STATISTICAL ANALYSIS PLAN

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-ASCENDING DOSE STUDY TO DETERMINE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF UV-4B SOLUTION ADMINISTERED ORALLY IN HEALTHY SUBJECTS

Statistical Analysis Plan Status: Final 1.0
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Study Drug: UV-4B

Sponsor Reference No.: DMID 15-0062
[redacted] No.: 8311270

Clinical Phase I

Sponsor:

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Study Site:

Multiple Sites

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1. STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted]

2. TABLE OF CONTENTS

3. ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	Analysis Data Model
AE	adverse event
AR	accumulation ratio
$AUC_{(0-8)}$	area under the concentration-time curve from time zero to 8 hours after first daily dose on Day 1 and after the final dose on Day 7
$AUC_{(0-24)}$	area under the concentration-time curve from time zero to 24 hours postdose (total daily exposure) calculated as AUC(0-8)*3 (Day 7 only)
$AUC_{(0-last)}$	area under the concentration-time curve from time zero to time of last quantifiable concentration
BLQ	below the level of quantification
CDISC	Clinical Data Interchange Standards Consortium
CL/F	apparent systemic clearance after a single dose
C_{max}	observed maximum plasma concentration
CRF	Case Report Form
CSR	Clinical Study Report
CV%	coefficient of variation expressed as a percentage
DMID	Division of Microbiology and Infectious Diseases
DN	Dose Normalized
EC	Early Clinical
ECG	electrocardiogram
FDA	Food and Drug Administration
ICH	International Council for/Conference on Harmonisation
ITT	Intent-to-Treat
LLOQ	lower limit of quantification
MAD	multiple ascending dose
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
NC	not calculated

NR	no result
PK	Pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
R^2	coefficient of determination
SAP	Statistical Analysis Plan
SD	standard deviation
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TID	three times a day
TFLs	tables, figures, and listings
t_{max}	time to reach maximum plasma concentration
$t_{1/2}$	apparent terminal half-life (Day 7 only)
UV-4B	UV-4 hydrochloride
UV-4 free base (also UV-4)	active component of the UV-4B hydrochloride salt, having a chemical structure consisting of a 1 deoxynojirimycin (DNJ) head group and a 9-carbon methoxy alkyl side chain attached to the nitrogen of the DNJ ring
V_z/F	apparent volume of distribution during the terminal phase

4. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Protocol Amendment 3, dated 10 January 2017).

This SAP describes the planned analysis of the safety, tolerability, and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Emergent Product Development Gaithersburg, Inc and [redacted]Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's analysis presentation in the CSR.

The principal features of the proposed statistical analysis for this study were specified in the protocol before study initiation. This SAP provides more detail on the statistical considerations identified in the protocol; where considerations are different from the protocol, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Emergent Product Development Gaithersburg, Inc and [redacted]EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5. STUDY OBJECTIVES

Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of UV-4B given 3 times a day (TID) for 7 days in healthy subjects.

Secondary Objective

The secondary objective of the study is to determine PK parameters describing absorption and clearance of UV-4B given TID for 7 days in healthy subjects.

Study Outcome Measures

Primary Outcome Measures

- Evaluation and occurrence of adverse events (AEs) and serious adverse events (SAEs);
- Determination of changes from baseline for clinical laboratory tests.

Secondary Outcome Measures

- Determination of changes from baseline for physical exam (PE), vital signs, and 12-lead electrocardiogram (ECG)
- UV-4 plasma concentrations and PK parameters, including (please refer to section 10.5.1 for detailed PK parameter definition):
  i) C_{max}
  ii) t_{max}
  iii) $AUC_{(0\text{-last})}$ (Day 7 only)
  iv) $AUC_{(0\text{-}8)}$ (Day 1 and Day 7)
  v) $AUC_{(0\text{-}24)}$ (Day 7 only)
  vi) CL/F (Day 7 only)
  vii) V_z/F (Day 7 only)
  viii) $t_{1/2}$ (Day 7 only) and
  ix) AR.

