ORBACTIV™ (oritavancin)

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

Protocol No.: MDCO-ORI-14-03
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PROTOCOL VERSION: 3.0

Drug Development Phase: IV

Sponsor: The Medicines Company
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PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Telephone Number
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PROTOCOL SYNOPSIS

Name of Sponsor/Company: The Medicines Company

Name of Finished Product: ORBACTIV™ (oritavancin)

Name of Active Ingredient: oritavancin diphosphate

Title of Study: An Open-Label Study to Evaluate the Safety of a Single 1200 mg IV Dose of Orbactiv (oritavancin) in Subjects on Concomitant Chronic Warfarin Therapy Being Treated For Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

Study Centers: Multicenter, at up to 10 centers in the United States

Phase of Development: IV

Objective:

Assess the safety and tolerability when a single 1200 mg IV infusion of oritavancin is given concomitantly in subjects on chronic warfarin therapy with ABSSSI.

Methodology: This is a Phase IV, multicenter, open-label safety study of a single 1200 mg intravenous (IV) infusion of oritavancin in adult subjects on chronic warfarin with acute bacterial skin and skin structure infection (ABSSSI) suspected or proven to be caused by Gram-positive pathogens. ABSSSI includes wound infections, infective cellulitis, and major cutaneous abscesses.

An additional group of patients with ABSSSI, who are not on concomitant warfarin therapy, will also be enrolled to obtain information regarding the potential for antibody production following a single dose of oritavancin administration in patients.

Subjects providing informed consent and meeting all study eligibility criteria will be enrolled in the study and will receive one 1200 mg dose of IV oritavancin.

Number of Subjects: Approximately 25 subjects on concomitant warfarin therapy will be enrolled in this study.

An additional group of 15 patients with ABSSSI, who are not on warfarin, will also be enrolled.

Diagnosis and Main Criteria for Inclusion:

Subjects who meet all of the following inclusion criteria are eligible for the study:

1. Males or females ≥18 years old
2. Diagnosis of ABSSSI (wound infection, cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen requiring IV therapy
3. Must be currently being treated with chronic warfarin therapy*:
    a. Warfarin therapy must have been initiated a minimum of 30 days prior to enrollment
    b. Current warfarin dosage must be stable for at least 14 days prior to enrollment
    c. At least one documented INR between 1.5 and 3.0 in the 30 days prior to screening
    d. The INR value at Screening must fall within 1.5 and 3.0 and also be within 25% of the prior documented value
4. Able to give informed consent and willing to comply with all required study procedures

*Patients in the non-warfarin group are not required to be on chronic warfarin therapy

Subjects who meet any of the following criteria are not eligible to participate in this study:

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 patient 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 intravenous 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. Significant change of any medications over the preceding 7 days that could interfere with the metabolism of warfarin (if patient is on chronic warfarin therapy)
16. 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)

Test Product, 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 Injection (D5W).

On Day 1 of the study, subjects will be administered a single 1200 mg IV dose of oritavancin in 1000 mL D5W. Oritavancin 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: Intravenous oritavancin will be administered in a single 1200mg intravenous dose.

Reference Therapy, Dose, and Mode of Administration: Not applicable.

Criteria for Evaluation:

Primary outcome:

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

Additional Safety Evaluation:

Any changes in warfarin dosing (for patients on warfarin therapy), based on the PT/INR results or safety data will be recorded. If the PT/INR has not returned to therapeutic baseline by Day 14, patient will be referred to and followed by their primary physician responsible for their PT/INR monitoring.

Secondary outcomes:

- Clinical cure as an assessment of efficacy, determined by the investigator at 48-72 hours after start of oritavancin dose and at Day 7

Exploratory Outcome:

- Potential for antibody development following a single dose oritavancin administration

Clinical evaluation time points:

- Assessment of safety (adverse events and PT/INR testing) Days 1, 2, 3, 7 and 14
- Early clinical efficacy evaluation at 48 to 72 hours from start of oritavancin administration
- Post-therapy efficacy evaluation at Day 7

Statistical Methods: Approximately 25 subjects on chronic warfarin therapy will be enrolled (ITT population). An additional group of 15 ABSSSI patients, who are not on chronic warfarin therapy, will also be enrolled.

