Statistical Analysis Plan: PTK0796-CABPPO-19109

Study Title:	A Phase 1 Multi-Center Study to Measure the Pharmacokinetics of Oral Omadacycline in Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)
Study Number:	PTK0796-CABPPO-19109
Study Phase:	1b
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Confidentiality Statement

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABG	arterial blood gas
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse Event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration time curve
AUC_{0-24}	AUC from time 0 to 24 hours after dosing
AUC_{last}	AUC from time 0 to the last quantifiable concentration
β-hCG	serum β-human chorionic gonadotropin
BP	blood pressure
CABP	community-acquired bacterial pneumonia
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CV	coefficient of variation
CXR	chest X-ray
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FFU	Follow-up visit
ICF	Informed Consent Form
IND	Investigational New Drug
ITT	intent-to-treat
IV	Intravenous
IxRS	interactive voice/web response system

MedDRA	Medical Dictionary for Regulatory Activities
PaO_2	partial pressure of arterial oxygen
PK	Pharmacokinetics
Po	per oral
PORT	Pneumonia Outcomes Research Team
PT	preferred term
PTE	Post Therapy Evaluation
QD	once per day
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed plasma concentration
$T_{1/2}$	terminal-phase elimination half-life
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell (Count)

1 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol PTK0796-CABPPO-19109, "A Phase 1 multi-center, open label study to measure the Pharmacokinetics of Oral Omadacycline in Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)." The statistical plan described is an *a priori* plan and no analysis prior to the preparation of this plan has been conducted. This SAP summarizes the study design and objectives and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol PTK0796-CABPPO-19109.

All decisions regarding final analysis, as defined in this SAP document, have been made prior to database freeze of the study data.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the PK of oral (po) only omadacycline in adults with CABP.	The following plasma PK parameters will be determined: • Area under the plasma concentration time curve (AUC) from time 0 to 48 hours after dosing (AUC_{0-48}) • Area under the plasma concentration time curve (AUC) from time 0 to 24 hours after dosing (AUC_{0-24}) • AUC from time 0 to the last quantifiable concentration (AUC_{last}) • Maximum observed plasma concentration (C_{max}) • Time to reach maximum observed plasma concentration (T_{max}) • Elimination half-life associated with the terminal slope of the semilogarithmic concentration-time curve ($T_{1/2}$)
Secondary Objective	**Secondary Endpoint**
• To evaluate the safety of omadacycline in the treatment of adults with CABP.	The following variables will be analyzed descriptively in the Safety population: • Adverse Events (AEs), and Serious Adverse Events (SAEs) • Vital signs (systolic and diastolic BP, pulse/heart rate, body temperature, pulse oximetry, RR), including change from Baseline by time point measured • Clinically notable vital signs (meeting predefined criteria as specified in the SAP) by time point measured • Laboratory parameters (Hematology and Serum Chemistry), including change

	from Baseline by visit and overall worst post-baseline • Clinically notable laboratory parameters (meeting predefined criteria as specified in the SAP) by visit and overall worst post-baseline • Concomitant Medications • Urinalysis and Pregnancy assessments (Screening only)
Exploratory Objectives	**Exploratory Endpoint**
• To evaluate the efficacy of oral only omadacycline in the treatment of adults with CABP.	The following is a list of key assessments that will be performed: • Assessment of signs and symptoms of CABP by the investigator • Clinical Stability • Final Follow-up Assessment of signs and symptoms of CABP by the investigator

3 STUDY DESIGN

This is an open-label Phase 1b study evaluating oral omadacycline in the treatment of adults with CABP.

This study is intended to evaluate the PK of an oral dosing regimen in adults with CABP. Subjects will initiate treatment with an oral loading dose of 300 mg BID on Day 1 followed by 300 mg on subsequent days.

Following a screening period of up to 24 hours, eligible subjects will be assigned to receive 7 to 10 days of po treatment. Subjects with baseline bacteremia (i.e., confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment after consultation with the medical monitor.

Subjects may receive oral treatment in either inpatient or outpatient settings, provided that all assessments can be completed at the timepoints required by protocol.

Eligible subjects will be assigned to the following treatment groups.

Test Article	Study Day 1	Study Day 2	Study Days 3-10
Omadacycline	300 mg po BID	300 mg po QC	300 mg po QC

po = per oral, a dosing day is a 24-hour day not a calendar day

a The total duration of treatment is 7 to 10 days. Treatment duration can be extended to up to 14 days for subjects with bacteremia that, in the opinion of the investigator, requires more than 10 days of treatment.

Refer to the Schedule of Events (Appendix 1) for the summary of subject visits and assessments through end of treatment (EOT).

Subjects will return to the study site for a Post Therapy Evaluation (PTE) 5 to 10 days after the last dose of test article. A Final Follow-up visit (FFU) will be conducted within 30 to 37 days following the first dose of test article. The FFU assessment may be conducted via telephone contact or by another interactive technology for subjects who had an outcome of Clinical Success in the opinion of the investigator at EOT and PTE and had no AEs or clinically significant laboratory or electrocardiogram (ECG) abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in-person study visit.

