Statistical Analysis Plan

Initial U.S. Approval: 2014

ORBACTIV® (oritavancin)

A Randomized, Open-label, Pharmacokinetics and Safety Study to Evaluate the Relative Exposure and Safety of a New Formulation Versus the Approved Formulation of a Single 1200 mg Intravenous (IV) Dose of ORBACTIV® (oritavancin) in Subjects Being Treated for Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

Protocol Number.: **ML-ORI-102**

U.S. IND Number: **51,292**

EudraCT Number.: **Not Applicable**

Development Phase:	Phase I
Sponsor:	Melinta Therapeutics, Inc. 300 Tri-State International Suite 272 Lincolnshire, IL 60069
Statistician:	Junming Zhu Edetek, Inc
Version 2.0	October 7, 2019

1. SIGNATURE PAGE

The signature of the Investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. This trial will be conducted in compliance with the protocol and all applicable regulatory requirements, in accordance with Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Statistician

Junming Zhu
Printed Name

Signature

07OCT2019
Date

Representatives of Melinta Therapeutics who agree to the terms and conditions of the SAP include:

Melinta Representative

Karen Fusaro
Printed Name

Signature

07 October 2019
Date

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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABSSSI	Acute Bacterial Skin and Skin Structure Infection
AE	adverse event
AESI	Adverse Event of Special Interest
AUC	Area under the curve of plasma concentrations
BE	Bioequivalence
CE	Clinical Evaluable
CI	confidence interval
CL	clearance
C_{max}	maximal plasma concentrations
CV	coefficient of variation
D5W	dextrose 5% in water
EC	Ethics Committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	General Linear Model
HPβCD	Hydroxypropyl-β-cyclodextrin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
h	hour
kg	kilograms(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MIC	minimum inhibitory concentration
mg	milligram(s)
mL	milliliter(s)
mm	millimeter(s)

min	minute(s)
NOAEL	no-observed-adverse-effect level
PK	pharmacokinetic
PCS	potentially clinically significant
s	second(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOP	standard operating procedures
SWFI	sterile water for injection
$t_{½}$	half-life
TEAE	treatment emergent AE
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WHO	World Health Organization
y	year

5. INTRODUCTION

The statistical analysis plan (SAP) describes the statistical analysis methods and the planned deliverables for the ML-ORI-102 study. This protocol is a randomized, open-label, multi-center, study evaluating the pharmacokinetics (PK) and safety of a new formulation versus the approved oritavancin formulation in adult subjects with acute bacterial skin and skin structure infections (ABSSSI). The new formulation adjusts the infusion time, concentration and reconstitution/administration solutions of a single 1200 mg intravenous (IV) infusion of oritavancin.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective

The primary objective is to determine the relative AUC exposure of the new formulation of oritavancin compared to the currently approved formulation based on area under the plasma concentration-time curve (AUC) after a single 1200 mg IV infusion of oritavancin in male and female subjects with ABSSSI.

6.2. Secondary Objective

The secondary objective is to evaluate the safety and tolerability of the new formulation of oritavancin by the incidence of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory abnormalities, including the results of Direct and Indirect Coombs test and oritavancin antibody assay as applicable, and by vital signs.

Safety and tolerability assessments will be evaluated through Day 15 following the oritavancin infusion.

6.3. Exploratory Objectives

An exploratory objective is the evaluation of pharmacokinetic parameters (including, but not limited to: C_{max}, time of observed C_{max} (T_{max}), AUC, and, where they can be calculated, elimination half-life [$t_{½}$], volume of distribution at steady state [V_{ss}], and CL) after a single 1200 mg IV infusion of oritavancin in male and female subjects with ABSSSI.

Correspondingly the study endpoints are defined below.

6.4. Primary Endpoint(s)

The primary endpoint of this trial is:

Relative AUC exposure of the new formulation of oritavancin to the approved formulation of oritavancin based on areas under the plasma concentration-time curve from time zero to 72 hr (AUC_{0-72}) and time zero to 168 hr (AUC_{0-168}).

