

TARGANTA THERAPEUTICS CORPORATION

**Briefing Document for the
Anti-Infective Drugs Advisory Committee
Discussion on Noninferiority Margin Justification**

November 18, 2008

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Introduction

The Anti-Infective Drugs Advisory Committee (AIDAC) scheduled a meeting for 18 November 2008 to discuss noninferiority (NI) margin justifications for studies involving complicated skin and skin structure infections (cSSSI). Targanta Therapeutics Corporation (Targanta) is invited to participate in this discussion and will give a 15-minute presentation that includes a rationale for the selection of NI margins for its two Phase 3 cSSSI studies, H4Q-MC-ARRD (Study ARRD) and H4Q-MC-ARRI (Study ARRI). As a supplement to its presentation, Targanta is also providing this introduction and two attachments.

[Attachment 1](#) consists of a document titled “*Overview of Oritavancin Complicated Skin and Skin Structure Infection Studies and NI Margins*,” which was written in response to an FDA request and follows the October 2007 Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval (FDA 2007¹). The same NI overview document was included in Section 2.7.3.6.1 of Targanta’s NDA 22-153. As specified in International Conference of Harmonisation Guidance Document (E10), the document addresses the following four aspects that a sponsor should consider when selecting NI margins:

- **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 minimum size).
- **Study design characteristics:**
The details of the study design should adhere closely to that of the relevant historical studies.
- **Defining an acceptable noninferiority margin:**
The considerations should be based upon acceptable clinical AND statistical criteria.
- **Study oversight:**
The study conduct should adhere closely to the relevant historical studies and be of high quality.

¹ [FDA] Food and Drug Administration. 2007. Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval. Available at: <http://www.fda.gov/cder/guidance/7884dft.pdf>

Targanta proposes that severity of illness plays a role in the selection of an acceptable NI margin in cSSSI studies; therefore, additional data characterizing disease and severity of illness in Targanta's Phase 3 cSSSI studies are presented in [Attachment 2](#), further supporting the selected NI margins in the two studies (Study ARRD 15%; Study ARRI 10%). This second attachment defines "severity," "complicated," and disease categories (as specified in the protocols of these two studies) and presents a variety of patient population characteristics from the combined data of the two studies that serve as indicators of cSSSI disease severity. Finally, the document compares these indicators of disease severity with those obtained from published cSSSI studies of daptomycin, linezolid, tigecycline, telavancin, and ceftobiprole.

**Attachment 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

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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 2001](#); [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 Wangenstein 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; Meloney 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, monomicrobial) 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 monomicrobial 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 polymicrobial 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 cm²) 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 ($>38^{\circ}\text{C}$ [$>100.4^{\circ}\text{F}$] rectal, or $>37.5^{\circ}\text{C}$, [$>99.5^{\circ}\text{F}$] oral) or subjective fever within 3 days before enrollment or elevated white blood cell (WBC) count $\geq 10.0 \times 10^3/\text{mm}^3$ or $\geq 10\%$ 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.

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**Attachment 2:
Description of Patient Population in Oritavancin's
Phase 3 cSSSI Studies and Indicators of Disease**

1 Disease Diagnostic Criteria

In both of Targanta Therapeutics Corporations' (Targanta) Phase 3 complicated skin and skin structure infections (cSSSI) studies (Studies H4Q-MC-ARRD [ARRD] and H4Q-MC-ARRI [ARRI]), a patient was defined as having a cSSSI if all three of the following definitions (severity, complicated disease, and disease categories) were satisfied.

1.1 Definition of Severity

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

1.2 Definition of Complicated

Skin and skin-structure infections 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).

1.3 Definition of Disease Categories

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

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 ($>38^{\circ}\text{C}$ rectal or $>37.5^{\circ}\text{C}$ 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.

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.

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 ($>38^{\circ}\text{C}$ rectal or $>37.5^{\circ}\text{C}$ oral) or subjective fever within three days prior to enrollment or elevated white blood cell count $\geq 10.0 \times 10^3/\text{mm}^3$ or $\geq 10\%$ bands.