Subjects will participate in the study for up to 37 days. Following a screening period of up to 24 hours, eligible subjects will be assigned to receive treatment. Eligible subjects will be assigned to receive 7 to 10 days of po treatment. Subjects with baseline bacteremia (i.e., confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment after consultation with the medical monitor.

The study is expected to be complete in approximately 6 months.

4 ASSESSMENT OF CABP SYMPTOM SEVERITY FOR EFFICACY

The investigator will specifically assess the presence and severity level of the subject's symptoms of cough, sputum production, pleuritic chest pain, and dyspnea on a 4-point scale (absent, mild, moderate, or severe) based upon the Community Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment (see Protocol Appendix 2) and enter the symptom severity level into the eCRF. Subjects must have at least 3 of these 4 symptoms of CABP to be eligible for the study.

5 GENERAL STATISTICAL CONSIDERATIONS

All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

During the analysis and reporting process, any deviations from the statistical analysis plan designed for this protocol will be described and justified in the final clinical study report (CSR).

Unless specified otherwise, baseline will be defined as the last non-missing assessment prior to the study drug administration for each treatment period. Unscheduled visits will be used in determining baseline.

Missing values will not be imputed for safety endpoints. The handling rule for missing PK concentration will be described in Section 6.2.

5.1 Sample Size Determination

This study is designed to evaluate the PK profile of an oral dosing regimen, 300mg BID on Day 1 and QD on Day 2, in adults with CABP. The sample size determination is based on consideration of the precision of the estimate, GMR of $AUC_{(0-48)}$ for 300mg po to 100mg IV, derived from model-based simulations of omadacycline concentration data (Phase I studies).

With 20 subjects evaluable for PK population, there will be 90% probability that the 90% CIs of the GMR for $AUC_{(0-48)}$ will be within 80% and 125%. Up to 30 subjects will be enrolled so that at least 20 subjects are evaluable for bioavailability estimation.

The total number of subjects may be adjusted to ensure that there are 20 subjects evaluable for PK population.

5.2 Study Analysis Populations

5.2.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all enrolled subjects regardless of whether the subject received test article.

5.2.2 Safety (SAF) Population

The Safety population will consist of all enrolled subjects who receive test article. All safety analyses will be conducted in this population.

5.2.3 Pharmacokinetic (PK) Population

The pharmacokinetic population is defined as subjects who receive test article and have at least 1 evaluable PK parameter. If any subject has an emesis within 4 hours after dosing, the subject will be excluded from PK Analysis. If any subject discontinues dosing before 48 hours with incomplete PK profile for 0-24 or 0-48 hours, the subject will be excluded from the PK analysis for AUC_{0-24} and $AUC_{0-48,}$ respectively.

This population will be used for listings, summary tables, and plotting of individual and mean/median concentration-time profiles.

6 STUDY POPULATION SUMMARIES

6.1 Disposition

The number of subjects included in each of the analysis populations (i.e., ITT, Safety, and PK) will be summarized. A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion in/exclusion from the populations and the reason for exclusion from each of the populations.

A listing will be provided of enrolled subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met. The number and percentage of subjects completing the study (defined as receiving at least 1 dose of test article and returning for all the EOT, PTE, and Follow-up Visits), not completing the study, missing each of the EOT and PTE Visits, and prematurely discontinuing from test article will be presented for the ITT population. Reasons for premature discontinuation of test article, not completing the study, and for missing each of the visits, as recorded on the eCRF will be summarized (number and percentage) for the ITT populations. A listing of all subjects who prematurely discontinued from test article or not completing the study will be presented, and the primary reason for discontinuation of test article or not completing the study, as well as the visit(s) missed and the reason for missing the visit(s), will be provided.

6.2 Demographics and Baseline Characteristics

Except where indicated, demographic data and baseline characteristics will be presented for the ITT population. A table will present the subject demographics (e.g., gender, age, ethnicity, and race) and baseline characteristics (height, weight, BMI, and creatinine clearance categorized before the start of test article as:

- severe renal impairment [< 30 mL/min],
- moderate renal impairment [30-50 mL/min],
- mild renal impairment [> 50-80 mL/min], and
- normal renal function [> 80 mL/min]).

Age will be calculated from the date of birth to the informed consent date. Age will be summarized as a continuous variable and in the categories, 18-45, >45-65, and > 65 years.

Creatinine clearance will be calculated from the local laboratory data since these data were used for determination of the inclusion and exclusion criteria and will be determined from the Cockcroft-Gault equation.

A table will provide the frequency counts and percentages for subjects who received prior antibiotics, and PORT Risk Class (from the eCRF) for the ITT population. PORT score will also be summarized as a continuous variable.

Baseline assessments of clinical symptoms, clinical signs, abnormal vital signs, and abnormal laboratory signs of CABP will be presented for the ITT, and PK populations.

