Treatment of Nonalcoholic Steatohepatitis (NASH)

Protocol Number:	JKB-121-001
Current Protocol:	V4.0 / March 2, 2016
SAP:	V1.0 / March 31, 2017

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1 SUMMARY OF CHANGES

SAP Version History		
Version	**Date**	**Description of Changes**
1.0	March 31, 2017	Original Document

2 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical and pharmacokinetic (PK) methods and procedures to be implemented for the analyses of data from TaiwanJ Pharmaceuticals Protocol JKB-121-001. Any deviations from this analysis plan will be substantiated by sound statistical/PK rationale and will be documented in the final clinical study report.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the safety and potential efficacy of two dose levels of JKB-121 (5 mg twice daily and 10 mg twice daily) in reducing liver fat compared to placebo.

3.2 Secondary Objectives

The secondary objectives are:

- Determine the pharmacokinetic profile of JKB-121 in nonalcoholic steatohepatitis (NASH)
- Assess the impact of treatment with JKB-121 on metabolic markers
- Assess the impact of treatment on liver enzymes (serum alanine aminotransferase [ALT]) over 24 weeks.
- Establish the recommended dose for future NASH treatment studies.
- To evaluate changes of NASH related biomarkers such as adiponectin, leptin, ghrelin, tumor necrosis factor alpha (TNF-alpha), TGF-beta, hyaluronic acid and matrix metallopeptidase 2 (MMP-2).

3.3 Exploratory Objective

Investigate the impact of treatment of potentially relevant inflammatory and metabolic biomarkers associated with NASH.

4 STUDY OVERVIEW

4.1 Study Design

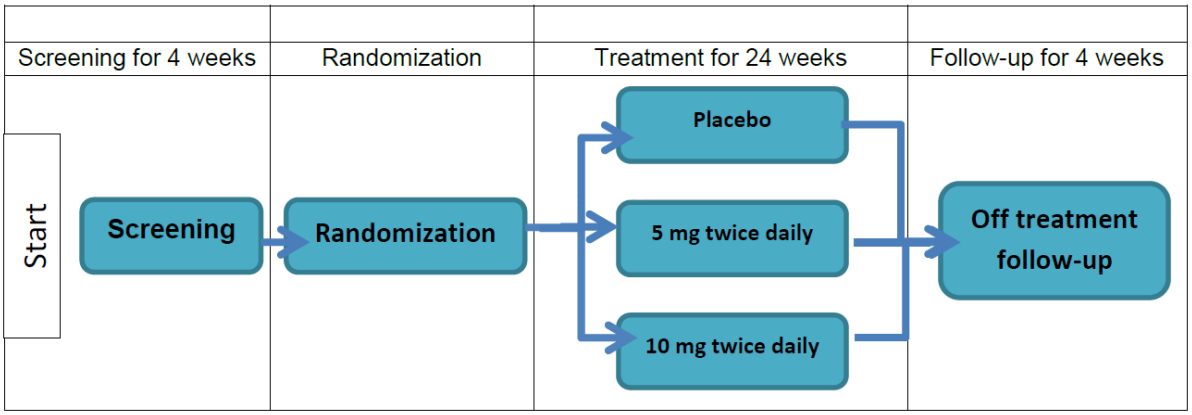
This is a randomized, double-blind, placebo controlled, parallel-group, phase II trial of JKB-121 in treating subjects with biopsy-proven NASH.

Subjects will be randomized at study entry to placebo twice daily, 5 mg twice daily, or 10 mg twice daily of JKB-121 orally to improve NASH with regard to biochemical and MRI/MRS features of NASH in a 1:1:1 ratio.

- Treatment Group 1: placebo twice a day orally
- Treatment Group 2: 5mg of JKB-121 twice a day orally
- Treatment Group 3: 10 mg of JKB-121 twice a day orally

The maximum time on study drug for each subject is 24 weeks with an additional 4 weeks of follow-up.

