TARGANTA THERAPEUTICS CORPORATION

Briefing Document for the Anti-Infective Drugs Advisory Committee

November 19, 2008

NUVOCID® (oritavancin diphosphate for injection) for Treatment of Complicated Skin and Skin Structure Infections

NDA 22-153

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table of Contents

1 Executive Summary 11
1.1 Introduction 11
1.2 Nonclinical 12
1.3 Clinical Pharmacology 13
1.4 Clinical 13
1.4.1 Phase 3 Study Designs 13
1.4.2 Phase 3 Results 14
1.4.2.1 Phase 3 Efficacy 14
1.4.2.2 Phase 3 Safety 14
1.5 Conclusions 15
2 Introduction 16
2.1 Background and Medical Need in Complicated Skin and Skin Structure Infections 18
2.2 Oritavancin 19
2.2.1 History 19
2.2.1.1 Development History 19
2.2.1.2 Regulatory History Relating to the cSSSI Indication 22
3 Nonclinical 25
3.1 Pharmacology 25
3.1.1 Primary Pharmacodynamics 25
3.1.1.1 Mechanisms of Action 25
3.1.1.2 In Vitro Activity 27
3.1.1.3 Activity of Oritavancin in Animal Models of Infection 34
3.1.1.4 In Vitro Attempts to Select for Resistance 42
3.1.2 Safety Pharmacology 42
3.1.2.1 In Vitro Studies 42
3.1.2.2 Animal Studies 42
3.1.2.3 Clinical Follow-Up Based on Nonclinical Safety Findings 42
3.2 Pharmacokinetics 43
3.2.1 Absorption and Bioavailability 43
3.2.2 Distribution 43

3.2.3 Metabolism 44
3.2.4 Elimination 45
3.3 Toxicology 45
4 Overview of Clinical Studies 50
5 Clinical Pharmacology 59
5.1 Pharmacokinetic Characteristics 59
5.1.1 Absorption 60
5.1.2 Distribution 61
5.1.3 Metabolism 61
5.1.4 Elimination 62
5.2 Special Populations 62
5.3 Potential for Drug Interactions 63
5.4 Pharmacokinetics-Pharmacodynamics 63
5.4.1 Potential for Oritavancin Resistance Development 63
5.4.2 Dose Justification 65
5.4.2.1 Animal models and Phase 2 Study ARRL 65
5.4.2.2 Study ARRD 66
5.4.2.3 Study OCSI-001 (Phase 1 Skin Blister Study) 68
5.4.2.4 Breakpoint Analysis 68
5.4.2.5 Final Dose Selection for Study ARRI 69
5.4.2.6 ARRI Pharmacokinetic-Pharmacodynamic Exploratory Analyses by Targanta 70
5.5 Clinical Pharmacology and Microbiology Conclusions 72
6 Clinical Efficacy 74
6.1 Disease Diagnostic Criteria 75
6.1.1 Severity 75
6.1.2 Definition of Complicated 75
6.1.3 Disease Categories 75
6.1.3.1 Wound Infection at the Site of Surgical Incision or Trauma (Including Burn Wounds) or Infected Ulcers 76
6.1.3.2 Major Abscess (No Open Wound) 76
6.1.3.3 Cellulitis 76
6.2 Study Design 77

6.3 Selection of Comparator: Vancomycin/Cephalexin 79
6.4 Noninferiority Margin Justification 80
6.4.1 Discussions with the FDA 80
6.4.2 Historical, Statistical, and Clinical Considerations 81
6.5 Sample Size 82
6.6 Evaluation Criteria for Efficacy 82
6.6.1 Patient Populations 82
6.6.2 Definitions of Efficacy Outcome Variables 83
6.6.2.1 Investigator-Defined Clinical Outcome 83
6.6.2.2 Sponsor-Defined Clinical Outcome 83
6.6.2.3 Pathogen Level Microbiological Outcome 83
6.6.2.4 Patient Level Microbiological Outcome 84
6.7 Individual Phase 3 Study Results 84
6.7.1 Phase 3 Study ARRD 84
6.7.1.1 Demographics 85
6.7.1.2 Baseline Disease 86
6.7.1.3 Comorbidities and Severity of Illness 88
6.7.1.4 Disposition 89
6.7.1.5 Efficacy Results 90
6.7.2 Phase 3 Study ARRI 93
6.7.2.1 Demographics 93
6.7.2.2 Baseline Disease 94
6.7.2.3 Comorbidities and Severity of Illness 96
6.7.2.4 Disposition 97
6.7.2.5 Efficacy Results 98
6.8 Pooled Phase 3 Study Results 100
6.9 Characterization of Clinical Trial Isolates with Apparent Decreased Susceptibility to Oritavancin 105
6.10 Efficacy Conclusions 105
7 Clinical Safety 107
7.1 Extent of Exposure 107
7.2 Adverse Events 107
7.2.1 Deaths and Serious Adverse Events 107

7.2.2 Treatment-Emergent Adverse Events 114
7.2.3 Timing of Onset and Time to Resolution of Adverse Events 119
7.3 Potential Glycopeptide-Related Effects 123
7.3.1 Injection Site Phlebitis 123
7.3.2 Histamine-Like Infusion Reactions 124
7.3.3 Nephrotoxicity 126
7.3.4 Ototoxicity 128
7.3.5 Vestibular Toxicity 128
7.3.6 Hematological Effects 128
7.3.6.1 Neutropenia 130
7.3.6.2 Thrombocytopenia and Pancytopenia 131
7.4 Potential Antibiotic-Related Effects: *Clostridium Difficile* Infection 131
7.5 Hepatic Evaluation 132
7.5.1 Phase 3 Liver Function Test Results 132
7.5.2 Potential Drug-Induced Liver Injury 134
7.6 Additional Laboratory Evaluations 135
7.7 Vital Signs 135
7.8 ECG/QT Interval 137
7.9 Drug Interactions 138
7.10 Overdose 139
7.11 Safety Conclusions 140
8 Benefit/Risk Summary 142
8.1 Medical Need 142
8.2 Potential Benefits and Risks of Oritavancin Therapy 143
8.2.1 Nonclinical Studies 143
8.2.2 Clinical Studies 144
8.2.2.1 Pharmacology 144
8.2.2.2 Efficacy 146
8.2.2.3 Safety 147
9 Conclusions 150
10 References 152
11 Appendices 166

List of Tables

Table 3-1 Summary Table - Spectrum of Activity of Oritavancin against Gram-Positive Pathogens 29

Table 3-2 Oritavancin Exhibits Anti-biofilm Activity In Vitro Against *S. aureus* Strains of Varying Resistance Phenotypes 33

Table 3-3 Animal Infection Model Studies in Which Oritavancin Has Demonstrated Efficacy 35

Table 3-4 Toxicology Program for Oritavancin 46

Table 3-5 Nonclinical Toxicology Findings That Provided Guidance for Clinical Investigation 49

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date 51

Table 5-1 Mean Pharmacokinetic Parameters of Oritavancin in Patients in Phase 2 and Phase 3 Studies (N=360) 60

Table 6-1 Phase 3 Complicated Skin and Skin Structure Infection Study Descriptions.74

Table 6-2 Patient Populations for Efficacy Analysis 83

Table 6-3 Patient Evaluation Groups for Study ARRD 84

Table 6-4 Reasons for Nonevaluability for Study ARRD (Intent-to-Treat Population) 85

Table 6-5 Baseline Patient Demographics for Study ARRD (Intent-to-Treat Population) 86

Table 6-6 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRD (Intent-to-Treat Population) 87

Table 6-7 Incidence of Clinically Relevant Comorbid Conditions in the Intent-to-Treat Population for Study ARRD 88

Table 6-8 Number of Comorbidities per Patient in the Intent-to-Treat Population for Study ARRD 89

Table 6-9 Primary Reasons for Discontinuation of Study Drug in Study ARRD (Intent-to-Treat and Clinically Evaluable Populations) 90

Table 6-10 Cure/Success Rates[a] at Test-of-Cure Visit for Study ARRD 91

Table 6-11 Patient Evaluation Groups for Study ARRI 93

Table 6-12 Reasons for Nonevaluability for Study ARRI (Intent-to-Treat Population) 93

Table 6-13 Baseline Patient Demographics for Study ARRI (Intent-to-Treat Population) 94

Table 6-14 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRI (Intent-to-Treat Population) 95

Table 6-15 Incidence of Clinically Relevant Comorbidities in the Intent-to-Treat Population for Study ARRI 96

Table 6-16 Number of Comorbidities per Patient in the Intent-to-Treat Population for Study ARRI 97

Table 6-17 Primary Reasons for Discontinuation of Study Drug in Study ARRI (Intent-to-Treat and Clinically Evaluable Populations) 98

Table 6-18 Cure/Success Rates[a] at Test-of-Cure Visit for Study ARRI 98

Table 6-19 Clinical Cure Rates[a] at Test-of-Cure Visit for the Analysis of Pooled Data (Studies ARRD and ARRI) 101

Table 6-20 Clinical Cure Rates[a] at Test-of-Cure Visit by Disease Category in the Clinically Evaluable Population for the Analysis of Pooled Data (Studies ARRD and ARRI) 101

Table 6- 21 Cure Rates for Sponsor-Defined Clinical Outcomes by Duration of Active IV Therapy for the Pooled Phase 3 Studies (Clinically Evaluable Population) 102

Table 6-22 Clinical and Microbiological Outcomes at First Follow-Up by Special Population for the Pooled Phase 3 Studies 103

Table 6-23 Patient Level Microbiologic Success Rates by Sponsor-Defined Pathogens in Microbiologically Evaluable Patients in the Pooled Analysis (Studies ARRD and ARRI) 104

Table 6-24 Summary of Minimum Inhibitory Concentration Data by Baseline Isolate within the Modified Intent-to-Treat Population in the Analysis of Pooled Data (Studies ARRD and ARRI) 104

Table 7-1 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 3 Intent-to-Treat Population 109

Table 7-2 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 2[a] Intent-to-Treat Population 112

Table 7-3 Summary of Adverse Events by Treatment Group During the Phase 3 Studies (Intent-To-Treat Population) 115

Table 7-4 Treatment-Emergent Adverse Events of Special Interest by Decreasing Frequency Reported in ≥1% of Complicated Skin and Skin Structure Infection Intent-to-Treat Patients in Each Treatment Group in the During IV Therapy Period 118

Table 7-5 Summary of Possible Histamine-Like Infusion Reaction Subgroup Analyses (Phase 3 Intent-to-Treat Population) 126

Table 7-6 Summary of Clinically Relevant Renal Laboratory Test Results During the Phase 3 Studies (Intent-to-Treat Population) 127

Table 7-7 Summary of Clinically Relevant Hematology Laboratory Test Results during the Phase 3 Studies (Intent-to-Treat Population) 130

Table 7-8 Summary of Clinically Relevant Liver Function Laboratory Test Results During the Phase 3 Studies (Intent-to-Treat Population) 133

Table 7-9 Baseline and Postbaseline Liver Function Test Results for Patient ARRD-039-3205 135

Table 7-10 Baseline and Postbaseline Liver Function Test Results for Patient ARR1-006-0001 135

Table 7-11 Clinically Significant Vital Signs Value Criteria 136

Table 7-12 Summary of Vital Signs Results during Study by Treatment Group (Phase 3 Intent-to-Treat Population) 137

Table 7-13 Serious Adverse Events with Onset after Exposure to Substrate (Concomitant Medication) of CYP450 Isoenzyme of Interest (Phase 3 ITT Population) 139

List of Figures

Figure 2-1 Chemical structure of oritavancin diphosphate with the lipophilic aryl methylene side chain identified. 16

Figure 2-2 Oritavancin development history. 21

Figure 3-1 Representation of the multiple mechanisms of action of oritavancin. 26

Figure 3-2 Oritavancin exerts concentration-dependent activity in vitro against linezolid-nonsusceptible methicillin-resistant *S. aureus* isolate NRS 127. 31

Figure 3-3 Oritavancin exhibits rapid, bactericidal activity against linezolid-nonsusceptible methicillin-resistant *S. aureus* isolate NRS 121 when tested in vitro at its predicted fC_{max} in plasma following standard clinical doses in proposed prescribing information for complicated skin and skin structure infections. 32

Figure 3-4 Observed average 24-hour AUC:MIC ratios versus log10 colony-forming unit at 48 hours across five *S. aureus* strains, with a predicted overlay using the overall population mean values. 37

Figure 3-5 Efficacy of single oritavancin doses against S. aureus ATCC 13709 (methicillin-sensitive *S. aureus*) compared to the untreated group in the rat granuloma pouch model at 72 hours posttherapy. 39

Figure 3-6 Histogram of oritavancin MIC distribution against 4442 strains of S. aureus collected in the United States in 2005 and 2006. 41

Figure 5-1 Investigator-defined clinical outcome and microbiological outcome at pathogen level by baseline minimum inhibitory concentration (*S. aureus*, microbiologically evaluable population). 69

Figure 5-2 Study ARRI: Estimated probability of *S. aureus* eradication for predicted area under the time-concentration curve on Day 1 dose/weight (mg/kg) over minimum inhibitory concentration (328 observations; p=0.046). 71

Figure 5-3 Study ARRI: Estimated probability of *S. aureus* eradication for predicted cumulative treatment area under the time-concentration curve (dose/weight (mg/kg) x accumulation factor/minimum inhibitory concentration) (328 observations; p=0.65). 72

Figure 6-1 Studies ARRD and ARRI study designs. 77

Figure 7-1 Most common adverse events occurring in ≥2% of Phase 3 oritavancin patients. 116

Figure 7-2 Most common adverse events with significant differences between treatment groups..... 116

Figure 7-3 Rate of onset of treatment-emergent adverse events per patient by study day (Phase 3 intent-to-treat population)..... 120

Figure 7-4 Time to adverse event resolution of the adverse event of longest duration per patient (Phase 3 intent-to-treat population). 121

Figure 7-5 Time to adverse event resolution of the adverse event of longest duration per patient for treatment-emergent adverse events of special interest (Phase 3 intent-to-treat population). 122

Figure 7-6 Percentages of Phase 3 oritavancin-treated and vancomycin/cephalexin-treated patients with adverse events mapped to renal failure and impairment. 128

1 Executive Summary

1.1 Introduction

In February 2008, Targanta Therapeutics Corporation (Targanta) submitted New Drug Application (NDA) 22-153 to the Food and Drug Administration (FDA) for the use of oritavancin diphosphate (a semisynthetic lipoglycopeptide antibiotic hereafter referred to as oritavancin) in the treatment of complicated skin and skin structure infections (cSSSI). That NDA is the focus of this Advisory Committee meeting.

Complicated skin and skin structure infections (cSSSI) are primarily caused by gram-positive organisms. They require immediate and appropriate systemic antimicrobial therapy and frequently require appropriate surgical intervention to minimize tissue damage and prevent further spread of infection. Improperly treated or untreated cSSSI can lead to local spread, secondary bacteremia with potential for distant metastatic foci of infection, systemic effects of bacterial infection, gangrene, amputation, and even death. Resistant pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA]) are becoming global and are associated with increasing morbidity and mortality. Therapeutic failures, emerging resistance, and safety and tolerability issues with older antibiotics have necessitated development of therapeutic alternatives. However, all of the currently available agents have potential limitations that span safety and efficacy, including emerging resistance or restricted spectrum of activity, toxicities and safety concerns, drug interactions, lack of data regarding efficacy in complicated infections, and the risk of development of resistance while on therapy. Consequently, additional alternatives in the armamentarium for the treatment of cSSSI are needed.

Vancomycin has long been, and continues to be, a standard-of-care treatment for MRSA cSSSI suspected or known to be caused by multidrug-resistant, gram-positive bacteria. Since the early 1990s, resistance to vancomycin has become an increasing concern. Oritavancin, a semisynthetic product of chloroeremomycin, was developed as a new antibiotic agent that would feature potent activity against both MRSA and vancomycin-resistant enterococcus (VRE). Two Phase 3 studies (H4Q-MC-ARRD [ARRD] and H4Q-MC-ARRI [ARRI]) have demonstrated that once-daily intravenous (IV) oritavancin was noninferior to a course of twice-daily IV vancomycin followed by a course of twice-daily oral cephalexin (hereafter referred to as vancomycin/cephalexin) in treating serious, gram-positive cSSSI. Furthermore, data from these two studies demonstrated that oritavancin was effective with a 3- to 7-day course of treatment, had a favorable safety

profile, and exhibited a statistically significantly lower overall incidence of treatment-emergent adverse events (TEAEs) compared to vancomycin/cephalexin.

1.2 Nonclinical

The core heptapeptide aglycone of oritavancin, which oritavancin shares with vancomycin, confers inhibition of cell wall synthesis, a characteristic of glycopeptides. However, unlike vancomycin, oritavancin inhibits multiple cell wall synthesis activities by virtue of physicochemical and functional characteristics that collectively are not shared by other approved injectable antibiotics. In addition to oritavancin's inhibition of cell wall synthesis, the drug also disrupts membranes of gram-positive bacteria in a concentration-dependent manner. These two principal mechanisms of action (inhibition of cell wall synthesis and disruption of gram-positive membranes) confer upon oritavancin its concentration-dependent bactericidal activity and its extended gram-positive spectrum, both of which distinguish the molecule from vancomycin and other single-mechanism therapeutic agents for MRSA. Multiple mechanisms of action also may reduce the potential for oritavancin to engender resistance during therapy.

Oritavancin exerts persistent, concentration-dependent bactericidal activity in vitro. Furthermore, its demonstrated activity in vitro against stationary-phase cells, biofilms, and intracellular pathogens may be of benefit in recurrent staphylococcal and enterococcal infections.

Parenterally administered oritavancin is active in numerous animal models of infection that are applicable to cSSSI, including neutropenic mouse models of *S. aureus* and *Streptococcus pyogenes* thigh infection, a rat model of methicillin-sensitive *S. aureus* (MSSA) granuloma pouch infection, mouse models of *S. aureus* and VRE bacteremia, and rabbit models of MRSA and VRE endocarditis. Pharmacodynamic studies in these and other models suggest that once-daily dosing regimens and other less frequent regimens are predicted to be efficacious in humans.

Toxicology studies of oritavancin were conducted using rats, rabbits, and dogs. This series of studies included acute (single dose), subacute (14-day dosing), and subchronic (1-month and 3-month daily dosing) studies, as well as genotoxicity, reproductive, immunotoxicity, and local tolerance studies. Overall, the nonclinical safety studies indicate that oritavancin has an acceptable safety profile for the proposed clinical indication, dosage, and treatment duration.

1.3 Clinical Pharmacology

Oritavancin, in its current formulation, is administered intravenously to achieve systemic exposure effective for cSSSI; its oral bioavailability is low, but not completely characterized. Like other glycopeptides, it is expected to be poorly absorbed across an intact gastrointestinal tract due to its high molecular weight (1989.1 Daltons). Oritavancin is extensively distributed in tissues, including those relevant to cSSSI, and is concentrated in macrophages. It is 86% to 90% bound to human plasma proteins. Although oritavancin binds primarily to albumin, the impact of human serum albumin on oritavancin's in vitro activity is modest. There is no in vitro or in vivo evidence that oritavancin is metabolized. It is excreted unchanged in feces and urine. Mean population-predicted half-lives in the Phase 2 and 3 patients are similar to those in healthy subjects with predicted α, β, and γ half-lives of approximately 2, 31, and 393 hours, respectively. At up to 2 weeks after administration, ≤5% of the dose of oritavancin is recovered in urine and feces due to the drug's extensive tissue distribution and low rate of clearance.

1.4 Clinical

1.4.1 Phase 3 Study Designs

Two randomized, double-blind, comparator-controlled, Phase 3 clinical studies of the safety and efficacy of oritavancin in patients with cSSSI (Studies ARRD and ARRI) were conducted. The primary objective of both studies was to test the hypothesis that 3 to 7 days of once-daily oritavancin is noninferior to 10 to 14 days of twice-daily vancomycin/cephalexin in the treatment of patients with gram-positive bacterial cSSSI. Stratified randomization was applied where patients were assigned to one of three disease categories: wound infection, major abscess, or cellulitis. Patients were enrolled with cirrhosis, renal insufficiency, no limitation on the anticipated length of hospitalization, and no limitation on severity of important comorbidities (including bacteremia, polymicrobial infection, diabetes, HIV/AIDS, and/or neutropenia), all of which may complicate response to therapy. In addition, all patients were to have had cSSSI that required ≥3 days of IV antibiotic therapy.

In both studies, patients were randomized to either oritavancin/placebo or vancomycin/cephalexin (in a 1:1:1 fashion [2 oritavancin groups to 1 vancomycin/cephalexin group] in Study ARRD and in a 2:1 fashion [oritavancin fixed-dose:vancomycin] in Study ARRI) for a total duration of therapy of 10 to 14 days as determined by the investigator. After 3 days of IV study drug, patients who met all predefined criteria could be switched from IV to oral therapy (oral placebo for

oritavancin treatment group). The oritavancin dose for Study ARRD included two weight-based dose groups (1.5 and 3.0 mg/kg/day with a median daily dose of 115.1 and 232.7 mg/day, respectively); the oritavancin dose for Study ARRI was fixed at 200 mg/day (300 mg/day for patients weighing more than 110 kg [242 lbs]) based on the results of a pharmacokinetic-pharmacodynamic analysis of Study ARRD. Patients with baseline pathogens of MRSA or enterococci were to receive 10 to 14 days of IV therapy (no oral). Such patients who were assigned to oritavancin received 7 days of IV treatment with active drug followed by 3 to 7 days of IV placebo; such patients who were assigned to vancomycin/cephalexin received 10 to 14 days of IV vancomycin.

1.4.2 Phase 3 Results

1.4.2.1 Phase 3 Efficacy

Both Phase 3 studies met their primary efficacy outcome, the establishment of noninferiority between oritavancin and vancomycin/cephalexin in the clinical response at the first follow-up (test of cure) visit in clinically evaluable (CE) patients.

In the analysis of the combined Phase 3 studies, clinical cure rates and microbiological success rates were comparable between the oritavancin and vancomycin/cephalexin treatment groups across all the evaluability populations. When analyzed by disease category, cure rates were also comparable between the oritavancin and vancomycin/cephalexin treatment groups in each of the populations. The mean duration of total active therapy in the oritavancin-treated patients of the CE population was 5.2 days compared to 11.3 days in the vancomycin/cephalexin-treated patients (with mean duration of active IV treatment of 5.2 days for oritavancin and 6.1 days for vancomycin).

The efficacy of oritavancin was analyzed by baseline demographic characteristics of gender, age class, weight, race, and geographic region. There were no significant differences between the oritavancin and vancomycin/cephalexin groups for these subgroups. When analyzed by renal, hepatic, and diabetes status, there were no treatment group differences between oritavancin and vancomycin/cephalexin.

There was no evidence of development of resistance to oritavancin in either of the studies.

1.4.2.2 Phase 3 Safety

The clinical development of oritavancin included standard evaluations of adverse events, laboratory measures, and vital signs. Safety was monitored during treatment through the final follow-up visit (Days 50 to 90 for Study ARRD and Days 39 to 46 for Study ARRI).

Overall, the safety profile of oritavancin was comparable to vancomycin/cephalexin with oritavancin having an overall statistically significantly lower incidence of TEAEs, including histamine-like infusion reactions (HLIRs). Study completion rates were similar across all treatment groups. However, the discontinuation rates from study drug and due to adverse events were lower for oritavancin relative to comparator.

The numbers of deaths and significant adverse events were comparable between the oritavancin and vancomycin/cephalexin treatment groups.

The most common TEAEs in the Phase 3 studies were, in decreasing order of frequency, headache, nausea, insomnia, constipation, diarrhea, vomiting, and dizziness. There did not appear to be any clinically relevant treatment group differences in changes in blood pressure, heart rate, temperature, or any indication of unexpected adverse systemic effects of treatment. Furthermore, there was no evidence of an oritavancin effect consistent with renal or hepatic toxicity.

No oritavancin-associated cardiac-related adverse events likely related to QT/QTc prolongation have been reported in the oritavancin clinical development program. Study QT002, a thorough QT/QTc study, demonstrated no clinically relevant effect on QTc at the therapeutic and at a supratherapeutic dose.

In summary, Studies ARRI and ARRD demonstrated that oritavancin has a favorable safety profile compared to comparable therapy with vancomycin/cephalexin. No safety-related findings, patterns, or data trends have been observed during active therapy or final final follow-up that would preclude the use of oritavancin to treat cSSSI or warrant focused initiatives for mitigating any potential adverse effect. There is no indication of a need for special laboratory monitoring for safety or for dose adjustment in special populations.

1.5 Conclusions

Oritavancin at the recommended dose of IV oritavancin 200 mg (300 mg for patients >110 kg [242 lbs]) was as effective as vancomycin/cephalexin in two pivotal Phase 3 cSSSI studies. Furthermore, oritavancin therapy in these two studies was effective with a 3- to 7-day course of treatment, with less frequent dosing than vancomycin/cephalexin, with a comparable adverse event profile, with a statistically significantly lower percentage of patients with TEAEs, and with no need for special laboratory monitoring.

2 Introduction

Oritavancin is a semisynthetic lipoglycopeptide antibiotic (empirical formula: $C_{86}H_{97}N_{10}O_{26}Cl_3 \bullet 2H_3PO_4$; molecular weight: 1989.1 Daltons) derived from glycopeptide nucleus factor B, a component present in the fermentation culture of *Kibdelosporangium aridum*. The chemical name for oritavancin is: [4"R]-22-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl- α -L-arabino-hexopyranosyl)-N3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl] vancomycin phosphate [1:2] [salt]. Figure 2-1 illustrates the structure of the molecule.

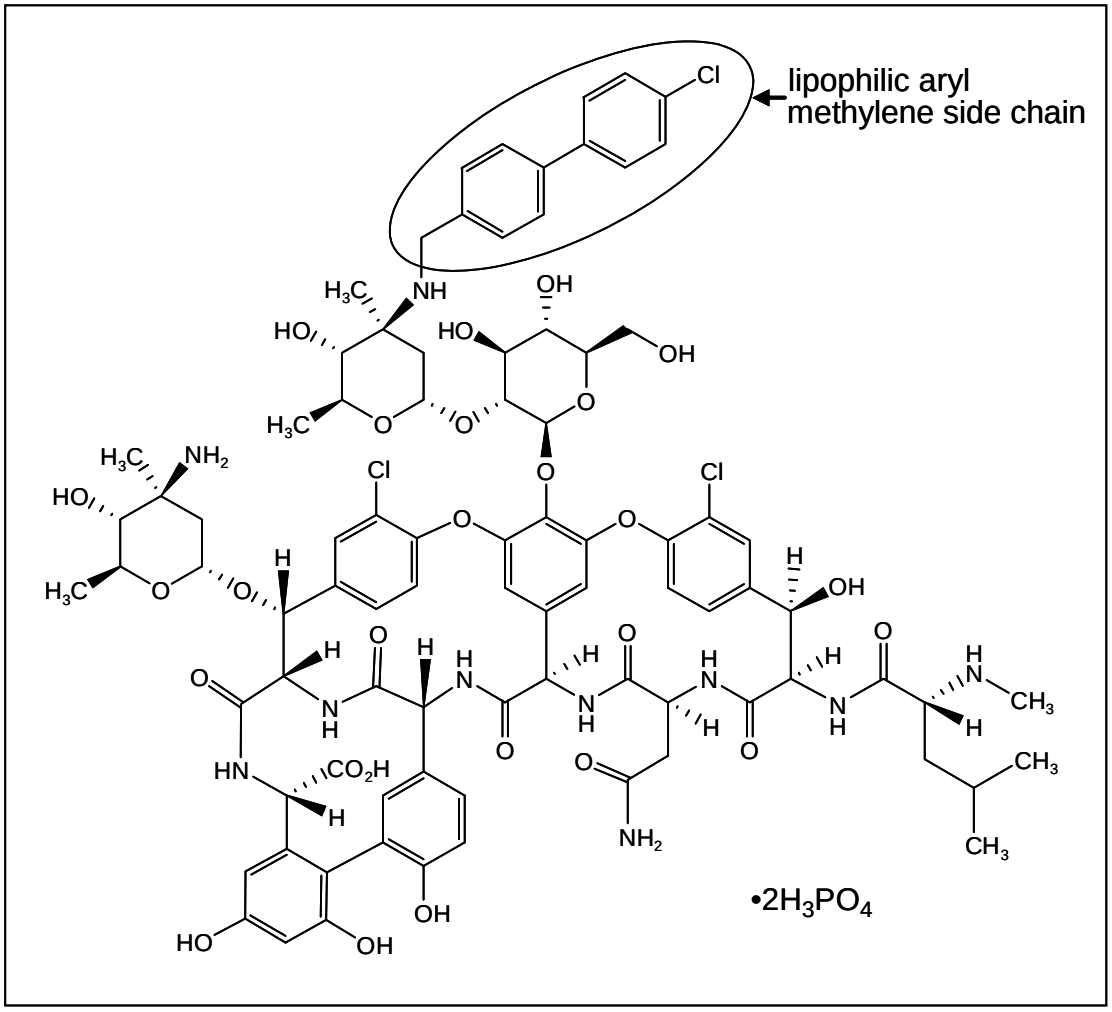


Figure 2-1 **Chemical structure of oritavancin diphosphate with the lipophilic aryl methylene side chain identified.**

The presence of the lipophilic aryl methylene side chain classifies oritavancin as a lipoglycopeptide antibiotic; this unique structure contributes to its multiple mechanisms of action. These multiple mechanisms of action result in potent in vitro bactericidal activity against clinically relevant gram-positive pathogens, including MRSA, vancomycin-resistant microorganisms, and isolates that are nonsusceptible to daptomycin

and linezolid (see Table 3-1 in Section 3.1.1.2). In addition to conferring activity against drug-resistant microorganisms, the multiple mechanisms of action also may reduce the probability that oritavancin resistance will develop during clinical use.

Targanta submitted an NDA seeking FDA approval for oritavancin in the treatment of cSSSI based on the results of two Phase 3 studies (Studies ARRD and ARRI). Both of these studies met their primary endpoint of clinical response at first follow-up visit by demonstrating that once-daily IV oritavancin was noninferior to a course of twice-daily vancomycin/cephalexin in treating cSSSI. Furthermore, oritavancin therapy was effective with less frequent dosing and a 3- to 7-day course of treatment. Oritavancin showed consistent efficacy across subpopulations (including patients with preexisting and/or concurrent comorbidities) and across disease categories (wound, major abscess, and cellulitis) in both of the individual Phase 3 studies as well as in the pooled analysis. Oritavancin was effective against clinically relevant gram-positive pathogens and demonstrated clinical cure and bacterial eradication. In general, adverse events were mild to moderate, and the adverse event profile observed in patients receiving oritavancin was comparable to the adverse event profile observed in patients receiving vancomycin/cephalexin with respect to event type, timing of onset, and intensity. Notably, overall incidence of TEAEs, including histamine-like infusion reactions (HLIRs), was statistically significantly lower for oritavancin than for vancomycin/cephalexin. With 1540 individuals exposed to oritavancin (as of the NDA submission data cutoff date of September 17, 2007), the compound has shown a favorable safety profile with no renal signals, hepatic signals, cardiac effects, or other toxicities that may require monitoring.

Based on the results of the clinical studies, the proposed therapeutic indication for oritavancin is as follows:

> Treatment of cSSSI, including patients with diabetes and/or human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), caused by susceptible isolates of the following gram-positive microorganisms:
>
> - *Staphylococcus aureus* (methicillin-susceptible and -resistant strains)
> - *Streptococcus pyogenes*
> - *Streptococcus agalactiae*
> - *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius*, and *S. constellatus*)

- *Streptococcus dysgalactiae* (includes *S. dysgalactiae* subsp. *S. equisimilis*)
- *Enterococcus faecalis* (vancomycin-susceptible strains only)

Combination therapy may be clinically indicated if documented or presumed pathogens include gram-negative or anaerobic organisms.

The proposed dosing recommendation is as follows:

> Oritavancin 200 mg (300 mg for patients weighing more than 110 kg [242 lbs]) is to be administered by IV infusion over approximately 60 minutes every 24 hours for 3 to 7 days. Patients with MRSA should be treated for 7 days. Oritavancin is intended for IV administration only. Dosage adjustment is not required for patients with renal insufficiency or for patients with mild to moderate hepatic insufficiency.

2.1 Background and Medical Need in Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections (cSSSI) are primarily caused by gram-positive organisms. Skin and skin structure infections (SSSI) are considered complicated when the infection involves deeper skin or soft tissue structures, requires significant surgical interventions, and/or arises in the presence of significant comorbidities. These infections are a common cause of morbidity and mortality (Rybak and Akins 2001) and require immediate and appropriate systemic antimicrobial therapy and frequently require appropriate surgical intervention to minimize tissue damage and prevent further spread of infection. Complications of improperly treated or untreated cSSSI include persistant infection, secondary bacteremia, and, in some cases, gangrene, limb amputation, or death (Rybak and Akins 2001).

Bacteria are becoming increasingly resistant to existing antibacterial agents, causing rising morbidity and mortality around the world (Weinberg and Scheinfeld 2003; Wilcox 2003; Lee et al. 2005; MacKenzie et al. 2005; Rice 2006; Schito 2006). One of the more concerning resistant bacteria is MRSA (CA-MRSA). Initially, MRSA was primarily nosocomial; more recently, CA- MRSA infections have become common and are rapidly increasing worldwide (Drew 2007; Boucher and Corey 2008). The incidence of MRSA has reached 60% to 74% in some large US teaching hospitals and is being reported with increasing frequency in outpatient infections (Moran et al. 2006; Daum 2007; Klevens et al. 2007). Clinical outcomes in patients infected with MRSA are generally worse than in patients infected with MSSA (Engemann et al. 2003; Lodise and McKinnon 2005).

The burden of therapeutic failures and the emerging resistance to the older antibiotics with favorable in vitro activity against resistant *S. aureus* infections (such as vancomyicn, trimethoprim-sulfamethoxazole, fluoroquinolones, erythromycin, clindamycin, rifampin, aminoglycosides, and tetracyclines) have necessitated development of therapeutic alternatives. More recently introduced alternatives for treatment of resistant gram-positive infections are linezolid, quinupristin-dalfopristin, daptomycin, and tigecycline. All of these agents have potential limitations due to emerging resistance or restricted spectrum of activity, toxicities and safety concerns, drug interactions, lack of data regarding efficacy in complicated infections, and the risk of development of resistance while on therapy (Drew 2007; Micek 2007).

Because the morbidity and mortality of improperly treated or untreated cSSSI is high, and because gram-positive bacterial pathogens such as MRSA are increasingly resistant to a number of standard antibiotics, new choices in the armamentarium for the treatment of serious gram-positive infections are needed (IDSA 2004; Brown et al. 2006; Carlet and Benali 2006; Drees and Boucher 2006; Finch 2006; Gosbell et al. 2006; Talbot et al. 2006; Theuretzbacher and Toney 2006; Drew 2007).

2.2 Oritavancin

2.2.1 History

2.2.1.1 Development History

Vancomycin has long been, and continues to be, a standard-of-care treatment for MRSA cSSSI suspected or known to be caused by multidrug-resistant, gram-positive bacteria. In the early 1990s, reports of emerging resistance to vancomycin spurred chemists at Eli Lilly and Company (Lilly) to modify chloroeremomycin (a naturally occurring glycopeptide antibiotic that had been earlier discovered by Lilly) in an effort to create a new antibiotic agent that retained potent activity against both MRSA and VRE. The result of this chloroeremomycin modification program was the semisynthetic lipoglycopeptide, oritavancin. Lilly submitted investigational new drug ([IND] application 51,292) to the FDA on August 12, 1996 and subsequently initiated six Phase 1 studies, one Phase 2 uncomplicated SSSI (uSSSI)/cSSSI study, two Phase 2 bacteremia studies, and two Phase 3 cSSSI studies. After completing the first of the two Phase 3 studies (Study ARRD) in 2001, Lilly made the business decision to end its infectious disease drug development program to focus on other therapeutic areas. As part of this change in corporate strategy, Lilly transferred the oritavancin IND to InterMune, Incorporated (InterMune) effective January 2, 2002.

InterMune completed the second Phase 3 cSSSI study (Study ARRI), the second Phase 2 bacteremia study, and 5 additional Phase 1 studies. In two of those Phase 1 studies (OCSI-007 and OCSI-008), injection site phlebitis was observed in numbers that were judged at the time to be greater in incidence and severity than previously observed. Both of the studies were voluntarily discontinued prior to completion. InterMune decided to focus its resources on therapies for pulmonary and hepatic diseases, effectively placing oritavancin on voluntary clinical hold. On February 27, 2006, Targanta acquired the oritavancin IND from InterMune.

Upon acquiring oritavancin, Targanta reviewed and evaluated all of the available data and then met with the FDA on several occasions to discuss the events of injection site phlebitis. Targanta demonstrated that the injection site phlebitis encountered in Studies OCSI-007 and OCSI-008 was due to a combination of high infusion rates and high drug concentrations administered to healthy subjects – a finding common to vancomycin and other glycopeptides antibiotics (Murray and Nannini 2005). Targanta further showed that the incidence of injection site phlebitis after oritavancin administration was comparable to that of equipotent therapeutic doses of vancomycin, and that the events were not due to the putative causes offered by InterMune. Based on review of the data provided by Targanta, the FDA agreed to lift the voluntary clinical hold imposed by InterMune.

In February 2008, Targanta submitted NDA 22-153 seeking FDA approval for the use of oritavancin in the treatment of cSSSI. In April 2008, Targanta was notified that a meeting of the Anti-Infective Drugs Advisory Committee would be scheduled prior to the Prescription Drug User Fee Act date.

Figure 2-2 illustrates oritavancin's path toward registration. Descriptions of each of the 19 clinical studies are provided in Table 4-1 of Section 4.

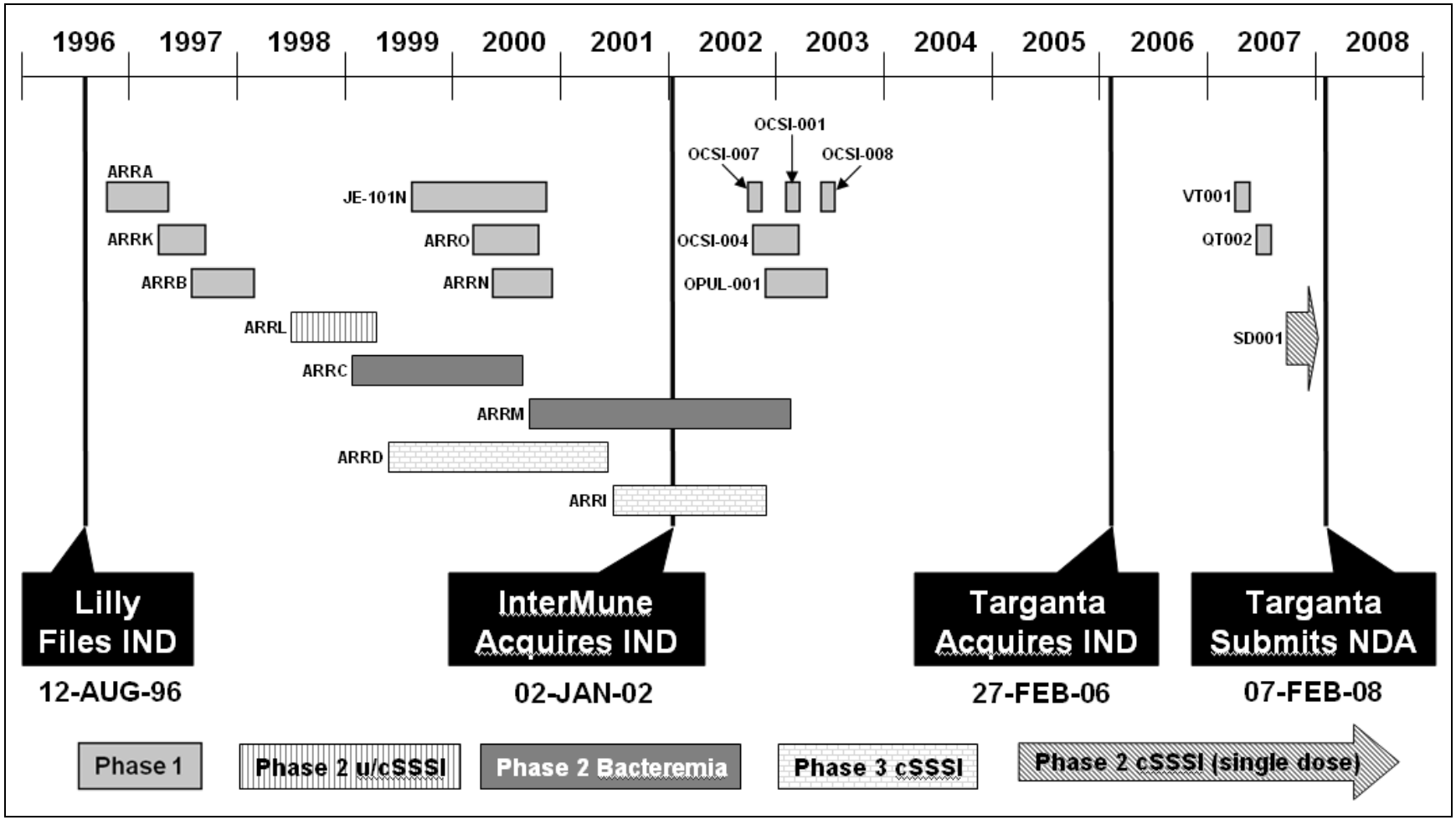


Figure 2-2 **Oritavancin development history.**

2.2.1.2 Regulatory History Relating to the cSSSI Indication

This section summarizes key FDA-sponsor meetings related to the cSSSI indication that have occurred during the oritavancin development history following the initiation of the first Phase 3 clinical study.

March 12, 2001 - Meeting between Lilly and FDA (NI Margin): As Study ARRD (the first Phase 3 pivotal cSSSI study) was nearing completion, Lilly requested this meeting to discuss the potential impact of a new recommendation for a 10% delta published by the FDA on February 12, 2001 in a revision to the FDA Division of Anti-Infective Drug Products' 1992 Points to Consider Guidance document: Clinical Development and Labeling of Anti-Infective Drug Products (FDA 1992b, disclaimer). Study ARRD was initiated in early 1999 and had been designed with a 15% delta based on the previous guidance document (FDA 1992a). After a face-to-face meeting, the FDA agreed to take this information and any other information that Lilly would submit to the Agency on the appropriateness of a 15% delta for Study ARRD under advisement and provide a response in the next several weeks.

March 23, 2001 - Teleconference between Lilly and FDA (NI Margin): In this teleconference, an agreement was reached to complete Study ARRD as planned (that is, approximately 500 patients targeted for completion in April 2001), with an understanding that the strength of the results from Study ARRD would not be judged solely on the lower limit, but also on the point estimate of the confidence interval (CI) and the safety profile with respect to the comparator. Lilly agreed with the FDA request to power the second pivotal study (Study ARRI) to meet the delta of 10%.

December 13, 2001 - Lilly notified the FDA of their intent to transfer sponsorship of the oritavancin IND to InterMune effective January 2, 2002: Lilly had made the decision to end its infectious diseases drug development effort.

June 14, 2002 - Meeting between InterMune and FDA: This meeting was requested by InterMune to discuss the clinical development program for oritavancin. The FDA stated that they would accept an NDA application seeking only the cSSSI indication for oritavancin. The FDA also agreed that the study design and patient numbers from Studies ARRD and ARRI, if successfully completed, would support an indication of cSSSI for oritavancin.

August 7, 2003 - Pre-NDA Meeting between InterMune and FDA: The goal of the meeting was to discuss the content and format of the NDA, the strategy around a potential Priority Review, and the pediatric study plan. FDA agreed to the strategy for the Integrated Summary of Efficacy and Integrated Summary of Safety analyses proposed by InterMune and encouraged InterMune to conduct a pediatric study, but noted that this study was not required prior to NDA submission.

November 20, 2003 - Teleconference Meeting between InterMune and FDA: The objective of this meeting was to review the injection site phlebitis and serious adverse events (SAEs) in Study OCSI-008, which had been submitted to FDA on October 8, 2003. InterMune proposed that no further clinical studies would be initiated until this issue was resolved, effectively placing oritavancin on voluntary clinical hold. InterMune agreed to submit updated data for Study OCSI-008, additional Chemistry, Manufacturing, and Control (CMC) evaluations, and a draft protocol of a proposed new study to address FDA's safety concerns.

March 10, 2004 - FDA Requested Meeting with InterMune: FDA invited InterMune to have an open discussion of the status of the CMC investigations and the systemic adverse events/injection site reactions observed in Studies OCSI-007 and OCSI-008.

July 6, 2004 - InterMune Letter to FDA: InterMune notified the FDA that they were seeking a partner for oritavancin and were discontinuing clinical development.

February 27, 2006 - InterMune Letter to FDA: InterMune notified the FDA of their intent to transfer sponsorship of the oritavancin IND to Targanta, effective immediately.

July 20, 2006 - Teleconference Meeting between Targanta and FDA: The primary goal of this first meeting between the FDA and Targanta was to discuss the InterMune voluntary clinical hold and determine whether this hold could be lifted so that Targanta could initiate new clinical studies with oritavancin to continue the development plan. Both the CMC data and the safety data from the two studies that precipitated the voluntary clinical hold (Studies OCSI-007 and OCSI-008) were discussed. The safety discussion focused on Targanta's reanalysis of the injection site phlebitis. Targanta agreed to submit responses to comments and requests from the CMC reviewer, to provide a table identifying the drug substance and drug product used in the nonclinical animal safety studies, and to provide the final study reports for Studies OCSI-007 and OCSI-008.

November 27, 2006 - Pre-NDA CMC Meeting between Targanta and FDA: The objective of this meeting was to confirm the submission strategy for the CMC section of the NDA submission. The FDA acknowledged that there did not appear to be any CMC issues that would prevent an NDA submission. The reviewer noted that it was difficult to follow the development path for oritavancin over the 10-year span since the IND was opened, owing in large part to the multiple sponsors. Targanta agreed to provide a simplified overview of the drug substance and drug product development process. That information was provided to the CMC reviewer on December 21, 2006.

January 31, 2007 - Pre-NDA Meeting between Targanta and FDA: Targanta requested a pre-NDA meeting to confirm the content and submission strategy for an NDA for oritavancin for the treatment of cSSSI. The FDA noted that two Phase 3 studies could be used to support the indicaton and requested that Targanta provide an in-depth justification for the noninferiority margins used in Studies ARRD and ARRI. Additionally, based on discussions at the July 20, 2006 Targanta-FDA meeting, the FDA review of the final study reports for OCSI-007 and OCSI-008, and evaluation of other documents provided to the FDA by Targanta, the FDA agreed to lift the voluntary clinical hold imposed by InterMune.

February 7, 2008 - Targanta submitted NDA 22-153 to the FDA for oritavancin for the treatment of cSSSI.

May 28, 2008 - Targanta submitted the 4-Month Safety Update to the FDA.

3 Nonclinical

Results of the nonclinical studies, summarized below, provided guidance for the design and conduct of the clinical development program of oritavancin. The combined nonclinical and clinical data support the intended clinical use of oritavancin at a daily dose of 200 mg (300 mg for patients weighing more than 110 kg [242 lbs]) for 3 to 7 days for the treatment of cSSSI.

3.1 Pharmacology

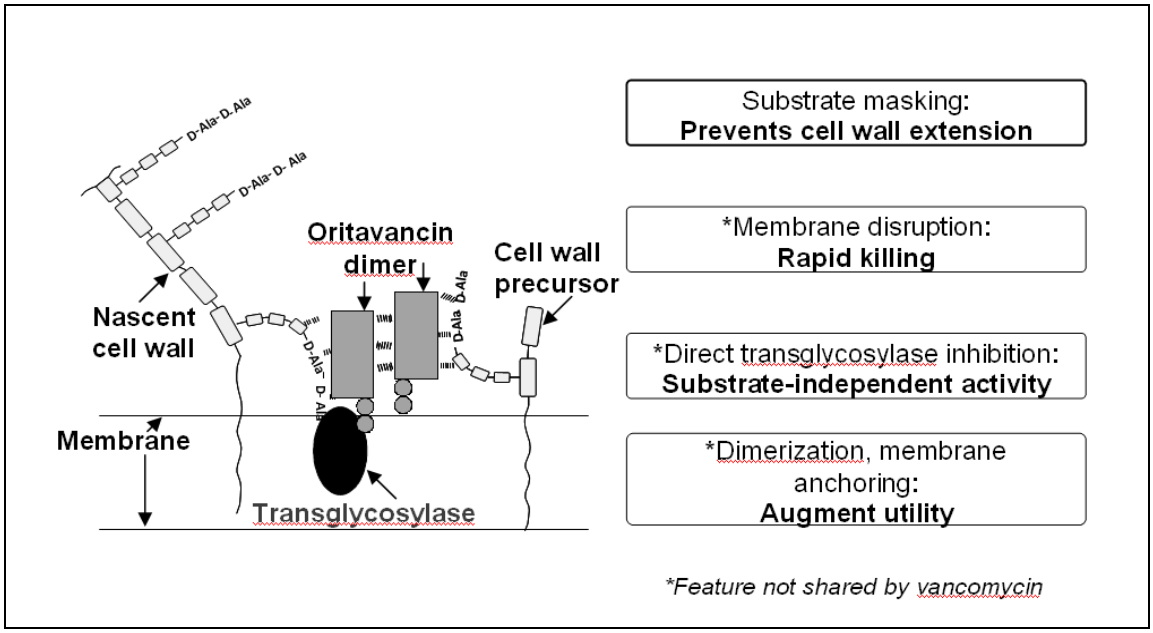
The primary pharmacology studies focused on in vitro microbiological profiling, efficacy studies in animal models of infection, and pharmacodynamic studies correlating efficacy with pharmacokinetic parameters. A variety of safety pharmacology studies (in vitro and animal) were also conducted to ensure appropriate safety and toxicology of the drug.