The number and percentage of subjects with each of the CABP symptoms (cough, pleuritic chest pain, dyspnea, and phlegm/sputum production) by severity (absent, mild, moderate, severe) will be presented. The number and percentage of subjects with the presence by severity (i.e., absent, mild, moderate, severe) of the following clinical signs will be provided: rales, rhonchi, dullness on percussion, bronchial breath sounds, wheezing, decreased breath sounds, and egophony. The number and percentage of subjects with fever (defined as body temperature > 38°C [100.4°F] oral or rectal), hypothermia (defined as body temperature < 36°C [95.5°F] oral or rectal), hypotension with systolic blood pressure < 90 mmHg, heart rate > 90 bpm, respiratory rate > 20 breaths/min, hypoxemia (defined as PaO_2 < 60 mmHg by arterial blood gas or oxygen saturation < 90% by pulse oximetry), elevated total WBC count (> 12,000 cells/mm^3), leucopenia (WBC < 4,000 cells/mm^3), elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count) and any of elevated total WBC count, leucopenia or elevated immature neutrophils will be summarized.

Risk factors for CABP will be presented for the ITT population. Risk factors include smoking (current, past, and descriptive statistics of the number of years since quitting for those subjects who were previous smokers), receipt of pneumococcal vaccine, prior lung infection, whether the subject had mild to moderate COPD, symptomatic asthma with wheezing, and chronic cough with or without sputum production.

Readings of baseline chest radiographs, including the type of assessment (CXR or CT scan), presence of pleural effusion, whether the pleural effusion is unilateral or bilateral, whether the pulmonary infiltrate was uni- or multi-lobar and the location of the pulmonary infiltrate (combining left upper lobe and lingula) will be summarized for all subjects in the ITT population.

A listing will be provided that includes all baseline microbiology isolates.

6.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the CSR). Medical history will be presented in a data listing.
Other medical and surgical history will be summarized based on MedDRA system organ class for the ITT and Safety populations.

6.4 Inclusion and Exclusion Criteria

All inclusion/exclusion criteria deviations recorded in the electronic case report form (eCRF) will be presented in a data listing.

6.5 Treatment Compliance and Exposure

Exposure summary will be presented for the Safety population. The distribution of subjects by the total number of days on therapy, will be presented.

Treatment compliance is defined as the number of oral doses received divided by the number of doses expected (× 100) over the time period defined by the first dose date and the last dose date. Descriptive statistics for treatment compliance and the number and percentage of subjects at least 80% compliant will be presented for the ITT population.

7 PHARMACOKINETIC ANALYSIS

7.1 Pharmacokinetic Sample Concentrations

Blood samples for PK assessments of omadacycline will be collected from all subjects at the following time points:

- Day 1: within an hour prior to Dose 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours (12 hour taken immediately before Dose 2);

  Dose 2 administered (times relative to Dose 1); 13, 13.5, 14, 14.5, 15, 16, 24 hours post dose

- Day 2: within an hour prior to dose, 1, 1.5, 2, 2.5, 3, 4, 6 hours
- Day 3: prior to the Day 3 dose
- EOT: anytime during the visit

Individual plasma concentration of omadacycline and time deviation data for Safety Analysis Set will be presented in data listings. Plasma concentration data will be summarized by scheduled time point for the PK Analysis Set for each treatment using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Concentrations that are below the limit of quantification (BLQ) before the first quantifiable concentration will be treated as zero for descriptive statistics. Below the limit of quantification values after the first quantifiable concentration will be set as missing and excluded for summary statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable, if all individual values are BLQ.

Mean (±SD) plasma concentrations versus nominal time will be plotted by treatment on both linear and semi-logarithmic scales for the PK Analysis Set. Individual plasma concentrations versus actual time will be plotted on both linear and semi-logarithmic scales for the Safety Analysis Set.

7.2 Pharmacokinetic Parameters

Individual plasma concentration versus actual time data will be used to estimate the PK parameters of omadacycline in plasma by standard noncompartmental methods using WinNonlin (Phoenix) validated SAS programs. For the calculation of PK parameters, BLQ values before the first quantifiable concentration will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

The following PK parameters will be calculated for omadacycline in plasma, if data permits:

Parameter	**Description**
C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach maximum observed plasma concentration
AUC_{0-48}	Area under the plasma concentration versus time curve (AUC) from time 0 to 48 hours after dosing, calculated using the linear trapezoidal linear interpolation method
AUC_{0-24}	Area under the plasma concentration versus time curve (AUC) from time 0 to 24 hours after dosing, calculated using the linear trapezoidal linear interpolation method
AUC_{last}	AUC from time 0 to the time of last quantifiable concentration (Excluding the PK concentration at EOT timepoint), calculated using the linear trapezoidal linear interpolation method
$T_{1/2}$	Plasma terminal elimination half-life, calculated as $T_{1/2}= \ln (2)/ \lambda_z$ λ_z = Terminal elimination rate constant calculated by linear regression of the terminal portion of the natural log-plasma concentration versus time curve. This will be calculated after third dose of administration.

The individual PK parameters will be presented in the data listings for the PK Analysis Set. The PK parameters will be summarized using the PK Analysis Set with the following descriptive statistics: n, mean, SD, CV, median, minimum and maximum. Descriptive statistics will include geometric mean and geometric mean CV for AUC (0-48), AUC (0-24), AUC (last) and Cmax. For individual parameters that are listed but not summarized in the descriptive statistics due to Rsq < 0.8, a footnote will be added.

7.3 Treatment Comparison

The comparison of interest is the comparative bioavailability assessment between the test, 300mg po in CABP patients, and the reference, 100mg IV in healthy subjects. The comparison will be based on 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of $AUC_{(0-48)}$ for the two dosing regimens being within 80% and 125%.

