CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

Clinical Studies

NDA/Serial Number:	22-110 / N000
Drug Name:	Telavancin for Injection (10 mg/kg IV q24h)
Indication(s):	Complicated skin and skin structure infection
Applicant:	Theravance Inc.
Date(s):	3/13/09
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products (DAIOP)
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Keywords: active control/non-inferiority, pooling

Table of Contents

1 Conclusions and Recommendations

The Applicant provided evidence of the effectiveness of telavancin in the treatment of complicated skin and skin structure infections (cSSSI). Based on a 10% noninferiority (NI) margin, telavancin was noninferior to vancomycin in the two Phase 3 studies (Studies 0017 and 0018) for clinical response at Test-of-Cure (TOC). However, it is noted that the Applicant did not provide evidence that telavancin is more effective than vancomycin in the treatment of cSSSI for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pathogens isolated at baseline.

An NI margin of 10% for cSSSI was deemed reasonable by the Anti-Infective Drugs Advisory Committee (AIDAC) at their 11/18/08 meeting for patients with cellulitis, who have systemic symptoms, and also those with serious wound infections. There were concerns raised at the meeting about the inclusion of patients with major abscesses in NI studies of cSSSI with the thought that patients with this type of wound infection should be excluded from studies. Historical studies have shown no quantifiable treatment effect with antibacterial agents following primary incision and drainage in patients with superficial or simple abscesses — a type of uncomplicated skin and skin structure infection. Similarly, quantification of a treatment effect in patients with major abscesses — a type of cSSSI — is also uncertain.

A sensitivity analysis removing patients with major abscesses (~40% of the data), found that telavancin was noninferior to vancomycin in both co-primary populations for Study 0017 and for the AT population in Study 0018 using a 10% NI margin. In the other co-primary population for Study 0018, the CE population, there was a -5% difference (telavancin – vancomycin) in success rates between telavancin and vancomycin with a 95% CI of (-12.3%, 2.3%) and thus did not demonstrate noninferiority of telavancin to vancomycin using a 10% NI margin. Further details can be found in Table 3.

Finally, there are concerns that the relative effect of telavancin compared to vancomycin decreases as the level of baseline renal impairment increases. Both the Applicant and the reviewer agree that the cause of this observation is unclear and appears to be multifactorial and the attributable factors are unknown. Given that this is an exploratory subgroup finding, the significance of the finding is not clear. Note, there was a similar decrease in relative efficacy of telavancin compared to vancomycin in older patients, ≥65 years, compared to younger patients, <65 years. This is likely due to the fact that age and baseline renal impairment are highly correlated, as would be expected.

2 Submission Overview

This submission contains the Applicant's response to the complete response letter that was issued on 2/20/08 (submission date: 1/21/08).

On 1/21/08, the Applicant submitted a response to the approvable letter that was issued on 10/19/07 (submission date 12/19/06). Subsequently, a complete response letter was sent on 2/20/08. The deficiencies were:

1. Safety issues for patients in the two Phase 3 hospital-acquired pneumonia trials were not sufficiently detailed,
2. Patients in the two cSSSI trials (0017 and 0018) whose test-of-cure or follow-up laboratory data indicated a serum creatinine level of greater than two times the baseline value should be identified, and follow-up information for such subjects including creatinine levels and renal related adverse events (e.g., need for dialysis or death) should be obtained and submitted,
3. A proposed Risk Evaluation and Mitigation Strategy (REMS) should be submitted,
4. The following labeling issues were identified:
    a. Need for inclusion of a boxed warning about the potential for teratogenicity,
    b. Need for inclusion of a warning on nephrotoxicity,
    c. Need for inclusion of language in the Warnings and Precautions section to advise physicians of the potential risk due to efficacy and safety in patients with moderate or several renal impairment,
    d. Need for inclusion of a statement in the Warning and Precautions section regarding the incidence, nature and reversibility of the nephrotoxicity, populations at increased risk, and recommended avoidance of other concomitant nephrotoxic drugs (such as non-steroidal anti-inflammatory drugs) where alternative therapies may be substituted
    e. Need for a bolded statement or appropriate alternative to the carton and container labels that alert the pharmacist to give each patient the medication guide,
5. Postmarketing requirements,
6. Contents of Safety update