6.5. Secondary Endpoint(s)

The secondary endpoints of this trial are:

Safety and tolerability of the new formulation of oritavancin assessed according to AEs and SAEs, clinical laboratory parameters (including Direct and Indirect Coombs development and oritavancin antibody assay as applicable), and vital signs, through Day 15 following completion of study drug infusion.

6.6. Exploratory Endpoint(s)

The exploratory endpoints of this trial are:

An evaluation of pharmacokinetic parameters (including, but not limited to: C_{max}, T_{max}, AUC, and, where they can be calculated, elimination half-life [$t_{½}$], V_{ss}, and CL) after a single 1200 mg IV infusion of oritavancin in male and female subjects with ABSSSI.

7. STUDY DESIGN

This study will be a randomized, open-label, multi-center, study evaluating the PK and safety of the new formulation compared to the currently-approved formulation of oritavancin.

Approximately 100 subjects at about 5 centers will be randomized in a 1:1 ratio to the currently approved formulation of oritavancin versus the new formulation. Fifty (50) subjects will be administered the currently approved formulation of oritavancin, using the approved dosing regimen in which SWFI is used for reconstitution and D5W is used for further dilution to a final volume of 1000 mL. This formulation will be infused over 3 hours per the approved label. An additional fifty (50) subjects will be administered the new formulation of oritavancin. This formulation will also be reconstituted with SWFI and further diluted in 0.9% sodium chloride to a final volume of 250 mL. This formulation will be infused over 60 minutes.

Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Subjects will be screened up to 48 hours prior to the initiation of study drug. Subjects will receive their dose of oritavancin on Day 1 and will be asked to return to the study center on Day 2, Day 4, Day 8 and Day 15 for collection of additional blood samples and procedure assessments. The subject's participation is approximately 17 days.

Safety of the new formulation of oritavancin will be assessed according to AEs and SAEs, clinical laboratory parameters (including Direct and Indirect Coombs development and oritavancin antibody assay as applicable), and vital signs.

This is an unblinded, open label study. The primary endpoint is based on a pharmacokinetic assessment, a measurement that is not subject to interpretation bias.

The schedule of study assessments is provided in Table 1, and PK sampling time points are provided in Table 2.

Table 1: Schedule of Events/Assessments

Study Procedures	Screening	Day 1			Follow-up Visit				Unscheduled
	≤ 48 hrs prior to Day 1	Pre-Dose	Dosing	Post-Dose (1 hr or 3 hrs)	Day 2 (24 hrs)	Day 4 (72 hrs)	Day 8 (168 hrs)	Day 15[9] (336 hrs)	Unscheduled Visit
Informed consent	X								
Assess inclusion/exclusion	X	X							
Medical history, including microbiology results if available	X								
Randomize subject		X							
Physical exam including height & weight	X								X
Vital signs[1]	X	X		X			X		X
Urine pregnancy test[2]	X	X						X	X
Chemistry and hematology laboratory assessments[3]	X						X	X	X
Record prior or concomitant medications and surgical procedures	X	X		X	X	X	X	X	X
Administer IV oritavancin[4]			X						
Direct & Indirect Coombs Test[5]		X					X	X	X
Collect serum for oritavancin antibody assay[6]		X					X	X	X
Collect plasma for PK[7]		X		X	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.
2. At Screening and Day 15, perform a local urine pregnancy test for female subjects of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile). A urine pregnancy test will be performed again on Day 1 for female subjects of childbearing potential if the screening pregnancy test was performed > 24 hours prior to dosing.
3. Unless otherwise indicated, all chemistry and hematology laboratory tests will be performed by the site's local laboratory.

4. Start time of study drug infusion is Hour 0 (study drug will be administered over 1 hour or 3 hours)
5. Direct and Indirect Coombs testing will be done at the local laboratory. Samples will be collected at Day 1 (pre-dose), Day 8 and Day 15. If a subject has a change in Direct or Indirect Coombs results at Day 8, subjects may be asked to return for subsequent labs in order to investigate this change. Subjects with a positive Direct or Indirect Coombs test at the Day 15 visit must have the test repeated every 2 weeks until it returns to baseline or stabilizes.
6. Serum samples will be stored and tested for oritavancin antibody only if the subject(s) experience unexpected adverse events that may be associated with antibody production.
7. Time points for PK sample collection are Day 1 pre-dose and at the end of infusion (1 hour or 3 hours), and then at 3 hours (for 1 hour infusions), 6 hours, 12 hours, 24 hours, 72 hours, and 168 hours after the start of the infusion. See Table 2 for windows for PK draws and visits.
8. Adverse events and serious adverse events will be assessed from the time of study drug administration through Day 15 post administration of oritavancin.
9. The Day 15 visit may be performed within a ± 3 day window. If the subject is required to terminate the study early, the subject must complete the Day 15 assessments at the time of the Early Termination Visit.