This allocation is shown diagrammatically below:



4.2 Randomization and Treatments

Patients will be randomized in the order in which they are enrolled into this double-blind study by using a computer-generated randomization schedule. TaiwanJ Pharmaceuticals prepared the schedule prior to the start of the study. This number will designate which allocated treatment a patient will receive. The randomization schedule will be a ratio of 1:1:1 to one of the following three treatment groups:

- JKB-121 5 mg tablet twice daily orally
- JKB-121 10 mg tablet twice daily orally
- Placebo as tablet twice daily orally

Treatment allocation will be stratified by known diagnosis of diabetes status. Nondiabetic status will be defined as HbA1c ≤ 6.0 and absence of any medications to treatment diabetes. Diabetic status will be defined as HbA1c > 6.0 and/or requiring medication for treatment of diabetes mellitus.

Subjects who are withdrawn from the study will not be replaced.

Until formal conclusion of the study, subjects, investigators and all site study personnel will be remain blinded as to treatment allocation, except in the event of a medical emergency which necessitates unblinding.

5 EFFICACY ENDPOINTS

5.1 Primary Efficacy Endpoint

Mean and absolute changes from baseline in the percentage fat content of the liver measured by magnetic resonance imaging (MRI) at week 24.

5.2 Secondary Efficacy Endpoints

- Mean and absolute changes from baseline in the percentage fat content of the liver measured by magnetic resonance imaging (MRI) at week 12.
- Time to remission (TTR) defined as the time in weeks from randomization to liver function remission as defined as two consecutive ALT values within normal range (<20 U/L for women and <30 U/L for men). The time of the first of the two consecutive ALT values within normal range will be used as the TTR.
- Percentage of subjects reaching liver function remission as defined as two consecutive ALT values within normal range (<20 U/L for women and <30 U/L for men).
- Percentage of subjects at each scheduled visit whose ALT level is within normal range (<20 U/L for women and <30 U/L for men).
- Percentage of subjects whose ALT level is within normal range (<20 U/L for women and <30 U/L for men) at any time within the following time intervals which will be derived using actual study days:
    - Baseline to Week 12
    - Week 12 to Week 24
- Percentage of subjects achieving a 20% reduction in ALT from baseline at any time during the study period.
- Change from baseline in serum ALT at each scheduled visit.

- Serum aspartate aminotransferase (AST), ALT, and gamma-glutamyl transpeptidase (GGT) at each scheduled visit and the corresponding changes from baseline.

All endpoints which define the normal range as <20 U/L for women and <30 U/L for men will be repeated with the normal range defined as <40 U/L.

5.3 Other Efficacy Endpoints

- Metabolic Marker Endpoints
    - Body mass index (BMI) at each scheduled visit and the corresponding changes from baseline.
    - HbA1c and the homeostatic model assessment of insulin resistance (HOMA-IR) at each scheduled visit and the corresponding changes from baseline.
    - Serum lipid profile (total cholesterol, triglycerides, low density lipoprotein [LDL], and high density lipoprotein [HDL]) at each scheduled visit and the corresponding changes from baseline.
- Biomarker Endpoints
    - Biomarkers such as adiponectin, leptin, ghrelin, TNF-alpha, TGF-beta, hyaluronic acid and MMP-2 at each scheduled visit and the corresponding changes from baseline.
- Exploratory Outcome Measures
    - Mean serum concentrations of lipopolysaccharide (LPS), c-reactive protein (CRP), cytokeratin (CK)-18 fragments, proinsulin c-peptide, glucagon-like polypeptide (GLP-1) and adiponectin.
    - Relative levels of inflammatory cytokines, interferon gamma (IFN-γ), and TNF-alpha
    - Relative levels of regulatory T cells in the peripheral blood mononuclear cells (PBMC) samples including CD4, CD8, CD 25, Fox P3, NKT, and CD62 T cells.

6 STATISTICAL METHODOLOGY

6.1 Sample Size Determination

An approximate total of 60 subjects will be enrolled. Subjects will be randomized into three treatment groups in a ratio of Group 1 (5 mg twice daily): Group 2 (10 mg twice daily): Group 3 (placebo twice daily) = 1:1:1. No empirical power calculation is performed. The sample size is based on the best medical judgment.

The power to detect a difference between placebo and active treatment with respect to change from baseline in liver fat content and serum ALT has been determined for a sample size of 20 patients per arm to assess safety and potential efficacy. Fat quantification by MRI is very sensitive with as small as a 5% detectable change in fat quantification.