The PK parameter data for 100mg IV in healthy subjects comes from PTK 0796-SDES-0501(n=5), PTK 0796-BEQU-0801(n=11), PTK 0796 WOIV-0703(n=12), CPTK796A2104(n=21), CPTK796A2201(n=6), PTK 0796-RENL-15102(n=8). Using the

day 1 plasma concentration profile of the 100mg IV QD dosing from these studies, a BID dosing on day 1 and a QD dosing on day 2 was simulated using the superposition principle. The simulation model-based AUC $_{(0\text{-}48)}$ characteristics for each study are shown in the table below:

Study	n	Mean ln (AUC $_{(0\text{-}48)}$)	SD ln (AUC $_{(0\text{-}48)}$)
SDES-0501	5	9.5968	0.1896
BEQU-0801	11	9.8702	0.1467
WOIV-0703	12	10.017	0.1630
A2104	21	10.043	0.1649
A2201	6	10.129	0.1752
RENL-15102	8	10.039	0.1838
Total	63	9.9800	0.2091

The 90% CI of the GMR will be formed as follows: let $\bar{y}$, s, and n represent the average, standard deviation, and sample of the log (AUC $_{(0\text{-}48)}$) data observed in the current study. The pooled standard deviation is $s_p = \sqrt{\frac{(63-1)0.2091117^2+(n-1)s^2}{63+n-2}}$; the number of degrees of freedom is $df = 63 + n - 2$; and critical value for the CI is 95th percentile of a t-distribution, $t_{df,0.95}$. The 90% confidence interval on the log scale is

$$\bar{y} - 9.980044 \pm t_{df,0.95} s_p \sqrt{\frac{1}{63} + \frac{1}{n}} = (Lower, Upper)$$

and the CI for the GMR is $(e^{Lower}, e^{Upper}) \times 100\%$.

The following SAS code will be used:

[redacted]

7.4 Analysis of EOT PK concentration data

The sample at the EOT will be collected during the patient's visit. The patients' last dose will be recorded in a dosing diary and the time of sample collection will be recorded by the site during their visit. Since patients will be outpatient at their EOT visit and must be in a fasted state when dosing, dosing is likely to occur at home prior to their site visit.

Therefore, the data collected at EOT will be used to qualitatively assesses patient's compliance by using the concentration of the EOT sample taken at the recorded time after the last dose and compared to initial dose as the clinical efficacy is an exploratory endpoint that will be evaluated. If the EOT visit is not completed on the day of last dose but within the 2-day window as specified in the protocol, then the initial dose profile will be extrapolated using the terminal elimination rate constant and will be used to make the comparison.

8 SAFETY AND TOLERABILITY

All safety analyses will be conducted in the Safety population. Safety parameters include adverse events (AEs), vital signs, and clinical laboratory parameters.

8.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 17.1 or higher of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs), but all AEs will be provided in a listing. A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity on or after the initiation of active test article. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first dose of active test article. If time of the AE is missing and it occurred on the same date as the first dose of active test article, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first dose of test article, the AE should be defined as treatment emergent.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, any drug-related SAE, any serious TEAE leading to death, any TEAE leading to premature discontinuation of test article, any TEAE leading to premature discontinuation from the study, any TEAE leading to dose interruption of test article, and any serious TEAE leading to premature discontinuation of test article.

The number and percentage of subjects reporting a TEAE will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated or related to test article). The incidence of TEAEs will be summarized by preferred term, sorted by decreasing frequency, for all TEAEs, related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation. The incidence of serious TEAEs, TEAEs leading to premature discontinuation of test article, and TEAEs leading to a dose interruption of test article will be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to test article.

In addition, all AEs (including non-TEAEs), serious TEAEs, TEAEs leading to discontinuation of test article, and TEAEs leading to dose interruption of test article will be provided in listings by subject, verbatim term, MedDRA system organ class and preferred term, start and end date, seriousness flag, severity, relationship to test article, relationship to study protocol, action taken with test article, non-test article action taken and outcome.

8.2 Vital Signs

Vital signs include blood pressure (BP), heart rate, pulse oximetry, RR, and body temperature.

Descriptive statistics of the change from baseline to each post-baseline time point and the highest and lowest post-baseline value will also be provided. Baseline is defined as the value closest to but prior to the initiation of test article administration.

Post-baseline vital signs will be defined as clinically notable (CN) if they meet the criterion value or both the criterion value and the change from baseline criterion listed in Appendix 4. The incidence of CN vital signs will be summarized by time point and will be listed and flagged in by-subject listings. The overall post-baseline incidence of CN values for each vital sign parameter, which includes values from unscheduled post-baseline visits, will also be summarized. A listing will also be provided of subjects with a CN vital sign and will list all values for a vital sign noted as CN.

8.3 Laboratory Values

Summaries of laboratory data will include hematology, and chemistry, parameters. Laboratory parameters will be presented in alphabetic order with the following exceptions: differentials of white blood cell (WBC) counts will be presented following the WBC results, and chemistry parameters will first be grouped by organ class (renal, liver, electrolytes, and other) and presented alphabetically within each of these classes, as shown below.

