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 1	
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Version/Date:	Date:	Original Protocol dated 16 April 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.

Principal Investigator

Printed Name _____

_____ _____

Signature Date

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

Melinta Medical Monitor

16 APR 2019

Signature Date

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Melinta Therapeutics, Inc.

Name of Study Drug: ORBACTIV® (oritavancin)

Title of Study: 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)

Phase of Development: 1

Planned Number of Investigational Sites: Multi-center study in approximately 5 centers in the United States.

Number of Subjects: Approximately 100 subjects will be randomized in a 1:1 ratio to the currently approved formulation of oritavancin versus a new formulation containing hydroxypropyl-β-cyclodextrin (HPβCD)

Study Period: The estimated study period for the study will be approximately 5 months from the time the first subject is enrolled until the last subject is completed.

Rationale: Single IV dose oritavancin (1200 mg) has been approved in the U.S. for the treatment of adult patients with ABSSSI caused or suspected to be caused by Gram-positive microorganisms. The current study is being conducted to evaluate the relative exposure, pharmacokinetics (PK) and safety of a new formulation of oritavancin by adjusting infusion time, concentration and reconstitution/administration solutions, of a single 1200 mg IV infusion of oritavancin in adult subjects with ABSSSI.

The approved formulation of oritavancin requires reconstitution of oritavancin for injection with Sterile Water for Injection (SWFI) and then further dilution in dextrose 5% in Water (D5W) prior to infusing a total volume of 1000 mL over 3 hours. The outcome of this study will provide data to determine whether oritavancin can be infused in less than 3 hours, in a reduced volume, with potential to use normal saline or D5W for dilution. This would reduce the burden for patients by shortening infusion time and allowing flexibility for pharmacies to use D5W or normal saline. By decreasing the volume from 1000 ml to 250 ml, it reduces the amount of fluid that is given to the patient, which is especially important for renally impaired patients or patients with compromised cardiac function.

Objectives: To compare the relative AUC exposure, safety and tolerability of the new formulation to the approved formulation of oritavancin, with both administered as a single 1200 mg IV infusion in subjects with ABSSSI.

Methodology: This is a Phase 1 randomized, open-label, multi-center, study evaluating the PK and safety of a new formulation versus the approved oritavancin formulation. The new formulation enables a shorter infusion time and a smaller volume for reconstitution/administration of a single 1200 mg IV infusion of oritavancin in subjects with ABSSSI.

Fifty (50) subjects will be administered the currently approved formulation of oritavancin, using the approved dosing regimen in which SWFI is the reconstituting agent and D5W is used for further dilution for a total volume of 1000 mL. This formulation will be infused per the approved label over 3 hours. An additional 50 subjects will be administered a new formulation of oritavancin which contains HPβCD. This formulation will be reconstituted with SWFI and further diluted in 0.9% sodium chloride (saline) for a total volume of 250 mL. This formulation will be infused over 60 minutes.

Subject Participation: Subjects will be screened up to 48 hours prior to the initiation of study drug. Oritavancin will be administered on Day 1. The total duration of the study is up to approximately 17 days, including the Post-treatment follow-up.

- Screening: ≤ 48 hours prior to first dose
- Treatment: Day 1
- Follow-up Visits: Day 2, Day 4, Day 8 and End of Study Day 15

Diagnosis and Main Criteria for Selection:

Subjects may be included in the study if they meet all of the following criteria:

1. Subject must be 18 years of age or older, male or female, and of any race.
2. Subject must give written informed consent before initiation of any study-related procedures.
3. Diagnosis of ABSSSI (wound infections, cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen requiring IV therapy.
4. If female, the subject is surgically sterile, postmenopausal, or, if of childbearing potential, agrees to use at least 2 highly effective methods of birth control (e.g. prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier methods, abstinence) for the duration of the study until 60 days after study drug administration, or male partner sterilization alone.
5. Subject must express a commitment to comply with all study visits, procedures and requirements for the duration of the study.

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

1. Infections associated with, or in close proximity to, a prosthetic device.
2. Severe sepsis or refractory shock.
3. Known or suspected bacteremia at time of screening.
4. ABSSSI due to or associated with any of the following:
    a. Infections suspected or documented to be caused by only Gram-negative pathogens (i.e., infections acquired during prolonged admission in hospital or long-term care facilities).
    b. Diabetic foot infections (infection extending distal to the malleoli in a subject with diabetes mellitus and peripheral neuropathy and/or vascular insufficiency or any ulceration of their foot).
    c. Concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis).
    d. Infected burns.
    e. A primary infection secondary to a pre-existing skin disease with associated inflammatory changes such as atopic dermatitis, eczema, or hidradenitis suppurativa.
    f. Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous).
    g. Any evolving necrotizing process (i.e., necrotizing fasciitis), gangrene or infection suspected or proven to be caused by Clostridium species (e.g., crepitance on examination of the ABSSSI site and/or surrounding tissue(s) or radiographic evidence of subcutaneous gas in proximity to the infection).
    h. Infections known to be caused by an organism resistant to oritavancin.
    i. Catheter site infections.
5. Treatment with investigational medicinal product within 30 days or 5 half-lives, whichever is longer, before enrollment and for the duration of the study.
6. Subjects currently receiving anticoagulant therapy.
7. Known liver function tests (LFTs) $\geq$ 3 times the upper limit of normal (ULN) or total bilirubin $\geq$ 2 times ULN.

8. Any medical condition, which in the judgment of the Investigator, might interfere with the pharmacokinetics, distribution, metabolism, or excretion of the study drug.
9. Any planned, major surgical procedure during the study period (Day 15).
10. Subject is the Investigator or his/her deputy, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
11. Known hypersensitivity to oritavancin, glycopeptides or HPβCD.
12. Female subject who has a positive pregnancy test or is breastfeeding.
13. Previous use of oritavancin or anticipated need to use a long acting glycopeptide during the study.

Subjects excluded for any of the above reasons may be re-screened for participation at any time if the exclusion characteristic has changed.

Investigational Product, Dose and Mode of Administration, Batch Number(s):

One of two formulations of oritavancin diphosphate (oritavancin) will be administered intravenously to all subjects.

Current Formulation: Composed of 3 single-use vials, each containing 400 mg of oritavancin and the inactive component mannitol. Oritavancin vials will be reconstituted with SWFI and further diluted in D5W for a total volume of 1000 mL and infused intravenously over 3 hours. Oritavancin Batch Number 00018 will be used.

New Formulation: Composed of a single vial containing 1200 mg of oritavancin, HPβCD, and mannitol. Oritavancin vials will be reconstituted with SWFI and further diluted with 0.9% sodium chloride (saline) for a total volume of 250 mL and infused intravenously over 1 hour. Oritavancin Batch Number 00003 will be used.

No other material or diluent may be substituted or concomitantly infused through the same IV line.

Duration of Treatment:

The dosing period is either three hours (Current Formulation) or one hour (New Formulation).

Criteria for Evaluation:

Primary endpoint:

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

Secondary endpoint:

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

Exploratory endpoint:

- Pharmacokinetic parameters (including, but not limited to: C_{max}, T_{max}, AUC, and, where they can be calculated, elimination half-life [$t_{½}$], volume of distribution [V_d], and clearance).

Pharmacology: Blood samples for the analysis of oritavancin in plasma will be collected on Day 1 pre-dose and at the end of infusion (1 hour or 3 hours), and then 3 hours (for 1 hour infusions), 6 hours, 12 hours, 24 hours, 72 hours, and 168 hours **after the start of the infusion**.

Statistical Methods and Data Analysis: Descriptive statistics include means, medians, standard deviations and ranges for continuous variables, as well as frequency and percentage for categorical variables. Descriptive statistics will be provided for demographic, baseline characteristics, and prior and concomitant medications. Summary tables and listings of safety data, including AEs, laboratory results (including Direct and Indirect Coombs) and vital signs will be provided for the Safety Population.

A general linear model 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_{0-72} and AUC_{0-168}) 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.

Sample size: Using combined results from selected Phase 1 studies on oritavancin pharmacokinetics with the approved formulation (MDCO-ORI-14-01, MDCO-ORI-14-02, MDCO-ORI-15-01, MDCO-ORI-15-02), the observed coefficients of variation (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%

Analysis population: The subject populations are defined as follows:

Intent-to-Treat (ITT) Population: The ITT population will include all subjects randomized.

Pharmacokinetics (PK) Population: All subjects who received the full dose of oritavancin and have any valid samples measured for study drug levels. The PK population will be the primary population for the PK analysis.

Safety Population: All subjects who received any amount of IV oritavancin. The safety population will be the primary population for all the safety analyses.