Sample size: The sample size of 25 subjects is chosen based on feasibility and clinical judgment to provide adequate safety information on the administration of oritavancin to subjects with an ABSSSI who are on chronic warfarin. An additional group of 15 ABSSSI patients who are not on chronic warfarin therapy was added to obtain information regarding potential for antibody production related to oritavancin administration.

Analysis population: The patient populations are defined as follows:

- Intent-to-Treat (ITT) Population: The ITT population will include all subjects screened and enrolled
- 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 adverse events, laboratory results (prothrombin time (PT)/international normalized ratio (INR), direct and indirect Coombs, 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 3 and Day 7 will be provided for the ITT population.

Table 1: SCHEDULE OF EVENTS

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

[1] If subject has abnormal laboratory values that have not returned to a therapeutic baseline by Day 14, additional follow up visits may be required.
[2] Vitals signs include blood pressure, temperature, respiratory rate and heart rate.
[3] Perform a local urine pregnancy test for female patients of childbearing potential (may be omitted for females > 2 years postmenopausal or surgically sterile).
[4] This includes but is not limited to aspiration, debridement, incision and drainage.
[5] Blood chemistry and hematology (Section 7.2.4 for listing of tests to be performed). Unless otherwise indicated all laboratory tests will be performed by site's local laboratory.
[6] Microbiology testing should be performed per institutions Standard of Care (SOC).
[7] Patients on warfarin are required to have at least one documented INR between 1.5 and 3.0 in the 30 days prior to screening. The INR value at Screening must fall within 1.5 and 3.0. After dosing with oritavancin, the next PT/INR should be collected with 18-36 hours of start of oritavancin infusion. If PT/INR has not returned to baseline at Day 3, more frequent PT/INR testing prior to Day 7 may be required.
[8] Clinical cure should be assessed by investigator at Day 3 (48-72 hours after start of oritavancin administration) and at Day 7.
[9] Patients with a negative Coombs Test at Day 14 test must have test repeated every 2 weeks until return to baseline or stable.
[10] Adverse events and serious adverse events will be assessed from the time of informed consent through 14 days post first administration of Oritavancin.
[11] Blood will be collected immediately after the completion of the infusion to prepare three plasma sample for Ex Vivo Study investigating the effects of Oritavancin on Antibody Formation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

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

Abbreviation	Explanation
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
$T_{1/2}$	Half-life
T1/2,α	Half-life for the alpha phase
T1/2,β	Half-life for the beta phase
T1/2,γ	Half-life for the gamma phase
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
Vss	steady-state volume of distribution
WHO	World Health Organization

1. INTRODUCTION

This protocol describes a multicenter, open-label study to evaluate the safety of a single 1200 mg IV dose of Orbactiv (oritavancin) for the treatment of subjects on concomitant chronic warfarin therapy being treated for an acute bacterial skin and skin structure infection (ABSSSI). An additional group of fifteen patients will also be enrolled that are being treated for an ABSSSI and are NOT on concomitant chronic warfarin therapy.

Oritavancin has been approved in the United States for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs) 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 4 Phase III studies, 4 Phase II studies and 15 Phase I studies completed in adults. A safety and pharmacokinetic study in the pediatric population is ongoing. A total of 3042 subjects have been exposed to oritavancin to date, including 1075 adult subjects with ABSSSI treated with a 1200 mg single dose regimen.

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 *S. 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

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 methicillin resistant *Staphylococcus aureus* [ORBACTIV™ Package Insert 2014].

1.2.1. Preclinical Studies

Oritavancin has been extensively studied pre-clinically. The results from the safety, toxicology, pharmacokinetic, 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. Summary of Clinical Pharmacology

The pharmacokinetics of a single 1200 mg dose of oritavancin in ABSSSI subjects were determined from population pharmacokinetic analysis of pooled data from 297 adult subjects and are presented in Table 2. 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 2 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; $T_{1/2,\alpha}$, Half-life for the alpha phase, $T_{1/2,\beta}$, Half-life for the beta phase; $T_{1/2,\gamma}$, Half-life for the gamma phase; CV% = Percent Coefficient of variation.

1.2.3. Clinical Studies

The clinical program of oritavancin comprises four completed Phase III studies, four Phase II studies, fourteen 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) [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 patients demonstrate that a single 1200 mg IV dose of oritavancin is 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 is well tolerated and has 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, Serious Adverse Events (SAEs) and Adverse Events (AEs) leading to discontinuation reported by patients (Table 3).