6. STUDY DESIGN

This is a multiple ascending dose (MAD) study with up to 5 cohorts of healthy subjects planned. Each cohort will consist of 8 subjects (6 active; 2 placebo). Within each cohort, subjects will be randomized to receive UV-4B oral solution or placebo TID for 7 days (every 8 hours ± 0.5 hours). Subjects will be randomized immediately prior to dosing on Day 1, and no subjects will be replaced following randomization.

Safety assessments will include telemetry, ECG measurements, vital signs, PE, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, vomitus occult blood, and fecal occult blood), and AEs. For PK assessment, blood samples will be collected at multiple time points until clinic discharge. Subjects will return to the clinic on Day 10 (±1) for additional safety assessments and blood draws for laboratory assessments as well as a final PK assessment, and on Day 15 (±1) for the final study follow-up visit. A summary of dosing and PK sampling is provided in the following table; see Appendix D in the protocol for the full study schedule.

Visit number	Visit 2 Residential Period								Visit 3
	Dosing (TID)							Discharge From Clinic	Follow-up
Activity\Day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 10 ± 1**
Administration of the investigational product	X	X	X	X	X	X	X		
PK blood sampling	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[c]	X[c]	X[d]

[a] Blood samples for PK analysis will be collected at pre-dose (0 hour) and after the first dose at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min) hours (8 hour sample to be collected immediately before the second dose),

[b] One trough sample daily within 15 minutes before the first dose each day

[c] immediately (within 15 minutes) before the final dose, and at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min), 10 (±30 min), 12 (±30 min), and 14 (±30 min) hours after the final dose;

[d] One sample.

All safety and exposure data from Cohorts 1 through 3, along with a protocol amendment for further dose escalations (Cohorts 4 and 5) will be submitted to the FDA for review.

If any of the halting criteria (Protocol Section 9.6) are met, the study dosing will be halted for all subjects under treatment, although safety evaluation will continue. The SMC will review the data to determine if the study should proceed, and if any subjects need to be replaced at the same dose level.

7. TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Study Treatment Name	Treatment Abbreviation on TFL	Treatment Order on TFL	Cohort
Pooled Placebo TID	Pooled Placebo	1	1-5
30 mg UV-4B TID	UV-4B 30 mg	2	1
75 mg UV-4B TID	UV-4B 75 mg	3	2
150 mg UV-4B TID	UV-4B 150 mg	4	3
XX mg UV-4B TID	UV-4B XX mg	5	4
XX mg UV-B TID	UV-4B XX mg	6	5

8. SAMPLE SIZE JUSTIFICATION

The sample size chosen for this study is not based on statistical considerations. The number of subjects within each dose group was chosen based on historical experience with safety and tolerance trials. The sample size falls within the range of those used in other studies of this nature.

9. DEFINITION OF ANALYSIS POPULATIONS

The **All Subjects Population** will consist of any subjects who signed informed consent (excluding screen failures), and had study data recorded on the database as per the protocol.

The Intent to Treat Population (ITT Population) will consist of all randomized subjects in the groups to which they are randomly assigned, regardless of their adherence to the inclusion-exclusion criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug (UV-4B, placebo). The safety population will be analyzed according to the treatment and dose level into which the subjects are enrolled.

The **PK Population** will be defined as all subjects who received at least 1 dose of study drug (UV-4B) and have evaluable PK data, and complete scheduled post-dose PK measurements without protocol deviations, violations, or events thought to significantly affect the PK of the drug. Examples of significant protocol deviations, violations, or events include, but may not be limited to, vomiting occurring within 30 minutes following oral dosing, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK sampling. In the case of a significant protocol deviation, PK data collected during the affected treatment period will be excluded from summary statistics, but will be included in individual subject listings.

All protocol deviations that occur during the study will be considered for their severity/impact and the assignments of subjects to analysis populations will be finalized prior to database lock and unblinding. Details of subject assignment to the analysis populations will be listed.

10. STATISTICAL METHODOLOGY

10.1 General

Data listings and summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (All Subjects/ITT/Safety/PK).