3.1.1 Primary Pharmacodynamics

In vitro and in vivo studies adequately demonstrate that oritavancin, a lipoglycopeptide antibiotic, has potent activity against gram-positive bacteria of relevance to cSSSI including MRSA, *S. pyogenes*, and VRE. Oritavancin also has substantial in vitro activity against vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA).

3.1.1.1 Mechanisms of Action

The unique chemical moieties of oritavancin, namely the 4-*epi*-vancosamine at the ring six amino residue and the N-substituted-*p*-chlorobiphenylmethyl (lipophilic aryl methylene) side chain attached to the disaccharide (Figure 2-1), confer in vitro activity against glycopeptide-resistant gram-positive bacteria (Allen and Nicas 2003). Oritavancin has thus been termed a lipoglycopeptide as have teicoplanin, dalbavancin, and telavancin (Kahne et al. 2005; Van Bambeke 2006; CLSI 2008). Oritavancin exerts two principal mechanisms of action against gram-positive pathogens, namely, inhibition of cell wall synthesis (Cegelski et al. 2006; Arhin et al. 2007a) and disruption of membrane integrity (McKay et al. 2006; 2008b). Multiple mechanisms of oritavancin action are expected to reduce the potential for emergence of resistance. These mechanisms are displayed graphically in Figure 3-1 and further described below.



References: Allen and Nicas 2003; Cegelski et al. 2006; McKay et al. 2006; Arhin et al. 2007a; Kim et al. 2007; Wang et al. 2007; Kim et al. 2008; McKay et al. 2008b.

Figure 3-1 Representation of the multiple mechanisms of action of oritavancin.

The core heptapeptide aglycone of oritavancin is shared with vancomycin and confers inhibition of cell wall synthesis, which is characteristic of glycopeptides (Reynolds 1989) via binding to the acyl-D-alanyl-D-alanine terminus of the cell wall precursor, lipid II (Nicas and Allen 1994; Allen et al. 1996; Cegelski et al. 2006; Kim et al. 2006; Arhin et al. 2007a). Unlike vancomycin, oritavancin exists predominantly as noncovalent dimers that associate strongly with the cell wall precursor-membrane target (Beauregard et al. 1995; Allen et al. 1997; Allen and Nicas 2003); indeed, oritavancin is approximately 12,000-fold more strongly dimerized than vancomycin (Allen et al. 1997). Its physicochemical properties also promote binding to bacterial cytoplasmic membranes. These multiple cooperative effects likely contribute to the overall bactericidal mechanism of oritavancin. Wang et al. (2007) provided data supporting the claim that oritavancin directly inhibits transglycosylation, in the absence of a requirement to bind cell wall precursors. Oritavancin inhibits both transglycosylation and transpeptidation through its interactions with both lipid II and nascent cell wall, including interactions with the pentaglycyl bridge (Kim et al. 2007, 2008). Thus, oritavancin inhibits multiple cell wall synthesis activities by virtue of physicochemical and functional characteristics that collectively are not shared by other glycopeptides and lipoglycopeptides.

Oritavancin disrupts membranes of gram-positive isolates including MSSA, MRSA, VISA, VRSA, vancomycin-sensitive enterococcus (VSE), and VRE in a concentration-dependent manner (McKay et al. 2006; Belley et al. 2007a; Belley et al 2008c; McKay et al. 2008a, 2008b). This activity comprises collapse of transmembrane potential and perturbation of the membrane barrier function (McKay et al. 2006; Domenech et al. 2008). Disruption of bacterial membranes by oritavancin is tightly linked with cell killing: as an example, challenge of *S. aureus* ATCC 29213 (MSSA) with 0.5 µg/mL oritavancin fully collapsed the transmembrane potential within 10 minutes and correspondingly decreased viable cell counts by 3.5 ± 0.2 log (McKay et al. 2006) in the same period. In vitro studies with a diverse set of drug-resistant isolates of *S. aureus* and enterococci support the claim that cell killing by oritavancin is tightly linked with its disruption of membrane potential (McKay et al. 2008b).

The combination of two principal mechanisms of action, namely, inhibition of cell wall synthesis and disruption of gram-positive membranes, are predicted to confer upon oritavancin its concentration dependent activity and its extended gram-positive spectrum, both of which distinguish oritavancin from vancomycin and other single-mechanism therapeutic agents for MRSA. Multiple mechanisms of action are also believed to reduce the potential for oritavancin to engender resistance during therapy. This prediction is supported by evidence from Phase 3 studies in cSSSI and from in vitro studies (Section 3.1.1.4).

3.1.1.2 In Vitro Activity

Before 2007 it was not appreciated that oritavancin binds avidly and saturably to plasticware and glassware used in in vitro studies; therefore, oritavancin susceptibility studies conducted prior to 2007 likely substantially underestimate the drug's in vitro potency (Arhin et al. 2007b; 2008b). The addition of 0.002% polysorbate-80 to broth microdilution assays has been shown to promote near-quantitative recovery of oritavancin from solution and therefore to most accurately reflect oritavancin potency in vitro (Arhin et al. 2008b). Quality control ranges based on this methodology have been defined by the Clinical and Laboratory Standards Institute (CLSI 2008).

This recent optimization of oritavancin susceptibility testing methods prompted a re-assessment of its in vitro activity profile in a large surveillance initiative with geographically diverse clinical isolates of staphylococci, enterococci, and streptococci that were collected between 2005 and 2006 (reviewed in Poulakou and Giamarellou 2008). This study employed the broth microdilution method with polysorbate-80 for

testing of oritavancin (CLSI 2008). As shown in Table 3-1, key findings of these studies, with particular focus on organisms of heightened relevance to cSSSI, include the following:

- The activity of oritavancin against *S. aureus* and coagulase-negative staphylococci isolates remained consistent regardless of oxacillin-susceptibility status. The minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) values for MSSA, MRSA, and coagulase-negative staphylococci ranged from 0.06 to 0.25 µg/mL.

- Oritavancin MIC_{90} values remained at or below 1 µg/mL against *S. aureus* strains that were nonsusceptible to daptomycin and vancomycin, including for the latter group, heteroresistant vancomycin-intermediate *S. aureus* (hVISA) and VISA. Similarly, oritavancin maintained potent activity against VRSA and linezolid-nonsusceptible *S. aureus*, with minimum inhibitory concentration (MIC) ranges of 0.12 to 0.5 µg/mL (VRSA; n=5 strains) and of 0.06 to 0.25 µg/mL (linezolid nonsusceptible; n=9 strains).

- Oritavancin was active against *S. pyogenes*, *S. agalactiae*, and other beta-haemolytic streptococci, with MIC_{90}s between 0.12 and 0.5 µg/mL. Erythromycin susceptibility phenotype had no substantial impact upon oritavancin susceptibility.

- Oritavancin was active against both VSE and VRE (VRE includes both VanA and VanB isolates), including *E. faecalis*, *E. faecium*, and other *Enterococcus* spp. Oritavancin MIC_{90} values ranged from 0.03 to 0.06 µg/mL for VanB strains and from 0.25 to 1 µg/mL for the highly glycopeptide-resistant (vancomycin and teicoplanin resistant) VanA strains of VRE. This feature distinguishes oritavancin in vitro activity from that of lipoglycopeptides telavancin and dalbavancin, which lose substantial activity against VanA strains (Billeter et al. 2008; Krause et al. 2008).

- Oritavancin is inactive against gram-negative bacteria.

Table 3-1 Summary Table - Spectrum of Activity of Oritavancin against Gram-Positive Pathogens

Organism	Category	Total n	µg/mL MIC Range	MIC Mode	MIC_{50}	MIC_{90}
Aerobic/facultative						
Staphylococcus aureus	All	5008	≤0.004-4	0.06	0.06	0.12
	Oxacillin S	2518	≤0.004-0.5	0.06	0.06	0.12
	Oxacillin R	2490	≤0.004-4	0.06	0.06	0.25
	Daptomycin NS[a]	16	0.015-1	1	0.5	1
	Linezolid NS[b]	9	0.06-0.25	NA	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
Staphylococcus epidermidis	All	802	≤0.004-2	0.12	0.12	0.25
	Oxacillin S	183	0.008-1	0.12	0.12	0.25
	Oxacillin R	618	≤0.004-2	0.12	0.12	0.25
	VICNS[e]	11	0.12-2	1	0.5	1
Staphylococcus haemolyticus	All	72	0.008-1	0.03	0.03	0.12
	Oxacillin S	25	0.008-0.12	0.015	0.03	0.06
	Oxacillin R	47	0.015-1	0.03	0.06	0.12
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 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
Streptococcus mitis	All	12	0.015-1	0.015	0.03	0.5
	Erythromycin S	3	0.03-1	NA	NA	NA
	Erythromycin NS	9	0.015-0.5	NA	NA	NA
Viridans group *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
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[f]	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

(continued)

Table 3-1 Summary Table - Spectrum of Activity of Oritavancin against Gram-Positive Pathogens (Concluded)

Organism	Category	Total n	µg/mL MIC Range	MIC Mode	MIC_{50}	MIC_{90}
Aerobic/facultative (concluded)						
Enterococcus faecium	All	423	≤0.0005-2	0.015	0.03	0.25
	Vancomycin S	136	≤0.0005-0.06	0.015	0.015	0.015
	Vancomycin NS	287	≤0.0005-2	0.12	0.06	0.25
	Daptomycin NS	15	0.015-0.5	0.015	0.015	0.25
	Linezolid NS[g]	16	0.004-0.25	0.12	0.03	0.25
	VanA	250	0.004-2	0.12	0.12	0.25
	VanB	29	≤0.0005-0.06	0.008	0.008	0.03
Enterococcus gallinarum	All	10	0.004-0.25	0.03	0.03	0.12
	Vancomycin S	1	0.03-0.03	NA	NA	NA
	Vancomycin NS	9	0.004-0.25	NA	NA	NA
Bacillus species	All	22	≤0.004-0.12	0.06	0.015	0.06
Corynebacterium species	All	20	0.008-2	0.015	0.03	0.25
Leuconostoc species	All	22	1-8	4	4	8
Listeria monocytogenes	All	12	0.002-0.004	0.002	0.002	0.004
Pediococcus species	All	17	1-8	4	4	8
Anaerobic[h]						
Clostridium difficile	All	32	0.25-1	0.25	0.5	1
Clostridium perfringens	All	31	0.25-1	1	1	1
Lactobacillus species	All	12	0.004-8	8	1	8
Peptostreptococcus spp.	All	31	≤0.004-0.5	0.12	0.12	0.5
Propionibacterium acnes	All	22	0.12-0.5	0.25	0.25	0.25
Propionibacterium species	All	10	0.06-0.25	0.12	0.12	0.25

Abbreviation: hVISA = heteroresistant vancomycin-intermediate *S. aureus*; VICNS = vancomycin emerged in coagulase-negative staphylococci; VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*.

[a] Isolated between 1998 and 2006 (6 isolates isolated prior to 2005 and 3 unknown dates of isolation).
[b] Isolated between 2001 and 2006 (5 isolates isolated prior to 2005 and 1 unknown date of isolation).
[c] Isolated between 1997 and 2003 (13 isolates isolated prior to 2005).
[d] Isolated between 2002 and 2005 (4 isolates isolated prior to 2005).
[e] Isolated between 1996 and 2002 (11 isolates isolated prior to 2005);VICNS included 7 *S. epidermidis* isolates and 4 *S. haemolyticus* isolates.
[f] Isolated between 2002 and 2005 (8 isolates isolated prior to 2005 and 2 unknown dates of isolation).
[g] Isolated between 2004 and 2005 (9 isolates isolated prior to 2005).
[h] Anaerobes were tested by agar dilution according to CLSI guidelines.

Additional broth microdilution studies with polysorbate-80 have further characterized the spectrum of in vitro activity of oritavancin against isolates collected from the US, Canada, Europe, and Asia in 2007-2008 (Bouchillon et al. 2008; Draghi et al. 2008; Fritsche et al. 2008; Sahm et al. 2008a, 2008b; Vashisht et al. 2008) and against resistant

phenotypes of particular interest to cSSSI including hVISA, VISA, CA-MRSA, and daptomycin-nonsusceptible MRSA (Grover et al. 2007; Arhin et al. 2008a; Pankuch and Appelbaum 2008; Saravolatz et al. 2008; Vaudaux et al. 2008).

Further in vitro studies demonstrate that oritavancin exerts a long, concentration-dependent, postantibiotic effect (Mercier and Rybak 1997; Novelli et al. 1997; Baltch et al. 1998; Zhanel et al. 1998; McKay et al. 2007b). This finding is consistent with nonclinical in vivo and clinical data showing that oritavancin remains effective even following once-daily or infrequent dosing (Lehoux et al. 2006).

Oritavancin exerts concentration-dependent activity in vitro. In one example, progressively greater extent of kill of a linezolid-nonsusceptible MRSA clinical isolate is evident as the concentration of oritavancin increases from 0.5 to 8 µg/mL (Figure 3-2; McKay et al. 2007a). This feature suggests that measures of area under the oritavancin concentration-time curve (AUC) and peak concentration (C_{max}) rather than time above minimum inhibitory concentration (T>MIC) should be predictive of efficacy in vivo. This suggestion is supported by data from animal models of infection as described in Section 3.1.1.3.

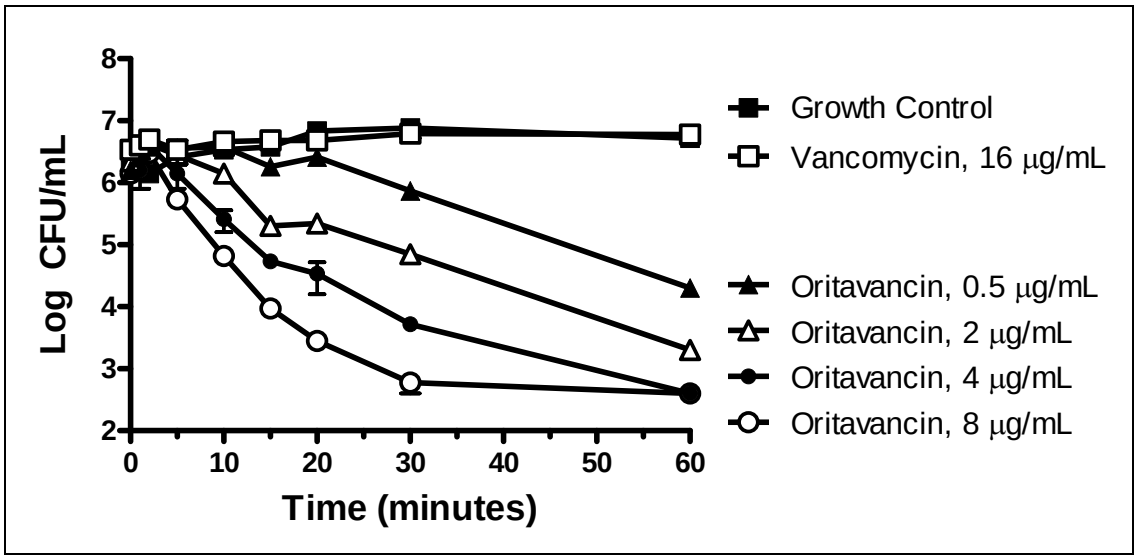


Figure 3-2 **Oritavancin exerts concentration-dependent activity in vitro against linezolid-nonsusceptible methicillin-resistant *S. aureus* isolate NRS 127.**

Agents that exhibit bactericidal rather than bacteriostatic activity may provide advantages in treating certain difficult infections caused by MRSA (Finberg et al. 2004; Sakoulas et al. 2004; Daum 2007; Moise et al. 2007) and other gram-positive bacteria (Pankey and

Sabath 2004). Oritavancin activity in vitro is bactericidal (defined as 99.9% killing of inoculum) against *S. aureus* including MRSA (Figure 3-2 and Figure 3-3; McKay et al. 2007a), VISA (McKay et al. 2008a), and enterococci (McKay et al. 2007a). The rapid rate of cell eradication by oritavancin distinguishes it from several other anti-MRSA agents including teicoplanin, linezolid, vancomycin, and daptomycin, which generally exhibit bacteriostatic or slower bactericidal activity (Figure 3-3; McKay et al. 2007a, 2008a) when tested at physiologically relevant free-drug levels anticipated in plasma following approved doses for cSSSI.

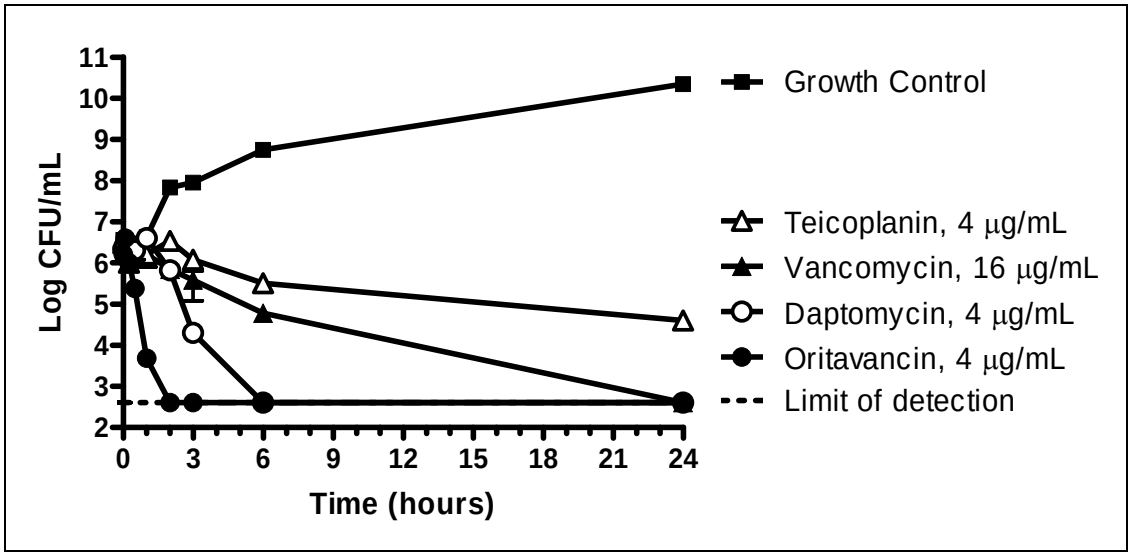


Figure 3-3 **Oritavancin exhibits rapid, bactericidal activity against linezolid-nonsusceptible methicillin-resistant *S. aureus* isolate NRS 121 when tested in vitro at its predicted *f*C_{max} in plasma following standard clinical doses in proposed prescribing information for complicated skin and skin structure infections.**

Retention of antibacterial activity against non-dividing bacteria, bacteria in a biofilm state, and bacteria growing intracellularly is a desirable characteristic because such pathogens are associated with recurrent and relapsing infections in the clinical setting (Stewart and Costerton 2001; Darouiche 2004; Lemaire et al. 2008). The bactericidal activity of oritavancin in vitro extends to stationary-phase cells (Belley et al. 2007b). In contrast, vancomycin activity was bacteriostatic in this test system.

Furthermore, oritavancin cell eradication activity is readily demonstrated against in vitro biofilms. In a representative example of this activity, oritavancin showed the smallest proportional reduction in activity relative to linezolid and vancomycin for biofilm versus planktonic cultures of MSSA, MRSA, and VRSA. Ratios of the minimum biofilm

eradication concentration (MBEC):MIC were lower for oritavancin (MBEC:MIC ratios from 1 to 4) than for vancomycin and linezolid (MBEC:MIC ratio from >32 to >128 and from >8 to >64, respectively) (Table 3-2; Belley et al. 2007b). Indeed, these latter two agents lacked measurable anti-biofilm activity against the three tested strains. Oritavancin's activity against in vitro biofilms extends to *S. epidermidis* and enterococci including VRE (Belley et al. 2007b; Belley et al. 2008a, 2008b).

Table 3-2 Oritavancin Exhibits Anti-biofilm Activity In Vitro Against *S. aureus* Strains of Varying Resistance Phenotypes

	MSSA ATCC 29213[a]		MRSA ATCC 33591[a]		VRSA VRS5[a]	
Agent	**MIC[b] (µg/mL)**	**MBEC[c] (µg/mL)**	**MIC[b] (µg/mL)**	**MBEC[c] (µg/mL)**	**MIC[b] (µg/mL)**	**MBEC[c] (µg/mL)**
Oritavancin	2	2-8	0.5-1	0.5-1	2-4	2-4
Linezolid	8	>128	2	>128	4-16	>128
Vancomycin	1-4	>128	2	>128	>128	>128

Abbreviations: MBEC = minimal biofilm eradication concentration; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; VRSA = vancomycin-resistant *S. aureus*.

[a] Typical CFU/peg for MSSA ATCC 29213, MRSA ATCC 33591, and VRSA VRS5 were $8.1 \pm 3.6 \times 10^5$, $3.9 \pm 2.5 \times 10^5$, and $3.7 \pm 1.4 \times 10^5$, respectively.

[b] MICs (µg/mL) were determined in MBEC plates and represent the antibacterial activity against planktonic cells shed from the peg biofilms. This methodology is not identical to CLSI broth microdilution testing methods for these compounds.

[c] MBEC (µg/mL) determinations followed manufacturer's protocols.

Intracellular penetration and bactericidal activity of an antimicrobial agent against intracellular bacteria are desirable properties since they may contribute to eradication of recurrent infections (Alexander and Hudson 2001). Oritavancin has shown substantial in vitro activity against *S. aureus* and enterococci in models of intracellular infection (Al-Nawas and Shah 1998; Al-Nawas et al. 2000; Van Bambeke et al. 2001, 2004; Seral et al. 2003; Baudoux et al. 2008). In these experiments, oritavancin challenge at concentrations relevant to the recommended clinical therapeutic dose typically reduced intracellular bacterial loads by 2- to 3-log colony forming units (CFU) over 24 hours. Recently, oritavancin intracellular activity has also been demonstrated against small colony variants of *S. aureus* (Nguyen et al. 2007, 2008a, 2008b). The intracellular bactericidal activity of oritavancin is related to its accumulation in lysosomes within macrophages and fibroblasts in tissue culture (Van Bambeke et al. 2001; Seral et al. 2002, 2003; Van Bambeke et al. 2004).

In summary, oritavancin exerts sustained, concentration-dependent bactericidal activity. Furthermore, its demonstrated activity in vitro against stationary-phase cells, biofilms,

and intracellular pathogens is anticipated to be of benefit in recurrent staphylococcal and enterococcal infections.

3.1.1.3 Activity of Oritavancin in Animal Models of Infection

Oritavancin, administered parenterally, is active in numerous animal models of infection that are pertinent to cSSSI, including neutropenic mouse models of *S. aureus* and *S. pyogenes* thigh infection, a rat model of MSSA granuloma pouch infection, mouse models of *S. aureus* and VRE bacteremia, and rabbit models of MRSA and VRE endocarditis. Pharmacodynamic studies in these and other models suggest that once-daily dosing regimens and other less frequent regimens may be possible in humans. Additional details of oritavancin activity in animal models can be found in the references cited in Table 3-3.

Table 3-3 Animal Infection Model Studies in Which Oritavancin Has Demonstrated Efficacy

Host	Disease	Pathogen	Endpoint	Reference
Mouse	Systemic Infection	*E. faecalis*, *E. faecium*	Bacterial burden in tissues	Boylan et al. 1995
Mouse	Systemic Infection	*S. pneumoniae*, *S. aureus*	Survival	Knudsen et al. 1997
Neutropenic Mouse	Thigh Infection	*S. aureus*	Bacterial burden in thigh	Boylan et al. 2003; Okusanya et al. 2008
Mouse	Bacteremia	*S. aureus*	Bacterial burden in blood and spleen	Lehoux et al. 2008a
Neutropenic Mouse	Thigh Infection	*S. pyogenes*	Bacterial burden in thigh	ICPD-00180
Mouse	Pneumonia	*S. pneumoniae*	Bacterial burden in lung	Lehoux 2007a, 2007b
Neutropenic Mouse	Bacteremia	*E. faecium*	Survival; bacterial burden in blood	Schwalbe and Iarocci 1997
Mouse	Inhalation Anthrax	*Bacillus anthracis*	Survival; bacterial burden in lung	Heine et al. 2008
Syrian hamster	*Clostridium difficile* lethal enteritis	*C. difficile*	Survival; toxin production	Lehoux et al. 2008b
Rat	Line Bacteremia	*S. aureus*	Bacterial burden in catheter, blood, tissue	Rupp and Ulphani 1998
Rat	Line Bacteremia	*E. faecalis*, *E. faecium*	Bacterial burden in catheter, blood, tissue	Rupp et al. 2001
Rat	Granuloma Pouch Infection	*S. aureus*	Bacterial burden in blood, pouch exudate	Lehoux et al. 2006
Rat	Endocarditis	*S. aureus*	Bacterial burden in endocardial vegetations; cardiac bioluminescence	Xiong et al. 2008
Rabbit	Endocarditis	*S. aureus*	Bacterial burden in endocardial vegetation, tissue	Kaatz et al. 1998
Rabbit	Endocarditis	*E. faecalis*	Survival	Saleh-Mghir et al. 1999
Rabbit	Endocarditis	*E. faecalis*	Bacterial burden in endocardial vegetation	Lefort et al. 2000
Rabbit	Meningitis	*S. pneumoniae*	Bacterial burden in cerebrospinal fluid	Cabellos et al. 1998
Rabbit	Meningitis	*S. pneumoniae*	Bacterial burden in cerebrospinal fluid	Gerber et al. 2001

3.1.1.3.1 Murine Septicemia Infection Models

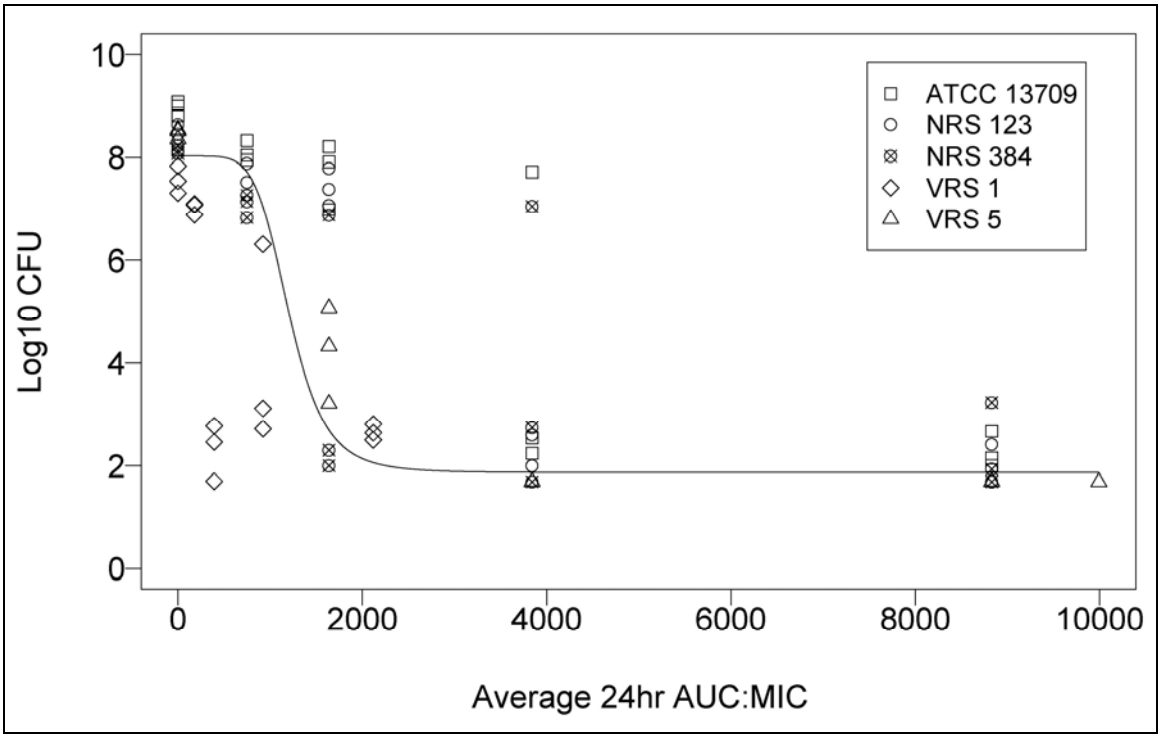
Boylan et al. (1995) compared the efficacy of oritavancin and vancomycin in a murine model of *E. faecium* and *E. faecalis* septicemia. Oritavancin was approximately 100-fold more potent than vancomycin by weight, with a ≥4 $\log_{10}$ reduction in CFU relative to untreated controls at doses of up to 0.16 mg/kg. Subsequently, Knudsen et al. (1997) found that oritavancin was 2- to 3-fold more active by weight than teicoplanin and vancomycin in the pneumococcal murine septicemia model. The effective dose for half-maximal effect (ED_{50}) of oritavancin after single or multiple doses ranged from 0.18 to 2.0 mg/kg.

3.1.1.3.2 Murine Thigh Infection Models

Dose-fractionation design murine thigh infection models serve at least two useful functions, namely, to identify the pharmacokinetic-pharmacodynamic index that is most closely associated with efficacy, and to determine the magnitude of the pharmacokinetic-pharmacodynamic index that is necessary for a given level of effect. Whereas glycopeptides, such as vancomycin, display time-dependent bactericidal activity in vitro against gram-positive pathogens (Chambers and Kennedy 1990; Peetermans et al. 1990), oritavancin displays concentration-dependent bactericidal activity in vitro (Zelenitsky et al. 1997; McKay 2007a). Oritavancin $AUC_{0\text{-}24}$:MIC or C_{max}:MIC ratios are, therefore, expected to be predictive of oritavancin efficacy in animal models of infection (Boylan et al. 2003).

A murine neutropenic thigh model study (Report ICPD 00159; Okusanya et al. 2008) examined oritavancin PK and efficacy against five strains of *S. aureus*, with oritavancin MICs (with polysorbate-80) of either 0.06 µg/mL (ATCC 13709 [MSSA], NRS 123 [USA 400; CA-MRSA], NRS 384 [USA 300; CA-MRSA]) or 0.25 µg/mL (VRS 5 [VRSA] and VRS 1 [VRSA]). One hour after inoculation, neutropenic mice were administered oritavancin in bolus IV doses anticipated to result in oritavancin 24-hour AUC values representative of those expected in human patients administered oritavancin bolus doses of 100, 200, 400, or 800 mg once daily for 3 days or a single 1200-mg dose. Mice were sacrificed up to 72 hours postdose (n=3 per time point) and bacterial burden in infected thighs was determined by serial dilution plating of thigh homogenates.

Figure 3-4 shows a plot of the observed average 24 hour AUC:MIC ratio versus $\log_{10}$ CFU at 48 hours, with a predicted overlay using the overall population mean values. Overall, the correlation coefficient for the fit of the model to the average 48-hour time point data was 0.456.



Abbreviations: AUC = area under the plasma concentration-time curve; hr = hour; MIC = minimum inhibitory concentration.

Figure 3-4 Observed average 24-hour AUC:MIC ratios versus log10 colony-forming unit at 48 hours across five *S. aureus* strains, with a predicted overlay using the overall population mean values.

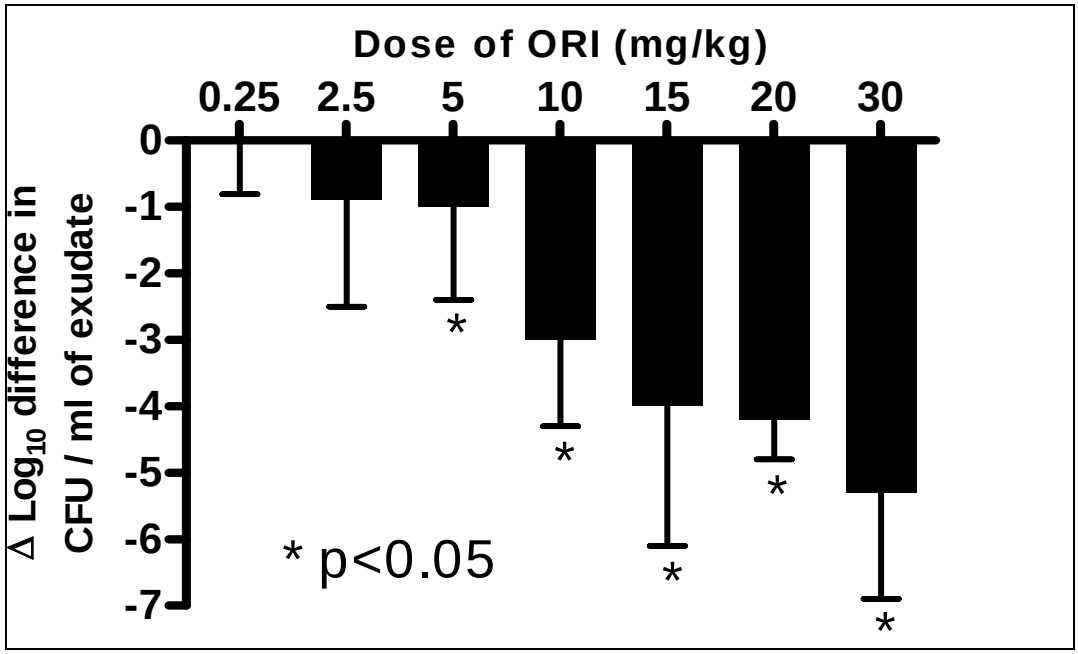
These data and data from an earlier study of *S. aureus* thigh infection in neutropenic mice (Boylan et al. 2003) demonstrated the activity of oritavancin in treating *S. aureus* infections in a model that is of particular relevance to cSSSI. They also showed that a higher, less frequent dose of oritavancin is more active than the same total dose when divided, supporting the conclusion that the AUC:MIC ratio is predictive of oritavancin efficacy. This conclusion is further supported by data from subsequent studies in a mouse model of PSSP pneumonia (Lehoux et al. 2007a, 2007b). These data are consistent with the exposure targets seen in the population pharmacokinetic analysis of the Phase 3 clinical trials (Bhavnani et al. 2008).

A recent study extended the murine neutropenic thigh model data to demonstrate efficacy of humanized dosing regimens of oritavancin against five strains of *S. pyogenes* (ICPD-00180). The oritavancin MICs of the test strains varied between 0.016 and 0.5 µg/mL and therefore represented the range of oritavancin MICs that has been encountered both in clinical studies and in contemporary surveillance (Poulakou and Giamarellou 2008). Interestingly, the MIC appeared to be of little value in predicting the

activity of oritavancin against *S. pyogenes*; as such, efficacy targets were calculated based on AUC alone rather than AUC:MIC. Because doses of oritavancin that in mice provided exposures equivalent to doses of 50 mg in humans were active against all five strains of *S. pyogenes*, the AUC targets obtained suggest that doses of 50 mg a day in humans should be adequate to treat *S. pyogenes* infections.

3.1.1.3.3 Rat Granuloma Pouch Infection Models

The rat granuloma pouch model is useful to evaluate pharmacokinetics and pharmacodynamics in experimentally induced soft-tissue abscesses, which are often associated with human SSSI. Lehoux et al. (2006) explored the relationship between vancomycin and oritavancin doses and in vivo efficacy in the rat granuloma pouch model of MSSA infection. Figure 3-5 shows the dose-response relationship of oritavancin-treated animals relative to untreated controls. The difference in bacterial burden in granuloma pouch exudates between oritavancin-treated and untreated animals was statistically different ($p<0.05$) at doses >2.5 mg/kg. Moreover, a single 30-mg/kg oritavancin dose provided a prolonged reduction in bacterial burden (≥4 log unit CFU/mL) compared with that for a single 100-mg/kg vancomycin dose (96 versus 24 hours; Lehoux et al. 2006). These data demonstrate oritavancin activity against *S. aureus* in an infection model related to cSSSI at daily or less frequent dosing intervals.



Abbreviations: CFU = colony-forming unit; h = hours; ORI = oritavancin.

Figure 3-5 **Efficacy of single oritavancin doses against S. aureus ATCC 13709 (methicillin-sensitive *S. aureus*) compared to the untreated group in the rat granuloma pouch model at 72 hours posttherapy.**

3.1.1.3.4 Rat Bacteremia Models

Rupp and Ulphani (1998) evaluated oritavancin in the rat intravascular catheter-associated *S. aureus* bacteremia model. Of the oritavancin-treated animals, 40%, 80%, 30%, and 30% of the 2.5-, 5-, 10-, and 20-mg/kg groups developed central venous catheter infections, respectively. Higher, infrequent dose regimens tended to be more efficacious than lesser, more frequent regimens. Further, Rupp et al. (2001) evaluated oritavancin against *E. faecium* in the rat intravascular catheter-associated bacteremia model. Of the oritavancin-treated animals, only one animal developed central venous catheter infection.

3.1.1.3.5 Murine Inhalational Anthrax Models

The activity of oritavancin against *Bacillus anthracis* was compared to that of ciprofloxacin, which has FDA approval for infections involving *B. anthracis*. In murine post-exposure prophylaxis and post-exposure treatment models of inhalation anthrax, oritavancin provided similar efficacy to that of ciprofloxacin but with a significantly lower number of doses. In one post-exposure prophylaxis study, a single dose of oritavancin (50 mg/kg) provided 100% 30-day survival and 28 doses of ciprofloxacin (30 mg/kg) provided equivalent survival (90%) (Heine et al. 2008). Further, a single

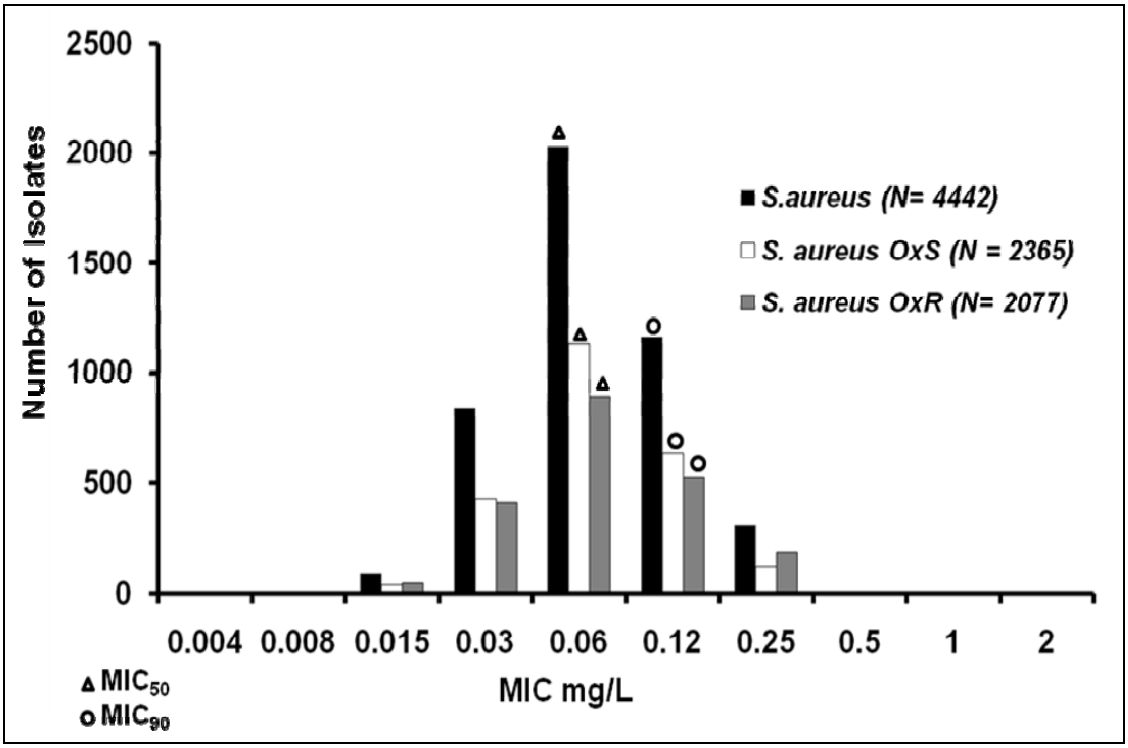
dose of oritavancin administered 14 days prior to lethal challenge provided complete protection in a preexposure anthrax prophylaxis model while single dose ciprofloxacin provided no protection.

3.1.1.3.6 Derivation of Proposed Susceptibility Breakpoints

Oritavancin susceptibility breakpoint proposals were made on the basis of consideration of three principal sources of data, namely, (i) oritavancin MIC distributions against key pathogens encountered in Phase 3 studies of cSSSI and in contemporary surveillance, (ii) pharmacokinetic-pharmacodynamic data from murine neutropenic thigh infection model with *S. aureus* in conjunction with Monte Carlo simulation to assess the probability of pharmacokinetic-pharmacodynamic target attainment by MIC value for *S. aureus* following an oritavancin 200-mg once-daily regimen, and (iii) clinical and microbiological outcome statistics in Phase 3 studies of cSSSI. Derivation of susceptibility breakpoint proposals using these data sources is supported by guidance from the FDA (FDA 2005a), by guidance from standards-setting institutes (NCCLS 2001), and by literature (Mouton et al. 2007; Turnidge and Paterson 2007).

3.1.1.3.6.1 Oritavancin Minimum Inhibitory Concentration Distributions

Oritavancin MIC distributions (as determined by broth microdilution with polysorbate-80; CLSI 2008) for 4442 US isolates of *S. aureus* isolated between 2005 to 2006 show that distributions for oxacillin-susceptible and -resistant isolates are superimposable, with MIC_{50} and MIC_{90} values of 0.06 and 0.12 μg/mL, respectively, for both populations (Figure 3-6). Minimum inhibitory concentrations (MICs) are normally distributed without evidence of a second subpopulation. The oritavancin MIC range of the wild-type population against *S. aureus* extends to at least an MIC value of 0.25 μg/mL.



Abbreviations: MIC = minimum inhibitory concentration; OxR = oxacillin-resistant; OxS = oxacillin-susceptible.

Figure 3-6 Histogram of oritavancin MIC distribution against 4442 strains of S. aureus collected in the United States in 2005 and 2006.

The maximum oritavancin MIC for any gram-positive pathogen in Phase 3 studies for cSSSI was 2 µg/mL for a single isolate of MRSA; this isolate was successfully eradicated following oritavancin treatment. All other baseline cSSSI pathogens (n=802) were inhibited in vitro by ≤0.5 µg/mL oritavancin: maximum oritavancin MICs were 0.25 µg/mL (staphylococci), 0.5 µg/mL (streptococci), and 0.25 µg/mL (enterococci).

3.1.1.3.6.2 Pharmacokinetic-Pharmacodynamic and Target Attainment Modeling

The pharmacokinetic-pharmacodynamic and target attainment modeling is best understood within the overall context of dose justification. Please refer to Section 5.4.2.4.1 for this discussion.

3.1.1.3.6.3 Clinical and Microbiological Outcome Statistics

The clinical and microbiological outcome statistics are best understood within the overall context of dose justification. Please refer to Section 5.4.2.4.2 for this discussion.

3.1.1.4 In Vitro Attempts to Select for Resistance

Studies describing attempts to develop resistance in vitro are described in Section 5.4.1.

3.1.2 Safety Pharmacology

3.1.2.1 In Vitro Studies

In vitro studies were conducted to determine the potential human cardiac ion channel blocking profile of oritavancin. Effects on cardiac sodium current (I_{Na}), transient outward potassium current (I_{to}), sustained current (I_{sus}), inwardly rectifying potassium current (I_{K1}) recorded from isolated human atrial myocytes, or human Ether-a-go-go-Related Gene (hERG) (a stable expressed human I_{Kr} clone) were determined.

Oritavancin blocked the human cardiac INa, Ito, and hERG (I_{Kr}) channels with IC_{50} values of 0.51 µM (1.0 µg/mL), 4.2 µM (8.2 µg/mL), and 22 µM (42.8 µg/mL), respectively. Of note, these in vitro studies were conducted in serum-free media and, therefore, represent free-drug concentration and do not account for plasma protein binding. At ^{14}C-oritavancin concentrations of 1, 10, and 91 µg/mL, binding to human plasma proteins was determined to occur in a range of 86% to 90%. Thus, free-drug concentrations, the parameter most likely to correlate with cardiac tissue concentrations, are 10% to 14% of total plasma concentrations. Furthermore, oritavancin does not appear to accumulate in cardiac tissue (Study R20595 ADME Report 9).

3.1.2.2 Animal Studies

Studies on gastrointestinal motility and on cardiac, renal, and behavioral effects in animals showed no findings that indicate a substantive safety risk for the proposed use of the drug. Significant HLIRs, similar to those observed with vancomycin, occurred in dogs administered doses ≥15 mg/kg as a 30-minute IV infusion, but these reactions were manageable with antihistamines and supportive therapy. Like the reactions associated with vancomycin administration in man (Polk 1991), the severity of these reactions increased with higher doses, concentrations, or faster infusion rates and lessened with repeated administrations.

3.1.2.3 Clinical Follow-Up Based on Nonclinical Safety Findings

As mentioned above, the only notable safety finding in pharmacology studies with oritavancin was a hERG blockage observed in vitro at high concentrations. However, prolongation of the QT/QTc interval did not occur in vivo in dogs. Because of the uncertainty regarding the clinical relevance of the in vitro hERG data, clinical evaluations of the effect of oritavancin on QT were also carried out. An initial QT study

(Study H4Q-LC-ARRO [ARRO]) demonstrated no relationship between QTc and plasma concentrations. An extensive evaluation of cardiovascular safety (including 81 subjects from healthy subject studies, 471 subjects from patient studies, and 58 subjects from the QT/QTc Study OCSI-008) as well as a concentration/effect analysis exploring the relationship between oritavancin concentrations and selected electrocardiogram (ECG) parameters in Study OCSI-008 alone were performed. No clinically relevant effect of oritavancin was observed on QT/QTc interval in either of these analyses. In addition, Targanta conducted Study QT002, a thorough QT/QTc study (FDA 2005b), which demonstrated the expected effect of moxifloxacin (the positive control) on QTc and the absence of consistent, significant effects of 200- and 800-mg IV doses of oritavancin on QTc. The final clinical study report and datasets for Study QT002 were submitted to the NDA as part of the 4-Month Safety Update on May 28, 2008.

3.2 Pharmacokinetics

Absorption, distribution, metabolism, and elimination characteristics of oritavancin have been investigated following IV injection in mice, rats, and dogs, species identical to those used for the toxicological evaluation of the compound.

3.2.1 Absorption and Bioavailability

Due to limitations in sampling and assay sensitivity only a portion of the full pharmacokinetic profile could be determined in rats and dogs. Following single IV doses of oritavancin in rats and beagle dogs the apparent elimination half-lives were 10.8 and 52.5 hours, respectively. After 2 weeks of daily dosing in dogs, maximal plasma concentrations did not change although there were increases in both plasma AUC and the 24-hour trough plasma concentrations from Days 0 to 14, suggesting oritavancin may accumulate in the plasma as suggested from single-dose pharmacokinetics. In rats there was no evidence of plasma accumulation after either 2 weeks or 1 month of daily dosing as suggested from single-dose pharmacokinetics.

3.2.2 Distribution

Distribution of oritavancin was characterized by in vitro plasma protein binding and in vivo tissue evaluations. In vitro plasma protein binding of ^{14}C-oritavancin was investigated. At the clinically relevant ^{14}C-oritavancin concentrations of 1, 10, and 91 μg/mL, binding to human plasma proteins was determined to be 85.7 ± 0.7%, 88.8 ± 0.4%, and 89.9 ±0.9% (average ± standard error of the mean), respectively.

Tissue distribution was characterized in quantitative whole-body autoradiography studies using a 5-mg/kg dose of ^{14}C-oritavancin as well as single- and repeat-dose studies in rats, gravid rats, and dogs using ^{14}C-oritavancin. A 5-mg/kg dose in rats and dogs is approximately 0.2 and 1.2 times the daily human exposure, respectively, based on AUC. Radioactivity associated with ^{14}C-oritavancin was readily distributed from blood to tissues. Peak radiocarbon concentrations in most tissues occurred at 1 or 6 hours postdose; however, radioactivity remained relatively constant in many tissues from 12 to 168 hours postdose. The highest concentrations of radiocarbon were found in liver and intestinal wall, with concentrations ranging from 46.51 to 91.38 µg-equiv/g, respectively. Many tissues including adrenal gland, bone marrow, cecal wall, kidney, salivary glands, and spleen contained moderate concentrations of radioactivity (7.24 to 28.32 µg-equiv/g). Microscopic analyses in repeat-dose toxicity studies have shown that oritavancin is primarily associated with macrophages present in these tissues, hepatocytes, and kidney proximal tubular cells. Brain, eye, and testes contained low or background levels of radioactivity (≤1 µg-equiv/g), indicating that oritavancin does not cross either the blood-brain or the blood-testis barrier in healthy animals. The retention of radiocarbon in tissues following a single IV dose suggests the potential for tissue accumulation after multiple dosing.

In gravid rats, moderate concentrations of radioactivity were present in the placenta and ovary, similar to that observed in other tissues of non-gravid rats. Maternal tissue concentrations remained constant at most time points with detectable concentrations remaining at 24 hours. Radioactivity associated with ^{14}C-oritavancin did not appear to have crossed the placenta. No detectable concentrations were seen in the fetuses by this method of analysis. In lactating rats, radiocarbon associated with ^{14}C-oritavancin was excreted in milk following a single 5-mg/kg IV dose of ^{14}C-oritavancin. The radioactivity associated with ^{14}C-oritavancin excreted in milk was absorbed by nursing pups. Concentrations peaked in nearly all pup tissues at 24 hours with the exception of the pup stomach wall, which peaked at 6 hours. The tissue concentrations were generally low compared to maternal plasma concentration.