Table 3 Overview of Adverse Events from SOLO Pooled Data (Safety Population)

	SOLO Pool			
Category	**Oritavancin (N=976) n (%)**		**Vancomycin (N=983) n (%)**	
No. of Subjects with any AE	540	(55.3%)	559	(56.9%)
No. of Subjects with any AE Leading to Study Drug Discontinuation	36	(3.7%)	41	(4.2%)
No. of Subjects with SAE	57	(5.8%)	58	(5.9%)
No. of Subjects with any AE Leading to Death	2	(0.2%)	3	(0.3%)

AE = adverse event; SAE = serious adverse event.

Table 4 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%)

1.2.4. Known and Potential Risks and Benefits

Twenty three clinical trials, including four Phase III, four Phase II, and fifteen 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 4.

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 ORBACTIV infusion in patients with a history of glycopeptide allergy. In the Phase III 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 or anaphylactoid reactions have been reported with oritavancin including pruritus, urticaria or flushing. If reactions do occur, slowing or interrupting the infusion should be considered to mitigate the reaction.

Oritavancin is a mild inhibitor of Cytochrome P450 2C9 enzyme (CYP2C9), and therefore, has the potential to increase warfarin concentrations when administered concomitantly. Oritavancin has been shown to artificially prolong PT and 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

who are on warfarin (including all subjects in this trial) should be closely monitored for signs of bleeding.

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).

1.3. STUDY RATIONALE

As noted above, oritavancin is a weak inhibitor of CYP2C9 based on a 31% increase (90% confidence interval (CI) [1.294, 1.345]) in the systemic exposure of S warfarin (TMC-ORI-12-03). Two additional studies are ongoing; MDCO-ORI-14-01 is a Phase I study in healthy volunteers to assess the magnitude and duration of the effect of a single 1200 mg intravenous dose on numerous coagulation tests, including PT/INR, and MDCO-ORI-14-02 which is an additional Phase I study in healthy volunteers assessing the magnitude and duration of the pharmacokinetic (PK) interaction between warfarin and oritavancin. Since warfarin is a drug with a narrow therapeutic index and some patients with ABSSSI may receive oritavancin while on warfarin treatment, this study is being conducted to characterize the effect of oritavancin on clinical care and warfarin dosing. The intention is to determine the magnitude and duration, if any, of alterations to warfarin dosing or of clinically important consequences of dosing with oritavancin.

In the SOLO and SIMPLIFI trials, a total of 16 patients with ABSSSI received concomitant warfarin while treated with a single 1200 mg dose of oritavancin. Of these 16 patients, 10 were on warfarin prior to starting oritavancin, 4 received warfarin therapy after starting oritavancin therapy and for 2 patients the timing of warfarin therapy is unknown. None of these 16 patients discontinued from the study early due to adverse events. One patient experienced an event of infusion site thrombosis 2 days prior to the administration of warfarin therapy but there were no other bleeding or thrombotic related events. Additionally, no abnormal prothrombin time coagulation tests were reported in the oritavancin treated patients.

This study will extend the above safety data in patients with ABSSSI when oritavancin and warfarin are given concomitantly.

In addition, a group of patients with ABSSSI, who are not on concomitant warfarin therapy, have been added to this study to obtain information regarding the potential for antibody production following a single dose of oritavancin administration in patients. This has not been previously tested, therefore plasma will be collected at regular intervals after oritavancin dosing to test for immunoglobulins, direct and indirect Coombs, and presence of oritavancin antibodies.

The 1200 mg dose of oritavancin is the United States (US) approved therapeutic dose.

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

1.4. STUDY POPULATION

Subjects at least 18 years of age with an ABSSSI, on concomitant warfarin therapy, suspected or confirmed to be caused by Gram-positive pathogens. An ABSSSI includes the following infections: Wound infections, cellulitis/erysipelas and major cutaneous abscess. An additional group of patients with ABSSSI, who are not on concomitant warfarin therapy, will also be enrolled.

2. TRIAL OBJECTIVE AND PURPOSE

The primary objectives of this study are:

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

3. TRIAL DESIGN

3.1. PRIMARY OUTCOME

The primary outcome of this trial will be:

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

3.2. SECONDARY OUTCOME

The secondary outcome of this trial will be:

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

3.2.1. Exploratory Outcome:

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

3.3. MEASURES TO MINIMIZE/AVOID BIAS

3.3.1. Unblinded Study

This is an open label study. The primary endpoints are safety and laboratory measurements, primarily change in PT/INR, which is not likely to be subject to interpretation bias.