Further, since the endpoint is the change from baseline, plausible estimates of the degree of correlation between pre-and post-baseline measurements will be incorporated into the variance estimates. Given the wide range of results observed in the literature, several "what-if" scenarios were examined. As such, the current sample size was considered sufficient for the exploratory objectives of the study for the given range of plausible treatment effects and variance estimates. Due to the exploratory objects of the protocol, no adjustment for the two co-primary endpoints was made. Additionally, there will be no adjustments for multiple comparisons between the 3 treatment groups.

Assuming the observed difference between two treatment groups is 20%, then the 95% confidence interval for the true mean is given by (2.5%, 37.5%) with 20 subjects in each group.

Fat Liver Content Change from Baseline:

The current sample size of 20 subjects per group should yield approximately 85% power to detect a treatment effect of at least ~ 5% with respect to the difference in the mean change from baseline between one of the JKB-121 treatment groups and placebo

ALT change from Baseline:

The current sample size of 20 subjects per group should yield approximately 73% power to detect a treatment effect of at least 30 U/L assuming a SE of 50 U/L (α= 0.05; two tailed; unpaired t-test). The SD of 50 U/L for the change from baseline endpoint was derived assuming SDs of 40 for the pre-and post-baseline measurements with a correlation of 0.25.

Sample size and power estimates have not been adjusted for multiple comparisons or multiple endpoints, dropouts or stratifications.

The analysis of each primary endpoint will be based on a linear model that incorporates the baseline measures as a covariate, the stratification factor and randomization treatment group. Pairwise comparisons of each active treatment group to control will be conducted vial linear contrasts.

6.2 Baseline, Endpoint, and Other Statistical Considerations

The clinical statistical analyses will be performed by Medpace.

Baseline will be the measurement at Day 1. If missing, the last valid measurement on or prior to the first date administration of study medication will be used as baseline.

Unless specified otherwise, the order of the columns in descriptive summaries will be placebo, JKB-121 5 mg, JKB-121 10 mg, and total.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize the continuous efficacy and safety data by treatment group. The count and frequency will be used to tabulate the categorical measurements.

Scheduled visits will be used according to their visit label. Unscheduled visits will be used if the scheduled visit is unavailable and the unscheduled visit is within the visit window. The window is defined as the halfway point between the previous (or subsequent) scheduled visit and the expected day of the visit.

Data will be used as it is reported. Last observation carried forward (LOCF) or multiple imputation may be used when specified.

6.3 Analysis Populations

6.3.1 Full Analysis Set Population

The Full Analysis Set Population includes all subjects who received at least one dose of study medication. Only subjects with clear documentation that no study medication was received may be excluded. The Full Analysis Set Population will be the primary population for the efficacy analyses. In the event of allocation errors, subjects will be analyzed for efficacy according to the treatment to which they were randomized.

6.3.2 Modified Intent-to-Treat Analysis Population

The Modified Intent-to-Treat (mITT) Population will consist of all patients who receive at least one dose of study medication, have a valid baseline and at least 1 post-baseline MRI or ALT assessment. In the event of allocation errors, subjects will be analyzed for efficacy according to the treatment to which they were randomized.

6.3.3 Safety Population

The Safety Population includes all subjects who received at least one dose of study medication. Only subjects with clear documentation that no study medication was received may be excluded. In the event of treatment allocation errors, subjects will be analyzed for safety according to the treatment group they received.

6.3.4 Per Protocol Population

The Per Protocol Population includes all subjects who complete 24 weeks of study treatment and have MRI and ALT measured at baseline and at week 24 and no major protocol violations, determined prior to break of the treatment blind.

6.3.5 PK Substudy Population

The PK Substudy Population will consist of all patients who receive at least one dose of JKB-121, have no significant deviation in dosing that will affect PK evaluation, and have sufficient evaluable plasma PK concentrations to calculate PK parameters.

6.4 Subject Disposition

Subject disposition information will be summarized by randomized treatment group and total. Number and percentage of subjects who are randomized, who are in each analysis population, who complete the study, and who withdraw early from the study will be presented. The primary reasons for early withdrawals will also be tabulated. The number of randomized patients within each treatment group will be used as the denominator for the percentage calculations.

6.5 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment group and total for the Safety Population and mITT Population.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, body mass index (BMI), and baseline efficacy measures (percentage fat content of the liver measured by MRI, ALT, AST, GGT). Randomization stratum (diabetic status) will also be summarized. Continuous variables will be summarized by descriptive statistics. Categorical variables will be summarized by the number and percentage of patients in corresponding categories. The baseline is defined in Section 6.2, Baseline, Endpoint, and Other Statistical Considerations.

