Oritavancin for the Treatment of Complicated Skin and Skin Structure Infections

FDA Briefing Document for
Anti-Infective Drugs Advisory Committee Meeting
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I. BACKGROUND

Targanta Therapeutics Corp. submitted New Drug Application NDA 22-153, for oritavancin diphosphate on February 7, 2008. Oritavancin is a semisynthetic lipoglycopeptide antibacterial that inhibits cell wall biosynthesis through a similar mechanism of action as vancomycin. Oritavancin is microbiologically active against Gram-positive bacteria, including streptococci, methicillin resistant staphylococci, and some isolates of vancomycin-resistant enterococci. The sponsor's proposed indication for oritavancin is treatment of adults with complicated Skin and Skin Structure Infections (cSSSI) caused by susceptible isolates of the following Gram-positive organisms: *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius* and *S. constellatus*), *Streptococcus dysgalactiae* (includes *S. dysgalactiae* subsp. *equisimilis*) and *Enterococcus faecalis* (vancomycin-susceptible strains only).

The drug product is supplied in single dose vials of lyophilized powder containing 100 mg of oritavancin base. The powder can be reconstituted with 10 mL of sterile water for injection. The product is administered by slow IV infusion over 60 minutes in at least 250 mL of D5W. Because of precipitation, oritavancin should not be diluted in saline solutions, and the catheter should be flushed with D5W before and after oritavancin administration.

The proposed dose regimen for oritavancin is 200 mg (300 mg for patients weighing >110 kg) daily for 3 to 7 days.

This briefing document summarizes the information submitted in the oritavancin NDA. The last section of this document (**VIII**) highlights the expected issues for discussion at the advisory committee.

II. CLINICAL DEVELOPMENT

Oritavancin has been administered to 1540 patients: two Phase 3 clinical studies assessed the efficacy of oritavancin in the treatment of cSSSI (ARRI and ARRD), one Phase 2 study assessed patients with cSSSI and uncomplicated SSSI (ARRL), and two Phase 2 studies assessed patients with bacteremia (ARRM and ARRC).

Descriptions of these Phase 3 studies from which data were drawn to support the proposed labeling of oritavancin are given in Table 2.1 on the following page:

Table 2.1: Overview of Clinical Efficacy Studies

Study	Total N	Description	Treatment Regimens	Treatment n
ARRI	1246	Randomized, double-blind, multicenter, comparator-controlled study in cSSSI patients	Oritavancin IV 200 mg QD (300 mg QD for weight >110 kg) Treatment Duration: 3 to 7 days	831
			Vancomycin IV 15 mg/kg q12 hrs, followed by Cephalexin PO 1000 mg BID Treatment Duration: 10 to 14 days	415
ARRD	517	Randomized, double-blind, multicenter, comparator-controlled study in cSSSI patients	Oritavancin IV 3.0 mg/kg QD (max dose 400 mg) Treatment Duration: 3 to 7 days	169
			Oritavancin IV 1.5 mg/kg QD Treatment Duration: 3 to 7 days	173
			Vancomycin IV 15 mg/kg q12 hrs, followed by Cephalexin PO (one or two 500 mg capsules BID) Treatment Duration: 10 to 14 days	175

III. PHARMACOLOGY-TOXICOLOGY

Oritavancin as a single dose had minimal effects on the CNS, cardiovascular, renal or gastrointestinal systems. In toxicology studies in the dog, where ECGs were measured within 10 minutes of the end of infusion, no changes in ECGs were noted. However, in patch clamp studies in human myocytes, the IC50 values ranged from 1 to 43 µg/mL. Human Cmax values were 27 µg/mL, suggesting that QT prolongation could be an issue in clinical use. Clinical evaluation of the potential for QT prolongation with oritavancin was conducted.

Single dose pharmacokinetics, as well as toxicokinetics, were studied primarily in the rat and dog (with a few studies in the mouse). There were no remarkable differences in pharmacokinetics or toxicokinetics based on gender. No significant plasma accumulation of drug was noted. AUC, whether measured by radiolabel or HPLC, did not differ greatly, suggesting minimal metabolism. Further analysis of plasma and bile for oritavancin products confirmed this conclusion. Infection, neutropenia, and pregnancy did not significantly change the AUCs or Cmax levels of oritavancin in animal models. Clearance decreased over exposure time, leading to longer half-lives (initial half-life for rats on day 1 was generally between 3 and 6 hours, while after multiple days of exposure ranged from 5-10 hours). The half life in dogs was between 8 and 17 hours. In humans, the distribution half-life was approximately 31 hours, with the elimination half-life at 393 hours. The AUC in humans, normalized to a dose of 200 mg, was 139 ± 60 µg·h/mL. Elimination was minimal via the urine and feces (<5% urine, 10-30% fecal). Six weeks after a dose in the rat, approximately 70% of the dose was still associated with the carcass. In the 13 week dog and rat studies, levels of oritavancin in the liver 2 months after the cessation of dosing did not differ significantly from the levels immediately after the end of

treatment. Levels of oritavancin in milk were roughly 1/5th that in maternal plasma. Little distribution into the brain was seen. Highest concentrations of oritavancin were in the liver with significant amounts in the intestine, marrow, kidney, spleen and adrenals. With multiple administrations, liver levels rose at a disproportionate extent. Protein binding in animals was low, but may have been associated with oritavancin binding to glassware. Protein binding in the human was near 90%.

The toxicities seen in the rat and dog were similar. In the dog, emesis, histamine release (manifested as facial reddening, welts, increased blood pressure), and stool changes were noted. In rats, death during the toxicity studies was much more common. Otherwise, both species showed decreases in red blood cells, increases in BUN, AST/ALT, histiocytosis (macrophages) with eosinophilic/acidophilic granules in liver, kidney, spleen, injection site, and lymph nodes. The histiocytosis did not resolve over the 1-2 month recovery period and correlates well with the persistent levels of oritavancin in the liver and carcass. The ratio between the AUC at the NOAEL in the dog (13 week study) and the AUC at the clinical dose in humans was slightly greater than 3.

Oritavancin was negative in the genotoxicity studies conducted (Ames, mouse lymphoma, chromosomal aberrations and mouse micronucleus tests). Oritavancin did not affect fertility in the rat (doses up to 30 mg/kg), fetal development in the rat and rabbit (doses up to 30 and 15 mg/kg respectively), or pre and post-natal development (doses up to 30 mg/kg). Given a human plasma AUC after a 200 mg dose of 139 µg·h/mL, and plasma AUCs in the rat of 340 to 520 µg·h/mL, a margin of safety of approximately 2.4 to 3.7 was seen. Oritavancin was minimally irritating to the eye and to the injection site, but was a moderate irritant to skin. Immunotoxicity studies were contradictory, although oritavancin clearly induced histamine release in the dog.

Nonclinical safety issues relevant to clinical use: The finding of persistent histiocytosis in multiple organs including liver, kidney, spleen, and lymph nodes, as well as at the injection site is troubling. While the renal and hepatic changes can be associated with increases in serum BUN and AST/ALT, the persistence at the injection site may be responsible for phlebitis observed in clinical trials.

IV. MICROBIOLOGY

Antimicrobial Spectrum of Activity

Table 4.1 on the following pages provides *in vitro* susceptibility data for oritavancin against various bacterial isolates.

Table 4.1: Spectrum of Activity of Oritavancin

			Oritavancin µg/mL			
Organism	**Category**	**Total n**	**MIC Range**	**MIC Mode**	**MIC_{50}**	**MIC_{90}**
Staphylococcus aureus	All	5046	≤0.004-4	0.06	0.06	0.12
	Oxacillin S	2526	≤0.004-2	0.06	0.06	0.12
	Oxacillin R	2518	≤0.004-4	0.06	0.06	0.25
	Daptomycin NS[a]	14	0.06-1	1	0.5	1
	Linezolid NS[b]	9	0.06-0.25	NA[f]	NA	NA
	hVISA	11	0.25-1	1	0.5	1
	VISA[c]	13	0.5-1	1	1	1
	VRSA[d]	5	0.12-0.5	NA	NA	NA
Enterococcus faecalis	All	925	≤0.0005-4	0.03	0.03	0.12
	Vancomycin S	862	≤0.0005-0.5	0.03	0.03	0.06
	Vancomycin NS	63	0.015-4	0.5	0.5	1
	Linezolid NS[e]	13	0.015-0.5	0.03	0.03	0.25
	VanA	51	0.03-4	0.5	0.5	1
	VanB	11	0.015-0.12	0.03	0.03	0.06
Streptococcus pyogenes	All	309	0.008-0.5	0.03	0.06	0.25
	Erythromycin S	260	0.008-0.5	0.03	0.06	0.25
	Erythromycin NS	47	0.008-0.25	0.03	0.03	0.12
Streptococcus agalactiae	All	101	0.03-0.5	0.06	0.06	0.12
	Erythromycin S	67	0.03-0.5	0.06	0.06	0.12
	Erythromycin NS	34	0.03-0.5	0.06	0.06	0.25
Streptococcus Group C	All	22	0.001-0.25	0.008	0.008	0.12
	Erythromycin S	16	0.001-0.25	0.002	0.008	0.12
	Erythromycin NS	6	0.008-0.25	NA	NA	NA
Streptococcus Group F	All	5	0.008-0.015	NA	NA	NA
	Erythromycin S	5	0.008-0.015	NA	NA	NA
Streptococcus Group G	All	33	0.008-1	0.25	0.12	0.5
	Erythromycin S	27	0.008-1	0.25	0.25	0.5
	Erythromycin NS	6	0.015-0.12	NA	NA	NA
Viridans *Streptococcus*	All	16	0.004-1	0.12	0.06	0.5
	Erythromycin NS	4	0.004-0.12	NA	NA	NA
	Erythromycin S	8	0.004-0.25	NA	NA	NA