3.4. TYPE/DESIGN OF TRIAL

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

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

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

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

A description of each study period and the assessments that will be performed at each time point is detailed in Section 6.

4. SUBJECT POPULATION

4.1. NUMBER OF SUBJECTS

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

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. Must be currently being treated with chronic warfarin therapy*:
    a. Warfarin therapy must have been initiated a minimum of 30 days prior to enrollment
    b. Current warfarin dosage must be stable for at least 14 days prior to enrollment
    c. At least one documented INR between 1.5 and 3.0 in the 30 days prior to Screening
    d. The INR value at Screening must fall within 1.5 and 3.0 and also be within 25% of the prior documented value
4. Able to give informed consent and willing to comply with all required study procedures

*Patients in the non-warfarin sub-group are not required to be on chronic warfarin therapy

4.3. EXCLUSION CRITERIA

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

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 patient 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 intravenous unfractionated heparin sodium within 48 hours after oritavancin administration
7. Last known cluster of differentiation 4 (CD4) count <200 cells/mm3 in subjects with known human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)
8. Neutropenia with absolute neutrophil count (ANC) <500 cells/mm3
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. Significant change of any medications over the preceding 7 days that could interfere with the metabolism of warfarin (if patient is on chronic warfarin therapy)
16. 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)

Subjects excluded for any of the previous criteria may only be rescreened 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 the study without prejudice. The investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completes the clinical study. If for any reason study treatment or observations are discontinued, the reason will be recorded and the Sponsor should be notified. Reasons that a subject may discontinue participation in this clinical study include the following:

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

It is imperative to obtain safety follow-up information for all subjects whether or not they discontinue oritavancin. Every attempt should be made to collect follow-up information except for those subjects who specifically withdraw consent for release of such information.

5. TREATMENT OF SUBJECTS

5.1. STUDY MEDICATIONS

Each subject will receive a single 1200 mg IV dose of oritavancin. 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, 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.

Each subject will receive a single oritavancin dose of 1200 mg in 1000 mL of D5W administered as a constant-rate IV infusion over 3 hours via a single dedicated peripheral IV line. 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. Packaging and Labeling

Oritavancin will be provided by the Sponsor. Warfarin will be supplied by the site. 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.

5.1.3. 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 intravenous 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.

5.1.4. 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 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.

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 the drug lot number(s) to be returned and the reason for the return request.

5.2. CONCOMITANT MEDICATIONS

5.2.1. Prohibited Concomitant Medications

If possible, patients on chronic warfarin therapy should not take any new medications that could interfere with warfarin metabolism, other than oritavancin, during this study. Any concomitant medications will be recorded in the electronic case report form (eCRF) according to the Schedule of Events.

5.2.2. Permitted Concomitant Medications

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

5.2.3. Warfarin Therapy

Any changes in warfarin dosing (for patients on concomitant chronic warfarin), based on the PT/INR results or safety data will be captured.

5.3. 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.

6. SEQUENCE OF PROCEDURES

A summary of clinical assessments and procedures is provided before the contents in Schedule of Events.

This study consists of four periods: Screening, Pre-Dose, Treatment, and Follow-up. The maximum duration of a patient's participation in this study is approximately 14 days post first administration of oritavancin.

6.1. 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.

6.2. SCREENING PERIOD (≤24 HRS 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
- Obtain height and weight to determine body mass index (BMI)
- Perform a physical examination
- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, PT/INR coagulation test, direct and indirect Coombs 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 ABSSI surgical procedures

6.3. DAY 1 PRE-DOSE

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

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

6.4. 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.

6.4.1. Day 1

Ideally, treatment should be initiated within 4 to 6 hours after the patient 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
- Collect blood sample for Drug Dependent Antibody Ex Vivo Study (immediately after the completion of the oritavancin infusion).

6.5. FOLLOW UP

6.5.1. Day 2

- Collect blood sample for PT/INR coagulation test (window: 18-36 hours after the start of the oritavancin infusion).