Table 2: PK Blood Draw Schedule

PK Blood Draw Schedule		
Optimal Sample Time from START of infusion	**Sample Time Window**	
	Lower Limit	**Upper Limit**
Pre-Dose (-30 minutes)	Any time prior to dose administration	Any time prior to dose administration
1 hour (end of infusion) **New Formulation Arm Only**	End of Infusion	End of Infusion + 5 min
3 hours **New Formulation Arm Only**	2 hrs 50 min	3 hrs 10 min
3 hours (end of infusion) **Current Formulation Arm Only**	End of Infusion	End of Infusion + 5 min
6 hours	5 hrs 45 min	6 hrs 15 min
12 hours	10 hrs	14 hrs
24 hours (Day 2)	20 hrs	28 hrs
72 hours (Day 4)	60 hrs	84 hrs
168 hours (Day 8)	Day 7	Day 9

8. STATISTICAL PLAN

8.1. Sample Size Determination

Using combined results from selected Phase 1 studies on oritavancin pharmacokinetics with the approved formulation, the observed CV of AUC_{0-72} and AUC_{0-168} were 25.4% and 26.3%, respectively. Using a slightly larger CV value of 30% to be conservative, the table below shows estimated power values in a parallel study design to demonstrate equivalence of AUC of the new formulation (test, T) relative to the approved formulation (reference, R), assuming various true T/R ratios of geometric means of AUC_{0-72} and AUC_{0-168}. The table uses a sample size of 100 subjects randomized in 1:1 ratio to the test and reference groups and uses the standard 80% to 125% equivalence limits. A study design of 50 subjects in each of the test and reference groups should have ≥ ~90% power to demonstrate AUC equivalence, if the true T/R ratios are within 0.95 to 1.05.

True T/R Ratio	Power
0.95	89.5%
1.0	96.7%
1.05	90.2%

8.2. Randomization

With a sample size of approximately 100, subjects will be randomized in 1:1 ratio in a parallel fashion to the test (new formulation) and reference (approved formulation) groups.

8.3. Analysis Population

8.3.1. Intent-to-Treat (ITT) Population

All subjects randomized will be analyzed according to the treatment arm to which they were randomized. Subject disposition, demographic, and baseline characteristics will be summarized by treatment using the ITT population

8.3.2. Pharmacokinetics (PK) Population

All subjects who have received the full dose of oritavancin and have one valid sample measured for study drug levels. The PK population will be the primary population for the PK analysis.

8.3.3. Safety Population

All subjects who have received any amount of IV oritavancin will be included in the safety population. Treatment group will use it as actually received. The safety population will be the primary population for all the safety analyses.

8.4. General Statistical Considerations and Definitions

8.4.1. Software

All data listings, summaries and statistical analyses will be generated using SAS® Version 9.4 or above, or equivalent statistical software. PK analysis (including the calculation of PK parameters such as AUC, C_{max}, $T_{1/2}$, etc.) will use WinNonlin or relevant software, and will be performed by PK vendor.

8.4.2. General Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Unless otherwise specified, descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage. For the summary by visit analysis, graphic display using box-whisker or mean +/- standard error plot will be generated.

8.4.3. Analysis Windows and Baseline

All data collected in the study will be included in the analysis. Unless otherwise specified, the last evaluation prior to the initiation of study drug will be considered the "Baseline" evaluation for analysis. For microbiologic assessments, any pathogen identified from within 72 hours prior to screening up to and including Day 2 will be considered as baseline.