6.6 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers and percentages of subjects in each treatment group and in total having medical/surgical history will be summarized by system organ class and preferred term for the Safety Population. All medical history will be listed.

Liver histology scoring (steatosis grade, ballooning, lobular inflammation, fibrosis stage, and NAS score) will be summarized with numbers and percentages of subjects in each treatment group.

6.7 Prior and Concomitant Medications

Medication start and stop dates that are recorded on the Prior & Concomitant Medications case report form will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of study treatment. Prior medications are defined as those used prior to and stopped

before the first dose of study treatment. All prior and concomitant medication verbatim terms will be coded using the World Health Organization Drug Dictionary. The numbers and percentages of subjects taking concomitant medications in each treatment group and in total will be summarized by anatomic and therapeutic chemical term and preferred term for the Safety Population. All prior and concomitant medications will be listed.

6.8 Study Medication Exposure and Compliance

Subjects' exposure to randomized study medication will be summarized with descriptive statistics for the Safety Population.

Days of exposure is defined as:

$$\textit{date of last dose of study drug} - \textit{date of first dose} + 1$$

If a subject has been instructed to stop dosing for any portion of the study, for example due to AE, then the days of interruption will be subtracted from the days of exposure. The days of interruption is defined as:

$$\textit{last date of interruption} - \textit{first date of interruption} + 1$$

If the last dose of study drug is missing, the date of completion/early termination will be used. In addition, a contingency table will be provided to display the number and percentage of subjects in each treatment group with exposure in the following categories: 1-56 days (1-8 weeks), 57-112 days (8-16 weeks), 113-168 days (16-24 weeks), 169-196 days (24-28 weeks), and ≥197 days (>28 weeks).

Summary statistics will be presented for percent compliance to study medication by treatment group and total. The count and percentage of subjects will also tabulated by groups with overall compliance < 80%, 80% to 120%, and > 120%.

The percent compliance to study medication will be calculated as:

$$100 \times \frac{\textit{total number of tablets dispensed} - \textit{total number of tablets returned}}{\textit{days of exposure} \times 2 - \textit{days of interruption}}$$

If a subject has been instructed to take half dose (1 tablet per day) for any portion of the study, for example due to AE, then the percent compliance will be calculated as:

$$100 \times \frac{\textit{total number of tablets dispensed} - \textit{total number of tablets returned}}{\textit{days of regular exposure} \times 2 + \textit{days of half dose exposure} - \textit{days of interruption}}$$

6.9 Efficacy Analysis

6.9.1 Primary Efficacy Endpoint

The change from baseline at Week 24 of the percentage fat content of the liver measured by MRI will be analyzed by analysis of covariance (ANCOVA) in the Full Analysis Set Population with treatment group and diabetes stratum as factors and baseline MRI value as a covariate. The comparisons will be (1) between the response of the JKB-121 5 mg group and the response of the Placebo group and (2) between the response of the JKB-121 10 mg group and the response of the Placebo group. The least-squares means, standard errors, and 95% confidence intervals for each treatment group and for each comparison will be provided. The two-sided p-values testing for significance within treatment group change from baseline and comparisons between treatment groups will be presented. No multiple comparisons techniques will be applied. The sample SAS code can be found below:

```
**********************************************************************
Note:
  TREATMENT = 0, (placebo), 1 (JKB-121 5 mg), 2 (JKB-121 10 mg)
  DIABSTAT = nondiabetic, diabetic
  BASE: baseline percentage fat content of the liver measured by MRI
  CHG: change from baseline to Week 24 in the percentage fat content of
       the liver measured by MRI
**********************************************************************;
proc glm data=MRI;
  class TREATMENT DIABSTAT;
  model CHG = TREATMENT DIABSTAT BASE / ss1 ss3;
  means TREATMENT;
  lsmeans TREATMENT / cov stderr pdiff cl;
  estimate "JKB-121 5 mg : Placebo" TREATMENT -1 1 0;
  estimate "JKB-121 10 mg : Placebo" TREATMENT -1 0 1;
run;
```

The data and model residuals will be inspected for normality and homogeneity of variance, and a logarithmic transformation will be applied if necessary.

