STATISTICAL ANALYSIS PLAN
(SAP)

A DOUBLE-BLIND, RANDOMIZED STUDY TO EVALUATE THE SAFETY OF EITHER A SINGLE 1200-MG INTRAVENOUS (IV) DOSE OF ORBACTIV™ (ORITAVANCIN) AND PLACEBO OR TWO IV DOSES OF ORBACTIV™ IN SUBJECTS BEING TREATED FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION

Protocol No.: MDCO-ORI-16-02
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
BMI	body mass index
CrCl	creatinine clearance
CRF	case report form
CS	clinically significant
CV	coefficient of variation
eCRF	electronic case report form
ITT	Intent-to-Treat
IV	intravenous
LLN	lower limit of the standard reference (normal) range
LLOQ	lower limit of quatification
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
No.	Number
PK	pharmacokinetic
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
ULN	Upper limit of the standard reference (normal) range
US	United States
USPI	United States Package Insert
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-16-02, Version 1.0 (19 October 2016).

The analysis plan will be finalized prior to database lock, but may change thereafter 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 of two 1200-mg IV infusions of oritavancin when administerd one week apart in subjects with acute bacterial skin and skin structure infection (ABSSSI).

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 will be assessed according to vital signs, laboratory abnormalities, and the incidence of adverse events (AEs) and serious adverse events (SAEs).

2.3.2 Secondary Endpoint

The secondary endpoint of this trial is:

- Clinical cure determined by the investigator at the Day 8 visit.

2.3.3 Exploratory Endpoint:

The exploratory endpoint of this trial is:

- Additional information collected will include (a) potential for antiglobulin development (direct and indirect), (b) change or increase in immunoglobulin profile, and (c) development of drug-specific antibody in response to two 1200mg IV infusions of oritavancin.

3 STUDY DESIGN

3.1 Number of Subjects

Approximately 20 subjects will be studied at 1-2 centers located in the United States (US).

3.2 Sample Size Considerations

Approximately 20 ABSSSI subjects will be evaluated to obtain safety information including the potential for antibody production related to oritavancin administration. Study subjects will be randomized in a 3:1 ratio to all receive oritavancin with the first dose (20 subjects) and receive oritavancin with the second dose (15 subjects) or placebo (5 subjects).

3.3 Study Design

This will be a Phase IV, randomized, double-blind trial in subjects with ABSSSI. Approximately 20 subjects will be enrolled at approximately 1-2 centers in the US. Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Eligible subjects will be randomized to receive either two doses of oritavancin one week apart or one dose of oritavancin and a single dose of placebo one week apart in a 3:1 ratio.

The study will consist of four periods: Screening (≤24 hours prior to Day 1), Pre-Dose (Day 1), Treatment (Day 1, Day 8), and Follow-up (Day 15, Day 22).

Safety assessments will include vital signs, laboratory abnormalities, and the incidence of AEs and SAEs (see Section 6 for assessment details).

The maximum duration of a subject's participation in this study is approximately 22 days after the first administration of oritavancin.

Infusion-related reactions will be considered an AE of Special Interest within the protocol and will be followed until resolution. This designation will require that any reports (whether serious or non-serious) will be submitted to the Sponsor within 24 hours, along with a narrative and all necessary information to complete a CIOMS/MedWatch form, ensuring that complete and detailed information is obtained on the event. Furthermore, any clinically significant lab data or adverse events occurring after the second dose will be required to be entered in the database within 24 hours in order to facilitate the Sponsor's ongoing review of safety data. The Sponsor will be conducting ongoing review of the safety data within Study MDCO-ORI-16-02 (AEs, vital signs and labs).

Table 1: Schedule of Events

Study procedures	SCREENING	Pre-Dose	Post-Dose	Pre-Dose	Post-Dose	FOLLOW UP	
	≤24 hrs from 1st dose	Day 1	Day 1	Day 8	Day 8	Day 15 Follow up Visit (±2 days)	Day 22 Follow up Visit (± 2 days)
Informed Consent	x						
Assess Inclusion/Exclusion	x	x					
Medical History	x						
Physical Exam	x						
Vital Signs[1]	x	x	x	x[1]	x[1]	x	x
Pregnancy test[2]	x			x			x
Record ABSSSI surgical procedures[3]	x						
Chemistry and Hematology laboratory assessments[4]	x			x	x	x	x
Microbiology testing[5]	x						
Record prior or concomitant medications	x	x	x	x	x	x	x
Administer IV oritavancin			x		x[9]		
Assess clinical cure[6]				x		x	x
Immunoglobulin panel	x			x	x	x	x
Direct and Indirect Antiglobulin Test[7]	x			x		x	x
Plasma Storage Samples for oritavancin antibody assay	x			x	x		
Collect blood specimen for complement profile (C3, C4, CH50), serum tryptase, erythrocyte sedimentation rate (ESR), Haptoglobin level and C-reactive protein				x	x		
Collect plasma for PK[10]				x	x	x	x
Assessment of adverse events[8]	x	x	x	x	x	x	x