For continuous data, summary statistics will include number of observations (n), the arithmetic mean, arithmetic standard deviation (SD), median, minimum (Min), and maximum (Max); for log-normal data (eg, the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation expressed as a percentage (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Baseline is defined as the last value for each assessment prior to the subject's first dose, including unscheduled values. Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual

subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using appropriate SAS® procedures such as Proc Univariate.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.3.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Version 2.1.0 or higher will be utilized to ensure compliance with CDISC standards.

10.1.1 Unscheduled Readings

Unscheduled readings are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. Unscheduled readings are labelled as 'Unscheduled' in the listings.

10.2 Protocol Deviations

Protocol deviations will be reviewed for their impact on the study data, and will be listed and tabulated.

10.3 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. Subject disposition will be summarized and listed.

10.4 Medical History, and Previous and Concomitant Medications

Subjects' medical history will be listed. Previous and concomitant medications will also be listed. Prior medication includes medication taken and ended before the initiation of study drug. Concomitant medication includes medication started after the first dose of study, or taken prior to the first dose of study drug and that is continued during the study.

10.5 Pharmacokinetic Assessment

10.5.1 Pharmacokinetic Analysis

Where possible, the following PK parameters will be determined from UV-4 plasma concentrations on Day 1 and Day 7 and using non-compartmental methods[3] performed in Phoenix WinNonlin (Certara USA, Inc., Version 6.4 or higher):

Parameter	Definition
C_{max}	Observed maximum plasma concentration
t_{max}	Time to reach maximum plasma concentration
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from time zero to time of last quantifiable concentration after the final dose on Day 7, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

$AUC_{(0-8)}$	Area under the concentration-time curve from time zero to 8 hours after first daily dose on Day 1 and after the final dose on Day 7, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{(0-24)}$	Total daily exposure at steady state, calculated as $AUC_{(0-8h)} \times 3$ (Day 7 last dose only)
CL/F	Apparent systemic clearance at steady state (Day 7 only), calculated as dose divided by $AUC_{(0-8)}$
V_z/F	Apparent volume of distribution during the terminal phase, calculated as $CL/F / \lambda_z$ after multiple doses (Day 7 only)
$t_{1/2}$	Apparent terminal half-life (Day 7 only), calculated as $\ln(2)/\lambda_z$
AR	Accumulation ratio, calculated as $AUC_{(0-8)}$ after last dose/$AUC_{(0-8)}$ after first dose

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out using actual sampling times.

Concentrations for PK analyses will be used as supplied by the analytical laboratory. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

If multiple peaks occur, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

10.5.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

- Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;
    - Any embedded BLQ value (BLQ value occurring between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
    - If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
    - If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
    - If a predose concentration is missing prior to the first daily dose on Day 1, these values will be set to zero.

10.5.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-life

10.5.3.1 Number of Data Points

- At least 3 data points will be included in the regression analysis and, preferably, should not include C_{max}. Cmax may be included if needed to provide 3 data points.

10.5.3.2 Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient of determination of exponential fit (R^2 adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.
- An elimination half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

10.5.3.3 Period of Estimation

- The $t_{1/2}$ will be estimated over a time period of at least two half-lives, where possible.
- Where a $t_{1/2}$ is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value will be discussed in the CSR.

10.5.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

10.5.5 Anomalous Values

- If a value is considered to be anomalous by being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and CSR.
- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.
- Positive predose value(s) greater than 5% of C_{max} on Day 1 may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

10.6 Presentation of Pharmacokinetic Data

10.6.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in a plasma concentration data series to be summarized.
    - For the calculation of summary statistics, BLQ values will be set to half the LLOQ
    - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
    - Where there is NR, values will be set to missing.

- If there are fewer than 3 values in the data series, only the Min, Max and n will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, Min and Max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is BLQ, it will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.

10.6.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max}.

10.6.3 Pharmacokinetic Statistical Methodology

All UV-4 plasma concentration data and derived PK parameters will be summarized by cohort.

If applicable, the PK parameters $AUC_{(0\text{-}8)}$, $AUC_{(0\text{-last})}$, and C_{max} will be assessed for dose proportionality using the data from the last dose on Day 7.