Abbreviations: hVISA = heterointermediately resistant to vancomycin; MIC = minimum inhibitory concentration; NS = not susceptible; R = resistant; S = susceptible; VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus.*
[a] Isolated between 1998 and 2006 (six isolates isolated prior to 2005 and three unknown dates).
[b] Isolated between 2001 and 2006 (five isolates isolated prior to 2005 and one unknown date of isolation).
[c] Isolated between 1997 and 2003 (13 isolates isolated prior to 2005).
[d] Isolated between 2002 and 2005 (four isolates isolated prior to 2005).
[e] Isolated between 2002 and 2005 (eight isolates isolated prior to 2005 and two unknown dates).
[f] Isolated between 2002 and 2005 (eight isolates isolated prior to 2005 and two unknown dates of isolation).
Source: Table 2.5-3 Clinical Overview; NDA 22-153

Table 4.1: Continued

			Oritavancin µg/mL			
Organism	**Category**	**Total n**	**MIC Range**	**MIC Mode**	**MIC_{50}**	**MIC_{90}**
E. faecium	All countries	644	0.06 - 2	1	0.5	2
	Vancomycin S	329	0.06 - 2	0.5	0.5	1
	Vancomycin I	10	0.25 - 1	0.5	0.5	0.5
	Vancomycin R	305	0.06 - 2	1	1	2
E. faecium	United States	342	0.06 - 2	1	2	2
	Vancomycin S	139	0.06 - 2	0.5	1	1
	Vancomycin I	2	0.25 - 0.25	0.25	0.5	0.25
	Vancomycin R	201	0.06 - 2	1	1	1
S. epidermidis	All countries	784	0.015 - 1	0.12	0.12	0.25
	Oxacillin S	183	0.06 - 1	0.12	0.12	0.5
	Oxacillin R	601	0.015 – 0.5	0.12	0.12	0.25
S. epidermidis	United States	718	<0.004 - 1	0.12	0.12	0.25
	Oxacillin S	165	0.008 - 1	0.12	0.12	0.25
	Oxacillin R	553	0.004 - 1	0.12	0.12	0.25
S. haemolyticus	All countries	106	<0.004 - 0.5	0.06	0.06	0.06
	Oxacillin S	19	0.008 - 0.25	0.06	0.03	0.03
	Oxacillin R	87	0.008 - 0.5	0.06	0.06	0.06
S. haemolyticus	United States	36	0.008 - 0.5	0.06	0.06	0.12
	Oxacillin S	11	0.008 - 0.25	0.03	0.03	0.06
	Oxacillin R	25	0.15 - 0.5	0.06	0.06	0.12

Abbreviations: I = Intermediate; MIC = minimum inhibitory concentration; R = resistant; S = susceptible;

Agency's Proposed Target Pathogens for cSSSI Indication
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus pyogenes
Streptococcus agalactiae
Enterococcus faecalis (vancomycin-susceptible isolates only)

Additional Organisms Proposed by Agency Based on In Vitro MICs without Evidence from Clinical Trials
Enterococcus faecium (vancomycin-susceptible and -resistant isolates)
Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)
Staphylococcus haemolyticus

Mechanism of Action
Oritavancin acts at the same site in peptidoglycan biosynthesis as vancomycin. In addition, studies suggest that the chlorophenyl group of oritavancin is a key determinant of biological activity, with a mechanism independent of peptide binding. It is thought that oritavancin may interact directly with immature peptidoglycan and enzymes involved in the transglycosylation step of cell wall biosynthesis.

In vitro, oritavancin appears to be bactericidal against methicillin-susceptible and resistant staphylococci, *S. pyogenes*, *S. agalactiae* and penicillin-susceptible and resistant *S. pneumoniae*.

In the case of enterococci (both *E. faecium* and *E. faecalis*) bactericidal activity is isolate and method dependent. The clinical significance of this bactericidal activity is not known.

Mechanism(s) of Resistance
At least two potential routes exist for oritavancin resistance development; namely, the evolution of current glycopeptide resistance mechanisms (e.g., Van operons) and the VISA-type cell wall thickening mechanism resulting in isolates not carrying any other pre-existing glycopeptide resistance. The oritavancin MIC_{90s} and MIC distributions of the staphylococcal and enterococcal surveillance isolates suggest an absence of cross-resistance with VanA, VanB, or VanC phenotypes and for staphylococci with vancomycin-intermediate (VISA) phenotype.

Cross resistance to oritavancin has not been associated with other antimicrobials including vancomycin.

Interaction of Oritavancin with Other Antimicrobials
In vitro studies have shown that oritavancin is synergistic with gentamicin, linezolid, daptomycin and rifampin against some isolates of *S. aureus* including methicillin- resistant isolates and enterococci including vancomycin-resistant isolates. However, this data is limited in scope. Studies did show that oritavancin was not antagonistic with these antimicrobials.

In Vitro Antimicrobial Susceptibility Testing
Minimal Inhibitory Concentration (MIC) Susceptibility Testing Interpretive Criteria

The determination of oritavancin MICs is done by using cation supplemented Mueller Hinton broth with the addition of 0.002% polysorbate 80. The polysorbate 80 is added to the Mueller Hinton broth to prevent binding of the oritavancin to the plastic of the microtiter trays.

Based on the results obtained from antimicrobial surveillance data, clinical trials and PK/PD analysis, the FDA proposed MIC susceptibility test interpretive criteria are shown in Table 4.2 with the sponsor's proposed MIC interpretive criteria shown in **bold**.

Table 4.2: Susceptibility Interpretive Criteria for Oritavancin[a]

Pathogen	Minimum Inhibitory Concentrations (MIC in mcg/mL)		
	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.25 **(0.25)**	(b)	(b)
Streptococcus pyogenes and S. agalactiae	≤0.25 **(0.5)**	(b)	(b)
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.06 **(0.12)**	(b)	(b)

[a] As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay [1, 2].
[b] The current absence of resistant isolates precludes defining any results other than "susceptible." Isolates yielding test results suggestive of "nonsusceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

Disk Diffusion Susceptibility Testing
Disk diffusion susceptibility testing with oritavancin is not reliable; therefore, disks will not be available for disk diffusion susceptibility testing.

V. CLINICAL PHARMACOLOGY

Summary of Pharmacokinetic Characteristics of Oritavancin
The single-dose pharmacokinetics of oritavancin are linear at doses ranging from 0.05 mg/kg to 10 mg/kg and at fixed doses from 100 to 800 mg. In most subjects, plasma concentrations declined to <11% of the maximum concentration within the first 24 hours. Oritavancin pharmacokinetics were best described with a three compartment model with a mean $t_{½,\alpha}$ of 2.8 hours, a $t_{½,\beta}$ of approximately 33 hours, and a $t_{½,\gamma}$ of 320 hours in Phase 1 studies. Once-daily IV administration of 200 mg for up to 10 days demonstrated that maximum concentration (C_{max}) and $t_{½}$ values were consistent with oritavancin single-dose pharmacokinetics. There was no substantial increase in C_{max} (approximately 30% increase) after 10 days of dosing; however, there was an approximate 2.8 fold increase in minimum concentration (C_{min}), which likely reflects an overall tissue accumulation of oritavancin. Accumulation appeared to be dose-independent over the dose range of 100 mg to 200 mg.

The population pharmacokinetics of oritavancin in patients with uncomplicated or complicated skin and skin structure infections or with bacteremia were similar to those of healthy volunteers, with the exception that plasma clearance was increased in Phase 2 and Phase 3 patients by an average of 30% after accounting for differences in body weight. The pharmacokinetic parameters of oritavancin in the Phase 2 and Phase 3 studies are presented in Table 5.1.

Table 5.1: Pharmacokinetic parameters of oritavancin in Phase 2 and Phase 3 studies

	Phase 2 and Phase 3 studies (N=360)	
	Mean (SD)	Median (Min – Max)
CL (L/h)	0.601 (0.204)	0.584 (0.172 to 1.45)
V_c (L)	7.10 (2.46)	6.79 (1.17 to 18.3)
$T_{1/2,\alpha}$ (h)	2.04 (0.440)	2.04 (0.910 to 4.08)
$T_{1/2,\beta}$ (h)	31.2 (11.4)	29.2 (8.37 to 86.3)
$T_{1/2,\gamma}$ (h)	393 (73.5)	394 (142 to 602)
AUC_{0-24} (mg·h/L)[a]	139 (60.2)	129 (42.2 to 618)
C_{max} (mg/L)[a]	27.3 (12.1)	25.2 (10.2 to 131)
C_{min} (mg/L)[a]	1.90 (1.02)	1.62 (0.463 to 8.07)

[a] AUC_{0-24}, C_{max}, and C_{min} have been normalized to a dose of 200 mg to ease comparisons across groups.

Distribution: Oritavancin is approximately 86% to 90% protein-bound in human plasma. Oritavancin exhibits extensive tissue distribution, and accumulates in macrophages. Based on the population pharmacokinetic analysis of healthy and infected subjects, the central volume of distribution (V_c) in humans is 5.9 L, which is similar to plasma volume. The total volume of distribution ($V_c + V_2 + V_3$) is approximately 100 L, which is indicative of the wide tissue distribution of oritavancin. The penetration of oritavancin into skin blister fluid ($AUC_{0-24blister}$:$AUC_{0-24plasma}$ ratio) was approximately 20% for two different dosing regimens (i.e., 800 mg single dose and 200 mg QD for 3 days).

Metabolism: An *in vitro* human hepatic microsomal metabolism study showed that there was no evidence that oritavancin is metabolized by the cytochrome P450 system. There have been no

radio-labeled studies conducted in humans to confirm that oritavancin does not undergo metabolism. However, no metabolite of oritavancin has been detected in urine or plasma. Based on the extensive animal data and on the structural similarity of oritavancin to other drugs that are minimally metabolized, it appears unlikely that oritavancin is metabolized. No oritavancin metabolites have been identified in plasma or bile from rats, mice, and dogs receiving single IV doses of ^{14}C-oritavancin in nonclinical work.

Excretion: Oritavancin is excreted unchanged in feces and urine. Approximately 5% of the oritavancin dose was excreted in the urine, and ~1% in the feces up to 2 weeks after administration of a single dose of oritavancin. The remainder of the dose remains in phagocytic cells in tissues after 2 weeks.