To handle missing results such as due to early termination, multiple imputation will be performed. The detailed steps are specified below.

> Step 1: Prepare the data for multiple imputation. Since there is only one intermediate visit (Week 12) for MRI collection, the missing pattern would be monotone if endpoint values are not available.

Step 2: PROC MI would be used to impute the missing MRI values. The treatment, diabetes stratum, and MRI values at baseline and all available post-baseline visits would be included. The SAS code can be found as below:

```
PROC MI data=MRI out=MI_OUT nimpute=1000 seed=12345 minimum=0;
  var TREATMENT DIABSTAT BASE WEEK12 WEEK24;
  mcmc initial=em prior=jeffreys nbiter=200 niter=500 chain=single;
run;
```

Step 3: Endpoint would be calculated by averaging the values of Week 12 and Week 24. For each imputation, the ANCOVA model specified above would be performed to compare the change from baseline to Week 24 endpoint between JKB-121 5 mg group the placebo group, and between JKB-121 10 mg group and the placebo group.

Step 4: The procedure PROC MIANALYZE would be used with estimated statistics ("least-squares means") and associated standard error from each simulation for overall testing results. The overall least-squares means, standard errors, 95% confidence intervals, and p-values would be reported.

The same analysis will be repeated for the mITT and Per Protocol Populations. Multiple imputation will not be performed for the Per Protocol Population; only subjects with both baseline and endpoint will be included in the analysis.

The percentage of fat content of the liver measured by MRI at Baseline and Week 24 will be summarized descriptively, as well as the change from baseline.

The same descriptive statistics and ANCOVA model as the primary efficacy endpoint will be applied to the percentage of fat content of the liver measured by MRI at Baseline and Week 12.

6.9.2 Secondary Endpoints

6.9.2.1 ALT Remission

All TTR and responder analyses described below will be repeated for both ALT normal range definitions:

- <20 U/L for women and <30 U/L for men
- <40 U/L

Time to Remission

TTR defined as the time in weeks from randomization to liver function remission, defined as two consecutive ALT values within normal range during the treatment period (i.e. excluding Week 28 follow-up visit), will be assessed by survival analysis. The time to the first of the two consecutive ALT values within normal range will be used for the TTR. The time in weeks will be calculated as (sample date – first dose date + 1)/7. For those reaching

remission, the Hodges-Lehmann estimator of the "location shift" between each dose group and placebo will be presented. The asymptotic (Moses) 95% confidence limits for the location shift will also be presented. The cumulative portion of the time-to-remission of each treatment group will be determined by Kaplan-Meier estimates. The time-to-remission will be analyzed using Cox proportional hazards model with treatment and diabetes stratum as explanatory variables. The following SAS code was used for the analyses of proportional hazards models:

```
proc phreg;
  Model TIME*CENSOR(0) = TREATMENT DIABSTAT / risklimits;
run;
```

Subjects who discontinue from the study before remission and subjects who complete the study without reaching remission will be assigned a TTR equal to the larger of the following two quantities:

- (Maximum TTR in days observed for all subjects in the study + 1 day) / 7;
- (Time to censoring (last ALT assessment during the treatment period) + 2 days) / 7.

Responder Analysis

The number and percentage of responders will be provided by treatment group. A subject who had as two consecutive ALT values within normal range during the treatment period will be defined as a responder. Subjects who are not responders and early withdraw will be considered as non-responders. Cochran-Mantel-Haenszel statistics will be provided adjusting for diabetes stratum.

```
*********************************************************************
Note:
  TREATMENT = 0, (placebo), 1 (JKB-121 5 mg), 2 (JKB-121 10 mg)
  DIABSTAT = nondiabetic, diabetic
  RESPONDER: Y/N responder
  COUNT: number of subjects
*********************************************************************;
      proc freq data=ALT;
         tables DIABSTAT*TREATMENT*RESPONDER / cmh;
         weight COUNT;
      run;
```

Sensitivity analyses will be conducted using subjects who complete the study.

Similar summaries and analyses will be provided for:

- Subjects whose ALT level at each scheduled visit during the treatment period is within normal range.
- Subjects whose ALT level is within normal range at any time within the following time intervals which will be derived using actual study days:
    a. Baseline to Week 12

b. Week 12 to Week 24

- Subjects achieving a 20% reduction from baseline at any time during the treatment period.

