NCT #: NCT02452918

STATISTICAL ANALYSIS PLAN
(SAP)

AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY OF A SINGLE 1200 MG IV DOSE OF ORBACTIV (ORITAVANCIN) IN PATIENTS ON CONCOMITANT CHRONIC WARFARIN THERAPY BEING TREATED FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION

Protocol No.: MDCO-ORI-14-03

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ANC	absolute neutrophil count
AUC	area under the plasma concentration time curve
AUC_{0-24}	Area under the drug concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	Area under the concentration-time curve from zero to infinity
BMI	body mass index
CD4	cluster of differentiation 4
CI	confidence interval
C_{max}	maximum plasma concentration
CrCl	creatinine clearance
CS	clinically significant
CV	coefficient of variation
CYP2C9	Cytochrome P450 2C9 enzyme
DAT	Direct Coombs Test
D5W	5% dextrose in water
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, throat
HIV	Human Immunodeficiency Virus
IAT	Indirect Coombs Test (DAT)
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	institutional review board
ITT	Intent-to-Treat
IV	intravenous
LLN	lower limit of the standard reference (normal) range
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MIC	Minimum Inhibitory Concentration
MRSA	methicillin-resistant *S. aureus*
No.	Number

Abbreviation	Explanation
OTC	over the counterPotentially clinically significant (PCS)
PCS	Potentially clinically significant
PK	pharmacokinetic
PT	prothrombin time
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
$T_{1/2}$	Half-life
T1/2,α	Half-life for the alpha phase
T1/2,β	Half-life for the beta phase
T1/2,γ	Half-life for the gamma phase
ULN	Upper limit of the standard reference (normal) range
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
Vss	steady-state volume of distribution
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used for the analysis and summarization of safety data from Protocol MDCO-ORI-14-03, Amendment 2 (17 March 2016).

The analysis plan will be finalized prior to database lock, but may change due to unforeseen circumstances. Any changes made after finalization of the analysis plan will be documented. Related documents are the study protocol and electronic case report forms (eCRFs).

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

- To assess the safety and tolerability when a single 1200 mg intravenous (IV) infusion of oritavancin is given concomitantly in subjects on chronic warfarin therapy with acute bacterial skin and skin structure infection (ABSSSI).
- An additional group of patients with ABSSSI, who are not on concomitant warfarin therapy, will be enrolled to obtain information regarding the potential for antibody production following a single dose of oritavancin administration in patients.

2.2 Secondary Objective

Not applicable.

2.3 Endpoint

2.3.1 Primary Endpoint

The primary endpoint of this trial is:

- Safety of the administration of oritavancin in subjects on chronic warfarin will be assessed according to vital signs, laboratory abnormalities, and the incidence of AEs and SAEs.

2.3.2 Secondary Endpoint

The secondary endpoint of this trial is:

- Clinical cure determined by the Investigator at 48-72 hours after start of oritavancin dose and Day 7 visit.

2.3.3 Exploratory Endpoint:

An exploratory outcome of this trial is to evaluate the potential for antibody development following a single dose oritavancin administration.

3 STUDY DESIGN

3.1 Number of Subjects

Up to forty subjects will be enrolled at up to 10 centers in the United States (US). Approximately 25 subjects on concomitant warfarin therapy will be enrolled in this study. An additional 15 patients with ABSSSI, who are not on warfarin, will also be enrolled.

3.2 Sample Size Considerations

The sample size of 25 subjects on concomitant warfarin therapy is chosen based on feasibility and clinical judgment to provide adequate safety information on the administration of oritavancin with an ABSSSI who are on chronic warfarin.

An additional group of 15 ABSSSI patients, who are not on chronic warfarin therapy, was added to obtain information regarding potential for antibody production related to oritavancin administration.

3.3 Study Design

This will be a Phase IV, open-label study evaluating the safety and tolerability when a single 1200 mg dose of oritavancin is given concomitantly in subjects on chronic warfarin therapy with ABSSSI. An additional group of patients with ABSSSI, who are not on concomitant warfarin therapy, will also be enrolled.

Up to 40 subjects will be enrolled at up to 10 centers in the United States. Informed consent will be obtained from subjects meeting all inclusion and no exclusion criteria before the initiation of any study-specific procedures.

Eligible subjects will be enrolled and receive a single 1200 mg dose of oritavancin IV.

Adverse events and SAEs will be assessed from the time of informed consent through 14 days post administration of oritavancin.

The schedule of events is shown in Table 1. This schedule is based on Protocol MDCO-ORI-14-03, Amendment 2 (17 March 2016). In Protocol Amendment 1 (dated 16 December 2015), Direct Coombs Test (DAT) was added to the schedule of events; in Protocol Amendment 2, Indirect Coombs Test (IAT) and the drug dependent antibody was added to the schedule of events.