Effects of Intrinsic Factors on Oritavancin PK
Based on the results of the population pharmacokinetic covariate analysis, age, gender, and race have no clinically significant effect on the PK of oritavancin.

Renal Impairment: Based on the results of the population pharmacokinetic covariate analysis, the concentration-time profiles and the relevant PK parameters (i.e., AUC, C_{max}, C_{min}, $t_{1/2}$, and CL) of oritavancin were not significantly altered in patients with mild (CL_{CR} 50 to ≤80 mL/min), moderate (CL_{CR} 30 to ≤50 mL/min) and severe (CL_{CR} ≤30 mL/min) renal impairment compared to subjects with normal renal function (CL_{CR} >80 mL/min).

Hepatic Impairment: The impact of moderate hepatic impairment (Child-Pugh B) on the pharmacokinetics of a single 800 mg dose of oritavancin was investigated in a clinical study comparing twenty adult subjects with hepatic impairment with 20 matched healthy subjects with normal hepatic function. Oritavancin plasma concentrations were approximately 10-15% lower at every time point in the population of subjects with hepatic impairment. The mean C_{max} and AUC_{0-24} were 18% and 12% lower in subjects with hepatic impairment compared to healthy subjects with normal hepatic function, respectively. Severe hepatic impairment has not been evaluated.

Overall, oritavancin dose adjustments are not needed for patients with mild, moderate, or severe renal impairment; for patients with mild to moderate hepatic impairment; or for other intrinsic factors (age, gender, or race).

Drug Interaction Assessment
In vitro metabolism studies with human liver microsomes demonstrated that the potential order of CYP inhibition was CYP2D6 > CYP3A > CYP1A2 > CYP2C9. Oritavancin inhibited CYP2D6 with a K_i of 12.6 μM (25.1 mg/L) *in vitro* which is near the mean C_{max} achieved in the Phase 3 trials of 27.3 mg/L. Since a concentration of 12.6 μM is physiologically achievable with the proposed dosing regimen, drug-drug interaction studies with the CYP2D6 model substrate desipramine were conducted.

Desipramine: The design of the desipramine drug-drug interaction trial was to evaluate the effect of oritavancin on the steady-state pharmacokinetics of desipramine in 32 subjects. Subjects were

allowed to reach desipramine steady-state (7 days of monotherapy), and were then scheduled to begin receiving 800 mg QD of oritavancin for 14 days while continuing on desipramine. Although the trial was terminated by the sponsor's decision due to the incidence and severity of injection site phlebitis, analysis after one day of oritavancin dosing showed no significant difference in the AUC and C_{max} of either desipramine or its metabolite 2'OH-desipramine.

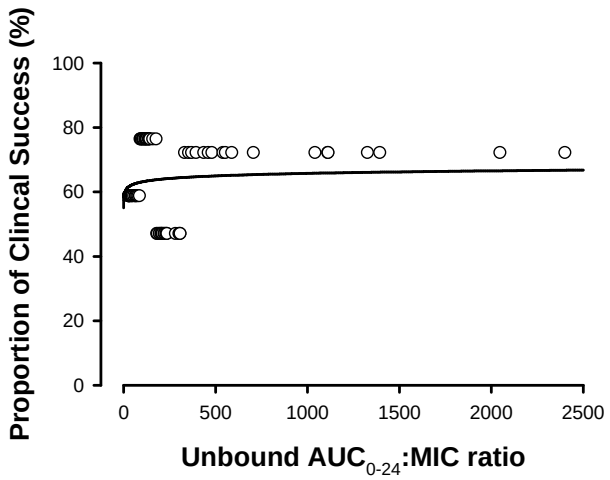
Clinical Dose and Regimen Selection

The proposed clinical dose of oritavancin for the treatment of cSSSI is 200 mg QD for patients under 110 kg, and 300 mg QD for patients over 110 kg. Dose fractionation studies in animal models suggest that the PK-PD parameter best correlated with efficacy is the AUC_{0-24}/MIC. An analysis of nonclinical data by the Agency gives an unbound AUC_{0-24} target of approximately 7 µg·hr/mL for bacterial stasis. The MIC of oritavancin for *S. aureus* in that study was 0.06, leading to a target of approximately 117. The MIC_{90} of oritavancin for *S. aureus* as determined from over 5,000 clinical isolates was 0.12, and the mean unbound AUC_{0-24} in Phase 2 and 3 studies was 17.4 µg·hr/mL, so the mean AUC_{0-24}/MIC_{90} for oritavancin patients would be 145 (17.4/0.12). This result suggests that the proposed dosing regimen exceeds the nonclinical PK-PD target predicted to be required for efficacy in a majority of patients.

Exposure-Response Relationship

The relationship between the probability of clinical success (i.e. clinical cure and clinical improvement) and the unbound AUC_{0-24}:MIC ratio for patients in Study ARRD (1.5 mg/kg or 3.0 mg/kg QD for 3-7 days) is shown in Figure 1. Each open circle corresponds to the individual patient AUC_{0-24}:MIC ratio and the proportion of clinical successes for patients belonging to the corresponding AUC_{0-24}:MIC quartile. The lack of a statistically significant relationship ($p>0.83$) between oritavancin exposure and clinical success is likely due to proportionately high AUC values relative to the MIC values.

Figure 5.1: Relationship between the probability of clinical success and unbound AUC_{0-24}: MIC ratio for patients with cSSSI (Study ARRD: N=69, p=0.95)



Cardiac Repolarization
A double blind, randomized, placebo- and positive-controlled, single dose, parallel design thorough QTc study was performed in healthy adults to evaluate the impact of oritavancin on cardiac repolarization. Two hundred forty subjects were randomized to receive a single dose of oritavancin (200 mg or 800 mg), positive control (moxifloxacin 400 mg PO), or placebo (vehicle). The upper limits of the 90% CI for the baseline-corrected, placebo-corrected QTcF (ΔΔQTcF) were 8.1 msec for oritavancin 200 mg and 5.7 msec for oritavancin 800 mg. In comparison, the largest lower limit of the 90% CI for ΔΔQTcF was 7.8 msec for moxifloxacin. No clinically relevant changes in ECG, including QT interval, were observed in the thorough QTc study.

VI. EFFICACY

Two phase 3 studies were submitted to demonstrate the efficacy of oritavancin for the treatment of complicated skin and skin structure infections. The two studies (ARRI and ARRD) differed in design as described in the following sections.

In order to be enrolled in either Study ARRI or Study ARRD, patients had to meet criteria for the definition of cSSSI and required a minimum level of disease severity. The cSSSI must have been of sufficient severity to anticipate 3 or more days of parenteral antibiotic therapy.

Study Descriptions for ARRI and ARRD:

Study ARRI
Study ARRI was a Phase 3, randomized, double-blind, multicenter study in patients with cSSSI presumed or proven to be caused by Gram-positive bacteria. Patients who met the criteria for enrollment were randomly assigned to receive either 200 mg oritavancin intravenously once daily (300 mg for patients weighing more than 110 kg [242 lbs]) followed by oral placebo, or 15 mg/kg vancomycin intravenously twice daily (or less in patients with reduced creatinine clearance) followed by oral cephalexin (1 gram twice daily) in a ratio of two oritavancin patients to one vancomycin patient. Randomization was stratified by disease category (wound infection, major abscess, or cellulitis). Enrollment of patients with cellulitis was limited to 25% of the population.

The primary objective of Study ARRI was to test the hypothesis that oritavancin is as clinically effective as vancomycin/cephalexin in the treatment of patients with Gram-positive bacterial cSSSI, even when administered for a shorter duration.

Eligible patients included those who were at least 18 years of age, weighed at least 37 kg (81 lbs), and had a cSSSI presumed or proven to be caused by a Gram-positive pathogen.

Patients randomly assigned to oritavancin received intravenous (IV) infusions for a minimum of 3 days and a maximum of 7 days, followed by oral placebo until at least Day 10, but no longer than Day 14. Patients randomly assigned to vancomycin received IV infusions for a minimum of

3 days and a maximum of 7 days, followed by oral cephalexin until at least Day 10, but no longer than Day 14. Patients who did not meet the criteria for IV-to-oral switch or patients with methicillin-resistant Gram-positive bacteria or enterococci isolated at baseline received 10 to 14 days of IV therapy (7 days of oritavancin followed by 3 to 7 days of Dextrose 5% in Water [D5W] or 10 to 14 days of vancomycin). Use of aztreonam and/or metronidazole was allowed for suspected or proven polymicrobial infections that included Gram-negative pathogens and/or anaerobes.

Assessments were conducted at Baseline, Day 3/4, Day of IV-to-Oral Switch/Day 7, First Follow-up (Day 21 to Day 29, Test-of-Cure), and Late Follow-up (Day 39 to Day 46). Assessments included signs and symptoms of cSSSI, vital signs, clinical laboratory tests, and blood and/or infection site cultures as appropriate. Safety data were collected through the Late Follow-up Visit.

Study ARRD

Study ARRD was a Phase 3, randomized, double-blind, multicenter study in patients with cSSSI presumed or proven to be caused by Gram-positive bacteria (Study ARRD). Originally, Study ARRD was developed by Eli Lilly and Company (Lilly) as a Phase 2/3 protocol. After a protocol-defined blinded interim analysis directed the company to continue the study without change, Lilly designated it a Phase 3 study. Since then, Study ARRD has been referred to as a Phase 3 study and is used to support the requested cSSSI indication.

Patients who met the criteria for enrollment into Study ARRD were randomly assigned in a ratio of 1:1:1 to one of the following three treatment groups: oritavancin 1.5 mg/kg IV once daily followed by oral placebo, oritavancin 3.0 mg/kg IV once daily (maximum dose 400 mg) followed by oral placebo, or vancomycin 15 mg/kg IV twice daily (or less in patients with reduced creatinine clearance) followed by oral cephalexin (one or two 500-mg capsules twice daily). As in Study ARRI, randomization was stratified by disease category (wound infection, major abscess, or cellulitis).