8.4.4. Missing Data Handling

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

Partial dates: Dates missing the day of the month, or both the day and month of the year will adhere to the following conventions:

- The missing day of onset of an adverse event or start date of a concomitant medications will conservatively be set to the earlier of:
  - first day of the month that the event occurred, as long as it is after the date of the start of first treatment
  - one day after the first dose, if this is the same month that the event occurred
- The missing day of resolution of an adverse event or end date of a concomitant medications will be set to the last day of the month of the occurrence.
- If the onset date of an adverse event or start date of a concurrent therapy is missing both the day and month, the onset date will be set to the earliest of:
  - January 1 of the year of onset, as long as it is after the first dose
  - one day after the first treatment, if this is the same year that the event occurred

- If the resolution date of an adverse event or end date of a concomitant medications is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence, if the patient is continuing treatment
  - The date of patient discontinuation, if the event is not ongoing

8.5. Statistical Analyses

8.5.1. Subject Disposition

A disposition table will summarize the number of patients screened, randomized, treated, discontinued from study treatment and reasons for discontinuation from study and study drug by treatment groups. The table will define the ITT, PK, and Safety Populations. Indicator variables (Yes/No) will be presented in listings to identify the population flag. The reason for discontinuation from study and study drug will be summarized using the categories specified in the case report form (CRF), by treatment group.

8.5.2. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by treatment groups using the ITT population. Unless the PK, and Safety population is significantly different from the ITT population (> 5% in total number of patients), the demographic and baseline characteristics table will not be duplicated.

Demographic and baseline variables will include:

- Age
- Sex
- Race
- Ethnicity
- Height
- Weight
- BMI
- ABSSSI Disease Status

Baseline pathogens and medical/surgical history will also be summarized.

8.5.3. Prior and Concomitant Medications

Summary of each prior medication, and concomitant medication will be provided by treatment group separately for the safety population. Medication will be coded with World Health Organization Drug Dictionary Enhanced (WHODrug March 1, 2019)[2] and summarized using ATC Level 4 and generic drug names. Subjects will be counted only once within each period by medication.

8.5.4. Study Drug Exposure

Extent of exposure including dose amount and duration of treatment (minutes) will be summarized for the Safety population. The number and percentage of subjects who completed treatment, and who experienced dose interruptions and discontinuations will be summarized for the Safety population.

All study drug administration data will be presented in a listing.

8.5.5. Safety Analysis

Safety will be assessed according to adverse clinical events, clinical laboratory evaluations (including Coombs anti-globulin tests and oritavancin antibody assay, as applicable), and vital signs. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline value for all analyses.

8.5.5.1. Adverse Events

The MedDRA Version 22.0[3] or later will be used for coding AEs. Adverse events (AEs) will be graded using the 5-point Common Terminology Criteria for Adverse Events (CTCAE) criteria (Version 5)[1]. An AE (classified by preferred term) occurring from the start of study drug will be counted as treatment emergent AE (TEAE) either if it was not present at baseline or if it was present at baseline but increased in severity during the period of observation.

An overall summary of subjects reporting a TEAE in each treatment group will be provided for the Safety population. This analysis will include: the number and percentage of subjects reporting any TEAE, any TEAE presented by maximum severity, any TEAE related to study drug, any SAE, any SAE related to study drug, any SAE leading to premature discontinuation of study drug, any SAE with an outcome of death, any TEAE leading to study discontinuation, any TEAE leading to study drug discontinuation or interruption, and any TEAE of special interest will be summarized for the Safety population.

The number and (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. A summary of TEAEs occurring in ≥ 5% (or >=2 subjects) of either formulation group (based on MedDRA preferred term) sorted by decreasing frequency in the new formulation arm will also be provided. Likewise, the number and percentage of subjects reporting a serious TEAE and reporting a study-drug related SAE in each treatment group will be tabulated separately by system organ class and preferred term. Likewise, summaries of TEAEs leading to study discontinuation or study drug discontinuation or interruption will also be provided by system organ class and preferred term. For all analyses of TEAEs if the same event (based on preferred term) occurred for the same subject more than once, 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.

A listing of all serious TEAEs will be provided and will include subject ID, study day(s) of event, duration of study drug administered prior to onset (minutes), system organ class, preferred term, verbatim term, severity, relationship to study drug, action taken with study drug, and outcome.