To investigate the dose proportionality[4] of AUCs and C_{max}, a statistical analysis using the power model[4] will be conducted. The power model will have the form:

$$Y = a*(dose)^b$$

where Y is the PK parameter, and a and b are the coefficient and exponent, respectively, of the power equation.

By taking the natural logarithm (ln), the power model can be analyzed using linear regression and has the form:

$$\ln(Y) = \ln(a)+b*\ln(dose) + error$$

$$=\alpha + \beta*\ln(dose) + error,$$

where α is the intercept, and β is the slope, and ln(dose) is based on the dose size for each subject. Estimates of slope and intercept along with their 90% confidence intervals will be reported. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality using the power model.

For dose proportionality, the slope of the regression line (b) = 1 and for dose independence b = 0.

An additional classification term for treatment will be added to the above model to assess departure from linearity. Linearity, and hence the power model, will be assumed appropriate if the treatment term is not significant at the 5% significance level and the diagnostic plots seem reasonable. The assessment

of linearity may also be determined visually from plots by the Pharmacokineticist. This assessment may override the statistical assessment; where this occurs; it will be detailed in the CSR.

In previous single-dose escalation study[5], it was concluded that UV-4 was dose proportional over the 30- to 1000-mg range in $AUC_{(0\text{-}inf)}$ where the 90% CI of the slope is (0.984, 1.043). The 90% CI of the slope for C_{max} was (1.048, 1.157), which was considered to be approximately dose-proportional. For the current study, if the assumption of linearity is considered acceptable and if the 90% CI for b is entirely with (0.8, 1.25), the relationship between dose and the PK parameter will be concluded to be dose proportional for the dose range studied. Caution should be used when interpreting results, since this study is not based on power calculations.

Scatter plots with regression lines will be presented with ln(dose) as the x-axis versus the ln(PK parameter) as the y-axis.

10.7 Safety and Tolerability Assessments

10.7.1 Drug Exposure and Compliance

Treatment exposure and compliance will be summarized descriptively by treatment group for the Safety population.

10.7.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs after administration of the first dose of study product or that is already present prior to the first dose of study product and becomes more severe postdose. In this study AEs will be evaluated from time of the first dose administration through the last follow-up visit. A medical condition that exists at the time of screening will be recorded as an AE only when it deteriorates at any time after the first study dose administration.

All AEs must be graded for severity and relationship to study product per Section 9.2.1 of the Protocol. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) AE coding system, version 19.0.

All TEAEs will be summarized for all subjects in the safety population by maximum severity, relationship to the study drug (as assessed by the Principal Investigator [PI]), and initial onset day. Serious TEAEs will be summarized by maximum severity, and relationship to the study drug. TEAEs leading to treatment discontinuation will also be summarized by maximum severity and relationship to the study drug. The frequency including the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE will also be summarized and displayed. TEAEs summaries will be presented by treatment, and by MedDRA (Version 19.0) system organ class and preferred term.

All AEs, severe AEs, serious AEs, deaths (if any), and events resulting in study discontinuation will be listed. Any individual dose-limiting toxicity (Protocol Section 9.7) will also be listed.

10.7.3 Physical Examination

Physical examination findings from subjects will be listed by treatment, study day and exam type.

10.7.4 Clinical Laboratory Parameters

Observed values and change from baseline data for clinical laboratory parameters (hematology, serum chemistry, coagulation, urinalysis) will be summarized by treatment. Baseline is considered as the last laboratory test result collected before the first dose.

Shift tables will be presented for serum chemistry, hematology, coagulation, and urinalysis parameters according to laboratory toxicity grading. The grading of laboratory findings was based on the *FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and *Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study (found in Appendix II of the protocol). A summary of clinical laboratory values of toxicity Grade 1 or higher will also be provided by parameter and treatment.

Individual subject data listings (serum chemistry, hematology, coagulation, and urinalysis) will be provided to summarize all laboratory values including change from baseline, all laboratory values outside the clinical reference ranges, and all laboratory values of toxicity Grade 1 or higher.