The primary objective of Study ARRD was to test the hypothesis that oritavancin is as clinically effective as vancomycin/cephalexin in the treatment of patients with cSSSI.

Eligible patients included those who were at least 18 years of age, weighed at least 37 kg (81 lbs), and had a cSSSI, presumed or proven to be caused by a Gram-positive pathogen.

Patients randomly assigned to receive oritavancin were dosed for a minimum of 3 days and up to a maximum of 7 days, followed by oral placebo until at least Day 10, but no longer than Day 14. Patients randomly assigned to receive vancomycin were dosed for a minimum of 3 days and up to a maximum of 7 days, followed by oral cephalexin until at least Day 10, but no longer than Day 14. Parenteral study drug therapy was limited to a maximum of 7 days, except in patients infected with MRSA. Patients with MRSA randomly assigned to one of the oritavancin treatment groups received 7 days of oritavancin followed by 3 to 7 days of placebo infusions (D5W) and patients randomly assigned to the vancomycin treatment group received 10 to 14 days of vancomycin.

Patients who did not meet the IV-to-oral switch criteria at Day 7 were assigned a clinical response of failure, with the exception of patients with MRSA or those who could not tolerate the IV-to-oral switch. Use of aztreonam and/or metronidazole was allowed for suspected or proven polymicrobial infections that included Gram-negative pathogens and/or anaerobes.

After randomization (Day 1), efficacy was assessed on Day 3/4, at End of IV Therapy, at First Follow-up (which could have occurred between Day 21 to Day 35, Test-of-Cure), and at Late Follow-up (which could have occurred between Day 40 to Day 90). Safety data were collected through the Late Follow-up Visit.

Evaluation Criteria for Efficacy:

Patient Populations
The efficacy data presented for both studies includes results for the following patient subsets: Intent-to-Treat (ITT), Modified Intent-to-Treat (MITT), Clinically Evaluable (CE), and Microbiologically Evaluable (ME) patient populations. The populations used for efficacy analyses are described below.

Intent-to-Treat Population: The ITT population includes all patients who were randomly assigned to a study treatment and who took any amount of study drug. Patients were analyzed in the treatment group according to what treatment they actually received, even if they were randomly assigned to a different study treatment.

Modified Intent-to-Treat Population: The MITT population includes those patients in the ITT subset who also had a Gram-positive sponsor-defined pathogen isolated at Baseline.

Clinically Evaluable Population: The CE population included those patients in the ITT subset who also met the following criteria:

- Enrollment Criteria - met pre specified protocol enrollment criteria,
- Sufficient Therapy - received all active study drug doses during the first 3 days of treatment unless discontinued early due to lack of efficacy,
- Clinical Response - had an SDCO that was not Indeterminate or Missing at the First Follow-up Visit (Test of Cure), or
- Assessment Window - had an SDCO at the Test-of-Cure Visit. Patients who had an SDCO of Failure carried forward from a prior visit were considered to have met the Test-of-Cure Visit window requirement.

Microbiologically Evaluable Population: The ME population includes all patients in the CE patient subset who also had a Gram-positive sponsor-defined pathogen isolated at Baseline. This population was identified as Bacteriologically Evaluable (BE) in both of the Phase 3 study reports.

Definitions of Efficacy Outcome Variables

The efficacy endpoints evaluated for both studies included Investigator-Defined Clinical Outcome (IDCO) and Sponsor-Defined Clinical Outcome (SDCO). These assessments are analyzed at the First Follow-up Visit (Test-of-Cure) which is the primary time point reported in the Summary of Clinical Efficacy. For the original analysis of Study ARRD, clinical outcomes were only determined by the investigator (IDCO) and not by the sponsor (SDCO). For the Summary of Clinical Efficacy, the SDCO was derived, analyzed, and reported for Study ARRD.

Investigator-Defined Clinical Outcome: Clinical response was assessed by the Investigator at each study visit as directed in the individual studies. Each patient was assigned one of the following clinical outcomes: Cure, Improvement, Failure, or Indeterminate.

Sponsor-Defined Clinical Outcome: The Sponsor-Defined Clinical Outcome (SDCO) at each visit is based primarily on the evaluations made by the Investigator at these visits. The SDCO is a calculated variable derived from the Investigator's assessment of outcome as recorded on the case report form (CRF) with conservative review and revision assessed by the sponsor in order to avoid inconsistency among the Investigators in rating clinical responses. The SDCO was defined as follows:

- *Cure:* The SDCO was classified as a Cure if the Investigator's assessment was classified as a Cure and was not superseded by any of the following conditions.
- *Failure:* The SDCO was classified as a Failure if the IDCO was a Failure or any of the following conditions occurred:
    - If a patient was given a systemic antibiotic with activity against Gram-positive pathogens at any time after first dose of study medication for lack of efficacy.
    - If a patient had any procedures performed to treat the primary study condition, which started >48 hours after start of study medication. Procedures, whether for primary study condition or not, that were performed within 48 hours after first dose of study drug and repeated after the 48-hour window, were considered planned and did not cause a patient to be assigned a SDCO of Failure.
    - If the Investigator's assessment was either Missing or Indeterminate at a visit, an assessment of Failure was made at that visit if the patient died before or at the time of the visit.
    - If a patient failed at a previous visit due to any of the reasons in the preceding bullet points, then the Failure was carried forward to all subsequent visits, except Late Follow-up.

- *Indeterminate:* The SDCO was classified as indeterminate if a clinical response could not be evaluated due to any of the following situations.

    - If a patient received a systemic antibiotic with activity against Gram-positive pathogens for an infection before the start of study medication and continued to use that antibiotic during treatment.

- If a patient received a systemic antibiotic with activity against Gram-positive pathogens other than study drug for 2 or more days during the study for an infection other than the primary study indication.
- If a patient discontinued study drug due to an adverse event.

Summary of Results of Individual Studies:

The following sections provide overviews of the individual results of the two Phase 3 cSSSI studies (ARRI and ARRD).

The primary analysis for the primary efficacy endpoint in both Study ARRI and Study ARRD was performed in the ITT and clinical evaluable population (CE) as co-primary populations. The missing or indeterminate values were considered as failures in the ITT co-primary analysis.

Study ARRI

Baseline patient demographic data for Study ARRI for the ITT and CE populations are summarized as follows:

Table 6.1: Baseline Patient Demographics (study ARRI)

Demographic	ITT		CE	
	Oritavancin N=831 n (%)	**Vancomycin N=415 n (%)**	**Oritavancin N=675 n (%)**	**Vancomycin N=328 n (%)**
Sex				
Male	463 (55.7)	230 (55.4)	370 (54.8)	176 (53.7)
Female	368 (44.3)	185 (44.6)	305 (45.2)	152 (46.3)
Ethnic Origin				
Caucasian	413 (49.7)	208 (50.1)	351 (52.0)	172 (52.4)
African Descent	174 (20.9)	87 (21.0)	142 (21.0)	69 (21.0)
Hispanic	119 (14.3)	54 (13.0)	87 (12.9)	34 (10.4)
Other	125 (15.0)	66 (15.9)	95 (14.1)	53 (16.2)
Age (years)				
Mean (+SD)	48.0 (16.95)	48.7 (16.77)	48.2 (17.05)	49.4 (16.32)
Age Groups				
<45 years	372 (44.8)	184 (44.3)	299 (44.3)	139 (42.4)
>45 – <65 years	307 (36.9)	152 (36.6)	247 (36.6)	123 (37.5)
>65 – <75 years	97 (11.7)	46 (11.1)	82 (12.1)	42 (12.8)
>75 years	55 (6.6)	33 (8.0)	47 (7.0)	24 (7.3)
Weight				
<110 kg	773 (93.0)	373 (89.9)	625 (92.6)	297 (90.5)
>110 kg	58 (7.0)	42 (10.1)	50 (7.4)	31 (9.5)
Region[b]				
US/Canada	241 (29.0)	119 (28.7)	170 (25.2)	79 (24.1)
Latin America	88 (10.6)	42 (10.1)	69 (10.2)	31 (9.5)
Europe	244 (29.4)	123 (29.6)	224 (33.2)	110 (33.5)
Other	258 (31.0)	131 (31.6)	212 (31.4)	108 (32.9)

Abbreviations: CE = clinically evaluable; ITT = intent-to-treat; N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; Van = vancomycin.

[a] Regions: Latin America = Argentina, Brazil, Chile, and Mexico; Europe = Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Italy, Russia, Slovakia, Spain, and United Kingdom; Other = Australia, India, Malaysia, Singapore, South Africa, and Taiwan.

Source: **Sponsor's Table 2.7.3-4**

The baseline disease categories and characteristics for the ITT and CE patient populations are for study ARRI is summarized as follows:

Table 6.2: Baseline Disease Categories and Characteristic (Study ARRI)

	ITT		CE	
	Oritavancin n (%)	**Vancomycin n (%)**	**Oritavancin n (%)**	**Vancomycin n (%)**
ARRI				
N	831	415	675	328
Disease Category				
Wound Infection	265 (31.9)	139 (33.5)	228 (33.8)	115 (35.1)
Major Abscess	366 (44.0)	177 (42.7)	279 (41.3)	129 (39.3)
Cellulitis	200 (24.1)	99 (23.9)	168 (24.9)	84 (25.6)
Deepest Tissue Involved				
Skin	26 (3.1)	19 (4.6)	21 (3.1)	
Subcutaneous	432 (52.0)	215 (51.8)	357 (52.9)	17 (5.2)
Muscle	94 (11.3)	48 (11.6)	68 (10.1)	171 (52.1)
Fascial Plane	273 (32.9)	131 (31.6)	225 (33.3)	34 (10.4)
Bone	0	0	0	104 (31.7)
Other	6 (0.7)	2 (0.5)	4 (0.6)	0 2 (0.6)
Duration of Disease				
Mean (+SD) - Days	5.4 (5.20)	6.0 (8.96)	5.1 (4.98)	5.8 (8.99)

Source: Sponsor's Table 2.7.3-7

A summary of primary reasons for discontinuation of study drug in the ITT and CE co-primary populations are as follows:

Table 6.3: Primary Reasons for Discontinuation of Study Drug (Study ARRI)

	ITT		CE	
	Oritavancin n (%)	**Vancomycin n (%)**	**Oritavancin n (%)**	**Vancomycin n (%)**
ARRI				
N	831	415	675	328
Discontinued	95 (11.4)	52 (12.5)	63 (9.3)	41 (12.5)
Lack of Efficacy	32 (3.9)	12 (2.9)	28 (4.1)	12 (3.7)
Death	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Adverse Event	16 (1.9)	20 (4.8)	14 (2.1)	18 (5.5)
Other	47 (5.7)	19 (4.6)	21 (3.1)	10 (3.0)

Sponsor's table (edited)

Statistical Methodology

Primary Efficacy Analysis of the Primary Efficacy Endpoint in Study ARRI

In Study ARRI, the primary efficacy endpoint was the Sponsor-Defined Clinical Outcome (SDCO) at the First Follow-up Visit (TOC visit).