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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABSSSI	Acute bacterial skin and skin structure infection
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve of plasma concentrations
CDAD	Clostridium difficile-associated diarrhea
CI	Confidence interval
CL	Clearance
C_{max}	Maximal plasma concentrations
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D5W	Dextrose 5% in water
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	General linear model
GPV	Global Pharmacovigilance
HPβCD	Hydroxypropyl-β-cyclodextrin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
hr	Hour
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MIC	Minimum inhibitory concentration

Abbreviation	Definition
min	Minute(s)
NOAEL	No-observed-adverse-effect level
PK	Pharmacokinetic
PCS	Potentially clinical significant
PT	Prothrombin time
RSI	Reference safety information
s	Second(s)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard operating procedure
SWFI	Sterile water for injection
$t_{½}$	Half-life
TEAE	Treatment emergent adverse event
T_{max}	Time of observed C_{max}
TMF	Trial Master File
ULN	Upper limit of normal
V_d	Volume of distribution
V_z	Volume of distribution
WHO	World Health Organization
y	Year

5. INTRODUCTION

This protocol describes a randomized, open-label, multi-center, study evaluating the pharmacokinetic (PK) and safety of a new formulation versus the approved oritavancin formulation in subjects with acute bacterial skin and skin structure infection (ABSSSI). The new formulation adjusts the infusion time, concentration and reconstitution/administration solutions of a single 1200 mg intravenous (IV) infusion of oritavancin.

Oritavancin has been approved in the United States for the treatment of adult patients with ABSSSI caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms. An extensive clinical development program has been conducted to evaluate the safety and effectiveness of oritavancin, comprising 3198 oritavancin-treated subjects from 29 completed clinical trials in adults, including two Phase 4 studies, four Phase 3 studies, four Phase 2 studies, 19 Phase 1 studies and one ongoing Phase 1 trial in pediatrics.

Oritavancin has been well tolerated in these studies. More details may be found in the Investigator's Brochure (Oritavancin Investigator's Brochure Edition 12.0).

In a previous study (MDCO-ORI-15-01), the area under the curve (AUC) generated with a single 1200 mg dose of the new formulation of oritavancin administered as an IV infusion over 30, 60, 90 minutes, or 2 hours in healthy volunteers was comparable with previous exposure data with a 1200 mg dose of the approved formulation of oritavancin administered over 3 hours. The purpose of the current study is to determine the (a) relative AUC exposure (b) safety and tolerability and (c) pharmacokinetic profile using the new single vial formulation of oritavancin following a single IV dose in subjects with ABSSSI.

5.1. Background on Oritavancin

Oritavancin is a novel semi-synthetic, lipoglycopeptide antibiotic that has three principal mechanisms of action: 1) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; 2) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and 3) disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and rapid cell death. These multiple mechanisms contribute to the rapid, concentration-dependent bactericidal activity of oritavancin.

Oritavancin has been approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of Gram-positive microorganisms including *Staphylococcus aureus* (including methicillin-susceptible and methicillin–resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (includes *S. anginosus, S. intermedius, and S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only) (ORBACTIV® Package Insert 2018). The currently approved formulation of oritavancin is obtained by reconstitution and dilution of three ORBACTIV® 400 mg vials to prepare a single 1200 mg intravenous dose. Reconstitution is by sterile water for injection (SWFI), and dilution is by dextrose 5% in water (D5W), yielding a final concentration of 1.2 mg/ml. The currently approved formulation of oritavancin is infused over 3 hours.

This new formulation is reconstituted using a combination of hydroxypropyl-β-cyclodextrin (HPβCD) in SWFI instead of SWFI only. Hydroxypropyl-β-cyclodextrin is the most widely used

modified cyclodextrin and has been shown to change the physicochemical properties of lipophilic and other insoluble compounds when co-formulated in combination. HPβCD functions by forming an inclusion complex with the active pharmaceutical agent that increases aqueous solubility and stability (Loftsson 2005). Solutions of cyclodextrin-drug complexes may be lyophilized to produce freely soluble powders as drug products.

The current formulation of oritavancin has limited solubility in solutions containing sodium chloride and must be diluted in 1000 mL of D5W and infused over 3 hours. As HPβCD has been shown to improve the solubility and formulation characteristics of numerous compounds including anti-infectives such as Sporanox® (itraconazole) and Vibativ® (telavancin), this excipient was tested with oritavancin. In HPβCD, oritavancin is significantly more soluble at physiologic pH and in 0.9% sodium chloride (normal saline) (MDCO Internal Report SR15-30 2015), allowing for smaller infusion volumes using in diluents other than D5W.

5.2. Nonclinical Studies

Oritavancin has been extensively studied pre-clinically. The results from the safety, toxicology, pharmacokinetic, and pharmacodynamic studies demonstrate that oritavancin does not appear to induce any biologically significant toxicity. An overview of relevant nonclinical study results is presented in the Investigator's Brochure (Oritavancin Investigator's Brochure Edition 12.0).

5.2.1. HPβCD Nonclinical Summary

HPβCD is quickly cleared after parenteral administration. After a single intravenous dose of 14C labeled HPβCD, the half-life in plasma was 0.4 and 0.8 hours in rats and dogs, respectively. The plasma clearance (CL) was 0.51 and 0.19 L/hr/kg in rats and dogs, respectively (Gould 2005).

In acute toxicology studies in rats, there was no toxicity at 2 g/kg. In cynomolgus monkeys, a single dose of 10 g/kg was tolerated (Gould 2005).

In sub-acute toxicity studies in rats over 90 days with doses of 50, 100, or 400 mg/kg, the no-observed-adverse-effect-level (NOAEL) was 50 mg/kg/day. At 100 mg/kg/day, there were minimal histological changes in the epithelial cells of the bladder, changes in tubular cells of the kidney and in the liver. At 400 mg/kg/day, there were decreases in body weight and food consumption, changes in some clinical chemistry parameters and some increases in organ weights. These changes were reversible after one month (Gould 2005).

In a second sub-acute toxicity study in rats over 90 days with every other day dosing at 200 mg/kg/dose there was no toxicity observed (Gould 2005).

In sub-acute toxicity studies in dogs over 90 days with doses of 50, 100, or 400 mg/kg, the NOAEL was 100 mg/kg/day. At 400 mg/kg/day, there were histological changes in the lung and epithelial cells of the bladder and renal pelvis. All changes were reversible after one month (Gould 2005).

In a second sub-acute toxicity study in dogs over 90 days at doses of 700 – 1000 mg/kg, the only signs of toxicity were vacuolation of renal tubular cells which was reversible (Gould 2005).

In a sub-acute toxicity study in cynomolgus monkeys with 200 mg/kg dosing every other day for 91 days, there was no toxicity observed (Gould 2005).

5.2.2. PK and Toxicity of Oritavancin with HPβCD (Study SR15-030)

The pharmacokinetics of oritavancin formulated in D5W or HPβCD in normal saline were compared after a one-hour intravenous infusion of 50 or 100 mg/kg in male Sprague-Dawley rats. Data indicate that the formulation does not have an impact on the pharmacokinetics of oritavancin. Rats infused with 50 mg/kg of oritavancin in D5W or HPβCD had maximum concentrations (C_{max}) of 160 and 138 mg/L, respectively. Rats infused with 100 mg/kg of oritavancin in D5W or HPβCD had C_{max} of 244 and 280 mg/L, respectively. The whole blood AUCs at 100 mg/kg were 1992.15 and 1964.47 mg*hr/L and the estimated plasma AUCs at 100 mg/kg were 3172.21 and 3128.14 mg*hr/L for oritavancin in D5W and HPβCD, respectively. The concentrations of oritavancin in both formulations increased proportionally with dose.

In the toxicity study, there were no clinical observations, hematology or clinical chemistry changes due to oritavancin formulated in D5W or in HPβCD over 8 days following single 1-hour intravenous infusions of 50 or 100 mg/kg. There was no treatment related macroscopic or microscopic changes in tissues collected at any dose with either formulation.

Based on the lack of any significant findings with either formulation of oritavancin, the NOAEL for oritavancin in D5W or in HPβCD in normal saline was found to be ≥ 100 mg/kg following a single 1-hour infusion.

The plasma AUC of oritavancin formulated in HPβCD in the rat following a 100 mg/kg dose was 3128.14 mg*h/L. This exposure level is roughly equivalent to a 1200 mg dose in man (~2800 mg*h/L).

The dose of HPβCD in the control group and the 100 mg/kg oritavancin in HPβCD group was 400 mg/kg. There were no adverse findings associated with either group.

5.3. Summary of Clinical Pharmacology

5.3.1. Currently Approved Formulation of Oritavancin

The pharmacokinetics of a single 1200 mg dose of oritavancin in ABSSSI subjects were determined using the currently approved formulation from population pharmacokinetic analysis of pooled data from 297 adult subjects, and are presented in Table 1. At steady-state, oritavancin exhibits linear pharmacokinetics at a dose up to 1200 mg. The mean, population-predicted oritavancin concentration-time profile displays a multi- exponential decline and a long terminal half-life of 245 hours. Normal Healthy Volunteers administered a single 1200 mg dose of oritavancin experience higher oritavancin exposure when compared to patients; mean C_{max} was approximately 25% higher in healthy volunteers and $AUC_{0-\infty}$ was approximately 40% higher in healthy volunteers when compared to patients.

