Initial U.S. Approval: 2014

ORBACTIV™ (oritavancin)

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

Protocol No.: MDCO-ORI-16-02
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EudraCT No.: Not Applicable

PROTOCOL VERSION: 1.0

Development Phase: IV

Sponsor: The Medicines Company
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PROCEDURES IN CASE OF EMERGENCY

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: The Medicines Company
Name of Finished Drug/Device: ORBACTIV™ (oritavancin)
Name of Active Ingredient: Oritavancin diphosphate
Title of Study: A Double-Blind, Randomized Study to Evaluate the Safety of either a Single 1200-mg Intravenous (IV) Dose of Orbactiv™ (oritavancin) and Placebo or two IV Doses of Orbactiv™ in Subjects Being Treated for Acute Bacterial Skin and Skin Structure Infection (ABSSSI)
Phase of Development: IV
Study Centers: Multicenter study in up to 5 centers in the United States
Central Facilities: This list is maintained by the Sponsor
Number of Subjects: 20 planned; 20 evaluable
Principal Investigator: [redacted]
Study Period: The estimated study period for the study will be approximately 3 weeks from first subject enrolled to last subject completed.
Objectives: Assess the safety and tolerability of two 1200-mg intravenous (IV) infusions of oritavancin when administered one week apart in subjects with acute bacterial skin and skin structure infection (ABSSSI).
Methodology: This study will be a randomized, double-blind study. Subjects with will be randomized (3:1) to receive either two doses of oritavancin or one dose of oritavancin and a single dose of placebo one week apart in order to obtain safety information. This safety information will include information regarding the potential for antibody production following one or two doses of 1200 mg oritavancin.
Diagnosis and Main Criteria for Selection: **Key inclusion criteria:** • Males or females ≥18 years old • Diagnosis of ABSSSI (wound infections, cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen requiring IV therapy **Key exclusion criteria:** • Infections associated with, or in close proximity to, a prosthetic device • Severe sepsis or refractory shock • Known or suspected bacteremia at time of screening • ABSSSI due to or associated with any of the following:

– Infections suspected or documented to be caused by Gram-negative pathogens (i.e., human or animal bites, injuries contaminated with fresh or salt water, external malignant otitis) – Wound infections (surgical or traumatic) and abscesses with only Gram-negative pathogens – 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) – Concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis) – Infected burns – A primary infection secondary to a pre-existing skin disease with associated inflammatory changes such as atopic dermatitis, eczema, or hidradenitis suppurativa – Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous) – 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) – Infections known to be caused by a Gram-positive organism with a vancomycin minimum inhibitory concentration (MIC) >2 μg/mL or clinically failing prior therapy with glycopeptides – Catheter site infections • Treatment with investigational medicinal product within 30 days or 5 half-lives, whichever is longer, before enrollment and for the duration of the study. • Prior exposure to oritavancin alone or in combination with another product.
Test Drug, Dose and Mode of Administration: The investigational drug oritavancin diphosphate (oritavancin) will be administered intravenously to all subjects. The dose is made up of three single-use vials, each containing 400 mg of oritavancin and the inactive component mannitol. At the time of use, each vial should be reconstituted by adding 40 mL of Sterile Water for Injection, United States Pharmacopeia (USP). After reconstitution, oritavancin should be further diluted in approximately 1000 mL of 5% Dextrose Water Injection (D5W). On Day 1 of the study, subjects will be administered a single 1200-mg IV dose of oritavancin in 1000 mL D5W. On Day 8, an additional 1200-mg IV dose of oritavancin in 1000 mL D5W or placebo (D5W) will be administered. Oritavancin or placebo must be infused over 3 hours. No other material or diluent may be substituted or concomitantly infused through the same IV line.
Duration of Treatment: The study will consist of four periods: Screening (≤24 hours prior to Day 1), Pre-Dose (Day 1), Treatment (Day 1, Day 8), and Follow-up (Day 15, Day 22).
Reference Therapy, Dose and Mode of Administration: Five subjects will be administered a placebo (1000 mL of D5W) infused over 3 hours for the second dose.
Criteria for Evaluation:

Primary outcome:

- Safety of the administration of oritavancin in subjects will be assessed according to vital signs, laboratory abnormalities, and the incidence of adverse events (AEs) and serious adverse events (SAEs).

Secondary outcome:

- Clinical cure, as an assessment of efficacy, determined by the investigator at Day 8.

Exploratory outcome:

- Antibody development following a single dose and multiple doses of oritavancin administration.

Clinical evaluation time points:

- Assessment of safety (AEs) through Day 22
- Post-therapy efficacy evaluation at Day 8

Efficacy: Clinical cure

Safety: AEs, vital signs, clinical laboratory assessments

Statistical Methods: Approximately 20 ABSSSI subjects will be enrolled. All 20 subjects will receive a single dose of oritavancin on Day 1, 15 subjects will receive a second 1200-mg dose of oritavancin and 5 subjects will receive a placebo infusion on Day 8.

Sample size: Twenty ABSSSI subjects were added to obtain safety information and to assess the potential for antibody production related to oritavancin administration.

Analysis population: The subject populations are defined as follows:

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

Safety Population: All subjects dosed with IV oritavancin. The safety population will be the primary population for all the safety analyses.

Descriptive statistics will be provided for demographic, baseline characteristics, medical history, prior and concomitant medications. Descriptive statistics include means, medians, standard deviations and ranges for continuous variables, as well as frequency and percentage for categorical variables. Summary tables and listings of safety data, including AEs, laboratory results (direct and indirect antiglobulin, immunoglobulin panel, oritavancin antibody assay) and vital signs will be provided for the Safety Population. Summaries of clinical cure as assessed by the investigator at Day 8 will be provided for the ITT Population.