The primary efficacy analysis was to test if the proportions of patients who had a successful SDCO at the TOC visit in the oritavancin-treated patients would not be lower than the SDCO in the vancomycin-treated patients by a non-inferiority margin (NI) of 10% in the ITT and CE co-primary populations. The testing procedure was based on a two-sided 95% CI for the difference of success rates between the treatment groups (oritavancin minus vancomycin). The method of

constructing the 95% CI was based on a normal approximation to the binomial distribution. If the lower limit of the 95% CI was above -10%, the oritavancin treatment would demonstrate non-inferiority to vancomycin treatment based on a margin of 10%.

Study Results:
For the primary efficacy endpoint of sponsor-defined clinical outcome, the success rates in the Intent-to-treat (ITT) population at the TOC Visit were 594/831 (71.5%) in the oritavancin group and 284/415 (68.4%) in the vancomycin group; and the rate difference and the corresponding 95% CI between the treatment groups were 3% (-2.4%, 8.5%). The clinical cure rate in the Clinically Evaluable (co-primary population) in the oritavancin treated patients was 78.5% (530/675) as compared with 75.9% (249/328) in the vancomycin treated patients and the treatment difference and the corresponding 95% CI were; 2.6%(-3.0%, 8.2%) respectively.

The success rates in the modified intent-to-treat (MITT) population at the TOC Visit were 70.9% (398/561) in the oritavancin group and 68.6% (205/299) in the vancomycin group; and the rate difference and the 95% CI between the treatment groups were 2.4% (95% CI: -4.1%, 8.8%). The success rates of the sponsor-defined clinical outcome in the microbiologically evaluable population (ME) at TOC Visit were 78.9% (362/459) in the oritavancin group and 76.8% (182/237) in the vancomycin group; and the rate difference and the 95% CI between the treatment groups were 2.1% (95% CI: -4.5%, 8.6%).

Table 6.4: Success/Cure Rates at Test-of-Cure Visit for Study ARRI

Efficacy Endpoint /Patient Population	**Oritavancin n/N (%)**	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin**
Study ARRI			**(95% CI)**
Sponsor-Defined Clinical Outcome			
ITT	594/831 (71.5)	284/415 (68.4)	3.0 (-2.4, 8.5)
MITT	398/561 (70.9)	205/299 (68.6)	2.4 (-4.1, 8.8)
ME	362/459 (78.9)	182/237 (76.8)	2.1 (-4.5, 8.6)
CE	530/675 (78.5)	249/328 (75.9)	2.6 (-3.0, 8.2)
Investigator-Defined Clinical Outcome			
ITT	608/831 (73.2)	291/415 (70.1)	3.0 (-2.3, 8.4)
MITT	407/561 (72.5)	211/299 (70.6)	2.0 (-4.4, 8.3)
ME	363/459 (79.1)	187/237 (78.9)	0.2 (-6.2, 6.6)
CE	534/675 (79.1)	254/328 (77.4)	1.7 (-3.8, 7.1)

Missing data and indeterminate values were treated as failures. Data source: Sponsor's NDA efficacy-information-amendment.
ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CE = Clinically Evaluable; ME = Microbiologically Evaluable; N = total number of patients; CI = Confidence Interval.; All confidence intervals were calculated based on a normal approximation to the binomial distribution.

Table 6.5 illustrates the clinical outcomes for patients with the identified baseline pathogens for the MITT population of Study ARRI. Note that for subjects from whom MRSA was isolated, a lower percentage of oritavancin-treated subjects met the protocol definition of success.

Table 6.5: Sponsor-defined Clinical Outcomes for Patients with Identified Baseline Pathogens (MITT Population: Study ARRI)

Organism	Oritavancin n/N (%)	Vancomycin n/N (%)
***Staphylococcus aureus* (All)** Sponsor-Defined Clinical Outcome	303/429 (70.6%)	158/222 (71.2%)
Methicillin-sensitive (MSSA) Sponsor-Defined Clinical Outcome	219/286 (76.6%)	116/156 (74.4%)
Methicillin-resistant (MRSA) Sponsor-Defined Clinical Outcome	66/118 (55.9%)	36/53 (67.9%)
Streptococcus pyogenes Sponsor-Defined Clinical Outcome	74/96 (77.1%)	36/62 (58.1%)
Streptococcus agalactiae Sponsor-Defined Clinical Outcome	20/35 (57.1%)	6/8 (75.0%)
***Streptococcus anginosus* group**[a] Sponsor-Defined Clinical Outcome	25/38 (65.8%)	13/19 (68.4%)
Streptococcus dysgalactiae[b] Sponsor-Defined Clinical Outcome	8/12 (66.7%)	2/5 (40.0%)
Other *Streptococcus* spp[c] Sponsor-Defined Clinical Outcome	21/28 (75.0%)	12/21 (57.1%)
Enterococcus faecalis Sponsor-Defined Clinical Outcome	23/34 (67.6%)	16/24 (66.7%)
Other *Enterococcus* spp[d] Sponsor-Defined Clinical Outcome	6/12 (50.0%)	3/7 (42.9%)
Enterococcus faecalis Sponsor-Defined Clinical Outcome	23/34 (67.6%)	16/24 (66.7%)

a Streptococcus anginosus group includes Streptococcus anginosus, intermedius, and constellatus
b Streptococcus dysgalactiae includes Streptococcus dysgalactiae and dysgalactiae subsp. Equisimilis
c Other Streptococcus spp includes Streptococcus bovis, equinus, oralis, parasanguinis, salivarius, sanguinis, and unspeciated Streptococcus
d Other Enterococcus spp includes Enterococcus avium, casseliflavus, faecium, hirae, and unspeciated Enterococcus
Missing and Indeterminate Treated as Failures.

Study ARRD

Baseline patient demographic data for Study ARRD for the ITT and CE populations are summarized as follows:

Table 6.6: Baseline Patient Demographics (Study ARRD)

	ITT			CE		
	Oritavancin		Vancomycin	Oritavancin		Vancomycin
	1.5 mg/kg N=173 n (%)	3.0 mg/kg N=169 n (%)	Van N=175 n (%)	1.5 mg/kg N=136 n (%)	3.0 mg/kg N=128 n (%)	Van N=130 n (%)
Sex						
Male	109 (63.0)	106 (62.7)	116 (66.3)	82 (60.3)	74 (57.8)	87 (66.9)
Female	64 (37.0)	63 (37.3)	59 (33.7)	54 (39.7)	54 (42.2)	43 (33.1)
Ethnic Origin						
Caucasian	97 (56.1)	95 (56.2)	106 (60.6)	75 (55.1)	72 (56.3)	82 (63.1)
African Descent	21 (12.1)	23 (13.6)	13 (7.4)	15 (11.0)	14 (10.9)	10 (7.7)
Hispanic	49 (28.3)	49 (29.0)	51 (29.1)	41 (30.1)	41 (32.0)	34 (26.2)
Other	6 (3.5)	2 (1.2)	5 (2.9)	5 (3.7)	1 (0.8)	4 (3.1)
Age (years) Mean (±SD)	48.6 (15.60)	49.3 (15.74)	48.6 (16.29)	48.3 (14.56)	50.6 (15.58)	48.3 (16.17)
Age Groups						
<45 years	72 (41.6)	78 (46.2)	82 (46.9)	53 (39.0)	54 (42.2)	61 (46.9)
>45 – <65 years	68 (39.3)	60 (35.5)	62 (35.4)	60 (44.1)	51 (39.8)	48 (36.9)
>65 – <75 years	21 (12.1)	22 (13.0)	19 (10.9)	18 (13.2)	15 (11.7)	14 (10.8)
>75 years	12 (6.9)	9 (5.3)	12 (6.9)	5 (3.7)	8 (6.3)	7 (5.4)
Weight						
<110 kg	151 (87.3)	147 (87.0)	148 (85.1)[a]	118 (86.6)	111 (86.7)	109 (84.5)[a]
>110 kg	22 (12.7)	22 (13.0)	26 (14.9)	18 (13.2)	17 (13.3)	20 (15.5)
Region[b]						
US/Canada	123 (71.1)	116 (68.6)	118 (67.4)	98 (72.1)	83 (64.8)	90 (69.2)
Latin America	37 (21.4)	35 (20.7)	44 (25.1)	30 (22.1)	30 (23.4)	34 (26.2)
Europe	13 (7.5)	18 (10.7)	13 (7.4)	8 (5.9)	15 (11.7)	6 (4.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CE = clinically evaluable; ILDR = intended label dose range; ITT = intent-to-treat; n = number of patients; N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; Van = vancomycin.

[a] One patient in the vancomycin group did not have weight collected at Baseline; therefore, the N for the ITT Van group is 174 and the N for the CE vancomycin group is 129.

[b] Regions: Latin America = Argentina, Mexico, and Puerto Rico; Europe = Germany and Spain.