2 Description of Patient Population in Oritavancin's Phase 3 Studies

[Table 1](#) summarizes baseline disease categories and characteristics in the intent-to-treat (ITT) population of the pooled Phase 3 studies (Studies ARRD and ARRI).

Table 1 Baseline Disease Categories and Characteristics for Pooled Studies ARRD and ARRI (Intent-to-Treat Population)

	ORI % (n) N=1173	VAN/CEPH % (n) N=590
<u>Disease Category</u>		
Wound infection	28.5% (334)	30.0% (177)
Major abscess	42.0% (493)	40.8% (241)
Cellulitis	29.5% (346)	29.2% (172)
<u>Deepest Tissue Involved</u>		
Skin	4.3% (51)	5.3% (31)
Subcutaneous	55.4% (650)	55.1% (325)
Fascial plane	29.3% (344)	27.5% (162)
Muscle	9.7% (114)	11.4% (67)
Bone	0.3% (3)	0.2% (1)
Other	0.9% (1)	0.7% (4)
<u>Location of Infection</u>		
Head and neck	6.7% (79)	7.3% (43)
Torso	25.0% (293)	21.9% (129)
Upper extremity	22.6% (265)	22.5% (133)
Lower extremity ^a	46.5% (545)	49.0% (289)
Foot	9.8% (115)	10.3% (61)
Lower leg	30.9% (362)	29.3% (173)
Upper leg	7.6% (89)	11.5% (68)
Other ^b	1.5% (17)	1.5% (9)
<u>Duration of Disease in Days</u>		
Mean (SD)	5.4 (5.77)	5.7 (7.88)
Minimum to maximum	1 to 92	1 to 140
SIRS ^c	25.9% (304)	27.3% (161)
<u>Concomitant antibacterial therapy</u>		
aztreonam	14.7% (173)	18.3% (108)
metronidazole	14.2% (167)	18.0% (90)
Surgery/Debridement/Drainage	61.0% (716)	61.0% (360)

Abbreviations: 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 In Study ARRD, 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 "Other" includes lower extremity infections such as whole leg, knee, heel, etc. identified in Study ARRI.

^c Presence of ≥ 2 of the following variables: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, 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).

Table 2 shows the incidence of selected comorbidities in the ITT population of the pooled Phase 3 studies (Studies ARRD and ARRI).

Table 2 Incidence of Clinically Relevant Comorbidities in Pooled Studies ARRD and ARRI (Intent-to-Treat Population)

Comorbidity	ORI N=1173 % (n)	VAN/CEPH N=590 % (n)
Age \geq 75	6.5% (76)	7.6% (45)
Diabetes	22.2% (260)	21.4% (126)
Renal insufficiency ^a /dialysis	5.1% (60)	5.4% (32)
Hepatic insufficiency	3.2% (38)	3.6% (21)
Vascular ^b	5.8% (68)	5.4% (32)
Immunologic ^c	5.0% (59)	4.4% (26)
Cancer ^d	2.1% (25)	2.2% (13)
Cardiac ^e	5.1% (60)	4.9% (29)
Respiratory ^f	6.0% (70)	6.9% (41)
Transplantation	0.1% (1)	0% (0)

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

^a Creatinine clearance \leq 30.

^b Arterial insufficiency and/or venous stasis.

^c ANC <1000, neutropenic event, HIV/AIDS, and/or immunosuppressive concomitant medications.

^d Except basal cell carcinoma of skin.

^e Congestive heart failure, myocardial infarction, and/or other cardiac conditions likely to reduce cardiac output.

^f Severe asthma, chronic obstructive pulmonary disease, and/or other respiratory conditions likely to decrease blood oxygenation.

Table 3 shows the number of clinically relevant comorbidities (the same comorbidities presented in Table 2 above) per patient in the ITT population of the pooled Phase 3 studies (Studies ARRD and ARRI).