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LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
AESI(s)	Adverse Event of Special Interest(s)
AIDS	Acquired Immune Deficiency Syndrome
ANC	absolute neutrophil count
AUC	area under the plasma concentration time curve
AUC_{0-24}	area under the drug concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	area under the concentration-time curve from zero to infinity
BMI	body mass index
CD4	cluster of differentiation 4
C_{max}	maximum plasma concentration
CS	clinically significant
CV	coefficient of variation
DAT	direct antiglobulin testing
D5W	5% dextrose in water
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour

HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IAT	indirect antiglobulin testing
ID	Identification number
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
kg	kilograms(s)
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	myocardial infarction
MIC	minimum inhibitory concentration
mL	milliliter(s)
mm	millimeter(s)
min	minute(s)
MRSA	methicillin-resistant *Staphylococcus aureus*
No.	number

OTC	over-the-counter
PK	pharmacokinetic
Q1	first quartile
Q3	third quartile
s	second(s)
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
$t_{½}$	half-life
$t_{½,\alpha}$	half-life for the alpha phase
$t_{½,\beta}$	half-life for the beta phase
$t_{½,\gamma}$	half-life for the gamma phase
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
V_{ss}	steady-state volume of distribution
WHO	World Health Organization
y	years(s)

1. INTRODUCTION

This protocol describes a multicenter, double-blind, randomized study to evaluate the safety of two 1200-mg intravenous (IV) doses of Orbactiv™ for the treatment of subjects with an acute bacterial skin and skin structure infection (ABSSSI).

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. Background

ABSSSIs are common infections that include cellulitis, major cutaneous abscesses, and wound infections. ABSSSIs are inflammatory microbial invasions of the epidermis, dermis, and subcutaneous tissues [Dryden, 2009]. These infections are frequently caused by Gram-positive bacteria including methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, and other β-hemolytic streptococcal species and enterococci. The clinical complications of improperly treated or untreated ABSSSIs may include local expansion and spread, secondary bacteremia with potential for distant metastatic foci of infection, and systemic effects of bacterial infection.

1.2. Oritavancin (ORBACTIV™)

Oritavancin is a novel semi-synthetic, lipoglycopeptide antibiotic that has three 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 Food and Drug Administration (FDA) for the treatment of adult subjects with ABSSSIs caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms including MRSA [ORBACTIV™ Package Insert 2016].

1.2.1. Nonclinical Studies

Oritavancin has been extensively studied pre-clinically. The results from the safety, toxicology, pharmacokinetic (PK), and pharmacodynamic studies demonstrate that oritavancin does not induce any biologically significant toxicity. An overview of relevant nonclinical study results is presented in the Investigator's Brochure [Oritavancin Investigator's Brochure Version 10].

1.2.2. Clinical Pharmacology

The PK of a single 1200-mg dose of oritavancin in ABSSSI subjects were determined from population PK analysis of pooled data from 297 adult subjects and are presented in Table 1. At steady state, oritavancin exhibits linear PK 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 ($t_{½}$) of 245 hours. Normal healthy volunteers administered a single 1200-mg dose of oritavancin experience higher oritavancin exposure when compared to subjects; mean C_{max} was approximately 25% higher in healthy volunteers, and $AUC_{0-\infty}$ was approximately 40% higher in healthy volunteers when compared to subjects.

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} (µg•h/mL)	1110	(33.9%)
AUC_{0-72} (µg•h/mL)	1530	(36.9)
$AUC_{0-\infty}$ (µg•h/mL)	2800	(28.6%)
$T_{1/2,\alpha}$ (h)	2.29	(49.8%)
$T_{1/2,\beta}$ (h)	13.4	(10.5%)
$T_{1/2,\gamma}$ (h)	245	(14.9%)

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; $AUC_{0-\infty}$, 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.

1.2.3. Clinical Studies

An extensive clinical development program has been conducted to evaluate the safety and effectiveness of oritavancin comprising 4 completed Phase III studies, 4 Phase II studies, 14 Phase I studies in healthy subjects, and one Phase I study in both healthy and hepatically impaired subjects. Throughout the completed studies, IV oritavancin was administered to 3042 individuals (2632 subjects and 410 healthy subjects) including 1075 adult subjects with ABSSSI treated with a 1200-mg single-dose regimen. [Oritavancin Investigator's Brochure Version 10].

Efficacy and safety findings of the intended treatment dose in adult subjects with ABSSSI are summarized below:

Efficacy

The results from SOLO I and SOLO II in 1959 adult subjects demonstrated that a single 1200-mg IV dose of oritavancin was clinically non-inferior to 7 to 10 days of IV vancomycin (1 g or 15 mg/kg twice daily) using a pre-specified non-inferiority margin of 10% for both early clinical response and clinical cure at post-therapy evaluation. The subject population was representative of ABSSSIs with *S. aureus* the common causative pathogen isolated; a large subset of subjects (N=405) had documented MRSA infections. Efficacy in MRSA subjects was similar to that observed in the overall population for all endpoints.

Safety

The SOLO I and SOLO II studies demonstrated that a single 1200-mg IV dose of oritavancin was well tolerated and had a similar safety profile to 7 to 10 days of IV vancomycin treatment as demonstrated by the similar frequency and nature of treatment-emergent adverse events

(TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation reported by subjects.

1.2.4. Known and Potential Risks and Benefits

SINGLE DOSE

Twenty three clinical trials, including 4 Phase III, 4 Phase II, and 15 Phase I studies have been completed to date in which 3042 subjects were exposed to oritavancin. The most common adverse events (>3%) by preferred term in either treatment group, in the SOLO I or SOLO II studies were nausea, headache, vomiting, cellulitis, diarrhea, constipation, infusion site extravasation, pyrexia and pruritus, as outlined in Table 2.