Table 1: Mean Pharmacokinetic Parameters for ABSSSI Subjects Receiving a Single 1200 mg Dose (n = 297)

Parameter	Mean	(CV%)
V_{ss} (L)	97.8	(56.4%)
C_{max} (µg/mL)	138	(23.0%)
AUC_{0-24} (h*µg/mL)	1110	(33.9%)
AUC_{0-72} (h*µg/mL)	1530	(36.9%)
$AUC_{0-\infty}$ (h*µg/mL)	2800	(28.6%)
$t_{½\alpha}$ (h)	2.29	(49.8%)
$t_{½\beta}$ (h)	13.4	(10.5%)
$t_{½\gamma}$ (h)	245	(14.9%)

Abbreviations: V_{ss} = Steady-state volume of distribution; C_{max} = Maximum plasma concentration; AUC_{0-24} = Area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-72} = Area under the plasma concentration-time curve from time zero to 72 hours; $AUC_{0-\infty}$ = Area under the plasma concentration time curve from time zero to infinity; $t_{½\alpha}$ = Half-life for the alpha phase; $t_{½\beta}$ = Half-life for the beta phase; $t_{½\gamma}$ = Half-life for the gamma phase; CV% = Percent coefficient of variation

5.3.2. New Formulation of Oritavancin

A multi-vial version of the new formulation (HPβCD solution was provided as a diluent) was tested in Study MDCO-ORI-15-01 to determine whether oritavancin could be infused in less than 3 hours, in a reduced volume, with potential to use normal saline instead of D5W for dilution.

Study MDCO-ORI-15-01 was a Phase 1, single-center, double-blind cohort study evaluating the pharmacokinetics and safety of a new formulation of oritavancin by adjusting infusion time, concentration, and reconstitution/administration solutions, of a single 1200 mg IV infusion of oritavancin in healthy adult subjects. Fifty-six (56) subjects (46 received oritavancin and 10 received placebo) with a median age of 40.5 years (range: 19-65 years) participated in the study. The study consisted of six cohorts (subjects in Cohort 6 received the new formulation over 60 minutes using normal saline as the diluent, which is the formulation which will be studied in this trial). Oritavancin C_{max} generally increased as the infusion duration decreased from 3 hours to 60 minutes, while the mean AUC, CL, and volume of distribution (V_z) estimates were comparable between the approved formulation and the new formulation (Table 2).

Table 2: Summary of Mean (CV%) Oritavancin PK Parameters in Healthy Adult Subjects by Cohort (PK Population; Study MDCO-ORI-15-01)

PK Parameter (units)	Cohort 1 (n = 6)	Cohort 2 (n = 8)	Cohort 3 (n = 8)	Cohort 4 (n = 8)	Cohort 5 (n = 8)	Cohort 6* (n = 8)
IV infusion duration:	3 hours	2 hours	90 minutes	60 minutes	30 minutes	60 minutes
$AUC_{0\text{-last}}$ (h*µg/mL)	3278 (18.6)	2377 (22.7)	2509 (29.0)	2535 (32.2)	2807 (14.7)	2719 (20.5)
$AUC_{0\text{-inf}}$ (h*µg/mL)	3537 (16.7)	2617 (23.9)	2727 (28.0)	2756 (31.1)	3063 (14.3)	2962 (20.7)
C_{max} (µg/mL)	182.8 (11.4)	152.5 (17.5)	176.8 (15.5)	201.9 (20.5)	199.1 (11.8)	205.8 (7.3)
T_{max} (h)	3.040 (3.00-3.08)	2.000 (2.00-2.02)	1.465 (1.44-1.51)	1.025 (1.00-1.04)	0.490 (0.48-0.51)	0.970 (0.96-1.00)
$t_{½}$ (h)	47.807 (32.6)	60.694 (14.6)	61.264 (21.7)	62.968 (24.7)	57.479 (14.7)	52.608 (19.5)
CL (L/h)	0.3483 (18.6)	0.4871 (29.0)	0.4729 (29.3)	0.4783 (33.7)	0.3988 (14.2)	0.4238 (24.9)
V_z (L)	24.00 (40.7)	42.13 (26.0)	42.01 (36.1)	45.63 (57.9)	33.24 (24.4)	32.49 (32.9)

Abbreviations: CV% = percent coefficient of variation; h = hour(s); IV = intravenous; PK = pharmacokinetic; CL = clearance; C_{max} = Maximum plasma concentration; $AUC_{0\text{-last}}$ = Area under the plasma concentration time curve from time zero to the time of the last measurable concentration; $AUC_{0\text{-}\infty}$ = Area under the plasma concentration time curve from time zero to infinity; $t_{½}$, = Half-life; T_{max} = Time of observed C_{max}; V_z = volume of distribution
Cohort 1: 1200 mg of oritavancin diluted in 1000 mL of dextrose 5% in water (D5W).
Cohort 2: 1200 mg of oritavancin diluted in 250 mL of D5W with hydroxypropyl-β-cyclodextrin (HPβCD) or placebo of 250 mL of D5W.
Cohort 3: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 4: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 5: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
*Cohort 6 differs from Cohort 4 as this cohort administered a 60-minute infusion diluted in 250 mL of normal saline instead of D5W.
Note: T_{max} reported as median (minimum-maximum).
Source: MDCO-ORI-15-01

For Cohort 1, the currently approved formulation, the mean C_{max} was 182.8 µg/mL with a coefficient of variation (CV)% of 11.4%. The mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were 3278 and 3537 h*µg/mL, respectively, which were higher (approximately 1.2- to 1.4-fold) than the AUC values for all other cohorts and the $AUC_{0\text{-inf}}$ estimate listed in the product label (2800 h*µg/mL). Compared with Cohorts 2 through 6, the mean CL and V_z for Cohort 1 were slightly lower (approximately 0.5- to 0.8-fold).

For Cohorts 2 through 5, the mean C_{max} generally increased as the infusion duration decreased, as would be expected. The mean C_{max} estimates for Cohorts 2 through 5 were 152.5, 176.8, 201.9, and 199.1 µg/mL, respectively, and the CV% ranged from 11.8% to 20.5%. The mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were similar across Cohorts 2 through 5, ranging from 2377 h*µg/mL to 2807 h*µg/mL for $AUC_{0\text{-last}}$ and 2617 h*µg/mL to 3063 h*µg/mL for $AUC_{0\text{-inf}}$. The mean CL, and V_z estimates were also similar across Cohorts 2 through 5.

For Cohort 6, the new formulation in 0.9% sodium chloride instead of D5W, the mean C_{max} was 205.8 µg/mL, which was comparable to the mean C_{max} for Cohort 4 (201.9 µg/mL). The mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were 2719 and 2962 h*µg/mL, respectively, which were also similar to the mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for Cohort 4.

The oritavancin plasma exposures following 60-minute infusions of the new formulation (Cohorts 4 and 6) from Study MDCO-ORI-15-01 were compared to the plasma exposures following 3-hour infusions of the currently approved formulation from completed Phase 1 and ABSSSI studies. The results of this analysis found that oritavancin exposures, as measured by AUC, were comparable between the two formulations.

5.4. Clinical

5.4.1. Currently Approved Formulation of Oritavancin

As of 12 March 2019, oritavancin has been studied in 3198 oritavancin-treated subjects from 29 completed clinical trials in adults, including two Phase 4 studies, four Phase 3 studies, four Phase 2 studies, 19 Phase 1 studies and one ongoing Phase 1 trial in pediatrics.

5.4.1.1. Known and Potential Risks from Phase 3 ABSSSI Clinical Trials

In the pooled ABSSSI clinical trials, there were 540 (55.3%) subjects in the oritavancin arm and 559 (56.9%) subjects in the vancomycin arm, who reported ≥ 1 adverse reaction. Serious adverse reactions were reported in 57/976 (5.8%) subjects treated with oritavancin and 58/983 (5.9%) treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in oritavancin and 12/983 (1.2%) in the vancomycin arms, respectively.

The most commonly reported adverse reactions (≥ 3%) in subjects receiving a single 1200 mg dose of oritavancin in the pooled ABSSSI clinical trials were: nausea, headache, vomiting, limb and subcutaneous abscesses, and diarrhea.

In the pooled ABSSSI clinical trials, oritavancin was discontinued due to adverse reactions in 36/976 (3.7%) of subjects; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 0.3%) (Orbactiv® Package Insert 2018).

5.4.1.2. Hypersensitivity and Infusion Related Reactions

Serious hypersensitivity reactions have been reported with the use of oritavancin. If an acute hypersensitivity reaction occurs during oritavancin infusion, discontinue oritavancin immediately and institute appropriate supportive care. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during oritavancin infusion in patients with a history of glycopeptide allergy. In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in oritavancin-treated patients was 1.2 days and the median duration of these reactions was 2.4 days.

Infusion related reactions have been reported with the glycopeptide class, including oritavancin. The reactions resemble "Red-man Syndrome", including pruritus, urticaria and/or rash and flushing of the upper body. If infusion-related reactions occur, slowing or interrupting the infusion could stop the reaction.