On 12/19/06, the Applicant submitted an original new drug application (NDA) for telavancin. Subsequently, an approvable letter was issued on 10/19/07 to the Applicant listing the deficiencies requiring response prior to approval. The deficiencies were 1) significant deviations from Current Good Manufacturing Practice regulations at the proposed manufacturing facility, 2) benefit to risk ratio of the drug product is in question because of the following: a) decreased efficacy in clinical cure rates were noted to occur in patients with decreased baseline creatinine clearance, b) relative to vancomycin, decreased efficacy in clinical cure rates was noted to occur in patients with increasing age, c) relative to vancomycin, there is an imbalance in the reported rate of serious renal disorders and vascular disorders, d) thorough QT/QTc study demonstrated that the baseline and placebo corrected QTcF interval was lengthened greater than 10 milliseconds, e) drug product appears to be a teratogen in at least one and possibly three species, and f) there is insufficient information to recommend a dosing regimen for patients with a creatinine clearance of less than 10 mL/min including patients on hemodialysis.

In my review of the original submission, (submitted: 12/06/06), data from Site 38091 were excluded because of data integrity issues raised during site inspection by the Division of Scientific Investigations (DSI). Based on this finding and a subsequent inspection of the clinical research organization (CRO), there was a question of the adequacy of study monitoring. DSI conducted additional site inspections and determined that the study monitoring was adequate. In addition, the Applicant conducted an internal audit which was consistent with DSI's findings. During the audit, two additional sites, 37004 and 38020, were identified and it was determined that data from these sites should also be excluded. The revised analyses in this review exclude the data from all three sites (38091, 37004, and 38020) in Study 0018.

3 Brief Overview of Clinical Studies

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains, [redacted] *Streptococcus* pyogenes, *Streptococcus* agalactiae, *Streptococcus* anginosus grp. (including *S.* anginosus, *S.* intermedius and *S.* constellatus), and *Enterococcus* faecalis (vancomycin-susceptible isolates only). The proposed dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous (IV) infusion once every 24 hours for 7 to 14 days. b(4)

The two Phase 3 studies (Studies 0017 and 0018) were randomized, double blind, double-dummy, active-controlled, parallel group, multicenter, multinational trials. Patients with complicated Gram-positive skin and skin structure infections (primarily due to MRSA) were randomized to receive either telavancin 10 mg/kg IV once daily or vancomycin 1g q12 hours. Treatment duration was to be from 7 to 14 days. Investigators were encouraged to administer aztreonam and/or metronidazole in patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. In the Phase 3 studies, 862 (429 telavancin and 433 vancomycin) and 1035 (517 telavancin and 518 vancomycin) patients were enrolled in Studies 0017 and 0018 respectively. Study 0017 was conducted in 29 countries with approximately 73% of the patients enrolled in the United States, while Study 0018 was conducted in 17 countries with a slightly lower percentage (66%) of the patients enrolled from the United States.

The primary efficacy variable in the studies was the Clinical Response at Test-of-Cure. The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary and a 10% noninferiority margin was used. For the superiority analysis, the AT analysis population was the population of interest.

If the two studies were able to demonstrate the noninferiority of telavancin to vancomycin, an additional goal was to demonstrate the superiority of telavancin 10 mg/kg over vancomycin in patients infected with MRSA pathogens at baseline. This analysis was to be performed pooled across Studies 0017 and 0018 in the AT population.

If telavancin is shown to have superior efficacy in patients infected with MRSA at baseline, then the efficacy and safety of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) will be examined to demonstrate that the advantages in the MRSA subpopulation do not occur to the detriment of the complementary subpopulation.

4 Statistical Issues and Findings

In this section only selected results will be presented, please see my earlier reviews of the 12/19/06 and 1/21/08 submissions for additional analyses.

In this section, revised results, excluding the three sites (38091, 37004, and 38020) with data integrity issues have been excluded. In addition, the following statistical issues will discussed in this review– the 10% noninferiority margin used in the studies and the inconsistency of the treatment effect across levels of baseline renal impairment. These issues will be discussed and their impact assessed.