A listing of all TEAEs leading to study discontinuation, and all TEAEs leading to study drug discontinuation or interruption and will include subject ID, study day(s) of event, duration of study drug administered prior to onset (minutes), system organ class, preferred term, verbatim term, severity, relationship to study drug, action taken with study drug, and outcome.

8.5.5.2. Laboratory Tests

Laboratory values presented will include: serum chemistry, hematology, direct/indirect Coombs test, and oritavancin antibody assay. Descriptive statistics (number of subjects with a reported value, mean, SD, median, minimum, and maximum) will be presented for quantitative laboratory parameters. Laboratory data will be summarized by visit using descriptive statistics (including absolute values and change from baseline). For qualitative laboratory parameters, tables will display the number of subjects with a reported value and percentage in each category. Laboratory results will be classified as low (L), normal (N), or high (H) according to the laboratory-supplied reference ranges from the local laboratories.

There will be separate data listings for each category of laboratory test results. Subjects with values above or below the reference range, regardless of clinical significance, will be identified in the data listings with flags for high and low values. Potentially clinically significant (PCS) values will be flagged in the listings of chemistry and hematology data.

8.5.5.3. Chemistry and Hematology Laboratory Parameters,

Laboratory values descriptive statistics will be summarized by treatment group, including absolute value and changes from baseline at each scheduled time point. Graphic display of change over time using box-whisker plot or mean +/- standard error by visit will be generated. A shift table from baseline to overall worst post-baseline (which will include values from unscheduled post-baseline visits) by category (low, normal, high) will be generated. Subjects with missing data for a given visit will not contribute to the summary statistics for that visit. Tables showing shift from baseline will also be presented.

Analyses will also be performed for each lab parameter by treatment group for incidence rates of PCS values abnormalities for subjects without a PCS value at baseline. PCS values are defined in Table 3. Listings of subjects with treatment-emergent PCS (Grade 3 and 4) post-baseline laboratory abnormalities will be provided.

Table 3: Criteria for Potentially Clinically Significant Abnormal Lab Tests

Parameter	Lower limit	Upper limit
Hematology		
Red Blood Cell Count	≤ 0.75 × LLN	≥ 1.25 × ULN
WBC's Count	< 2.0×10^9/L	
Neutrophil Count	< 1.0×10^9/L	
Lymphocyte count	< 0.5×10^9/L	
Hematocrit	≤ 0.75 × LLN	≥ 1.25 × ULN
Hemoglobin	≤ 11.5 g/dL Male ≤ 9.5 g/dL Female	≥ 18.0 g/dL Male ≥ 16.0 g/dL Female
Platelet count	≤ 75×10^9/L	≥ 700×10^9/L
Absolute Reticulocyte Count[1]		> ULN
Serum Chemistry		
BUN		≥ 10.7 mmol/L
Calcium	≤ 7.0 mg/dL	≥ 15.5 mg/dL
CPK		≥ 3 × ULN
Creatinine		≥ 2.0 mg/dL
Glucose	≤ 50 mg/dL	≥ 180 mg/dL
Haptoglobin	< LLN or decrease of 50% from Baseline	
Potassium	≤ 3.0 mmol/L	≥ 5.5 mmol/L
Sodium	≤ 125 mmol/L	≥ 150 mmol/L
Liver Function Tests (LFTs):		
Alanine Transaminase (ALT/SGPT)	≥ 3×, 5×, 10× and 20× ULN	
Aspartate Transaminase (AST/SGOT)	≥ 3×, 5×, 10× and 20× ULN	
ALT or AST	≥ 3×, 5×, 10×, or 20× ULN	
Total bilirubin	≥ 1.5× and 2× ULN	
Alkaline Phosphatase (ALP)	≥ 1.5× and 3× ULN	
ALT/AST ≥ 3 × ULN and Total bilirubin ≥ 2 × ULN		
Potential Hy's Law cases:	ALT or AST ≥ 3 × ULN, Total bilirubin ≥ 2 × ULN, and ALP ≤ 2 × ULN	

1. If reticulocytes are reported in % by local laboratory, these results will be converted to absolute count in the unit of 1000/mcl for this analysis.