3.2.3 Metabolism

Comparison of plasma concentrations of oritavancin to plasma radioequivalent concentrations of ^{14}C-oritavancin suggested there were no circulating metabolites of oritavancin in the plasma. Furthermore, plasma and bile from rats, mice, and/or dogs receiving single IV doses of ^{14}C-oritavancin were evaluated for the presence of

metabolites of oritavancin. These evaluations provided no indication of metabolism of oritavancin in any of the animal species examined (rats, mice, or dogs).

3.2.4 Elimination

The routes of oritavancin's elimination were adequately characterized in animal studies using rats, mice, and dogs. Recovery studies in these three species demonstrated slow elimination of oritavancin via the bile in the feces and retention of radioactivity after single doses of ^{14}C-oritavancin.

3.3 Toxicology

Oritavancin has been evaluated in a comprehensive series of toxicity studies in laboratory animals and in vitro test systems (Table 3-4). The doses were selected for each of the toxicity studies to provide substantial challenge to test animals and cause systemic toxic effects. Low doses were selected to provide a no-observed-effect and/or no-observed-adverse-effect levels. The goal of this program was to adequately characterize the nonclinical toxicity of oritavancin for clinical use. Adequate exposure that mimicked or exceeded the anticipated clinical dose was achieved in the animal studies, as described in this document. Pivotal toxicity and toxicokinetic studies were performed in accordance with Good Laboratory Practice regulations. Applicable International Conference of Harmonisation (ICH), Committee for Medicinal Products for Human Use, and FDA guidance documents were also referred to during the development of the compound.

Table 3-4 Toxicology Program for Oritavancin

Study Type and Duration	Route of Administration	Species	Compound Administered
Single-dose toxicity	Intravenous	Rat, Mouse	Oritavancin
Single-dose toxicity with reversibility	Intravenous	Rat	Oritavancin
Repeat-dose toxicity			
2 weeks	Intravenous	Rat, Dog	Oritavancin
1 month	Intravenous	Rat, Dog	Oritavancin
Repeat-dose toxicity with reversibility			
2 weeks	Intravenous	Rat, Dog	Oritavancin
1 month	Intravenous	Rat, Dog	Oritavancin
13 weeks	Intravenous	Rat, Dog	Oritavancin
Genotoxicity			
Bacterial mutation	In vitro	*Salmonella. typhimurium Escherichia. coli*	Oritavancin
Chromosomal aberration	In vitro	Chinese hamster ovary cells	Oritavancin
Mammalian mutation	In vitro	L5178Y TK+/- cells	Oritavancin
Micronucleus	In vitro	Mouse (bone marrow)	Oritavancin
Reproductive/developmental toxicity			
Fertility/early embryonic development	Intravenous	Rat	Oritavancin
Embryo-fetal development	Intravenous	Rat, Rabbit	Oritavancin
Prenatal/postnatal development	Intravenous	Rat	Oritavancin
Juvenile animals (1 month)	Intravenous	Neonatal rat, Neonatal dog	Oritavancin
Humoral immunotoxicity	Intravenous	Rat	Oritavancin
Cell-mediated immunotoxicity	Intravenous	Rat	Oritavancin
Dermal irritation/toxicity	Dermal	Rabbit	Oritavancin
Ocular irritation/toxicity	Ocular	Rabbit	Oritavancin
Studies on impurities			
14 days	Intravenous	Rat	Oritavancin spiked with impurities
28 days	Intravenous	Rat	Oritavancin spiked with impurities
Bacterial mutation	In vitro	*S. typhimurium E. coli*	Oritavancin spiked with impurities
Micronucleus	In vitro	Mouse (bone marrow)	Oritavancin spiked with impurities

The most important nonclinical safety findings in repeat-dose rat and dog studies were the effects on liver and kidneys and the presence of eosinophilic granules observed in tissue macrophages and liver and kidney cells. In repeat-dose studies in rats, dogs, and rabbits, a dose-related accumulation of cytoplasmic granules was observed in hepatocytes, renal cortical epithelial cells, adrenal cells, and macrophages of the reticuloendothelial system. Ultrastructurally, the granules were identified as secondary lysosomes, containing amorphous electron-dense material and parallel arrays of membranes. The findings were reversible after cessation of treatment. In macrophage cell cultures, high intracellular concentrations of oritavancin were associated with lysosomes (Van Bambeke et al. 2004). Moderate, dose-related increases in liver enzymes (ALT and AST) were observed in rats and dogs and were shown to be reversible upon cessation of treatment.

Clinical signs consistent with histamine-mediated anaphylactoid reactions or inflammatory responses were observed in dogs administered ≥15 mg/kg as a 30-minute infusion (15-mg/kg dose for 14 days produced mean C_{max} = 207.6 μg/mL in dogs and 139.7 μg/mL in rats).

In immunotoxicity studies in rats, no consistent effect on antibody response was seen, but reversible decreases in host resistance and a nonspecific increase in total serum immune globulin M and immune globulin G were observed.

Oritavancin was not genotoxic.

The no-observed-adverse-effect level in the 1-month repeat-dose studies was 5 mg/kg/day for both rats and dogs. A 5-mg/kg dose in rats and dogs is approximately 0.2 and 1.2 times the daily human exposure, respectively, based on AUC. Based on body surface area comparisons, the 5-mg/kg dose is 0.3 and 0.9 times the recommended human dose, respectively. Studies in neonatal rats and dogs for 30 days showed similar effects as those seen in adult animals.

No mutagenic or clastogenic potential was found in a battery of tests, including an Ames assay, in vitro chromosome aberration assay in Chinese hamster ovary cells, in vitro forward mutation assay in mouse lymphoma cells and an in vivo mouse micronucleus assay. Daily doses up to 30 mg/kg of oritavancin administered intravenously did not affect the fertility or reproductive performance of male and female rats. The maximum exposure in rats was approximately 0.5 and 1.1 times the human exposure, respectively, based on the AUC. Based on body surface area comparisons, the 30-mg/kg dose is

1.6 times the recommended human dose. Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of oritavancin.

A number of the toxicology findings summarized above provided guidance for safety assessment in subsequent clinical studies. Table 3-5 presents the relevant nonclinical toxicology findings and how they relate to findings from the clinical investigation of oritavancin.

Table 3-5 Nonclinical Toxicology Findings That Provided Guidance for Clinical Investigation

Toxicity End Point	Nonclinical Findings	Clinical Investigation
Injection-site inflammation	Injection-site inflammation was noted in all repeat-dose studies in rats and dogs.	Results: Section 7.3.1 In patients with cSSSI the incidence of injection site phlebitis was comparable between oritavancin and vancomycin given at equipotent doses.
Histamine-like infusion reactions (HLIRs)	In all repeat-dose studies in dogs, HLIRs were more pronounced at the beginning of the study and were treated with antihistaminics.	Results: Section 7.3.2 and Table 7-5 Lower but not significantly different percentages of HLIRs compared to vancomycin.
Possible adverse effect on renal function	In some repeat-dose studies in rats and dogs, there were sporadic minimal increases in blood urea nitrogen, minimal urine changes and degeneration and mineralization of tubular cells, the presence of granular material in tubular cells, and moderate oritavancin tissue distribution to kidney.	Results: Section 7.3.3, Table 7-6, and Figure 7-6 No evidence of a clinically relevant effect on renal function.
Possible inflammatory effect associated with the presence of ORI	In some repeat-dose studies in rats and dogs, there were slight decreases in red blood cells, white blood cells, and thrombocytes, increases in serum globulin, and nonspecific increase in total serum immune globulin M and immune globulin G in rat immunotoxicity studies.	Results: Section 7.3.6 and Table 7-7 No evidence of a clinically relevant effect on hematology parameters.
Hepatotoxicity	In all repeat-dose studies in rats and dogs, consistent mild to moderate increases in ALT and AST, single cell necrosis and presence of granular material in hepatocytes, and high oritavancin tissue distribution to liver.	Results: Section 7.4 and Table 7-8 No evidence of an effect consistent with hepatic toxicity or altered hepatic function.
Potential for QT/QTc prolongation	In vitro oritavancin blocked Ina, Ito, and hERG (Ikr) cardiac ion channels in serum free media. In vivo dog studies did not show any evidence of QT/QTc interval prolongation.	Results: Section 7.7 No evidence of a clinically relevant effect on QT/QTc interval.
Potential for Immunosuppression	A host resistance study in rats showed an approximately 30% decrease in survival at 5 mg/kg after a *Candida albicans* challenge. The effect was fully reversible upon cessation of treatment. Repeat-dose studies up to 3 months did not show any increased mortality due to infection. No histological evidence of lymphoid tissue or bone marrow atrophy was observed in vivo in rats or dogs.	Results: Section 7.2.1 No difference in mortality between treatment groups. No evidence of a clinically relevant effect on white blood cell parameters.

4 Overview of Clinical Studies

As of the NDA submission data cutoff date of September 17, 2007, there were 16 completed clinical studies:

- Two Phase 3 studies demonstrating the safety and efficacy of oritavancin for the treatment of cSSSI (Studies ARRD and ARRI).
- Three Phase 2 studies, one demonstrating the safety and efficacy of oritavancin for the treatment of cSSSI and uSSSI (Study H4Q-MC-ARRL [ARRL]) and two demonstrating initial safety and efficacy of oritavancin for the treatment of bacteremia (H4Q-MC-ARRM [ARRM] and H4Q-MC-ARRC [ARRC]).
- Eleven other supportive clinical studies in humans, evaluating safety and pharmacokinetics.

Table 4-1 presents a summary of the 16 clinical studies that were completed at the time of the NDA submission data cutoff date.

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
H4Q-LC-ARRA	Phase 1, single-dose escalation, open-label, non-controlled study in healthy subjects	15	Single IV dose of oritavancin from 0.02 mg/kg to 0.5 mg/kg, administered in D5W over 60 min. The primary objective was to evaluate the safety of single doses of oritavancin in healthy subjects.	The doses studied appeared to be safe and were well-tolerated. The pharmacokinetic parameters were linear within the dose range. The mean plasma half-life of oritavancin was 195 hours (about 8 days) and systemic clearance was very slow.
H4Q-LC-ARRK	Phase 1, single-dose escalation, open-label, non-comparator-controlled study in healthy subjects	11	Single IV dose of oritavancin of 0.5, 1, 2, and 3 mg/kg, administered in D5W over 30 min. The primary objective was to evaluate the safety and tolerability of oritavancin in healthy subjects.	The doses studied appeared to be safe and were well-tolerated. The pharmacokinetic parameters were linear within the dose range. Clearance was low and the steady-state volume of distribution was modest.
H4Q-LC-ARRB	Phase 1, multiple-dose escalation, open-label, non-comparator-controlled study in healthy subjects	10	Multiple once-daily IV doses of oritavancin 1.5 mg/kg for 2, 3, 5, or 7 days. All doses were administered in D5W over 30 min. The primary objective was to evaluate the safety and tolerability of oritavancin in healthy subjects.	The doses studied appeared to be safe and were well-tolerated. Inspection of ECGs and other safety measures revealed no clinically relevant safety concerns. Oritavancin mean maximum plasma concentrations did not increase with multiple dosing. The mean minimum plasma concentrations increased >2-fold with multiple dosing.
H4Q-JE-101N	Phase 1, single-dose, open-label, non-comparator-controlled Japanese study in healthy subjects	26	Single IV dose of oritavancin of 0.02, 0.08, 0.2, 0.5, 1.0, 2.0, or 3.0 mg/kg administered in D5W over approximately 30 min. The primary objective was to evaluate the safety and tolerability of oritavancin in healthy Japanese subjects.	The doses studied appeared to be safe and were well-tolerated. The pharmacokinetic parameters in Japanese males were consistent with the previous US-based clinical pharmacology studies in healthy subjects.

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Continued)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
H4Q-LC-ARRO	Phase 1, subject-blind, dose-escalation study of single-dose placebo lead-in followed by single-dose oritavancin in healthy subjects	16	Single dose of placebo, followed by single IV dose of oritavancin 100, 200, 400, or 600 mg (unit dose). All doses were administered in D5W as follows: 100 and 200 mg over 30 min, 400 mg over 60 min, and 600 mg over 75 min. The primary objective was to evaluate the effect of oritavancin on the QTc interval in healthy male and surgically sterile or anovulatory female subjects.	The doses studied appeared to be safe and were well-tolerated. No relationship was observed between QTc and plasma concentrations. The pharmacokinetic parameters were linear within the dose range. No effect of either body weight or gender on clearance or volume of distribution. Clearance and steady-state volume of distribution were consistent with previous studies.
H4Q-LC-ARRN	Phase 1, subject-blind, placebo lead-in, multiple-dose, dose-escalation study in healthy subjects	20	Two doses of IV placebo followed by 10 daily IV doses of oritavancin at 100, 150, or 200 mg unit doses. All doses were administered in D5W over 60 min. The primary objective was to evaluate the effect of oritavancin on ECG intervals (including the QTc interval) in healthy male or surgically sterile or anovulatory female subjects.	The doses studied appeared to be safe and were well-tolerated. There was a trend toward a lower number of adverse events with a slower and/or more dilute infusion. No relationship was observed between QTc and plasma concentrations. Accumulation appeared to be dose-independent.
OCSI-004	Phase 1, single-dose, open-label, parallel study of oritavancin in moderately hepatically impaired subjects compared to matched healthy subjects	40 (20 healthy and 20 hepatically impaired)	Single IV dose of oritavancin 800 mg administered in D5W over 90 min. The objective was to evaluate and characterize the pharmacokinetics and safety of oritavancin in subjects with moderate liver insufficiency (Child-Pugh Class B) compared with healthy subjects.	A single IV infusion of oritavancin appeared to be safe and was well-tolerated by both hepatically impaired subjects and healthy subjects. Observed differences in plasma pharmacokinetics in hepatically impaired subjects and in healthy subjects do not indicate a necessity of a dose adjustment for hepatically impaired subjects.

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Continued)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
OCSI-007	Phase 1, open-label, drug-interaction study to assess the effect of oritavancin on the pharmacokinetics of desipramine in healthy subjects	31	Desipramine 50 mg PO daily Days 1–21 and oritavancin 800 mg IV daily Days 8-21. All IV doses were administered in D5W over 90 min. The primary objective was to assess the effect of oritavancin on the pharmacokinetics of desipramine.	Oritavancin administration was associated with mild to severe injection site phlebitis, which led to early termination of study drug administration by InterMune. No pharmacokinetic conclusions can be drawn due to the lack of blood samples collected in this terminated study.
OPUL-001	Phase 1, multiple-dose, open-label, study assessing drug levels in bronchoalveolar lavage and alveolar macrophages of oritavancin and vancomycin in normal healthy adults	32 (20 ORI and 12 VAN)	Oritavancin 800 mg IV daily x 5d administered in D5W at an infusion rate not to exceed 10 mg/kg/h; vancomycin 1000 mg IV every 12h x 5d administered in D5W at an infusion rate not to exceed 30 mg/kg/h. The primary objective was to determine and compare the steady-state concentrations of oritavancin and vancomycin in plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM) in healthy, nonsmoking adults who underwent bronchoscopy and bronchoalveolar lavage (BAL) at selected time intervals	Oritavancin penetrates into the ELF and the AM at doses that are safe and well-tolerated in healthy volunteers. During the 24 hours following the last dose, mean ELF concentrations ranged from 3.1 to 6.3 μg/mL and were similar in magnitude to vancomycin while mean AM concentrations ranged from 113.1 to 179.4 μg/mL and were nearly 3-fold higher than vancomycin. Seven days after the last dose, the mean values for concentrations of oritavancin in ELF and AM of all subjects were 1.7 and 557.9 μg/mL, respectively. The highest concentrations of oritavancin in ELF and AM were observed at 24 hours and 7 days, respectively.

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Continued)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
OCSI-001	Phase 1, open-label, skin-blister study of single and multiple doses of oritavancin in healthy male subjects 19 to 51 years	17 (8 in Group A and 9 in Group B)	**Group A:** Oritavancin 200 mg IV daily x 3d administered in D5W over 60 min **Group B:** Oritavancin 800 mg IV daily x 1d administered in D5W over 90 min. **Primary objective:** To evaluate and characterize the pharmacokinetic profile of oritavancin penetration into skin blister fluid after administration in normal healthy male subjects.	Total-drug oritavancin exposure in interstitial fluids was approximately 20% of that in plasma, regardless of dosing regimen tested. Oritavancin levels are maximal in blister fluid 9 to 10 h after dosing and decrease to undetectable levels 100 to 150 h after the last dose. Oritavancin AUC_{0-24}:MIC ratios associated with in vivo efficacy were met or exceeded in blister fluid, supporting a 200-mg, once-daily regimen.
OCSI-008	Phase 1, open-label, drug-interaction study to assess the effect of oritavancin on the pharmacokinetics of desipramine and on the QTc interval of healthy adults	64 (32 in Arm A and 32 in Arm B)	**Arm A:** Desipramine 50 mg PO daily from Day 1 to 7 followed by desipramine 50 mg PO daily and oritavancin 800 mg IV (administered in D5W over 90 min) daily for 14 consecutive days (Days 8 to 21). **Arm B:** Placebo PO daily from Day 1 to 7 followed by placebo PO daily and oritavancin 800 mg IV (administered in D5W over 90 min) daily for 14 consecutive days (Days 8 to 21). **Primary objectives:** To assess the effect of IV oritavancin on the pharmacokinetics of oral desipramine and to assess the effect of oritavancin on the QTcF.	The study was halted due to higher rates of injection phlebitis than previously observed. Therefore, the second cohort of patients received only 3 to 4 doses of oritavancin. Given these facts, the primary pharmacokinetic assessments were limited to the comparison of Day 8 with Day 7 data (that is, after subjects had received a single 800-mg dose of oritavancin). Nevertheless, 800-mg IV dose of oritavancin did not appear to influence the metabolism of desipramine in this study; additionally, oritavancin pharmacokinetics were not affected by the administration of desipramine. Oritavancin did not have a clinically relevant effect on the QTc interval.

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Continued)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
H4Q-MC-ARRL	Phase 2, open-label, non-comparator-controlled, dose escalation study in patients with SSSI	29	QD doses of: 1.5 mg/kg x 7d, 2.0 mg/kg x 7d, 3.0 mg/kg x 7d, 3.0 mg/kg x 3d, 3.0 mg/kg x 1d, 6.0 mg/kg x 1d, and 9.0 mg/kg x 1d. The primary objective was to establish the safety of up to 7 dose regimens of oritavancin in patients with SSSI.	Oritavancin was generally well-tolerated without any serious adverse events ascribed to study drug. Favorable clinical responses (cure or improvement) were noted in 20 (69.0%) of 29 patients over the multiple dose regimens at the end of therapy.
H4Q-MC-ARRC	Phase 2, open-label, multicenter, dose escalation study in patients with gram-positive bacteremia	27	Three oritavancin regimens: 3.0 mg loading dose the first day followed by 2.0 mg/kg/day (3/2 dose group); 4.0 mg loading dose the first day followed by 3.0 mg/kg/day (4/3 dose group); and 5.0 mg loading dose the first day followed by 4.0 mg/kg/day (5/4 dose group). The primary objective was to establish the safety and efficacy of up to 3 dose regimens of oritavancin in patients with gram-positive bacteremia.	Oritavancin was generally well-tolerated. Twenty-seven patients were entered into the study and evaluated for safety but only 15 patients met the specific requirements for inclusion in the efficacy analysis. The limited number of data obtained in the 3/2 (3 patients) and 4/3 (2 patients) dose groups did not support expansion of those treatments; thus, the 5/4 (10 patients) dose group was selected for expansion. Favorable bacteriologic response was observed in 9 of the 10 patients in the 5/4 dose group, mostly with enterococci (both VRE and VSE bacteremia).

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Continued)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
H4Q-MC-ARRM	Phase 2, randomized, open-label, multicenter, active-comparator study in patients with *S. aureus* bacteremia	123 (86 ORI and 37 VAN)	Oritavancin was given at the following doses: 5.0, 6.5, 8.0, 10.0, 12.0, or 14.0 mg/kg/d. The positive control group was given IV vancomycin every 12 hours; patients with MSSA may also have received a cephalosporin or another β-lactam antibiotic. The primary objective was to test the hypothesis that the safety of up to six different dose levels of oritavancin in the treatment of subjects with *S. aureus* bacteremia is at least equivalent to that of the positive control.	Oritavancin was well-tolerated compared with the positive control with no indication of any unexpected adverse systemic effects. All doses of oritavancin were noninferior to the vancomycin control.
H4Q-MC-ARRD	Phase 3, double-blind, randomized, multicenter, active-comparator study in patients with cSSSI	517 (173 ORI 1.5; 169 ORI 3.0; and 175 VAN)	Oritavancin was administered in two regimens, 1.5 and 3.0 mg/kg/day. Vancomycin/cephalexin were dosed at 15 mg/kg twice daily and 500 to 1000 mg twice daily, respectively. The primary objective of the study was to test the hypothesis that once-daily infusions of oritavancin provide clinically successful treatment equivalent to that of vancomycin/cephalexin in the treatment of patients with gram-positive cSSSI.	Oritavancin efficacy was comparable to that of vancomycin and met the primary and secondary endpoints. Both regimens of oritavancin were safe, well-tolerated, and demonstrated adverse event profiles similar to vancomycin/cephalexin.

(continued)

Table 4-1 Completed Studies in the Oritavancin Clinical Development Program at the Submission Data Cutoff Date (Concluded)

Protocol	Design	N	Treatment Groups/Primary Objective	Conclusions
H4Q-MC-ARRI	Phase 3, double-blind, randomized, multicenter, active-comparator study in patients with cSSSI	1246 (831 ORI and 415 VAN)	**ORI:** IV phase: Oritavancin was administered as a daily infusion of 200 mg followed approximately 12 h later by an infusion of 250 mL D5W. Oral phase: To maintain the study blind, patients who met the IV-to-oral switch criteria were to receive two placebo capsules every 12 hours. **VAN:** IV phase: Patients with normal creatinine clearance received infusions of 15 mg/kg of vancomycin twice daily while patients with reduced creatinine clearance received 10 to 12 mg/kg. Oral phase: Patients who met the IV-to-oral switch criteria were to receive two 500-mg capsules of cephalexin every 12 hours for up to 11 days. **Primary objective:** To determine whether oritavancin was as clinically effective as vancomycin/cephalexin in the treatment of patients with cSSSI caused by gram-positive bacteria.	Oritavancin efficacy was comparable to that of vancomycin and met the primary and secondary endpoints. Oritavancin had superior tolerability compared with vancomycin/cephalexin.

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; cSSSI = complicated skin and skin structure infections; d = day; D5W = 5% dextrose solution; h = hour; IV = intravenous; MIC = minimum inhibitory concentration; min = minutes; MSSA = methicillin-sensitive *S. aureus*; N = number of individuals enrolled; ORI = oritavancin; PK = pharmacokinetics; PO = oral; QD = once daily; QTc = QT interval corrected for heart rate; QTcF = QTc interval using the Fridericia method; SSSI = skin and skin structure infections; VAN = vancomycin; VRE = vancomycin-resistant enterococci; VSE = vancomycin-sensitive enterococci; x = times.

In addition to the 16 completed clinical studies, there were 3 ongoing clinical studies at the time of the submission data cutoff date of September 17, 2007, Study VT001 (a Phase 1 vein tolerance study), Study QT002 (a Phase 1 thorough QT/QTc study), and Study SD001 (a Phase 2 single- and infrequent-dose cSSSI study). All of these studies are now completed and there are no active clinical studies at this time. Because Studies VT001 and QT002 were completed prior to the NDA submission date of February 7, 2008, the final clinical study report for Study VT001 and the ECG expert report for Study QT002 were both included in the NDA. Under an agreement with FDA, the final clinical study report and datasets for Study QT002 as well as a safety update on Study SD001 were submitted as part of the 4-Month Safety Update on May 28, 2008.

5 Clinical Pharmacology

Oritavancin pharmacokinetics have been characterized in healthy subjects, subjects with hepatic cirrhosis, patients with uSSSI, patients with cSSSI, and patients with bacteremia in 15 clinical studies:

- Eleven Phase 1 clinical pharmacology studies (ARRA, ARRK, ARRB, JE-101N, ARRO, ARRN, OCSI-004, OCSI-007, OPUL-001, OCSI-001, and OCSI-008)
- Three Phase 2 studies (ARRL, ARRC, and ARRM)
- One Phase 3 study (ARRD)

Note: Phase 3 Study ARRI did not include pharmacokinetic endpoints.

The individual pharmacokinetic results from these 15 studies are augmented by the results of a population pharmacokinetic analysis of data pooled from a total of 560 subjects from 12 of the 15 studies: 200 from the Phase 1 studies, 86 from one of the two Phase 2 bacteremia studies, 29 from the Phase 2 SSSI study, and 245 from the Phase 3 cSSSI study.

Pharmacokinetic analyses from the individual study reports demonstrate that the pharmacokinetic profile of oritavancin is similar in healthy volunteers and in patients with uSSSI, cSSSI, or bacteremia. Based on the integrated population pharmacokinetic analysis, however, patients in the Phase 2 and 3 studies have an increased clearance by an average of 30% when compared to subjects in Phase 1 studies. Overall, oritavancin pharmacokinetics are comparable in animals (observed from the nonclinical studies) and humans.

5.1 Pharmacokinetic Characteristics

The initial Phase 1 clinical studies in healthy subjects demonstrated that oritavancin is well-tolerated with single doses at all doses tested (up to 800 mg), with repeated doses at all doses tested (up to 800 mg) for up to 4 days, and with repeated doses of 200 mg for up to 10 days. The single-dose pharmacokinetics of oritavancin were linear at all doses tested (ranging from 0.05 to 10 mg/kg and from 100 to 800 mg.) In most subjects, plasma concentrations declined to <11% of the C_{max} within the first 24 hours. Predicted pharmacokinetic parameters following multiple doses demonstrated a mean alpha half-life ($t_{½,\alpha}$) of 2.8 hours, a beta half-life ($t_{½,\beta}$; tissue distribution phase) of approximately 33 hours, and a gamma half-life ($t_{½,\gamma}$; terminal phase) of 320 hours in Phase 1 studies. Plasma pharmacokinetics of oritavancin after multiple doses was consistent with the

single-dose pharmacokinetics. Once-daily IV administration of 200 mg for up to 10 days demonstrated that C_{max} and $t_{½}$ values were consistent with oritavancin single-dose pharmacokinetics. There was no increase in C_{max}; however, there was an approximate 2.8-fold increase in minimum concentration (C_{min}). Accumulation appeared to be dose independent over the dose range studied.

The population pharmacokinetics of oritavancin in patients with uSSSI, cSSSI, or bacteremia were similar to those of healthy volunteers, with the exception that clearance was increased in Phase 2 and 3 patients by an average of 30% after accounting for differences in body weight. The pharmacokinetic parameters of oritavancin in the Phase 2 and 3 studies are presented in Table 5-1.

Table 5-1 Mean Pharmacokinetic Parameters of Oritavancin in Patients in Phase 2 and Phase 3 Studies (N=360)

Variable	Mean (SD)
CL (L/h)	0.601 (0.204)
V_c (L)	7.10 (2.46)
$T_{1/2,\alpha}$ (h)	2.04 (0.440)
$T_{1/2,\beta}$ (h)	31.2 (11.4)
$T_{1/2,\gamma}$ (h)	393 (73.5)
AUC_{0-24} (mg•h/L)[a]	139 (60.2)
C_{max} (mg/L)[a]	27.3 (12.1)
C_{min} (mg/L)[a]	1.90 (1.02)

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; CL = total clearance; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; min = minimum; h = hour; max = maximum; SD = standard deviation; $T_{1/2,\alpha}$ = alpha elimination half-life; $T_{1/2,\beta}$ = beta elimination half-life; $T_{1/2,\gamma}$ = gamma elimination half-life; Vc = central volume of distribution.

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

5.1.1 Absorption

Oritavancin, in its current formulation, is administered intravenously to achieve systemic concentrations effective for cSSSI; its oral bioavailability is low, but not completely characterized. Like other glycopeptides, it is expected to be poorly absorbed across an intact gastrointestinal tract due to its high molecular weight (1989.1 Daltons).

Oritavancin is excreted in breast milk; nonclinical radioactivity data in nursing rats indicate that oritavancin is orally absorbed by these neonatal animals. Caution should be exercised if oritavancin is administered to nursing women.

5.1.2 Distribution

Oritavancin is extensively distributed in tissues, including those relevant to cSSSI, and is concentrated in macrophages. Oritavancin is 86% to 90% protein bound in human plasma. Although oritavancin binds primarily to albumin, the impact of human serum albumin on oritavancin's activity in vitro is modest. Based on the integrated population pharmacokinetic analysis (which included Phase 1, 2, and 3 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 + V2 + V3) is approximately 110 L, further suggesting that oritavancin is widely distributed to tissues.

Distribution of oritavancin was examined in two Phase 1 studies that evaluated the oritavancin pharmacokinetic profile and penetration into skin blister fluid and in the lungs of healthy volunteers. Study OCSI-001 demonstrated that blister fluid concentrations exceeded the MIC_{90} of oritavancin against *S. aureus* (0.25 ug/mL) for more than 72 hours when oritavancin was administered 200 mg once daily for 3 days or as a single 800-mg dose. Study OPUL-0001 demonstrated that oritavancin, given at 800 mg once daily for 5 consecutive days, is distributed into and out of lung epithelial lining fluid, and that the mean concentrations of oritavancin in alveolar macrophages (113 to 179 ug/ml) were higher than those of the epithelial lining fluid (3.1 to 6.3 ug/ml).

5.1.3 Metabolism

There is no evidence in any in vitro, animal, or human study that oritavancin is metabolized.

Due to the very long residence time of oritavancin in the body (~40 weeks), the challenges of collecting urine and feces for several months, as well as the inability to gain IRB approval for administering a radioactive substance to humans with such a long residence time, no radio-labeled studies have been conducted in humans. However, urine and feces were collected in several Phase 1 studies (Studies ARRA, ARRK, and JE-101N), which assisted with evaluating oritavancin's disposition and elimination profile. The inability to detect metabolites in human urine and plasma is consistent with the lack of metabolism of oritavancin in humans. Based on the extensive animal data, and because drugs that are structurally similar to oritavancin are only minimally metabolized, if at all, it is reasonable to conclude that oritavancin is unlikely metabolized in humans.

5.1.4 Elimination

Oritavancin is excreted unchanged in feces and urine. Mean population-predicted half-lives in the Phase 2 and 3 patients are similar to those in healthy volunteers with predicted α, β, and γ serum half-lives of approximately 2, 31, and 393 hours, respectively.

Studies ARRA, ARRK, and JE-101N provide information on the elimination of oritavancin in humans. Due to the tissue accumulation and slow elimination of oritavancin, very little oritavancin was excreted in the urine and feces (≤5% total) up to 2 weeks after administration of a single dose of oritavancin. This observation suggests that the terminal elimination half-life of oritavancin is in excess of 2 weeks.

5.2 Special Populations

A population pharmacokinetic model was developed to describe the disposition of oritavancin using data from a pooled population of Phase 1 subjects and Phase 2 and 3 patients with uSSSI, cSSSI, or bacteremia. The population pharmacokinetic analysis pooled data from 12 studies: nine Phase 1 studies conducted in healthy subjects (ARRA, ARRB, ARRK, ARRN, ARRO, OCSI-001, OCSI-004, OCSI-008, and OPUL-001); two Phase 2 studies in subjects with uSSSI and cSSSI (ARRL) or bacteremia (ARRM); and one Phase 3 study in patients with cSSSI (ARRD).

The population pharmacokinetic model combined data from a total of 560 subjects (with a total of 6336 oritavancin plasma concentrations) and assessed the impact of subject demographic and disease characteristics on intersubject variability for selected pharmacokinetic parameters. The model demonstrated that gender, race, hepatic impairment, and renal impairment had no effect on the pharmacokinetics of oritavancin; thus, there is no need to adjust dose based on those demographics. Age had a minimal impact on dose-normalized C_{max} and does not warrant dosage adjustment in elderly patients. Body size had a clinically relevant impact on the pharmacokinetics of oritavancin. For clearance, the most significant relationship was observed in subjects with >80 kg of total body weight, with clearance increasing linearly above 80 kg. There was no relationship between total body weight and clearance in subjects of ≤80 kg. As expected given the relationship between clearance and total body weight, the heaviest individuals have the fastest apparent clearance of oritavancin from the plasma and lowest exposure (in terms of $AUC_{0\text{-}24}$). The magnitude of this drop is sufficient to warrant a higher dose in the heaviest individuals (that is, those >110 kg [242 lbs]). Proposed labeling recommendations state that patients over 110 kg (242 lbs) should receive 300 mg oritavancin.

The population pharmacokinetic data were sufficient to develop the model and support prescribing information for the populations who will need this therapy.

5.3 Potential for Drug Interactions

The in vitro and in vivo cytochrome P450 interaction studies and the lack of metabolism observed for oritavancin indicate a low likelihood of drug interactions through these mechanisms. The order of potential inhibition by oritavancin of the metabolism of coadministered drugs by the cytochrome P450 isoforms was determined to be CYP2D6>CYP3A4>CYP1A2>CYP2C9. The clinical relevance of these predictions depends on the concentration of oritavancin available to the active site of these enzymes.

Study OCSI-008 was designed to assess the effect of oritavancin on the pharmacokinetics of desipramine, a CYP2D6 substrate. Although the study was terminated early by InterMune due to the incidence and severity of injection site phlebitis, the data gathered were adequate to investigate the interaction of the drugs and to conclude that an 800-mg IV dose of oritavancin (4 times the intended label dose of 200 mg oritavancin in cSSSI) did not influence the metabolism of desipramine in healthy subjects. This conclusion provides evidence that oritavancin has no clinically relevant effect on CYP2D6 enzyme activity. In addition, desipramine did not influence the disposition of oritavancin.

5.4 Pharmacokinetics-Pharmacodynamics

The pharmacokinetics-pharmacodynamics of oritavancin in patients with cSSSI were evaluated in the Phase 3 study, ARRD. The pharmacokinetic-pharmacodynamic analyses were conducted to evaluate the relationships between clinical response at the first follow-up visit (assessed at end of therapy + 21 to 35 days) and oritavancin exposure for patients with cSSSI, particularly those associated with *S. aureus* and/or *S. pyogenes*. In animal models of gram-positive bacterial infection, both AUC:MIC and C_{max}:AUC are predictors of efficacy (Boylan et al. 2003; Lehoux 2007a; Report ICPD-00159; Report ICPD-00180). At the time of this writing, the pharmacokinetic-pharmacodynamic relationship (in particular, the $AUC_{0–24}$:MIC ratio or the C_{max}:MIC ratio) that is the best predictor for the effectiveness of oritavancin in patients with cSSSI has not been fully defined. The following sections present the microbiologic profile of oritavancin in vitro and are the basis for determining what constituted an adequate exposure for microbiological efficacy.

5.4.1 Potential for Oritavancin Resistance Development

At least two potential routes exist for oritavancin resistance development; namely, the evolution of current glycopeptide resistance mechanisms (that is, Van operons and the

possibility that thicker cell walls that are seen in some VISA isolates are causally related to higher glycopeptide MICs) and development of a new mechanism in strains not exhibiting preexisting glycopeptide resistance. Several lines of evidence support the propositions that oritavancin is unlikely to engender high-level resistance and that resistance to oritavancin is not pervasive in contemporary, clinically relevant gram-positive bacteria, including glycopeptide-resistant strains.

The multiple mechanisms of action of oritavancin (Section 3.1.1.1) are likely to impede the emergence of oritavancin resistance because bacteria would need to overcome two or more mechanisms while retaining viability and fitness. Upregulation of efflux mechanisms is not predicted to reduce oritavancin susceptibility since the targets for oritavancin are cell-surface located.

Broth microdilution studies have demonstrated that elevated oritavancin MICs are rare among current gram-positive cSSSI pathogens, including glycopeptide-intermediate and -resistant strains (Arhin et al. 2008a; Bouchillon et al. 2008; Draghi et al. 2008; Fritsche et al. 2008; Pankuch and Appelbaum 2008; Poulakou and Giamarellou 2008; Sahm et al. 2008a, 2008b; Saravolatz et al. 2008; Vashisht et al. 2008; Vaudaux et al. 2008). The maximum oritavancin MIC observed for any gram-positive pathogen from surveillance of approximately 9000 recent isolates was 4 µg/mL (Table 3-1) and from Phase 3 studies in cSSSI, 2 µg/mL (Section 3.1.1.3.6). Furthermore, results from 20-step selection experiments in vitro based on broth microdilution methodology with polysorbate-80 (Study TT004) predict that emergence of strains with high-level oritavancin resistance will be rare among clinically relevant bacteria. In these experiments, oritavancin MICs against representative oritavancin-selected MSSA, MRSA, and vancomycin-nonsusceptible strains of *S. aureus* were increased maximally by three doubling dilutions with respect to naïve MICs, with oritavancin MICs of any selectant not exceeding 1 µg/mL. The oritavancin MIC_{90}s and MIC distributions from surveillance with contmporary clinical isolates suggest an absence of cross-resistance with VanB and VanC phenotypes in enterococci (Draghi et al. 2007) and with vancomycin resistance in *S. aureus* (Grover et al. 2007). Isolates of hVISA, VISA, and VanA VRE typically demonstrate oritavancin MIC_{90} values of 1 µg/mL (Draghi et al. 2007; Arhin et al. 2008a; Pankuch and Appelbaum 2008; Poulakou and Giamarellou 2008; Saravolatz et al. 2008; Vashisht et al. 2008).

5.4.2 Dose Justification

The rationale for the selection of oritavancin's final recommended dosing regimen (200 mg/day [300 mg/day for patients weighing more than 110 kg (242 lbs)] for 3 to 7 days) takes into account results obtained both prospectively and retrospectively from Study ARRI, the Phase 3 study that used that same dosing regimen.

Pre-Study ARRI results taken into consideration include:

- Results of animal models and Phase 2 Study ARRL (Lilly)
- Phase 3 Study ARRD pharmacokinetic-pharmacodynamic results (Lilly)

Post-Study ARRI results taken into consideration include:

- Phase 3 Study ARRD pharmacokinetic-pharmacodynamic results (Targanta and the Institute for Clinical Pharmacodynamics [ICPD])
- Phase 1 skin blister study, Study OCSI-001 (InterMune)
- Breakpoint analysis (Targanta and ICPD)
- Phase 3 Study ARRI pharmacokinetic surrogates–pharmacodynamic results (Targanta).

Retrospective pharmacokinetic-pharmacodynamic results based on MIC values determined in the absence of polysorbate-80 were reconducted based on MICs determined with the new broth dilution method, which now includes 0.002% polysorbate-80 and for which quality control ranges have been defined by the Clinical and Laboratory Standards Institute (CLSI 2008). A correction factor could not simply account for the differences in MICs between the two methods.

5.4.2.1 Animal models and Phase 2 Study ARRL

Early studies conducted in the neutropenic mouse thigh model (and recently reconfirmed, Section 3.1.1.3.2) suggested that a dose of 1.5 mg/kg/day in man would provide plasma concentrations sufficient for effective treatment of SSSI (Boylan et al. 2003). These studies also showed that a higher, less frequent dose of oritavancin would be more active than the same total dose when divided, supporting the hypothesis that both the C_{max}:MIC and AUC:MIC ratios would be more predictive of oritavancin efficacy in the clinic, a hypothesis concordant with views generally held about the pharmacokinetic-

pharmacodynamic parameters most relevant for concentration-dependent antibacterial agents such as oritavancin.

Data from Study ARRL, the Phase 2 study of SSSI, suggested that seven doses of oritavancin 1.5 mg/kg/day would be expected to provide plasma concentrations of oritavancin similar to those associated with efficacy in the neutropenic mouse thigh model. Flexible dosing regimens of 3 to 7 doses of 1.5 or 3 mg/kg were tested in the first of the two Phase 3 studies, Study ARRD.

5.4.2.2 Study ARRD

5.4.2.2.1 Exposure-Response Relationship Study by Lilly

The bulk of the efforts on understanding exposure-response relationships were spent on the first Phase 3 study, Study ARRD, which included blood sampling for pharmacokinetic-pharmacodynamic exploration (PKPD Report EDMS 2981-v1). Most patients on oritavancin could be switched to oral placebo after a minimum of 3 days of therapy based on pre-specified criteria surrounding patient improvement. Patients with MRSA or enterococci identified as baseline were to receive oritavancin for 7 days, but, in the study practice, half these patients were switched to placebo before completing their 7 days of active drug. Because duration of active therapy ranged from 3 to 7 days to an improvement endpoint, cumulative exposure over treatment duration was viewed as a relevant pharmacokinetic parameter.

Individual predicted concentrations in the central compartment were integrated over time to calculate cumulative AUC values over the treatment duration. Relationships of individual cumulative AUC and C_{max} values to clinical and bacteriologic outcome were explored graphically and statistically. There was extensive overlap in the distributions of AUC for the patients with or without a successful clinical or microbiological outcome. In the absence of an evident relationship between the pharmacokinetic exposure parameters (cumulative AUC, C_{max}) and microbiologic or clinical outcome, explorations with logistic regression analysis were conducted to evaluate the ability of dose, weight, cumulative AUC, and C_{max} to predict outcome. The analysis of the clinical outcome suggested that cumulative AUC was marginally significant ($p=0.0726$). As expected, the addition of weight to AUC for the prediction of clinical outcome was not statistically significant.

The conclusions of Lilly's population pharmacokinetic-pharmacodynamic analysis for Study ARRD were:

- Although weight appears to have a modest effect on the estimate of central compartment volume (Vc), this effect does not appear to be clinically relevant and, therefore, oritavancin does not require dosing based on weight.

- In the absence of a clear relationship between exposure parameters, MIC-derived parameters, and efficacy, the data suggest that a fixed dose of oritavancin 200 mg will give adequate drug levels to treat the pathogens involved in cSSSI.

5.4.2.2.2 Exposure-Response Relationship Study by Targanta

Targanta and ICPD reexamined the data utilized for Lilly's pharmacokinetic-pharmacodynamic analysis of Study ARRD using MIC values determined in the presence of polysorbate-80 for all pathogens that could be retested. The need to retest isolates for susceptibility considerably reduced the sample size of evaluable patients (n=243) at the time Lilly conducted the study. Only 43 cases had *S. aureus* and/or *S. pyogenes* isolates viable for susceptibility testing with the new method. To examine exposure-response relationships, a more comprehensive population pharmacokinetic model developed by ICPD (Report ICPD-00142) was utilized. Because clinical outcomes were in agreement with bacteriologic outcomes for all analysis groups, the pharmacokinetic-pharmacodynamic analyses for efficacy were focused to clinical outcomes.

The AUC_{0-24} was viewed as likely to be estimated with more precision than AUC for the duration of individualized treatment or $AUC_{0-\infty}$, but this approach de facto ignored the potential contribution of treatment duration (and cumulative AUC) to outcome. Independent variables that were considered included the following: 1.) AUC_{0-24}:MIC ratio using MIC value for pathogens isolated at baseline and 2.) Patient demographics (such as age, weight, and creatinine clearance) that could have affected the pharmacokinetics of oritavancin. Disease-related characteristics and underlying comorbidities were also included in the model.

The final mulitivariate logistic regression models did not support a significant relationship between AUC_{0-24}:MIC and clinical outcome in patients without diabetes, suggesting that these patients were in the flat portion or plateau of the exposure-response relationship. In the few evaluable patients with diabetes (n=16), an AUC_{0-24}:MIC ratio of 2253 or greater was associated with a higher probability of clinical success relative to that of patients in whom lower ratios were attained, suggesting that greater oritavancin daily exposure might be required in diabetic patients.

5.4.2.3 Study OCSI-001 (Phase 1 Skin Blister Study)

Complicated skin and skin structure infections (cSSSI) involve tissues beyond the central blood compartment. Drug concentration in the extracellular skin compartment can be measured to confirm that a given drug is appropriate for treating these infections. In Phase 1 Study OCSI-001, oritavancin was administered to healthy volunteers at 200 mg IV daily for 3 days or 800 mg IV daily for 1 day to evaluate the pharmacokinetic profile of drug penetration into skin blister fluid. Total drug oritavancin exposure in the interstitial fluids was approximately 20% of that in plasma. Oritavancin levels reached maximal levels in blister fluid 9 to 10 hours after dosing and decreased to undetectable levels at 100 to 150 hours following the last dose. Oritavancin AUC_{0-24}:MIC ratios associated with in vivo efficacy were met or exceeded in blister fluid, supporting a 200-mg, once-daily regimen.

5.4.2.4 Breakpoint Analysis

5.4.2.4.1 Target Attainment Modeling

In mice treated with a regimen to approximate AUC values seen in humans on Day 2 or Day 3 of treatment (Report ICPD 00159), 24-hour free drug AUC:MIC ratios that correspond to net bacterial stasis and to a 1- and 2- $\log_{10}$ CFU reduction from baseline of *S. aureus* (targets) were 69.0, 77.1, and 86.0, respectively (Report ICPD 00160).

Monte Carlo simulations were performed to test oritavancin plasma concentration-time data from 360 patients enrolled in Phase 2 and 3 studies (Report ICPD-00142) against susceptibility data for 4442 strains of *S. aureus* collected from 2005 to 2006 in the US (Sahm et al. 2007). Average free-drug AUC_{0-24}:MIC ratios were calculated for each simulated patient by dividing individual average free-drug AUC_{0-24} values over 48 hours by each MIC in the *S. aureus* MIC distribution. For an oritavancin 200-mg once-daily dosing regimen, the probabilities of pharmacokinetic-pharmacodynamic target attainment for stasis, 1-log kill, and 2-log kill were 0.97, 0.95, and 0.91, respectively, for an MIC value of 0.12 µg/mL. At an MIC value of 0.25 mg/L, the probability of attaining an AUC_{0-24}:MIC ratio associated with net bacterial stasis was 0.60. These probabilities of target attainment were derived from target attainment estimates based on 0-24 hours exposure on Day 2 or Day 3 of treatment. The estimated probabilities were not adjusted to the expected or observed treatment duration and, therefore, can be viewed as conservative. Potential limitations in applicability of this model to human cSSSI include the difference of this model from the general cSSSI disease process in humans in that a major component of the immune response to pyogenic infection is profoundly blunted or absent.

5.4.2.4.2 Clinical Experience

Examination of microbiological and clinical outcomes from oritavancin therapy in the total Phase 3 clinically evaluable and microbiologically evaluable populations does not suggest that response rates are impacted by oritavancin MIC of causative *S. aureus* clinical isolates (Figure 5-1). Furthermore, the response rate for MRSA isolates with an oritavancin MIC of 0.25 μg/mL or above was equivalent to that for MSSA isolates at this MIC, and overall response rates demonstrate a consistent therapeutic benefit of oritavancin over the range of *S. aureus* MICs encountered in these studies and in recent surveillance studies.

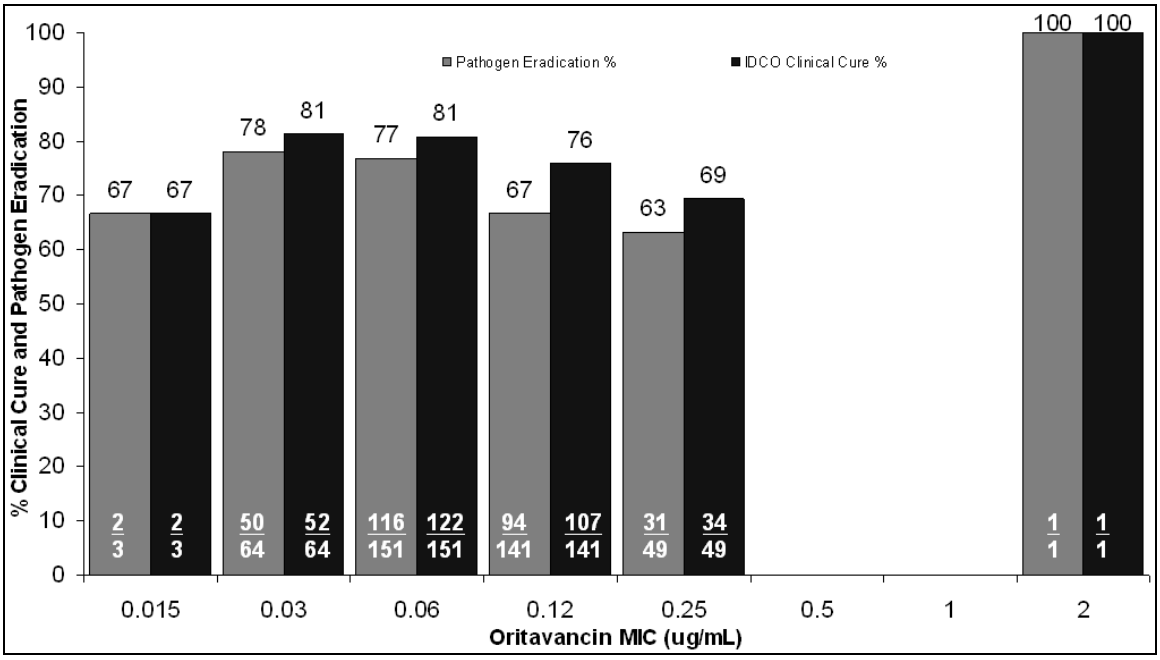


Figure 5-1 Investigator-defined clinical outcome and microbiological outcome at pathogen level by baseline minimum inhibitory concentration (*S. aureus*, microbiologically evaluable population).

5.4.2.5 Final Dose Selection for Study ARRI

Although Lilly's population pharmacokinetic-pharmacodynamic analysis of Study ARRD concluded that a fixed dose of oritavancin 200 mg would give adequate drug levels to treat the pathogens involved in cSSSI, the dose selected by Lilly for the subsequent Phase 3 study (Study ARRI) was 200 mg/d for patients ≤110 kg and 300 mg/day for patients >110 kg. Targanta believes that the decision was made in order to better equalize exposure across the range of weights encountered in clinical practice. Indeed, a regimen in which subjects ≤110 kg receive 200 mg/day and those >110 kg

receive 300 mg/day results in a tighter distribution of predicted steady-state AUC_{0-24} values than a regimen in which all patients are given a fixed 200 mg/day. What is not apparent, however, is whether this dosage adjustment was necessary.