5.4.1.3. Other Potential Risks

Oritavancin has been shown to artificially prolong prothrombin time (PT) and International Normalized Ratio (INR) for up to 24 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 24 hours after an oritavancin dose. Subjects currently receiving anticoagulant therapy are excluded from this study at Screening.

Infusing oritavancin in a shorter duration may result in a higher C_{max}. A higher C_{max} may produce adverse events (AEs) similar to those observed in the oritavancin cardiac safety study (MDCO-ORI-12-02) where 1600 mg infused over three hours was selected as the supra-therapeutic dose. In this study, forty-eight healthy volunteers were administered the 1600 mg supratherapeutic oritavancin dose (current formulation) and seven reported oral paresthesia or oral hypoesthesia. They were of mild intensity as were most of the events reported from the 1600 mg dose.

There are no additional AEs expected from using HPβCD as the excipient in this trial.

A complete description of relevant risks of oritavancin can be found in the Investigator's Brochure (Oritavancin Investigator's Brochure Edition 12.0).

5.4.2. New Formulation of Oritavancin

As described in Section 5.3.2, Study MDCO-ORI-15-01 was a Phase 1, single-center, double-blind cohort study evaluating the pharmacokinetics and safety of a new formulation of oritavancin by adjusting infusion time, concentration, and reconstitution/administration solutions, of a single 1200 mg IV infusion of oritavancin in healthy adult subjects. The new formulation was well tolerated by the healthy male and female subjects with no evidence of an increase in incidence or severity of treatment-emergent adverse events (TEAEs) with shorter infusion times and new formulation.

5.4.2.1. Safety in Study MDCO-ORI-15-01 with Oritavancin New Formulation

Overall, 10 subjects (17.9%) reported at least one TEAE and 8 subjects (14.3%) reported a TEAE considered related to study drug. All TEAEs were mild in severity. There were no deaths, serious adverse events (SAEs), or TEAEs leading to study drug or study discontinuation.

Overall, a higher percentage of subjects (4 subjects, 50.0%) reported TEAEs in Cohort 3 (90-minute IV infusion) followed by subjects (3 subjects, 37.5%) in Cohort 4 (60-minute IV infusion). Similar percentages of subjects reported TEAEs considered related to study drug in Cohorts 3 and 4 (3 subjects each, 37.5%). No TEAEs were reported by subjects in Cohort 1 (3-hour IV infusion) or Cohort 2 (2-hour IV infusion). There was no evidence of an increase or change in TEAEs with a decrease infusion time response in Cohorts 1 through 5, and no evidence of a response to switching to normal saline between Cohorts 4 and 6.

TEAEs reported by more than 1 subject included diarrhea, oral paresthesia, and headache (2 subjects each, 3.6%) (Table 3). All TEAEs of oral paresthesia occurred in Cohort 4 (60-minute IV infusion) and all TEAEs of headache occurred in Cohort 3 (90-minute IV infusion). The TEAEs of diarrhea occurred in Cohort 3 (90-minute IV infusion) and Cohort 6 (60-minute IV infusion). All other TEAEs were reported by one subject (1.8%) each. Based on the findings in these studies and the safety of HPβCD in other formulations, there is limited safety risk with use with oritavancin and thus further evaluation in human trials is warranted.

Table 3: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population; Study MDCO-ORI-15-01)

System Organ Class Preferred Term	Cohort 1 (3-hour IV) (n = 6) n (%)	Cohort 2 (2-hour IV) (n = 8) n (%)	Cohort 3 (90-min IV) (n = 8) n (%)	Cohort 4 (60-min IV) (n = 8) n (%)	Cohort 5 (30-min IV) (n = 8) n (%)	Cohort 6* (60-min IV) (n = 8) n (%)	Placebo (n = 10) n (%)	Overall (N = 56) n (%)
Number of subjects with at least 1 TEAE	0	0	4 (50.0)	3 (37.5)	1 (12.5)	1 (12.5)	1 (10.0)	10 (17.9)
Number of TEAEs	0	0	7	4	4	4	1	20
Gastrointestinal disorders	**0**	**0**	**2 (25.0)**	**2 (25.0)**	**0**	**1 (12.5)**	**0**	**5 (8.9)**
Abdominal pain	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Constipation	0	0	1 (12.5)	0	0	0	0	1 (1.8)
Diarrhea	0	0	1 (12.5)	0	0	1 (12.5)	0	2 (3.6)
Nausea	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Paresthesia oral	0	0	0	2 (25.0)	0	0	0	2 (3.6)
General disorders and administration site	**0**	**0**	**0**	**2 (25.0)**	**0**	**0**	**1 (10.0)**	**3 (5.4)**
Injection site injury	0	0	0	1 (12.5)	0	0	0	1 (1.8)
Injection site pain	0	0	0	1 (12.5)	0	0	0	1 (1.8)
Medical device reaction	0	0	0	0	0	0	1 (10.0)	1 (1.8)
Infections and infestations	**0**	**0**	**1 (12.5)**	**0**	**0**	**0**	**0**	**1 (1.8)**
Pharyngitis	0	0	1 (12.5)	0	0	0	0	1 (1.8)
Injury, poisoning, and procedural complications	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Infusion related reaction	0	0	0	0	1 (12.5)	0	0	1 (1.8)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Muscle tightness	0	0	0	0	1 (12.5)	0	0	1 (1.8)
Nervous system disorders	**0**	**0**	**2 (25.0)**	**0**	**0**	**1 (12.5)**	**0**	**3 (5.4)**
Dizziness	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Headache	0	0	2 (25.0)	0	0	0	0	2 (3.6)

System Organ Class Preferred Term	Cohort 1 (3-hour IV) (n = 6) n (%)	Cohort 2 (2-hour IV) (n = 8) n (%)	Cohort 3 (90-min IV) (n = 8) n (%)	Cohort 4 (60-min IV) (n = 8) n (%)	Cohort 5 (30-min IV) (n = 8) n (%)	Cohort 6* (60-min IV) (n = 8) n (%)	Placebo (n = 10) n (%)	Overall (N = 56) n (%)
Psychiatric disorders	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Anxiety	0	0	0	0	1 (12.5)	0	0	1 (1.8)
Respiratory, thoracic, and mediastinal disorders	**0**	**0**	**2 (25.0)**	**0**	**0**	**0**	**0**	**2 (3.6)**
Nasal congestion	0	0	1 (12.5)	0	0	0	0	1 (1.8)
Pharyngeal inflammation	0	0	1 (12.5)	0	0	0	0	1 (1.8)

Abbreviations: IV = intravenous; min = minute; TEAE = treatment-emergent adverse event
Cohort 1: 1200 mg of oritavancin diluted in 1000 mL of dextrose 5% in water (D5W).
Cohort 2: 1200 mg of oritavancin diluted in 250 mL of D5W with hydroxypropyl-β-cyclodextrin (HPβCD).
Cohort 3: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 4: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 5: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
*Cohort 6 differs from Cohort 4 as this cohort administered a 60-minute infusion diluted in 250 mL of normal saline instead of D5W.
Placebo: Cohorts 2-6 each had 2 subjects who were administered placebo (250 mL of normal saline). These subjects are pooled together in the placebo column.

5.5. Rationale for the Present Study

Single IV dose oritavancin (1200 mg) has been approved in the U.S. for the treatment of adult patients with ABSSSI caused or suspected to be caused by Gram-positive microorganisms. The current study is being conducted to evaluate the relative exposure, PK and safety of a new formulation of oritavancin by adjusting infusion time, concentration and reconstitution/ administration solutions, of a single 1200 mg IV infusion of oritavancin in adult subjects with ABSSSI.

The approved formulation of oritavancin requires reconstitution of oritavancin for injection with SWFI and then further dilution in D5W prior to infusing a total volume of 1000 mL over 3 hours. The outcome of this study will provide data to determine whether oritavancin can be infused in less than 3 hours, in a reduced volume, with potential to use normal saline or D5W for dilution. This would reduce the burden for patients by shortening infusion time and give flexibility for pharmacies to use D5W or normal saline. By decreasing the volume from 1000 ml to 250 ml, it reduces the amount of fluid that is given to the patient, which is especially important for renally impaired patients or patients with compromised cardiac function.

In a prior study (MDCO-ORI-15-02) using the current approved formulation, elevated immunoglobulin levels and a positive Indirect Coombs test were observed in several healthy volunteers after a second dose of oritavancin (two weeks apart). Another study (MDCO-ORI-16-02) was subsequently completed with ABSSSI patients who received two doses of oritavancin one week apart (also with the current approved formulation). None of the patients in that study had a positive Indirect Coombs result.

As a result of these findings and to verify whether this might occur with the new formulation in ABSSSI patients, plasma will be collected from subjects in this study before and after oritavancin dosing to test for Direct and Indirect Coombs.

5.6. Study Population

Male or female subjects at least 18 years old (inclusive) with ABSSSI who meet all the inclusion and none of the exclusion criteria.