Source: Sponsor's Table 2.7.3-5

The baseline disease categories and characteristics for the ITT and CE patient populations are for study ARRD is summarized in Table 6.7, as follows:

Table 6.7: Baseline Disease Categories and Characteristic

	ITT			CE		
	Oritavancin n (%)		Vancomycin n (%)	Oritavancin n (%)		Vancomycin n (%)
ARRD	**1.5 mg/kg**	**3.0 mg/kg**		**1.5 mg/kg**	**3.0 mg/kg**	
N	173	169	175	136	128	130
Disease Category						
Wound Infection	35 (20.2)	34 (20.1)	38 (21.7)	28 (20.6)	26 (20.3)	30 (23.1)
Major Abscess	66 (38.2)	61 (36.1)	64 (36.6)	50 (36.8)	47 (36.7)	48 (36.9)
Cellulitis	72 (41.6)	74 (43.8)	73 (41.7)	58 (42.6)	55 (43.0)	52 (40.0)
Deepest Tissue Involved						
Skin	14 (8.1)	11 (6.5)	12 (6.9)	11 (8.1)	9 (7.0)	9 (6.9)
Subcutaneous	107 (61.8)	111 (65.7)	110 62.9)	87 (64.0)	87 (68.0)	80 (61.5)
Muscle	9 (5.2)	11 (6.5)	19 (10.9)	5 (3.7)	8 (6.3)	15 (11.5)
Fascial Plane	38 (22.0)	33 (19.5)	31 (17.7)	30 (22.1)	23 (18.0)	25 (19.2)
Bone	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)
Other	3 (1.7)	2 (1.2)	2 (1.1)	2 (1.5)	1 (0.8)	1 (0.8)
Duration of Disease						
Mean (+SD) - Days	6.4 (9.22)	4.8 (3.17)	4.9 (4.27)	6.3 (9.40)	4.9 (3.35)	4.9 (4.74)

Source: Sponsor's Table 2.7.3-7

A summary of primary reasons for discontinuation of study drug in the ITT and CE co-primary populations are as follows:

Table 6.8: Primary Reasons for Discontinuation of Study Drug (Study ARRD)

	ITT			CE		
	Oritavancin n (%)		Vancomycin n (%)	Oritavancin n (%)		Vancomycin n (%)
ARRD	**1.5 mg/kg**	**3.0 mg/kg**		**1.5 mg/kg**	**3.0 mg/kg**	
N	173	169	175	136	128	130
Discontinued	47 (27.2)	53 (31.4)	48 (27.4)	22 (16.2)	23 (18.0)	17 (13.1)
Lack of Efficacy	8 (4.6)	12 (7.1)	6 (3.4)	8 (5.9)	11 (8.6)	5 (3.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event	6 (3.5)	13 (7.7)	13 (7.4)	0 (0.0)	4 (3.1)	3 (2.3)
Other	33 (19.1)	28 (16.6)	29 (16.6)	14 (10.3)	8 (6.3)	9 (6.9)

Primary Efficacy Analysis of the Primary Efficacy Endpoint in Study ARRD

In Study ARRD, the primary efficacy endpoint was the Investigator-Defined Clinical Outcome (IDCO) at the TOC Visit. The efficacy analysis methods used in this study were the same as in Study ARRD except for the non-inferiority margin. The non-inferiority margin (NI) used in Study ARRD was 15%.

Although two interim analyses were planned, no adjustment to the nominal 0.05 alpha level at the final analysis was made. The sponsor's justification for not adjusting alpha was due to the fact that the trial would not be stopped at either interim analysis for superior performance of

either of the oritavancin treatment groups, and furthermore, that there was an increased probability of making a Type II error, that is, stopping the trial for lack of demonstration of therapeutic equivalence at the interim analysis when, in truth, the treatments were equivalent.

Multiplicity Issues in the primary analysis:

Study ARRD compared the efficacy results of the two oritavancin regimens with the oritavancin treatment. Multiplicity could be an issue if the intent of this study was to determine which or both the two oritavancin regimens were non-inferior to the vancomycin treatment. Simply calculating the 95% CI for the success rate differences between treatment groups, as was done in the sponsor's clinical study report, will not address this potential multiplicity issue. Thus, the 97.5% CI were calculated for the rate differences to adjust for this potential multiplicity issue.

Study Results:
The original primary efficacy outcome variable for Study ARRD was the Clinical Response (Investigator-Defined Clinical Outcome) at the First Follow-Up Visit (Test-of-Cure). Although clinical outcomes were not determined by the sponsor (SDCO) in the original analysis of Study ARRD, they were derived for the Summary of Clinical Efficacy.

For the primary efficacy endpoint of the investigator-defined clinical outcome, the success rates in the ITT population at the TOC Visit were 58.4% (101/173) in the oritavancin 1.5 mg/kg group, 57.4% (97/169) in the oritavancin 3.0 mg/kg group, and 60.6% (106/175) in the vancomycin group. The differences in cure rates and the 97.5% CI comparing the two oritavancin groups with the vancomycin group were -2.2% (97.5% CI: -14%, 9.6%) and -3.2 (97.5% CI: -13.6%, 7.2%), respectively. The success rates of the investigator-defined clinical outcome in the CE population (co-primary) at the TOC Visit were 73.5% (100/136) in the oritavancin 1.5 mg/kg group, 74.2% (95/128) in the oritavancin 3.0 mg/kg group, and 76.9% (100/130) in the vancomycin group. The rate differences and the 97.5% CI comparing the two oritavancin groups with the vancomycin group were -3.4% (97.5% CI: -15.2%, 8.5%) and -2.7% (97.5% CI: -14.7%, 9.3%), respectively.

Similarly, the success rates based on the investigator-defined clinical outcome in the MITT population at the TOC Visit were 54.5% (55/101) in the oritavancin 1.5 mg/kg group, 59.8% (58/97) in the oritavancin 3.0 mg/kg group, and 59.3% (64/108) in the vancomycin group. The differences in cure rates were -3.4% (97.5% CI: -15.2%, 8.5%) and 0.5 (97.5% CI: -14.9%, 15.9%), respectively, for comparing the two oritavancin groups with the vancomycin group. The success rates of the investigator-defined clinical outcome in the ME population at the TOC Visit were 69.6% (55/79) in the oritavancin 1.5 mg/kg group, 75.3% (58/77) in the oritavancin 3.0 mg/kg group, and 73.5% (61/83) in the vancomycin group. The rate differences and the 97.5% CI were -3.9% (97.5% CI: -19.8%, 12%) and 1.8% (97.5% CI: -13.6%, 17.3%), respectively, for comparing the two oritavancin groups with the vancomycin group.

The clinical cure (based on sponsor-defined outcome) was also assessed since it was the primary endpoint in Study ARRI. However, the results and conclusions based on this endpoint were consistent with investigator-defined clinical outcome in study ARRD.

Table 6.9: Success/Cure Rates at Test-of-Cure Visit for Study ARRD

Efficacy Endpoint /Patient Population	Oritavancin n/N (%)		Vancomycin n/N (%)	Difference between Oritavancin and Vancomycin	
Study ARRD	**1.5 mg/kg**	**3.0 mg/kg**		**1.5 mg/kg (97.5% CI)**	**3.0 mg/kg (97.5% CI)**
Sponsor-Defined Clinical Outcome					
ITT	98/ 173 (56.6)	95/169 (56.2)	101/175 (57.7)	-1.1 (-13, 10.8)	-1.5 (-13.5, 10.5)
MITT	53/101 (52.5)	57/ 97 (58.8)	63/108 (58.3)	-5.9 (-21.3, 9.5)	0.4 (-15.0, 15.9)
ME	53/ 79 (67.1)	57/ 77 (74.0)	61/ 83 (73.5)	-6.4 (-22.5, 9.7)	0.5 (-15.1, 16.1)
CE	98/136 (72.1)	94/128 (73.4)	98/130 (75.4)	-3.3 (-15.4, 8.8)	-1.9 (-14.1, 10.2)
Investigator-Defined Clinical Outcome					
ITT	101/173 (58.4)	97/169 (57.4)	106/175 (60.6)	-2.2 (-14, 9.6)	-3.2 (-15.1, 8.7)
MITT	55/101 (54.5)	58/97 (59.8)	64/108 (59.3)	-4.8 (-20.2, 10.5)	0.5 (-14.9, 15.9)
ME	55/ 79 (69.6)	58/77 (75.3)	61/ 83 (73.5)	-3.9 (-19.8, 12)	1.8 (-13.6, 17.3)
CE	100/136 (73.5)	95/128 (74.2)	100/130 (76.9)	-3.4 (-15.2, 8.5)	-2.7 (-14.7, 9.3)

Missing data and indeterminate values were treated as failures. Data source: Sponsor's NDA efficacy-information-amendment.
ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CE = Clinically Evaluable; ME = Microbiologically Evaluable; N = total number of patients; CI = Confidence Interval.
All confidence intervals were calculated based on a normal approximation to the binomial distribution. For Study ARRD, the 97.5% confidence intervals were calculated to adjust for multiplicity arising from multiple comparisons (two test drug doses vs. active control).

In general, the outcomes for oritavancin and vancomycin/cephalexin patients with cSSSI were comparable in subgroup analyses for age, gender, ethnic group, region, and disease category.

Table 6.10 shows the clinical outcomes by baseline pathogen for the MITT population of Study ARRD. Note that there were few subjects from whom certain pathogens were isolated, such as *S. agalactiae, E. faecalis, and other Enterococcus species*, which limits the ability to make definitive conclusions regarding these organisms.