5.4.2.6 ARRI Pharmacokinetic-Pharmacodynamic Exploratory Analyses by Targanta

Because of its fixed-dose design, Study ARRI provided a range of dose/weight values as potential predictors of outcome. In the absence of pharmacokinetic sampling from this study, Targanta used dose/weight as a proxy for AUC_{0-24} and calculated cumulative treatment AUCs for each patient by multiplying weight (kg) by a factor representing oritavancin accumulation (in the central compartment) resulting from 3, 4, 5, 6, or 7 days of dosing from the ICPD model. Targanta also used this approach to verify or validate Lilly's population pharmacokinetic-pharmacodynamic analysis (PKPD Report EDMS 2981-v1).

As previously observed in Study ARRD, there was extensive overlap in the distributions of estimated cumulative treatment AUC for the patients with and without a successful clinical or microbiological outcome.

In the absence of an evident relationship between cumulative treatment AUC and microbiologic or clinical outcomes, explorations with logistic regression analysis were conducted to evaluate cumulative treatment AUC or cumulative treatment AUC:MIC as predictors of clinical and bacteriological outcomes in the microbiologically evaluable (ME) population infected with *S. aureus* at baseline. Figures 5-2 and 5-3 illustrate that, although there is an exposure response relationship for the probability of *S. aureus* eradication when using AUC_{0-24} as the independent measure of exposure, the relationship disappears when using cumulative treatment AUC. The relationship also disappears when using cumulative dose as an independent measure of exposure.

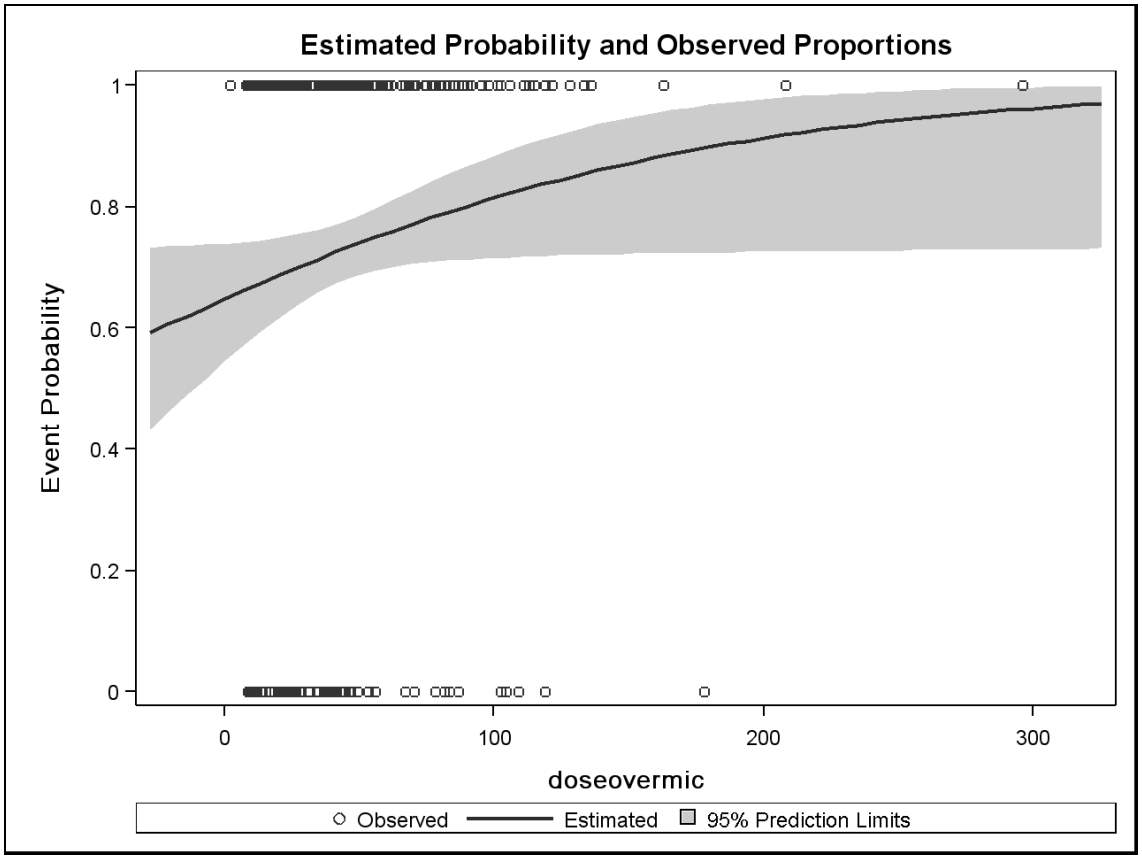


Figure 5-2 **Study ARRI: Estimated probability of *S. aureus* eradication for predicted area under the time-concentration curve on Day 1 dose/weight (mg/kg) over minimum inhibitory concentration (328 observations; p=0.046).**

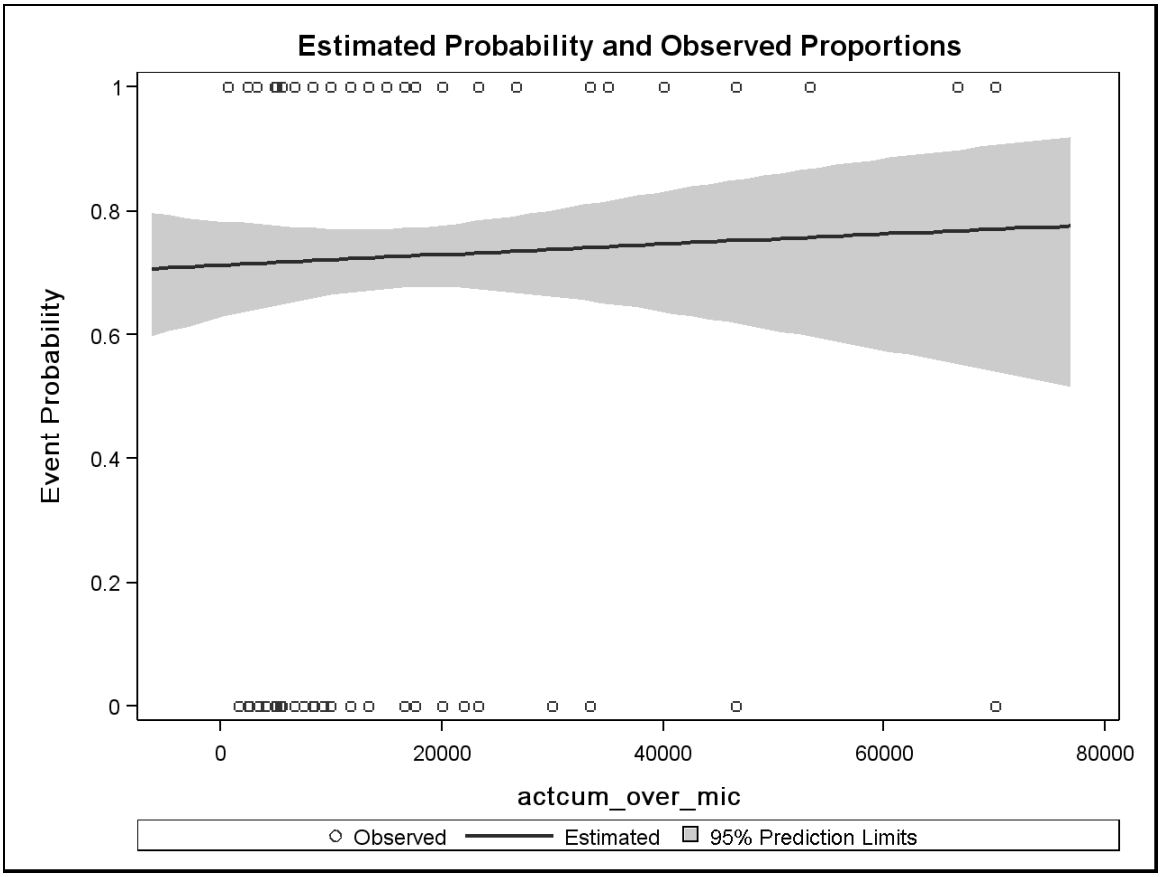


Figure 5-3 **Study ARRI: Estimated probability of *S. aureus* eradication for predicted cumulative treatment area under the time-concentration curve (dose/weight (mg/kg) x accumulation factor/minimum inhibitory concentration) (328 observations; p=0.65).**

These results suggest that the exposure resulting from a single day of treatment is an independent predictor of outcome and that a better microbiological result could be achieved with higher exposure on a single day of treatment. These results also suggest that microbiological response for the most frequent cSSSI pathogen is independent of cumulative exposure achieved by 3 to 7 days of treatment. The same pattern of insensitivity is also observed with clinical response. All these results appear to confirm the Lilly conclusion that a fixed dose of oritavancin 200 mg would give adequate drug levels to treat the pathogens involved in cSSSI.

5.5 Clinical Pharmacology and Microbiology Conclusions

The clinical pharmacokinetic properties of oritavancin have been well characterized and support a lack of dose adjustments due to renal or hepatic insufficiency and a low likelihood of drug-drug interactions at the recommended doses. In addition, the

pharmacokinetic properties provide evidence that oritavancin remains in the plasma and the tissue (including the target tissues of skin and skin structures) for an appropriate period of time at clinically relevant concentrations to provide necessary therapeutic effect (that is, killing at >0.25 ug/mL). The clinical pharmacology studies and microbiology investigations summarized above support the proposed IV dose of 200 mg (300 mg for patients weighing more than 110 kg [242 lbs]) daily for 3 to 7 days.

Surveillance studies with recent clinical strains show that oritavancin demonstrates significant activity across a broad range of gram-positive pathogens, including those with specific resistance phenotypes that are associated with cSSSI. Oritavancin MIC_{90}s against these pathogens generally remain pharmacokinetically accessible at the intended label dose (of 200 mg [300 mg for patients >110 kg (242 lbs)]). Susceptibility distributions are typically narrow; with oritavancin MICs above 1 µg/mL being encountered only rarely (Table 3-1). These findings from surveillance initiatives are consistent with susceptibility data from cSSSI Studies ARRI and ARRD, and suggest that existing clinical outcome data would be predictive for organisms that would be encountered currently in clinical settings.

6 Clinical Efficacy

The pivotal efficacy data supporting the cSSSI submission are based on two randomized, double-blind, comparator-controlled, Phase 3 clinical studies, Study ARRD (which utilized weight-based dosing) and Study ARRI (which utilized fixed dosing). The primary objective of both studies was to test the hypothesis that 3 to 7 days of once-daily oritavancin is noninferior to 10 to 14 days of twice-daily vancomycin/cephalexin in the treatment of patients with gram-positive bacterial cSSSI. Stratified randomization was applied where patients were assigned to one of three disease categories: wound infection, major abscess, or cellulitis. Patients were allowed to be enrolled with cirrhosis, renal insufficiency (patients requiring dialysis were excluded from Study ARRD but not Study ARRI), with no limitation on the anticipated length of hospitalization, and with no limitation on severity of important comorbidities (including bacteremia, polymicrobial infection, diabetes, HIV/AIDS, and/or neutropenia), which may complicate response to therapy. Table 6-1 describes these two Phase 3 studies.

Table 6-1 Phase 3 Complicated Skin and Skin Structure Infection Study Descriptions

Study (years of study)	Total N	Description	Treatment Regimens (1:1:1 for ARRD; 2:1 for ARRI)	Treatment n
ARRD (1999 to 2001)	517	Randomized, double-blind, multicenter, comparator-controlled study in patients with cSSSI	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
ARRI (2001 to 2002)	1246	Randomized, double-blind, multicenter, comparator-controlled study in patients with cSSSI	Oritavancin IV 200 mg QD (300 mg QD for weight >110 kg [242 lbs]) 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

Abbreviations: BID = twice daily; cSSSI = complicated skin and skin structure infections; hrs = hours; IV = intravenous; N = total number of intent-to-treat patients; n = number of intent-to-treat patients per regimen; PO = by mouth; q = every; QD = once daily.

The next several sections of the briefing document provide information relating to the disease diagnostic criteria for the Phase 3 cSSSI studies (Section 6.1), the study designs for both studies (Section 6.2), the selection of the comparator for those studies (Section 6.3), the justification of the NI margins (Section 6.4), the explanation of the sample sizes (Section 6.5), and the definitions for the various patient populations and efficacy outcome variables (Section 6.6). Section 6.7 presents individual efficacy results for Studies ARRD and ARRI while Section 6.8 presents the efficacy results for both Phase 3 cSSSI studies combined.

6.1 Disease Diagnostic Criteria

In both Phase 3 cSSSI studies, a patient was defined as having cSSSI if all three of the following definitions (severity, complicated disease, and disease categories) were satisfied.

6.1.1 Severity

Complicated skin and skin structure infections (cSSSI) were of sufficient severity to anticipate three or more days of IV antibiotic therapy.

6.1.2 Definition of Complicated

Skin and skin structure infections (SSSI) were classified as complicated if one or more of the following criteria were met:

- Infection required significant surgical intervention within 48 hours of enrollment (36 hours in Study ARRD).
- Infectious process was suspected or confirmed to involve deeper soft tissue (fascia and/or muscle layers).
- Infections occurred in patients with significant underlying diseases or conditions that are known to complicate the response to treatment (such as diabetes mellitus, bacteremia, cirrhosis, neutropenia, organ transplantation, immunosuppressive disease or conditions, and so forth).

6.1.3 Disease Categories

For purposes of stratified randomization, patients were grouped into one of three disease categories and must have met the following defined criteria.

6.1.3.1 Wound Infection at the Site of Surgical Incision or Trauma (Including Burn Wounds) or Infected Ulcers

The patient must meet all of the following criteria (adapted from Horan et al. 1992):

- Purulent drainage from the wound or ulcer but not from the organ/space component of the injury.
- At least one of the following: fever (>38°C rectal or >37.5°C oral), localized pain or tenderness, erythema extending at least 1 cm beyond the wound edge, or localized swelling.
- Wound infections must occur within 30 days after an operative procedure or trauma. In the case of infected ulcers, the underlying lesion may have been present >30 days.

6.1.3.2 Major Abscess (No Open Wound)

The patient must have all of the following:

- Acute onset within seven days prior to enrollment.
- Purulent drainage or purulent aspirate.
- Erythema, induration (≥2 cm in diameter), or tenderness.
- Evidence of loculated fluid by physical examination, blind aspiration, or ultrasound that requires intervention (such as aspiration, incision and drainage, excision) within 48 hours of enrollment.

6.1.3.3 Cellulitis

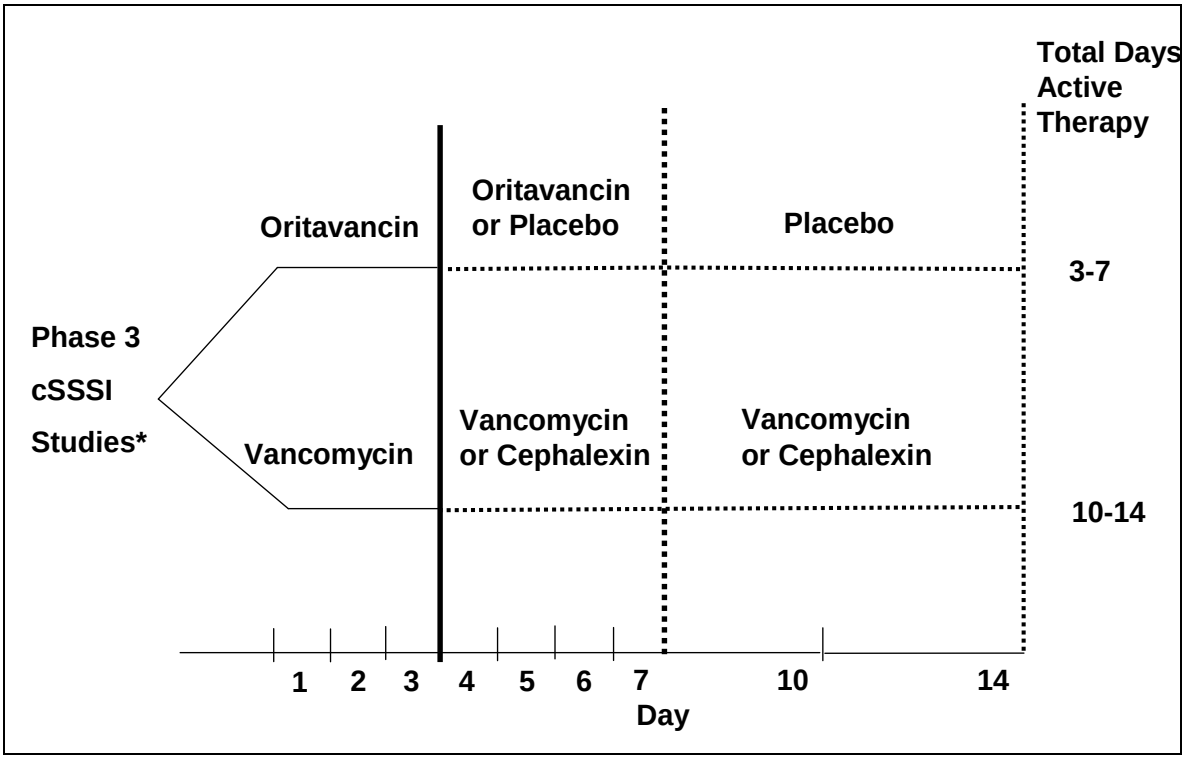
The patient must have all of the following (adapted from Gorbach 1997 and Ginsberg 1981):

- Acute onset within seven days prior to enrollment.
- Pain or tenderness.
- Cutaneous erythema.
- Advancing edema or induration.

- History of measured (>38°C rectal or >37.5°C oral) or subjective fever within three days prior to enrollment or elevated white blood cell count ≥10.0 x 10^3/mm^3 or ≥10% bands.

6.2 Study Design

Figure 6-1 illustrates the study designs for Studies ARRD and ARRI.



* In the Phase 3 Study ARRD, there were three treatment groups: oritavancin 1.5 mg/kg/day, oritavancin 3.0 mg/kg/day, and comparator. In the Phase 3 Study ARRI, there were two treatment groups: oritavancin 200 mg/day (300 mg for patients weighing more than 110 kg [242 lbs]) and comparator.

Figure 6-1 Studies ARRD and ARRI study designs.

In both Studies ARRD and ARRI, patients were randomized to either oritavancin/placebo or vancomycin/cephalexin (in a 1:1:1 fashion in Study ARRD [2 oritavancin groups to 1 vancomycin/cephalexin group] and in a 2:1 fashion in Study ARRI) for a total duration of therapy of 10 to 14 days as determined by the investigator. In these double-blind studies, each dose of IV study drug was to be reconstituted by a nonblinded pharmacist and each bag was to be identified as a dose of study drug without identification of the drug or dose. To maintain blinding while on IV therapy, patients randomized to oritavancin received dextrose 5% in water infusions approximately 12 hours after the oritavancin infusions. Cephalexin monohydrate capsules appeared identical to placebo

capsules. After 3 days of IV study drug, patients who met all predefined criteria (afebrile for 24 hours, no clinical indication for further IV therapy, ability to take oral medications, and a response of "cure" or "improved") could be switched from IV to oral therapy. The oritavancin dose for Study ARRD included two weight-based dose groups (1.5 and 3.0 mg/kg/day with a median daily dose of 115.1 and 232.7 mg/day, respectively); the oritavancin dose for Study ARRI was fixed at 200 mg/day (300 mg/day for patients weighing more than 110 kg [242 lbs]).

In both studies, patients could receive concomitant aztreonam (for gram-negative organisms) and/or metronidazole (for anaerobic organisms) if clinically indicated. Use of aztreonam and/or metronidazole was allowed for suspected or proven polymicrobial infections that included gram-negative pathogens and/or anaerobes. Patients with MRSA who were assigned to oritavancin received a minimum of 7 days of IV treatment with active drug followed by 3 to 7 days of IV placebo whereas patients with MRSA who were assigned to vancomycin/cephalexin received 10 to 14 days of IV treatment of active drug.

During the course of Study ARRD, two planned interim analyses were performed under the auspices of an external Data Monitoring Board (DMB). No adjustment to the nominal 0.05 alpha level at the final analysis was made. The justification for not adjusting alpha was two-fold: 1.) that the trial would not be stopped at either interim analysis for superior performance of either of the oritavancin treatment groups and 2.) 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). The DMB was asked to report on predetermined decision-making criteria based on unblinded data. To preserve the study blind and integrity, a separate, predefined data analysis group performed the interim analysis, the results of which were presented to the DMB. Following the DMB's review of the data, recommendations were presented to a Portfolio Management Committee, which had the authority to disseminate the results in a controlled manner.

At the first planned interim analysis, the DMB reported the following after 97 patients had completed treatment:

- Cure rates >80% for all treatment arms at first follow-up.
- Excluded a -20% percent difference in cure rates with an 80% CI.

- Rate of discontinuation due to adverse events for oritavancin was not >3 times that of vancomycin/cephalexin.

Other recommendations (such as to continue study, supporting another interim analysis, ECG monitoring, and reporting of no deaths) were also reported.

At the second planned interim analysis, the DMB reported the following after 201 patients completed treatment:

- Identified no safety concerns.
- Commented on the lower oritavancin group efficacy concerns for those with *S aureus*, *S pyogenes*, and *S agalactiae*.
- Recommended to continue study.

6.3 Selection of Comparator: Vancomycin/Cephalexin

Because the comparator selection can directly affect study feasibility, data assumptions, and credibility, choosing a comparator regimen is a critical decision in designing an appropriate clinical study. Three basic questions (derived from ICH Guidelines) need to be addressed when selecting an appropriate antibiotic comparative agent (Hwang and Morikawa 1999):

1. Is a proven effective treatment available?
2. Is the standard treatment life-saving and/or known to prevent irreversible morbidity?
3. Do studies for the standard treatment have sensitivity-to-drug effects and does the particular study have assay sensitivity?

In addition, technical issues related to clinical trial conduct (such as the blinding of study medication) must also be considered.

After evaluating and addressing the questions mentioned above, vancomycin/cephalexin (with or without aztreonam for gram-negative organisms and/or metronidazole for anaerobic organisms) was selected as a suitable comparator in Studies ARRD and ARRI.

Vancomycin has a proven track record from clinical studies as well as continued use in clinical practice and is highly effective for treatment of severe infections, including

cSSSI. It has gained the reputation as a "drug of choice" for difficult-to-treat, complicated, gram-positive infections likely due to MRSA, and continues to be widely used for treatment of cSSSI (Jones 2006; Levine 2006; Moellering 2006; Scheinfeld 2007). At the time, Studies ARRD and ARRI were designed and conducted, vancomycin was, and continues to be, a standard-of-care treatment of MRSA cSSSI, and it continues to be appropriate empiric therapy for cSSSI in patients at increased risk of MRSA (Stevens et al. 2005).

Over time, the safety and efficacy of vancomycin have been demonstrated as part of several worldwide registration studies for treatment of cSSSI. Most recently, quinupristin/dalfopristin, daptomycin, tigecycline, linezolid, and telavancin have included the use of vancomycin as a comparator agent. Of note, however, Studies ARRD and ARRI were initiated in 1999 and 2001, respectively, before these newer alternative therapies were commercially available or were considered to be appropriate drugs for cSSSI. Therefore, these newer treatment options (which were approved in the US in 2000 or later) were not considered in the selection of comparator agents for Studies ARRD and ARRI.

Cephalexin was chosen as an oral step down (following vancomycin treatment) for those patients that were demonstrating signs and symptoms of improvement and were without evidence of MRSA as a cSSSI pathogen. Cephalexin is indicated for the treatment of SSSI caused by most gram-positive pathogens (excluding enterococci and MRSA) (Kumar et al. 1988; Powers et al. 1991; Tack et al. 1998).

Lastly, technical issues related to clinical trial conduct and the blinding of study medication (the route of delivery, side effect and drug interaction profiles, patient allergies, and pharmacodynamics) also favor use of vancomycin as a comparator to oritavancin. In particular, while oritavancin is dosed once daily, the ß-lactam antibiotics most appropriately used in treatment of non-MRSA gram-positive cSSSI are dosed 3 to 6 times a day. As a result, blinding is more easily maintained with vancomycin, which is administered every 12 hours.

6.4 Noninferiority Margin Justification

6.4.1 Discussions with the FDA

The initial sponsor, Lilly, began enrolling patients in Study ARRD in February 1999. Based on the FDA guidance contained in the Division of Anti-Infective Drug Products' 1992 Points to Consider, Clinical Development and Labeling of Anti-Infective Drug

Products (FDA 1992a), Lilly selected a 15% delta for NI using a 95% 2-sided CI based on their expectation that the comparator response rate would be between 80% and 90%.

In March 2001, Lilly became aware of differences between the method used to select the delta for Study ARRD, and the new recommendation for a 10% delta published in a revision to the FDA Division of Anti-Infective Drug Products' 1998 Points to Consider, Clinical Development and Labeling of Anti-Infective Drug Products, posted on February 12, 2001 (FDA 1992b, disclaimer).

Lilly met with the FDA in March 2001 to discuss the potential impact of this new guidance on Study ARRD. After discussions with the FDA, an agreement was reached to complete Study ARRD as planned (that is, approximately 500 patients targeted for completion in April 2001). Lilly was asked by the FDA to power the subsequent Study ARRI to meet the delta of 10%, with an understanding that the strength of the results from Study ARRD would not be judged solely on the lower limit, but also on the point estimate of the CI and the safety profile with respect to the comparator.

6.4.2 Historical, Statistical, and Clinical Considerations

The preponderance of historical evidence from the preantibiotic era demonstrates that the use of antibiotics provide substantially more effect than placebo or surgery alone. Based upon both statistical and clinical review of the historical data for cSSSI, it was determined that a placebo response >35% is unlikely. To maintain at least 50% of the treatment effect with an assumed placebo cure response of 35% and an active-control effect of 45% (for a combined observed effect of 80%), an NI margin of 22.5% could be acceptable from a statistical standpoint.

The smaller NI margins selected for Study ARRD (NI=15%) and Study ARRI (NI=10%) were statistically and clinically relevant. Both studies adhered to the NI margin components of consideration and the regulatory guidance principals and standard of clinical studies at the time of the protocols' inceptions. Study ARRD was powered for and achieved the primary endpoint within a 15% NI margin (95% CI for 1.5 mg/kg-group was [-14.4, 5.9] and 95% CI for 3.0-mg/kg group was [-14.9, 5.7]). Study ARRI was powered for and achieved the primary endpoint (clinical efficacy comparable to that of vancomycin/cephalexin) within a 10% NI margin (95% CI; -3.0, 8.2).

Additional historical information demonstrating that the use of antibiotics provides substantially more effect than placebo or surgery alone as well as the specific points of justification for the selection of the 15% (Study ARRD) and the 10% (Study ARRI) NI

margins was included in Targanta's NDA submission and is provided in Appendix 11.1 of this briefing document.

6.5 Sample Size

For Study ARRD, the sample size calculation was determined using the following assumptions to rule out a difference in cure rates using a 2-sided 95% CI: 80% cure rate, randomization ratio 1:1:1 (2 oritavancin groups to 1 vancomycin/cephalexin group), and a noninferiority margin of 15%. A total of 405 CE patients would provide a power of approximately 80%. Assuming an evaluability rate of 60%, the total number of enrolled patients was 675. After the interim analysis revealed a higher evaluability rate (74%), the study closed enrollment after 517 patients.

For Study ARRI, the sample size calculation was determined using the following assumptions to rule out a difference in cure rates using a 2-sided 95% CI: 80% cure rate, randomization ratio 2:1 oritavancin to vancomycin/cephalexin, and a noninferiority margin of 10%. A total of 758 CE patients would provide a power of approximately 90%. Assuming an evaluability rate of 60%, the total number of enrolled patients was 1250.

6.6 Evaluation Criteria for Efficacy

6.6.1 Patient Populations

Efficacy analyses were performed for 4 patient populations in Studies ARRD and ARRI: intent to treat (ITT), modified intent to treat (MITT), clinically evaluable (CE), and microbiologically evaluable (ME). Table 6-2 defines these populations.

Table 6-2 Patient Populations for Efficacy Analysis

ITT Patients who received any study drug	**MITT** ITT patients with a gram-positive baseline pathogen
CE ITT patients who: • Met the enrollment criteria • Received at least 3 days of treatment • Had a clinical assessment that was not indeterminate or missing at the TOC • Had a clinical assessment in the TOC Visit analysis window of Day 21 to Day 35 (ARRD) or Day 21 to Day 29 (ARRI)	**ME** CE patients with a gram-positive baseline pathogen

Abbreviations: CE = clinically evaluable; ITT = intent to treat; ME = microbiologically evaluable; MITT = modified intent to treat; TOC = test of cure.

6.6.2 Definitions of Efficacy Outcome Variables

6.6.2.1 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.

6.6.2.2 Sponsor-Defined Clinical Outcome

The sponsor-defined clinical outcome (SDCO) at each visit was 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 with a thorough, by-patient review and revision assessed by the sponsor to avoid inconsistency among the investigators in rating clinical responses. Each patient was assigned one of the following clinical outcomes: cure, failure, or indeterminate. When calculating the SDCO, the sponsor assessment was more conservative and thus, could only downgrade patients from the investigator-defined clinical outcome (from cure to failure or indeterminate), not upgrade them (from failure or indeterminate to cure). Factors taken into consideration when deriving the SDCO were the use of concomitant effective antibiotics and procedures performed to treat the primary study condition which started >48 hours after the start of study medication.

6.6.2.3 Pathogen Level Microbiological Outcome

Microbiological outcomes were assigned at the individual pathogen level for each baseline gram-positive pathogen. Multiple pathogens identified from the same patient were assigned separate outcomes. These assignments were based on results obtained from culture and susceptibility testing and the SDCO. Each baseline pathogen was

assigned one of the following microbiological outcomes: documented eradication, presumed eradication, documented persistence, presumed persistence, indeterminate, or missing.

6.6.2.4 Patient Level Microbiological Outcome

For each patient, an overall microbiologic response was assigned based on the pathogen level microbiological outcome and the SDCO. If a patient had multiple pathogen level microbiological outcomes, the worst-case outcome was used. Selection of the worst-case outcome was to follow the order: documented persistence, presumed persistence, superinfection, colonization, presumed eradication, and documented eradication.

6.7 Individual Phase 3 Study Results

Overall, the individual results of the two Phase 3 studies (Studies ARRD and ARRI) demonstrate that the clinical efficacy of oritavancin 200 mg (300 mg for patients weighing more than 110 kg [242 lbs]) infused once daily for 3 to 7 days is noninferior to the combination antibiotic regimen of vancomycin/cephalexin every 12 hours for 10 to 14 days in the treatment of subjects with cSSSI caused by gram-positive pathogens.

6.7.1 Phase 3 Study ARRD

Table 6-3 presents the patient evaluation groups for Study ARRD. The percentages of patients in the four populations were comparable between treatment groups.

Table 6-3 Patient Evaluation Groups for Study ARRD

Patient Population	ORI % (n)[a]		VAN/CEPH % (n)[a]
	1.5 mg/kg	3.0 mg/kg	
ITT	97.7% (173)	95.5% (169)	98.9% (175)
MITT	57.1% (101)	54.8% (97)	61.0% (108)
CE	76.8% (136)	72.3% (128)	73.4% (130)
ME	44.6% (79)	43.5% (77)	46.9% (83)

Abbreviations: CE = clinically evaluable; ITT = intent to treat; ME = microbiologically evaluable; MITT = modified intent to treat; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Percentages are based on numbers randomized.

Table 6-4 presents the reasons for nonevaluability in the ITT population for Study ARRD.

Table 6-4 Reasons for Nonevaluability for Study ARRD (Intent-to-Treat Population)

	ORI 1.5 mg/kg N=173 % (n)	ORI 3.0 mg/kg N=169 % (n)	VAN/CEPH 15 mg/kg N=175 % (n)
Clinically nonevaluable patients	21.4% (37)	24.3% (41)	25.7% (45)
Reasons for nonevaluability[a]			
Clinical assessment missing or indeterminate at test of cure	22.5% (39)	24.9% (42)	22.9% (40)
Did not receive at least 3 days of treatment	5.8% (10)	7.1% (12)	8.0% (14)
Inclusion criteria not met	3.5% (6)	1.8% (3)	1.7% (3)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Patients may have had multiple reasons for nonevaluability. All reasons are summarized; therefore, percentages may total more than 100%.

6.7.1.1 Demographics

Baseline patient demographic data for Study ARRD are summarized in Table 6-5 for the ITT population. Patient demographic characteristics were comparable between the oritavancin and vancomycin/cephalexin treatment groups.

Table 6-5 Baseline Patient Demographics for Study ARRD (Intent-to-Treat Population)

Demographic	ORI 1.5 mg/kg N=173 % (n)	ORI 3.0 mg/kg N=169 % (n)	VAN/CEPH N=175 % (n)
Sex			
Male	63.0% (109)	62.7% (106)	66.3% (116)
Female	37.0% (64)	37.3% (63)	33.7% (59)
Ethnic Origin			
Caucasian	56.1% (97)	56.2% (95)	60.6% (106)
African Descent	12.1% (21)	13.6% (23)	7.4% (13)
Hispanic	28.3% (49)	29.0% (49)	29.1% (51)
Other	3.5% (6)	1.2% (2)	2.9% (5)
Age (years)			
Mean (±SD)	48.6 (15.60)	49.3 (15.74)	48.6 (16.29)
Age Groups			
<45 years	41.6% (72)	46.2% (78)	46.9% (82)
>45 – <65 years	39.3% (68)	35.5% (60)	35.4% (62)
>65 – <75 years	12.1% (21)	13.0% (22)	10.9% (19)
>75 years	6.9% (12)	5.3% (9)	6.9% (12)
Weight			
<110 kg	87.3% (151)	87.0% (147)	85.1%[a] (148)
>110 kg	12.7% (22)	13.0% (22)	14.9% (26)
Region[b]			
US/Canada	71.1% (123)	68.6% (116)	67.4% (118)
Latin America	21.4% (37)	20.7% (35)	25.1% (44)
Europe	7.5% (13)	10.7% (18)	7.4% (13)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; VAN/CEPH = vancomycin/cephalexin.

[a] One patient in the VAN/CEPH group did not have weight collected at baseline; therefore, the N for the VAN group is 174.

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

6.7.1.2 Baseline Disease

Table 6-6 presents the baseline disease categories, characteristics, and pathogens for patients in the ITT population in Study ARRD. The numbers of patients within each disease category as well as the duration of the disease and extent of tissue involvement were comparable between the oritavancin and vancomycin/cephalexin treatment groups. The most common pathogen isolated at baseline was *S. aureus*.

Table 6-6 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRD (Intent-to-Treat Population)

	ORI % (n)		VAN/CEPH % (n)
	1.5 mg/kg N=173	3.0 mg/kg N=169	N=175
Disease Category			
Wound infection	20.2% (35)	20.1% (34)	21.7% (38)
Major abscess	38.2% (66)	36.1% (61)	36.6% (64)
Cellulitis	41.6% (72)	43.8% (74)	41.7% (73)
Deepest Tissue Involved			
Skin	8.1% (14)	6.5% (11)	6.9% (12)
Subcutaneous	61.8% (107)	65.7% (111)	62.9% (110)
Muscle	5.2% (9)	6.5% (11)	10.9% (19)
Fascial plane	22.0% (38)	19.5% (33)	17.7% (31)
Bone	1.2% (2)	0.6% (1)	0.6% (1)
Other	1.7% (3)	1.2% (2)	1.1% (2)
Location of Infection			
Head and neck	4.0% (7)	6.5% (11)	3.4% (6)
Torso	19.1% (33)	20.2% (34)	18.9% (33)
Upper extremity	32.4% (56)	23.2% (39)	28.6% (50)
Lower extremity[a]	48.0% (83)	52.4% (88)	51.4% (90)
Foot	9.8% (17)	16.7% (28)	13.7% (24)
Lower leg	38.2% (66)	35.7% (60)	33.1% (58)
Upper leg	9.8% (17)	12.5% (21)	17.1% (30)
Duration of Disease in Days			
Mean (SD)	6.4 (9.22)	4.8 (3.17)	4.9 (4.27)
Minimum to maximum	1 to 92	1 to 20	1 to 35
SIRS[b]	17.3% (30)	21.3% (36)	22.9% (40)
Concomitant antibacterial therapy			
aztreonam	15.0% (26)	16.0% (27)	14.9% (26)
metronidazole	11.0% (19)	13.0% (22)	10.9 (19)
Baseline Pathogen[c]	N = 101[c]	N = 97[c]	N = 108[c]
S. aureus	67.3% (68)	64.9% (63)	60.2% (65)
MSSA	36.6% (37)	44.3% (43)	43.5% (47)
MRSA	19.8% (20)	16.5% (16)	13.0% (14)
S. pyogenes	13.9% (14)	14.4% (14)	18.5% (20)
S. agalactiae	5.0% (5)	8.2% (8)	7.4% (8)
S. anginous group[d]	13.9% (14)	15.5% (15)	21.3% (23)
Other *Streptococcus* spp.[e]	12.9% (13)	12.4% (12)	13.0% (14)
E. faecalis	8.9% (9)	5.2% (5)	5.6% (6)
Other *Enterococcus* spp.[f]	2.0% (2)	3.1% (3)	1.9% (2)

(continued)

Table 6-6 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRD (Intent-to-Treat Population) (Concluded)

Abbreviations: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; SIRS = systemic inflammatory response syndrome; VAN/CEPH = vancomycin/cephalexin.

[a] Patients may have had infection identified at more than one location. All locations are summarized; therefore, total of foot, lower leg, and upper leg infections may not be equivalent to number of lower extremity infections.

[b] Presence of ≥2 of the following variables: temperature >38°C or <36°C, heart rate >90 beats/min, PaCO2 <32 mmHg (calculated using the Henderson-Hasselbalch equation and serum bicarbonate), and abnormal white blood cell count (>12,000 cells/mm3 or <4,000 cells/mm3 or >10% bands).

[c] Baseline pathogens are derived from the modified intent-to-treat population, not the intent-to-treat population.

[d] *S. anginous* group includes *S. anginosus*, *S. constellatus*, and *S. intermedius*.

[e] Other *Streptococcus* spp. includes *S. bovis*, *S. oralis*, and unspeciated *Streptococcus*.

[f] Other *Enterococcus* spp. includes *E. avium*, *E. faecium*, and unspeciated *Enterococcus*.

6.7.1.3 Comorbidities and Severity of Illness

Table 6-7 shows the incidence of clinically relevant comorbidities in the ITT population for Study ARRD.

Table 6-7 Incidence of Clinically Relevant Comorbid Conditions in the Intent-to-Treat Population for Study ARRD

Comorbidity	ORI 1.5 mg/kg N=173 % (n)	ORI 3.0 mg/kg N=169 % (n)	VAN/CEPH N=175 % (n)
Age ≥75	6.9% (12)	5.3% (9)	6.9% (12)
Diabetes	26.6% (46)	32.0% (54)	21.1% (37)
Hepatic insufficiency	5.2% (9)	3.0% (5)	2.9% (5)
Renal insufficiency[a]/dialysis	3.5% (6)	6.5% (11)	7.4% (13)
Vascular[b]	7.5% (13)	7.1% (12)	4.6% (8)
Immunologic[c]	6.4% (11)	7.1% (12)	4.6% (8)
Cancer	1.7% (3)	2.4% (4)	3.4% (6)
Cardiac[d]	2.9% (5)	6.5% (11)	4.6% (8)
Respiratory[e]	5.2% (9)	8.9% (15)	8.6% (15)
Transplantation	0% (0)	0.6% (1)	0% (0)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Creatinine clearance ≤30.

[b] Arterial insufficiency and/or venous stasis.

[c] ANC <1000, neutropenic event, HIV/AIDS, and/or immunosuppresive concomitant medications.

[d] Congestive heart failure, myocardial infarction, and/or other cardiac conditions.

[e] Severe asthma, chronic obstructive pulmonary disease, and/or other respiratory conditions.

Table 6-8 shows the number of comorbidities per patient in the ITT population for Study ARRD.

Table 6-8 Number of Comorbidities per Patient in the Intent-to-Treat Population for Study ARRD

Number of Comorbidities	ORI 1.5 mg/kg N=173 % (n)	ORI 3.0 mg/kg N=169 % (n)	VAN/CEPH N=175 % (n)
Patients with zero	54.9% (95)	48.5% (82)	58.9% (103)
Patients with one	29.5% (51)	35.5% (60)	26.9% (47)
Patients with two	11.6% (20)	10.1% (17)	9.1% (16)
Patients with three or more	4.0% (7)	5.9% (10)	5.1% (9)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

6.7.1.4 Disposition

Table 6-9 presents the primary reasons for discontinuation of study drug for Study ARRD for both the ITT and CE populations. The reasons for discontinuation were generally similar between the groups with the exception of discontinuation due to lack of efficacy. Greater percentages of patients in the oritavancin 3.0-mg/kg group were discontinued from treatment with study drug due to lack of efficacy compared to the vancomycin/cephalexin-treated patients in both the ITT and CE populations.

Table 6-9 Primary Reasons for Discontinuation of Study Drug in Study ARRD (Intent-to-Treat and Clinically Evaluable Populations)

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

Abbreviations: CE = clinically evaluable; ITT = intent to treat; N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Percentages are based on ITT population.

[b] Percentages are based on CE population.

[c] The other reasons for discontinuation (and the numbers of ITT patients per reason) are: patient decision (5 ORI 1.5 mg/kg, 6 ORI 3.0 mg/kg, 8 VAN), physician decision (11 ORI 1.5 mg/kg, 8 ORI 3.0 mg/kg, 8 VAN), protocol violation (4 ORI 1.5 mg/kg, 1 ORI 3.0 mg/kg, 1 VAN), protocol entry criteria not met (4 ORI 1.5 mg/kg, 2 ORI 3.0 mg/kg, 3 VAN), sponsor decision (1 ORI 1.5 mg/kg, 1 ORI 3.0 mg/kg, 0 VAN), and unable to contact patient/lost to follow-up (8 ORI 1.5 mg/kg, 10 ORI 3.0 mg/kg, 9 VAN)

6.7.1.5 Efficacy Results

The original primary efficacy outcome variable for Study ARRD was the clinical response (IDCO) of patients in the CE population at the first follow-up visit (test of cure). Additional efficacy outcome variables for this study included patient level microbiological outcome and pathogen level outcome. Although SDCO was not determined in the original analysis of Study ARRD, this assessment was derived for the cSSSI submission. Table 6-10 presents the efficacy analysis of Study ARRD.

Table 6-10 Cure/Success Rates[a] at Test-of-Cure Visit for Study ARRD

Efficacy Endpoint (Patient Population)	ORI 1.5 mg/kg % (n/N)	ORI 3.0 mg/kg % (n/N)	VAN/CEPH % (n/N)
Investigator-defined clinical outcome[b] (CE)	75.8% (100/132)[c]	75.4% (95/126)[d]	80.0% (100/125)
Sponsor-defined clinical outcome (CE)	72.1% (98/136)	73.4% (94/128)	75.4% (98/130)
Wound	75.0% (21/28)	76.9% (20/26)	66.7% (20/30)
Abscess	74.0% (37/50)	76.6% (36/47)	79.2% (38/48)
Cellulitis	69.0% (40/58)	69.1% (38/55)	76.9% (40/52)
Patient level microbiological outcome (ME)	65.8% (52/79)	72.7% (56/77)	74.7% (62/83)

Abbreviations: CE = clinically evaluable; ME = microbiologically evaluable; N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Excludes missing and indeterminate.

[b] For Study ARRD, investigator-defined clinical outcome in the clinically evaluable population was the primary efficacy endpoint.

[c] ORI 1.5 mg/kg – VAN: 95% CI (-14.4, 5.9).

[d] ORI 3.0 mg/kg – VAN: 95% CI (-14.9, 5.7).

For the IDCO, the overall clinical cure rates in the CE population at the test-of-cure visit were comparable between treatment groups: 75.8% (100/132) for the oritavancin 1.5-mg/kg dose group and 75.4% (95/126) for the oritavancin 3.0-mg/kg dose group as compared with 80.0% (100/125) for vancomycin/cephalexin-treated patients (95% CIs: [-14.4, 5.9] and [-14.9, 5.7], respectively). Similar results were observed across all four populations (ITT, MITT, CE, and ME).

The overall clinical cure rates for the more conservative SDCO in the CE population at the test-of-cure visit support the IDCO findings with cure rates of 72.1% (98/136) for the oritavancin 1.5-mg/kg dose group and 73.4% (94/128) for the oritavancin 3.0-mg/kg dose group as compared with 75.4% (98/130) for the vancomycin/cephalexin-treated patients. These findings were also comparable across all four populations.

In addition, the SDCO cure rates were comparable for oritavancin versus vancomycin/cephalexin in the CE population at the test-of-cure visit for the three disease categories of wound, abscess, and cellulitis.

The patient level microbiological outcomes further support the comparability of oritavancin to vancomycin/cephalexin with microbiologic success rates of 72.7% (56/77) for oritavancin 3.0-mg/kg patients compared with 74.7% (62/83) for the vancomycin/cephalexin patients at the test-of-cure visit in the ME population. In addition, the success rate for oritavancin 1.5-mg/kg patients was 65.8% (52/79).

S. aureus was the most common pathogen isolated from baseline cultures. The eradication rates for all baseline pathogens were generally comparable between the 2 treatment groups. Eradication rates in the oritavancin 1.5 mg/kg and oritavancin 3.0-mg/kg groups compared to the vancomycin/cephalexin group for the ME population for *S. aureus* were 66.0% (35/53) and 67.3% (33/49) versus 72.0% (36/50), respectively. For MSSA, the eradication rates were 65.6% (21/32) and 63.6% (21/33) versus 69.4% (25/36), respectively. For MRSA, the eradication rates were 61.5% (8/13) and 76.9% (10/13) versus 72.7% (8/11), respectively. The eradication rates for *S. pyogenes* were 50.0% (5/10) for oritavancin 1.5 mg/kg and 90.0% (9/10) for oritavancin 3.0 mg/kg versus 58.8% (10/17) for vancomycin/cephalexin and for *E. faecalis* 62.5% (5/8) for oritavancin 1.5 mg/kg and 75.0% (3/4) for oritavancin 3.0 mg/kg versus 80.0% (4/5) for vancomycin/cephalexin.

The clinical and microbiological effectiveness of oritavancin and vancomycin/cephalexin in treating patients with cSSSI was comparable in subgroup analyses for age, gender, ethnic group, and region.

Overall, efficacy results in Study ARRD were consistent and comparable across the primary and secondary efficacy variables in all patient populations evaluated. Oritavancin was shown to be noninferior to vancomycin/cephalexin in the treatment of patients with cSSSI, with statistical analyses revealing that treatment with oritavancin was noninferior to vancomycin/cephalexin.

Although oritavancin 1.5 mg/kg and oritavancin 3.0 mg/kg were not directly compared for the analyses for the NDA submission, the original analyses of Study ARRD included this comparison. No statistical differences were observed between the two oritavancin dose groups; however, trends for higher success rates in several subsets were more frequently seen with the 3.0-mg/kg/day dose group, providing evidence to support the higher regimen.

At the conclusion of Study ARRD, a pharmacokinetic-pharmacodynamic analysis was performed on the weight-based dosing data obtained from the study. Results of this analysis led Lilly to use a fixed-dose regimen (200 mg/day [300mg/day for patients weighing >110 kg (242 lbs)]) in Study ARRI. The subsequently developed population-pharmacokinetic model using data from healthy subjects in Phase 1 studies and patients in Phase 2 and 3 studies (see Section 5.2) supports Lilly's dose selection for Study ARRI.

6.7.2 Phase 3 Study ARRI

Table 6-11 presents the patient evaluation groups for Study ARRI. The percentages of patients in the four populations were comparable between treatment groups.

Table 6-11 Patient Evaluation Groups for Study ARRI

Patient Population	ORI % (n)[a]	VAN/CEPH % (n)[a]
ITT	98.7% (831)	97.6% (415)
MITT	66.6% (561)	70.4% (299)
CE	80.2% (675)	77.2% (328)
ME	54.5% (459)	55.8% (237)

Abbreviations: CE = clinically evaluable; ITT = intent to treat; ME = microbiologically evaluable; MITT = modified intent to treat; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Percentages are based on numbers randomized.

Table 6-12 presents the reasons for nonevaluability in the ITT population for Study ARRI.

Table 6-12 Reasons for Nonevaluability for Study ARRI (Intent-to-Treat Population)

	ORI N=831 % (n)	VAN/CEPH N=415 % (n)
Clinically nonevaluable patients	18.8% (156)	21.0% (87)
Reasons for nonevaluability[a]		
Clinical assessment missing or indeterminate at test of cure	10.6% (88)	12.8% (53)
Clinical assessment did not occur in protocol-specified window (Day 21 to Day 29)	9.9% (82)	14.2% (59)
Did not receive at least 3 days of treatment	7.5% (62)	8.2% (34)
Inclusion criteria not met	2.4% (20)	1.9% (8)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Patients may have had multiple reasons for nonevaluability. All reasons are summarized; therefore, percentages may total more than 100%.

6.7.2.1 Demographics

Baseline patient demographic data for Study ARRI are summarized in Table 6-13 for the ITT population. Patient demographic characteristics were comparable between the oritavancin and vancomycin/cephalexin treatment groups.