6. STUDY OBJECTIVES

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 AEs and 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 [V_d], 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 Phase 1, 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 five 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.

Detailed descriptions of the assessments are provided in Section 10.

7.1. 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}).

7.2. 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.

7.3. 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_d, and CL) after a single 1200 mg IV infusion of oritavancin in male and female subjects with ABSSSI.

7.4. Measures to Minimize/Avoid Bias

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.

8. SELECTION OF SUBJECT POPULATION

The following criteria for enrollment must be followed explicitly. The subject will not be enrolled unless the inclusion/exclusion criteria are met. The Investigator or other study site personnel must document in the source documents that the informed consent form (ICF) was signed and dated prior to any study screening procedures. The presence of inclusion criteria and absence of exclusion criteria will be verified in the electronic case report form (eCRF).

8.1. Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Subject must be 18 years of age or older, male or female, and of any race.
2. Subject must give written informed consent before initiation of any study-related procedures.
3. Diagnosis of ABSSSI (wound infections, cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen requiring IV therapy.
4. If female, the subject is surgically sterile, postmenopausal, or, if of childbearing potential, agrees to use at least 2 highly effective methods of birth control (e.g. prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier methods, abstinence) for the duration of the study until 60 days after study drug administration, or male partner sterilization alone.
5. Subject must express a commitment to comply with all study visits, procedures and requirements for the duration of the study.

8.2. Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

1. Infections associated with, or in close proximity to, a prosthetic device.
2. Severe sepsis or refractory shock.
3. Known or suspected bacteremia at time of screening.
4. ABSSSI due to or associated with any of the following:
    a. Infections suspected or documented to be caused by only Gram-negative pathogens (i.e., infections acquired during prolonged admission in hospital or long-term care facilities).
    b. Diabetic foot infections (infection extending distal to the malleoli in a subject with diabetes mellitus and peripheral neuropathy and/or vascular insufficiency or any ulceration of their foot).
    c. Concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis).
    d. Infected burns.

e. A primary infection secondary to a pre-existing skin disease with associated inflammatory changes such as atopic dermatitis, eczema, or hidradenitis suppurativa.

f. Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous).

g. Any evolving necrotizing process (i.e., necrotizing fasciitis), gangrene or infection suspected or proven to be caused by *Clostridium* species (e.g., crepitance on examination of the ABSSSI site and/or surrounding tissue(s) or radiographic evidence of subcutaneous gas in proximity to the infection).

h. Infections known to be caused by an organism resistant to oritavancin.

i. Catheter site infections.

5. Treatment with investigational medicinal product within 30 days or 5 half-lives, whichever is longer, before enrollment and for the duration of the study.
6. Subjects currently receiving anticoagulant therapy.
7. Known liver function tests (LFTs) ≥ 3 times the upper limit of normal (ULN) or total bilirubin ≥ 2 times ULN.
8. Any medical condition, which in the judgment of the Investigator, might interfere with the pharmacokinetics, distribution, metabolism, or excretion of the study drug.
9. Any planned, major surgical procedure during the study period (Day 15).
10. Subject is the Investigator or his/her deputy, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
11. Known hypersensitivity to oritavancin, glycopeptides or HPβCD.
12. Female subject who has a positive pregnancy test or is breastfeeding.
13. Previous use of oritavancin or anticipated need to use a long acting glycopeptide during the study.

Subjects excluded for any of the above reasons may be re-screened for participation at any time if the exclusion characteristic has changed.

8.3. Prior and Concomitant Treatment

Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments) received by the subject within 14 days before administration of the first dose of study drug through the last study visit. These medications/treatments will be recorded in the eCRF. The medication name, route of administration, dose, unit, frequency and indication and duration of the treatment/procedure (start and stop dates) will be recorded in the eCRF.

8.3.1. Permitted Adjunctive Therapies

Minor surgical or bedside procedures (including incision and drainage, aspiration, lavage, etc.) are allowed during the study. However, planned major surgical procedures during the study that

could incur blood loss or fluid shifts are not permitted as this may impact the safety and PK analysis.

8.3.2. Prohibited Medications

As the safety data collection in this trial is extremely important, use of additional antibiotics during the study period should be minimized unless the patient is a treatment failure requiring unexpected rescue antibiotics or requires additional antibiotics to treat a new infection during the study.

9. STUDY DRUGS

9.1. Method of Assigning Subjects to Treatment Groups

The study is randomized 1:1 (Current Formulation:New Formulation). Randomization will take place in the electronic data capture (EDC) system once the subject is screened and confirmed to be eligible for participation.

9.2. Treatments Administered

After randomization, dosing will be performed on Day 1. All participants will receive a single intravenous infusion of oritavancin, either the current formulation or the new formulation, diluted as indicated below. A pharmacist or qualified designee will prepare the study drug infusions. No other material or diluent may be substituted or concomitantly infused through the same IV line. Refer to the Pharmacy Manual for further details regarding dose preparation and administration.

9.2.1. Current Oritavancin Formulation

The currently approved formulation is composed of 3 single-use vials, each containing 400 mg of oritavancin diphosphate (as the free base) and the inactive component mannitol. Oritavancin vials will be reconstituted with SWFI and further diluted in D5W for a total volume of 1000 mL and infused intravenously over 3 hours.

9.2.2. New Oritavancin Formulation

The new formulation is composed of a single vial containing 1200 mg of oritavancin, HPβCD, and mannitol. Oritavancin vials will be reconstituted with SWFI and further diluted with 0.9% sodium chloride (saline) for a total volume of 250 mL and infused intravenously over 1 hour.

9.3. Packaging and Labeling

The Sponsor will provide the current and new formulation. Infusion bags of D5W and 0.9% sodium chloride will be provided by the study site pharmacy.

Vial labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

This study is open-label and therefore, the site personnel and study subject will know which formulation they are receiving and the infusion duration (3 hours or 1 hour). The pharmacist will label the infusion bag with the oritavancin 1200 mg (new formulation or current approved formulation) and will include the infusion time (1 hour or 3 hours).

9.4. Study Drug Storage Conditions

Oritavancin lyophilized powder should be stored at controlled room temperature (20°C to 25°C; 68°F to 77°F) in a secure cabinet. Diluted intravenous solution in an infusion bag should be used **within 6 hours when stored at room temperature, or within 12 hours when refrigerated.** The combined storage time (reconstituted solution in the vial and diluted solution in the bag) and infusion time should not exceed 6 hours at room temperature or 12 hours when refrigerated (see Pharmacy Manual). Access should be strictly limited to the study pharmacists and their designees.

9.5. Blinding

The study is open-label and therefore, there is no blinding of the study drug or study drug infusion time.

9.6. Receipt of Supplies

Upon receipt of the investigational drug, the pharmacist or designated study site personnel will visually inspect the shipment and verify the drug information, quantity, and condition of the kits received. The Investigational Drug Transmittal and Receipt Form will be completed and signed by the pharmacist and retained in the pharmacy binder. In addition, receipt of the study drug shipment will be sent to Melinta for placement in the Trial Master File (TMF).

9.7. Study Drug Accountability

It is the responsibility of the Investigator to ensure that a current record of inventory/drug accountability is maintained. The investigator or designee must maintain an inventory record of all study medications received and administered to assure the regulatory authorities and the Sponsor that the drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Drug accountability forms and/or specific instructions can be found in the Pharmacy Manual. Inventory records must be readily available for inspection by the study monitor and available to Regulatory Agencies for inspection at any time.

The oritavancin supplied for use in this study is to be prescribed only by the Principal Investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

During the study, all used oritavancin containers (e.g., empty vials) will be kept until the monitor has reviewed the accountability records. If this is not permitted by the institution's Standard Operating Procedures (SOP), this should be discussed with the monitor prior to study start.

9.8. Study Drug Handling and Return

Upon the completion or termination of the study, and upon written authorization from Melinta or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Melinta. It is the Investigator's responsibility to ensure that Melinta or its representative has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Melinta monitor (or designee).

9.9. Product Complaints

Sites are required to report any product complaints to Melinta immediately but no later than 24 hours from the time of awareness, by phone or e-mail as follows:

US Phone: 1-844-MED-MLNT (1-844-633-6569)

Email: medinfo@melinta.com

Product Complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, durability, reliability, quality, safety, effectiveness or

performance of a product, after it is released for distribution (EU DIR 2001/83/EC). (Derived from Ref US 21 CFR 211.198)

There are two types of Product Complaints: Technical Quality Complaints and Preference Complaints.

Technical Quality Complaint: A report of dissatisfaction with the product with regard to its efficacy, strength, integrity, purity, or quality; thus, a potential failure to meet product specifications. Examples include:

- An indication that there is an unexpected physical change in the drug product such as discoloration, change in shape of the drug product, presence of particulates or any other physical change that might indicate contamination, a manufacturing defect or any other event that might indicate a compromise in product quality.
- An indication that the content does not meet its labeled volume, count, etc.
- An indication that there is an unexpected physical change in any part of the container (this includes the bottle, any part of the seal, the cap or the label).
- An indication that the product is mislabeled.
- An indication that there is an unexpected physical change of the product or container once the product is diluted or reconstituted (the container includes the vial, bag, IV-line, syringe or any other item that is in contact with the product).
- An indication that the product is falsified, tampered with or adulterated.
- An indication that the product did not meet its pharmacologic effect, i.e. lack of efficacy.