Table 1. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Renal	Creatinine
Renal	Urea
Liver	Alkaline phosphatase (ALP)
Liver	ALT
Liver	AST
Liver	Total Bilirubin
Liver	GGT
Electrolytes	Bicarbonate
Electrolytes	Calcium
Electrolytes	Chloride
Electrolytes	Magnesium
Electrolytes	Potassium
Electrolytes	Sodium
Other	Albumin
Other	Amylase
Other	Blood glucose
Other	Cholesterol
Other	CK
Other	LDH

Table 1. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Other	Lipase
Other	Phosphate
Other	Total protein
Other	Uric acid

Baseline is defined the local lab value that is closest to and prior to the first dose of study drug.

Several analyses of the laboratory data will be presented. Descriptive statistics (based on International System [SI] units) for chemistry, hematology and the change from baseline will be summarized by treatment group at each time point (EOT Visit and PTE Visit), and for the overall worst value post-baseline (which includes unscheduled visits).

Clinically notable laboratory values will be defined as any lab values with at least a 2-grade increase from baseline. Shift tables will be presented to show the number of subjects with a laboratory value with a grade of 0, 1, 2, 3 or 4 at baseline versus the value at each visit and the worst post-baseline value. Number and percentage of subjects with at least a 2-grade increase from baseline (based on DMID criteria shown in Appendix 3) will be summarized. Percentages for each laboratory test will be based on the number of subjects with a baseline and post-baseline evaluation of the specific laboratory test. A listing will be provided which gives all laboratory results for a given laboratory test for subjects who have at least one 2-grade increase from baseline.

Detailed subject listings of all laboratory data collected during the study will be provided, including calculated creatinine clearance (using the Cockcroft-Gault equation). Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable thresholds (CN) of at least a 2-grade increase from baseline.

8.4 Physical Examinations

Subject listings of all physical examination results by body system will be provided. Any clinically significant changes from baseline will be recorded as adverse events.

9 EXPLORATORY EFFICACY MEASURES

9.1 Investigator's Assessment of Clinical Response

9.1.1 Investigator's Assessment of Clinical Response at EOT

EOT assessments should be performed on the calendar day of, or within 2 days following the last dose of any test article. If a subject withdraws prematurely or terminates participation in the study prior to completion of the planned antibiotic therapy, the EOT visit should be conducted.

The investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

Clinical Success: the subject is alive, and the infection is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual findings related to infection (i.e., cough) requiring ancillary (i.e., non-antibiotic) treatment (e.g., expectorant). For the subject to be considered a Clinical Success at EOT, the subject may not meet any criteria for Clinical Failure or Indeterminate at EOT.

Clinical Failure: the subject requires alternative antibacterial treatment for CABP prior to EOT related to either (a) progression or development of new symptoms of CABP or (b) development of infectious complications of CABP (e.g., empyema, lung abscess) or (c) subject developed an AE that required discontinuation of study therapy. Other reasons for Clinical Failure are:

- Subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to EOT visit.
- Other specified reason.

Indeterminate: the clinical response to test article could not be adequately inferred due to:

- Subjects were not seen for EOT evaluation because they withdrew consent or were lost to follow-up,
- Other specified reason.

9.1.2 Investigator's Assessment of Clinical Response at PTE

The PTE assessment is to be performed 5 to 10 days after the subject's last day of therapy. The investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

Clinical Success: survival after completion of a test article regimen without receiving any systemic antibacterial therapy other than test article, resolution of signs and symptoms of the infection present at Screening with no new symptoms or complications attributable to CABP and no need for further antibacterial therapy.

Clinical Failure: the subject requires alternative antibacterial treatment for CABP prior to PTE related to either (a) progression or development of new symptoms of CABP or (b) development of infectious complications of CABP (e.g., empyema, lung abscess).

- The subject is receiving antibiotics that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to PTE.
- Other specified reason.

Indeterminate: the clinical response to test article could not be adequately inferred due to:

- Subjects were not seen for PTE evaluation because they withdrew consent or were lost to follow-up.
- Other specified reason.

9.2 Clinical Stability

The formal determination of the subject's Clinical Stability will be done programmatically using the investigator's assessment of the subject's vital signs entered into the eCRF. The investigator is not responsible for categorizing the subject's Clinical Stability. Clinical Stability will be determined daily and analyzed by day, early clinical response window, EOT, and PTE.

Patients will be considered clinically stable if they achieve all the following criteria:

- temperature ≤37.8°C (100°F);
- heart rate ≤100 beats/minute;
- RR ≤24 breaths/minute;
- systolic blood pressure ≥ 90 mmHg; and
- arterial oxygen saturation ≥ 90% or PaO2 ≥ 60 mmHg on room air.

9.3 Clinical Outcomes

The number and percentage of subjects classified as a Clinical Success, Clinical Failure, and Indeterminate by the Investigator's Assessment at EOT in the ITT population will be presented. The number and percentage of subjects in each response category for the overall assessment of Clinical response at PTE (based on the investigator's assessment) in the ITT population will also be presented.