6.9.2.2 Liver Function

The same descriptive statistics, ANCOVA model, and multiple imputation as the primary efficacy endpoint will be applied to serum aspartate aminotransferase (AST), ALT, and gamma-glutamyl transpeptidase (GGT) at each scheduled visit for the Full Analysis Set Population and the mITT Population.

As a sensitivity analysis, the change from baseline in AST, ALT, and GGT will be analyzed using a mixed-model repeated-measures (MMRM) ANCOVA model for the Full Analysis Set Population, implemented using SAS® Proc Mixed. The factors in the model will be diabetes stratum, treatment group, baseline value, visit, and the treatment group by visit interactions. An unstructured covariance matrix will be used (TYPE=UN). No imputation will be performed. The sample SAS code can be found below:

```
*********************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0, (placebo), 1 (JKB-121 5 mg), 2 (JKB-121 10 mg)
  DIABSTAT = nondiabetic, diabetic
  VISIT = visit
  BASE = baseline value
  CHG = change from baseline to the specified visit
*********************************************************************;
      proc mixed;
        class USUBJID DIABSTAT TREATMENT BASE VISIT;
        model CHG = DIABSTAT TREATMENT BASE VISIT TREATMENT*VISIT;
        Repeated VISIT / TYPE=UN sub=USUBJID;
        lsmeans VISIT*TREATMENT / cl pdiff slice=VISIT;
      run;
```

6.9.2.3 Other Endpoints

The same descriptive statistics and ANCOVA model as the primary efficacy endpoint will be applied to metabolic marker endpoints, biomarker endpoints, and other secondary outcome measures will be summarized and analyzed in the same manner as the primary efficacy endpoint. LOCF will be used in place of multiple imputation.

6.10 Pharmacokinetic Analysis

6.10.1 Sample Collections for Pharmacokinetic Analysis

Six mL of blood will be collected from fasting (at least 8 hours) subjects on Day 1 prior to dosing, and during Visits 4, 6, and 8 for measurements of the plasma concentrations of

JKB-121. In a subset of volunteers who consent to participate in PK Substudy, blood samples will be collected on Day 1 pre-dose and at each sampling point post-dose for PK evaluation.

From volunteered subjects for intensive PK studies: Blood samples will be obtained on Day 1 prior to 12 hour dosing (predose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, and 24 (next day) hours post dose administration in three volunteered subjects from each treatment group (5 mg and 10 mg bid). Additional pre-dose blood sample for trough PK level at Day 1, weeks 8, 16, and 24 will be collected for assessment of steady state PK analysis as well as biomarker study.

6.10.2 Pharmacokinetic Variables

The following noncompartmental PK parameters will be calculated from plasma samples prior to the 12 hour dosing collected for the PK Substudy Population if data allows:

- Area under concentration-time (AUC) curve from time 0 to infinity (AUCinf)
- AUC curve from time 0 to time of last quantifiable concentration (AUClast)
- AUC curve from time 0 to 12 hours (AUC12h)
- Minimum post-dose concentration (Cmin)
- Maximum post-dose concentration (Cmax)
- Time of Cmax (Tmax)
- Apparent first-order terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration vs. time curve (Kel)
- Terminal phase elimination half-life (t½)
- Clearance (CL/F)
- Volume of Distribution (Vz/F)
- Percent AUC Extrapolated (AUC%extrap)

Parameters Kel, t½, and AUCinf will not be presented for those subjects who do not exhibit a terminal elimination phase in their concentration versus time profiles. In order to estimate the constant Kel, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate Kel. The constant Kel will not be assigned if the terminal elimination phase is not linear (as appears in a semi-logarithmic scale), the terminal elimination rate constant indicates a positive slope (Kel < 0), if the Tmax is one of the 3 last data points, or the regression coefficient (R^2) is less than 0.8.

The actual time relative to dosing will be used in the PK parameter calculation. The Linear Up/Log Down method will be used in the computation of all AUC values. The AUClast will

be calculated from 0 hour to the last time point with quantifiable concentration. The AUCinf will be calculated as AUClast + Clast/Kel, where Clast is the last quantifiable plasma concentration.