6.5.2. Day 3

- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Assessment of early clinical cure at 48-72 hours after start of infusion of Oritavancin
- Assessment of AEs and SAEs
- Collect blood specimens for immunoglobulin panel, oritavancin antibody assay, PT/INR coagulation test, direct and indirect Coombs test
- Collection of concomitant medication information

6.5.3. Day 7

- Obtain vital sign measurements (blood pressure, heart rate, respiratory rate and temperature)
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, PT/INR coagulation test, direct and indirect Coombs 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.
- Assessment of clinical cure
- Collection of concomitant medication information
- Assessment of AEs and SAEs

6.5.4. Day 14 (±2 days)

- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Collection of concomitant medication information
- Collect blood specimens for hematology, serum chemistry, immunoglobulin panel, oritavancin antibody assay, PT/INR coagulation test*, direct and indirect Coombs test
- Assessment of AEs and SAEs
- Patients with a negative Coombs Test at Day 14 test must have test repeated every 2 weeks until return to baseline or stable.

*If a subject's PT/INR has not returned to therapeutic baseline by Day 14, patient will be referred to and followed by their primary physician responsible for their PT/INR monitoring.

7. PROTOCOL ASSESSMENTS

7.1. TREATMENT, DAY 1

7.1.1. 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.

If a patient has an infusion reaction with oritavancin the infusion may be slowed or stopped. The patient should be treated as necessary. The infusion may be resumed at half the previous infusion rate with continued monitoring for signs or symptoms of a histamine infusion reaction.

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

7.1.1.1. 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.

7.2. ASSESSMENT OF SAFETY

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

7.2.1. Adverse Events

Subjects will be carefully monitored for adverse events by the investigator during the designated study period.

7.2.2. Physical Examinations

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

7.2.3. 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.

Blood pressure and pulse must always be taken after the subject has been resting supine for 5 minutes.

7.2.4. Laboratory assessment

Specimens will be obtained at the designated time periods as indicated in the Schedule of Events. All clinical laboratory assessments 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 to resolution per the Investigator/Sponsor's decision. If the PT/INR has not returned to baseline by Day 14, patient will be followed until PT/INR has returned to therapeutic baseline.

- **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
- **Coagulation Tests:** PT/INR
- **Urine Pregnancy Test**
- **Direct and Indirect Coombs 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**

7.3. ASSESSMENT OF EFFICACY

Definition of clinical response:

Assessment of clinical cure at 48 to 72 hours:

A patient 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

A patient cannot be classified as a "success" at 48-72 hours (i.e., patient is a failure) if:

- Death (all-cause mortality) from the start of oritavancin administration
- Fever (one or more temperature readings of ≥37.7°C between 48 and 72 hours)
- Spread of lesion defined as an increase in size (length, width, or area) of the redness, edema, and/or induration such that the size of the lesion is greater than the size at baseline
- Administration of rescue antibacterial drug therapy or any non-trial antibacterial drug therapy for the treatment of ABSSSI prior to the 48-72 hours clinical cure evaluation
- Requires an additional unplanned surgical procedure after start of therapy as described below under: "A patient cannot be classified as clinical cure if"

Investigator assessment of clinical cure:

At Day 7: Complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further treatment with antibiotics is needed

A patient cannot be classified as clinical cure if:

- Patient did not fulfill criteria for clinical cure above
- Investigator assignment of failure any time prior to Day 7
- Patient 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 infection 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 patient who is not classified as clinical cure will be classified as failure.

8. ADVERSE EVENTS

8.1. DEFINITIONS

8.1.1. Adverse Event

An adverse event (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 drug was given or the subject was enrolled in a clinical study are not to be considered AEs.

Subjects experiencing adverse events 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 case report form. 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 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

A serious adverse event (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-patient 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 product as per instructions in the protocol. Medication Errors generally fall into 4 categories as follows:

1. wrong medication

2. wrong dose (including dosing regimen, strength, form, concentration, amount);

3. wrong route of administration;

4. wrong patient (i.e. not administered to the intended patient)

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 authorised 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. Reporting Medication Errors

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 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.

8.1.5. Reporting Events of Pregnancy

Occurrences of pregnancy 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 a Serious Adverse Event, the Serious Adverse Event reporting form should be used to report the SAE and the Pregnancy Reporting form should be used to report the pregnancy. Any spontaneous abortion must be captured as a 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 Institutional Review Board (IRB)/Ethics Committee (EC) and/or national or local regulatory authorities.