Table 6-13 Baseline Patient Demographics for Study ARRI (Intent-to-Treat Population)

Demographic	ORI N=831 % (n)	VAN/CEPH N=415 % (n)
Sex		
Male	55.7% (463)	55.4% (230)
Female	44.3% (368)	44.6% (185)
Ethnic Origin		
Caucasian	49.7% (413)	50.1% (208)
African Descent	20.9% (174)	21.0% (87)
Hispanic	14.3% (119)	13.0% (54)
Other	15.0% (125)	15.9% (66)
Age (years)		
Mean (+SD)	48.0 (16.95)	48.7 (16.77)
Age Groups		
<45 years	44.8% (372)	44.3% (184)
>45 – <65 years	36.9% (307)	36.6% (152)
>65 – <75 years	11.7% (97)	11.1% (46)
>75 years	6.6% (55)	8.0% (33)
Weight		
<110 kg	93.0% (773)	89.9% (373)
>110 kg	7.0% (58)	10.1% (42)
Region[a]		
US/Canada	29.0% (241)	28.7% (119)
Latin America	10.6% (88)	10.1% (42)
Europe	29.4% (244)	29.6% (123)
Other	31.0% (258)	31.6% (131)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; VAN/CEPH = vancomycin/cephalexin.

[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.

6.7.2.2 Baseline Disease

Table 6-14 presents the baseline disease categories, characteristics, and pathogens for patients in the ITT population in Study ARRI. The numbers of patients within each disease category as well as the duration of the disease and extent of tissue involvement were comparable between the oritavancin and vancomycin/cephalexin treatment groups. The most common pathogen isolated at baseline was *S. aureus*.

Table 6-14 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRI (Intent-to-Treat Population)

	ORI % (n) N=831	VAN/CEPH % (n) N=415
Disease Category		
Wound infection	31.9% (265)	33.5% (139)
Major abscess	44.0% (366)	42.7% (177)
Cellulitis	24.1% (200)	23.9% (99)
Deepest Tissue Involved		
Skin	3.1% (26)	4.6% (19)
Subcutaneous	52.0% (432)	51.8% (215)
Muscle	11.3% (94)	11.6% (48)
Fascial plane	32.9% (273)	31.6% (131)
Bone	0% (0)	0% (0)
Other	0.7% (6)	0.5% (2)
Location of Infection		
Head and neck	7.3% (61)	8.9% (37)
Torso	27.2% (226)	23.1% (96)
Upper extremity	20.5% (170)	20.0% (83)
Lower extremity	45.0% (374)	48.0% (199)
Foot	8.4% (70)	8.9% (37)
Lower leg	28.4% (236)	27.7% (115)
Upper leg	6.1% (51)	9.2% (38)
Other[a]	2.0% (17)	2.2% (9)
Duration of Disease in Days		
Mean (SD)	5.4 (5.20)	6.0 (8.96)
Minimum to maximum	1 to 88	1 to 140
SIRS[b]	28.6% (238)	29.2% (121)
Concomitant antibacterial therapy		
aztreonam	14.4% (120)	19.8% (82)
metronidazole	15.2% (126)	17.1% (71)
Baseline Pathogen[c]	N=561[c]	N=299[c]
S. aureus	76.5% (429)	74.2% (222)
MSSA	51.0% (286)	52.2% (156)
MRSA	21.0% (118)	17.7% (53)
S. pyogenes	17.1% (96)	20.7% (62)
S. agalactiae	6.2% (35)	2.7% (8)
S. anginous group[d]	6.8% (38)	6.4% (19)
S. dysgalactiae	2.1% (12)	1.7% (5)
Other *Streptococcus* spp.[e]	5.2% (29)	7.0% (21)
E. faecalis	6.1% (34)	8.0% (24)
Other *Enterococcus* spp.[f]	2.1% (12)	2.3% (7)

(continued)

Table 6-14 Baseline Disease Categories, Characteristics, and Pathogens for Study ARRI (Intent-to-Treat Population) (Concluded)

Abbreviations: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; N = total number of patients; n = number of patients treated; ORI = oritavancin; SD = standard deviation; SIRS = systemic inflammatory response syndrome; VAN/CEPH = vancomycin/cephalexin.

[a] "Other" includes lower extremity infections such as whole leg, knee, heel, etc.

[b] Presence of ≥2 of the following variables: temperature >38°C or <36°C, heart rate >90 beats/min, PaCO2 <32 mmHg (calculated using the Henderson-Hasselbalch equation and serum bicarbonate), and abnormal WBC count (>12,000 cells/mm3 or <4,000 cells/mm3 or >10% bands).

[c] Baseline pathogens are derived from the modified intent-to-treat population, not the intent-to-treat population.

[d] *S. anginous* group includes *S. anginosus*, *S. constellatus*, and *S. intermedius*.

[e] Other *Streptococcus* spp. includes *S. bovis*, *S. canis*, *S. equinus*, *S. oralis*, *S. parasanguinus*, *S. salivarius*, *S sanguinus*, and unspeciated *Streptococcus*.

[f] Other *Enterococcus* spp. includes *E. avium*, *E. casseliflavus*, *E. faecium*, *E. hirae*, and unspeciated *Enterococcus*.

6.7.2.3 Comorbidities and Severity of Illness

Table 6-15 shows the incidence of clinically relevant comorbidities in the ITT population for Study ARRI.

Table 6-15 Incidence of Clinically Relevant Comorbidities in the Intent-to-Treat Population for Study ARRI

Comorbidity	ORI N=831 % (n)	VAN/CEPH N=175 % (n)
Age ≥75	6.6% (55)	8.0% (33)
Diabetes	19.3% (160)	21.4% (89)
Hepatic insufficiency	2.9% (24)	3.9% (16)
Renal insufficiency[a]/dialysis	5.2% (43)	4.6% (19)
Vascular[b]	5.2% (43)	5.8% (24)
Immunologic[c]	4.3% (36)	4.3% (18)
Cancer	2.2% (18)	1.7% (7)
Cardiac[d]	5.3% (44)	5.1% (21)
Respiratory[e]	5.5% (46)	6.3% (26)
Transplantation	0% (0)	0% (0)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Creatinine clearance ≤30.

[b] Arterial insufficiency and/or venous stasis.

[c] ANC <1000, neutropenic event, HIV/AIDS, and/or immunosuppresive concomitant medications.

[d] Congestive heart failure, myocardial infarction, and/or other cardiac conditions.

[e] Severe asthma, chronic obstructive pulmonary disease, and/or other respiratory conditions.

Table 6-16 shows the number of comorbidities per patient in the ITT population for Study ARRI.

Table 6-16 Number of Comorbidities per Patient in the Intent-to-Treat Population for Study ARRI

Number of Comorbidities	ORI N=831 % (n)	VAN/CEPH N=175 % (n)
Patients with zero	62.3% (518)	58.3% (242)
Patients with one	25.0% (208)	27.0% (112)
Patients with two	8.4% (70)	11.1% (46)
Patients with three or more	4.2% (35)	3.6% (15)

Abbreviations: N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

6.7.2.4 Disposition

Table 6-17 presents the primary reasons for discontinuation of study drug for Study ARRI for both the ITT and CE populations. The reasons for discontinuation were generally similar between the groups with the exception of discontinuation due to adverse event. A significantly greater percentage of patients were discontinued from treatment with study drug due to an adverse event in the vancomycin/cephalexin-treated group (4.8%, 20/415) as compared to the oritavancin-treated patients (1.9%, 16/831). A single death was reported in the vancomycin/cephalexin group that resulted in discontinuation of study drug.

Table 6-17 Primary Reasons for Discontinuation of Study Drug in Study ARRI (Intent-to-Treat and Clinically Evaluable Populations)

	ITT		CE	
	ORI **%** (n)[a]	**VAN/CEPH** **%** (n)[a]	**ORI** **%** (n)[b]	**VAN/CEPH** **%** (n)[b]
N	831	415	675[a]	328
Discontinued	11.4% (95)	12.5% (52)	9.3% (63)[a]	12.5% (41)
Lack of efficacy	3.9% (32)	2.9% (12)	4.1% (28)[a]	3.7% (12)
Death	0.0% (0)	0.2% (1)	0.0% (0)[a]	0.3% (1)
Adverse event	1.9% (16)	4.8% (20)	2.1% (14)[a]	5.5% (18)
Other[c]	5.7% (47)	4.6% (19)	3.1% (21)[a]	3.0% (10)

Abbreviations: CE = clinically evaluable; ITT = intent to treat; N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Percentages are based on the ITT population.

[b] Percentages are based on the CE population.

[c] The other reasons for discontinuation (and the numbers of involved ITT patients) are: patient decision (21 ORI, 9 VAN), physician decision (13 ORI, 6 VAN), protocol violation/entry criteria not met (10 ORI, 3 VAN), and sponsor decision (3 ORI, 1 VAN).

6.7.2.5 Efficacy Results

The primary efficacy outcome variable for Study ARRI was the SDCO of patients in the CE population at the first follow-up visit (test of cure). Additional efficacy outcome variables for this study included the IDCO, pathogen level outcome, and patient level microbiological outcome. Table 6-18 presents the efficacy analysis of Study ARRI.

Table 6-18 Cure/Success Rates[a] at Test-of-Cure Visit for Study ARRI

Efficacy Endpoint (Patient Population)	**ORI[a]** **% (n/N)**	**VAN/CEPH** **% (n/N)**
Investigator-defined clinical outcome (CE)	82.3% (534/649)	82.5% (254/308)
Sponsor-defined clinical outcome[b] (CE)	78.5% (530/675)[c]	75.9% (249/328)
Wound	75.9% (173/228)	72.2% (83/115)
Abscess	81.0% (226/279)	78.3% (101/129)
Cellulitis	78.0% (131/168)	77.4% (65/84)
Patient level microbiological outcome (ME)	74.1% (340/459)	71.7% (170/237)

Abbreviations: CE = clinically evaluable; ME = microbiologically evaluable; N = total number of patients; n = number of patients treated; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

[a] Excludes missing and indeterminate.

[b] For Study ARRI, sponsor-defined clinical outcome in the CE population was the primary efficacy endpoint.

[c] 95% CI (-3.0, 8.2).

The overall clinical cure rate (SDCO, the primary efficacy result) for oritavancin patients was 78.5% (530/675) compared with 75.9% (249/328) for the vancomycin/cephalexin patients (95% CI: [-3.0, 8.2]) in the CE population at the test-of-cure visit. This finding

of comparable efficacy was consistent across the other three populations as well: ITT (78.8% [594/754] for oritavancin patients compared with 76.3% [284/372] for vancomycin/cephalexin patients), MITT (78.7% [398/506] for oritavancin patients compared with 76.8% [205/267] for vancomycin/cephalexin patients), and ME (78.9% [362/459] for oritavancin patients compared with 76.8% [182/237] for vancomycin/cephalexin patients).

The IDCO was consistent with the primary endpoint with cure rates at the test-of-cure visit of 82.3% (534/649) in the oritavancin group and 82.5% (254/308) in the vancomycin/cephalexin group in the CE population, with similar results observed in the other populations.

In addition, the SDCO cure rates were comparable for oritavancin versus vancomycin/cephalexin in the CE population at the test-of-cure visit for the three disease categories of wound, abscess, and cellulitis.

The patient level microbiological outcomes further support the comparability of oritavancin and vancomycin/cephalexin with similar microbiological success rates of 74.1% (340/459) for oritavancin patients compared with 71.7% (170/237) for the vancomycin/cephalexin patients at the test-of-cure visit in the ME population.

S. aureus and *S. pyogenes* were the most common pathogens isolated from baseline cultures. Overall, the eradication rates for all baseline pathogens were generally comparable between the two treatment groups, with eradication rates in the oritavancin group compared to the vancomycin/cephalexin group for the ME population as follows: *S. aureus* 72.2% (252/349) versus 74.1% (129/174); MSSA 76.7% (184/240) versus 76.0% (98/129); MRSA 61.4% (54/88) versus 65.8% (25/38); *S. pyogenes* 84.5% (71/84) versus 73.5% (36/49); and *E. faecalis* 86.2% (25/29) versus 65.0% (13/20), respectively.

The clinical and microbiological effectiveness of oritavancin and vancomycin/cephalexin in treating patients with cSSSI was comparable in subgroup analyses for age, gender, ethnic group, and geographic region.

Overall in Study ARRI, as in Study ARRD, efficacy results were consistent and comparable across the primary and secondary efficacy variables in all of the patient populations evaluated in this study. Oritavancin was as clinically effective as vancomycin/cephalexin in the treatment of patients with cSSSI, with statistical analyses revealing that treatment with oritavancin was noninferior to vancomycin/cephalexin.

6.8 Pooled Phase 3 Study Results

Because patient demographics, criteria for evaluability, and treatment duration were similar in the two Phase 3 studies, the data were pooled to allow a comprehensive evaluation of the findings, to support the conclusions of the two studies individually, and to pull together a larger database for subgroup analyses. However, because the initial Phase 3 study (Study ARRD) included two weight-based dosages (1.5 and 3.0 mg/kg), patients in that study could have received doses higher than or lower than the intended label dose studied in Study ARRI of 200 mg/day (300 mg/day for patients weighing more than 110 kg [242 lbs]). To determine whether the receipt of doses outside the proposed label dose had an impact on efficacy outcomes, a dose range was selected to encompass the proposed two doses of 200 and 300 mg that would exclude patients who received more than or less than the intended label dose. This dose range, labeled the intended label dose range (ILDR), included patients from Study ARRD who received a dose of oritavancin between 180 and 330 mg per day. The lower and upper bounds of this range were determined by including patients who received a dose that incorporated ±10% of the dose contained in the proposed label (that is, 200 mg - 10% to 300 mg +10%). The majority of oritavancin patients from the combined Phase 3 studies (81.5% [956 of 1173]) received oritavancin in the ILDR of 180 to 330 mg/day. Only a small percentage (1.9%) of the oritavancin population received oritavancin at a dose greater than this range, while 16.6% received oritavancin at a dose less than this range.

As shown in Table 6-19, outcomes are comparable between the ORI-ALL (all patients receiving oritavancin in either Studies ARRD or ARRI) and ORI-ILDR treatment groups for both measures of clinical outcome (SDCO and IDCO) as well as for microbiological outcome. Because outcomes are comparable between the ORI-ALL and the ORI-ILDR treatment groups, the pooling of all the oritavancin treatment groups from Studies ARRD and ARRI was determined to be appropriate; therefore, subsequent efficacy outcomes for the combined data will be presented using the ORI-ALL population.

Table 6-19 Clinical Cure Rates[a] at Test-of-Cure Visit for the Analysis of Pooled Data (Studies ARRD and ARRI)

Outcome Parameter/ Study Population	ORI-ALL	ORI-ILDR	VAN/CEPH
	% (n/total)		
SDCO			
ITT	76.6% (787/1027)	77.6% (662/853)	75.6% (385/509)
CE	76.9% (722/939)	77.7% (597/768)	75.8% (347/458)
IDCO			
ITT	80.6% (806/1000)	81.4% (676/830)	82.0% (397/484)
CE	80.4% (729/907)	81.3% (601/739)	81.8% (354/433)
Patient Level Microbiological Outcome			
MITT	72.5% (483/666)	73.5% (413/562)	73.1% (258/353)
ME	72.8% (448/615)	74.0% (378/511)	72.5% (232/320)

Abbreviations: CE = clinically evaluable; ITT = intent to treat; ME = microbiologically evaluable; MITT = modified intent to treat; n = number of patients; ORI-ALL = oritavancin all doses; ORI-ILDR = oritavancin intended label dose range; VAN/CEPH = vancomycin/cephalexin.

[a] Results exclude assessments of indeterminate or missing.

As shown in Table 6-20, analysis by disease category showed similar clinical cure rates as those observed in the individual study populations.

Table 6-20 Clinical Cure Rates[a] at Test-of-Cure Visit by Disease Category in the Clinically Evaluable Population for the Analysis of Pooled Data (Studies ARRD and ARRI)

Disease Category	ORI-ALL	VAN/CEPH
	% (n/total)	
Wound infection	75.9% (214/282)	71.0% (103/145)
Major abscess	79.5% (299/376)	78.5% (139/177)
Cellulitis	74.4% (209/281)	77.2% (105/136)

Abbreviations: n = number of patients; ORI-ALL = oritavancin all doses; VAN/CEPH = vancomycin/cephalexin.

[a] Sponsor-defined clinical outcome (SDCO).

Clinical cure rates by the subgroups of age, sex, and weight were similar in all treatment groups and to the overall population. Clinical cure rates for patients ≥75 years of age were lower than patients <75 years of age; however, comparable cure rates were observed in all treatment groups for this older population. In CE patients with an outcome of cure at the test-of-cure visit, relapse rates at the late follow-up visit were 2.4% (16/663) in the ORI-ALL doses and 1.9% (6/315) in the vancomycin/cephalexin group.

In the pooled analysis, the mean duration of active IV dosing in the CE population was approximately 1 day shorter for oritavancin-treated patients compared with the vancomycin-treated patients (5.2 days and 6.1 days, respectively). Further, the mean duration of total active therapy (IV and oral) in the vancomycin/cephalexin-treated

patients was 11.3 days compared to 5.2 days of total active therapy in the oritavancin-treated patients. Even with therapy durations shorter than the mean of 5.2 days (3 or 4 days), clinical cure rates for oritavancin remained consistent (Table 6-21). Because the recommended treatment durations are different for oritavancin (3 to 7 days) as compared to vancomycin/cephalexin (10 to 14 days), comparison of outcomes between treatment groups on a daily basis is not valid. However, it is appropriate to look at the clinical outcomes for oritavancin alone by treatment duration without a direct comparison to vancomycin/cephalexin.

Table 6-21 Cure Rates for Sponsor-Defined Clinical Outcomes by Duration of Active IV Therapy for the Pooled Phase 3 Studies (Clinically Evaluable Population)

Duration of Active IV Therapy	ORI-ALL % (n/N)
3 days	83.2% (84/101)
4 days	83.9% (239/285)
5 days	78.1% (89/114)
6 days	81.6% (71/87)
7 days	78.9% (105/133)
7 days plus additional IV placebo[a]	65.5% (133/203)

Abbreviations: IV = intravenous; N = total number of patients; n = number of patients cured; ORI-ALL = oritavancin all doses.

[a] Includes patients receiving 7 days of active oritavancin therapy plus an additional 1 to 9 days of IV placebo.

In both Studies ARRD and ARRI, patients were allowed to be enrolled with significant comorbidities including all levels of renal and hepatic insufficiency, diabetes, HIV/AIDS, polymicrobial infection, and bacteremia, all of which may complicate response to therapy. The clinical outcome at first follow-up by these special populations is presented in Table 6-22 for the pooled Phase 3 studies.

Table 6-22 Clinical and Microbiological Outcomes at First Follow-Up by Special Population for the Pooled Phase 3 Studies

Underlying Disease/ Study Population[a]	Cure Rate	
	ORI-ALL % (n/N)	VAN/CEPH[b] % (n/N)
Creatinine Clearance		
>80 mL/min		
ITT	78.0% (605/776)	76.8% (307/400)
CE	78.1% (557/713)	77.2% (281/364)
>30 to ≤80 mL/min		
ITT	74.6% (153/205)	73.3% (63/86)
CE	75.7% (140/185)	71.1% (54/76)
>10 to ≤30 mL/min		
ITT	64.7% (11/17)	50.0% (1/2)
CE	60.0% (9/15)	0% (0/1)
Hepatic Insufficiency[c]		
ITT	76.5% (26/34)	57.9% (11/19)
CE	77.4% (24/31)	60.0% (9/15)
Diabetes		
ITT	61.9% (143/231)	64.6% (73/113)
CE	62.2% (125/201)	62.9% (61/97)
HIV/AIDS		
ITT	70.0% (14/20)	62.5% (5/8)
CE	73.7% (14/19)	66.7% (4/6)

Abbreviations: AIDS = acquired immune deficiency syndrome; CE = clinically evaluable; HIV = human immunodeficiency virus; ITT = intent to treat; N = total number of patients; n = number of patients cured; ORI-ALL = oritavancin all doses; VAN/CEPH = vancomycin/cephalexin.

[a] Special population as defined at baseline; patients who had a response of missing or indeterminate are not included.

[b] Vancomycin dosed intravenously at 15 mg/kg twice daily.

[c] Patients were identified with hepatic insufficiency through an examination of preexisting conditions or adverse events mapped to MedDRA 10.0 preferred terms.

The microbiological success rate in the ME population at the test-of-cure visit was 72.8% in the ORI-ALL group and 72.5% in the VAN/CEPH group (Table 6-19). As presented in Table 6-23, the microbiological success rates by individual pathogens for the ME population were comparable between treatment groups including all *S. aureus*, MRSA, and *S. pyogenes*. Baseline pathogen distribution and MIC_{50} and MIC_{90} values for oritavancin and vancomycin/cephalexin are summarized in Table 6-24.

Table 6-23 Patient Level Microbiologic Success Rates by Sponsor-Defined Pathogens in Microbiologically Evaluable Patients in the Pooled Analysis (Studies ARRD and ARRI)

Baseline pathogen	ORI-ALL	VAN/CEPH
	% (n of pathogens/total)	
S. aureus	70.7% (319/451)	72.8% (163/224)
MSSA	74.1% (226/305)	74.5% (123/165)
MRSA	63.2% (72/114)	67.3% (33/49)
S. pyogenes	77.9% (81/104)	66.7% (44/66)
S. agalactiae	66.7% (24/36)	85.7% (12/14)
S. anginosus[a]	79.6% (43/54)	81.5% (22/27)
S. dysgalactiae[b]	50.0% (6/12)	33.3% (1/3)
E. faecalis[c]	75.6% (31/41)	68.0% (17/25)

Abbreviations: ORI-ALL = oritavancin all doses; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; n = number of patients cured; VAN/CEPH = vancomycin/cephalexin.

[a] *S. anginosus* group includes *S. anginosus, intermedius, and constellatus*

[b] *S. dysgalactiae includes S. dysgalactiae and dysgalactiae* subsp. *Equisimilis*

[c] Vancomycin-susceptible strains only.

Table 6-24 Summary of Minimum Inhibitory Concentration Data by Baseline Isolate within the Modified Intent-to-Treat Population in the Analysis of Pooled Data (Studies ARRD and ARRI)

		Antibiotic Tested					
		ORI			VAN/CEPH		
Baseline Isolates	N	MIC Range Min-Max	MIC_{50}	MIC_{90}	MIC Range Min-Max	MIC_{50}	MIC_{90}
S. aureus	768	0.008-2.0[a]	0.06	0.25	0.25-2.0	1	1
MSSA	545	0.008-0.25	0.06	0.12	0.25-2.0	1	1
MRSA	215	0.015-2.0	0.06	0.25	0.5-2.0	1	1
S. pyogenes	184	0.004-0.5	0.06	0.25	0.25-0.5	0.25	0.25
E. faecalis	70	0.015-0.25	0.06	0.12	0.5-4.0	1	2

Abbreviations: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; Max = maximum; MIC = minimum inhibitory concentration; Min = minimum; N = total number of patients; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.

a When tested by broth microdilution including polysorbate-80, the maximum oritavancin MIC for any gram-positive complicated skin and skin structure (cSSSI) pathogen in Phase 3 studies for cSSSI was 2µg/mL (MRSA; n=1); this isolate was successfully eradicated following oritavancin treatment. All other baseline cSSSI pathogens were inhibited in vitro by <0.5µg/mL.

There were a total of 21 oritavancin patients and 9 vancomycin/cephalexin patients enrolled in Studies ARRD and ARRI with concurrent bacteremia at baseline (allowed per the inclusion criteria) who had an assessed outcome for analysis. In this population of MITT patients, outcomes were similar between treatment groups with clinical cure rates of 61.9% (13/21) in the ORI-ALL group and 66.7% (6/9) in the VAN group.

For patients with cSSSI and concurrent bacteremia with a baseline blood pathogen of *S. aureus*, clinical cures were observed in 7/13 ORI-ALL patients and 4/4 VAN patients. Although the number of patients with *S. pyogenes* isolates was small, clinical cures were observed in ORI-ALL patients (2/2) and VAN patients (2/4).

6.9 Characterization of Clinical Trial Isolates with Apparent Decreased Susceptibility to Oritavancin

Sixteen patients treated with oritavancin in Studies ARRD and ARRI had isolates displaying an MIC dilution increase of ≥2-fold from baseline during the study period. However, no categorical susceptibility change appeared to have developed on therapy because the highest MIC encountered in all of these cases was at or below the proposed susceptibility breakpoints for oritavancin for the potentially indicated organisms. Of these 16 patients, 6 patients (4 failures, 1 cure, 1 indeterminate) had *S. aureus* as their baseline pathogen and an oritavancin MIC increase to 0.25 µg/mL, the proposed susceptible breakpoint for *S. aureus*. Oritavancin MICs against isolates from the Phase 3 studies of cSSSI were determined, once per isolate, by broth microdilution in the presence of polysorbate-80.

The oritavancin MIC against a subset of these isolates (isolates from oritavancin-treated patients with an MIC increase between baseline and terminal isolates) was reexamined in triplicate so as to assess the reproducibility of the observed stepwise increases in oritavancin MIC on therapy. Unexpectedly, the oritavancin MIC values against isolates from the patient's final visit were consistently lower upon re-test and, indeed, were comparable to (that is, generally identical to or within one doubling dilution of) the oritavancin MIC values observed at the patient's initial visit (Eurofins Report 500585). This observation suggests that the reported apparent increases in oritavancin MICs on therapy in clinical studies of cSSSI were not reproducible. Further, this observation suggests that oritavancin did not select for increased MICs on therapy, at least for the tested isolates.

6.10 Efficacy Conclusions

In summary:

- Studies ARRD and ARRI demonstrated that 3 to 7 days of oritavancin was noninferior to 10 to 14 days of vancomycin/cephalexin in treating cSSSI, either presumed or proven to be caused by susceptible gram-positive pathogens, within the prespecified noninferiority margins for each study.

- The overall response rates for both clinical and microbiological outcomes were similar between the oritavancin and vancomycin/cephalexin treatment groups and the effects were consistent across all populations, across baseline disease categories, and across preexisting comorbidities.

- The overall response rates for both clinical and microbiological outcomes were similar when the pooled analyses were conducted using ORI-ALL or ORI-ILDR.

- The efficacy of oritavancin was comparable to that of vancomycin/cephalexin for the subgroups of gender, age class, weight, ethnicity, geographic region, renal function, hepatic function, and for patients with diabetes.

- There was no evidence of increases in oritavancin MIC beyond the proposed oritavancin susceptibility breakpoints for proposed indicated organisms in either of the studies.

- Together, Studies ARRD and ARRI demonstrated that oritavancin was efficacious for the treatment of cSSSI at the recommended dose of IV oritavancin 200 mg (300 mg if patient weighs >110 kg [242 lbs]).

7 Clinical Safety

The clinical development of oritavancin included standard evaluations of adverse events, laboratory measures, and vital signs. Most of the following discussion (with the exception of deaths) will focus on the safety profile of oritavancin in patients with cSSSI, that is, the double-blind Phase 3 population from Studies ARRD and ARRI. Throughout this document, the relatedness of an adverse event to study drug is always based on the assessment of the investigator, unless otherwise noted. All cSSSI patients in Studies ARRD and ARRI who received any amount of study drug (ITT population) are included in the integrated safety analyses. In general, similar types of adverse events were seen in the three phases of clinical development.

7.1 Extent of Exposure

In the Phase 3 ITT population, 1173 patients from Studies ARRD and ARRI received oritavancin with a mean duration of oritavancin therapy of 5.1 days ± 1.6 days (median = 5.0 days). Of these 1173 patients, 956 (81%) received at least one dose of oritavancin in the ILDR of 180 to 330 mg/day. The safety findings in the ORI-ILDR treatment group were similar to and without clinically important differences from the ORI-ALL treatment group; therefore, this clinical safety section will primarily focus on the safety findings in the ORI-ALL group.

7.2 Adverse Events

7.2.1 Deaths and Serious Adverse Events

Among the 2176 individuals (1540 oritavancin- and 636 vancomycin-treated subjects and patients) who received study drug in the oritavancin clinical development program to date, 74 (3.4%) deaths occurred. Eight of those 74 deaths (10.8%) occurred either after completion of the study protocol (6 deaths [4 in the oritavancin treatment group and 2 in the vancomycin treatment group]) or after discontinuation from the study because of an adverse event (2 deaths, both in the oritavancin treatment group).

Of the 66 deaths that occurred during study participation, 31 occurred among Phase 3 ITT patients (19 [1.6%] of 1173 oritavancin- and 12 [2.0%] of 590 vancomycin/cephalexin-treated patients), 35 among Phase 2[1] ITT patients (27 [19.0%] of 142 oritavancin- and 8 [23.5%] of 34 vancomycin-treated patients), and 0 among Phase 1 ITT patients. None of the deaths that occurred among oritavancin-treated Phase 3 or Phase 2 ITT patients during study participation was investigator-assessed as related to study drug.

Table 7-1 and Table 7-2 present details on the deaths that occurred during study participation in the Phase 3 ITT population and the Phase 2 ITT population, respectively.

[1] Phase 2 ITT patients came from 3 diverse studies. Two of these studies (1 open-label, controlled [comparator: vancomycin] and 1 non-comparator-controlled) were conducted in patients who had bacteremia and a variety of profound comorbidities. The third Phase 2 study (non-comparator-controlled) was conducted in patients with skin and skin structure infections.

Table 7-1 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 3 Intent-to-Treat Population

Patient Number	Age/Race/ Gender	Days of IV Therapy	Relative Day of Death[a]	Verbatim Term	Adverse Event Preferred Term	Related to Study Drug
Oritavancin 1.5 mg/kg/d (N=3)						
ARRD-069-2871[b]	33/AF/M	1	54	Asystole (2)	Cardiac arrest	No
ARRD-705-7043	82/C/F	7	42	Cardiac arrest	Cardiac arrest	No
ARRD-705-7045	90/C/M	14	31	Cardiac arrest	Cardiac arrest	No
Oritavancin 3.0 mg/kg/d (N=3)						
ARRD-069-2864	39/HP/F	1	2	Idioventricular rhythm	Rhythm idioventricular	No
ARRD-069-3283	56/AF/F	7	44	Cardiopulmonary arrest	Cardio-respiratory arrest	No
ARRD-705-7200	71/H/F	2	2	Septic shock	Septic shock	No
Oritavancin 200 mg/d[c] (N=13)						
ARRI-005-0004	69/C/F	6	15	Bacteremia	Bacteremia	No
ARRI-005-0007	47/HP/M	6	12	Septic shock	Septic shock	No
ARRI-006-0002	64/C/M	11	29	Sepsis	Sepsis	No
ARRI-030-0001	87/C/M	4	11	Acute pulmonary edema	Acute pulmonary edema	No
ARRI-056-0003	85/HP/M	14	17	Cardiopulmonary arrest	Cardio-respiratory arrest	No
ARRI-065-0007	68/C/M	7	25	Intra-abdominal bleeding	Intra-abdominal hemorrhage	No
ARRI-130-0002	26/HP/F	6	25	Abdominal sepsis due to accidental perforation of the bowel	Abdominal sepsis Intestinal perforation	No
ARRI-151-0021	73/C/M	2	5	Cardiac insufficiency	Cardiac failure	No
ARRI-166-0033	55/AF/F	4	6	Pulmonary embolus	Pulmonary embolism	No
ARRI-167-0008	24/AF/M	5	22	Septicemia	Sepsis	No
ARRI-167-0042	24/AF/F	11	20	Death (Murder)	Accidental death	No
ARRI-234-0020	84/HP/F	9	16	Respiratory arrest	Respiratory arrest	No
ARRI-234-0027	35/HP/F	8	23	Obstructive upper airway	Obstructive airways disorder	No

(continued)

Table 7-1 Summary of During Study Deaths among Oritavancin-Treated Patients in the Phase 3 Intent-to-Treat Population (Concluded)

Patient Number	Age/Race/ Gender	Days of Therapy	Relative Day of Death[a]	Verbatim Term	Adverse Event Preferred Term	Related to Study Drug
Vancomycin (N=12)						
ARRD-702-7013	80/C/M	14	48	Irreversible respiratory failure	Respiratory failure	No
ARRD-703-7025	67/HP/F	7	18	Mediastinal follicular lymphoma	B-cell lymphoma	No
ARRD-705-7218	64/HP/M	7	20	Cardiac arrest	Cardiac arrest	No
ARRD-706-7060	43/HP/F	7	9	Heart arrest	Cardiac arrest	No
ARRD-901-9122	59/HP/M	8	12	Pulmonary embolism	Pulmonary embolism	No
ARRI-041-0003	67/O/F	4	5	Ventricular fibrillation	Ventricular fibrillation	Yes
ARRI-117-0002	63/C/M	2	20	Peritonitis	Peritonitis	No
ARRI-126-0003	59/A/F	9	10	Pneumonia	Pneumonia	No
ARRI-151-0022	75/C/F	4	12	Ischemic insult (stroke)	Ischemic stroke	No
ARRI-158-0014	56/C/F	7	14	Cardio pulmonary failure	Cardiopulmonary failure	No
ARRI-162-0024	72/C/F	3	31	Pulmonary distress	Respiratory distress	No
ARRI-234-0094	59/C/M	15	37	Cardiac arrest	Cardiac arrest	No

Abbreviations: A = Asian; AF = African descent; C = Caucasian; d = day; F = female; HP = Hispanic; IV = intravenous; M = male.

[a] Day 1 = first day of IV therapy.

[b] Patient ARRD-069-2871 died after completing the study but was included in the clinical trial database.

[c] 300 mg/day for patients weighing more than 110 kg (242 lbs).

Among the four post-protocol-completion deaths (as opposed to the during study deaths presented in the table above) in oritavancin-treated patients, one was investigator-assessed as related to study drug. A brief narrative of this case follows:

- ARRD-401-4205 (ORI) was a 65-year-old Caucasian male who received oritavancin IV 144 mg on Days 1 through 6 for a periumbilical abscess. Ongoing medical conditions at the time of study entry included gastric cancer, subtotal small bowel resection, protein C deficiency, ascites, and hypoalbulminemia. Historical diagnoses included cholecystectomy, deep vein thrombosis, femoral neck fracture, gastrectomy, and "herniotomy." Beginning approximately 6 weeks prior to study entry, the patient was hospitalized and treated with parenteral hyperalimentation. The day prior to study entry, the patient was treated for a periumbilical abscess with piperacillin/tazobactam and incision and drainage, with deepest tissue involvement reported as muscle. The investigator reported that the patient was improved on Day 6. Serious adverse events of candida pneumonia and candida sepsis were reported on Day 11. He received piperacillin/tazobactam for sepsis and pneumonia Days 15 through 21. The patient was treated with systemic antifungal treatment beginning Day 27, with fluconazole IV Days 27 through 31, flucytosine IV Days 31 through 46, and amphotericin B IV Days 32 through 46, as well as oral nystatin, reportedly for pneumonia, Days 27 through 30. Imipenem/cilastatin and vancomycin were added for sepsis and pneumonia Days 31 through 41. The patient developed a relapse of the abscess on Day 18 and was diagnosed with a fistula to the transverse colon, which was treated surgically; this information is not included in the case report form (CRF). The patient developed mild herpes simplex and mild impetigo on Day 48. The patient developed acute respiratory distress syndrome (ARDS) and died on Day 53, after completing the study, from multi-organ failure. The investigator could not exclude that oritavancin may have contributed to a decline in this patient's immune function, and that the events of candida sepsis, candida pneumonia, herpes simplex and impetigo were possibly related to study drug. The current sponsor notes multiple risk factors for systemic candida infection, including malnutrition, parenteral hyperalimentation, colonic fistula, abdominal surgeries, antibiotic administration, and the implanted subcutaneous port placed the month prior to study entry, which remained in place at the time of the patient's death.

Table 7-2 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 2[a] Intent-to-Treat Population

	Age/Race/ Gender	Days of IV Therapy	Relative Day of Death[a]	Verbatim Term	Adverse Event Preferred Term	Related to Study Drug
Oritavancin 3/2 mg/kg IV (Day 1 loading dose/remaining days; daily maintenance dose) (n/N=1/5)						
ARRC-012-1281	42/AF/M	7	45	Venoocclusive liver disease	Venoocclusive liver disease	No
Oritavancin 4/3 mg/kg IV (Day 1 loading dose/remaining days; daily maintenance dose) (n/N=2/5)						
ARRC-007-1181	77/HP/M	3	4	Sepsis syndrome	Sepsis syndrome	No
ARRC-010-1242	44/AF/M	3	5	Cardiac arrest	Cardiac arrest	No
Oritavancin 5/4 mg/kg IV (Day 1 loading dose/remaining days; daily maintenance dose) (n/N=2/17)						
ARRC-009-1225	48/HP/M	7	17	Respiratory distress	Respiratory distress	No
ARRC-009-1223	48/HP/F	7	48	Respiratory distress	Respiratory distress	No
Oritavancin 5.0 mg/kg/d (n/N=2/9)						
ARRM-085-1744	75/HP/F	5	11	Mediastinitis	Mediastinitis	No
ARRM-085-1746	82/A/M	3	4	Myocardial infarction	Myocardial infarction	No
Oritavancin 6.5 mg/kg/d (n/N=2/11)						
ARRM-705-7041	19/HP/M	13	18	Septic shock due to *Pseudomonas aeruginosa*	Septic shock Pseudomonal sepsis	No
ARRM-705-7043	28/HP/M	14	36	Septic shock due to *Staphylococcal epidermidis*	Septic shock Staphylococcal sepsis	No
Oritavancin 8.0 mg/kg/d (n/N=14/40)						
ARRM-085-1750	75/HP/F	11	35	Multisystem organ failure	Multi-organ failure	No
ARRM-085-1751	47/HP/M	4	4	Multisystem organ failure	Multi-organ failure	No
ARRM-086-1780	38/AF/M	14	27	Septic shock	Septic shock	No
ARRM-086-1782	79/A/F	14	36	Recurrent candida urosepsis	Candiduria Urosepsis	No
ARRM-303-3081	53/A/F	10	10	Worsening liver cirrhosis	Hepatic cirrhosis	No
ARRM-351-3140	23/A/F	5	61	Cardiogenic shock	Cardiogenic shock	No

(continued)

Table 7-2 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 2 Intent-to-Treat Population (Continued)

	Age/Race/ Gender	Days of IV Therapy	Relative Day of Death[a]	Verbatim Term	Adverse Event Preferred Term	Related to Study Drug
Oritavancin 8.0 mg/kg/d (concluded)						
ARRM-605-6040	76/C/F	1	6	Septic shock associated with endocarditis	Septic shock Endocarditis	No
ARRM-702-7002	70/C/M	3	3	Irreversible cardiac failure	Cardiac failure	No
ARRM-705-7051	32/HP/F	7	8	Nosocomial pneumonia	Pneumonia	No
ARRM-707-7124	71/C/M	9	17	Sudden death (cause unknown)	Sudden death	No
ARRM-707-7126	58/C/F	5	22	Uncontrolled sepsis	Sepsis	No
ARRM-708-7161	86/C/F	11	29	Worsening of esophagus neoplasm	Neoplasm progression	No
ARRM-708-7163	86/C/F	10	11	Worsening of pneumonia	Pneumonia	No
ARRM-706-7083	55/C/M	3	4	Severe hypotension	Hypotension	No
Oritavancin 10.0 mg/kg/d (n/N=4/26)						
ARRM-085-1760	54/C/F	10	23	Worsening respiratory failure	Respiratory failure	No
ARRM-085-1761	52/C/F	4	5	Massive pulmonary embolism	Pulmonary embolism	No
ARRM-707-7130	58/C/M	4	49	Cardiac arrest	Cardiac arrest	No
ARRM-708-7164	88/C/M	10	34	Worsening of rectal neoplasm	Neoplasm progression	No
Vancomycin (n/N=8/37)						
ARRM-082-1581	47/C/F	2	16	Worsening of end stage renal disease	Renal failure chronic	No
ARRM-085-1741	80/C/F	8	22	Septic shock	Septic shock	No
ARRM-085-1754	85/A/F	1	15	Multisystem organ failure	Multi-organ failure	No
ARRM-085-1755	90/HP/F	9	46	Acute non Q wave myocardial infarction	Acute myocardial infarction	No

Table 7-2 **Table 7-2 Summary of During Study Deaths among Oritavancin- and Vancomycin-Treated Patients in the Phase 2 Intent-to-Treat Population (Concluded)**

Patient Number	Age/Race/ Gender	Days of Therapy	Relative Day of Death[a]	Verbatim Term	Adverse Event Preferred Term	Related to Study Drug
Vancomycin (concluded)						
ARRM-302-3042[d]	68/A/M	12	14	Hypotension	Hypotension	No
ARRM-302-3045	70/A/M	3	28	Sepsis	Sepsis	No
ARRM-706-7080	58/HP/F	11	30	Worsening encephalic Metastatic cancer	Brain cancer metastatic	No
ARRM-804-8041	75/C/M	11	16	Multisystem organ failure	Multi-organ failure	No

Abbreviations: A = Asian; AF = African descent; C = Caucasian; d = day; F = female; HP = Hispanic; IV = intravenous; M = male; N = total number of patients.

[a] Phase 2 ITT patients came from 3 diverse studies. Two of these studies (one open-label controlled, [comparator: vancomycin and/or β-lactam], Study ARRM, and one non-comparator-controlled, Study ARRC) were conducted in patients who had bacteremia and a variety of profound comorbidities. The third Phase 2 study (non-comparator-controlled), Study ARRL, was conducted in patients with skin and skin structure infections.

Comparable percentages of patients in the oritavancin and vancomycin/cephalexin treatment groups (9.1% oritavancin and 11.4% vancomycin/cephalexin) had serious adverse events (SAEs) during the Phase 3 studies. The SAEs experienced by patients in the oritavancin studies did not suggest a specific pattern and do not suggest systemic drug toxicities from oritavancin.

7.2.2 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that was present at baseline and worsened in severity during a study or an event with onset after the beginning of the first infusion of active study drug. Throughout this section, all references to significant differences are to statistically significant differences ($p<0.05$). As Table 7-3 illustrates, a significantly lower percentage of patients in the oritavancin treatment group had at least 1 TEAE or a TEAE related to study drug during the Phase 3 studies compared with the vancomycin/cephalexin treatment group. A significantly lower percentage of oritavancin than vancomycin/cephalexin patients discontinued study drug due to an adverse event.

Table 7-3 Summary of Adverse Events by Treatment Group During the Phase 3 Studies (Intent-To-Treat Population)

Number of Patients Who	ORI N=1173 % (n)	VAN/CEPH N=590 % (n)	p-Value
Had at least 1 TEAE	53.5% (628)	62.4% (368)	<0.001
Had at least 1 related TEAE	18.0% (211)	25.3% (149)	<0.001
Had at least 1 SAE	9.1% (107)	11.4% (67)	0.150
Had at least 1 related SAE	0.9% (10)	1.2% (7)	0.606
Had a fatal SAE	1.6% (19)	2.0% (12)	0.566
Discontinued study drug due to an AE	3.0% (35)	5.8% (34)	0.006

Abbreviations: AE = adverse event; N = number of patients; n = number of patients with event; ORI = oritavancin; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VAN/CEPH = vancomycin/cephalexin.

Figure 7-1 summarizes the most common adverse events occurring in ≥2% of Phase 3 oritavancin patients. As Figure 7-2 shows, events of insomnia, pruritus, and rash occurred in significantly lower percentages of oritavancin-treated patients than vancomycin/cephalexin-treated patients while dizziness occurred in a significantly higher percentage of oritavancin-treated than vancomycin/cephalexin-treated patients. None of the events of dizziness that occurred in the oritavancin treatment group was associated with a central nervous system or cardiovascular adverse event, or with a concurrent clinically relevant decrease in blood pressure.

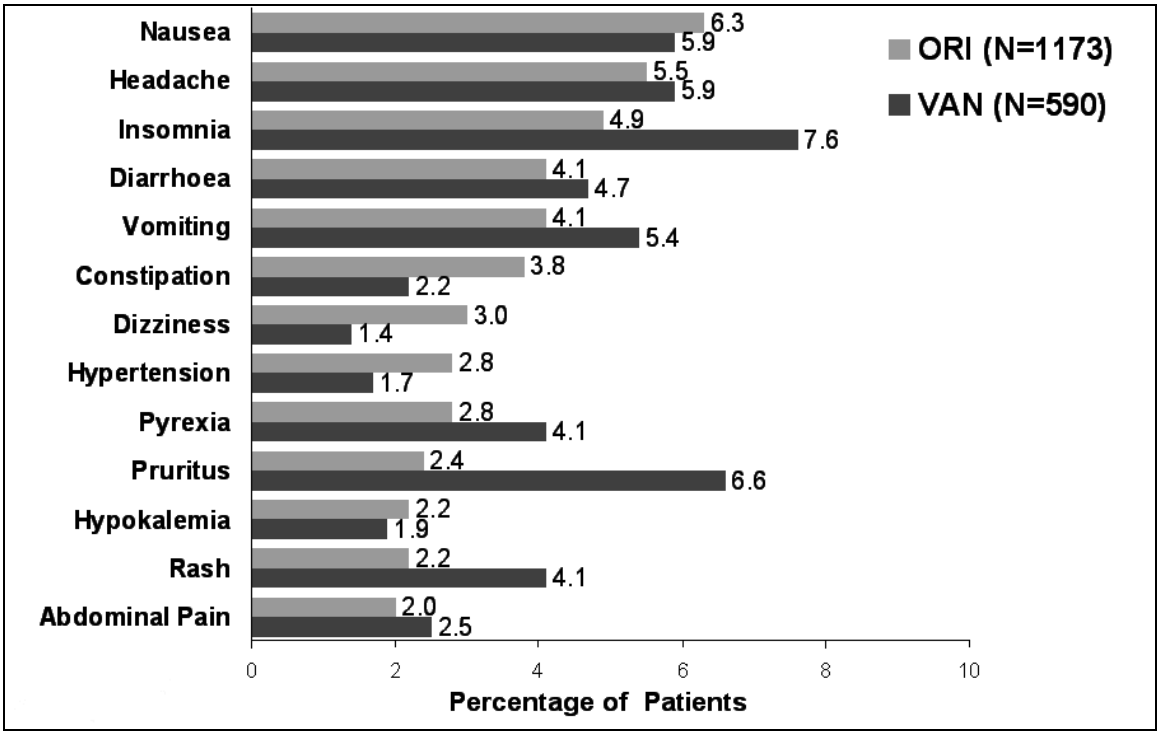


Figure 7-1 **Most common adverse events occurring in ≥2% of Phase 3 oritavancin patients.**

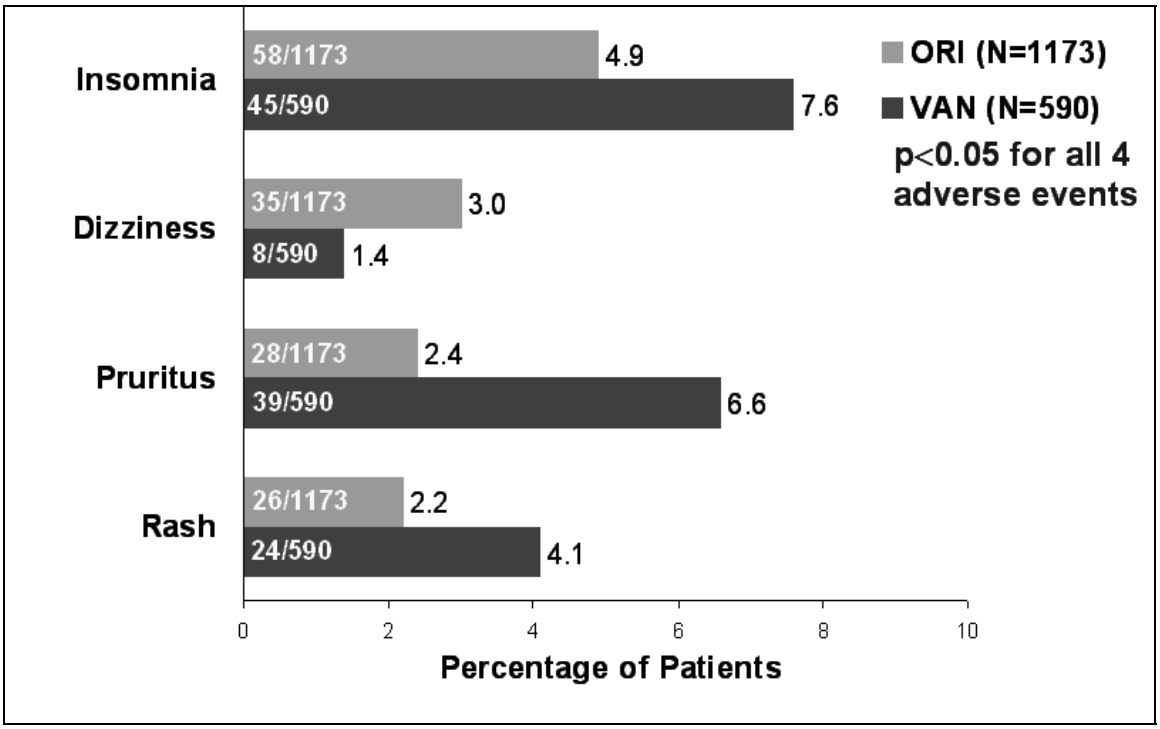


Figure 7-2 **Most common adverse events with significant differences between treatment groups.**

Treatment-emergent adverse events (TEAEs) of special interest in the oritavancin clinical development program were defined in an effort to identify those TEAEs most likely to be related to oritavancin therapy. These were defined as those TEAEs that occurred in the during IV therapy period that are considered to be potentially drug-class related, including injection site phlebitis, histamine-like infusion reaction (HLIR), or red man syndrome. Finally, any TEAEs that occurred in ≥1% of patients in the oritavancin treatment group in the during IV therapy period of the Phase 3 studies and at a significantly different incidence between the vancomycin/cephalexin group and the oritavancin group are also designated as TEAEs of special interest.

Table 7-4 summarizes the TEAEs of special interest that occurred in the during IV therapy period in ≥1% of patients in the Phase 3 ITT population, regardless of treatment group. The majority of TEAEs included in the table are drug-class related events. Of the TEAEs of special interest, seven (pruritus, erythema, pruritus generalized, flushing, red man syndrome, urticaria, and infusion site pruritus) occurred in significantly lower percentages of oritavancin than vancomycin/cephalexin patients. The five remaining TEAEs of special interest showed no significant differences between the treatment groups.