Preference Complaints: A report of dissatisfaction with service, delivery, packaging or other preference.

10. SCHEDULE OF ASSESSMENTS AND PROCEDURES

This study will consist of three periods:

1. Screening Period – within 48 hours prior to first dose
2. Day 1 (pre-dose, dosing, post-dose)
3. Follow-up Period – Day 2 through Day 15 (End of study visit)

The subject's participation from screening/informed consent to end of study will be up to approximately 17 days.

10.1. Schedule of Events/Assessments

The Schedule of Events/Assessments (Table 4) summarizes the study assessments by time point.

Table 4: 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 plasma 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]Plasma 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 5 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]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.

10.2. Screening Period (Within 48 Hours Prior to Day 1)

The following procedures will be performed within 48 hours prior to study drug administration to assess subject eligibility for the study:

1. Obtain written informed consent.
2. Assess inclusion/exclusion criteria.
3. Record medical history including microbiology results, if available.
4. Perform a physical examination (including height and weight).
5. Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature).
6. A local urine pregnancy test will be performed for female subjects of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile).
7. Collect blood specimens for hematology and serum chemistry tests.
8. Record prior and concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).

10.3. Randomization

Randomization should only occur once subject eligibility criteria are confirmed (see Section 9.4).

10.4. Day 1 (Pre-Dose)

The following assessments will be performed on Day 1 prior to dosing:

1. Assess inclusion/exclusion criteria.
2. Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature).
3. A local urine pregnancy test will be performed for female subjects of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile) if the screening pregnancy test was performed > 24 hours prior to dosing.
4. Record prior and concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).
5. Collect blood specimens for PK, Direct and Indirect Coombs testing and oritavancin antibody assay.

10.5. Day 1 (Dosing)

Oritavancin will be administered over 3 hours (if randomized to the current formulation) or over 1 hour (if randomized to the new formulation). The start time of study drug administration is Day 1 (Hour 0), and all subsequent visits and PK draws will be calculated from this start time.

All AEs and SAEs that occur during the infusion will be recorded. See Section 5.4.1.2 for guidance in the event a hypersensitivity or infusion-related reaction occurs during infusion.

10.6. Day 1 (Post-Dose)

The following assessments will be performed on Day 1 after dosing:

1. Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature).
2. Collect plasma for PK at the end of infusion (1 hour or 3 hours), and then at 3 hours (for 1 hour infusions), 6 hours, and 12 hours after the start of the infusion.
3. Record concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).
4. Assess AEs and SAEs.

10.7. Follow-up Visits Day 2 (24 Hours) and Day 4 (72 Hours)

The following assessments will be performed on follow-up visits at Day 2 and Day 4 (See Table 5 for the **visit window** for each visit):

1. Collect plasma for PK at 24 hours (Day 2) and 72 hours (Day 4) after the start of the infusion.
2. Record concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).
3. Assess AEs and SAEs.

10.8. Follow-up Visit Day 8 (168 Hours)

The following assessments will be performed on the follow-up visit at Day 8 (See Table 5 for the **visit window** for Day 8):

1. Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature).
2. Collect blood specimens for hematology and serum chemistry tests.
3. Record concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).
4. Collect blood specimens for Direct and Indirect Coombs testing and oritavancin antibody assay.
5. Collect plasma for PK at 168 hours after the start of the infusion.
6. Assessment of AEs and SAEs.

10.9. End of Study (Day 15/Early Termination Visit)

The following assessments will be performed on follow-up visit at Day 15 or the Early Termination Visit (See Table 5 for the **visit window** for Day 15):

1. A local urine pregnancy test will be performed for female subjects of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile).

2. Collect blood specimens for hematology and serum chemistry tests.
3. Collect blood specimens for Direct and Indirect Coombs testing and oritavancin antibody assay.
4. Record concomitant medications and surgical procedures (this includes, but is not limited to, aspiration, debridement, incision and drainage).
5. Assessment of AEs and SAEs.

A subject's participation in the study is complete when the subject has completed the Day 15 Visit or Early Termination Visit. However, if at this visit there is an ongoing SAE, or the subject has a positive Direct or Indirect Coombs test, then the SAE will be followed and/or Coombs test result will be repeated up to a return to baseline condition or stabilization.

10.10. Unscheduled Visit

If at any time the Investigator believes the subject requires additional testing/follow-up, an Unscheduled Visit may be performed.

11. PROTOCOL ASSESSMENTS

11.1. Demographic Data/Medical History

Demographic information will be recorded at Screening. A complete medical and surgical history, including past and current use/abuse of drugs, alcohol, and tobacco, and any available microbiology results, will be collected at Screening and reviewed for any changes at Day 1. The medical history should include clinically significant medical or surgical history ongoing at baseline or with onset in the previous 2 years.

11.2. Adverse Events

Subjects will be carefully monitored for AEs by the investigator during the designated study period (see Section 13 for details).

11.3. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate and temperature) will be assessed at the designated time periods as indicated in the Schedule of Events (Section 10.1). Blood pressure and pulse must always be taken after the subject has been resting supine for 5 minutes.

11.4. Physical Examination

A complete physical examination, including height (cm) and weight (kg), will be performed at Screening. The complete physical examination will include the following organ or body system assessments: skin; head, neurological; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities.

11.5. Laboratory Assessments

Specimens will be obtained at the designated time periods as indicated in the Schedule of Events (Section 10.1). All safety laboratory assessments and Direct and Indirect Coombs Testing will be performed by the site's local laboratory. Additional local laboratory testing may be performed at the discretion of the investigator. Any clinically significant lab findings that occur during the study should be followed until returning to normal or baseline, or to a level that is agreed upon by both the Principal Investigator and the Sponsor. Laboratory assessments include:

- Chemistry: Blood urea nitrogen, Serum creatinine, Total bilirubin, Direct bilirubin, Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Albumin, Total protein, Glucose, Calcium, Chloride, Sodium, Magnesium, Potassium, Uric acid, Lactate dehydrogenase, Bicarbonate, Phosphorus.
- Hematology: Hemoglobin, Hematocrit, White blood cell count (with automated differential), Red blood cell count, Platelet count, Absolute reticulocyte count, Haptoglobin.
- Pregnancy Test: A urine pregnancy test (human chorionic gonadotropin for female subjects of childbearing potential only) will be conducted at Screening (and possibly at Day 1 if the screening test was performed more than 24 hours prior to dosing) and Day 15. For information about reporting occurrences of pregnancy in a study subject or a

study subject's partner (to be followed until conclusion of pregnancy and reported on specific forms; see Section 13.4.5.2).

- Direct and Indirect Coombs Test: Direct and Indirect Coombs Test will be conducted at Day 1 (pre-dose), Day 8 and Day 15.
- Oritavancin Antibody Assay: Two plasma samples will be collected at each of the following time points: Day 1 (pre-dose), Day 8 and Day 15. These samples will be stored at the site, and sent to a Central Lab for oritavancin antibody testing only if the subject(s) experiences unexpected AEs that may be associated with antibody production.

11.6. Assessment of Pharmacodynamics

Pharmacodynamic assessments will not be performed in this study.

11.7. Assessment of Pharmacokinetics

Blood samples for the analysis of oritavancin in plasma will be collected on Day 1 pre-dose and at the end of infusion (1 hour or 3 hours), and then 3 hours (for 1 hour infusions), 6 hours, 12 hours, 24 hours, 72 hours, and 168 hours after the start of the infusion. Every effort should be made to collect all PK samples at the optimal sample time (within the window in Table 5 below). The date and time of each PK sample will be recorded on the eCRF.

Table 5: 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**	1 hr	1 hr 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**	3 hrs	3 hrs 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

Detailed collection, processing, storage, and shipment procedures will be provided in PK sample collection laboratory manual. Samples will be sent to a central laboratory for analysis. Plasma

concentrations will be determined using liquid chromatography-tandem mass spectroscopy methods.

12. STUDY AND SUBJECT DISCONTINUATION

A clear distinction will be made between subjects who discontinue study drug dosing and those who withdraw or are withdrawn from the study. Only those subjects who are lost to follow-up, are unwilling to comply with protocol procedures, or who withdraw consent and/or refuse any further contact with respect to the study will be withdrawn from the study.

12.1. Screening Failures

Subjects who sign and date the ICF but who fail to meet the inclusion and exclusion criteria are defined as screen failures.