8.5.5.4. Analysis of Coombs Test

Coombs Test (Indirect and Direct) results (positive or negative) will be summarized by treatment group, including changes from baseline (negative to positive) at each scheduled time point. A shift table from baseline to worst change (negative to positive) post-baseline will be generated. Subjects with missing data for a given visit will not contribute to the summary statistics for that visit.

8.5.5.5. Vital Signs

Systolic and Diastolic blood pressure (mmHg), heart rate (beats/minute, bpm), respiratory rate (breaths/minute, rpm), and temperature (°F) will be collected at Screening/Baseline, Day 1 (post-dose), Day 2, Day 4, and Day 8 and Day 15. Body height and weight will be collected at Screening/Baseline only.

Vital sign measurements and changes from baseline will be summarized descriptively at each scheduled timepoint and overall worst post-baseline (maximum and/or minimum) by treatment group. The number and percentage of subjects with treatment-emergent PCS changes will also be summarized by treatment group at each scheduled time point and overall worst post-baseline (which will include values from unscheduled post-baseline visits).

A treatment-emergent PCS vital sign is defined as: Baseline value is within the normal range and the post-Baseline value is PCS. Table 4 provides definitions for PCS vital sign values. For each treatment-emergent PCS vital sign, if criteria in both directions (low and high) are shown for a single parameter, then abnormalities in each direction will be summarized separately.

Table 4: Criteria for Potentially Clinically Significant Vital Signs Values

Vital Sign	Direction	Criterion
Systolic blood pressure	Low	Value ≤ 90 mmHg and decreased ≥ 20 mmHg from Baseline value
	High	Value ≥ 180 mmHg and increased ≥ 20 mmHg from Baseline value
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decreased ≥ 15 mmHg from Baseline value
	High	Value ≥ 105 mmHg and increased ≥ 15 mmHg from Baseline value
Heart Rate	Low	Value ≤ 45 bpm and decreased ≥ 10 bpm from Baseline value
	High	Value ≥ 120 bpm and increased ≥ 15 bpm from Baseline value
Respiratory Rate	Low	Decreased ≥ 6 rpm from Baseline value
	High	Increased ≥ 6 rpm from Baseline value

All vital sign data collected during the study will be presented in a listing including an indication of whether each value is PCS.

8.5.6. Pharmacokinetic Parameters

All the pharmacokinetic analyses including the calculation of PK parameters and comparison between the two formulations, will be performed by the Melinta designated vendors. This section will just show what PK analysis will be included, all the TFLs related to PK will be provided by a separate report from the vendor.

Oritavancin plasma (blood) concentration versus time data will be analyzed using noncompartmental pharmacokinetic analysis. The following pharmacokinetic parameters will be estimated where possible (additional parameters may be calculated):

- Area under the plasma concentration-time curve (AUC) from time zero to 72 hr ($AUC_{0\text{-}72}$), time zero to 168 hr ($AUC_{0\text{-}168}$), time zero to the time of the last measurable concentration ($AUC_{0\text{-}last}$) and, where possible, AUC from time zero to infinity ($AUC_{0\text{-}inf}$)
- Maximum observed measured plasma concentration (C_{max})
- Time of observed C_{max} (T_{max})
- Elimination half- life ($t_{½}$)
- Total body clearance (CL)
- Volume of distribution at steady state (V_{ss})

All concentration data will be presented descriptively for each formulation at each time point. All pharmacokinetic parameters will be summarized by formulation for the PK population. Descriptive statistics comprise N, mean, geometric mean, SD, SEM, median, %CV, minimum and maximum.

A general linear model (GLM) will be used to evaluate the relative AUC exposure of the new formulation (test) relative to the approved formulation (reference) based on a two-group parallel design. The primary PK parameters ($AUC_{0\text{-}72}$ and $AUC_{0\text{-}168}$) will be natural-logarithmically transformed and used as the dependent variable. The independent variable includes formulation. For each PK parameter, the estimate of the treatment difference (test minus reference) and the upper/lower bound of its 90% confidence interval (CI) will be obtained from the general linear model, and then exponentiated to obtain the ratio of the geometric means and its 90% CI in the original scale.