The number and percentage of subjects with stabilization of all vital signs associated with CABP at EOT will be presented for the ITT population as will the number and percentage of subjects with stabilization of each vital sign. These include temperature (no fever or hypothermia), SBP (> 90 mmHg), heart rate (< 90 bpm), RR (< 20 breaths/minutes), and PaO_2 (> 60 mmHg by pulse oximetry or ABG). WBC count (< 12,000 cells/mm^3 or ≥ 4,000 cells/mm^3) and immature neutrophils (< 15%).

10 DATA HANDLING CONVENTIONS

10.1 Premature Withdrawal and Missing Data

If available, pharmacokinetic parameters from the concentration-time profile data of patients who drop out or are withdrawn will be calculated but will be excluded from the final statistical analysis.

For all variables, only the observed data from the patients will be used in the statistical analyses, i.e., there is no plan to estimate missing data, unless otherwise specified.

Missing data occurs when any of the requested data is not provided, leading to blank fields on the collection of the instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as "Not applicable” and “Not evaluable” are not considered to be missing data and such be displayed as such.

All missing and partial dates for adverse events or for medications received after enrollment will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Appendix 2. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used in all listings.

Missing start and stop times for prior and concomitant antibiotics will be queried for a value. If no value can be obtained but the site indicates the antibiotic was received (onset time) prior to the first dose of test article, 00:01 will be used for the onset time. If the site also indicates that the end time was prior to the first dose of test article, 00:01 will be used for end time. The actual value (blank) will be recorded on the eCRF and will be used in the listings.

Subjects with the designation of treatment relationship of adverse event (AE) and serious adverse events (SAEs) missing will have the worst case assumed to impure the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. The severity and causality assessment for adverse events cannot be missing. Missing data will be queried for a value.

Missing times for assessments of CABP symptoms will be queried for a value. If minutes are not available, the time will be recorded to the closest hour.

If no value can be obtained for all other times for events and assessments occurring after enrollment, the time will not be imputed but will remain missing.

For clinical response, missing data will be handled as follows:
For investigator’s assessment of Clinical Response at the EOT and PTE Visits:

- Subjects will be defined as an Indeterminate if the investigator cannot determine whether the subject is a Clinical Success or Failure at the EOT or PTE Visits or the subject has a missing response. By definition, subjects with an Indeterminate response are included in the denominator for analyses in the ITT population, and thus, are considered Clinical Failures.

10.2 Derived and Transformed Data

10.2.1 Reference Dates

There are three reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of inform consent.
- The safety reference date is the treatment start date and will be used to calculate the study day for safety assessments.
- The efficacy reference date is the date of enrollment and will be used to calculate study day for efficacy measures and baseline characteristics (time since initial diagnosis)

10.2.2 Study day for Safety Measures and Efficacy

If the date of interest occurs on or after the safety or efficacy reference date, then the study day will be calculated as:

Study day = (date of interest – reference date) + 1

There is no safety or efficacy study day 0

10.2.3 Duration and Elapsed Time

Durations (e.g. duration of an adverse event, duration of exposure, etc.) are calculated as:

Duration = (Stop date – Start date) + 1

Elapse times (e.g. time since initial diagnosis) are calculated as:

- Reference date is on or after the event date = (reference date – event date) + 1
- Reference date is before the event date = reference date – event date

10.2.4 Creatinine Clearance (CrCl)

Cockcroft-Gault equation to calculate creatinine clearance (CrCl):

(140-age[yrs])*weight [kg]* (Z)	Z = 1.0, if Male
Cr (mg/dL) * 72	Z = 0.85, if Female

10.2.5 Baseline Definition

Baseline or pre-dose assessment is defined as the most recent, non-missing available assessment prior to time of first dose, unless is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the schedule assessments will be included in the summary tables.

10.2.6 Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-enrollment values. If either the baseline or the post-enrollment value is missing, the change from baseline is set to missing as well.

10.2.7 Pharmacokinetic Parameters

Plasma pharmacokinetic parameters will be summarized and analyzed after undergoing log-transformation (except tmax).

10.3 Assessment Windows

Actual dosing and PK sampling times will be used in the calculation of the PK parameters. Nominal times will be used for purposes of summarization.

EOT assessments should be performed on the calendar day of, or within 2 days following the last dose of any test article. If a subject withdraws prematurely or terminates participation in the study prior to completion of the planned antibiotic therapy, the EOT visit should be conducted on that day.

The PTE assessment is to be performed 5 to 10 days after the subject's last day of therapy.

The final follow up (FFU) assessment should be conducted within 30-37 days following the subject's first dose of test article.

For each safety outcome, analyses will utilize assessments occurring during the scheduled visit windows (provided below). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's last day of therapy, the assessment will not be summarized with the PTE Visit but will be considered an unscheduled assessment. If a subject does not have an assessment at a scheduled visit and an unscheduled assessment was taken within the window for the time point (for example, 5 to 10 days after the subject's last day of therapy for PTE), these assessments will be summarized in the by time point analyses. If more than one measurement is taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement in the visit window will be used. If more than one measurement is taken on the same day, the assessment closest to the start of the dose will be used for on treatment values and the last measurement on the day will be used for post-treatment values.

For worst overall post-baseline analyses, all assessments including those obtained from unscheduled visits will be included.