The baseline demographics are similar between treatment groups. Selected baseline demographics in the AT Population (Post-Amendment) are presented in Table 1. Please see my earlier review for more information.

Table 1: Baseline Demographics in the AT Population (Post-Amendment)

	Study 0017		Study 0018	
	Telavancin N=426	**Vancomycin N=429**	**Telavancin N=458**	**Vancomycin N=481**
Age (years)				
Mean (range)	48.9 (18-96)	47.7 (17-90)	49.2 (18-95)	49.9 (18-91)
Age Distribution				
<65 years	337 (79%)	357 (83%)	377 (82%)	379 (79%)
≥65 years	89 (21%)	72 (17%)	81 (18%)	102 (21%)
Sex				
Male	230 (54%)	248 (58%)	258 (56%)	294 (61%)
Female	196 (46%)	181 (42%)	200 (44%)	187 (39%)
Race				
Black, of African heritage	59 (14%)	52 (12%)	69 (15%)	74 (15%)
White	349 (82%)	353 (82%)	336 (73%)	343 (71%)
Other	18 (4%)	24(6%)	53 (12%)	64 (13%)
Description of cSSSI				
Major Abscess	179 (42%)	193 (45%)	196 (43%)	204 (42%)
Deep/Extensive Cellulitis	156 (37%)	161 (38%)	153 (33%)	176 (37%)
Wound Infection	72 (17%)	60 (14%)	67 (15%)	61 (13%)
Infected Ulcer	16 (4%)	12 (3%)	29 (6%)	36 (7%)
Infected Burn	3 (<1%)	3 (<1%)	13(3%)	6 (1%)
Baseline Creatinine Clearance (ml/min)				
>80	274 (64%)	291 (68%)	279 (61%)	286 (60%)
>50-80	85 (20%)	85 (20%)	112 (24%)	118 (25%)
30-15	41 (10%)	35 (8%)	32 (7%)	45 (9%)
<30	21 (5%)	12 (3%)	17 (4%)	16 (3%)
Missing	5 (1%)	6 (1%)	18 (4%)	16 (3%)

[1] Counts (and percentages) represent the number (percentage) of patients with each medical condition.
Source: CSR, Tables 8-3, 8-4, 8-5, 8-7, and 8-8 excluding Sites 38091, 37004, and 38020 from Study 0018

Noninferiority Margin

A major statistical issue was the size of the noninferiority margin used in the two Phase 3 studies. This topic was discussed at the November 18, 2008 meeting of the AIDAC. The AIDAC members felt that a 10% margin was a reasonable compromise as long as major abscesses are excluded and there are safety, cost, and/or antimicrobial benefits associated with the test product. The Agency also found that a 10% noninferiority margin for cSSSI was justifiable (see Appendix A-1 of my review of the 1/21/08 submission) for patients with cellulitis, who have systemic symptoms, and also those with serious wound infections.

Primary Analyses

Table 2: Clinical Success Rates at TOC in Post-Amendment Patients

	Applicant Analyses			FDA Analyses		
Population	**Telavancin n/N %**	**Vancomycin n/N %**	**Difference[2] % (95% CI[3])**	**Telavancin n/N %**	**Vancomycin n/N %**	**Difference[2] % (95% CI[3])**
All Treated						
Study 0017	323/426 (75.8)	321/429 (74.8)	1.0 (-4.8, 6.8)	309/426 (72.5)	307/429 (71.6)	0.9 (-5.3, 7.2)
Study 0018 [1]	358/458 (78.2)	364/481 (75.7)	2.5 (-2.9, 7.9)	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
Clinically Evaluable						
Study 0017	304/346 (87.9)	302/349 (86.5)	1.3 (-3.6, 6.3)	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)
Study 0018 [1]	327/368 (88.9)	334/371 (90.0)	-1.2 (-5.6, 3.3)	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)

[1] Excluded patients from Sites 38091, 37004, and 38020
[2] Difference is (telavancin – vancomycin)
[3] 95% CI calculated using a continuity correction

For Study 0017, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 1.0% with a corresponding 95% CI of (-4.8%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 1.0% with a corresponding 95% CI of (-5.3%, 7.2%) for the AT population. In the other co-primary analysis of the CE population, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 1.3% with a corresponding 95% CI of (-3.6%, 6.3%) while the Agency analysis found a similar result with a treatment difference of 1.5% with a corresponding 95% CI of (-4.3%, 7.3%).