Table 6.10: Sponsor-defined Clinical Outcomes for Patients with Identified Baseline Pathogens (MITT Population: Study ARRD)

Organism	ORI 1.5 mg/d n/N (%)	ORI 3.0 mg/d n/N (%)	Vancomycin n/N (%)
***Staphylococcus aureus* (All)** Sponsor-Defined Clinical Outcome	36/68 (52.9%)	34/63 (54.0%)	37/65 (56.9%)
Methicillin-sensitive (MSSA) Sponsor-Defined Clinical Outcome	22/37 (59.5%)	22/43 (51.2%)	26/47 (55.3%)
Methicillin-resistant (MRSA) Sponsor-Defined Clinical Outcome	8/20 (40.0%)	10/16 (62.5%)	8/14 (57.1%)
Streptococcus pyogenes Sponsor-Defined Clinical Outcome	5/14 (35.7%)	9/14 (64.3%)	11/20 (55.0%)
Streptococcus agalactiae Sponsor-Defined Clinical Outcome	2/5 (40.0%)	6/8 (75.0%)	7/8 (87.5%)
***Streptococcus anginosus* group**[a] Sponsor-Defined Clinical Outcome	7/14 (50.0%)	13/15 (86.7%)	11/23 (47.8%)
Other *Streptococcus* spp[c] Sponsor-Defined Clinical Outcome	7/13 (53.8%)	9/12 (75.0%)	8/14 (57.1%)
Enterococcus faecalis Sponsor-Defined Clinical Outcome	6/9 (66.7%)	3/5 (60.0%)	4/6 (66.7%)
Other *Enterococcus* spp[d] Sponsor-Defined Clinical Outcome	1/2 (50.0%)	1/3 (33.3%)	1/2 (50.0%)

a Streptococcus anginosus group includes Streptococcus anginosus, intermedius, and constellatus
b Streptococcus dysgalactiae includes Streptococcus dysgalactiae and dysgalactiae subsp. Equisimilis
c Other Streptococcus spp includes Streptococcus bovis, equinus, oralis, parasanguinis, salivarius, sanguinis, and unspeciated Streptococcus
d Other Enterococcus spp includes Enterococcus avium, casseliflavus, faecium, hirae, and unspeciated Enterococcus
Missing and Indeterminate Treated as Failure.

VII. SAFETY

The NDA database included 2176 individuals who received either oritavancin or a comparator. Of these, 1540 individuals (225 subjects and 1315 patients) received oritavancin and 636 (12 subjects and 624 patients) received vancomycin. In the two phase 3 studies (ARRI and ARRD), there were 1173 oritavancin-treated patients, and 590 vancomycin-treated patients. In study ARRI, 831 patients received oritavancin and 415 patients received vancomycin. 342 patients received oritavancin and 175 patients received vancomycin. In the oritavancin group, 173 patients received oritavancin 1.5 mg/kg and 169 patients received oritavancin 3.0 mg/kg.

Exposure

For step down therapy from IV to oral treatment, the oritavancin group received oral placebo and the vancomycin group received oral cephalexin. Due to this study treatment design, the total active therapy for the oritavancin group only includes the active IV treatment, whereas the total active therapy for the vancomycin group includes both the IV vancomycin treatment plus the oral step down to cephalexin. The mean duration of the total active dosing in the oritavancin-treated patients was 5.2 days as compared to 11.3 days in the vancomycin-treated patients in the CE population. In Study ARRI and Study ARRD combined, the mean duration of active IV dosing in the CE population was approximately 1 day shorter for oritavancin-treated patients as compared to the vancomycin-treated patients (5.2 days for oritavancin and 6.1 days for vancomycin).

Deaths
A total of 74 deaths (66 during study and 8 post study) occurred among oritavancin- and vancomycin-treated patients in the cSSSI and Phase 2 ITT populations. Two of the 74 (2.7%) deaths were investigator-assessed as related to study drug. One occurred post study in an oritavancin-treated cSSSI patient (multiple organ failure) and the other occurred during study in a vancomycin-treated cSSSI patient (ventricular fibrillation). Overall, the vast majority of deaths were found to be related to the underlying medical conditions of the patients.

In study ARRI, there were 16 oritavancin-treated patients and 9 vancomycin-treated patients who died during or soon after their participation in the study. Mortality rates were comparable for both treatment groups in this study. Table 7.1 provides a list of the patient deaths and adverse events associated with their fatal outcome. In the majority of cases, death occurred days to weeks after study drug had been completed. The investigator considered death to be possibly related to study drug treatment in only one case. This was a vancomycin-treated patient (41003) with a history of arrhythmia and pacemaker placement, who developed ventricular fibrillation and cardiac arrest on the fourth day of treatment.

Table 7.1 Patient Deaths in Study ARRI

Patient ID Number	Age/Gender/ Race	Relative Day of Death	Adverse Event
Oritavancin (16/831, 1.9%)			
5004	69/F/CA	15	Bacteremia
5007	47/M/HP	12	Septic Shock
6002	64/M/CA	29	Sepsis NOS
30001	87/M/CA	11	Acute Pulmonary Edema
56003	85/M/HP	17	Cardio-respiratory Arrest
65007	68/M/CA	25	Intra-abdominal Hemorrhage NOS
130002	26/F/HP	25	Sepsis NOS
151003	65/F/CA	12	Myocardial Infarction
151021	73/M/CA	5	Cardiac Failure NOS
163001	41/M/CA	68	*C. difficile* Diarrhea/Gram-negative Sepsis
166033	55/F/AF	6	Pulmonary Embolism
167008	24/M/AF	22	Sepsis NOS
167024	66/M/AF	54	Maxillary Carcinoma
167042	24/F/AF	20	Death (Murder)
234020	84/F/HP	16	Respiratory Arrest
234027	35/F/HP	23	Airway Obstruction NOS
Vancomycin (9/415, 2.2%)			
41003*	67/F/O	5	Ventricular Fibrillation
65004	78/F/CA	48	Cardiac Insufficiency
117002	63/M/CA	20	Gastrointestinal Infection NOS/ Sepsis NOS
126003	59/F/EA	10	Pneumonia NOS
151022	75/F/CA	12	Ischemic Stroke NOS
158014	56/F/CA	14	Cardio-respiratory Arrest
162024	72/F/CA	31	Respiratory Distress
199001	81/F/EA	44	Aspiration Pneumonia
234094	59/M/CA	37	Cardiac Arrest

NOS = not otherwise specified
Race: CA = Caucasian; HP = Hispanic; AF = African Descent; O = Other; EA = East/Southeast Asian
Note: Relative day = Date of death - Date of first IV infusion of study medication +1.
* AE considered possibly related to treatment by the investigator

In study ARRD, there were 7 deaths in oritavancin-treated patients and 5 deaths in vancomycin-treated patients. Mortality rates were comparable for both treatment groups in this study. Table 7.2 provides a list of the patient deaths and adverse events associated with their fatal outcome. The investigator could not exclude relationship to study drug for one patient. An oritavancin-treated patient (4205) who received 6 days of study drug for peri-umbilical abscess, developed candidal sepsis and pneumonia on day 11. His subsequent treatment course included relapse of his abscess, anti-fungal treatment, additional antibiotic treatments for pneumonia/sepsis, and acute respiratory distress syndrome. He died on day 53 due to multi-organ failure.

Table 7.2 Patient Deaths in Study ARRD

Patient ID Number	Age/Gender/Race	Relative Day of Death	Adverse Event
Oritavancin 1.5 mg/kg (3/173, 1.7%)			
2871	33/M/AF	44	Cardiac Arrest
7043	82/F/CA	11	Cardiac Arrest
7045	90/M/CA	30	Acinetobacter Sepsis/Cardiac Arrest
Oritavancin 3 mg/kg (4/169, 2.4%)			
2864	39/F/HP	2	Idioventricular Rhythm/Medication Error
3283	66/F/AF	43	Bowel Obstruction/Sepsis/Cardiac Arrest
4205*	65/M/CA	53	Multiple Organ Failure
7200	71/F/HP	2	Septic Shock
Vancomycin (5/175, 2.9%)			
7013	80/M/CA	47	Respiratory Failure
7025	67/F/HP	17	Non-Hodgkin's Lymphoma
7060	43/F/HP	8	Cardiac Arrest
7218	64/M/HP	19	ARDS/Cardiac Arrest
9122	59/M/HP	11	Pulmonary Embolism

Race: CA = Caucasian; HP = Hispanic; AF = African Descent; O = Other; EA = East/Southeast Asian
Note: Relative day = Date of death - Date of first IV infusion of study medication +1.
* AE considered possibly related to treatment by the investigator

Serious Adverse Events

Comparable percentages of oritavancin- and vancomycin-treated cSSSI patients had at least one serious adverse event (SAE) during the Phase 3 studies (9.1% [107 of 1173 for oritavancin]; 11.4% [67 of 590 for vancomycin]). Comparable percentages of oritavancin- and vancomycin-treated cSSSI patients had at least one SAE investigator-assessed as related to study drug (0.9% [10 of 1173 for oritavancin]; 1.2% [7 of 590 for vancomycin]).

Infections and infestations was the system organ class disorder in which the highest percentages of patients in both treatment groups had SAE (4.7% [55 of 1173 for oritavancin]; 4.2% [25 of 590 for vancomycin]), followed by, in decreasing order, cardiac disorders, gastrointestinal disorders, vascular disorders, and respiratory/thoracic/mediastinal disorders. Most of the reported SAE occurred in no more than 1 or two patients in the oritavancin or vancomycin treatment groups. Table 7.3 provides the list of individual SAE that were reported in 3 or more patients in either treatment group from the two cSSSI studies.

Table 7.3: Selected Serious Adverse Events in cSSSI patients

Serious AE	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)
Cellulitis	10 (0.9%)	3 (0.5%)
Abscess	7 (0.6%)	2 (0.3%)
Sepsis	7 (0.6%)	3 (0.5%)
Abscess Limb	6 (0.5%)	1 (0.2%)
Osteomyelitis	5 (0.4%)	0
Septic Shock	4 (0.3%)	0
Myocardial Infarction	3 (0.3%)	1 (0.2%)
Cardiac Arrest	3 (0.3%)	4 (0.7%)
Cardio-respiratory Arrest	3 (0.3%)	1 (0.2%)
Chest Pain	3 (0.3%)	1 (0.2%)
Pyrexia	2 (0.2%)	3 (0.5%)
Pulmonary Embolism	1 (0.1%)	4 (0.7%)
Vomiting	1 (0.1%)	4 (0.7%)

Discontinuations of Study Drug
In Study ARRI, 11.4% (95/831) of the oritavancin group and 12.5% (52/415) of the vancomycin group discontinued treatment with study drug. The reasons for discontinuation were generally similar between the groups with the exception of discontinuation due to adverse event. A greater percentage of patients were discontinued from treatment with study drug due to an adverse event in the vancomycin-treated group (4.8%, 20/415) as compared to the oritavancin-treated patients (1.9%, 16/831).