Scheduled Study Visits

Study Visit	Study Day	Notes
Baseline	Day -1 or Day 1	Except where indicated, last measurement prior to the first dose of test article. Screening assessments are to be taken within 24 hours prior to the first dose of test article. If no test article is taken, the date and time of enrollment is used in place of the first dose of test article.
On Treatment	Day 1-Day 10	A Day 10 visit will be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT Visit.
EOT		Within 2 days following the last dose of test article
PTE		5-10 days after the subject's last day of therapy
Final Follow-up	Day 30-37	30-37 days after the start of the first dose of test article

10.4 Clinically Notable Values

- Clinically notable laboratory parameters, meeting predefined criteria as values with 2 grade increases will be listed
- Clinically notable vital signs, meeting predefined criteria as specified in Appendix 4 by time point measured

11 OTHER RELEVANT DATA ANALYSES/SUMMARIES

11.1 Prior and Concomitant Medications

All medications taken within 7 days prior to the date of informed consent through the Final Follow-up Visit will be recorded on the eCRF. Prior medications will be summarized by WHODRUG (Version 01 Dec 2014) Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/pharmacologic subgroup) and generic medication name. Medications are considered prior if taken prior to the first dose of test article or if their start date is unknown. Subjects will be counted only once for an ATC class and generic medication name. Concomitant medications taken during and after the study treatment period will be similarly summarized. Medications are considered concomitant if taken on or after the first dose of test article, or if their stop date is unknown or marked as continuing.

The number and percentage of subjects who receive the following prior and concomitant medications will be summarized:

- Systemic antibacterial medications taken within 72 hours prior to first dose of test article and the reasons for receipt (ITT)

11.2 Resource Utilization Analyses

The number of subjects who are in-patient at the start of the treatment and how many days were spent in hospital will be summarized.

12 CHANGES FROM THE PROTOCOL

In the protocol, the PK Analysis Set was defined to include subjects who receive omadacycline and have PK samples collected. If any subject has an emesis within 2.5 x median T_{max} after dosing, the subject may be excluded from PK Analysis Set. In the SAP, the PK Analysis Set has been defined to include subjects who receive study drug and have at least 1 evaluable PK parameter. If any subject has an emesis within 4 hours after dosing, the subject will be excluded from PK Analysis Set.

Any changes from this statistical analysis plan will be documented in the CSR for this study.

13 REFERENCES

14 APPENDICES

Appendix 1 Schedule of Events

Study Phase	Screening[a]	Treatment Phase				Follow-up Phase	
Study Day[b]		Day 1	Day 2	Day 3	Day 7-10/ EOT[c]	PTE[d]	Final Follow-up[e]
Signed Informed Consent[f]	X						
Medical History, current medical conditions, demography	X						
Assessment of CABP symptom severity[g]	X		X	X	X	X	
Chest X-ray or CT scan[h]	X						
PORT Risk Class, ABG (or pulse oximetry) [i]	X						
Blood samples for local lab hematology/chemistry//pregnancy test[j]	X				X	X	
Urine samples for local lab urine tests/pregnancy test[j]	X						
Review of Inclusion and Exclusion criteria/Treatment Group Assignment (if Eligible)	X						
Test Article Administration and Accountability[l]		X	X	X	X		
Physical examination[m]	X		X	X	X	X	
Vital signs[n]							
Height and weight	X						
Body temperature	X	X	X	X	X	X	
Blood Pressure	X	X[o]	X	X	X	X	
Pulse Oximetry	X	X	X	X	X	X	
Pulse/Heart Rate	X	X[o]	X	X	X	X	
Respiratory Rate	X	X	X	X	X	X	
Plasma samples (in heparin) for PK analyses		X[p]	X[q]	X[r]	X[s]		
Assessment for need for continued therapy[t]		X ---------- X					
Investigator's Assessment of Clinical Response					X	X	
Adverse Events[u]	X ---------- X						
Prior/Concomitant Medications and Procedures[k]	X ---------- X						
Assessment of Resource Utilization	X ---------- X						

ABG = arterial blood gas, AE = adverse event, BP = blood pressure, β-hCG = beta – human Chorionic Gonadotropin, CABP = community-acquired bacterial pneumonia, CT = computed tomography, CXR = chest X-ray, eCRF = electronic case report form, EOT = end of treatment, ICF = informed consent form, IxRS = Interactive Voice Response System/Interactive Web Response System, PK = pharmacokinetics, PORT = Pneumonia Outcomes Research Team, PTE = post-therapy evaluation, RR = respiratory rate, SAE = serious adverse event.

[a] Following the signing of an ICF, all Screening evaluations, with the exception of the radiographic confirmation of pneumonia, should be completed within the 24 hours prior to treatment group assignment. The radiographic confirmation of pneumonia should be completed within the 48 hours prior to the first dose of test article.

[b] Study Day 1 is the first day of test article administration. Subsequent study visit days may be consecutive calendar days.

[c] To be conducted on the day of, or within 2 days following the last dose of test article. Should also be conducted for any prematurely withdrawn subject.

[d] To be conducted 5 to 10 days after the subject's last day of therapy.