Bioequivalence can be demonstrated if the 90% CI in the original scale is within the range of 80% to 125%.

8.5.7. Subgroup Analysis

No subgroup analysis is planned.

8.5.8. Interim Analysis

No interim analysis is planned.

9. REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
2. WHODrug, March 1, 2019 https://www.who-umc.org/whodrug/whodrug-portfolio/whodrug-global/
3. MEDDRA Version 22.0 https://www.meddra.org/news-and-events/news/english-meddra-version-220-available-download

10. PLANNED TABLES, LISTINGS, AND FIGURES

Table 5: Planned Tables

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Table 14.1.2	Significant Protocol Deviations (ITT Population)
Table 14.1.3.1	Demographic and Baseline Characteristics (ITT Population)
Table 14.1.3.2	Baseline Pathogens (ITT Population)
Table 14.1.3.3	Medical and Surgical History by MedDRA SOC and Preferred Term (ITT Population)
CSR Section 14.1.4	Prior Medications (ITT Population)
CSR Section 14.1.5	Concomitant Medications (ITT Population)
CSR Section 14.3.1	Dose Administration and Extent of Exposure (Safety Population)
CSR Section 14.3.2.1	Summary of Treatment Emergent Adverse Events (Safety Population)
CSR Section 14.3.2.2	Treatment Emergent Adverse Events by SOC and Preferred Term (Safety Population)
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CSR Section 14.3.3.5	Incidence of PCS Graded Abnormalities for Chemistry Local Laboratory Parameters (Safety Population)
CSR Section 14.3.3.6	Incidence of PCS Graded Abnormalities for Hematology Local Laboratory Parameters (Safety Population)
CSR Section 14.3.3.7	Listing of Subjects with Treatment-Emergent PCS Local Laboratory Chemistry Abnormalities (Safety Population)
CSR Section 14.3.3.8	Listing of Subjects with Treatment-Emergent PCS Local Laboratory Hematology Abnormalities (Safety Population)
CSR Section 14.3.4.1	Summary of Direct and Indirect Coombs Anti-globulin Local Laboratory Tests (Safety Population)
CSR Section 14.3.4.2	Shift Table of Direct and Indirect Coombs Anti-globulin Local Laboratory Tests from Baseline to Post-baseline (Safety Population)
CSR Section 14.3.5.1	Incidence of Treatment-Emergent PCS Vital Signs (Safety Population)
CSR Section 14.3.5.2	Vital Signs and Changes from Baseline by Visit (Safety Population)

Table 6: Planned Listings

Listing Number	Listing Title
Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Screen Failures (Eligibility Criteria Not Met)
Listing 16.2.1.3	Subject Inclusion for Analysis Sets and Reasons for Exclusion
Listing 16.2.2	Significant Protocol Deviations
Listing 16.2.3.1	Demographic and Baseline Characteristics
Listing 16.2.3.2	Microbiological Assessments
Listing 16.2.3.3	Prior and Concomitant Medications
Listing 16.2.3.4	Concomitant Surgical Procedures
Listing 16.2.3.5	Medical and Surgical History
Listing 16.2.4	Study Drug Administration
Listing 16.2.5.1	Plasma Oritavancin Concentration by Time Points
Listing 16.2.5.2	PK Parameters by Subject
Listing 16.2.6.1	Adverse Events by Subject
Listing 16.2.6.2	AE of Special Interest by Subject
Listing 16.2.7.1	Local Laboratory Results: Hematology

Listing Number	Listing Title
Listing 16.2.7.2	Local Laboratory Results: Chemistry
Listing 16.2.7.3	Local Laboratory Results: Direct/Indirect Coombs Anti-globulin Test
Listing 16.2.8	Vital Signs

Table 7: Planned Figures

Figure Number	Figure Title
CSR Section Figure 14.3.1	Clinical Chemistry Lab Mean +/- Standard Error Plot by Visit and Lab Parameters
CSR Section Figure 14.3.2	Clinical Hematology Lab Mean +/- Standard Error Plot by Visit and Lab Parameters
CSR Section Figure 14.3.3	Vital Signs Mean +/- Standard Error Plot by Visit and Parameters