Table 2: Adverse Events that Occurred in ≥3% of Subjects in the Oritavancin Treatment Group (Safety Population)

	SOLO Pool	
Preferred Term	**Oritavancin (N=976) n (%)**	**Vancomycin (N=983) n (%)**
Nausea	97 (9.9%)	103 (10.5%)
Headache	69 (7.1%)	66 (6.7%)
Vomiting	45 (4.6%)	46 (4.7%)
Cellulitis	37 (3.8%)	32 (3.3%)
Diarrhea	36 (3.7%)	32 (3.3%)
Constipation	33 (3.4%)	38 (3.9%)
Infusion site extravasation	33 (3.4%)	33 (3.4%)
Pyrexia	30 (3.1%)	31 (3.2%)
Pruritus	29 (3.0%)	73 (7.4%)

Serious hypersensitivity reactions have been reported with the use of oritavancin which could possibly have cross-sensitivity with hypersensitivity to glycopeptide drugs (e.g. vancomycin). In the Phase III ABSSSI clinical trials, the median onset of hypersensitivity reactions in oritavancin-treated subjects was 1.2 days and the median duration of these reactions was 2.4 days.

Infusion-related reactions or anaphylactoid reactions have been reported with oritavancin including pruritus, urticaria, or flushing.

MULTIPLE DOSE

In MDCO-ORI-15-02, a Phase I clinical study, 10 healthy volunteers received two doses of 1200 mg oritavancin given 14 days apart. Seven of the 10 subjects receiving oritavancin reported AEs during the second infusion with 5 prematurely discontinuing dosing during the second infusion. The predominant symptoms in the 7 subjects who experienced AEs were

musculoskeletal complaints (e.g., lower back pain) as well as gastrointestinal complaints (nausea, vomiting). Fever or rash was not reported in any subject. Symptoms developed in all 7 subjects within 30 to 90 minutes from the start of the infusion and resolved in all within a few hours of study drug discontinuation. None of the AEs experienced were deemed SAEs by the investigator, but in aggregate were considered by The Medicines Company (MDCO) as an important medical finding warranting of an IND Safety Report. Further dosing in this study was voluntarily terminated by MDCO in order to investigate further the observed AEs during the second dose. The key findings from these investigations are presented below.

- No correlation between immunoglobulin levels and subjects experiencing an AE in MDCO-ORI-15-02
- No pattern of cytokine/chemokine response in oritavancin-stimulated peripheral blood mononuclear cells from subjects with symptoms from MDCO-ORI-15-02
- No lymphoproliferative response in oritavancin-stimulated peripheral blood mononuclear cells from subjects with symptoms from MDCO-ORI-15-02
- No healthy subjects have developed a positive direct test for hemagglutination in the presence of drug testing and no subjects met clinical criteria for drug-induced autoimmune hemolytic anemia. In ex vivo testing of healthy subject plasma samples, administration of oritavancin (and development of a positive indirect antiglobulin test [IAT]) appears to be associated with a weakly positive indirect test for hemagglutination in the presence of drug.
- Administration of oritavancin to healthy subjects in 2 separate studies (MDCO-ORI-15-02 and MDCO-ORI-15-01) was associated with development of a positive IAT in the majority of oritavancin-treated subjects; the IAT result reversed to negative in all subjects within 30 to 60 days.
- None of the 15 subjects with ABSSSI infections treated with a single 1200-mg dose of oritavancin in the ongoing Study MDCO-ORI-14-03 (Warfarin Study in ABSSSI Subjects) in whom direct antiglobulin testing (DAT) or IAT was performed for up to 14 days developed a positive DAT or IAT.
- Results of recent post-marketing surveillance revealed 15 reports of subjects who received multiple doses of oritavancin. Two reports described the onset of back pain during the second infusion of oritavancin. In one report, the infusion was stopped and the subject was treated for symptoms; the subject was able to complete the infusion at a slower rate without further complications. In the second report, the subject was treated for symptoms at the end of the dose.

In summary, currently available data show that, in some healthy volunteer subjects, receipt of oritavancin was associated with a positive IAT (also called indirect Coombs test), which resolved over time, and a weakly positive indirect test for hemagglutination in the presence of drug with ex vivo testing . There have been no positive DATs and no similar AEs reported following a single dose. There is no evidence of autoimmune hemolytic anemia or definitive immune-related sequelae. In view of the difference in the rate of development of positive IAT between healthy

subjects and infected subjects, we believe that it is most appropriate to further evaluate multiple-dose administration in patients with ABSSSI infections rather than in healthy volunteer subjects. Subjects with ABSSSIs are to be enrolled to collect additional data on DAT and IAT, and to assess the safety of a second dose of oritavancin in these subjects in a controlled setting.

A complete description of relevant risks of oritavancin can be found in the Investigator's Brochure [Oritavancin Investigator's Brochure Version 10] and the United States Package Insert (USPI). More information regarding the events in Study MDCO-ORI-15-02 can be found in the Aggregate Report (dated August 26, 2015) of Infusion-Related Reactions Following the Second Infusion in Study MDCO-ORI-15-02 [Aggregate Report, 2015] and the subsequent follow up information dated July 22, 2016 [Follow-up Report, 2016].

1.3. Study Rationale

Clinical studies in adult subjects with ABSSSI have demonstrated that a single 1200-mg IV dose of oritavancin was clinically non-inferior, well tolerated, and had a similar safety profile to 7 to 10 days of IV vancomycin treatment (See Section 1.2.3 for additional details).

The rationale for selecting the 1200-mg IV dose of oritavancin is described in Section 1.2.2. The 1200-mg dose of oritavancin is the United States (US) approved therapeutic dose.

Subjects with ABSSSI will be enrolled in this study to obtain safety information of two 1200-mg IV infusions of oritavancin when administered one week apart.

Study Population

The study population will comprise of subjects who are at least 18 years of age with an ABSSSI suspected or confirmed to be caused by gram-positive pathogens. An ABSSSI includes the following infections: wound infections, cellulitis/erysipelas, and major cutaneous abscess.

2. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and tolerability of two 1200-mg IV infusions of oritavancin when administered one week apart.

2.1. Primary Objective

Assess the safety and tolerability of two 1200-mg IV infusions of oritavancin when administered one week apart in subjects with ABSSSI.