[e] To be conducted 30 to 37 days after the start of the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no AEs or clinically significant laboratory, or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

[f] Written and signed ICF must be obtained before any assessment is performed.

[g] The investigator should assess the severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain, and dyspnea based upon the Community Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment (Appendix 3).

[h] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 48 hours prior to the first dose of test article.

[i] Only subjects with a PORT Risk Class of II or III for whom oral only treatment for CABP is appropriate are eligible for enrollment.

[j] Hematology and serum chemistry evaluations will be performed at each of the timepoints indicated. A serum or urine pregnancy test (for women only) and urine dipstick will be performed only at Screening. The relevant local laboratory results from Screening will be used to assess eligibility as per the inclusion/exclusion criteria.

[k] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies administered after the first dose of test article must be recorded in the eCRF. Additional information, including start and stop time, will be collected for any prior or concomitant antibiotic.

[l] All oral doses should be taken in a fasted state (no food, antacids, or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours before dosing). Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit and site staff will perform accountability. The total duration of test article therapy for all subjects will be 7 to 10, up to 14 for bacteremia.

[m] A full physical examination will be completed at Screening, thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

[n] Vital signs include body temperature, BP, pulse oximetry, pulse/heart rate, and RR.

[o] BP and heart rate should be measured within 30 min before, and approximately (± 15 minutes) 1-hour after the completion of the doses on Day 1.

[p] PK sample collection on Day 1:within an hour prior to Dose 1, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours (12 hour taken immediately before Dose 2); Dose 2 administered (times relative to Dose 1); 13, 13.5, 14, 14.5, 15, 16, 24 hours post dose

[q] PK sample collection on Day 2:within an hour prior to dose, 1, 1.5, 2, 2.5, 3, 4, 6 hours

[r] PK sample collection on Day 3: prior to the Day 3 dose

[s] PK sample collection on EOT is anytime during the visit after the final dose.

Study Phase	Screening[a]	Treatment Phase	Follow-up Phase

[t] The total duration of test article therapy for all subjects will be 7 to 10 days, up to 14 days for bacteremia.

[u] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

Appendix 2 Adverse Event and Prior/Concomitant Medication Date Imputations

Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.

Prior and Concomitant Medication Start Date Imputation

Parameter	Type of Medication	Imputation
Start date for con meds	Non-Antibacterial	If it cannot be determined whether or not the start date of a medication (non-antibacterial) is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug.
	Antibacterial	Missing start dates for antibacterials will be queried for a value. If it cannot be determined whether or not the start date of an antibacterial is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug unless the indication notes that the medication was received after the first dose of study drug.
Stop date for con meds	Non-Antibacterial	If it cannot be determined whether or not the stop date of a medication (^{nonantibacterial}) is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug
	Antibacterial	Missing stop dates for antibacterials will be queried for a value. If it cannot be determined whether or not the stop date of an antibacterial is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug unless the indication notes that the medication was received prior to the first dose of study drug. If it cannot be determined whether the antibacterial was received prior to the assessment of Early Clinical Response, the EOT and/or the PTE Visit, the antibacterial will be assumed to have been received through the PTE Visit.

Appendix 3 Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table

The DMID Adult Toxicity Table (21-NOV-2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. Grades for enzymes were modified as indicated in the table below.

For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied.

For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

HEMATOLOGY					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (gm/dL)	> 10.5	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
Absolute Neutrophil Count (count/mm^3)	> 1500	1000-1500	750-999	500-749	< 500
Platelets (count/mm^3)	≥ 100,000	75,000-99,999	50,000-74,999	20,000-49,999	< 20,000
WBCs (count/mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	> 30,000 or < 1,000

CHEMISTRY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L)	> 135	130-135	123-129	116-122	< 116
Hypernatremia (mEq/L)	< 146	146-150	151-157	158-165	> 165
Hypokalemia (mEq/L)	> 3.4	3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Hyperkalemia (mEq/L)	< 5.6	5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Hypoglycemia (mg/dL)	≥ 65	55-64	40-54	30-39	< 30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)*	< 116	116-160	161-250	251-500	> 500
Hypocalcemia (mg/dL) (corrected for albumin)	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	< 6.1
Hypercalcemia (mg/dL) (correct for albumin)	≤ 10.5	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
Hypomagnesemia (mEq/L)	> 1.4	1.4- 1.2	1.1-0.9	0.8-0.6	< 0.6
Hypophosphatemia (mg/dL)	≥ 2.5	2.0-2.4	1.5-1.9	1.0-1.4	< 1.0
Hyperbilirubinemia (total bilirubin)	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.5×ULN	> 2.5-5×ULN	> 5×ULN
Urea	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Hyperuricemia (uric acid) (mg/dL)	< 7.5	7.5–10.0	10.1–12.0	12.1–15.0	> 15.0
Creatinine	< 1.1×ULN	1.1-1.5×ULN	> 1.5-3.0×ULN	> 3.0-6×ULN	> 6×ULN

*The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from subjects with no prior diabetes.

ENZYMES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
ALT (SGPT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
GGT	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Alkaline Phosphatase	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Amylase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN
Lipase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN

Appendix 4 Criteria for Clinically Notable Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 15 bpm
	Low (CL)	≤ 50	Decrease of ≥ 15 bpm