[1] Vital signs include blood pressure, temperature, respiratory rate and heart rate. On Day 8 vitals will be collected at pre-dose, 1.5 hours after the start of infusion, at the end of the infusion, and 4 hours after the start of infusion.
[2] Perform a local urine pregnancy test for female subjects of childbearing potential (may be omitted for females >2 years postmenopausal or surgically sterile).
[3] This includes but is not limited to aspiration, debridement, incision and drainage.
[4] Blood chemistry and hematology (Section 7.1.4 for listing of tests to be performed). Unless otherwise indicated all laboratory tests will be performed by the site's local laboratory.
[5] Microbiology testing should be performed per institution's Standard of Care (SOC).
[6] Clinical cure should be assessed by the investigator at Day 8.
[7] Direct and indirect antiglobulin testing will be done both at the local lab and also sent frozen to a central Lab. Subjects with a positive direct or indirect antiglobulin test at the Day 22 visit must have the test repeated every 2 weeks until it returns to baseline or stabilizes.
[8] Adverse events and serious adverse events will be assessed from the time of informed consent through 22 days post first administration of oritavancin.
[9] Subjects should remain at the clinic for observation for at least 3 hours post the completion of this IV infusion or until all adverse events have resolved or stabilized. A medically qualified team member must be onsite during this time to assess any adverse events.
[10] Time points for pharmacokinetic (PK) sample collection are Day 8 (pre-dose, end of infusion (3 hr.), 6-hr. post infusion start), and on Day 15 and Day 22.

4 GENERAL STATISTICAL CONSIDERATIONS

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

All summaries will be presented by group.

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 randomized. This will be the primary population for efficacy analysis.

5.2 Safety Population

The safety population will include all subjects who are dosed with intravenous (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 Analysis Windows and Baseline

The observational period for the study includes Day 22 ±2 days. Any event occurring beyond the defined observational period, even if collected on the case report form (CRF), will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

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

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. 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 Protocol Deviations

Deviations from the protocol will be presented in a data listing.

6.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for the Safety Population. Descriptive statistics (i.e., mean, median, standard deviation (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 group and overall.

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

6.4 Medical History

Medical history data will be mapped with the current version of Medical Dictionary for Regulatory Activities (MedDRA, version 19.1) and summarized by system organ class (SOC) and preferred term for each treatment and overall. Medical history data will be listed by subject identification, medical condition reported term, SOC, preferred term, onset date, and ongoing status/resolution date.

6.5 Prior and Concomitant Medications

Separate summary of prior (pre-baseline) and concomitant (baseline or later) medications will be provided by age cohort and group for the safety population. Medications will be coded with the latest World Health Organization (WHO) Drug Dictionary Enhanced (released in Sept 2016) and presented as ATC 2. 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.

6.6 Extent of Exposure

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

7 EFFICACY ANALYSIS

Efficacy results for all subjects will be summarized by group as well as provided in data listings.

8 SAFETY ANALYSIS

8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA, version 19.1) will be used for coding AEs. An AE (classified by system organ class and preferred term) that occurs during the treatment period will be counted as a treatment-emergent adverse event (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 oritavancin. 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.

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, including direct and indirect antiglobulin, immunoglobulin panel, and oritavancin antibody assay, will be summarized descriptively. Clinically significant values will also be flagged in a listing. The criteria for potentially clinical significant laboratory tests are displayed in Table 2.

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

Table 2-1: Potentially Clinically Significant Hematology Laboratory Values

	Lower limit	Upper limit
Basophils		≥5%
Eosinophils		≥10%
Lymphocytes	<10%	≥80%
Monocytes		≥20%
Neutrophils	< 10%	≥90%
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
Mean Corpuscular Volume (MCV)	≤0.75x LLN	≥1.25x ULN
Red Blood Cell Count	≤ 0.75× LLN	≥ 1.25×ULN
WBC's	≤3 x 10^9/L	≥20 x 10^9/L

Table 2-2: Potentially Clinically Significant Chemistry Laboratory Values

	Lower limit	Upper limit
BUN		≥10.7 mmol/L
Calcium	≤7.0 mg/dL	≥12 mg/dL
CPK		≥3x ULN
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

Table 2-3: Potentially Clinically Significant Abnormal 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;
ALT >= 3x ULN and TBIL >= 2x ULN and ALP < 2x ULN;
ALT >= 3x ULN and TBIL >= 2x ULN and (ALT/ULN)/(ALP/ULN) <=5;

where ULN is the upper limit of the standard reference (normal) range

8.3 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at the designated time periods as indicated in the Assessment Schedule. Blood pressure and heart rate must always be taken after the subject has been resting supine for 5 minutes.

Vital sign measurements and changes from baseline will be summarized descriptively at each scheduled time point. Potentially clinically significant changes will also be flagged in a listing. The criteria for potentially clinical significant vital signs are displayed in Table 3.

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

Table 3: Potentially clinically significant values for vital sign changes

Variable	Criterion value	Change relative to baseline
Systolic blood pressure	>140 mmHg	Increase of >20 mmHg
	<90 mmHg	Decrease of >20 mmHg
Diastolic blood pressure	>90 mmHg	Increase of >15 mmHg
	<50 mmHg	Decrease of >15 mmHg
Pulse	>100 bpm	Increase of >15 bpm
	<50 bpm	Decrease of >15 bpm

9 PHARMACOKINETIC ANALYSES

Plasma concentrations of oritavancin will be summarized at the scheduled timepoints by group using descriptive statistics (n, mean, median, coefficient of variation, standard deviation, minimum, and maximum). Values below Lower Limit of Quatification (LLOQ) will be set to zero for the summary tables. Mean concentrations that are below LLOQ will be presented as such, and the standard deviation (SD) and coefficient of variation (CV) will be reported as not applicable.

Mean (±SD) plasma concentration-time profiles will be displayed graphically with a line representing each group, where applicable. Individual plots for each subject will also be presented. Mean and individual plots will be presented on linear and semilogarithmic scales.

Plasma concentrations will be presented in a data listing.

10 EXPLORATORY ANALYSIS

Exploratory endpoints will be analyzed as described in Section 4 (general statistical considerations). No other exploratory analysis is planned.

11 REFERENCES

Not applicable