Table 1: Schedule of Events

Study procedures	SCREENING	Pre-Dose	Treatment	FOLLOW UP			
	≤24 hrs from 1st dose	Day 1	Day 1	Day 2	Day 3 Safety & Efficacy Visit	Day 7 Safety & Efficacy Visit	Day 14 Follow up Visit (± 2 days)[1]
Informed Consent	x						
Assess Inclusion/Exclusion	x	x					
Medical History	x						
Physical Exam (height and weight at Screening only)	x						
Vital Signs[2]	x	x	x		x	x	x
Pregnancy test[3]	x					x	
Record ABSSSI surgical procedures[4]	x						
Safety laboratory assessments[5]	x					x	x
Microbiology testing[6]	x						
Record prior or concomitant medications	x	x	x	x	x	x	x
Administer IV oritavancin			x				
PT/INR Test[7]	x			x	x	x	x
Assess clinical cure[8]					x	x	
Immunoglobulin panel and plasma for oritavancin antibody assay	x				x	x	x
Direct and Indirect Coombs Test[9]	x				x	x	x
Assessment of adverse events[10]	x	x	x	x	x	x	x
Plasma Storage Samples for Drug Dependent Antibody Ex Vivo Study[11]			x				

[1] If subject has abnormal laboratory values that have not returned to a therapeutic baseline by Day 14, additional follow up visits may be required.
[2] Vitals signs include blood pressure, temperature, respiratory rate and heart rate.
[3] Perform a local urine pregnancy test for female patients of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile).
[4] This includes but is not limited to aspiration, debridement, incision and drainage.
[5] Blood chemistry and hematology . Unless otherwise indicated all laboratory tests will be performed by site's local laboratory.
[6] Microbiology testing should be performed per institutions Standard of Care (SOC).
[7] Patients on warfarin are required to have at least one documented International Normalized Ratio (INR) between 1.5 and 3.0 in the 30 days prior to screening. The INR value at Screening must fall within 1.5 and 3.0. After dosing with oritavancin, the next Prothrombin Time/International Normalized Ratio (PT/INR) should be collected with 18-36 hours of start of oritavancin infusion. If PT/INR has not returned to baseline at Day 3, more frequent PT/INR testing prior to Day 7 may be required.
[8] Clinical cure should be assessed by investigator at Day 3 (48-72 hours after start of oritavancin administration) and at Day 7.
[9] Patients with a negative Coombs Test at Day 14 test must have test repeated every 2 weeks until return to baseline or stable.
[10] Adverse events and serious adverse events will be assessed from the time of informed consent through 14 days post first administration of Oritavancin.
[11] Blood will be collected immediately after the completion of the infusion to prepare three plasma sample for Ex Vivo Study investigating the effects of Oritavancin on Antibody Formation.

4 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to database lock. All other analyses, if any, designed subsequent to the database lock will be considered *post hoc* analyses and will be applied as exploratory methodology. All *post hoc* analyses will be identified as such in the clinical study report.

Continuous variables will be summarized using mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

Summary statistics will be presented as follows: number of observations will be presented without any decimal places, minimum/maximum in the same precision as reported values, arithmetic and geometric means/median to 1 more decimal place than the reported values, SD to 1 more decimal place than mean/median, and coefficient of variation (CV) to 1 decimal place.

Data will be summarized by cohort. Summary tables will only be provided for cohorts with more than 4 subjects. For cohorts with no more than 4 subjects, only listings will be provided.

All statistical analyses will be conducted using SAS® version 9.3 or later using procedures appropriate for the particular analysis.

5 ANALYSIS POPULATIONS

Two populations will be used for data analyses and/or presentation.

5.1 Intent-to Treat (ITT) Population

The ITT population will include all subjects screened and enrolled. This will be the primary population for efficacy analysis.

5.2 Safety Population

The safety population will include all subjects who are dosed with IV oritavancin. This will be the primary population for safety analysis.

5.3 Missing Data Handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

5.4 Key Definitions

Unless otherwise specified, the last evaluation prior to the initiation of study drug will be considered the "Baseline" evaluation for analysis.

6 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

6.1 Subject Discontinuation

The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented by cohort. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized for the safety population.

A data listing for subject disposition including study completion status and reason for study discontinuation will be provided. In addition, analysis populations and reasons for exclusion from the analysis population will be provided in a data listing.

6.2 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by cohort for the safety populations. Descriptive statistics (i.e., mean, median, SD, minimum, and maximum) will be calculated for continuous demographic and baseline characteristic variables (age, weight, height, and body mass index [BMI]) and frequency counts will be tabulated for categorical demographic variables (sex, race, and ethnicity) for each cohort and overall.

In addition to the summary tables, a data listing will be provided for all demographic data. The height, weight, and BMI will be provided in the vital sign data listing.

6.3 Study Drug and Concomitant Medications

Separate summary of prior (pre-baseline) and concomitant (baseline or later) medications will be provided for the safety population. Medications will be coded with the World Health Organization (WHO) Drug Dictionary Enhanced. Subjects will be counted only once within each period by medication.