3. TRIAL DESIGN

3.1. Type/Design of Trial

This will be a Phase IV, randomized, double-blind trial in subjects with ABSSSI. Approximately 20 subjects will be enrolled at approximately 5 centers in the US. Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Eligible subjects will be randomized to receive either two doses of oritavancin one week apart or one dose of oritavancin and a single dose of placebo one week apart in a 3:1 ratio.

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

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

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

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

3.2. Primary Endpoint

The primary endpoint of this trial is:

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

3.3. Secondary Endpoint

The secondary endpoint of this trial is:

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

3.4. Exploratory Endpoint

The exploratory endpoint of this trial is:

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

3.5. Measures to Minimize/Avoid Bias

3.5.1. Blinded Study Where Pharmacist is Unblinded

This is a double-blind study design to minimize bias on study outcomes potentially introduced by the study procedures. The placebo subjects also serve as a control for external factors that may exist at the time subjects are enrolled.

Subjects will be given a subject identification (ID) number sequentially according to the date and time when subjects sign the informed consent (screening number). The unblinded pharmacist will match the subject ID with the randomization schedule, which assigns treatment sequence based on 3:1 ratio. The oritavancin and placebo infusion arms will be double-blind; all study staff will be blinded to the treatment with the exception of the unblinded pharmacist.

The blinding of IV treatment assignment will be maintained until database lock.

4. SUBJECT POPULATION

4.1. Number of Subjects

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

4.2. Inclusion Criteria

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

1. Males or females ≥18 years old
2. Diagnosis of ABSSSI (wound infections, Cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen requiring IV therapy
3. Able to give informed consent and willing to comply with all required study procedures

4.3. 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 Gram-negative pathogens (i.e., human or animal bites, injuries contaminated with fresh or salt water, external malignant otitis)
    b. Wound infections (surgical or traumatic) and abscesses with only Gram-negative pathogens
    c. 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)
    d. Concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis)
    e. Infected burns
    f. A primary infection secondary to a pre-existing skin disease with associated inflammatory changes such as atopic dermatitis, eczema, or hidradenitis suppurativa
    g. Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)
    h. 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)
    i. Infections known to be caused by a Gram-positive organism with a vancomycin minimum inhibitory concentration (MIC) >2 μg/mL or clinically failing prior therapy with glycopeptides

j. Catheter site infections

5. Currently receiving chronic systemic immunosuppressive therapy such as chemotherapy or prednisone (prednisone at non-immunosuppressive doses of ≤15 mg/day is permitted)
6. Subjects who are likely to need treatment with IV unfractionated heparin sodium within 48 hours after oritavancin administration
7. Last known cluster of differentiation 4 (CD4) count <200 cells/mm^3 in subjects with known human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)
8. Neutropenia with absolute neutrophil count (ANC) <500 cells/mm^3
9. Significant or life-threatening condition (e.g., endocarditis) that would confound or interfere with the assessment of safety
10. Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least 2 acceptable methods of birth control: (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier method(s) or male partner sterilization). Women ≥2 years postmenopausal or surgically sterile are exempt from this exclusion
11. History of immune-related hypersensitivity reaction to glycopeptides (such as vancomycin, televancin, daptomycin, or dalbavancin) or any of their excipients. Note: subjects who have had histamine-like infusion reactions to a glycopeptide are not excluded
12. Subjects unwilling to forego blood and/or blood product donation for at least 1 month from initiation of oritavancin dose
13. Treatment with investigational medicinal product within 30 days or 5 half-lives, whichever is longer, before enrollment and for the duration of the study
14. Investigational device present, or removed within 30 days before enrollment, or presence of device-related infection
15. Subjects who the investigator considers unlikely to adhere to the protocol, comply with oritavancin administration, or complete the clinical study (e.g., unlikely to survive 90 days from initiation of oritavancin dosing)
16. Prior exposure to oritavancin alone or in combination with another product.

Subjects excluded for any of the above reasons may only be re-screened for participation after favorable discussion with Sponsor and principal investigator.

4.4. Withdrawal Criteria

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completed the clinical study. If for any subject study treatment or observations were discontinued, the reason will be recorded and the Sponsor should

be notified promptly. Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

- Adverse event(s)
- Death
- Withdrawal of consent by subject
- Physician decision
- Lost to follow-up

It is imperative to obtain complete safety follow-up information for all subjects whether or not they discontinue oritavancin. All data collected up until the time of subject withdrawal is to be entered into the eCRF. In addition, every attempt should be made to collect follow-up information except for those subjects who specifically withdraw consent for release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the study drug should be carried out when possible whether or not a subject continues to receive treatment according the protocol.

5. TREATMENT OF SUBJECTS

5.1. Study Medications

Subjects will receive either two IV doses of 1200 mg oritavancin one week apart or will receive a single dose of 1200 mg oritavancin and a placebo infusion one week apart. Oritavancin will be prepared by the study pharmacist/designee.

5.1.1. Oritavancin

Oritavancin will be supplied as a lyophilized powder in single-use glass vials. Each vial will contain 400 mg of oritavancin.

Three 400 mg vials will be required for each subject receiving oritavancin. At the time of use, each vial will be reconstituted by adding 40 mL of Sterile Water for Injection, United States Pharmacopeia (USP), to each 400 mg vial of oritavancin. Vials reconstituted in this manner will provide a 10 mg/mL solution. After reconstitution, oritavancin should be further diluted in 5% dextrose in water (D5W) to provide a total volume of approximately 1000 mL. Since the solubility of oritavancin is highly dependent upon pH, no other material or diluent may be substituted or concomitantly infused through the same IV line. The IV line should be flushed with D5W before and after; saline must not be used since it may cause precipitation.

Subjects will receive either one or two 1200 mg IV oritavancin doses in 1000 mL of D5W administered as a constant rate IV infusion over 3 hours via a single dedicated peripheral IV line or a single dose of placebo, one week apart. Oritavancin must be infused over 3 hours (6.7 mg/minute) to reduce the potential for histamine like infusion reactions or phlebitis.

5.1.2. Placebo

Placebo will be 1000 mL of D5W infused over 3 hours via a single dedicated peripheral IV line.