In Study ARRD, 29.2% (100/342) of all patients given oritavancin discontinued treatment with study drug (27.2% for oritavancin 1.5 mg/kg, 31.4% for oritavancin 3.0 mg/kg) as compared to 27.4% for vancomycin-treated patients. The reasons for discontinuation were generally similar between the groups with the exception of discontinuation due to lack of efficacy. A greater percentage of patients were discontinued from treatment with study drug due to lack of efficacy in the oritavancin 3.0 mg/kg group (7.1%, 12/169) as compared to the vancomycin-treated patients (3.4%, 6/175).

Treatment Emergent Adverse Events
All treatment emergent adverse events (TEAE) that occurred during the study were evaluated. However, the sponsor also performed a separate analysis of those TEAE that occurred during IV treatment with study drug. In the "during IV therapy" period:

- Lower percentages of cSSSI patients in the oritavancin group than the vancomycin group had at least one treatment-emergent adverse event (TEAE) (42.2% for oritavancin; 50.0% for vancomycin).
- The most common TEAE in this period (in ≥2.0% of oritavancin-treated patients) were in decreasing order of frequency: headache, nausea, insomnia, constipation, diarrhea,

vomiting, and dizziness. Of these, only insomnia showed a difference between treatment groups, as a higher percentage of vancomycin than oritavancin patients had this TEAE. The most common TEAE, headache, occurred in 4.3% of patients in the oritavancin treatment group.

- In the oritavancin clinical development program, seven TEAE (pruritus, erythema, pruritus generalized, flushing, red man syndrome, urticaria, and infusion site pruritus) occurred in significantly lower percentages of oritavancin than vancomycin cSSSI patients. Five other drug-class related TEAE (infusion site pain, infusion site phlebitis, phlebitis, infusion site thrombosis, and infusion site erythema) showed no significant differences between the treatment groups.

In the "during study" period:

- Lower percentages of cSSSI patients in the oritavancin group than the vancomycin group had at least one TEAE (53.5% for oritavancin; 62.4% for vancomycin).
- Of 13 TEAE that occurred in ≥2.0% of oritavancin patients in this period, three (insomnia, pruritus, rash) occurred in a significantly lower percentage of oritavancin than vancomycin patients, and one (dizziness) occurred in a significantly higher percentage of oritavancin than vancomycin patients. The nine remaining most common TEAE showed no significant difference between treatment groups. The most common TEAE, diarrhea, occurred in 21.1% of patients in the oritavancin treatment group.

Injection Site Phlebitis
Injection site phlebitis was identified as an adverse reaction for oritavancin based on results of two phase 1 studies that showed phlebitis occurred in a majority of healthy subjects in the trials. The sponsor conducted a review of available safety data about phlebitis from 15 oritavancin clinical studies comprising 1962 patients and 243 healthy subjects.

- Oritavancin-treated patients with cSSSI or bacteremia demonstrated injection site phlebitis at an incidence and severity comparable to patients treated with equipotent therapeutic doses of the active-comparator, vancomycin.
- Healthy subjects administered multiple daily doses of oritavancin in all multiple-dose Phase 1 studies demonstrated an increased incidence and severity of injection site phlebitis compared with oritavancin-treated patients with cSSSI or bacteremia. InterMune, a previous sponsor, terminated two Phase 1 studies prior to completion largely because of these observations.
- No association between drug substance lot, or drug product lot, or date of manufacture and the incidence of injection site phlebitis.

Drug administration parameters most clearly related to the incidence and severity of injection site phlebitis were:

- The product of drug delivery rate (mg/min) x concentration of the infusate (mg/mL), expressed as ($mg^2/mL \cdot min$), and

- The delivery rate of oritavancin to the vein in mg/min, and, to a lesser extent, the concentration of oritavancin infusate in mg/mL.

These relationships were most clearly demonstrated in healthy subjects given multiple doses of oritavancin. In addition, in healthy subjects enrolled in multiple-dose cohorts, injection site phlebitis increased as daily dose (mg/day) increased.

Histamine-Like Infusion Reactions
Histamine-like infusion reaction (HLIR) symptoms and signs (e.g., flushing, erythema, wheezing, dyspnea, angioedema, urticaria, pruritus, pain or muscle spasm of the chest or back, or hypotension) were reported in some oritavancin clinical studies with administration of either oritavancin or vancomycin. Lower percentages of oritavancin than vancomycin cSSSI patients had at least one possible HLIR (3.2% [37 of 1173 for oritavancin]; 10.8% [64 of 590 for vancomycin]).

Among the 101 cSSSI patients who had at least one possible HLIR, the following was observed:

- Lower but not significantly different percentages of oritavancin patients (24.3%) than vancomycin patients (45.3%) received medication due to a possible HLIR, most commonly H1 receptor antagonists and/or corticosteroids
- Lower but not significantly different percentages of oritavancin than vancomycin patients discontinued study drug due to a possible HLIR
- 35.1% of oritavancin patients had a possible HLIR with their first oritavancin dose, while 57.8% of Van patients had a possible HLIR with their first vancomycin dose.

Clinical Laboratory Evaluations
No clinically relevant trends were observed in clinical laboratory results among oritavancin or vancomycin cSSSI patients. However, increases in mean uric acid concentration from baseline to last reported value were observed in the oritavancin group compared with the Van treatment groups (+41.1 µmol/L for oritavancin; +28.0 µmol/L for oritavancin). Gout was reported as an adverse event in two oritavancin patients. One patient had worsening of pre-existing gout on day 9 of IV therapy. The other patient was reported with gout 23 days after completion of four days of IV oritavancin. There were no vancomycin patients with gout as a TEAE.

No other statistically significant differences in change from baseline to last reported value were observed for any other chemistry, hematology, or liver function analyte in the cSSSI population.

Cardiac Safety
Overall, 81 subjects from healthy subject studies, 471 subjects from patient studies, and 58 subjects from the QT/QTc study OCSI-008 were included in analyses of the effect of oritavancin on QTc intervals. In addition, Phase 1, 2, and 3 studies were reviewed to identify oritavancin-treated subjects and patients who had serious cardiac adverse events.

- No evidence of clinically meaningful QT/QTc interval prolongation was observed in the oritavancin clinical studies at oritavancin doses up to 800 mg IV (2.6 to 4 times the intended label dose).
- No oritavancin-associated cardiac-related adverse events potentially related to QT/QTc prolongation were reported in the oritavancin clinical studies.
- Based on a concentration effect analysis, oritavancin has no apparent effect on the QTcF interval.

After the submission data cutoff date of 17 September 2007, Study TAR-ORI-QT002 (QT002), a Phase 1, double-blind, randomized, placebo- and positive-controlled, single dose, parallel design trial to assess the potential electrocardiographic effects of oritavancin in healthy adults was completed.

- No clinically or statistically significant change in QTcF was induced by a clinical (200 mg) or by a four-fold supraclinical (800 mg) dose of oritavancin, and
- Mean QTcF changes associated with oritavancin were below a 90% upper confidence limit of 10 msec at all time points, with no evidence of a dose-response relationship.

Safety in Subgroups
Targanta explored the subgroups of age, gender, race, hepatic function, renal function, diabetes, immunocompromised indicator, and weight group for potential safety differences. Although the number of patients in some of the subgroups was small and inferences from such small numbers can potentially be misleading, no consistent clinically relevant adverse trends were observed in the oritavancin treatment group compared with the vancomycin group.

Use in Pregnancy and Lactation
No adequate and well-controlled studies with oritavancin have been conducted in pregnant women.

To date, 2 healthy subjects, both of whom received oritavancin in Phase 1 clinical studies, and 2 patients, both of whom received vancomycin in a Phase 3 clinical study, became pregnant during or immediately after their participation in these studies. With regard to the pregnancies of the healthy Phase 1 subjects, one resulted in the birth of a healthy male infant and the second was electively terminated. Brief descriptions of both cases follow.

- Subject OCSI-007 001-0003 had a positive urine test for pregnancy on Study Day 15 (b)(6), 3 days after receiving her fifth and final oritavancin infusion. This subject had a negative serum test for pregnancy at screening and a negative urine test for pregnancy at baseline. She had received 13 days of desipramine plus five oritavancin infusions. Subject terminated pregnancy on (b)(6).
- Subject OPUL-002 01-016 became pregnant approximately 7 weeks after completing her last dose of oritavancin. She gave birth to a healthy male on(b)(6).

With regard to the pregnancies of the vancomycin cSSSI patients, one (Patient 162018 from Study ARRI) resulted in the birth of a healthy, full-term, female infant. The outcome of the

second (Patient 040001 [Study ARRI]) pregnancy is unknown but a prenatal ultrasound performed at 15 weeks of gestation suggested that conception occurred during the second month after administration of study drug.

VIII. ISSUES FOR DISCUSSION

1. Does study ARRI independently provide evidence of the effectiveness of oritavancin for cSSSI? In your response, discuss the following:

- The primary outcome and 95% CI for the study
- Outcomes for patients with known baseline pathogens, particularly MRSA

2. Does study ARRD independently provide evidence of the effectiveness of oritavancin for cSSSI? In your response, discuss the following:

- The primary outcome and 97.5% CI for the study
- The weight-based dosing regimen used in study ARRD

3. Do the data presented demonstrate the safety and effectiveness of oritavancin for the treatment of cSSSI?

- If your answer is yes, are there any specific issues that should be addressed in labeling?
- If your answer is no, what additional data/studies are needed?