Table 7-4 Treatment-Emergent Adverse Events of Special Interest by Decreasing Frequency Reported in ≥1% of Complicated Skin and Skin Structure Infection Intent-to-Treat Patients in Each Treatment Group in the During IV Therapy Period

Preferred Term	ORI N=1173 % (n)	VAN/CEPH N=590 % (n)	p-Value[a] ORI vs VAN
Patients with ≥ 1 TEAE	**42.2% (495)**	**50.0% (295)**	**0.002**
TEAEs of Interest Reported in ≥1% of Patients in the ORI Treatment Group			
Infusion site pain	1.7% (20)	1.9% (11)	0.848
Infusion site phlebitis	1.6% (19)	1.5% (9)	1.000
Pruritus	**1.6% (19)**	**5.4% (32)**	**<0.001**
Rash	1.6% (19)	2.5% (15)	0.200
Phlebitis	1.3% (15)	1.7% (10)	0.524
TEAEs of Interest Reported in ≥1% of Patients in the VAN Treatment Group but not the ORI Group			
Erythema	**0.6% (7)**	**2.2% (13)**	**0.007**
Pruritus generalised	**0.5% (6)**	**1.9% (11)**	**0.009**
Flushing	**0.2% (2)**	**1.4% (8)**	**0.003**
Red man syndrome	**0.0% (0)**	**1.4% (8)**	**<0.001**
Urticaria	**0.2% (2)**	**1.2% (7)**	**0.008**
Infusion site pruritus	**0.1% (1)**	**1.2% (7)**	**0.003**
Infusion site erythema	0.3% (3)	1.0% (6)	0.068

Abbreviations: N = number of patients; n = number of patients with TEAE; ORI = oritavancin all doses; TEAE = treatment-emergent adverse event; VAN/CEPH = vancomycin/cephalexin.

[a] p-Value from Fisher's exact test. Pairwise comparison is ORI vs VAN.

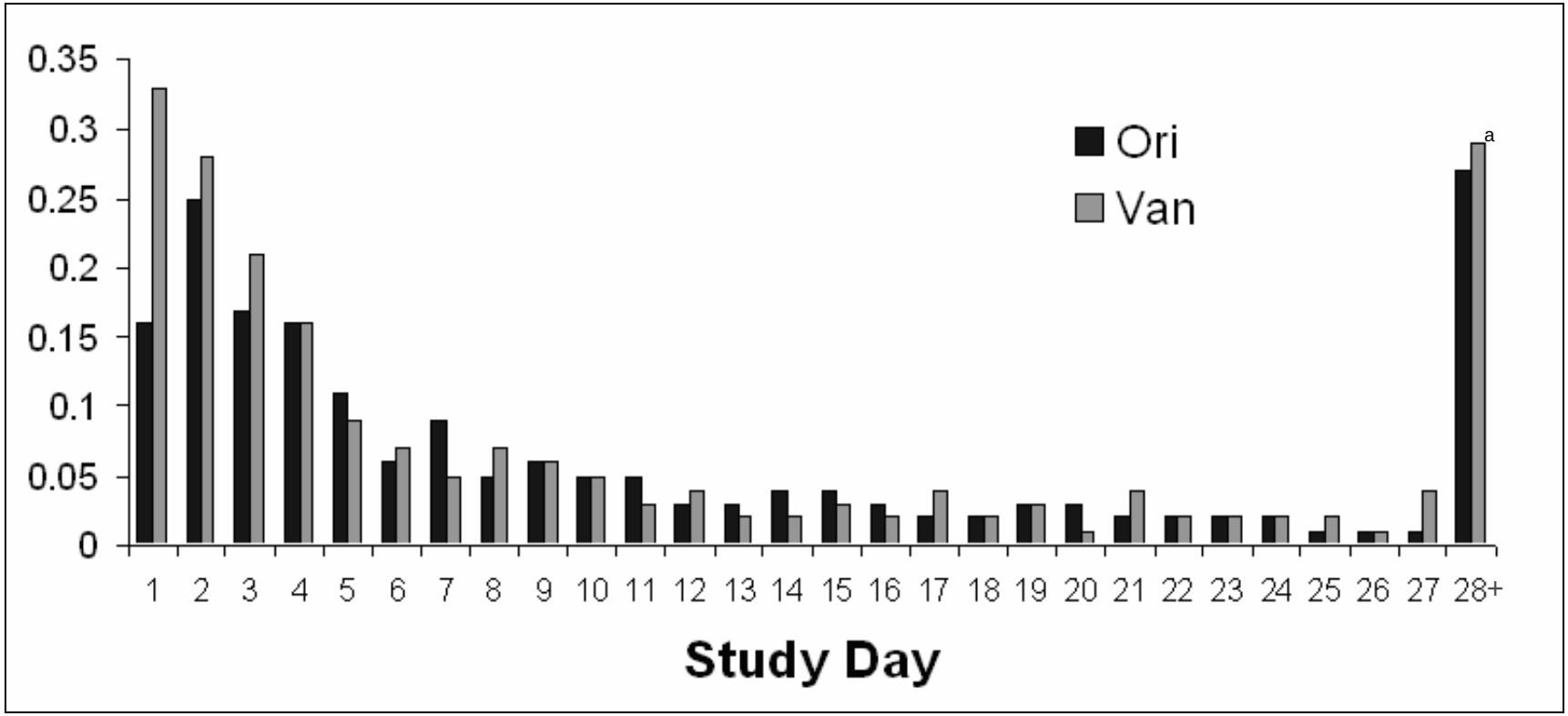
[b] Note: Shaded column indicates treatment group dictating the order of TEAEs by decreasing frequency. **Bolded** in-table numbers indicate significant between group differences.

The majority of TEAEs among oritavancin- and vancomycin-treated patients were mild or moderate in intensity (79.1% and 78.5%, respectively). Treatment-emergent adverse events (TEAEs) were evaluated by the subgroups of age, gender, race, hepatic function, renal function, diabetes, immunocompromised indicator, weight group, and ILDR group for potential safety differences. No particular subgroup appeared to be at an increased risk of adverse effects of drug treatment. Furthermore, the adverse event data across all studies were reviewed, focusing on the hepatic, renal, and cardiovascular systems as well as antibiotic-associated, and, more specifically, glycopeptide-associated effects. Overall, oritavancin appeared to have a comparable or, in some regards, an improved adverse event profile with respect to comparator.

7.2.3 Timing of Onset and Time to Resolution of Adverse Events

Figure 7-3 presents the rate of onset of TEAEs per patient by study day for oritavancin and vancomycin/cephalexin patients in the Phase 3 ITT population from the initiation of therapy through the final follow-up visit (Days 50 to 90 for Study ARRD and Days 39 to 46 for Study ARRI). Overall, the rates of onset of TEAEs per patient for oritavancin and vancomycin/cephalexin were comparable, and the rates of onset for both drugs decreased over time. The most notable difference in rate of onset of TEAEs per patient between oritavancin and vancomycin/cephalexin occurs on Day 1 and likely reflects the significantly higher incidence of HLIRs among vancomycin/cephalexin-treated patients (9% of the events on Study Day 1 were HLIR in the oritavancin group compared with 40% in the vancomycin/cephalexin group).

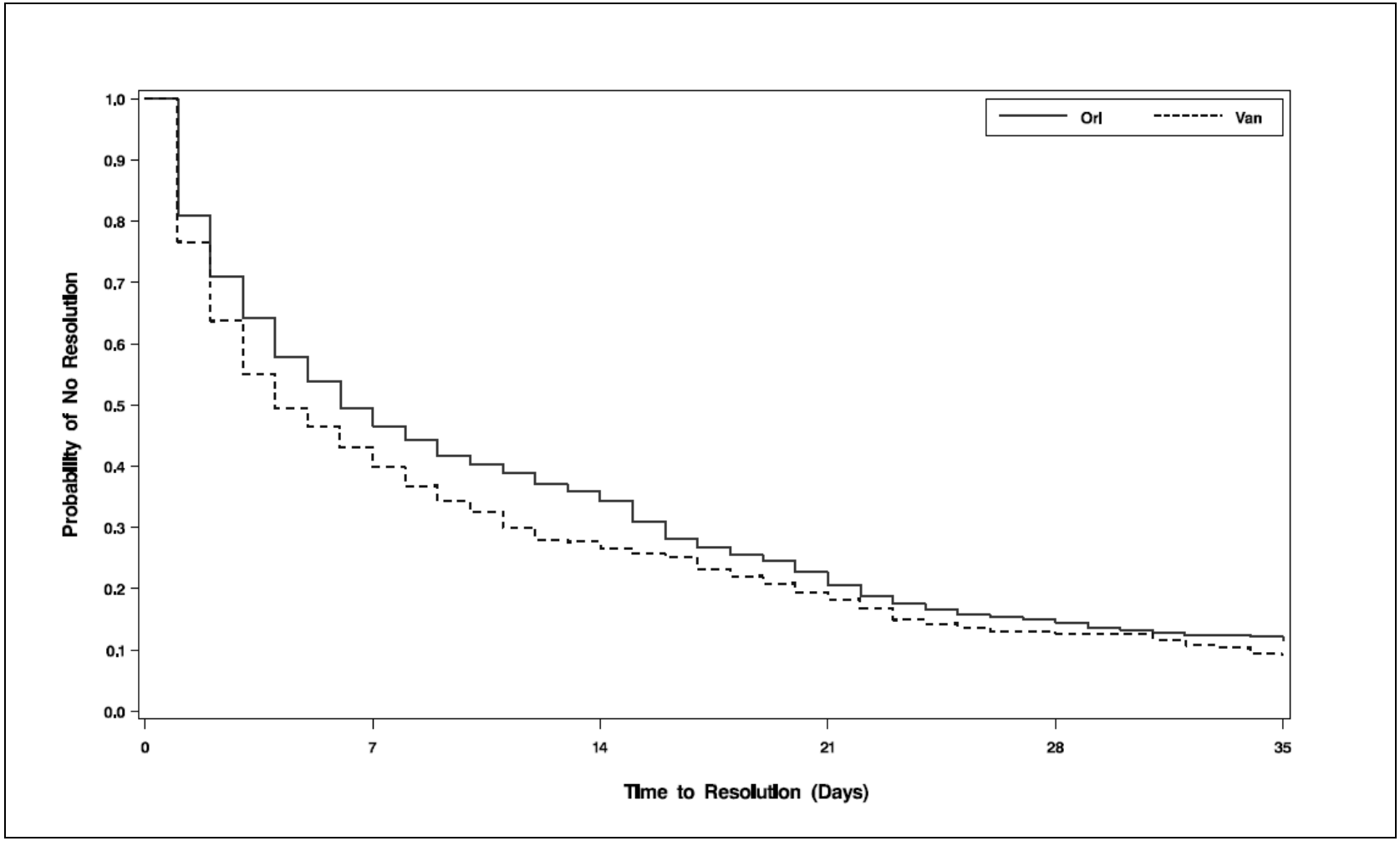
As Figure 7-4 illustrates, the time to resolution of the adverse event of longest duration per patient in the Phase 3 studies was similar in the oritavancin and vancomycin/cephalexin treatment groups. Further, the time to resolution of the adverse event of longest duration per patient for the 12 adverse events of special interest was comparable in the two treatment groups (Figure 7-5). Despite oritavancin's long residence time in the body, no clinically meaningful differences were observed in the time to onset or the time to resolution of TEAEs for oritavancin patients compared to vancomycin/cephalexin patients.



Abbreviations: Ori = oritavancin; Van = vancomycin/cephalexin.

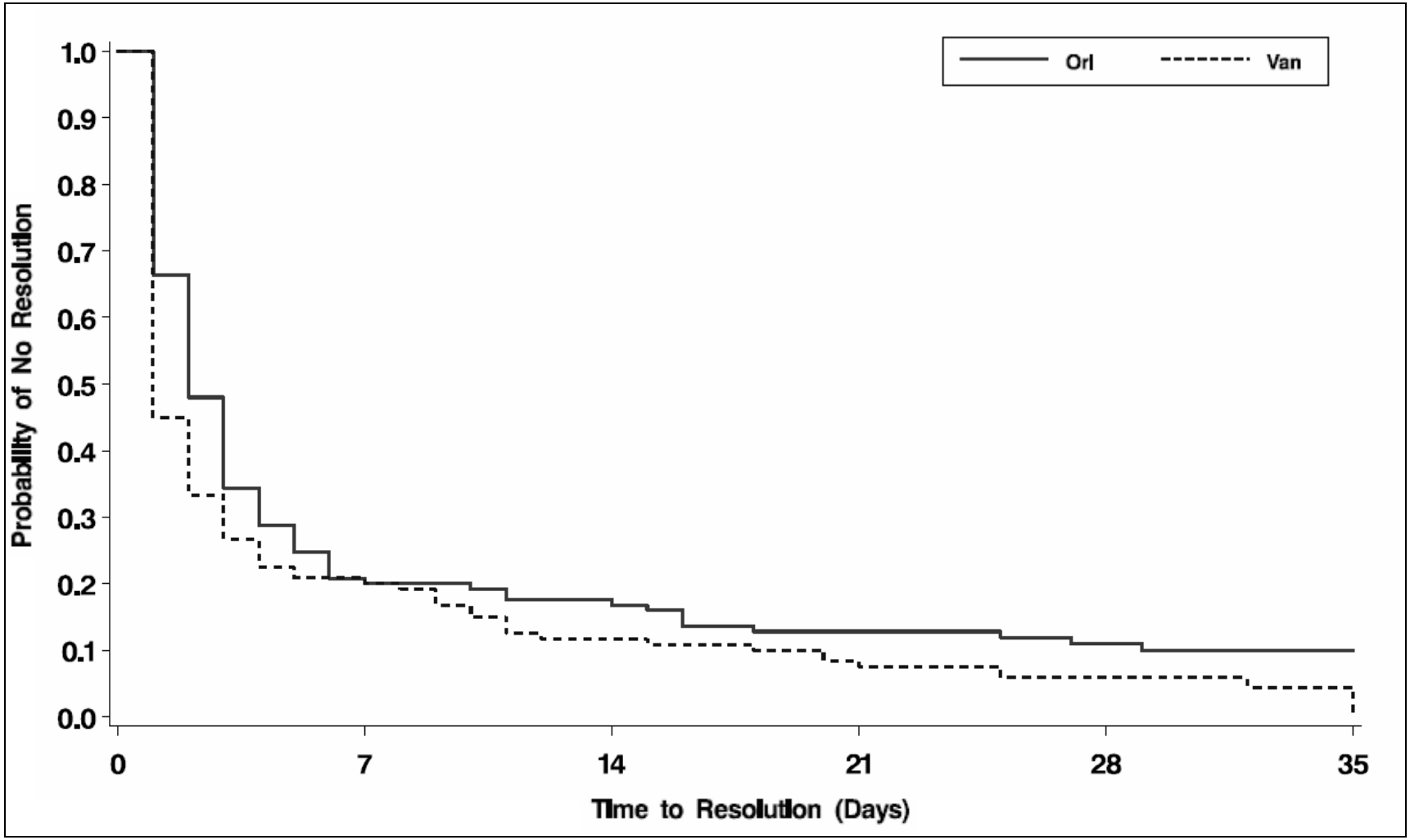
[a] The rate of treatment-emergent adverse events reported for "Day 28+" encompasses all events from Day 28 through the final follow-up visit (Days 50 to 90 for Study ARRD and Days 39 to 46 for Study ARRI).

Figure 7-3 Rate of onset of treatment-emergent adverse events per patient by study day (Phase 3 intent-to-treat population).



Abbreviations: Ori = oritavancin; Van = vancomycin/cephalexin.

Figure 7-4 **Time to adverse event resolution of the adverse event of longest duration per patient (Phase 3 intent-to-treat population).**



Abbreviations: Ori = oritavancin; Van = vancomycin/cephalexin.

Figure 7-5 **Time to adverse event resolution of the adverse event of longest duration per patient for treatment-emergent adverse events of special interest (Phase 3 intent-to-treat population).**

7.3 Potential Glycopeptide-Related Effects

The following sections review safety data potentially reflecting glycopeptide-related adverse events including injection site phlebitis, HLIRs, nephrotoxicity, ototoxicity, vestibular toxicity, and hematologic effects.

7.3.1 Injection Site Phlebitis

Targanta conducted a comprehensive review and analysis of safety data to explore potential factors contributing to injection site phlebitis. This review included 1962 patients and 243 healthy subjects. The conclusions of Targanta's review are summarized as:

- Oritavancin administration to patients with cSSSI and to patients with bacteremia resulted in an incidence of injection site phlebitis comparable with that of equipotent therapeutic doses of vancomycin (15 mg/kg [10 to 12 mg/kg for patients with reduced creatine clearance] every 12 hours).

- No association was observed between drug substance lot or drug product lot or date of manufacture and the incidence of injection site phlebitis.

- Oritavancin was well-tolerated in patients with bacteremia at doses up to 10 mg/kg/day for up to 14 days (maximum dose administered 1220 mg/day for 14 days), with an incidence of injection site phlebitis comparable with that of equipotent therapeutic doses of the active comparator, vancomycin.

- Oritavancin can be administered safely to patients in single doses up to at least 800 mg/day with a low incidence of injection site phlebitis (0.4% on first day of dosing in multiple-dose studies). In clinical studies of healthy subjects receiving multiple daily doses of oritavancin, injection site phlebitis was observed on the first day of dosing in 4.4% of subjects. Little or no associated injection site phlebitis was observed in healthy subjects receiving single doses of oritavancin.

- The 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·min).

- 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 drug administration 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.

7.3.2 Histamine-Like Infusion Reactions

Histamine-like infusion reactions (HLIRs) have been previously observed in animals and in humans with oritavancin administration (Murray and Nannini 2005). Often called red man syndrome and described as anaphylactoid reactions, HLIRs have also been observed with other glycopeptides, including vancomycin. With administration of vancomycin, these reactions might present as flushing, erythema, wheezing, dyspnea, angioedema, urticaria, pruritus, pain or muscle spasm, typically of the chest or back, and/or hypotension. When such reactions occur, slowing or interrupting the vancomycin infusion is generally considered to mitigate these reactions. Antihistamines (H1 receptor antagonists) may be administered to moderate the severity of a reaction (Murray and Nannini 2005). A significantly higher incidence of HLIRs has been reported with administration of vancomycin to healthy volunteers compared with administration to patients (Rybak et al. 1992). These reactions generally resolve within several hours after the vancomycin infusion is stopped or completed, and recurrence can be mitigated with subsequent doses by slowing of the infusion, without specific treatment. Pretreatment with H1 receptor antagonists has also been reported to decrease the incidence and severity of these reactions.

Targanta searched the integrated safety database of the Phase 3 ITT population for patients who had one or more adverse events that could represent symptoms or signs of HLIR. For this safety review, a possible HLIR was defined as the occurrence of at least one of the following events in a single patient, during or within 6 hours of completion of an active oritavancin or vancomycin infusion, and resolving within 24 hours of completion of infusion:

- Flushing, or erythema of the face, neck, shoulders, chest, back, or arms
- Rash, erythematous maculopapular, on face, neck, shoulders, chest, back, or arms

- Urticaria
- Pruritus
- Musculoskeletal pain or spasm, typically of chest or paraspinal muscles
- Angioedema
- Hypotension
- Wheezing, with or without dyspnea
- Chills, if concurrent with at least one other TEAE of HLIR, in association with the same dose

When times of onset and/or resolution were not reported, events possibly meeting the specified onset and resolution time frames were identified and included for medical review.

Of 104 patients whose TEAEs might have represented a possible HLIR, subsequent physician review excluded from further analyses 3 patients whose TEAEs were either non-specific (left shoulder discomfort [1 patient]; pain in left upper extremity intermittent [1 patient]) or investigator attributed to a specific etiology (wheezing and short of breath [1 patient] noted by investigator to begin immediately after smoking).

Table 7-5 summarizes the results of the HLIR analyses for the Phase 3 ITT population. Overall, significantly lower percentages of oritavancin ($p<0.001$) than vancomycin/cephalexin patients had at least one possible HLIR (3.1% [36 of 1173 oritavancin] and 11.0% [65 of 590 vancomycin/cephalexin]).

Table 7-5 Summary of Possible Histamine-Like Infusion Reaction Subgroup Analyses (Phase 3 Intent-to-Treat Population)

	ORI N=1173 % (n)	VAN/CEPH N=590 % (n)	p-Value[a]
Patients with HLIR	3.1% (36)	11.0% (65)	<0.001
HLIR Subgroup Analyses			
Of Patients with HLIR, Number of Patients Who:	**ORI N=36 % (n)**	**VAN N=65 % (n)**	**p-Value[a]**
Received medications due to HLIR	25.0% (9)	44.6% (29)	0.057
Discontinued therapy due to HLIR	8.3% (3)	16.9% (11)	0.368

Abbreviations: HLIR = histamine-like infusion reaction; N = number of patients; n = number of patients with finding; ORI = oritavancin; VAN/CEPH = vancomycin/cephalexin.
[a] p-Value from Fisher's exact test.

Among the 101 Phase 3 ITT patients who had at least one possible HLIR, the following was observed:

- Lower but not significantly different percentages of oritavancin (25.0%) than vancomycin/cephalexin (44.6%) patients received medication due to a possible HLIR, most commonly H1 receptor antagonists and/or corticosteroids.
- Lower but not significantly different percentages of oritavancin (8.3) than vancomycin/cephalexin (16.9) patients discontinued therapy due to a possible HLIR.

7.3.3 Nephrotoxicity

Table 7-6 presents a summary of the clinically relevant renal laboratory test results for the Phase 3 ITT population. There were no clinically relevant changes in blood urea nitrogen or creatinine in either treatment group. No safety signal was identified in the oritavancin group.

Table 7-6 Summary of Clinically Relevant Renal Laboratory Test Results During the Phase 3 Studies (Intent-to-Treat Population)

Test Result	ORI		VAN/CEPH	
Blood Urea Nitrogen (mmol/L)				
Change from BL to LOV	N=1106	Mean (SD) = 0.1 (2.7)	N=550	Mean (SD) = 0.2 (2. 6)
Low/normal BL shift to high - maximum[a] value	N=1036	% (n) = 4.9% (51)	N=515	% (n) = 5.2% (27)
Creatinine (µmol/L)				
Change from BL to LOV	N=1105	Mean (SD) = 0.5 (24.9)	N=550	Mean (SD) = 3.6 (34.7)
Low/normal BL shift to high - maximum[a] value	N=1020	% (n) = 3.7% (38)	N=505	% (n) = 4.2% (21)

Abbreviations: BL = baseline; LOV = last observed value; N = number of patients; n = number of patients with observed result; ORI = oritavancin; SD = standard deviation; VAN/CEPH = vancomycin/cephalexin.

[a] Most extreme.

As shown in Figure 7-6, the percentages of patients with any adverse events potentially representing nephrotoxicity were quite low (<1%). In short, upon review of laboratory and adverse event data, there is no evidence of renal toxicity with oritavancin administration.

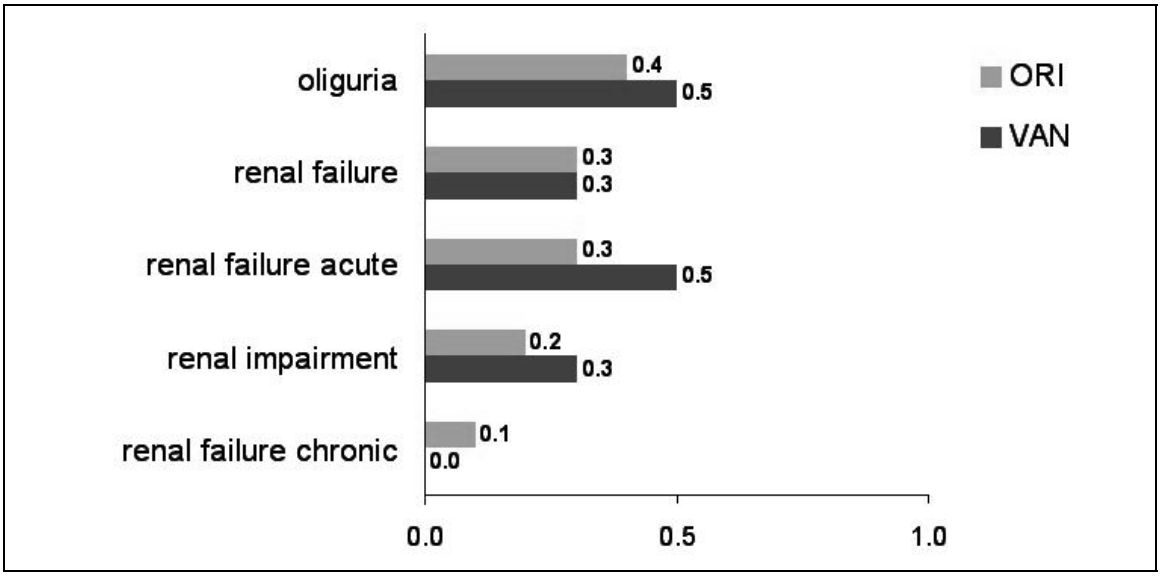


Figure 7-6 **Percentages of Phase 3 oritavancin-treated and vancomycin/cephalexin-treated patients with adverse events mapped to renal failure and impairment.**

7.3.4 Ototoxicity

No clinically relevant changes in audiograms were observed in the four Phase 1 studies (ARRA, ARRB, ARRK, and JE-101N) that included audiometric testing before and after oritavancin administration. A review of the adverse events potentially indicating hearing disorders or hearing loss in Phase 3 patients revealed one oritavancin patient with hypoacusis (which was mild and unrelated to study drug) and one vancomycin patient with dysacusis (which was possibly related to study drug and led to the patient's discontinuation from study drug). There was no treatment-emergent tinnitus in either treatment group.

7.3.5 Vestibular Toxicity

There was no treatment-emergent vertigo in either treatment group in the Phase 3 ITT population.

7.3.6 Hematological Effects

Because of oritavancin's uptake in bone marrow and long residence time in the body, as well as the hematologic effects reported with other glycopeptides, a thorough search of the safety data base for laboratory changes or adverse events indicating treatment-emergent neutropenia, thrombocytopenia, or pancytopenia was conducted.

Table 7-7 presents a summary of the clinically relevant hematology laboratory test results for the Phase 3 ITT population. There were no clinically relevant changes in hematocrit, hemoglobin, total neutrophils, or platelets in either treatment group. No safety signal was identified in the oritavancin group.

Table 7-7 Summary of Clinically Relevant Hematology Laboratory Test Results during the Phase 3 Studies (Intent-to-Treat Population)

Test Result	ORI		VAN/CEPH	
Hematocrit (%)				
Change from BL to LOV	N=916	Mean (SD) = 0.7 (4.6)	N=448	Mean (SD) = 0.6 (4.4)
High/normal BL shift to low - minimum[a] value	N=713	% (n) = 13.0% (93)	N=326	% (n) = 12.3% (40)
Normal BL shift to substantially abnormal low[b] minimum[a] value	N=701	% (n) = 16.4% (115)	N=323	% (n) = 15.8% (51)
Hemoglobin (mmol/L)				
Change from BL to LOV	N=963	Mean (SD) = 0.1 (0.9)	N=473	Mean (SD) = 0.1 (0.8)
High/normal BL shift to low - minimum[a] value	N=727	% (n) = 12.4% (90)	N=339	% (n) = 15.0% (51)
Normal BL shift to substantially abnormal low[c] minimum[a] value	N=723	% (n) = 6.4% (46)	N=337	% (n) = 9.2% (31)
Neutrophils total, Absolute (GI/L)				
Change from BL to LOV	N=961	Mean (SD) = -3.4 (4.5)	N=472	Mean (SD) = -3.7 (5.0)
Normal BL shift to substantially abnormal low[d] minimum[a] value	N=559	% (n) =	N=288	% (n) =
<1000/mm^3 to ≥500/mm^3		0.4% (2)		0.7% (2)
<500/mm^3		0.0 % (0)		0.0 % (0)
Platelets (GI/L)				
Change from BL to LOV	N=910	Mean (SD) = 19.0 (111.1)	N=448	Mean (SD) = 10.5 (113.8)
High/normal BL shift to low - minimum[a] value	N=866	% (n) = 1.4% (12)	N=431	% (n) = 2.1% (9)
Normal BL shift to substantially abnormal low[e] minimum[a] value	N=785	% (n) =	N=399	% (n) =
≤75,000/mm^3 to >40,000/mm^3		0.4% (3)		0.3% (1)
≤40,000/mm^3		0.0 % (0)		0.0 % (0)

Abbreviations: BL = baseline; LOV = last observed value; N = number of patients; n = number of patients with observed result; ORI = oritavancin; SD = standard deviation; VAN/CEPH = vancomycin/cephalexin.

[a] Most extreme.
[b] For males ≤37%; for females ≤32%.
[c] For males ≤11.5 g/dL; for females ≤9.5 g/dL.
[d] <1000/mm^3.
[e] ≤75,000/mm^3.

7.3.6.1 Neutropenia

No oritavancin- or vancomycin/cephalexin-treated patient shifted from a normal baseline to an absolute neutrophil count of <500/mm^3 at any time during the study. Three oritavancin-treated patients (0.3%) had neutropenia reported as an adverse event during

the Phase 3 studies. Two of the three events were reported as possibly related to study drug according to the investigator. One of these two possibly related events was reported as mild and one was reported as moderate by the investigator. Neither patient had an absolute neutrophil count of <1000/mm^3 reported in laboratory results. There was also one episode that was reported as unrelated to study drug according to the investigator. This event was reported as severe by the investigator and occurred in a patient with ongoing medical conditions of colon cancer, anemia, and leukopenia at study entry. No vancomycin/cephalexin-treated patient had an adverse event of neutropenia.

7.3.6.2 Thrombocytopenia and Pancytopenia

Regarding effects on platelets, the potential effect on bone marrow and potential immune-mediated destruction must be considered. No oritavancin- or vancomycin/cephalexin-treated patient shifted from a normal baseline to a platelet count of ≤40,000/mm^3 at any time during the study. Two oritavancin-treated patients and one vancomycin/cephalexin-treated patient had thrombocytopenia reported as an adverse event during the clinical trial, giving identical percentages for each treatment group (0.2%). In the oritavancin group, one event of thrombocytopenia was mild and possibly related to study drug and the other event was moderate and unrelated to study drug. The vancomycin/cephalexin patient had severe thrombocytopenia that was unrelated to study drug. There was no treatment-emergent pancytopenia reported in either treatment group. In summary, there was no clinically relevant safety signal detected regarding either thrombocytopenia or pancytopenia in the Phase 3 oritavancin safety data base.

7.4 Potential Antibiotic-Related Effects: *Clostridium Difficile* Infection

Clostridium difficile infection (CDI) has been reported with nearly all antibacterial agents, including oritavancin. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. Moreover, host and environmental factors also contribute to development of CDI (Thielman and Wilson 2005). Targanta considers all *C. difficile*-associated adverse events to be potentially related to study drug. Overall, a small percentage (0.5%) of both oritavancin- and vancomycin-treated patients in the Phase 3 ITT population had adverse events of pseudomembranous or *C. difficile* colitis.

Six (0.5%) oritavancin-treated patients had seven adverse events of pseudomembranous or C. difficile colitis. Of these, two were mild, four moderate, and one severe[2] in intensity. Event onset occurred between Day 5 to Day 48 and, in all cases, the patients had received other systemic antibiotics (from one to six), in addition to oritavancin, prior to event onset. Similarly, 3 (0.5%) vancomycin-treated patients had four adverse events of pseudomembranous or *C. difficile* colitis. All four adverse events were moderate in intensity. Event onset occurred between Day 22 to Day 32 and, in all cases, the patients had received other systemic antibiotics (from one to eight), in addition to vancomycin, prior to event onset.

7.5 Hepatic Evaluation

7.5.1 Phase 3 Liver Function Test Results

Table 7-8 presents a summary of liver laboratory test results for the Phase 3 ITT population. There was no evidence of a clinically relevant oritavancin effect on liver laboratory tests. There was also no evidence of an oritavancin effect consistent with hepatic toxicity.

[2] Event began on Day 39 of study, was considered unrelated to study drug, and listed as ongoing at time of study completion.

Table 7-8 Summary of Clinically Relevant Liver Function Laboratory Test Results During the Phase 3 Studies (Intent-to-Treat Population)

Test Result	ORI				VAN/CEPH			
Total Bilirubin (µmol/L)								
Change from BL to LOV	N=1073	Mean (SD) = -2.4* (8.4)			N=528	Mean (SD) = -1.7* (7.4)		
Low/normal BL shift to high - maximum[a] value	N=1030	% (n) = 0.7% (7)			N=510	% (n) = 1.8% (9)		
Normal BL shift to substantially abnormal - high[a] value	N=982	% (n) = 0.1% (1[b])			N=478	% (n) = 0.4% (2[b])		
Alkaline Phosphatase (U/L)								
Change from BL to LOV	N=1092	Mean (SD) = -1.9 (52.0)			N=544	Mean (SD) = -3.2 (41.5)		
Low/normal BL shift to high - maximum[a] value	N=974	% (n) = 8.5% (83)			N=492	% (n) = 7.3% (36)		
Normal BL shift to substantially abnormal - high[a] value	N=972	% (n) = 0.1% (1[c])			N=492	% (n) = 0.0% (0[c])		
ALT (SGPT) (U/L)								
Change from BL to LOV	N=1058	Mean (SD) = -0.6* (40.10)			N=524	Mean (SD) = 1.4* (26.66)		
Low/normal BL shift to high - maximum[a] value	N=983	% (n) = 9.0% (88)			N=481	% (n) = 9.4% (45)		
Normal BL shift to substantially abnormal - high[a] value	N=975	% (n) = 0.8% (8[d])	% (n) = 0.1% (1[e])	% (n) = 0.0% (0[f])	N=478	% (n) = 1.5% (7[d])	% (n) = 0.0% (0[e])	% (n) = 0.2% (1[f])
AST (SGOT) (U/L)								
Change from BL to LOV	N=1039	Mean (SD) = -1.6 (44.1)			N=518	Mean (SD) = -0.6 (29.7)		
Low/normal BL shift to high - maximum[a] value	N=948	% (n) = 11.1% (105)			N=467	% (n) = 11.1% (52)		
Normal BL shift to substantially abnormal - high[a] value	N=944	% (n) = 0.4% (4[d])	% (n) = 0.2% (2[e])	% (n) = 0.0% (0[f])	N=465	% (n) = 1.1% (5[d])	% (n) = 0.0% (0[e])	% (n) = 0.2% (1[f])

Abbreviations: ALT = Alanine transaminase; AST= aspartate aminotransferase; BL = baseline; LOV = last observed value; N = number of patients; n = number of patients with observed result; ORI = oritavancin; SD = standard deviation; ULN= upper limit of normal; VAN/CEPH = vancomycin/cephalexin.

[a] Most extreme.
[b] Number of patients with shifts to ≥2.0 mg/dL.
[c] Number of patients with shifts to ≥3x ULN.
[d] Number of patients with shifts to >3xULN to 5xULN.
[e] Number of patients with shifts to >5xULN to 10xULN.
[f] Number of patients with shifts to >10xULN.
* Indicates a statistically significantly different change within the dose group.

7.5.2 Potential Drug-Induced Liver Injury

To identify potential drug-induced liver injury cases, the following analytes of interest were examined: alanine transaminase (serum glutamic pyruvic transaminase) [ALT (SGPT)], aspartate transaminase (serum glutamic oxaloacetic transaminase) [AST (SGOT)], and total bilirubin. To meet screening criteria to qualify for review as a potential drug-induced liver injury case, a patient's ALT or AST values had to exceed 3 x ULN established for these analytes and the total bilirubin value had to exceed 34.2 µmol/L (or ≥2.0 mg/dL), regardless of alkaline phosphatase results. There were low and identical percentages (0.2%) of patients who met these initial screening criteria in the oritavancin (2/1171) and vancomycin/cephalexin (1/587) treatment groups. Both oritavancin-treated patients had ongoing, preexisting liver disease at the time of study entry and no clinically relevant worsening of liver laboratory test following oritavancin administration. The baseline and postbaseline liver function test results for both of these patients are shown below in Tables 7-9 and 7-10. The vancomycin/cephalexin patient had undergone a lung resection 20 days prior to study entry with a postoperative course marked by multiple complications. In summary, there were no oritavancin-treated patients meeting "Hy's Law" criteria for drug-induced liver injury (FDA 2007b).

Table 7-9 Baseline and Postbaseline Liver Function Test Results for Patient ARRD-039-3205

Study Day	ALT (0-47 U/L)	AST (0-37 U/L)	GGT (0-51 U/L)	ALKPHOS (40-135 U/L)	TBILI (0-19 µmol/L)	Albumin (37-49 g/L)
1 [a]	67	**134**	86	92	**51.0**	23.0
3	74	**119**	104	116	**50.0**	26.0
16	41	93	62	92	26.0	20.0

Abbreviations: ALKPHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; TBILI = total bilirubin.
[a] Baseline.
Note: **Bolded** values, in combination, meet the criteria for potential liver injury (ALT or AST >3 ULN and a total bilirubin >34.2 µmol/L). Shaded rows indicate period of active study drug treatment.

Table 7-10 Baseline and Postbaseline Liver Function Test Results for Patient ARR1-006-0001

Study Day	ALT (5-95 U/L)	AST (10-78 U/L)	GGT (6-193 U/L)	ALKPHOS (28-163 U/L)	TBILI (3-29 µmol/L)
1 [a]	143.0	NR	35.0	93.0	132.0
5	130.0	193.0	41.0	145.0	91.0
22	189.0	**243.0**	42.0	193.0	**62.0**
45	159.0	206.0	52.0	250.0	44.0

Abbreviations: ALKPHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; TBILI = total bilirubin.
[a] Baseline.
Note: **Bolded** values, in combination, meet the criteria for potential liver injury (ALT or AST >3 ULN and a total bilirubin >34.2 µmol/L). Shaded rows indicate period of active study drug treatment.

7.6 Additional Laboratory Evaluations

In addition to monitoring clinically relevant hematological, hepatic, and renal function laboratory test results, standard laboratory values were examined. Although a number of analytes revealed small but statistically significant instances of treatment-emergent high/low values, there was no discernable clinical pattern suggestive of a specific body system or toxicity. There was also no indication that laboratory monitoring for safety is indicated.

7.7 Vital Signs

For incidence of most extreme values and clinically significant changes in vital signs, Table 7-11 shows the direction of interest. To be considered clinically significant, abnormal changes had to meet criteria for absolute value and change relative to baseline.

Table 7-11 Clinically Significant Vital Signs Value Criteria

Vital Sign	Absolute Value	Change Relative to Baseline
Systolic Blood Pressure	≥180 mmHg ≤ 90 mmHg	Increase of ≥20 mmHg Decrease of ≥20 mmHg
Diastolic Blood Pressure	≥105 mmHg ≤50 mmHg	Increase of ≥15 mmHg Decrease of ≥16 mmHg
Heart Rate	≥120 beats/min ≤50 beats/min	Increase of ≥15 beats/min Decrease of ≥16 beats/min
Temperature	>101 °F	Increase of ≥2°F
Weight[a]	--	≥7% body weight ≤7% body weight

[a] Weight analyses in the cSSSI ITT population include data from Study ARRI only as postbaseline weights were not collected in Study ARRD.

Note: Clinically significant vitals signs values are from Leber's Guidelines.

Table 7-12 summarizes vital signs results during the Phase 3 studies for the ITT population. There were no clinically relevant trends or unexpected fluctuations in vital sign measurements among the oritavancin-treated or vancomycin/cephalexin-treated patients in the cSSSI studies.

Table 7-12 Summary of Vital Signs Results during Study by Treatment Group (Phase 3 Intent-to-Treat Population)

Vital Signs	ORI		VAN/CEPH	
Systolic Blood Pressure (mm Hg)				
	N	**Mean (SD)**	**N**	**Mean (SD)**
Change from BL to LOV	1092	-1.4 (18.3)	545	0.2 (18.3)
	N	**% (n)**	**N**	**% (n)**
Low/normal shift to high – maximum value[a]	1075	2.2% (24)	541	2.4% (13)
High/normal shift to low – minimum value[a]	1084	2.1% (23)	535	2.1% (11)
Clinically relevant values (high)	1092	1.8% (20)	545	2.4% (13)
Clinically relevant values (low)	1092	1.6% (17)	545	1.3% (7)
Diastolic Blood Pressure (mm Hg)				
	N	**Mean (SD)**	**N**	**Mean (SD)**
Change from BL to LOV	1092	1.5 (13.4)	545	2.5 (13.4)
	N	**% (n)**	**N**	**% (n)**
Low/normal shift to high – maximum value[a]	1081	2.0% (22)	539	1.7% (9)
High/normal shift to low – minimum value[a]	1061	4.8% (51)	525	4.6% (24)
Clinically relevant values (high)	1092	1.8% (20)	545	1.5% (8)
Clinically relevant values (low)	1092	3.2% (35)	545	3.7% (20)
Heart Rate (beats per minute)				
	N	**Mean (SD)**	**N**	**Mean (SD)**
Change from BL to LOV	1097	-4.1 (15.3)	547	-3.9 (14.6)
	N	**% (n)**	**N**	**% (n)**
Low/normal shift to high – maximum value[a]	1082	2.1% (23)	540	1.1% (6)
High/normal shift to low – minimum value[a]	1096	0.6% (7)	544	0.7% (4)
Clinically relevant values (high)	1097	1.7% (19)	547	0.7% (4)
Clinically relevant values (low)	1097	0.6% (7)	547	0.5% (3)

Abbreviations: BL = baseline; N= number of patients; n= number of patients with TEAEs in system organ class disorder; LOV= last observed value; ORI = oritavancin; SD = standard deviation; VAN/CEPH = vancomycin/cephalexin.

[a] Most extreme.

7.8 ECG/QT Interval

Study QT002, a phase 1, double-blind, randomized, placebo- and positive-controlled, parallel design trial to assess the potential electrocardiographic effects of oritavancin in healthy adults was conducted to meet current guidelines for the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (FDA 2005b). Adequate assay sensitivity was demonstrated by increase of ddQTcIb, the

primary QTc endpoint, for the active control (moxifloxacin) at Hour 1 with a lower confidence bound exceeding 5 msec (8.23 msec, 90% CI: 5.08, 11.40 msec). The ECG analysis of Study QT002 also demonstrated that no clinically relevant change in QTcF was induced by a clinical (200 mg) or by a supratherapeutic (800 mg) dose of oritavancin administered intravenously in healthy subjects. Mean QTcF changes associated with oritavancin were below a 90% upper confidence limit of 10 msec at all time points, and there was no evidence of a dose-response relationship.

Earlier in the oritavancin clinical development program, because of the preclinical findings in the hERG assay, Targanta completed an extensive evaluation of cardiovascular safety that included 81 subjects from healthy subject studies, 471 subjects from patient studies, and 58 subjects from the robust QT/QTc Study OCSI-008. All of these subjects had ECGs collected and interpreted by a central ECG laboratory before and after oritavancin administration. Furthermore, Targanta conducted a concentration effect analysis to explore the relationship between oritavancin concentrations and selected ECG parameters in Study OCSI-008. No clinically relevant effect of oritavancin was observed on QT/QTc interval in any of these analyses. Further, analysis of adverse events reported in these subjects demonstrated no oritavancin-associated cardiac-related event likely related to QT/QTc prolongation.

7.9 Drug Interactions

Based on in vitro and in vivo cytochrome P450 interaction studies and oritavancin's lack of metabolism (Section 5.1.3), oritavancin is unlikely to interact with other drugs. Oritavancin non-specifically binds to proteins at about 86% to 90%; the effect of this on other highly protein bound drugs is unknown.

In vitro studies demonstrated CYP2D6 to have the highest potential for inhibition by oritavancin. The Phase 1 Study OCSI-008 was designed to assess the effect of IV oritavancin administered at a dose of 800 mg daily for 14 days on the steady state pharmacokinetics of the CYP2D6 substrate desipramine. In that study, no effect of 800-mg oritavancin on the metabolism or elimination of desipramine was observed. Based on the population pharmacokinetic profile of patients at the recommended dose, the free plasma drug concentrations would be at or below the IC50 for CYP2D6 inhibition (12.6 μM) for 24 out of 24 hours. No other drug interaction studies with oritavancin were performed.

The effect of concomitant administration of oritavancin and medications metabolized by CYP450 isoenzymes was further explored by conducting analyses of SAEs among Phase 3 ITT patients who had taken these medications prior to adverse event onset.

Table 7-13 summarizes the results of the SAE analysis by specific CYP450 (CYP2D6, CYP1A2, CYP2C9, and CYP3A4) isoenzyme substrates. Overall, using SAE incidence as a measure of clinically relevant drug interaction, and vancomycin as a comparator, oritavancin has no apparent adverse effect on patients concomitantly taking medications metabolized by CYP2D6, or CYP1A2, CYP2C9, and CYP3A4 isoenzymes.

Table 7-13 Serious Adverse Events with Onset after Exposure to Substrate (Concomitant Medication) of CYP450 Isoenzyme of Interest (Phase 3 ITT Population)

	ORI N=1173				**VAN N=590**			
Patients with ≥1 SAE % (n)	9.1% (107[a])				11.4% (67[a])			
	ORI & 2D6 % (N) 18.2 (214)	**ORI & 1A2 % (N) 31.5 (370)**	**ORI & 2C9 % (N) 34.0 (399)**	**ORI & 3A % (N) 43.6 (511)**	**VAN & 2D6 % (N) 21.5 (127)**	**VAN & 1A2 % (N) 31.5 (186)**	**VAN & 2C9 % (N) 36.8 (217)**	**VAN & 3A % (N) 46.3 (273)**
Patients with ≥1 SAE[b] % (n)	13.1 (28)	13.0 (48)	9.3 (37)	12.5 (64)	20.5 (26)	15.6 (29)	8.3 (18)	15.8 (43)

Abbreviations: 1A2 = CYP1A2 enzyme; 2C9 = CYP2C9 enzyme; 2D6 = CYP2D6 enzyme; 3A= CYP3A enzyme; ORI = oritavancin; SAE = serious adverse event; VAN = vancomycin.

[a] All patients who received study drug, regardless of concomitant medication, who had an SAE during study.

[b] SAEs occurring at least 1 day after the earliest concomitant medication start date.

Furthermore, there is no evidence of oritavancin interaction with warfarin, a highly protein-bound medication, as indicated by the low and comparable adverse events of bleeding, hemorrhage, prolongation of prothrombin time or of international normalized ratio in oritavancin- compared with vancomycin-treated Phase 3 patients.

7.10 Overdose

In clinical studies, patients received up to 4 times the maximum proposed daily dose of 300 mg and up to 8 times the maximum proposed cumulative dose of 2100 mg. No clinically relevant differences in safety signals have been observed between patients

treated with oritavancin at these higher doses and those patients receiving lower doses of oritavancin or comparator.

7.11 Safety Conclusions

Overall, the safety profile of oritavancin was comparable to vancomycin/cephalexin with the exception of the following significant differences. A statistically significantly lower percentage of oritavancin-treated than comparator-treated patients had a TEAE, an investigator-assessed TEAE of possibly related to study drug, and/or a TEAE leading to study drug discontinuation.

The percentages of deaths and SAEs were comparable between the oritavancin and vancomycin/cephalexin treatment groups and the types of SAEs were not indicative of oritavancin systemic toxicity.

The thirteen most common TEAEs (those that occurred in ≥2.0% of oritavancin patients) were, in decreasing order of frequency: nausea, headache, insomnia, diarrhea, vomiting, constipation, dizziness, hypertension, pyrexia, pruritus, hypokalemia, rash, and abdominal pain. Three of those (insomnia, pruritus, and rash) occurred at a significantly higher rate in the vancomycin/cephalexin treatment group and one (dizziness) occurred at a significantly higher rate in the oritavancin treatment group. Of the twelve TEAEs of interest in the oritavancin clinical development program, seven (pruritus, erythema, pruritus generalized, flushing, red man syndrome, urticaria, and infusion site pruritus) occurred in significantly lower percentages of patients in the oritavancin than vancomycin/cephalexin treatment groups. The five remaining TEAEs of interest (infusion site pain, infusion site phlebitis, rash, phlebitis, and infusion site erythema) showed no significant differences between the treatment groups. There did not appear to be any clinically relevant treatment group differences in blood pressure, heart rate, temperature, or any indication of unexpected adverse systemic effects of treatment with oritavancin reflected in vital signs measurements. Furthermore, review of adverse events and laboratory studies demonstrated no evidence of renal or hepatic toxicity associated with oritavancin treatment.

Clinical and ECG data from healthy subjects and from patients, including a Phase 1 thorough QT/QTc study run in accordance with current regulatory guidelines, demonstrate no clinically relevant effect of oritavancin on cardiac repolarization, and no oritavancin-associated cardiac-related adverse events likely related to QT/QTc prolongation.

In summary:

- Studies ARRD and ARRI demonstrated that oritavancin has a favorable safety profile compared to vancomycin/cephalexin.
- No safety-related findings or patterns have been observed that would preclude the use of oritavancin to treat cSSSI or warrant focused initiatives for minimizing any adverse effect on public health.
- There is no indication for laboratory monitoring for safety or for dose adjustment in special populations, including patients with renal insufficiency or in patients with mild to moderate hepatic insufficiency.

8 Benefit/Risk Summary

8.1 Medical Need

With the increase in the prevalence of bacterial resistance that continues to threaten antibiotics for treating certain bacterial species, there exists a consensus regarding the critical need for the addition of new antimicrobial agents to the therapeutic armamentarium (Talbot 2006). Infections due to gram-positive bacterial species continue to be a leading problem in many institutions around the world (Wilcox 2003; Lee et al. 2005; Rice 2006; Boucher and Corey 2008). Methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *S. aureus* (GISA), and glycopeptide-resistant *enterococci* (GRE or VRE) are of specific concern.