5.1.3. Packaging and Labeling

Oritavancin will be provided by the Sponsor. Infusion bags of D5W will be provided by the study site pharmacy.

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

5.1.4. Storage

Oritavancin lyophilized powder should be stored in a secure cabinet or other enclosure at controlled room temperature (20°C to 25°C; 68°F to 77°F). Diluted IV solution in an infusion bag should be used within 6 hours when stored at room temperature, or used within 12 hours when refrigerated at 2 to 8°C (36 to 46°F). The combined storage time (reconstituted solution in the vial and diluted solution in the bag) and 3-hour infusion time should not exceed 6 hours at room temperature or 12 hours if refrigerated (see Pharmacy Manual). Access should be strictly limited to the study pharmacists and their designees.

5.1.5. Accountability

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 drugs 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.

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/bottles) will be kept until the monitor has reviewed the accountability records.

All used and unused oritavancin supplied for this study will be destroyed on site once inventoried and the monitor has reviewed the accountability records. In the event that oritavancin needs to be returned for any other reason, the site will receive a written request listing drug lot number(s) to be returned and the reason for the return request.

5.1.6. Product Complaints

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

United States of America: [redacted]
Contact information for all other geographic areas:
http://www.themedicinescompany.com/contact/global-medical-info
Email: [redacted]

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**: A report of dissatisfaction with product with regard to its efficacy, strength, integrity, purity, or quality; thus a potential failure to meet product specifications. **Preference Complaints**: A report of dissatisfaction with service, delivery, packaging or other preference.

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.
- Medical device incidents

5.2. Concomitant Medications

Any concomitant medications will be recorded in the electronic case report form (eCRF) according to the Schedule of Events.

5.2.1. Prohibited Concomitant Medications

There are no prohibited concomitant medications for this study.

5.2.2. Permitted Concomitant Medication(s)

Subjects enrolled and treated with oritavancin may receive additional antibiotic therapy with Gram-negative coverage if necessary.

5.3. Medical Management Guidelines

Other interventions to optimize the care of subjects will be left to the discretion of the attending physician and investigator. These include surgical/nonsurgical debridement of devitalized tissue, removal of prosthetic material, incision and drainage, suture removal, percutaneous aspiration, packing, dressings, or irrigation with normal saline to remove superficial slough, excess exudate or visible debris. Standard of care therapy (such as daily superficial debridements and dressing changes) are allowed.

The investigator will be given guidance to stop, slow, or possibly even interrupt and restart an infusion should an infusion-related reaction occur. In addition, at the investigator's discretion, patients who experience an infusion-related reaction may be given diphenhydramine or dexamethasone as treatment(s) for their symptoms. In Study MDCO-ORI-15-02, all adverse events observed that were associated with the second dose occurred within 30-90 minutes of the start of the 3 hour infusion and resolved within a few hours after the end of infusion. Therefore all infusions must be administered in the presence of a medically qualified team member and subjects will be required to remain in the administration setting for a minimum of 3 hours following the completion of the second IV infusion or until any AEs that occur are resolved or stable.

If a subject is classified as a treatment failure by the investigator at any time, the subject may be administered alternative antibiotic therapy according to clinical judgment.

5.3.1. Gram-negative pathogen ABSSSI infections

Subjects enrolled and treated with oritavancin before culture results are available and found to have a Gram-negative pathogen may receive additional antibiotic therapy with Gram-negative coverage.

5.4. Restrictions

Subjects will be encouraged to continue their usual diet and level of activity, as dictated by their clinical condition. Activities that would impact clinical outcome should be avoided during the study period.

5.5. Blinding

5.5.1. Method and Maintenance of Blinding

This is a randomized, double-blind study. Subjects will be given a subject identification (ID) number sequentially according to the date and time when subjects sign the informed consent (screening number). The unblinded pharmacist will match the subject ID with the randomization schedule, which assigns treatment sequence based on 3:1 ratio. The oritavancin and placebo infusion arms will be double-blind; all study staff will be blinded to the treatment with the exception of the unblinded pharmacist.

5.6. Unblinding

The blinding of IV treatment assignment will be maintained until database lock. However, if a subject has a safety event that meets any of the protocol-defined stopping criteria, the subject's treatment assignment will be unblinded after determining relatedness to the study drug. The blind may also be broken for a specific subject only in the case where knowledge of the treatment assignment is deemed essential to subject safety or the occurrence of a SAE that, in the opinion of the investigator, cannot be adequately treated without knowing the identity of the study drug. Any intentional or unintentional breaking of the blind should be immediately reported to the Sponsor.

The principal investigator will be provided with instructions/envelopes for subject unblinding.

6. SCHEDULE AND SEQUENCE OF PROCEDURES

The Schedule of Events/Assessments (Table 3) summarizes the study assessments by time point.

This study consists of 4 periods: Screening, Pre-Dose, Treatment, and Follow-up.

- The Screening Period occurs <24 hours prior to administration of study drug on Day 1.
- The Pre-Dose Period occurs at Day 1 prior to oritavancin administration.
- The Treatment Period occurs from the time of study drug administration through Day 8 following study drug administration.
- The Follow-up Period occurs from the end of the Treatment Period through Day 22 (±2 days).

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

6.1. Schedule of Events/Assessments

Table 3: Schedule of Events

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

[1] Vital signs include blood pressure, temperature, respiratory rate and heart rate. On Day 8 vitals will be collected at pre-dose, 1.5 hours after the start of infusion, at the end of the infusion, and 4 hours after the start of infusion.

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

6.2. General Conduct of the Trial

Written informed consent will be obtained from all subjects by the site staff member before any study specific procedure is performed.