For Study 0018, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 2.5% with a corresponding 95% CI of (-2.9%, 7.9%) while the Agency analysis found a similar result with a treatment difference of 0.7% with a corresponding 95% CI of (-5.1%, 6.5%) for the AT population. In the other co-primary analysis of the CE population, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of -1.2% with a corresponding 95% CI of (-5.6%, 3.3%) while the Agency analysis found a similar result with a treatment difference of -3.8% with a corresponding 95% CI of (-9.2%, 1.5%).

Thus, using a noninferiority margin of 10%, the Applicant was able to demonstrate the noninferiority of telavancin to vancomycin in both co-primary analysis populations for the two

Phase 3 studies. This was consistent for both the Applicant's analyses and the Agency's analyses.

As a sensitivity analysis, patients with major abscesses were removed from the analysis as the AIDAC had suggested. Major abscesses constituted 43.5% (372/458) of the AT patients in Study 0017 and 42.6% (400/939) of the AT patients in Study 0018. The results of these analyses are provided in Table 3.

Table 3: Clinical Success at TOC in Post-Amendment Patients Excluding Major Abscesses

	FDA Analyses			FDA Analyses Excluding Patients w/Major Abscesses		
Population	**Telavancin Success n/N %**	**Vancomycin Success n/N %**	**Difference (telavancin – vancomycin) % (95% CI[2])**	**Telavancin Success n/N %**	**Vancomycin Success n/N %**	**Difference (telavancin – vancomycin) % (95% CI[2])**
All Treated						
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)	176/247 (71.3)	166/236 (70.3)	0.9 (-7.6, 9.4)
Study 0018 [1]	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)	159/195 (81.5)	153/192 (79.7)	1.8 (-6.5, 10.2)
CE						
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)	196/262 (74.8)	208/277 (75.1)	-0.3 (-7.8, 7.4)
Study 0018 [1]	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)	169/205 (82.4)	188/215 (87.4)	-5.0 (-12.3, 2.3)

[1] Excluded patients from Sites 38091, 37004, and 38020
[2] 95% CI calculated using a continuity correction

When major abscesses are excluded, telavancin was noninferior to vancomycin in both co-primary populations for Study 0017 and for the AT population in Study 0018 using a 10% NI margin. In the other co-primary population for Study 0018, the CE population, the difference (telavancin – vancomycin) in success rates was -5.0% with a 95% CI of (-12.3, 2.3) and thus did not demonstrate noninferiority of telavancin to vancomycin using a 10% NI margin. In this analysis, the exclusion of patients with major abscesses increased the point estimate of the difference between the two groups from -3.8% to -5.0%. This was similar to the effect on the point estimate for the CE population in Study 0017 as well. However, because the two rates were more similar in Study 0017, this did not result in the lower confidence bound being lower than -10% for CE population as it did in Study 0018.

It should be noted that CE population in Study 0018 had low power to demonstrate noninferiority assuming the observed rates are the actual rates, this study had only 29% power to demonstrate noninferiority of telavancin to vancomycin using a 10% noninferiority margin. Alternatively, if one assumes that the response rates for both groups are those observed for vancomycin, i.e. 87.4%, then the study has 86% power to demonstrate noninferiority using a 10% margin

Efficacy in Patients with MRSA Isolated at Baseline

Table 4: Clinical Success at TOC in All-treated patients with MRSA at baseline (Post-Amendment)

Population	Telavancin Success n/N (%)	Vancomycin Success n/N (%)	Difference[2] (telavancin – vancomycin) % (95% CI)
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018 [1]	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
Pooled [1] (0017 + 0018)	227/301 (75.4)	242/323 (74.9)	0.9 (-5.8, 7.6) p-value 0.18

[1] Excluded patients from Sites 38091, 37004, and 38020

[2] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights.

p-value is a two-sided Mantel-Haenszel test based on a stratified analysis by study.