The majority of SSSI are caused by *S. aureus* or β-haemolytic streptococci. Complicated skin and skin structure infections (cSSSI) involve deeper skin structures (such as fascia or muscle layers), require significant surgical intervention, or arise in the presence of significant comorbidity (Rybak and Akins 2001). The medical need for newer agents in the treatment of cSSSI is substantiated by the persisting emergence of resistance, the continuing appearance of therapeutic failures, and increased morbidity and mortality (MacKenzie et al. 2005; Rice 2006; Schito 2006; Drew 2007; Micek 2007).

Resistance to existing therapies (including cross-resistance within and between classes) along with safety, tolerability, and drug-interaction limitations of existing therapies result in the continuing medical need for newer antibiotics. In addition, the more recently developed and approved antibiotics are not free from reports of emerging resistance and subsequent treatment failures (Schito 2006; Scheinfeld 2007; Saravolatz 2008). The safety, tolerability, and drug-interaction limitations of existing therapies restrict their utility in certain patient groups. All of these trends further necessitate the development of newer agents.

The unique properties of oritavancin are a major consideration in its addition to the therapeutic choices available to clinicians. Preclinical and clinical features suggest that oritavancin may address several areas of concern currently underscoring the medical need for newer antibiotics. The Phase 3 studies in patients with cSSSI were designed, executed, and analyzed in accordance to global regulatory (FDA 1992a, 1992b, 2005a, 2005b, 2007a) standards as well as key principles from therapeutic advisory groups (Stevens et al. 2005). These studies not only confirmed efficacy, but also demonstrated safety in a medically inclusive patient population, which should provide immediate

confidence for oritavancin's value to treating physicians. The key elements that comprise the benefit-risk assessment favoring oritavancin's addition to the available treatments for gram-positive cSSSI are presented below.

8.2 Potential Benefits and Risks of Oritavancin Therapy

8.2.1 Nonclinical Studies

Numerous nonclinical studies have asserted that oritavancin exhibits potent bactericidal activity through multiple mechanisms of action. Surveillance studies with recent clinical strains show that oritavancin demonstrates significant activity across a broad range of gram-positive pathogens including those with specific resistance phenotypes that are associated with cSSSI. The MIC_{90} for these species is typically ≤0.25 ug/mL (Poulakou and Giamarellou 2008). These findings from surveillance initiatives are consistent with susceptibility data from Phase 3 cSSSI Studies ARRI and ARRD and suggest that existing clinical outcome data would be predictive for organisms that would be encountered currently in clinical settings.

The antibacterial spectrum of oritavancin is not only a well-matched therapy for cSSSI (*S. aureus* and streptococci), but, because of its multiple mechanisms of action, there is also a lower probability for resistance development. The identified multiple mechanisms of action and the lack of observed emerging resistance from the clinical trials are reassuring.

Oritavancin exerts concentration-dependent activity as demonstrated from in vitro studies, including one presented in Section 3.1.1.2 (Figure 3-3) in which increasing oritavancin concentrations produced a progressively greater extent of kill of a linezolid-nonsusceptible MRSA clinical isolate. Additionally, this feature has been supported by animal models of infection that suggests the measures of AUC and C_{max} rather than T>MIC should be predictive of efficacy in vivo. These pharmacodynamic studies further support that once daily or perhaps other less frequent regimens may be possible in humans.

Oritavancin has been evaluated in a comprehensive series of toxicity studies in laboratory animals and in vitro test systems. The most important nonclinical safety findings in repeat-dose rat and dog studies were the effects on liver and kidneys and the presence of eosinophilic granules observed in tissue macrophages and liver and kidney cells. The findings were reversible after cessation of treatment. Any clinical manifestations that may be potentially related to these findings were not detected upon thorough review of

the integrated clinical data. Additionally, oritavancin was not found to be genotoxic, and no mutagenic or clastogenic potential was observed.

Although oritavancin's nonclinical spectrum of coverage offers a promising therapeutic option for infections caused by other resistant gram positive bacterial species (for example, VRE, GISA, VISA, and *C. difficile*) and agents of bioterrorism (for example, *Bacillus anthracis*), the current clinical data are limited and additional work is ongoing to further assess oritavancin's potential for addressing medical needs beyond cSSSI.

8.2.2 Clinical Studies

8.2.2.1 Pharmacology

Oritavancin is not metabolized and is not expected to be affected by drugs that inhibit or induce the activity of the CYP450 system. No depletion of oritavancin due to metabolism could be detected in an in vitro study using human liver microsomes. Additionally, the ability of oritavancin to inhibit the metabolism of marker catalytic activities for the CYP450 isoforms CYP3A4, CYP2D6, CYP2C9, and CYP1A2 was examined in vitro with human hepatocytes. The potential of oritavancin to inhibit the metabolism of coadministered drugs by the CYP450 isoforms was determined to be CYP2D6>CYP3A4>CYP1A2>CYP2C9. Based upon these findings, a single drug-drug interaction study was performed. In that study, there were no appreciable effects of oritavancin on the pharmacokinetics of desipramine, a CYP2D6 substrate, and desipramine did not influence the disposition of oritavancin. HPLC-based assays of the urine from Phase 1 subjects demonstrating the lack of observed additional peaks supports the conclusion that oritavancin is not metabolized; it is eliminated unchanged in feces and urine. This observation is consistent with the animal findings as well as characteristics of other glycopeptides.

A wide range of oritavancin doses (1 to 1220 mg) was administered across the Phase 1, 2, and 3 studies and was included in a population pharmacokinetic analysis (42% of 560 subjects received ≥400 mg while 25% received ≥800 mg). The pharmacokinetic data of healthy volunteers were found to be similar to that of patients. An assessment of dose-proportionality concluded that oritavancin pharmacokinetic data are linear and predictable over the dose range studied. Additionally, following 10 daily doses, plasma accumulation was less than 3-fold with a C_{min} increase of approximately 2.8-fold and no significant increase in C_{max}. No significant dose effect was observed on the accumulation ratios.

Oritavancin serum protein binding is approximately 88% at clinically relevant concentrations and it binds primarily to albumin. The plasma concentrations of oritavancin followed a multi-exponential decline. Mean population-predicted half-lives in patients were similar to those in healthy volunteers with predicted α, β, and γ half-lives of approximately 2, 31, and 393 hours, respectively. The 31-hour β half life allows for convenient once-daily dosing while offering an extended therapeutic effect following a shorter duration of therapy (3 to 7 days). The long residence time in the body is attributed to oritavancin's accumulation in phagocytic cells; this property is beneficial because it provides a mechanism for intracellular killing, although it also brings the potential risks of toxicity and resistance development, both of which were explored but not found in clinical studies. Targanta will discuss further with FDA the most effective approach to post-approval management of potential risks associated with oritavancin's long residence time in the body.

Based on population pharmacokinetic analysis, the Vc in humans is similar to plasma volume (6 L). The total volume of distribution is approximately 100 L, suggesting that oritavancin is widely distributed to tissues. These features are consistent with the pharmacokinetic findings in nonclinical studies. Complicated skin and skin structure infections (cSSSI) involve tissues beyond the central blood compartment. Study OCSI-001 was conducted to confirm the penetration of oritavancin beyond the central compartment to help anticipate appropriate dose levels needed to treat cSSSI. In that study, oritavancin was administered to healthy volunteers at 200 mg IV daily for 3 days or as a single 800-mg dose to evaluate the pharmacokinetic profile of drug penetration into skin blister fluid. Total drug oritavancin exposure in the blister fluid was approximately 20% of that in plasma. Oritavancin levels reached maximal levels in blister fluid 9 to 10 hours after dosing and decreased to undetectable levels at 100 to 150 hours following the last dose. Study OCSI-001 demonstrated that blister fluid concentrations exceeded the MIC_{90} (0.25 ug/mL) of oritavancin against *S. aureus* as well as other common cSSSI pathogens for more than 72 hours. Oritavancin AUC_{0-24}:MIC ratios associated with in vivo efficacy were met or exceeded in blister fluid, further supporting a 200-mg, once-daily regimen.

Oritavancin is only available as an intravenous formulation. The lack of an oral formulation may further reduce selective pressure that could be generated by community-based or protracted prescribing.

8.2.2.2 Efficacy

Data from two, double-blind, well-controlled, Phase 3 studies (Studies ARRI and ARRD) support the effectiveness of oritavancin 200 mg once daily (300 mg for patients >110 kg [242 lbs]) by IV infusion for 3 to 7 days. In both studies, 3 to 7 days of once-daily oritavancin achieved prespecified noninferiority criteria to the comparative regimen of vancomycin/cephalexin.

Targanta considers that the NI margins selected for the Phase 3 studies (Study ARRD [NI=15%] and Study ARRI [NI=10%]) to be clinically relevant and statistically sound and robust. Each study adhered to the NI margin components of considerations (per ICH and FDA guidelines) as well as the regulatory guidance principals and standard of clinical studies at the time the studies were designed. Noninferiority (NI) components of consideration included robust evidence that assay sensitivity to drug effects exists and selection of an appropriate active comparator was made. Study design characteristics were used for enrolling well-defined patients, and considerations for an acceptable NI margin were based upon relevant historical, clinical, and statistical criteria (conservative placebo cure rates of 20% to 75% were used for comparative evaluation). Lastly, the sponsor ensured that the conduct of the oritavancin studies adhered closely to the relevancy of historical studies and were of high quality.

From the combined data of these studies, treatment with the oritavancin regimen resulted in a cSSSI cure rate of 77.7% (597/768) compared with a twice-daily vancomycin/cephalexin cure rate of 75.8% (347/458) in the CE population. Observed microbiological success rates were 74.0% (378/511) for oritavancin as compared to 72.5% (232/320) for vancomycin/cephalexin-treated patients.

The mean duration of IV dosing was about 1 day shorter for oritavancin-treated patients compared with the vancomycin-treated patients (5.2 days and 6.1 days, respectively). The total therapy duration (IV and oral) in the vancomycin/cephalexin-treated patients was 11.3 days compared to 5.2 days in the oritavancin-treated patients. It is also notable that the rate of infection relapse was low for either treatment group despite the differences in total treatment duration (oritavancin 2.4% [16/663], vancomycin/cephalexin 1.9% [6/315]).

The efficacy and safety in the Phase 3 studies were demonstrated in cSSSI that included deep tissue involvement. In the combined studies, muscle or fascial plane involvement was seen in over one third of the patients in either treatment arm (9.7% [114/1173] and 29.3% [344/1173] of the oritavancin-treated patients versus 11.4% [67/590] and 27.5%

[162/590] of the vancomycin/cephalexin-treated patients, respectively). Additionally, patients with significant underlying diseases that can complicate treatment of cSSSI were included into both studies. Those patients with diabetes, HIV/AIDS, immunosuppresion (including those with ANC <1000 and/or on immunosuppresive concomitant medications), renal and hepatic insufficiency, cardiac conditions (such as congestive heart failure, myocardial infarction, and/or other) and severe asthma, chronic obstructive pulmonary disease, and/or other respiratory conditions were enrolled. Overall, the numbers of patients with at least one of these comorbid conditions was similar between treatment groups (27.2% [319/1173] of the oritavancin-treated patients compared to 26.9% [159/590] of the vancomycin/cephalexin-treated patients). The efficacy of oritavancin was comparable to that of the active comparator for these comorbid conditions as well as other subgroups including: gender, age class, weight, ethnicity, and geographic region. These data further support the efficacy of oritavancin in medically complex patient groups. Finally, they provide confidence to physicians that not only those patients who are allergic to or intolerant of other therapies, but those who have complicated infections may also benefit from oritavancin therapy.

8.2.2.3 Safety

The clinical development program included assessments with a wide range of doses in healthy subjects and in patients that exceeded the recommended doses and dosing duration for cSSSI. Although the safety database encompassed 2176 individuals (1540 individuals [225 subjects and 1315 patients] exposed to oritavancin and 636 individuals [12 subjects and 624 patients] exposed to vancomycin), there is always the risk, as with any new drug, for adverse events not observed in clinical studies. These unknown risks are most often identified and managed as a result of post-marketing surveillance.

Oritavancin appears to have favorable safety compared to vancomycin and to be well tolerated. The infusion-related adverse events that were observed in several Phase 1 studies have been well-characterized and appropriately resolved relative to the recommended dose, regimen, and intended patient population.

There were 66 deaths that occurred during study participation. Of these deaths, 31 occurred among Phase 3 ITT patients (19 [1.6%] of 1173 oritavancin- and 12 [2.0%] of 590 vancomycin/cephalexin-treated patients). Deaths were associated with the underlying disease, and upon thorough case review, none of the deaths were attributed to oritavancin by the investigator and none could be definitively associated with oritavancin treatment. The nondrug-related mortality rate in the oritavancin and in the comparator

treatment groups were higher than those in some of the more recently conducted Phase 3 trials in cSSSI, an observation that further underscores the disease severity of the patients enrolled in the oritavancin studies. There was one post-study death that an investigator assessed as possibly related to oritavancin. This investigator could not rule out that oritavancin may have contributed to a decline in this patient's immune function which, in turn, led to systemic candidiasis. However, multiple risk factors were well documented for systemic candidiasis.

From the totality of the safety database, there was no pattern to suggest specific end organ toxicity in the incidence and type of SAEs reported. The low incidence of SAEs potentially attributable to oritavancin is reassuring, especially in light of the severity of illness and comorbidities in these patients.

From the Phase 3 studies, a lower percentage of patients in the oritavancin treatment group compared to the vancomycin/cephalexin group had a TEAE, an investigator-assessed TEAE of possibly related to study drug, and/or a TEAE leading to study drug discontinuation. These differences were all statistically significant. Generally, the adverse events related to oritavancin were mild to moderate. The most common TEAEs were headache, nausea, insomnia, constipation, diarrhea, vomiting, and dizziness. In particular, those adverse events that are indicative of glycopeptide class effects (including possible HLIRs) occurred more frequently in the vancomycin/cephalexin treatment group, supporting an overall better tolerability profile in oritavancin-treated patients.

There was no evidence of an oritavancin effect on renal or hepatic function based on adverse events, and laboratory evaluations showed no evidence of an oritavancin effect consistent with renal or hepatic toxicity. Targanta completed an extensive evaluation of possible cardiovascular effects in healthy subjects and in patients, as well as a thorough QT/QTc study in compliance with current guidelines. In that thorough QT/QTc study, no clinically or statistically significant change in QTcF was induced by a clinical or by a supratherapeutic dose of oritavancin, whereas the expected effect of moxifloxacin (the positive control) on QTcF was demonstrated. Finally, the 90% upper confidence limit of ddQTcF changes associated with oritavancin was well below 10 msec at any timepoint with no evidence of a dose-response relationship. To date, no oritavancin-associated cardiac-related adverse events likely related to QT/QTc prolongation have been reported in the oritavancin clinical development program. In addition, oritavancin did not demonstrate an adverse effect on blood pressure or heart rate.

Given the exposure-response relationship across various subject populations as well as the balance achieved between safety and efficacy with the fixed dosage regimen (200 mg or 300 mg >110 kg [242 lbs]), monitoring of plasma concentrations is unnecessary. In particular, there is no indication for dose adjustments in patients with renal dysfunction or those with mild-to-moderate hepatic impairment (patients with severe hepatic impairment have not been studied extensively). This simplified dosing regimen may also result in fewer dosing errors and possibly higher compliance. In addition, there is no indication for special laboratory monitoring for safety.

9 Conclusions

Complicated skin and skin structure infections (cSSSI) are common clinical problems. These infections are a common cause of morbidity and mortality and require rapid and intensive antimicrobial and appropriate surgical intervention to minimize tissue damage and prevent further spread of infection. The clinical complications of improperly treated or untreated SSSI may include progressive and/or necrotizing soft tissue infection requiring extensive debridement and/or amputation, osteomyelitis, bacteremia with potential metastatic foci of infection, systemic inflammatory response syndrome, and death. The organisms responsible for these infections are increasingly resistant to the available antibiotics and many isolates are resistant to multiple antibiotics.

There are a number of drugs approved for treatment of cSSSI. Unfortunately, bacterial resistance has emerged following use of the approved drugs, including vancomycin. To date, no oritavancin-resistant strains have emerged in clinical trials. Therefore, a treatment for cSSSI with a reduced likelihood of emergence of resistance but with efficacy and safety comparable to vancomycin would be a benefit for patients with cSSSI. Because the morbidity and mortality of improperly treated or untreated cSSSI is high, and because gram-positive bacterial pathogens are increasingly resistant to a number of standard antibiotics, a need exists for additional antibiotic therapies with efficacy against these resistant gram-positive pathogens and with a favorable safety profile.

The clinical pharmacokinetic properties of oritavancin have been well characterized and support a lack of dose adjustments due to renal or hepatic insufficiency and a low likelihood of drug-drug interactions at the recommended doses. In addition, the pharmacokinetic properties provide evidence that oritavancin exposure in the plasma and the tissue (including the target tissues of skin and skin structures) resulting from 200-mg once-daily dosing is sufficient to provide necessary therapeutic effect against strains anticipated in the contemporary clinical setting.

Additionally, the clinical efficacy from the Phase 3 Studies ARRD and ARRI demonstrated that oritavancin was efficacious for the treatment of cSSSI at the recommended dose of IV oritavancin 200 mg (300 mg if patient weighs >110 kg [242 lbs]). The overall response rates for both clinical and microbiological outcomes were similar between the oritavancin and vancomycin/cephalexin treatment groups and the effects were consistent across all populations, across baseline disease categories, and across preexisting comorbidities. The efficacy of oritavancin was comparable to that of

vancomycin/cephalexin for the subgroups of gender, age class, weight, ethnicity, geographic region, renal function, hepatic function, and for patients with diabetes. There was no evidence of increases in oritavancin MIC beyond the proposed oritavancin susceptibility breakpoints for proposed indicated organisms in either of the studies.

Overall, the safety profile of oritavancin was comparable to vancomycin/cephalexin with the exception of the following statistically significant differences. A statistically signifcantly lower percentage of oritavancin-treated than comparator-treated patients had a TEAE, an investigator-assessed TEAE of possibly related to study drug, and/or a TEAE leading to study drug discontinuation.

The percentages of deaths and SAEs were comparable between the oritavancin and vancomycin/cephalexin treatment groups and the types of SAEs were not indicative of oritavancin systemic toxicity. Clinical and ECG data from healthy subjects and from patients, including a Phase 1 thorough QT/QTc study run in accordance with current regulatory guidelines, demonstrate no clinically relevant effect of oritavancin on cardiac repolarization and no oritavancin-associated cardiac-related adverse events likely related to QT/QTc prolongation.

In summary, oritavancin offers patients with cSSSI an efficacious treatment with fewer side effects, a short duration of treatment, and less frequent dosing than vancomycin/cephalexin. Overall, when compared with vancomycin/cephalexin, oritavancin is safe and well-tolerated with a favorable benefit-risk profile in patients with cSSSI. The increased safety of oritavancin is of therapeutic benefit to both patients and physicians and could contribute to decreased healthcare costs by allowing earlier discharge from the hospital and decreased need for follow-up home IV or oral antibiotics.

10 References

Alexander EH, Hudson MC. 2001. Factors influencing the internalization of *Staphylococcus aureus* and impacts on the course of infections in humans. Appl Microbiol Biotechnol 56:361-366.

Allen NE, Hobbs JN Jr, Nicas TI. 1996. Inhibition of peptidoglycan biosynthesis in vancomycin-susceptible and -resistant bacteria by a semisynthetic glycopeptide antibiotic. Antimicrob Agents Chemother 40:2356-2362.

Allen NE, LeTourneau DL, Hobbs JN, Jr. 1997. Molecular interactions of a semisynthetic glycopeptide antibiotic with D-alanyl-D-alanine and D-alanyl-D-lactate residues. Antimicrob Agents Chemother 41:66-71.

Allen NE, Nicas TI. 2003. Mechanism of action of oritavancin and related glycopeptide antibiotics. FEMS Microbiol Rev 26(5):511-532.

Al-Nawas B, Shah PM. 1998. Activity of vancomycin and LY333328, a new semisynthetic glycopeptide, against methicillin-resistant *Staphylococcus aureus.* Infection 26:165-167.

Al-Nawas B, Swantes J, Shah PM. 2000. In vitro activity of LY333328, a new glycopeptide, against extracellular and intracellular vancomycin-resistant enterococci. Infection 28:214-218.

Arhin FF, Sarmiento I, Parr TR Jr, Moeck G. 2007a. Mechanisms of action of oritavancin in *Staphylococcus aureus*. Presented at: the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster C1-1471.

Arhin FF, Sarmiento I, Parr TR, Jr., Moeck G. 2007b. Effect of polysorbate 80 on oritavancin binding to plastic surfaces: implications for susceptibility testing [abstract]. Presented in: Abstracts of the 25th International Congress of Chemotherapy and the 17th European Congress of Clinical Microbiology and Infectious Diseases; 2007 March 31-April 3; Munich, Germany. Poster 1112.

Arhin FF, Sarmiento I, Parr TR,Jr, Moeck G. 2008a. Activity of oritavancin against *Staphylococcus aureus* isolates that show heterogeneous resistance to vancomycin [poster]. Presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]; 19-22 April 2008; Barcelona (Spain). Poster P 584.

Arhin FF, Sarmiento I, Belley A, McKay GA, Draghi DC, Grover P, Sahm DF, Parr TR Jr, Moeck G. 2008b. Effect of polysorbate 80 on oritavancin binding to plastic surfaces: implications for susceptibility testing. Antimicrob Agents Chemother. 52(5):1597-1603.

Baltch AL, Smith RP, Ritz WJ, Bopp LH. 1998. Comparison of inhibitory and bactericidal activities and postantibiotic effects of LY333328 and ampicillin used singly and in combination against vancomycin-resistant *Enterococcus faecium.* Antimicrob Agents Chemother 42:2564-2568

Baudoux P, Tulkens PM, Van Bambeke F. 2008. Intracellular activity of oritavancin against MSSA, MRSA and VISA strains in a model of human macrophages. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Abstract A-971.

Beauregard DA, Williams DH, Gwynn MN, Knowles DJ. 1995. Dimerization and membrane anchors in extracellular targeting of vancomycin group antibiotics. Antimicrob Agents Chemother 39:781-785.

Belley A, Harris B, Beveridge T, Parr TR, Jr, Moeck G. 2007a. Differential targeting of cell wall assembly systems by oritavancin [poster]. Presented at the 47th annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICACC); 2007 September 17-20; Chicago (IL). Poster C-1472.

Belley A, Neesham-Grenon E, Parr TR, Jr, Moeck G. 2007b. Pharmacokinetic concentrations of oritavancin kill stationary-phase and biofilm *Staphylococcus aureus* in vitro [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster E-1620.

Belley A, Neesham-Grenon E, Parr TR, Jr, Moeck G. 2008a. Efficacy of oritavancin against in vitro biofilms derived from clinical isolates of *Staphylococcus epidermidis* [slide presentation/abstract]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Abstract C1-3711.

Belley A, Neesham-Grenon E, Parr TR, Jr, Moeck G. 2008b. Oritavancin sterilizes in vitro biofilms of *Staphlycoccus epidermis a*nd vancomycin-susceptible and -resistant Enterococci [poster]. Presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]; 19-22 April 2008; Barcelona (Spain). Poster P 597.

Belley A, Harris B, Beveridge T, Parr, TR Jr, Moeck G. 2008c. Cell wall and membrane effects of oritavancin on *Staphylococcus aureus* and *Enterococcus faecalis* [poster]. Presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]; 2008 April 19-22; Barcelona (Spain). Poster P 537.

Bhavnani SM, Rubino CM, Forrest A, Okusanya OO, Craig WA, Moeck G, Lehoux DE, Parr TR Jr, Ambrose PG. 2008. Pharmacokinetic-pharmacodynamic (PK-PD) target attainment (TA) as decision support for oritavancin (ORI) susceptibility breakpoints for *Staphylococcus aureus* (SA). Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster A-994.

Billeter M, Zervos MJ, Chen AY, Dalovisio JR, Kurukularatne C. 2008. Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. Clin Infect Dis 15;46(4):577-583.

Boucher HW, Corey GR. 2008. Epidemiology of methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis 46:S344–S349.

Bouchillon S, Badal R, Hoban D, Johnson A, Hackel M, Johnson J, Moeck G, Arhin FF. 2008. Oritavancin comparative in vitro activity against hospital-acquired enterococci from multicenter surveillance – the ORION study [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-145.

Boylan CJ, Campanale K, Iversen PW, Phillips DL, Zeckel ML, Parr TR, Jr. 2003. Pharmacodynamics of oritavancin (LY333328) in a neutropenic-mouse thigh model of *Staphylococcus aureus* infection. Antimicrob Agents Chemother 47:1700-1706.

Boylan CJ, Nicas TI, Preston DA, Zeckner DL, Boyll BJ, Raab PA, Mullen DL, Snyder NJ, Zornes LL, Stratford RE, Zweifel MJ, Wilkie SC, Rodriguez MJ, Thompson RC, Cooper RDG. 1995. Efficacy of semisynthetic glycopeptides active against vancomycin-resistant enterococci in a mouse infection model. Presented in: Abstracts of the 35th International Conference on Antimicrobiaol Agents and Chemotherapy (ICAAC); 1995 September 17-20; San Francisco (CA). p 157. Abstract F255.

Brown DF, Brown NM, Cookson BD, Duckworth G, Farrington M, French GL, King L, Lewis D, Livermore DM, Macrae B, Scott GM, Williams D, Woodford N. 2006. National Glycopeptides-Resistance Enterococcal Bacteraemia Surveillance Working Group report to the Department of Health – August 2004. J Hosp Infect 62(Suppl 1):S1-S27.

Cabellos C, Fernan Dez A, Maiques JM, Tubau F, Linares J, Viladrich PF, Gudiol F. 1998. Experimental study of LY333328 alone and in combination in the therapy of cephalosporin-resistant (CR) pneumococcal meningitis [abstract]. Presented in: Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1998 September 24-27; San Diego (CA). Abstract B-4.

Carlet J, Benali A. 2006. Existe-t-il une alternative aux glycopeptides pour le traitement des infections a *Staphylococcus aureus* résistant à la methicilline [Is an alternative to glycopeptides for treating methicillin-resistant *Staphylococcus aureus* infections available?] Reanimation 15(3):176-179.

Cegelski L, Steuber D, Mehta AK, Kulp DW, Axelsen PH, Schaefer J. 2006. Conformational and quantitative characterization of oritavancin-peptidoglycan complexes in whole cells of *Staphylococcus aureus* by in vivo 13C and 15N labeling. J Mol Biol 357:1253-1262.

Chambers HF, Kennedy S. 1990. Effects of dosage, peak and trough concentrations in serum, protein binding, and bactericidal rate on efficacy of teicoplanin in a rabbit model of endocarditis. Antimicrob Agents Chemother 34:510-514.

[CLSI] Clinical and Laboratory Standards Institute. 2008. M100-S18: Performance standards for antimicrobial susceptibility testing: approved standard. Clinical and Laboratory Standards Institute.

Darouiche RO. 2004. Treatment of infections associated with surgical implants. N Engl J Med 350(14):1422-1429.

Daum RS. 2007. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. N Engl J Med 357(4):380-390.

Domenech O, Van Bambeke F, Tulkens PM, Mingeot-Leclercq M, P. 2008. Comparative study of the membrane permabilization induced by oritavancin (ORI) vs. vancomycin (VAN) using a model of negatively-charged liposomes [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-199

Draghi DC, Moeck G, Arhin FF, Pillar CM, Sahm D. 2008. Anti-enterococcal and anti-streptococcal activity profile of oritavancin in Europe [poster]. Presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]; 19-22 April 2008; Barcelona (Spain). Poster P 538.

Draghi D, Sahm DF, Arhin FF, Moeck G. 2007. Anti-enterococcal activity profile of oritavancin, a potent lipoglycopeptide under development for use against gram-positive infections [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster E-1615.

Drees M, Boucher H. 2006. New agents for *Staphylococcus aureus* endocarditis. Curr Opin Infect Dis 19(6):544-550.

Drew RH. 2007. Emerging options for treatment of invasive, multidrug-resistant *Staphylococcus aureus* infections. Pharmacotherapy 27(2):227-249.

Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. 2003. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. Clin Infect Dis 36:592-598.

[FDA] Food and Drug Administration web site. 1992a. Division of Anti-Infective Drug Products: points to consider. Available at: http://www.fda.gov/CDER/guidance/old043fn.pdf. Accessed 02 October 2008.

[FDA] Food and Drug Administration web site. 1992b. Division of Anti-Infective Drug Products: points to consider. Points regarding clinical trial design/conduct: issues regarding adequacy of trials (2001 disclaimer, p 21). Available at: http://www.fda.gov/CDER/guidance/old043fn.pdf. Accessed 02 October 2008.

[FDA] Food and Drug Administration. 2005a. Division of Antiinfective and Ophthalmology Drug Products (HFD-520) Microbiological Data for Antibacterial Drug Products – Development, Analysis, and Presentation- October 20.

[FDA] Food and Drug Administration. 2005b. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-

antiarrhythimic drugs. Available at: http://www.fda.gov/cder/guidance/6922fnl.pdf. Accessed 22 September 2008.

[FDA] Food and Drug Administration. 2007a. Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval. Available at: http://www.fda.gov/cder/guidance/7884dft.pdf

[FDA] Food and Drug Administration. 2007b. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. Available at: http://www.fda.gov/Cber/gdlns/dili.pdf. Accessed 09 October 2008.

Finberg RW, Moellering R, Tally F, Craig W, Pankey GA, Dellinger EP, West M, Joshi M, Linden P, Rolston K, Rotschafer JC, Rybak MJ. 2004. The importance of bactericidal drugs: future directions in infectious disease. Clin Infect Dis 39:1314-1320.

Finch R. 2006. Gram-positive infections: lessons learnt and novel solutions. Clin Micobiol Infect 12:3-8.

Fritsche TR, Sader HS, Jones AL. 2008. Spectrum of activity of oritavancin and comparator agents tested against contemporary gram-positive pathogens submitted to a global surveillance program (2008) [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-142.

Gerber J, Smirnov A, Wellmer A, Ragheb J, Prange J, Schutz E, Wettich K, Kalich S, Nau R. 2001. Activity of LY333328 in experimental meningitis caused by a *Streptococcus pneumoniae* strain susceptible to penicillin. Antimicrob Agents Chemother 45:2169-2172.

Ginsberg MB. 1981. Cellulitis: analysis of 101 cases and review of the literature. South Med J 74:530-533.

Gorbach S. 1997. IDCP guidelines: superficial skin and soft tissue infections: part II. Infect Dis Clin Practice 6:6-11.

Gosbell IB, Fernandes LA, Fernandes CJ. 2006. In vitro antibacterial activity of beta-lactams and non-beta-lactams against *Streptococcus pneumoniae* isolates from Sydney, Australia. Pathology 38:343-348.

Grover PK, Draghi DC, Moeck G, Arhin F, Sahm DF. 2007. In vitro activity profile of oritavancin (ORI) against organisms demonstrating key resistance profiles to other antimicrobial agents [abstract]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20; Chicago (IL). Abstract E-1613.

Heine HS, Bassett J, Miller L, Bassett A, Ivins BE, Lehoux D, Arhin FF, Parr TR Jr, Moeck G. 2008. Efficacy of oritavancin in a murine model of *Bacillus anthracis* spore inhalation anthrax. Antimicrob Agents Chemother. Sep;52(9):3350-3357.

Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. 1992. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 13:606-608.

Hwang IK, Morikawa T. 1999. Design issues in non-inferiority trials. Drug Inf J 33:1205-1218.

[IDSA] Infectious Diseases Society of America. 2004. Bad bugs, no drugs: as antibiotic discovery stagnates a public health crisis brews. Available at: http://www.idsociety.org/WorkArea/showcontent.aspx?id=5554. Accessed 30 September 2008.

Jones RN. 2006. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin Infect Dis 42 Suppl 1:S13-S24.

Kaatz GW, Seo SM, Aeschlimann JR, Houlihan HH, Mercier RC, Rybak MJ. 1998. Efficacy of LY333328 against experimental methicillin-resistant *Staphylococcus aureus* endocarditis. Antimicrob Agents Chemother 42:981-983.

Kahne D, Leimkuhler C, Lu W, Walsh C. 2005. Glycopeptide and lipoglycopeptide antibiotics. Chem Rev 105:425-448.

Kim SJ, Cegelski L, Preobrazhenskaya M, Schaefer J. 2006. Structures of *Staphylococcus aureus* cell-wall complexes with vancomycin, eremomycin, and chloroeremomycin derivatives by 13C{19F} and 15N{19F} rotational-echo double resonance. Biochemistry 45:5235-5250.

Kim SJ, Dietrich E, Tanaka KSE, Rafai Far A, Schaefer J. 2007. Cell wall binding sites of desleucyl(flurophenyl)benzylchloroeremomycin, a damaged oritavancin analogue, in Staphylococcus aureus [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster C1-1473.

Kim SJ, Singh M, Dietrich E, Tanaka KSE, Parr TR, Jr, Rafai Far A, Schaefer J. 2008. Hexapeptide of oritavancin with damaged aglycon exhibits dual mode of action against cell-wall biosynthesis in *Staphylococcus aureus* [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster F1-366.

Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK. 2007. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 298(15):1763-1771

Knudsen JD, Raber S, Leggett J, Fuursted K, Espersen F, Frimodt-Moller N. 1997. Comparison of effect of LY333328 with teicoplanin and vancomycin against pneumococci in the mouse peritonitis model [abstract]. Presented in: Abstracts of the

37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1997 September 28-October 1; Toronto, Canada. p 147. Abstract F-10.

Krause KM, Renelli M, Difuntorum S, Wu TX, Debabov DV, Benton BM. 2008. In vitro activity of telavancin against resistant gram-positive bacteria. Antimicrob Agents Chemother 52(7):2647-2652.

Kumar A, Murray DL, Hanna CB, Kreindler TG, Jacobson KD, Bundy JM, Waxman K, Finnerty EF, Folan DW, Jr., Drucker WR, Kane JG, Durnell M, DiMattia A, Hill CD. 1988. Comparative study of cephalexin hydrochloride and cephalexin monohydrate in the treatment of skin and soft tissue infections. Antimicrob Agents Chemother 32:882-885.

Lee SY, Kuti JL, Nicolau DP. 2005. Antimicrobial management of complicated skin and skin structure infections in the era of emerging resistance. Surg Infect (Larchmt) 6:283-295.

Lefort A, Saleh-Mghir A, Garry L, Carbon C, Fantin B. 2000. Activity of LY333328 combined with gentamicin in vitro and in rabbit experimental endocarditis due to vancomycin-susceptible or -resistant *Enterococcus faecalis*. Antimicrob Agents Chemother 44:3017-3021

Lehoux D, Arhin FF, Fadhil I, Laquerre K, Ostiguy V, Sarmiento I, Moeck G, Parr TRJ. 2006. Oritavancin demonstrates rapid and sustained bactericidal activity in the rat granuloma pouch model of *Staphyloccocus aureus* infection [poster]. Presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2006 September 27-30; San Francisco (CA). Poster B-0404.

Lehoux D, Fadhil I, Gagne J, Bedard I, Ostiguy V, Malouin M, Cadieux C, Moeck G, Parr TR, Jr. 2008b. Efficacy of oritavancin against *Clostridium difficile* (CD) infection in the hamster model of CD infection (CDI) [abstract]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster B-067.

Lehoux D, Okusanya OO, Ostiguy V, Forrest A, Laquerre K, Bhavnani SM, Fadhil I, Malouin M, Arhin FF, Sarmiento I, Belanger O, Rafai Far A, Moeck G, Parr TR, Jr, Ambrose PG. 2007a. PK-PD of oritavancin against *S. pneumoniae* in a murine-pneumonia infection model [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster A-49.

Lehoux D, McKay GM, Fadhil I, Laquerre K, Malouin M, Ostiguy V, Moeck G, Parr TR, Jr. 2007b. Efficacy of oritavancin in a mouse model of *Streptococcus pneumoniae* pneumonia [abstract]. Presented at: The 25th International Congress of Chemotherapy and the 17th European Congress of Clinical Microbiology and Infectious Diseases; 2007 March 31-April 3; Munich, Germany. Poster P-1781.

Lehoux D, Ostiguy V, Fadhil I, Malouin M, Cadieux C, Bedard I, Laquerre K, Okusanya OO, Bhavnani SM, Moeck G, Parr TR, Jr. 2008a. Efficacy of oritavancin (ORI) in the

mouse bacteremia model. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster B-1009.

Lemaire S, Kosowska-Shick K, Julian K, Tulkens PM, Van Bambeke F, Appelbaum PC. 2008. Activities of antistaphylococcal antibiotics towards the extracellular and intraphagocytic forms of *Staphylococcus aureus* isolates from a patient with persistent bacteraemia and endocarditis. Clin Microbiol Infect 14(8):766-77.

Levine DP. 2006. Vancomycin: a history. Clin Infect Dis 42 Suppl 1:S5-S12.

Lodise TP, McKinnon PS. 2005. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. Diagn Microbiol Infect Dis 52:113-132.

MacKenzie FM, Struelens MJ, Towner KJ, Gould IM. 2005. Report of the Consensus Conference on Antibiotic Resistance; Prevention and Control (ARPAC). Clin Microbiol Infect 11:938-954.

McKay GA, Beaulieu S, Belley A, Arhin FF, Parr TR, Jr., Moeck G. 2007a. In vitro time kill studies of oritavancin against drug resistant isolates of *Staphylococcus aureus* and enterococci [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 September 17-20; Chicago (IL). Poster E-1614.

McKay GA, Beaulieu S, Parr TR, Jr., Moeck G. 2007b. In vitro post antibiotic effect studies of oritavancin against *S. aureus* and enterococci [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster A-50.

McKay GA, Beaulieu S, Parr TR, Jr, Moeck G. 2008b. Oritavancin disrupts membrane integrity to effect cell killing of vancomycin (VAN)-nonsusceptible *Staphylococcus aureus* (SA) and VAN-resistant *Enterococcus faecium* (VRE) [slide presentation/abstract]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Abstract C1-4182.

McKay GA, Beaulieu S, Sarmiento I, Arhin FF, Moraitis D, Parr TR, Jr, Moeck G. 2008a. In vitro time kill studies of oritavancin against vancomycin-intermediate *Staphylococcus aureus* (VISA) [slide presentation/abstract]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Abstract C1-3717.

McKay GA, Fadhil I, Beaulieu S, Ciblat S, Rafai Far A, Moeck G, Parr TR, Jr. 2006. Oritavancin disrupts transmembrane potential and membrane integrity concomitantly with cell killing in *Staphylococcus aureus* and vancomycin-resistant Enterococci

[abstract]. Presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Sept 27-30; San Francisco (CA). Abstract C1-682.

Mercier RC, Ryback MJ. 1997. Pharmacodynamic evaluation of new glycopeptides using in vitro models of infection against methicillin-resistant *Staphylococcus aureus*. Presented at the 8th European Congress of Clinical microbiology and Infectious Diseases (ECCMID); 1997 May 25-28; Lausanne, Switzerland. Abstract 202E.

Micek S. 2007. Alternatives to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis 45(Suppl 3):S184-S190.

Moellering RC, Jr. 2006. Vancomycin: a 50-year reassessment. Clin Infect Dis 42 Suppl 1:S3-4.

Moise PA, Sakoulas G, Forrest A, Schentag JJ. 2007. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 51:2582-2586.

Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan D. 2006. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med 355(7):666-674.

Mouton JW, Ambrose PG, Kahlmeter G, Wikler M, Craig WA. 2007. Applying pharmacodynamics for susceptibility breakpoint selection and susceptibility testing. In: Nightingale CH, Ambrose PG, Drusano GL, Murakawa, T, editors. Antimicrobial pharmacodynamics in theory and clinical practice, 2nd edition. New York (NY): Informa Healthcare. p 21-44.

Murray BE, Nannini EC. 2005. Glycopeptides (vancomycin and teicoplanin), streptogramins (quinupristin-dalfopristin), and lipopeptides (daptomycin). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases, sixth edition. Philadelphia: Elsevier Churchill Livingstone. p 417-434.

[NCCLS] National Committee for Clinical Laboratory Standards. 2001. M23-A2: Development of in vitro susceptibility testing criteria--2nd edition. Wayne (PA): National Committee for Clinical Laboratory Standards.

Nguyen HA, Denis O, Vergison A, Tulkens PM, Struelens M, Van Bambeke F. 2007. Comparactive intracellular activity of 10 antistaphylococcal antibiotics (AABS) against a stable small colony variant (SCV) of *S. aureus* in a model of human THP-1 macrophages [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster A-1437.

Nguyen HA, Denis O, Vergison A, Tulkens PM, Struelens MJ,Van Bambeke F. 2008a. Subcellular Localisation of *S. aureus* Small Colony Variant (SCV) versus its Normal Phenotype (NP) Counterpart in a Model of Calu-3 Airway Epithelial Cells: Impact on the Intracellular Activity of Oritavancin (ORI), Gentamicin (GEN), Oxacillin (OXA) and Moxifloxacin (MXF) [abstract]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual

Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Abstract A-972.

Nguyen HA, Huang TD, Tulkens PM, Van Bambeke F, Glupczynski Y. 2008b. SCV phenotype and reduced intracellular activity of antibiotics: a cause for persistent staphylococcal infection? [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster A-970.

Nicas TI, Allen NE. 1994. Resistance and mode of action. In: Glycopeptide antibiotics. Editor: Nagarajan R. New York (NY): Marcel Dekker. p 219-241.

Novelli A, Mazzei T, Fallani S, Cassetta M, Conti S. 1997. In vitro postantibiotic effect of the semisynthetic glycopeptide LY333328 on clinical gram positive infections. Program and Abstracts 20th International Congress of Chemotherapy. Sydney, Australia, June 1997. Abstract 4293.

Okusanya OO, Lehoux D, Van Wart SA, Bélanger O, Forrest A, Moeck G, Bhavnani SM, Parr Jr TR, Ambrose PG. 2008. Pharmacokinetics and Pharmacokinetics-Pharmacodynamics of Oritavancin against *Staphlyococcus aureus* in a Neutropenic Murine Thigh-Infection Model [poster]. Poster presented at the William A. Craig Symposium of the International Society of Anti-Infective Pharmacology (ISAP) 2008, Madison, WI, October 29, 2008.

Pankey GA, Sabath LD. 2004. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. Clin Infect Dis 38:864-870.

Pankuch GA, Appelbaum PC. 2008. Activity of oritavancin against 200 vancomycin susceptible And non-susceptible MRSA by MIC testing [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-186.

Peetermans WE, Hoogeterp JJ, Hazekamp-van Dokkum AM, van den Broek P, Mattie H. 1990. Antistaphylococcal activities of teicoplanin and vancomycin in vitro and in an experimental infection. Antimicrob Agents Chemother 34:1869-1874.

Polk RE. 1991. Anaphylactoid reactions to glycopeptide antibiotics. J Antimicrob Chemother 27(Suppl B):17-29.

Poulakou G, Giamarellou H. 2008. Oritavancin: a new promising agent in the treatment of infections due to Gram-positive pathogens. Expert Opin Investig Drugs 17:225-243.

Powers RD, Schwartz R, Snow RM, Yarbrough DR, III. 1991. Ofloxacin versus cephalexin in the treatment of skin, skin structure, and soft-tissue infections in adults. Clin Ther 13:727-736.

Reynolds PE. 1989. Structure, biochemistry and mechanism of action of glycopeptide antibiotics. Eur J Clin Microbiol Infect Dis 8:943-950.

Rice LB. 2006. Antimicrobial resistance in gram-positive bacteria. Am J Infect Control 34:S11-19; discussion S64-73.

Rupp ME, Fey PD, Longo GM. 2001. Effect of LY333328 against vancomycin-resistant *Enterococcus faecium* in a rat central venous catheter-associated infection model. J Antimicrob Chemother 47:705-707.

Rupp ME, Ulphani JS. 1998. Efficacy of LY333328 in a rat model of *Staphylococcus aureus* (SA) central venous catheter (CVC)-associated infection [abstract] Presented in: Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1998 September 24-27; San Diego (CA). Abstract nr F-111.

Rybak MJ, Akins RL. 2001. Emergence of methicillin-resistant *Staphylococcus aureus* with intermediate glycopeptide resistance: clinical significance and treatment options. Drugs 61:1-7.

Rybak MJ, Bailey EM, Warbasse LH. 1992. Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. Antimicrob Agents Chemother 36:1204-1207.

Sahm DF, Moeck G, Arhin FF, Draghi D. 2007. In vitro activity profile of oritavancin against resistant staphylococcal populations from a recent surveillance initiative [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 September 17-20; Chicago (IL). Poster E-1617.

Sahm DF, Pillar CM, Moeck G, Arhin FF, Draghi DC. 2008a. In vitro activity profile of oritavancin against resistant staphylococcal populations from a recent surveillance initiative in Europe [poster]. Presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]; 2008 April 19-22; Barcelona (Spain). Poster P 539.

Sahm DF, Moeck G, Arhin FF, Pillar CM, Draghi DC. 2008b. In vitro activity of oritavancin against gram-positive organisms in Europe: a comparative study of clinical trial and surveillance results [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-144.

Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Jr, Eliopoulos GM. 2004. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 42:2398-2402.

Saleh-Mghir A, Lefort A, Petegnief Y, Dautrey S, Vallois JM, Le Guludec D, Carbon C, Fantin B. 1999. Activity and diffusion of LY333328 in experimental endocarditis due to vancomycin-resistant *Enterococcus faecalis*. Antimicrob Agents Chemother 43:115-120.

Saravolatz LD, Pawlak J, Johnson L. 2008. In vitro activity of oritavancin against CA-MRSA, VISA and daptomycin-non-susceptible *Staphylococcus aureus* (DNSSA)

[poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-187.

Scheinfeld N. 2007. A comparison of available and investigational antibiotics for complicated skin infections and treatment-resistant Staphylococcus aureus and *Enterococcus.* J Drugs Dermatol 6:97-103.

Schito GC. 2006. The importance of the development of antibiotic resistance in *Staphylococcus aureus.* Clin Microbiol Infect 12 Suppl 1:3-8.

Schwalbe RS, Iarocci TR. 1997. Establishment of a neutropenic mouse model to characterize activity of LY333328 against vancomycin-resistant enterococci [abstract]. Presented in: Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1997 September 28-October 1; Toronto, Canada. p 148. Abstract F-113.

Seral C, Van Bambeke F, Tulkens PM. 2002. Activity of the new glycopeptide oritavancin (LY333328; ORI) in a model of *Staphylococcus aureus* intraphagocytic infection in comparison with telithromycin (TEL) and moxifloxacin (MXF) [abstract]. Presented in: Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 September 27-30; San Diego (CA). Abstract A-483.

Seral C, Van Bambeke F, Tulkens PM. 2003. Quantitative analysis of gentamicin, azithromycin, telithromycin, ciprofloxacin, moxifloxacin, and oritavancin (LY333328) activities against intracellular *Staphylococcus aureus* in mouse J774 macrophages. Antimicrob Agents Chemother 47:2283-2292.

Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. 2005. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 41:1373-1406.

Stewart PS, Costerton JW. 2001. Antibiotic resistance of bacteria in biofilms. Lancet. 14;358(9276):135-138.

Tack KJ, Littlejohn TW, Mailloux G, Wolf MM, Keyserling CH. 1998. Cefdinir versus cephalexin for the treatment of skin and skin-structure infections. The Cefdinir Adult Skin Infection Study Group. Clin Ther 20:244-256.

Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. 2006. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis 42:657-668.

Theuretzbacher U, Toney JH. 2006. Nature's clarion call of antibacterial resistance: are we listening? Curr Opin Investig Drugs 7(2):158-66.

Thielman NM, Wilson KH. 2005. Antibiotic-associated colitis. . In: Mandell GL, Bennet JE, Dolin R, eds. Principles and practice of infectious diseases. 6th edition. Philadelphia (PA): Elsevier, Inc.

Turnidge J, Paterson DL. 2007. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev 20(3):391-408.

Van Bambeke F. 2006. Glycopeptides and glycodepsipeptides in clinical development: a comparative review of their antibacterial spectrum, pharmacokinetics and clinical efficacy. Curr Opin Investig Drugs 7:740-749.

Van Bambeke F, Carryn S, Snoeck A, Mingeot-Leclercq M, Tulkens P. 2001. LY333328 (oritavancin) glycopeptide accumulates in cultured macrophages but is only bacteriostatic towards intracellular *Listeria monocytogenes* [abstract]. Presented in: Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 September 22-25; Chicago (IL). Abstract A-2069.

Van Bambeke F, Carryn S, Seral C, Chanteux H, Tyteca D, Mingeot-Leclercq MP, Tulkens PM. 2004. Cellular pharmacokinetics and pharmacodynamics of the glycopeptide antibiotic oritavancin (LY333328) in a model of J774 mouse macrophages. Antimicrob Agents Chemother 48:2853-2860.

Vashisht R, Weshnoweski B, Tailor F, Langner S, DeCorby M, Hoban DJ, Zhanel GG. 2008. Activity of oritavancin against *S. aureus*, *S. epidermidis*, *Enterococcus* spp. and *S. pneumoniae*, isolated from Canadian hospitals: results of CANWARD 2007 [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-146.

Vaudaux P, Huggler E, Arhin FF, Moeck G, Lew D. 2008. Comparative activity of oritavancin against methicillin-resistant Staphylococcus aureus (MRSA) bloodstream isolates from Geneva University Hospital [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster C1-143.

Wang T-SA, Kahne DE, Walker S. 2007. Probing the mechanism of ihibition of bacterial peptidoglycan glycotransferases by glycopeptide analogs [poster]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2007 Septemeber 17-20; Chicago (IL). Poster C1-1474.