6.3. Screening Period (24 hours Prior to Day 1)

The following procedures will be performed ≤24 hours prior to Day 1 to establish each candidate's general health and qualifications for enrollment into the study:

- Obtain written informed consent
- Verify inclusion/exclusion criteria
- Record medical history and demographics
- Perform a physical examination, including height and weight to determine body mass index (BMI)
- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, direct and indirect antiglobulin test
- A urine pregnancy test will be performed for female subjects of childbearing potential. This test may be omitted for females >2 years postmenopausal or surgically sterile.
- Microbiology samples, if obtained, per standard of care
- Record medication history over the past 14 days, including over-the-counter (OTC), prescription drugs, vitamins and nutraceuticals (e.g., herbal supplements)
- Assessment of AEs and SAEs starting from the time the informed consent form is signed
- Record planned ABSSSI surgical procedures

6.4. Day 1 Pre-dose

The following pre-dose procedures will be performed at Day 1 prior to administration of oritavancin:

- Confirm that the subject continues to meet inclusion and exclusion criteria including the verification of safety lab results
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Collection of concomitant medication information
- Assessment of AEs and SAEs
- Randomize the subject

6.5. Treatment Period

The enrollment process will be initiated only after confirmation of a subject's eligibility. Each successive subject will be assigned a unique subject identification number.

If a subject is found to be ineligible after signing the informed consent, but prior to dosing, he or she will be considered a screen failure, the subject will not be enrolled, and oritavancin will not be administered.

6.5.1. Day 1

Ideally, treatment should be initiated within 4 to 6 hours after the subject is first seen on Day 1.

- Administer oritavancin as a single IV infusion of 1200 mg over 3 hours
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Collection of concomitant medication information
- Assessment of AEs and SAEs

6.5.2. Day 8 Pre-dose

- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, direct and indirect antiglobulin test
- Collect blood specimen for complement profile (C3, C4, CH50) and serum tryptase, erythrocyte sedimentation rate (ESR), Haptoglobin level and C-reactive protein.
- Collect PK blood sample
- A urine pregnancy test will be performed for female subjects of childbearing potential. This test may be omitted for females >2 years postmenopausal or surgically sterile.
- Assessment of clinical cure
- Collection of concomitant medication information
- Assessment of AEs and SAEs

6.5.3. Day 8 Post-dose

- Administer oritavancin or placebo as a single IV infusion of 1200 mg over 3 hours
- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) at 1.5 hours after the start of the infusion, at the end of infusion and 4 hours after the start of the infusion.
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, direct and indirect antiglobulin test at the end of the infusion

- Collect blood specimen for complement profile (C3, C4, CH50) and serum tryptase, ESR, Haptoglobin level and C-reactive protein.
- Collect PK blood samples at 3 hours (end of infusion) and 6 hours after the start of the infusion.
- Collection of concomitant medication information
- Assessment of AEs and SAEs
- Subjects should remain in the administration setting for a minimum of 3 hours following the completion of the second IV infusion or until any AEs that occur are resolved or stable. A medically qualified team member must be onsite during this time to assess any adverse events.

6.6. Follow-up Period

6.6.1. Day 15 (±2 days)

- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, direct and indirect antiglobulin test
- Collect PK blood sample
- Collection of concomitant medication information
- Assessment of AEs and SAEs

6.6.2. Day 22 (±2 days)

- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, direct and indirect antiglobulin test
- Collect PK blood sample
- A urine pregnancy test will be performed for female subjects of childbearing potential. This test may be omitted for females >2 years postmenopausal or surgically sterile.
- Collection of concomitant medication information
- Assessment of AEs and SAEs

7. PROTOCOL ASSESSMENTS

7.1. Assessment of Safety

When blood draws and vital signs are done at the same time point, the following sequence should be followed: 1) vital sign assessment 2) blood draw for lab tests.

7.1.1. Adverse events

Subjects will be carefully monitored for AEs by the investigator during the designated study period (see Section 8 for details).

7.1.2. Physical examinations

A physical exam will include head, eyes, ears, nose, throat (HEENT), heart, lungs, abdomen, skin, and extremities. BMI will be calculated based on height and weight collected at the Screening Visit.

7.1.3. Vital signs

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

7.1.4. Laboratory assessments

Specimens will be obtained at the designated time periods as indicated in the Assessment Schedule. All clinical laboratory assessments will be performed by the site's local laboratory and shipped to the central laboratory for testing. Additional local laboratory testing may be performed at the discretion of the investigator. Any clinically significant (CS) laboratory findings that occur during the study should be followed to resolution per the Investigator/Sponsor's decision. If a subject has a positive indirect antiglobulin test at baseline, that subject will be replaced in the study.

- **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, reticulocyte count, complete blood count and manual blood smears
- **Additional Labs:** Complement profile (C3, C4, CH50) and serum tryptase, ESR, Haptoglobin level and C-reactive protein.
- **Urine pregnancy test**
- **Direct and Indirect antiglobulin test**
- **Immunoglobulin panel assays**: Immunoglobulin M (IgM), immunoglobulin G (IgG); immunoglobulin E (IgE), immunoglobulin A (IgA)

- **Assay for oritavancin antibodies**
- **Plasma storage samples for drug dependent antibody ex vivo study**

7.2. Assessment of Efficacy

Definition of clinical response

- A subject is classified as "success" if all of the following are met:
- Cessation of spread or reduction of the lesion defined as: Cessation of spread of the redness, edema, and/or induration, or reduction in size (length, width, and area) of the redness, edema, and/or induration such that the size of the lesion is less than or equal to the size at baseline
- Resolution (absence) of fever (temperature <37.7°C)
- No rescue antibiotic medication

Investigator assessment of clinical cure:

At Day 8: Complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further treatment with antibiotics is needed.

A subject cannot be classified as clinical cure if:

- Subject did not fulfill the criteria for clinical cure above
- Investigator assignment of failure any time prior to Day 8
- Subject dies (all-cause mortality) from the start of administration of oritavancin
- Incision and drainage after 48 hours of treatment that was unplanned prior to enrollment, with the exception of cellulitis where there is a conversion into an abscess or when an extension of the original incision is indicated
- Initiation of non-study antibacterial drugs for treatment of other infections unless antibiotic lacks efficacy in the treatment of ABSSSI
- Subjects who otherwise do not meet the definition of clinical cure (e.g., lost to follow-up; oritavancin discontinued secondary to adverse reaction)

A subject who is not classified as clinical cure will be classified as failure.