12.2. Premature Discontinuation from Study Drug

All subjects have the right to withdraw at any point during treatment or study participation without prejudice. The investigator can discontinue study drug at any time if medically necessary. If for any subject, study treatment is discontinued, the reason will be recorded, and the Sponsor should be notified promptly. Reasons that a subject may discontinue treatment:

- Adverse event(s)
- Death
- Subject wishes to withdraw consent
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol
- Investigator discretion
- Melinta Therapeutics request

In the event that study drug is discontinued prematurely, it is imperative that all safety procedures are completed.

12.3. Premature Discontinuation from Study

All subjects have the right to withdraw at any point during the study participation without prejudice or may be discontinued from the study for any of the following reasons:

- Adverse event(s)
- Death
- Subject wishes to withdraw consent
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol
- Investigator discretion
- Lost to follow-up
- Melinta Therapeutics request

In the event that a subject discontinues from the study, all data collected up until the time of study withdrawal is to be entered into the eCRF. Every attempt should be made to collect follow up information except for those subjects who specifically withdraw consent to release such information.

12.4. Study Site Discontinuation

Reasons for discontinuation of the study at an investigational site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Investigator request to withdraw from participation.
- Melinta Therapeutics decision.
- Serious and/or persistent non-compliance by the Investigator with the protocol, the clinical research agreement, and/or applicable regulatory guidelines in conducting the study.
- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) decision to terminate or suspend approval for the investigation or the Investigator.
- Investigator fraud (altered data, omitted data, or manufactured data).

13. ADVERSE EVENTS

13.1. Definitions

13.1.1. Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

13.1.2. Serious Adverse Event

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization (planned surgical procedures or hospitalization are NOT an SAE),
- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction (MI) that may be considered minor could also be an SAE if it prolonged hospitalization.

13.1.3. Adverse Event of Special Interest (AESI)

An AE of special interest (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program. Ongoing monitoring and rapid communication to the Sponsor is requested as such an event might warrant further investigation in order to further characterize it.

13.1.4. Special Situations

Information that is not necessarily considered an AE, but which can possibly contribute to the overall knowledge concerning the safety of the compound.

Examples include, but are not limited to, reports of pregnancy/lactation exposures with or without any AEs related to the parent or child; medication errors – actual and potential; accidental exposure; suspected transmission via an investigational product of an infectious agent; drug interaction.

13.2. Collection and Assessment of Data Evaluating Adverse Events

13.2.1. Pre-existing Conditions

Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should not be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of [condition]"). Planned hospital admissions and/or surgical procedures for an illness or disease that existed at baseline and did not aggravate during the study should not be reported as AEs. If the subject has a worsening of the Index Infection meeting the criteria for an AE during their study participation, the AE should be documented as 'Worsening of the Index Infection' and if a new infection develops, the AE term should be documented as 'New Infection with the type and location specified' (i.e., New Cellulitis on Right Arm).

13.2.2. AE Severity

The severity of an AE will be assessed by the Investigator using the grading system described below.

Adverse events (AEs) will be graded using the 5-point Common Terminology Criteria for Adverse Events (CTCAE) criteria (Version 5).

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2= Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL.

Grade 4 = Life-threatening consequences; urgent intervention indicated.

Grade 5 = Death related to AE.

For AE severity grading guidance organized by system organ class (SOC) refer to CTCAE (Version 5.0).

For AEs not listed in the CTCAE guidance, grading should be assigned using the 3-point scale below:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

Immediately life-threatening SAEs and fatal SAEs will be assigned a grade 4 or grade 5 respectively.

13.2.3. Relationship Assessment

For each AE, the Investigator must make an assessment of the relationship of the event to the study drug as:

Unrelated: There is no reasonable possibility that the administration of the study drug caused the AE; there is no temporal relationship between the investigational product and event onset, or an alternative etiology has been established.

Related: There is a reasonable possibility that the administration of the study drug caused the AE; there is evidence to suggest a causal relationship between the study drug and the AE.

13.3. Study Specific Safety Requirements for Additional Collection of Safety Data

13.3.1. Adverse Events of Special Interest (AESIs)

The following AESIs have been identified for oritavancin in this protocol:

- Hypersensitivity including Red Man Syndrome
- Pseudomembranous colitis/Clostridium difficile-associated diarrhea (CDAD)
- Osteomyelitis
- Hemolytic anemia:
  For the purpose of this study, the subjects will be monitored for signs of hemolysis. Subjects presenting with clinical signs of anemia should undergo a work-up that includes investigations of hemolytic anemia (absolute reticulocyte count, serum bilirubin <total and indirect>, lactic dehydrogenase, haptoglobin, alanine aminotransferase and a Direct and Indirect Coombs test).

13.3.2. Special Situations

Special Situations designated for this study are the following:

- Medication errors that fall into the following categories:
  - Wrong investigational product;
  - Wrong dose (including overdose, underdose, change in dosing regimen, strength, form, concentration, amount);

- Wrong route of administration;
- Wrong subject (i.e. not administered to the intended subject);
- Accidental exposure

- Pregnancy/lactation exposures with or without any AEs related to the parent or child
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions

13.4. Procedure for Adverse Event Recording

13.4.1. Serious Adverse Events (SAEs)

All SAEs that occur during the designated study period (from the time of study drug initiation to Day 15) must be reported to the Sponsor's Global Pharmacovigilance (GPV) Department within 24 hours of awareness of the event using the provided study specific SAE/AESI Report Form. Each SAE/AESI must also be recorded on the source documents and on the appropriate page of the eCRF.

The Investigator should provide any follow-up information for the event to the Sponsor on an updated SAE/AESI Report Form as soon as it becomes available. The Sponsor will contact the Investigator, if necessary, to clarify any of the event information or request additional information. All SAEs will be followed until satisfactory resolution or until the investigator or sub-investigator deems the event to be chronic or the subject to be stable. The timelines and procedure for follow-up reports are the same as those for the initial report.

If the Investigator is notified of a SAE/AESI that occurs post-study period that he or she wishes to report to the Sponsor (e.g., an event suspected to be causally related to investigational product), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the Investigator should report these events to the IRB/Ethics Committee (EC) and/or national regulatory authority in addition to the Sponsor.

13.4.2. Non-Serious AEs

All non-serious AEs that occur during the designated study period from the time of study drug initiation to Day 15 must be assessed and recorded on the source documents and the eCRF, regardless of causal relationship to the investigational product.

13.4.3. Laboratory Abnormalities

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or further diagnosis beyond repeat testing for confirmation alone.

13.4.4. Adverse Events of Special Interest (AESIs)

The SAE/AESI Report Form should be completed for reporting the AESI whether or not the event meets the criteria for a SAE. The SAE/AESI Report Form should indicate that the reported

event is an AESI. If applicable, the eCRF page or a targeted questionnaire associated with the AESI should also be completed and submitted with the SAE/AESI Report Form.

Non-serious AESIs should be reported to the Sponsor within 72 hours and serious AESIs should be reported to the Sponsor within 24 hours.

13.4.5. Special Situations

13.4.5.1. Medication Errors

Medication errors with or without an associated AE should be recorded as medication errors in the eCRF.

Medication errors and an associated SAE should be recorded in the eCRF and also reported to the Sponsor's GPV as described in Section 13.4.1.

Medication errors and an associated non-serious AE should be recorded in the eCRF as described in Section 13.4.2.

A mis-dosing protocol deviation (refer to Section 16.3) should be reported as a medication error if it was an "unintended error".

13.4.5.2. Pregnancy/Lactation Exposure

Occurrences of pregnancy/lactation exposure in a study subject or study subject's partner from the time of study drug initiation through the follow-up must be reported to the Sponsor within 24 hours using the Pregnancy/Lactation Exposure Report Form.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date of delivery, the Investigator should notify Melinta Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

In cases where a pregnancy/lactation exposure occurs with a SAE and/or AESI, the SAE/AESI Report Form should be used to report the SAE and/or AESI and the Pregnancy/Lactation Exposure Report Form should be used to report the pregnancy/lactation exposure. When a pregnancy/lactation exposure occurs without any concurrent SAE or AESI, the Pregnancy/Lactation Exposure Report Form must be submitted alone.

13.4.5.3. Suspected Transmission via a Medicinal Product of an Infectious Agent

Any suspected transmission of an infectious agent via a medicinal product should be considered an SAE and reported in accordance with Section 13.4.1 (SAEs).

If no other criterion is applicable, the seriousness of this report should be assessed as a 'medically significant event'.

13.4.5.4. Drug Interaction

An AE that occurs due to a suspected drug interaction, either serious or non-serious, should be recorded on the AE eCRF form and reported to the Melinta GPV Department using the SAE/AESI Report Form. The SAE/AESI Report Form should detail the investigational product, the interacting product and include the description of the alleged drug interaction.

13.5. Expectedness

Melinta GPV will be responsible for determining whether an AE is expected or unexpected for the purpose of SUSAR reporting. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information previously described for the investigational product in the Reference Safety Information (RSI).

For the investigational product and the approved product, the RSI will be the Investigator's Brochure current/approved at the time of expectedness assessment.