Table 3 Number of Clinically Relevant Comorbidities per Patient in the Pooled Studies ARRD and ARRI (Intent-to-Treat Population)

Number of Comorbidities	ORI N=1173 % (n)	VAN/CEPH N=590 % (n)
Patients with zero	59.2% (695)	58.5% (345)
Patients with one	27.2% (319)	26.9% (159)
Patients with two	9.1% (107)	10.5% (62)
Patients with three or more	4.4% (52)	4.1% (24)

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

3 Indicators of Severity of Disease in Complicated Skin and Skin Structure Infection Studies

Targanta compared the severity of illness in its two Phase 3 studies to other recently reported cSSSI studies.

[Table 4](#) summarizes the severity of illness across multiple cSSSI studies with a variety of antimicrobial agents.

Table 4 Indicators of Severity of Disease in cSSSI Studies

Indicator	Pooled ARRD and ARRI Studies		Arbeit et al. 2004		Stevens et al. 2000		Weigelt et al. 2005		Ellis-Grosse et al. 2005		Stryjewski et al. 2008		Noel et al. 2008 (CID)		Noel et al. 2008 (AAC)	
	ORI	COM	DAP	COM	LZD	COM	LZD	COM	TIG	COM	TEL	COM	CEF	COM	CEF	COM
Comorbidities																
Diabetes	22.2%	21.4%	30%	35%	---	---	---	---	19.7% ^a	20.7% ^a	24.9%	24.8%	---	---	16.6%	16.8%
PVD	5.8% ^b	5.4% ^b	19%	23%	---	---	---	---	6.9% ^a	6.8% ^a	---	---	---	---	---	---
Immuno- compromised	5.0%	4.4%	3%	3%	---	---	---	---	---	---	---	---	---	---	---	---
≥1 SAE	9.1%	11.4%	10.9%	8.8%	5.5%	4.5%	0.3%	1.4%	5.5% ^c	4.8% ^c	7%	4%	7%	9%	6%	6%
Death	1.6%	2.0%	1.5%	1.4%	0.8%	0.2%	1.5%	1.2%	1.1%	0.2%	0.9%	0.9%	0.6	0.4%	0%	0.8%
SIRS	26%	27%	36%	38%	---	---	---	---	---	---	---	---	19%	20%	---	---
Concomitant Antibacterial Therapy																
Aztreonam	14.7%	18.3%	---	---	---	---	---	---	---	---	32%	33%	---	---	---	---
Metronidazole	14.2%	18.0%	---	---	---	---	---	---	---	---	23%	22%	---	---	---	---
Aztreonam and/or Metronidazole	21.1%	24.1%	24%	27%	---	---	37%	39%	---	---	---	---	---	---	---	---
Depth of Tissue Involvement																
Muscle, fascia, and subcutaneous	94.5%	93.4%	---	---	80.4%	77.2%	---	---	---	---	---	---	---	---	---	---
Muscle and fascia	39.0%	38.8%	---	---	---	---	---	---	---	---	---	---	35%	37%	---	---
Procedures																
Surgery/ Debridement/ Drainage	61.0%	61.0%	29%	29%	---	---	---	---	25.8% ^a	29.0% ^a	---	---	40%	37%	24% ^d 6% ^e 15% ^f	28% ^d 5% ^e 14% ^f
Incision and drainage	47.4%	45.9%	---	---	---	---	---	---	---	---	16%	17%	---	---	---	---

(continued)

Table 4 Indicators of Severity of Disease in cSSSI Studies

Abbreviations and Footnotes

Abbreviations: DAP = daptomycin; COM = comparator; LZD = linezolid; TIG = tigecycline; TEL = telavancin; CEF = ceftabiprole; ORI = oritavancin; PVD = peripheral vascular disease; --- = not reported; SAE = serious adverse event; SIRS = systemic inflammatory response syndrome.

^a Arterial insufficiency and/or venous stasis.

^b Planned operative procedures.

^c Unplanned surgical interventions.

^d Debridement, not in operating room.

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