7.3. Assessment of Pharmacokinetics

Blood samples for pharmacokinetic analysis of oritavancin will be collected on Days 8 pre-dose, at 3 (end of infusion) and 6 hours after the start of study drug infusion. Subjects will have blood collected for PK on Day 15 and Day 22 as well.

Table 4: PK Blood Draw Schedule

	Sample Number	**Optimal Sample Time From Start of Infusion (h)**	**Sample Time Window**	
			Lower Limit (h)	**Upper Limit (h)**
DAY 8	1 (before start of study drug)	Pre-dose	-0.5	- 0.08
	2 (at end of infusion)	3 hours	3	3.5
	3	6 hours	5	7
DAY 15	4	PK sample at visit		
DAY 22	5	PK sample at visit		

8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation 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 (including 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.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the study drug was given or the subject was randomized in a clinical study are not to be considered AEs.

Subjects experiencing AEs should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject if necessary.

8.1.1.1. AE Severity

The severity of an AE will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

AEs will be graded on a 3-point scale and reported as indicated on the CRF. The intensity of an AE is defined as follows:

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.

8.1.1.2. Study Drug Causality

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject's clinical condition and medical history

Categorization of causality will be designated by the investigator as stated below:

1. **Unlikely related** - Lack of reasonable possibility of a causal relationship - causal relationship between the event and the Investigational Medicinal Product (IMP). This

means that there are little to no facts (evidence) or arguments to suggest a causal relationship.

2. **Reasonable possibility** - Reasonable possibility of a causal relationship - causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

8.1.2. Serious Adverse Event

An 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,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

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.

When death occurs with an SAE, the cause of death must be reported as an SAE. “Fatal” will be reported as the outcome for these events.

8.1.3. Medication Errors

Medication error refers to any unintended error in the dosing and administration of the study drug as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- wrong study medication
- wrong dose (including dosing regimen, strength, form, concentration, amount);

- wrong route of administration;
- wrong subject (i.e., not administered to the intended subject)

Medication errors include occurrences of overdose and underdose of the study product(s), and misuse.

Overdose: Administration of a quantity of the study product given per administration or per day which is above the maximum recommended dose according to the reference safety information or protocol for the investigational product or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Administration of a quantity of the study product given per administration or per day which is under the minimum recommended dose according to the reference safety information or protocol for the investigational product.

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply (e.g., without prescription for medicinal products subject to medical prescription).

8.1.4. Adverse Event of Special Interest (AESIs)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, which warrants ongoing monitoring and rapid communication by the investigator to the Sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESIs have been identified for the study drug in this protocol:

- Hypersensitivity/Infusion Related Reaction
- Pseudomembranous colitis/*Clostridium difficile*-associated diarrhea
- Osteomyelitis

8.2. Procedure for Non-Serious Adverse Event Recording

All non-serious AEs that occur during the designated study period (from signing the informed consent to 21 days following initial oritavancin administration) must be assessed and recorded on the source documents and eCRF, regardless of causal relationship to the study drug.

8.3. Procedure for Serious Adverse Event Reporting

All SAEs that occur during the designated study period (from signing the informed consent to 21 days following initial oritavancin administration) must be reported to MDCO within 24 hours of awareness of the event using the provided study specific SAE/AESI Report Form. The completion and processing of the SAE/AESI Report Form (paper) should follow the instructions provided in the SAE/AESI Report Form completion guidelines. In addition to completing the SAE/AESI Report Form, each SAE/AESI must be entered on the appropriate page of the eCRF.

When death occurs with an SAE, the cause of death must be reported as an SAE. "Fatal" will be reported as the outcome for these events

The investigator must assess the causality for each SAE/AESI.

MDCO will contact the investigator, if necessary, to clarify any of the event information. The investigator should provide any follow-up information for the event to MDCO as soon as it becomes available.

If the investigator is notified of a SAE/AESI that occurs during the post-study period, that he or she wishes to report to the Sponsor (e.g., an event suspected to be causally related to study drug), 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 Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority in addition to the Sponsor.

8.4. Procedure for Medication Error Reporting For Study Products

Medication errors, with or without an associated AE, need to be recorded as medication errors in the eCRF as described in Section 8.2.

Medication errors with an associated SAE need to be recorded as medication errors in the eCRF and reported to the MDCO Global Pharmacovigilance as described in Section 8.3.

A mis-dosing protocol deviation (refer to Section 12.3) would need to be reported as a medication error if it was an "unintended error" as defined in Section 8.1.3.

8.5. Procedure For Reporting Adverse Events Of Special Interest (AESIs)

All AESIs should be reported to MDCO within 24 hours. The SAE/AESI Report Form should be utilized for reporting the AESI even if a serious outcome may not apply. The SAE/AESI Report Form should indicate that the reported event is an AESI. The site will also be asked to complete a targeted questionnaire which obtains more information about the specific event.

8.6. Procedure For Reporting Pregnancies

Occurrences of pregnancy/lactation exposure in a study subject or study subject's partner, including pregnancies detected anytime from administration of oritavancin until 60 days after administration of oritavancin, must be reported within 24 hours using the Pregnancy Reporting form. In cases where a pregnancy occurs with an SAE, the SAE Reporting Form should be used to report the SAE/AESI and the Pregnancy Reporting Form should be used to report the pregnancy. Any spontaneous abortion must be captured as an SAE. When a pregnancy occurs without any intercurrent SAE, the Pregnancy Reporting Form may be submitted alone. Follow-up through pregnancy outcome is required if a pregnancy is detected during this study.

The Medicines Company or its designee will contact the investigator, if necessary, to clarify any of the pregnancy information. The investigator will provide follow-up information to MDCO or its designee as soon as it becomes available. Additionally, if required by local regulations or procedures, the investigator will report pregnancies to the IRB/EC and/or national or local regulatory authorities.