If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero. If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing). NQs which occur after the last measurable concentration will be omitted (set to missing).

6.10.3 Pharmacokinetic Summary and Analysis

PK concentration data will be summarized for each time point using descriptive statistics from the Safety Population and PK Substudy Population (i.e., Mean, SD, Minimum, Maximum, Median, %CV, Geometric Mean, Geometric %CV) by treatment group. Plots of mean concentrations of plasma concentrations (with standard deviation bars) versus nominal time will be generated for each treatment. Individual plasma concentration versus actual time plots will also be provided.

The PK parameters will be summarized by treatment group using the PK Substudy Population. Geometric mean and geometric coefficient of variation (CV%) will be added to the descriptive statistics for Cmin, Cmax, and all AUCs.

Trough (pre-dose) concentrations at Week 8, Week 16, and Week 24 will be summarized by treatment group for the Safety Population. If any trough concentration is NQ, it will be set to zero prior to summarization. Plots of mean trough concentrations (with standard deviation bars) by visit will be generated for each treatment.

The relationship between PK and efficacy may be explored as needed.

6.11 Safety Analyses

All safety analyses will be conducted on the Safety Population. The evaluation of safety will be based primarily on the frequency of adverse events (AEs), clinical laboratory assessments (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECG), physical examinations, weight, waist circumference, and vital signs (heart rate, blood pressures, respiratory rate, and temperature). Other safety data will be summarized as appropriate.

6.11.1 Adverse Events

For the purposes of this study, any sign (including a clinically significant laboratory result) or medical diagnosis noted by medical personnel, or symptom reported by the subject, regardless of relationship to investigational drug, that is treatment-emergent is considered to be an AE. All adverse events reported by the subject or observed by study site personnel from time of informed consent until completion of the study or premature withdrawal must

be recorded in the subject's CRF as per the CRF instructions. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) are defined as those AEs that have a start date on or after the first dose of study medication, or occur prior to the first dose and worsen in severity or relationship to study medication after the first dose. AEs beginning >7 days after last dose will not be considered treatment emergent. An overview of AEs will be provided by treatment group and in total for the following information:

- All TEAEs,
- Maximum severity of TEAEs,
- Study drug-related TEAEs,
- Maximum severity of drug-related TEAEs,
- All serious adverse events (SAEs),
- All treatment-emergent SAEs,
- Drug-related SAEs,
- Death due to AEs,
- Withdrawals due to AEs, and
- Withdrawals due to study drug-related AEs.

The numbers and percentages of subjects with TEAEs will be summarized for each treatment group and in total by MedDRA system organ class and preferred term. Similar summaries will be provided by maximum severity. Drug-related TEAEs will be summarized in the same manner. Listings of SAEs and AEs leading to study medication discontinuation will be provided.

6.11.2 Clinical Laboratory Evaluations

Summary statistics will be provided for safety laboratory tests at baseline and all scheduled post-baseline visits for chemistry, hematology, and urinalysis assessments by treatment group and in total. The change from baseline to post-baseline visits will also be presented.

The number and frequency of subjects with laboratory abnormalities (worst value post first dose for each subject) will be summarized by treatment group and in total. Shift tables from baseline to worst value post first dose will be presented for ALT and AST (>1xULN to ≤2xULN, >2xULN to ≤3xULN, >3xULN) and CK (>1xULN to ≤5xULN, >5xULN to ≤10xULN, >10xULN).

6.11.3 Vital Signs and ECG

Height, weight, waist circumference, and vital signs will be summarized at baseline and each scheduled post-baseline visit. The change from baseline will also be presented.

The overall ECG interpretation will be summarized by scheduled visit with counts and percentages by treatment group and in total.

6.11.4 Other Safety Parameters

All other safety parameters such as lifestyle, hospital anxiety and depression scale, Columbia-Suicide Severity Rating Scale, physical examination, and pregnancy tests will be listed.

7 GENERAL INFORMATION

The mock-ups for SAS-generated tables/figures/listings will be prepared in a separate document and finalized before database lock for the study.

7.1 Statistical Software

The creation of analysis datasets and all statistical analyses will be done using SAS® version 9.3. The PK parameters will be determined using Phoenix™ WinNonlin® version 6.3 or higher. The Medpace standard operating procedures will be followed for the validation of all SAS programs and outputs.