Prior medications are those with a start date occurring before the initiation of study drug on Day 1. Concomitant medications are those with a start date occurring on or after the initiation of study drug on Day 1 or that have unknown or ongoing end dates. In the event of a partial date, the medication will be classified as prior.

Prior and concomitant medications will be provided in a data listing by subject.

7 EFFICACY ANALYSIS

Efficacy results for all subjects will be provided in data listings.

8 SAFETY ANALYSIS

8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 18.0 or higher will be used for coding adverse events (AEs). Each verbatim term will be mapped to a preferred term and system organ class (SOC).

An AE (classified by system organ class and preferred term) that occurs during the treatment period will be counted as a treatment-emergent AE (TEAE) either if it is not present at Baseline or if it is present at Baseline but increased in severity during the treatment period or follow up period.

The number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to study drug. If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

Summaries of serious adverse events (SAEs) and AEs leading to study discontinuation will also be provided by system organ class and preferred term. Listings of SAEs and AEs leading to treatment or study discontinuation will also be provided.

In the presentation, SOC and preferred term will be sorted in alphabetical order.

All AEs captured in the database will be listed in by-subject data listings; however, only TEAEs will be summarized.

MedDRA version will be footnoted in both tables and data listings.

8.2 Clinical Laboratory Assessments

Clinical safety laboratory values and changes from baseline of hematology, serum chemistry, and urinalysis, including prothrombin time (PT)/international normalized ratio (INR), direct and indirect Coombs (DAT and IAT), Immunoglobulin panel, oritavancin antibody assay, will be summarized descriptively. Potentially clinically significant (PCS) values will also be flagged in a listing. The criteria for potentially clinical significant liver function tests are displayed in Table 2.

Unscheduled assessments that are not used for baseline will not be included in summary tables; however, all measurements will be listed.

Table 2: Criteria for Potential Clinically Significant Abnormal Lab Tests

Parameter	Lower limit	Upper limit
Hematology		
Red Blood Cell Count	≤ 0.75× LLN	≥ 1.25×ULN
WBC's Count	<2.0 x 10^9/L	
Hematocrit	≤0.75x LLN	≥1.25x ULN
Hemoglobin	≤11.5 g/dL Male	≥18.0 g/dL Male
	≤9.5 g/dL Female	≥16.0 g/dL Female
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
Serum Chemistry		
BUN		≥10.7 mmol/L
Calcium	≤7.0 mg/dL	≥15.5 mg/dL
Creatinine		≥2.0 mg/dL
Glucose	≤50 mg/dL	≥180 mg/dL
Potassium	≤3.0 mmol/L	≥5.5 mmol/L
Sodium	≤125 mmol/L	≥150 mmol/L
Liver Function Tests (LFTs)		
Alanine Transaminase (ALT/SGPT) ≥ 3x, 5x, 10x and 20x ULN		
Aspartate Transaminase (AST/SGOT) ≥ 3x, 5x, 10x and 20x ULN		
ALT or AST ≥ 3x, 5x, 10x, or 20x ULN		
Total bilirubin ≥ 1.5x and 2x ULN		
Alkaline Phosphatase (ALP) ≥ 1.5x and 3x ULN		
ALT/AST ≥ 3x ULN and Total bilirubin ≥ 2x ULN;		
Potential Hy's Law cases: ALT or AST ≥3×ULN, Total bilirubin ≥2×ULN, and ALP ≤ 2×ULN		

LLN: lower limit of the standard reference (normal) range.
ULN: upper limit of the standard reference (normal) range.

8.3 Vital Signs

Vital sign measurements and changes from baseline will be summarized descriptively at each scheduled timepoint. Potentially clinically significant changes will also be flagged in a listing based on the following thresholds:

- Respiratory Rate ≤10 rpm;
- Respiratory Rate ≥30 rpm;
- Systolic blood pressure ≥180 mm Hg and increase ≥20 mm Hg from Baseline;
- Diastolic blood pressure ≥110 mm Hg and increase ≥15 mm Hg from Baseline;
- Systolic blood pressure ≤90 mm Hg and decrease ≥20 mm Hg from Baseline;
- Diastolic blood pressure ≤50 mm Hg and decrease ≥15 mm Hg from Baseline;
- Heart rate ≥120 bpm with increase ≥15 bpm from Baseline;
- Heart Rate ≤50 bpm with decrease ≥15 bpm from Baseline.

Unscheduled assessments that are not used for baseline will not be included in summary tables; however, all measurements will be listed.

8.4 Extent of Exposure

Study drug administration dates and times will be provided in a data listing.

9 PHARMACOKINETIC ANALYSES

Not applicable as no pharmacokinetic sample was collected.

10 EXPLORATORY ANALYSIS

No exploratory analysis is planned.

11 REFERENCES

Not applicable