14. STATISTICAL PLAN

14.1. Sample Size

Using combined results from selected Phase 1 studies on oritavancin pharmacokinetics with the approved formulation (MDCO-ORI-14-01, MDCO-ORI-14-02, MDCO-ORI-15-01, MDCO-ORI-15-02), 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%

14.2. 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.

14.3. General Statistical Considerations and Definitions

14.3.1. 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. Descriptive statistics will be provided for demographic, baseline characteristics, and prior and concomitant medications. Summary tables and listings of safety data, including AEs, laboratory results (comprising results from Direct and Indirect Coombs and oritavancin antibody assay as applicable) and vital signs will be provided for the Safety Population.

14.3.2. Analysis Population

14.3.2.1. Intent-to-Treat (ITT) Population

All subjects randomized.

14.3.2.2. Pharmacokinetics (PK) Population

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

14.3.2.3. Safety Population

All subjects who have received any amount of IV oritavancin. The safety population will be the primary population for all the safety analyses.

14.3.2.4. 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.

14.3.3. Missing Data Handling

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

14.4. Statistical Analyses

14.4.1. Demographic and Background Characteristics

Subject demographics and baseline characteristics will be summarized by treatment using the ITT and safety populations.

14.4.2. Study Drug and Concomitant Medications

Summary of each prior (pre-baseline) medication and concomitant (baseline or later) medication will be provided by treatment for the safety population. Medication will be coded with World Health Organization (WHO) Drug Dictionary Enhanced. Subjects will be counted only once by medication.

14.4.3. Safety Analysis

14.4.3.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding AEs. An AE (classified by preferred term) occurring from the start of study drug will be counted as a 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.

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 SAEs and AEs leading to treatment or study discontinuation will also be provided by system organ class and preferred term.

14.4.3.2. Laboratory Tests

Laboratory values will be summarized by treatment group, including changes from baseline at each time point. Analyses will also be performed for each lab parameter by treatment group for incidence rates of potentially clinically significant (PCS) values for subjects without PCS value at baseline. PCS values will be defined in the Statistical Analysis Plan (SAP).

14.4.3.3. Vital Signs

Vital sign measurements and changes from baseline will be summarized descriptively at each scheduled timepoint by treatment. PCS changes will also be summarized by treatment group.

14.4.4. Pharmacokinetic Parameters

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_{0-72}), time zero to 168 hr (AUC_{0-168}), time zero to the time of the last measurable concentration (AUC_{0-last}) and. where possible, AUC from time zero to infinity ($AUC_{0-\infty}$)
- 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_d)

All concentration data will be presented descriptively for each formulation at each time point. All pharmacokinetic parameters will be descriptively analyzed 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_{0-72} and AUC_{0-168}) 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The Investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and Good Clinical Practice (GCP) requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

15.2. Auditing

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, study drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The Investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs and must permit regulatory authority inspections.

15.3. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. The Investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the Investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures.

The following Protocol Deviations will require additional information in the eCRF explaining why the deviation occurred and what will be done to prevent it from re-occurring:

- Any deviation in the Inclusion/Exclusion criteria.
- Subject is given an incorrect dose(s) of oritavancin (greater than 120% or less than 80%).
- If a subject misses 2 or more consecutive PK draws.

16. ADMINISTRATIVE ASPECTS

16.1. Ethics and Responsibility

This protocol will be conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

16.2. Institutional Review Board or Independent Ethics Committee Approval

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB/IEC for approval. IRB/IEC approval of the protocol, ICF, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The Investigator is responsible for keeping the IRB/IEC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The Investigator is also responsible for notifying the IRB/IEC of all unanticipated risks involving human subjects that occur during the study.

16.3. Informed Consent

It is the policy of Melinta Therapeutics that written informed consent is obtained from subjects. The ICF must be signed and dated prior to any study-related procedures being performed at screening/Baseline. The Investigator or designee must address all questions raised by the subject before the subject signs the consent form. The original signed ICF for each participating subject shall be filed with records kept by the Investigators(s). A copy of the ICF must be provided to the subject. Where applicable, it will be provided in a certified translation of the local language.

16.4. Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of Melinta Therapeutics, the IRB/IEC approving this research, and the US FDA, as well as any other applicable regulatory authorities, will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subject identities will remain confidential.

16.5. Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

16.6. Protocol Amendment

If a protocol has been filed with regulatory agencies or submitted to an IRB/IEC, and requires changes, a protocol amendment must be written. Any changes to the protocol will be made by

the sponsor. All amendments will be sent to the study sites who are then responsible for submitting the amendment to their IRB/IECs for approval prior to implementing the amendment changes or enrolling subjects under the amended protocol.

16.7. Data Collection

16.7.1. Case Report Forms: Electronic

For this trial, an EDC eCRF system which is 21 CFR Part 11 compliant will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. All users will be trained by qualified personnel on the technical features of the EDC, as well as the content of the eCRF, prior to gaining access to the EDC. A User ID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data.

It is the responsibility of the Principal Investigator to ensure the eCRFs are completed in an accurate and timely manner. The eCRF should be filled out by the site within 3 business days after a visit is completed (except for Randomization which needs to be completed in the eCRF prior to dosing in order to determine the treatment assignment and infusion time).

Prior to the database being locked, the Principal Investigator or a designated Sub-Investigator (listed on the Form FDA 1572) will review, approve and electronically sign/date each completed eCRF. This signature serves as attestation of the Investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic.

The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change and person making change). After the end of the trial, a copy of the data will be provided to the site, with the per-subject eCRF in an individual subject profile on disk or another electronic medium. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.

16.7.2. Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by Melinta Therapeutics representatives, the FDA, or other regulatory authorities.

It is not expected that the eCRF will serve as source for any data collected in this trial. If there is a reason for a site to do so, it must be approved by Sponsor and documented in the site files.

16.8. Study Monitoring Requirements

Site visits will be conducted by an authorized Melinta Therapeutics representative (the monitor) to inspect study data, subject medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The Investigator will permit representatives of Melinta Therapeutics, the US FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

16.9. Study File Management

It is the responsibility of the Investigator(s) to ensure that the study file at the site is maintained. The study file may contain, but not limited to:

1. Investigator's Brochure (including updated or revised versions)
2. Final study protocol
3. Protocol amendments (if applicable)
4. Fully executed Clinical Trial Agreement
5. ICF (blank)
6. Revised ICFs and/or all addenda (blank)
7. Copy of signed form(s) US FDA Form 1572
8. A completed and signed Health Canada QIU Form (if applicable)
9. DHHS number for IRB or other documentation of IRB/IEC compliance with FDA
10. Curricula Vitae (CV) of Investigators and Sub-Investigators
11. Financial disclosure information provided to the sponsors
12. A list of the IRB/IEC members and their qualifications
13. If the Investigator is a member of the IRB/IEC, documentation stating he/she did not vote on the study.
14. Documentation of IRB/IEC approval of protocol, ICF, any protocol amendments and any ICF revisions
15. Annual IRB/IEC updates and approvals
16. All correspondence between the Investigator, IRB/IEC and Melinta Therapeutics (or designee)
17. Copies of all Investigational New Drug (IND) Safety Reports submitted to the FDA or other regulatory agencies, and IRB/IEC correspondence documenting their submission (if applicable)
18. Laboratory certifications/normal laboratory value ranges
19. Screening log
20. Monitoring log
21. Drug accountability records and invoices for receipt/return of study drug
22. Protocol Signature Page
23. Laboratory Director's CV and medical/professional license, if available

16.10. Study Completion

Melinta Therapeutics requires that the following data and materials be on file at the study site before a study can be considered completed or terminated:

1. Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
2. eCRFs properly completed by appropriate study personnel and electronically signed and dated by the Investigator
3. Complete Drug Accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
4. Copies of protocol amendments and IRB/IEC approval/notification if appropriate
5. A summary of the study prepared by the Principal Investigator (an IRB/IEC summary letter is acceptable)

16.11. Audits

During the course of the study, or after completion of the study, each study site may be subject to an audit by a Melinta Therapeutics Quality Assurance Auditor (or an auditor appointed by Melinta Therapeutics or its authorized representative) and/or an inspector from the FDA and/or other regulatory authority. Every attempt will be made to notify the Investigator in writing in advance of the audit.

16.12. Retention of Records

Melinta Therapeutics follows US regulations and ICH guidelines in its retention policy.

US IND regulations (21 CFR 312.62) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs including CRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the Principal Investigator for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. ICH guidelines indicate that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies. No study records should be destroyed without prior authorization from Melinta Therapeutics.

16.13. Disclosure of Data

The Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of Investigators, their addresses, qualifications and extent of involvement. It is understood that the Investigator is required to provide Melinta Therapeutics with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the US FDA and other regulatory authorities, by Melinta Therapeutics, and the IRB as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

16.14. Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from Investigators participating in covered clinical studies; each Principal Investigator and Sub-investigator is required to provide the required financial information before participating in the study and to promptly update Melinta Therapeutics with any relevant changes to this information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all Investigators and Sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for marketing approval.

16.15. Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

17. REFERENCES

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