8.2. PROCEDURE FOR NON-SERIOUS ADVERSE EVENT RECORDING

All non-serious AEs that occur during the designated study period (from signing the inform consent to 14 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 14 days following initial warfarin administration) must be reported to The Medicines Company (MDCO) within 24 hours of awareness of the event using the provided study specific SAE Report Form. The completion and processing of the SAE Report Form (paper) should follow the instructions provided in the SAE Report Form completion guidelines. In addition to completing the SAE Report Form, each SAE must be entered on the appropriate page of the eCRF.

The investigator must assess the causality for each SAE.

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 an SAE that occurs during 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.

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 5 days after the Day 7 visit and 3 days after the Day 14 visit. 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 MDCO 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

The primary objective of this study is to assess the safety and tolerability when a single 1200 mg infusion of oritavancin is given concomitantly in subjects on chronic warfarin with ABSSSI. Statistical methods and data presentation will be described in more detail in the Statistical Analysis Plan (SAP) document.

10.1. SAMPLE SIZE

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

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

10.2. GENERAL STATISTICAL CONSIDERATIONS AND DEFINITIONS

10.2.1. General Statistical Methods

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

10.2.2. Analysis Population

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

10.2.2.1. Intent-to Treat (ITT) Population

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

10.2.2.2. Safety Population

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

10.2.3. Analysis Windows and Baseline

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

10.2.4. Missing Data Handling

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

10.3. STATISTICAL ANALYSES

All summaries will be presented by group.

10.3.1. Demographic and Background Characteristics

Subject demographics and baseline characteristics will be summarized using the safety population.

10.3.2. 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.

10.3.3. Safety Analysis

10.3.3.1. 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 treatment-emergent AE (TEAE) either if it is not present at Baseline or if it is present at Baseline but increased in severity during the treatment period or follow up period.

The number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system organ class, by system organ class and severity, and by system organ class and relationship to oritavancin. If more than 1 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.

10.3.3.2. Clinical Safety Laboratory Tests

Clinical safety laboratory values and changes from Baseline, including prothrombin time (PT)/international normalized ratio (INR), direct and indirect Coombs, Immunoglobulin panel, oritavancin antibody assay, will be summarized descriptively. Clinically significant (CS) values will also be flagged in a listing.

10.3.3.3. 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 Food and Drug Administration (FDA) regulations require all investigators participating in clinical 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, International Conference on Harmonization (ICH) guidelines require that essential documents 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.

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 any data clarification forms received from the Sponsor. 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 study center 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 will not be limited to, 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 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:

Inclusion/Exclusion Criteria deviations:

- Subject is < 18 years of age.
- Subject has a condition, including findings in the medical history or in pre-study assessments that constitutes a risk or a contraindication for the participation in the study or completing the study.
- Subject has a history of hypersensitivity to drugs with a similar chemical structure (i.e. glycopeptide antibiotics) to the investigational product or any of its excipients.

Dosing deviation:

- Subject is given an incorrect dose of oritavancin.

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States 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, as per IRB/EC guidelines, before any study-related procedures (including any pretreatment procedures) are performed. The investigator has both ethical and legal responsibilities to ensure that each subject 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/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/EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and the subject indicates an understanding of the implications of participation, the subject and the investigator (or designee) shall sign the IRB/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. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

This protocol, the written informed consent form, and any materials presented to subjects shall be submitted to the IRB/EC identified with this responsibility. Notification in writing of approval must come from the IRB/EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB/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/EC member, the written approval must indicate such nonparticipation in the voting session. The investigator will submit status reports to the IRB/EC as required by the governing body. The IRB/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/EC all changes in research (protocol amendments) and will not make such changes without IRB/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/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/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 Version 10) 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 investigational new drug oritavancin, the concurrent medications, and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the IRB/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/EC-approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms 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 enrolled 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)	
Institution Name	

16. REFERENCES

16.1. PUBLICATIONS

Dryden MS. Skin and soft tissue infection: microbiology and epidemiology. *Int J Antimicrob Agents*. 2009;34 (Suppl 1):S2-7.

ORBACTIV (oritavancin) [package insert] Parsippany, NJ: The Medicines Company; 2014.

Oritavancin Investigator's Brochure, Edition 10, March 2015.

16.2. STUDY REPORTS

TMC-ORI-12-03: An Open Label Study Evaluating the Effects of a Single Oritavancin Infusion on Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, N-Acetyltransferase-2, and Xanthine Oxidase Activities in Healthy Adults using the Cooperstown 5 + 1 Cocktail.