8.7. Ongoing Safety Monitoring and Stopping Rules

The Sponsor will be conducting ongoing review of the safety data (AEs, vitals and labs). The study will be terminated if any of the following criteria are met: 1) any death which is considered possibly related to oritavancin or 2) any two or more subjects who experience any serious adverse event possibly related to oritavancin or 3) any three or more subjects who experience any non-serious AE which is severe in intensity and considered possibly related to oritavancin.

8.8. Procedure For Reporting Special Situations

If there is an occurrence of a Special Situation event, defined in Section 8.1.4, report this occurrence to the Sponsor as per Section 8.3, Procedure for Serious Adverse Event Reporting. Note: The Special Situations event does not need to be serious to be reported on the SAE/AESI Report form.

9. DATA COLLECTION

An electronic data capture (EDC) system will be used for this trial. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel 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. The eCRF should be filled out by the site 3 days after the Day 15 visit and 3 days after the Day 22 visit. Any Clinically Significant lab data or AEs occurring after the second dose should be entered within 24 hours in order to facilitate the Sponsor's ongoing review of safety data. 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 DCO and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve, and 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. After the end of the trial, a copy of the data will be provided to the site. 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.

10. STATISTICAL PLAN

This is a 20 subject, randomized, double-blind trial. Subjects with ABSSSI will be included in this study. Subjects will be recruited from approximately 5 centers in the US. Subjects that qualify for entry into the study will be randomly assigned in a 3:1 ratio to receive either two IV doses of 1200 mg oritavancin one week apart or a single dose of 1200 mg oritavancin and a placebo infusion one week apart. The primary objective of this study is to evaluate the safety and tolerability of two 1200-mg IV infusions of oritavancin when administered one week apart. Statistical methods and data presentation will be described in more detail in the Statistical Analysis Plan (SAP) document.

10.1. Sample Size

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

10.2. Randomization

Subjects will be randomly assigned in a 3:1 ratio to receive either two doses of oritavancin one week apart or one dose of oritavancin and one dose of placebo one week apart.

10.3. General Statistical Considerations and Definitions

10.3.1. General Statistical Methods

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

10.3.2. Analysis Population

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

10.3.2.1. Intent-to-Treat (ITT) Population

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

10.3.2.2. Safety Population

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

10.3.3. Analysis Windows and Baseline

The observational period for the study includes Day 22±2 days. Any event occurring beyond the defined observational period, even if collected on the CRF, will not be included in the planned

statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

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

10.3.4. Missing Data Handling

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

10.4. Statistical Analyses

All summaries will be presented by group.

10.4.1. Demographic and Background Characteristics

Subject demographics and baseline characteristics will be summarized using the Safety Population.

10.4.2. Prior and Concomitant Medications

Separate summaries of prior and concomitant medications will be provided for the Safety Population. Prior medications are those received before the initiation of dosing on Day 1 while concomitant medications are those received after. Medications will be coded with the World Health Organization (WHO) Drug Dictionary Enhanced.

10.4.3. Safety Analysis

10.4.3.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding AEs. An AE (classified by system organ class and preferred term) that occurs during the treatment period will be counted as a TEAE either if it is not present at baseline or if it is present at baseline but increased in severity during the treatment period or follow-up period.

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

Listings of SAEs and AEs leading to treatment or study discontinuation will also be provided.

10.4.3.2. Clinical Safety Laboratory Tests

Clinical safety laboratory values and changes from baseline, including direct and indirect antiglobulin, immunoglobulin panel, and oritavancin antibody assay, will be summarized descriptively. Clinically significant values will also be flagged in a listing.

10.4.3.3. Vital Signs

Vital sign measurements and changes from baseline will be summarized descriptively at each scheduled time point. Potentially clinically significant changes will also be flagged in a listing.

11. RECORDS RETENTION

Current FDA regulations require all investigators participating in clinical study drug trials to maintain detailed clinical data for one of the following periods:

- At least 2 years following the date on which a New Drug Application is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA.

Similarly, current EU Directives / Regulations and International Conference on Harmonization (ICH) guidelines collectively require that essential clinical trial documents (including case report forms) other than patient's medical files must be retained for the following time period:

- — for at least 15 years after completion or discontinuation of the trial,
- — or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- — or for at least two years after formal discontinuation of clinical development of the study drug.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs received from the Sponsor of the final data. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. 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 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.

12.2. Auditing

The Sponsor may conduct audits at the study centers. 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.

12.3. 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 (Clinical Project Director, Medical Director or Clinical Research Associate) at the earliest possible time. 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.

Any protocol deviations that will affect the subject's safety or the study objectives may be considered a major protocol deviation upon review by the Sponsor. In addition, any of the following deviations will be considered major protocol deviations:

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:

- All Inclusion criteria violation
- All Exclusion criteria violation

- PK sample not collected due to site error
- Mis-Dosing: Subject was not dosed per the protocol instructions and therefore, greater than 120% or less than 80% of the correct dose was administered

*If the mis-dosing was unintended, i.e. a medication error, the error should be reported as per instructions in Section 8.4, Procedure for Medication Error Reporting.

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the US Food and Drug Administration (FDA) regulations, the ICH GCP guidelines, the Declaration of Helsinki and other local regulations, as applicable.

13.1. Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legally authorized representative) or, as per IRB guidelines, before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB- or EC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2. Institutional Review Board/Ethics Committee

This protocol, the written informed consent form and any materials presented to subjects shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

15. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the new study drug oritavancin, the concurrent medications, the safety parameters, and the conduct of the study in general. I am aware that this protocol must be approved by the IRB or EC responsible for such matters in the Clinical Study Facility where oritavancin will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB or EC approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on CRFs by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for subjects screened or randomized in the study.

I agree to provide all subjects with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11, and applicable local regulations.

Principal Investigator (Signature)	Date
Principal Investigator (Printed Name)	Original Protocol Version 1
Institution Name	

16. REFERENCES

16.1. Publications

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