Values for any serum chemistry, hematology, coagulation, and urinalysis values outside the clinical reference ranges and also meeting toxicity grading criteria will be flagged on the individual subject data listings.

Fecal and vomitus occult blood findings will be summarized and listed by treatment and study day.

10.7.5 Vital Signs

Routine vital signs data (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature) and orthostatic vital signs data (blood pressure and pulse rate) will be listed and summarized by treatment, along with changes from baseline, where baseline is defined as the last value prior to the first dose on Day 1, including unscheduled values. Orthostatic change is the standing value minus the supine value taken prior to the standing value.

A summary of vital signs values of toxicity Grade 1 or higher will also be provided by parameter and treatment. The grading of vital signs was based on the *FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* as modified for this study (found in Appendix II of the protocol).

For routine vital signs data, values outside the clinical reference ranges will be flagged on the individual subject data listing, as will the vital sign values meeting toxicity Grade 1 or higher.

The reference ranges for routine vital signs are: supine systolic blood pressure (90-140 mmHg), supine diastolic blood pressure (50-90 mmHg), supine pulse rate (40-100 bpm), respiratory rate (10-24 breaths/minute) and oral temperature (35.5°C -37.8°C).

Orthostatic decreases of ≥20 mmHg for systolic blood pressure or ≥10 mmHg for diastolic blood pressure or an increase in heart rate of >30 bpm are considered to be of potential clinical concern and will also be highlighted on the individual data listings. Repeat and unscheduled readings will be handled as defined in Section 10.1.1.

10.7.6 Electrocardiogram

Triplicate 12-lead ECGs will be collected at predose on Day 1 only, and a single ECG will be collected at all other scheduled times. The mean of these 3 values (including any unscheduled values) at Day 1 predose will be used in all subsequent calculations of changes from baseline.

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QTc interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, QRS duration, and heart rate. ECG data will be reviewed by the PI or designee to determine abnormal results and their clinical significance.

The ECG data will be summarized by treatment, together with changes from baseline.

An outlier analysis will be performed of all individual postdose measurements, including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: > 450 ms (male) or > 470 ms (female); > 500 ms; change from baseline > 30 ms to ≤ 60 ms; and change from baseline > 60 ms. Additionally, PR duration > 220 ms and QRS duration > 120 ms will be summarized.

Individual subject ECG data will be listed. Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listing. The reference ranges are 50-100 bpm for heart rate, 120-210 ms for PR interval, ≤120 ms for QRS duration, 340-450 ms for QT interval, >450 ms for QTcF interval. All incidences of QTcF >450, >480, and >500 ms will be flagged on the individual subject listing. All incidences of QTcF change from baseline >30 and >60 ms will be flagged on the individual subject listing.

10.7.7 Other Assessments

All other safety assessments not detailed in this section, including telemetry, will be listed.

10.7.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

The SMC review of all safety and PK data will be conducted after completion of each cohort. Interim PK data will be masked by the use of dummy coding to prevent unblinding of study subjects. Upon completion of review by the SMC, safety summary and PK data will be sent to the Food and Drug Administration (FDA), for review. The study will be paused during FDA review and dose escalation and subject enrollment into the next higher cohort will only proceed upon approval by the FDA. Details on the SMC review are presented in the SMC charter.

Interim safety TFLs will be produced for SMC review, including listings and summary tables of subject disposition, treatment exposure and compliance, AEs, SAEs, TEAEs, clinical laboratory data (including incidences of toxicity Grade 1 or higher), vital signs (including incidences of toxicity Grade 1 or higher), ECGs, and fecal and vomitus occult blood findings.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
3. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York, NY: Marcel Dekker; 1982.
4. Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L et al. Assessment of dose proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Information Journal 1995; 29: 1039-1048.
5. Emergent Product Development Gaithersburg Inc. Randomized, double-blind, placebo-controlled, parallel group, single ascending dose study to determine the safety, tolerability and pharmacokinetics of UV-4B solution administered orally in healthy subjects. Clinical Report for Study DMID 13-0001, issued 07 July 2016.