Weinberg JM, Scheinfeld NS. 2003. Cutaneous infections in the elderly: diagnosis and management. Dermatol Ther 16:195-205.

Wilcox MH. 2003. Efficacy of linezolid versus comparator therapies in Gram-positive infections. J Antimicrob Chemother 51(Suppl 2):ii27-ii35.

Xiong YQ, Li Y, Abdel Hady W, Lehoux D, Belanger O, Moeck G, Parr TRJ, Bayer AS. 2008. Efficacy of oritavancin (ORI), a lipoglycopeptide antibiotic, in a rat *Staphylococcus aureus* endocarditis (IE) model: microbiological and bioluminescent assessments [poster]. Presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2008 October 25-28; Washington (DC). Poster B-1011

Zelenitsky SA, Karlowsky JA, Zhanel GG, Hoban DJ, Nicas T. 1997. Time-kill curves for a semisynthetic glycopeptide, LY333328, against vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* strains. Antimicrob Agents Chemother 41:1407-1408.

Zhanel GG, Kirkpatrick IDC, Hoban DJ, Kabani AM, Karlowsky JA. 1998. Influence of human serum on pharmacodynamic properties of an investigational glycopeptide, LY333328, and comparator agents against *Staphylococcus aureus.* Antimicrob Agents Chemother 42(9):2427-2430.

11 Appendices

Appendix 11.1: Overview of Oritavancin Complicated Skin and Skin Structure Infection Studies and NI Margins

Overview of Oritavancin Complicated Skin and Skin Structure Infection Studies and Noninferiority Margins

Targanta Therapeutics Corporation
225 South East Street, Suite 390
Indianapolis, Indiana 46202

As part of the response to questions posed by Targanta Therapeutics Corporation (Targanta) prior to the Pre-NDA meeting held on January 1, 2007, the Food and Drug Administration (FDA) made the following statement:

> **"For both studies, the Sponsor should provide justification of their noninferiority margin(s) in terms of M1 (benefit of active drug over placebo) and M2 (acceptable loss of effect relative to control while preserving 50% of the effect of the control drug and controlling for the variability). More details are given in the ICH E9 and E10 guidelines. Note that citing summary bases of past approvals is not sufficient."**

The following constitutes the official reply by Targanta:

1 Overview of Oritavancin Complicated Skin and Skin Structure Infection Studies and Noninferiority Margins

The selection of a noninferiority (NI) margin for the oritavancin complicated skin and skin-structure infection (cSSSI) studies can be derived from concepts identified in several regulatory guidance documents, as well as expert proposals (Calandra et al. 1992; ESCMID 1993; FDA 1998; ICH 1998a, 1998b, 2000; Hwang and Morikawa 1999; Temple and Ellenberg 2000; Snapinn 200l; Wang et al. 2002; Blackwelder 2004; CPMP 2004; Stevens et al. 2005). It is important to note that the oritavancin clinical program for cSSSI was designed and initiated (1998) at a time when the FDA's view on selecting an NI margin was different than the current viewpoint.

The oritavancin Phase 2/3 Study H4Q-MC-ARRD (ARRD) began enrollment in February 1999 and completed in June 2001. The primary endpoint (clinical efficacy of oritavancin [two regimens] comparable to that of vancomycin/cephalexin) was achieved within a 15% NI margin (95% CI; -13.3, 4.2) (Wasilewski et al. 2001). A cornerstone for use of the 15% NI margin was built on principles from the 1998 FDA Points-to-Consider guidance document for the development of antimicrobial products.

This guidance document suggested use of an NI margin for study designs that were predetermined based on the study's expected cure rate. It suggested that for any product with an expected cure rate between 80% and 90%, a 15% NI margin was an appropriate choice. Additionally, NI margins of 20% or 10% would be appropriate for products with cure rates below 80% or above 90%, respectively.

However, early in 2001 the FDA decided that the statistical section of the 1998 Points-to-Consider document was no longer appropriate and proposed that Sponsors select an NI

margin which must be justified using clinical and statistical rationale (in alignment the recently developed ICH Guidance Documents, E9 and E10). With this consideration in mind, the subsequent Phase 3 cSSSI Study H4Q-MC-ARRI (ARRI) was designed and initiated in June 2001 and completed in November 2002 using an NI margin of 10%. The primary endpoint (clinical efficacy comparable to that of vancomycin/cephalexin) was achieved within a 10% NI margin (95% CI; -3.4, 7.8) (Giamarellou et al. 2003).

This document will therefore examine the rationale and provide evidence that supports the use of two NI study margins: Study ARRD (Phase 2/3, 15% NI margin) and Study ARRI (Phase 3, 10% NI margin). As outlined in the ICH Guidance Document (E10), appropriate considerations for selecting NI margins include the following:

1 Historical evidence of sensitivity-to-drug effect

The antimicrobial therapy standard (for example, vancomycin) provides an effect superior to that of placebo (of at least a minimum size).

2 Study design characteristics

The details of the study design should adhere closely to that of the relevant historical studies.

3 Defining an acceptable noninferiority margin

The considerations should be based upon acceptable clinical AND statistical criteria.

4 Study oversight

The study conduct should adhere closely to the relevant historical studies and be of high quality.

2 Discussion

2.1 Historical Evidence

2.1.1 The Preantibiotic Era, Magnitude of Effect, and Foundation for Active Control Studies

The literature holds striking examples of wound care, infections, and the resulting morbidity and mortality from the preantibiotic era. These types of observations are in sharp contrast to the current understanding of the benefits of antibiotic treatment. The determination of the antibiotic effect on outcome in cSSSI can be inferred from these sources and can also provide a basis for the use of active control studies in the development of new antibiotics for cSSSI.

The care of wounds has evolved over hundreds of years (Ferguson 1970; Forrest 1982). Armed conflicts have contributed significantly to this evolution (Schilling 1985; Haller 1992; Moore 1999; Blaisdell 2005). The Civil War preceded the antiseptic and aseptic surgery and bacterial theory of disease (Franchetti 1995). At this time, amputation was the most common operation carried out by surgeons. The most frequent indication was gunshot fracture, although extensive soft tissue injury, bleeding, or necrotizing infections were also common. Infection and death were often so synonymous that a long-term recovery was the only criterion of success. During this period, mortality rates associated with amputation were recorded to be in excess of 87% (Wangensteen and Wangensteen 1962; Blaisdell 1988).

At the time of the Civil War, amputation provided a clean wound that was associated with better chance of healing without the lethal complications of infection or secondary hemorrhage. By today's standards, amputation is considered an undesirable and often final option. It can be concluded that the functionality, loss of limb or extent of amputation, as well as the resulting mortality, has been dramatically reduced by the use of antibiotics in association with changing surgical practice.

In the early 1900s and during the First World War, surgical considerations from Alexis Carrel and Antoine Depage, with contributions from Alexander Fleming's bacteriological research, provided adjustment to the standards of wound care by adding debridement to the armamentarium of the surgeon (Limjoco et al. 1995; Helling and Daon 1998). Together with aseptic surgical practices and the liberal use of the then-new antiseptics (Illingworth 1964), debridement (including biological or "maggot" debridement) (Chernin 1986) were considered significant advances in wound care and provided a

foundation for today's medical practices. The personal experience of Depage included a significant reduction in the incidence of infectious complications of soft tissue injuries and the ensuing mortality (<50%, with surgical care + antiseptics); however, these wounds might not have been infected by today's clinical standards. This may be particularly true since other reports of mortality during this period suggest the rates remained close to 75% (Broughton et al. 2006). Thus, conversely, the anticipated survival rate/placebo cure rate was approximately 25% to 50% in soft tissue injuries sustained on the war front.

In 1943 when penicillin became available for clinical study, the Committee on Chemotherapy of the National Research Committee of the Office of Scientific Research and Development of the US government assigned a limited quantity of penicillin to several of the teaching hospitals to evaluate the use of penicillin for the treatment of surgical infections (Lockwood et al. 1944; Meleney 1946).

In this study, the estimate of the drug effect was based on the (clinical) judgment that the results were unparalleled and, therefore, had to be credited to the drug. The following case types were included:

1. cases of surgical infection that would have required a surgical procedure, in which that procedure was completely obviated
2. cases in which a limited surgical procedure plus drug were adequate to cure when formerly, without drug, a radical procedure would have been necessary
3. cases requiring a surgical procedure but in which the healing time was significantly shortened by the use of drug
4. cases permitting primary closure after incision or excision with the administration of drug
5. cases with drug administration permitting an earlier successful secondary closure than could have been obtained without drug. In addition, the value of drug treatment was clearly indicated by the disappearance of the causative organisms from the culture during the course of therapy. For those cases of non drug-treated patients, the cultures are almost invariably positive until the wound was healed.

There were 744 cases, including 82 cases of septicemia, of established surgical infections treated with penicillin in all the participating research units for which there were data judged sufficiently complete for analysis. Although no placebo or comparative arm was included, each patient acted as their own control. The results of penicillin in relationship to previous forms of treatment (that is, none, sulfonamides, other) and/or in relationship to cases with or without surgery when penicillin preceded, accompanied or followed the procedure were evaluated. Penicillin was administered by the intramuscular route in 438/744 cases, locally in 142/744 cases or both in 164/744. The dose of penicillin varied,

depending on drug supply (since drug was in scarce supply at the beginning of the study) and response to treatment.

For the series as a whole, 15% of the cases showed an excellent response and 50% showed a definite or good response for a combined estimated drug effect of 65%. Penicillin was reported to have no effect in only 131/744 cases or 13.4%. Of the 258 cases that had no primary surgical procedure while under treatment, 22.8% of the cases showed an excellent response and 43.8% showed a definite or good response for a combined estimated drug effect of 66.6%.

The clinical results in diagnoses of cSSSI, similar to those of the oritavancin studies, were interesting. From this study, an estimated drug effect (excellent plus good responders) was observed to be 91.7% (cellulitis), 81.3% (superficial abscess), 68.9% (deep abscess) and 64.8% (infected soft-part wound). Thus, the failure rate ranged from 8.3% (cellulitis) to 35.1% (infected soft-part wound). It should be noted that the lower failure rates observed in cases of cellulitis may be due to the relatively low organism load.

As a whole, the bacteriological results appeared to be concordant with the clinical results of this study, although these were not broken down by diagnoses. The highest percentages of favorable results were found in the pure (for example, monomicrobic) infections of coagulase-positive *Staphylococcus* infections (87.3%) followed by hemolytic *Streptococcus* (68.7%). These bacteriological results also support an estimate for the lack of drug effect. In the monomicrobic setting, this ranged from a low of 12.7% with coagulase-positive *Staphylococcus aureus* to a high of 31.3% with hemolytic *Streptococcus*.

Concurrent septicemia was observed in 82 cases of the surgical site infections. Only 8 of these cases were polymicrobic in nature. The hemolytic *Streptococcus* had the best results among the bacteria, with a favorable response of 87.5%. The *S. aureus* yielded a favorable response in 69% of patients. The authors note, that before the arrival of the sulfonamides, and subsequently penicillin, the mortality of hemolytic *Streptococcus* septicemia was approximately 50% and of *Staphylococcus* septicemia 80%. Therefore, in such cases, the non-drug effect may be estimated in the range 20% to 50%.

These examples provide dramatic evidence of the morbidity and mortality of cSSSI. In the preantibiotic and early antibiotic era, not only was mortality high, but recovery was often delayed for weeks in those that did survive. This suggests that in addition to a dual outcome of Cure:Failure, another benefit of antimicrobial therapy is a more rapid

resolution of infection and without amputation or functional loss. Given such large treatment effects with the use of antibiotics, these examples also set the basis for use of active- rather than placebo-controlled group studies (Collier 1995). Additionally, it is consistent with the recommendations of the Declaration of Helsinki, which considers such complicated patients and their treatment within a placebo-controlled study, unethical (WMA 1989).

Recently, however, the use of an active-control has been questioned in acute bacterial sinusitis and acute exacerbations of chronic bronchitis. These are infections that are viewed by some as self-limited diseases with minimal morbidity (DHHS 2006; FDA [WWW]). A similar question could be posed in the setting of uncomplicated SSSI (uSSSI) such as impetigo and single cutaneous abscess. Evidence for treatment of impetigo, supports a modest benefit of topical antibiotic therapy (George and Rubin 2003; Koning and van der Wouden 2004; Koning et al. 2005). Also, there is evidence suggesting that not all simple cutaneous abscesses require antimicrobial therapy in addition to an incision and drainage (Llera et al. 1984; Moran et al. 2006). Rajendran et al. (2007) conducted a randomized, double-blind trial of 166 out-patient subjects comparing placebo to cephalexin 500 mg orally four times for 7 days after incision and drainage of skin and soft tissue abscesses. The primary outcome was clinical Cure or Failure at 7 days after incision and drainage. The 90.5% Cure rate observed in the placebo arm and 84.1% Cure rate in the cephalexin arm provide strong evidence that antibiotics may be unnecessary after surgical drainage of uncomplicated skin and soft tissue abscesses caused by community strains of methicillin-resistant *Staphylococcus aureus* (MRSA) (Rajendran et al. 2007). For these types of simple infections, the use of antibiotics and the subsequent potential risk of adverse reactions is an additional ethical consideration.

In sharp contrast to these uncomplicated infections, the indication evaluated by the oritavancin studies was complicated SSSI. Because cSSSI includes diverse infection types which could exhibit a range of severity, the Sponsor constructed each Phase 3 study protocol to ensure enrollment of well-defined, clinically relevant cases of cSSSI. Patients were enrolled with substantial morbidity and intravenous (IV) antimicrobial therapy was considered a standard of care for the investigational studies (Swartz and Pasternak 2005; Nichols 1999; Nichols et al. 1999; Stryjewski et al. 2006; Arbeit et al. 2004; Ellis-Grosse et al. 2005; Merck 2005; Mohammedamin et al. 2006). Details of these study particulars, along with other study design criteria are discussed in Section 2.2.

In summary, the historical evidence from the preantibiotic and early postantibiotic era clearly demonstrates that the use of antibiotics in complicated infections provide substantially more effect than placebo or surgery alone. From this literature it may be surmised that for severe cSSSI infections, it is unlikely that a placebo response would be greater than 35%.

2.1.2 The Selection of a Comparator: Vancomycin/Cephalexin

A critical decision in designing an appropriate clinical study is the choice of comparator regimen, since the comparator can directly affect study feasibility, data assumptions, and credibility. Considerations for selecting an appropriate worldwide antimicrobial comparator in the oritavancin cSSSI studies were multifaceted. In addition to the spectrum of antimicrobial activity and resistance issues, the route of delivery, side effect and drug interaction profiles, patient allergies, pharmacodynamics, and cost, the need for historical evidence that similarly designed cSSSI studies could consistently distinguish effective treatment was of paramount importance.

There are three basic questions (derived from ICH Guidelines) that need to be addressed when selecting an appropriate antibiotic comparative agent (Hwang and Morikawa 1999).

The questions are as follows:

1. Is proven effective treatment available?
2. Is the standard treatment life-saving and/or known to prevent irreversible morbidity?
3. Do studies for the standard have sensitivity-to-drug effects and does the particular study have assay sensitivity?

In evaluating and addressing these questions, vancomycin/cephalexin (with or without aztreonam, for gram negative organisms and/or metronidazole for anaerobic organisms) was appropriately suited to be selected as the comparator for the oritavancin cSSSI studies for the following reasons:

1. Vancomycin has a proven track record from clinical studies as well as continued use in clinical practice and the therapeutic armamentarium. Vancomycin has been used as standard-of-care for the treatment of cSSSI and MRSA infections worldwide. Cephalexin is efficacious in the treatment of skin infections caused by gram-positive pathogens (excluding enterococci and MRSA).
2. Vancomycin is highly effective for treatment of severe infections, such as cSSSI. Efficacy rates range from 65% to 85% in clinical trials. Cephalexin was chosen as an oral step down (following vancomycin treatment) for those patients demonstrating signs and symptoms improvement and without evidence of MRSA.

3. Antibiotics versus placebo are highly effective with given effect sizes to support sensitivity-to-drug effects of the chosen comparator, vancomycin/cephalexin. Study design and quality of the historical studies appear to have adequate assay sensitivity.

In 1958, vancomycin was the first glycopeptide antibiotic developed for clinical use. The initial compound, labeled 05865, showed a high degree of bacteriocidal activity against staphylococci and was the primary reason that the US FDA quickly approved the compound (Griffith 1984; Levine 2006; Moellering 2006).

The bacterial spectrum and early clinical effects of vancomycin were investigated and reported in several studies (Griffith and Peck 1955; McGuire et al. 1955; Ziegler et al. 1956; Griffith 1956; Geraci et al. 1958; Geraci and Heilman 1960; Kirby et al 1960). In an early in vitro study, vancomycin was tested against fifteen species of organisms. Of note, 41 of 43 strains of *Staphylococcus aureus* (as *Micrococcus pyogenes* var. *aureus*) were inhibited by concentration of 0.156 to 1.87 µg/mL of the antibiotic (McGuire et al. 1955). Although the clinical significance of the development of antibiotic resistance was uncertain, in 1956 Ziegler and colleagues found striking results with vancomycin. While *M. pyogenes* var. *aureus* (209P ATCC strain) exhibited a 131,056 fold increase in concentration of penicillin after 25 exposures, the same bacterial culture was able to tolerate only 4- to 8-fold higher concentration of vancomycin after the same number of exposures. Other ATCC strains tested exhibited an almost identical pattern of resistance to vancomycin.

In 1958, Geraci and colleagues (Geraci and Heilman 1960) noted the utility and potency of vancomycin in a series of 6 patients with acute endocarditis caused by coagulase positive *M. pyogenes* (staphylococci, penicillin-resistant, and erythromycin-resistant micrococci). In all cases, vancomycin was used as monotherapy (0.5 gm every 6 hours) for 4 to 6 weeks in duration and provided a total killing effect in a dilution of 1:4 to 1:8. Four of the 6 patients (67%) were considered cured on the basis of follow-up periods (3 to 20 months). Two patients died, both from intractable congestive heart failure.

Despite the growing number of antibiotics that were currently available, in 1960 Kirby, Perry, and Bauer (Kirby et al. 1960) published their dissatisfaction of treatment with the current agents (due to rapid emergence of resistance) and their positive experience with newer antibiotic, vancomycin. They reported 33 cases of treatment of staphylococcal septicemia with vancomycin. The age of patients ranged from 10 to 90 years. Of the 33 cases, 22 were >50 yrs of age. In 19 of the 33 cases, staphylococcal infections were hospital-acquired in the patient who had serious underlying diseases on admission. Most

cases were associated with a major surgical procedure or with disease requiring IV infusion. The overall results showed 20 (60%) were cured, 6 improved but died due to underlying disease, and 7 were treatment failures. Of the 33 infections, 10 (30%) were associated with a source of infection to be the skin (wound infection, n=4, narcotic injection site, n=4, and skin infections, n=2). Cure rates of 70% were noted in the skin infection subgroup (cures for wound infection 50%, injection site 75% and skin infection 100%). Although case study evaluation and conclusion is difficult, the authors concluded that vancomycin was a potent weapon in the management of severe staphylococcal infections.

Although many of the clinical studies were conducted in the first half of the 20th century, vancomycin has gained the reputation as "drug of choice" for difficult to treat, complicated gram positive infections likely due to MRSA and continues to be widely used for treatment of cSSSI (Jones 2006; Levine 2006; Moellering 2006).

In addition, the safety and efficacy of vancomycin have been demonstrated as part of several worldwide registration studies for treatment of cSSSI. Most recently, quinupristin/dalfopristin, daptomycin, tigecycline, linezolid, and telavancin have included the use of vancomycin as the comparator agent of choice. The clinical cure rates for vancomycin in these studies range from 68% to 94% depending on the respective population that is analyzed. Specifically, within the respective clinically evaluable (CE) and intent-to-treat (ITT) populations the reported cure rates were as follows; 90%, 68% (quinupristin/dalfopristin) (Nichols et al. 1999); 84%, 71% (daptomycin) (Arbeit et al. 2004) to 89%, 80% (tigecycline) (Ellis-Grosse et al. 2005), to 90%, 70% (linezolid) (Weigelt et al. 2005) to 94%, 85% (telavancin) (Stryjewski et al. 2006). The cure rates for vancomycin (CE and ITT) observed in the oritavancin clinical studies were similar; 80%, 65% (Study ARRD) and 76%, 68% (Study ARRI). The predictability, reproducibility, and consistency among the vancomycin results, as well as its global therapeutic acceptance, further support the sensitivity-to-drug effect requirement for an active control agent used in an NI study.

Cephalexin was chosen as an oral step-down therapy for those patients meeting a protocol, predefined criteria. Cephalexin is efficacious in the treatment of skin and skin-structure infections caused by most gram-positive pathogens (excluding enterococci and MRSA) (Powers et al. 1991; Kumar et al. 1988; Tack et al. 1998). Additionally, aztreonam and/or metronidazole were allowed to provide coverage in patients with suspected or microbiologically proven polymicrobial infections that included gram-negative pathogens and/or anaerobes. For the cSSSI indication, it must be recognized

that the combination of vancomycin with aztreonam (and/or metronidazole) is not commonly used in the clinic, but has become a recognized gold standard active comparator for conducting clinical studies.

In summary, vancomycin is a globally accepted standard of care for treatment of cSSSI. It is an appropriate choice for an active control that is has been well studied, is highly effective and adequately demonstrates the requirements for sensitivity-to-drug effects.

2.2 Oritavancin Study Design Characteristics

2.2.1 Optimizing Patient Safety and Efficacy

The oritavancin studies were designed and remain in accordance with current global regulatory guidance documents, as well as the recognized experts and expert organization guidelines, such as the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology. The enrollment criteria were well defined to optimize potential benefit-risk ratio for the patients, as indicated in the general guidelines for the Clinical Evaluations of Anti-infective Drugs (FDA 1998).

2.2.2 Well Characterized Patients and Similarity to Historical Studies

As mentioned in Section 2.1, because cSSSI includes diverse infection types which could exhibit a range of severity, the Sponsor constructed each study protocol to ensure enrollment of well-defined, clinically relevant cases of cSSSI that would be reflective of the patient severity observed in early studies of vancomycin.

As observed in the historical cases of cSSSI, patients were enrolled with substantial morbidity, in which IV antimicrobial therapy was considered an appropriate standard of care (Bertoni et al. 2001; Blot et al. 2002; Laube and Farrell 2002; Engemann et al. 2003). The protocols provided the investigators with clear, concise definitions of the common types of infections observed in the cSSSI category including wound infections, major abscess, and cellulitis. It should be noted that enrollment of patients with cellulitis was limited to 25%. This ensured a wide range of complicated patients in which an adequate number of microbiologic specimen could be obtained.

A patient was defined as having a cSSSI in the oritavancin clinical trials if all of the following criteria for disease severity, complication, and category were met:

1. Severity — cSSSI were of sufficient severity to anticipate 3 or more days of IV antibiotic therapy.

2. Complicated disease — One or more of the following criteria were met:
    a. infection required significant surgical intervention (such as debridement of devitalized tissue, drainage of major abscess, removal of foreign body implicated in infection, or fasciotomy) within 48 hours of enrollment
    b. infection process was suspected or confirmed to involve deeper soft tissue (fascia and/or muscle layers), such as infected ulcers, burns, and major abscesses, without extending into body cavities or involving bony tissues
    c. significant underlying diseases or conditions that complicated the response to treatment were present, including: diabetes mellitus, bacteremia, cellulitis with an involvement of >3% (>510 cm^2) of the body surface area, corticosteroid therapy (>7.5 mg/day equivalent of prednisone), burn (>10% of body surface area), radiation therapy (local or systemic), history of alcoholism (within prior 6 months), neutropenia, organ transplantation, malnutrition, immunosuppressive therapy, known human immunodeficiency virus (HIV) infection, or other immunosuppressive disease.
3. Disease Categories — For purposes of stratified randomization, patients were grouped into one of three disease categories. If a patient had more than one of the following diseases, the hierarchy was wound infection, then major abscess then cellulitis (for example, if a patient had a wound surrounded with cellulitis, then wound infection was chosen as the disease category).
    a. Wound Infection at the Site of Surgical Incision or Trauma (Including Burn Wounds) or Infected Ulcers. The patient was to have met all of the following criteria (Horan et al. 1992):
        i. purulent drainage from the wound or ulcer, but not from the organ/space component of the injury.
        ii. at least one of the following:
            1. fever (>38°C [>100.4°F] rectal, or >37.5°C [>99.5°F] oral);
            2. localized pain or tenderness;
            3. erythema extending at least 1 cm beyond the wound edge;

4. localized swelling.

iii. wound infections that occurred within 30 days after an operative procedure or trauma. In the case of infected ulcers, the underlying lesion may have been present >30 days.

b. Major Abscess (no open wound). The patient was to have all of the following:

i. acute onset within 7 days before enrollment;

ii. purulent drainage or purulent aspirate;

iii. erythema, induration (≥2 cm in diameter), or tenderness;

iv. evidence of loculated fluid by physical examination, blind aspiration, or ultrasound that required intervention (such as aspiration, incision and drainage, or excision) within 48 hours of enrollment.

c. Cellulitis. Cellulitis is a spreading inflammatory process involving the deep dermis and subcutaneous fat developing from an initial portal of entry: Local (traumatic injury, puncture wound, insect bite, or surgical incision) or distant (foot lesion such as interdigital tinea pedis or skin fissures, or a deep hand wound that can spread to cause cellulitis of the limb). The patient was to have all of the following (Gorbach 1997; Ginsberg 1981):

i. acute onset within 7 days before enrollment.

ii. pain or tenderness.

iii. cutaneous erythema.

iv. advancing edema or induration.

v. history of measured (>38°C [>100.4°F] rectal, or >37.5°C, [>99.5°F] oral) or subjective fever within 3 days before enrollment or elevated white blood cell (WBC) count ≥10.0 x 103/mm3 or ≥10% bands.

Upon review of published literature for other products (for example, daptomycin, linezolid, tigecycline, and televancin) that have been approved for use in cSSSI, a similar

construct of study design, as well as patient definitions (including study populations, concomitant therapy and endpoints) have been used. Notable entry criteria differences with Study ARRI and Study ARRD included; no restriction on human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), neutropenia, or duration of hospitalization. No limitations in these criteria assisted with the enrollment of a truly severe patient population. Reference to these recent clinical studies shows consistency to the oritavancin Phase 3 study designs and outcome, particularly since vancomycin was used as the study comparator for all of these FDA approved products.

In summary, the oritavancin study protocols were designed to ensure enrollment of well-defined, clinically relevant cases of complicated disease (cSSSI) that would be reflective of the patient severity observed in early studies of vancomycin.

2.3 Definition of an Acceptable Noninferiority Margin

2.3.1 Historical, Clinical and Statistical Considerations

As discussed in the background section above, the selection of 15% margin for the Phase 2/3 oritavancin cSSSI Study ARRD (initiated in 1999) was based upon the FDA's recommendation from the 1998 Points to Consider guidance document, suggesting a fixed NI margin of 15% for drugs with an expected cure rate of approximately 80% to 90%. In support of the FDA's request, in 2001, the follow-on Phase 3 protocol (ARRI) incorporated the use of a 10% NI margin. In both Study ARRI and Study ARRD, considerations for historical study evidence, clinical judgment, and statistical reasoning were also applied in order to ensure patient safety, as well as the successful study outcome.

In selecting a NI margin, reference to historic placebo-controlled studies performed with the chosen comparator (for example, vancomycin) should be used. However, there are several issues that can undermine this assumption, particularly for those drugs that are considered pioneering antibiotics, such as vancomycin. Although vancomycin was developed in the mid 1950's, much of the information about its utility has evolved in the more recent years. The evolution of vancomycin use has successfully met the needs of current medicine's treating physicians and continued its frontline use in the therapeutic armamentarium (Jones 2006; Moellering 2006).

There are some potential differences in the historical design features; therefore, prudence was exercised regarding their interpretation. These differences include: evolving patient population definitions and classification of severity, biased reporting of successes, changing epidemiology, increasing rates of resistance, different and evolving dosing

recommendations, changes in medical practice, concomitant therapies, and evolving end-point definitions and regulatory requirements. Therefore, clinical considerations of these items, as well as comparison to recent registration studies (as discussed in Section 2.1, The Selection of a Comparator: Vancomycin/Cephalexin) were used to confirm rates of clinical cure, historical reliability, and reproducibility. This approach is consistent with the recommendation from Dr. Robert O'Neil (Director, Office of Biostatistics, CDER, FDA) (O'Neil 2001). In addressing the question "How is the margin delta chosen based upon prior study data," Dr. O'Neil states that for large treatment effects (for example, anti-infectives), it is a clinical decision of how similar a response rate is needed to justify efficacy of a test treatment. These components are consistent with the Sponsor's assessment that a placebo cure rate was unlikely to be greater than 35% for cSSSI patients meeting disease severity criteria and underlying co-morbidities.

2.3.2 Noninferiority Margin Definitions

As cited by Temple and Ellenberg (Temple and Ellenberg 2000), the NI margin must be no larger than the smallest treatment difference between standard therapy and placebo, and exclusion of a difference greater than the non inferiority margin would imply that at least part of the treatment effect of the standard therapy was preserved for the test drug.

These quantities are expressed as M1 and M2, such that:

M1 = the smallest treatment effect of active or standard therapy over that of placebo

M2 = a fraction of M1, chosen because the test drug should retain some substantial fraction (1-M1) of the effect of the standard drug.

For Study ARRD, the sample size was based upon a point estimate of the clinical cure rate of 80% in both oritavancin and the vancomycin/cephalexin groups and an evaluability rate of 60%. Using the Farrington and Manning method (Farrington and Manning 1990) the 95% CI for the difference in success rates was calculated and the statistical goal of these studies was to demonstrate the NI of oritavancin to that of the comparator agents, within a NI margin of 15%. With a sample size of at least 135 subjects per treatment arm the study was estimated to have a power of 82% to detect NI. Study ARRD enrolled 517 patients that received at least one dose, comprising the ITT group. Of these, 74% (n=384) were deemed clinically evaluable. In this group, the successful clinical response rates were 75.6%, 75.6%, and 80.2% for oritavancin 1.5 mg/kg, 3.0 mg/kg and vancomycin/cephalexin, respectively. Oritavancin (both regimens)

was successful in meeting the prespecified NI to vancomycin/cephalexin with the 95% CI, -13.3 to 4.2.

For Study ARRI, following the successful assumptions of Study ARRD, the sample size calculation for this study used similar assumptions: 80% efficacy for both oritavancin and the vancomycin/cephalexin groups and a 60% evaluability rate. The statistical goal of these studies was to demonstrate the NI of oritavancin to that of the comparator agents, within a NI margin of 10%. With patients randomized in a 2:1 (oritavancin:vancomycin) ratio, a sample size of at least 1250 subjects were to be enrolled for the study to have an estimated power of 90% to detect NI. Study ARRI enrolled 1246 patients that received at least one dose, comprising the ITT population. Of these, 80% (n=1000) were deemed clinically evaluable. In this group the cure rate for oritavancin patients was 78.6% compared with 76.2% for the vancomycin/cephalexin patients. Oritavancin was successful in achieving the pre-specified NI to vancomycin/cephalexin with the lower bound of 95% CI, -3.4 to 7.8.

Table 2-1 provides M1 and M2 assuming an 80% cure rate in the standard therapy group for differing rates of clinical cure in a placebo group. Per the comments and requests from the FDA, a fraction of 50% is used for M2. For additional comparative purposes, M2 of 66% and 75% retention of M1 is also displayed.

Table 2-1 M1 and M2 Assuming 80% Cure Rate in Standard Therapy Group

PLACEBO CURE RATE	EFFECT OF COMPARATOR (M1)	NI MARGIN AT 50% M1 (M2)	NI MARGIN AT 66% M1 (M2)	NI MARGIN AT 75% M1 (M2)
20%	60%	*30%*	20%	15%
25%	55%	*27.5%*	19%	14%
30%	50%	*25%*	17%	12%
35%	45%	*22%*	15%	11%
40%	40%	*20%*	14%	10%
45%	35%	*18%*	12%	9%
50%	30%	*15%*	10%	8%
55%	25%	*12%*	8%	6%
60%	20%	*10%*	7%	5%
65%	15%	*8%*	5%	
70%	10%	*5%*		
75%	5%			

Abbreviations: M1 = the smallest treatment effect of active or standard therapy over that of placebo; M2 = a fraction of M1, chosen because the test drug should retain some substantial fraction (1-M1) of the effect of the standard drug; NI = noninferiority.

For Study ARRD, an NI margin of 15% assured that the test therapy (oritavancin) maintained at least 50% of the treatment effect of the standard therapy (vancomycin) over placebo, when the standard therapy and placebo cure rates are 80% and 50%, respectively. Similarly, for Study ARRI, a NI margin of 10% assured that oritavancin maintained at least 50% of the treatment effect of the standard therapy (vancomycin) over placebo, when the standard therapy and placebo cure rates are 80% and 60%, respectively.

The placebo rates in Table 2-1 represent a conservative range of 20% to 75%. These rates were derived from the historical literature, as well as clinical considerations of the historic design feature caveats as discussed above. If one considers another example of maintaining at least 50% of the treatment effect in which the historical placebo cure response of 35% is used with an active-control effect (M1) of 45%; an NI margin of 22.5% would be acceptable. Consequently, the oritavancin NI margins of 15% (for Study ARRD) and 10% (for Study ARRI), respectively, would be considered to have exceeded the necessary power to detect appropriate differences.

It should also be noted that the requirement to maintain at least 50% of the control effect may be reconsidered in some situations (Snapinn 2000; Wang et al. 2002; Blackwelder 2004). A more rigid or conservative M2 could be applied. As in Table 2-1, use of 66% or 75% retention of standard drug effect, would have differing effects on the suitability of the desired NI margins. One could argue that given patient baseline severity (as observed in the oritavancin studies), and a historical placebo cure rate of 35% (including adequate surgical intervention), an M1 of 45% and a more conservative M2 of 66%, an NI margin of 15% should be suitable and appropriate to distinguish test drug effects.

Additionally, efficacy is not the exclusive consideration when evaluating benefit:risk. A larger NI margin may be considered clinically acceptable if a new therapy provides advantages of safety and/or tolerability over existing therapies.

Vancomycin, the standard of care, can be associated with several adverse events, including nephrotoxicity (Levy et al. 1990; Rybak et al. 1990 Khurana and deBelder 1999; James and Gurk-Turner 2001). As shown in Study ARRI and Study ARRD, oritavancin may provide a safe and effective alternative to vancomycin. The lack of nephrotoxic effects, in addition to exquisite bactericidal activity could offset a conservative efficacy NI margin.

2.4 Study Oversight

Study conduct and oversight are the final considerations for noninferior margin. A basic assumption is that the standard therapy should have retained its known (historical) effect and patients participating in the current study should be as similar as possible to the historic patients with respect to all baseline values and treatment variables that might influence outcome (see Section 2.2). A failure to achieve this similarity from the outset, a failure to ensure high-quality study conduct, or both, can introduce bias into the study and compromise assay sensitivity.

The classical method to minimize systematic differences between study groups is randomization. Further, double-blinding is intended to minimize potential biases resulting from differences in management, treatment, or assessment of patients, or differences in interpretation of results that could arise as a result of the subject's or investigator's knowledge of the assigned treatment.

The oritavancin studies incorporated both randomization and double-blinding methods to minimize potential bias (ICH 1998b). In addition, Studies ARRD and ARRI were carefully conducted using Good Clinical Practices (ICH 1996).

3. Summary and Conclusions

The Sponsor considers that the NI margins selected for Study ARRD (Phase 2/3, NI=15%) and Study ARRI (Phase 3, NI=10%) were clinically relevant, and statistically sound and robust. Each study adhered to the NI margin components of considerations, as well as the regulatory guidance principals and standard of clinical studies outlined in this document. In summary, the following components were considered:

3.1 Historical Evidence that Assay Sensitivity to Drug Effect Exists

The preponderance of historical evidence from the preantibiotic era demonstrates that the use of antibiotics provide substantially more effect than placebo or surgery alone. For severe cSSSI infections, it is unlikely that a placebo response would be greater than 35%. Given such large treatment effects with the use of antibiotics, these examples also set the basis for use of active rather than placebo control group studies.

The antimicrobial therapy standard chosen for the oritavancin trials was vancomycin/cephalexin, a globally accepted regimen for treating serious gram-positive infections. Vancomycin, a gold standard agent, has been well studied in both historical and recent registration trials. Cephalexin is also indicated for treatment of skin infections and was chosen as an oral step down (following vancomycin treatment) for those patients demonstrating signs and symptoms improvement and without evidence of MRSA.

3.2 Study Design Characteristics

The oritavancin study protocols were designed to ensure enrollment of well-defined, clinically relevant cases of cSSSI that would be reflective of the patient severity observed in relevant historical, as well as recent registration studies of vancomycin.

3.3 Defining an Acceptable Noninferiority Margin

Considerations for an acceptable NI margin were based upon relevant historical, clinical, and statistical criteria. Placebo cure rates of 20% to 75% were used for comparative evaluation. These rates are considered conservative and were derived from the historical literature, as well as clinical considerations of the historic design feature caveats.

In maintaining at least 50% of the treatment effect in which the historical placebo cure response of 35% is used with an active-control effect (M1) of 45%; an NI margin of 22.5% would be acceptable. Consequently, the oritavancin study's NI margins of 15% (Study ARRD) and 10% (Study ARRI), respectively, would be considered to have exceeded the necessary power to detect appropriate differences.

3.4 Study Oversight

The Sponsor ensured that the conduct of the oritavancin studies adhered closely to the relevant historical studies and were of high quality.

In conclusion, the oritavancin Phase 3 studies, if viewed alone or in concert, have confirmed that oritavancin, as compared to a standard of care, vancomycin/cephalexin, is efficacious (and demonstrated a clinically meaningful treatment effect) for the treatment of patients with cSSSI.

4 References

Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. 2004. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 38:1673-1681.

Bertoni AG, Saydah S, Brancati FL. 2001. Diabetes and the risk of infection-related mortality in the U.S. Diabetes Care 24:1044-1049.

Blackwelder WC. 2004. Current issues in clinical equivalence trials. J Dent Res 83 Spec No C:C113-115.

Blaisdell FW. 2005. Civil War vascular injuries. World J Surg 29 Suppl 1:S21-24.

Blaisdell FW. 1988. Medical advances during the Civil War. Arch Surg 123:1045-1050.

Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. 2002. Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Arch Intern Med 162:2229-2235.

Broughton G, 2nd, Janis JE, Attinger CE. 2006. A brief history of wound care. Plast Reconstr Surg 117:6S-11S.

Calandra GB, Norden C, Nelson JD, Mader JT. 1992. Evaluation of new anti-infective drugs for the treatment of selected infections of the skin and skin structure. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 15 Suppl 1:S148-154.

Chernin E. 1986. Surgical maggots. South Med J 79:1143-1145.

Collier J. 1995. Confusion over use of placebos in clinical trials. BMJ 311:821-822.

[CPMP] Committee for Proprietary Medicinal Products. 2004. Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections. Committee for Proprietary Medicinal Products. CPMP/EWP/558/95 rev 1.

[DHHS] Department of Health and Human Services, [FDA] Food and Drug Administration, [CDER] Center for Drug Evaluation and Research,. 2006. Minutes from: anti-infective drugs advisory committee (ADAC) held September 12, 2006. Available at: http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4232t1-part1.pdf. Accessed 10 August 2007.

Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E. 2005. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 41 Suppl 5:S341-353.

Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. 2003. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis 36:592-598.

[ESCMID] European Society of Clinical Microbiology and Infectious Disease. 1993. European guideline for the clinical evaluation of anti-infective drug products. 354 p.

Farrington CP, Manning G. 1990. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 9:1447-1454.

[FDA] Food and Drug Administration. Clinical trial design in studies of acute bacterial sinusitis. Available at: http://www.fda.gov/OHRMS/DOCKETS/AC/03/briefing/3997B2_01_FDA-AcuteBacterialSinusitis.pdf. Accessed 10 August 2007.

[FDA] Food and Drug Administration. 1998. Guidance for industry: developing antimicrobial drugs--general considerations for clinical trials. [FDA] Food and Drug Administration.

Ferguson DJ. 1970. Pareian and Listerian slants on infection in wounds. Perspect Biol Med 14:63-68.

Forrest RD. 1982. Development of wound therapy from the Dark Ages to the present. J R Soc Med 75:268-273.

Franchetti MA. 1995. Civil War antisepsis and infection. Md Med J 44:372-376.

George A, Rubin G. 2003. A systematic review and meta-analysis of treatments for impetigo. Br J Gen Pract 53:480-487.

Geraci JE, Heilman FR. 1960. Vancomycin in the treatment of staphylococcal endocarditis. Prog Neurobiol 35:316-326.

Geraci JE, Heilman FR, Nichols DR, Wellman WE. 1958. Antibiotic therapy of bacterial endocarditis. VII: Vancomycin for acute micrococcal endocarditis: preliminary report. Mayo Clin Proc 33:172-181.

Giamarellou H, O'Riordan W, H. H, Owen S, Porter S, Loutit JS. 2003. Phase 3 trial comparing 3-7 days of oritavancin vs. 10-14 days of vancomycin/cephalexin in the treatment of patients with complicated skin and skin structure infections (cSSSI). Presented at: 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2003 Sep 14-17; Abstract nr L-739a.

Ginsberg MB. 1981. Cellulitis: analysis of 101 cases and review of the literature. South Med J 74:530-533.

Gorbach S. 1997. IDCP guidelines: superficial skin and soft tissue infections: part II. Infect Dis Clin Practice 6:6-11.

Griffith RS. 1984. Vancomycin use--an historical review. J Antimicrob Chemother 14 Suppl D:1-5.

Griffith RS. 1956. Vancomycin; continued clinical studies. Antibiot Annu:118-122.

Griffith RS, Peck FB, Jr. 1955. Vancomycin, a new antibiotic. III. Preliminary clinical and laboratory studies. Antibiot Annu 3:619-622.

Haller JS, Jr. 1992. Treatment of infected wounds during the Great War, 1914 to 1918. South Med J 85:303-315.

Helling TS, Daon E. 1998. In Flanders fields: the Great War, Antoine Depage, and the resurgence of debridement. Ann Surg 228:173-181.

Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. 1992. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 13:606-608.

Hwang IK, Morikawa T. 1999. Design issues in non-inferiority trials. Drug Information Journal 33:1205-1218.

[ICH] International Conference on Harmonisation. 1996. Guidance for industry (E6). Good clinical practice: consolidated guidance. [ICH] International Conference on Harmonisation.

[ICH] International Conference on Harmonisation. 1998a. ICH Topic E8: General considerations for clinical trials. [CPMP] Committee for Proprietary Medicinal Products. CPMP/ICH/291/95.

[ICH] International Conference on Harmonisation. 1998b. ICH Topic E9: Statistical principles for clinical trials. [CPMP] Committee for Proprietary Medicinal Products. CPMP/ICH/363/96.

[ICH] International Conference on Harmonisation. 2000. ICH Topic E10: Note for guidance on choice of control group in clinical trials. [CPMP] Committee for Proprietary Medicinal Products. CPMP/ICH/364/96.

Illingworth C. 1964. The Lister Lecture, 1964: Wound Sepsis-from Carbolic Acid to Hyperbaric Oxygen. Can Med Assoc J 91:1041-1045.

James CW, Gurk-Turner C. 2001. Recommendations for monitoring serum vancomycin concentrations. Proc (Bayl Univ Med Cent) 14:189-190.

Jones RN. 2006. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin Infect Dis 42(Suppl 1):S13-24.

Khurana C, de Belder MA. 1999. Red-man syndrome after vancomycin: potential cross-reactivity with teicoplanin. Postgrad Med J 75:41-43.

Kirby WM, Perry DM, Bauer AW. 1960. Treatment of staphylococcal septicemia with vancomycin: report of thirty-three cases. N Engl J Med 262:49-55.

Koning S, van der Wouden JC. 2004. Treatment for impetigo. BMJ 329:695-696.

Koning S, Verhagen AP, van Suijekom-Smit LWA, Morris A, Butler CC, van der Wouden JC. 2005. Interventions for impetigo. Oxford (UK): Cochrane Database for Systematic Reviews. Issue 2, 71 p.

Kumar A, Murray DL, Hanna CB, Kreindler TG, Jacobson KD, Bundy JM, Waxman K, Finnerty EF, Folan DW, Jr., Drucker WR, et al. 1988. Comparative study of cephalexin

hydrochloride and cephalexin monohydrate in the treatment of skin and soft tissue infections. Antimicrob Agents Chemother 32:882-885.

Laube S, Farrell AM. 2002. Bacterial skin infections in the elderly: diagnosis and treatment. Drugs Aging 19:331-342.

Levine DP. 2006. Vancomycin: a history. Clin Infect Dis 42 Suppl 1:S5-12.

Levy M, Koren G, Dupuis L, Read SE. 1990. Vancomycin-induced red man syndrome. Pediatrics 86:572-580.

Limjoco UR, Landon CW, Ragland JJ. 1995. The contributions of Alexis Carrel to the management of contaminated wounds. Can J Surg 38:183-187.

Llera JL, Levy RC, Staneck JL. 1984. Cutaneous abscesses: natural history and management in an outpatient facility. J Emerg Med 1:489-493.

Lockwood JS. 1944. The use of penicillin in surgical infections. Ann Surg 120:311-344.

McGuire JM, Wolfe RN, Ziegler DW. 1955. Vancomycin, a new antibiotic. II. In vitro antibacterial studies. Antibiot Annu 3:612-618.

Meleney FL. 1946. Penicillin in the treatment of established surgical infections: a systematic study of 744 including 82 septicemias. Ann Surg 124:962-978.

Merck and Co. 2005. Section 10: dermatological disorders, bacterial skin infections. In The Merck manual. Available at: http://www.merck.com/mmpe/sec10/ch119/ch119a.html. Accessed 15 August 2007.

Moellering RC, Jr. 2006. Vancomycin: a 50-year reassessment. Clin Infect Dis 42 Suppl 1:S3-4.

Mohammedamin RS, van der Wouden JC, Koning S, Willemsen SP, Bernsen RM, Schellevis FG, van Suijlekom-Smit LW, Koes BW. 2006. Association between skin diseases and severe bacterial infections in children: case-control study. BMC Fam Pract 7:52.

Moore FD. 1999. Then and now: treatment volume, wound coverage, lung injury, and antibiotics: a capsule history of burn treatment at mid-century. Burns 25:733-737.

Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA. 2006. Methicillin-resistant S. aureus infections among patients in the emergency department. N Engl J Med 355:666-674.

Nichols RL. 1999. Optimal treatment of complicated skin and skin structure infections. J Antimicrob Chemother 44 Suppl A:19-23.

Nichols RL, Graham DR, Barriere SL, Rodgers A, Wilson SE, Zervos M, Dunn DL, Kreter B. 1999. Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. Synercid Skin and Skin Structure Infection Group. J Antimicrob Chemother 44:263-273.

O'Neil R. 2001. An update on statistical issues associated with the International Harmonization of Technical Standards for Clinical Trials (ICH). Presentation: 22nd Spring Symposium, New Jersey Chapter of ASA, June 2001. Available at: http://stat.rutgers.edu/njasa/Presentations/NJASAmeetinged.ppt. Accessed 04 October 2007.

Powers RD, Schwartz R, Snow RM, Yarbrough DR, III. 1991. Ofloxacin versus cephalexin in the treatment of skin, skin structure, and soft-tissue infections in adults. Clin Ther 13:727-736.

Rajendran PM, Young D, Maurer T, Chambers H, Perdreau-Remington F, Ro P, Harris H. 2007. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community methicillin-resistant Staphylococcus aureus infection. Antimicrob Agents Chemother.

Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. 1990. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J Antimicrob Chemother 25:679-687.

Schilling JA. 1985. Advances in knowledge related to wounding, repair, and healing: 1885-1984. Ann Surg 201:268-277.

Snapinn SM. 2000. Noninferiority trials. Current Controlled Trials in Cardiovascular Medicine 1:19-21.

Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. 2005. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 41:1373-1406.

Stryjewski ME, Chu VH, O'Riordan WD, Warren BL, Dunbar LM, Young DM, Vallee M, Fowler VG, Jr., Morganroth J, Barriere SL, Kitt MM, Corey GR. 2006. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 50:862-867.

Swartz MN, Pasternack MS. 2005. Skin and soft tissue infections. Mandell, Douglas, and Bennett's principles and practice of infectious disease. 6th edition. Philadelphia (PA): Elsevier, Inc.

Tack KJ, Littlejohn TW, Mailloux G, Wolf MM, Keyserling CH. 1998. Cefdinir versus cephalexin for the treatment of skin and skin-structure infections. The Cefdinir Adult Skin Infection Study Group. Clin Ther 20:244-256.

Temple R, Ellenberg SS. 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med 133:455-463.

Wang SJ, Hung HM, Tsong Y. 2002. Utility and pitfalls of some statistical methods in active controlled clinical trials. Control Clin Trials 23:15-28.

Wangensteen OH, Wangensteen S.D. 1962. Military surgeons and surgery, old and new: an instructive chapter in management of contaminated wounds. Surgery 62:1102-1124.

Wasilewski MM, Disch DP, Mcgill JM, Harris HW, O'Riordan W, Zeckel ML. 2001. Equivalence of Shorter Course Therapy with Oritavancin vs. Vancomycin/Cephalexin in Complicated Skin/Skin Structure Infections (CSSI) [abstract]. Presented in: Abstracts of the 41st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 December 16-19; Chicago (IL). Available at: http://gateway.nlm.nih.gov/MeetingAbstracts/102269584.html. Accessed 12 March 2007. Abstract nr UL-18.

Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C. 2005. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 49:2260-2266.

[WMA] World Medical Association. 1989. Declaration of Helsinki: ethical principles for medical research involving human subjects.

Ziegler DW, Wolfe RN, McGuire JM. 1956. Vancomycin, a new antibiotic. II. In vitro antibacterial studies. Antibiot Annu 3:612-618.