As it was the Applicant's objective to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population has been demonstrated, the discussion of these results will follow. The analysis plan was to pool data across Studies 0017 and 0018 to perform the analyses. The results of the two studies were not found to be substantially dissimilar (FDA Analysis: Breslow-Day statistic=1.81, p=0.18) so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses.

In AT patients with MRSA isolated as a pathogen at baseline, the Applicant failed to demonstrate that telavancin was superior to vancomycin (p=0.18) in clinical response at TOC (see Table 4).

The analysis of the efficacy of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) was examined to demonstrate that the potential advantages in the MRSA subpopulation are not observed at the detriment of the complementary subpopulation. In this subpopulation, the response rates in the two treatment groups were similar. However, since there was no evidence of the superiority of telavancin to vancomycin, the analysis of the MRSA-complement is less critical.

Decreased relative efficacy of telavancin compared to vancomycin for patients with renal impairment and age.

This finding was noted in the review of the initial submission and was one of the issues included in the approvable letter.

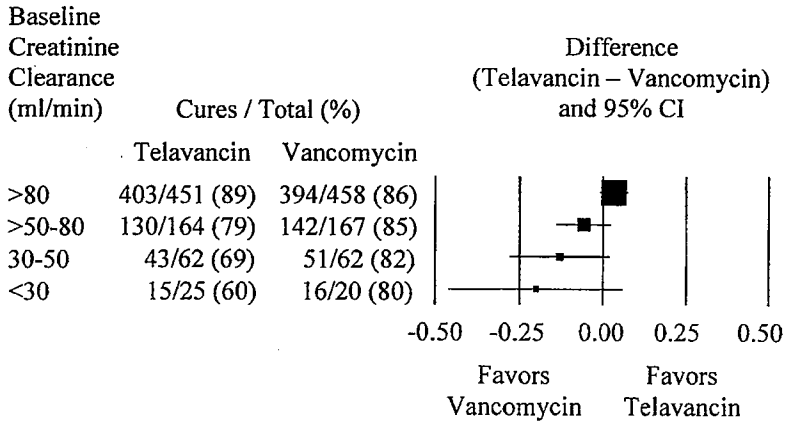
Table 5: Subgroup Analyses in the CE Population (Post-Amendment)

	Telavancin[1] % (n/N)	Vancomycin[1] % (n/N)	Difference[2] (TLV-Comparator) (95% CI)
Age			
<65 years	503/581 (86.6)	492/570 (86.3)	0.2 (-3.8, 4,1)
≥65 years	88/122 (72.1)	111/137 (81.0)	-8.6 (-19.1, 1.8)
Baseline Creatinine Clearance			
> 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
> 50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
< 30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018
[2] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights

There was a significant difference (decrease) in clinical response rates between patients with baseline renal impairment treated with telavancin compared to those treated with vancomycin. Patients with progressive degrees of baseline renal impairment had a greater decline in clinical response rate when treated with telavancin (see Figure 1). This decline in clinical response rate seen with telavancin treatment in patients with progressive levels of baseline renal impairment is of some concern. However, conclusions regarding this finding are limited by the exploratory nature of the post hoc analyses of subgroups and small numbers. A similar pattern of decrease in clinical response rates was seen in older patients treated with telavancin while clinical response rates in patients treated with vancomycin did not decrease. The decline in response rates may be related to decreased efficacy in older patients, since aging is correlated with a decline in creatinine clearance. The decrease in apparent response rates may be related to the failure to adjust (increase) the telavancin dose in response to improving renal function.

Figure 1: Clinical Response at TOC in the FDA CE Population for Studies 0017 + 0018 -- By Baseline Renal Impairment



Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

Efficacy by Baseline Pathogen

Clinical response at TOC in the Microbiological All-treated (MAT) and Microbiological Evaluable (ME) populations broken down by baseline pathogen are presented for both treatment arms in Table 6 and Table 7 respectively. The results are presented by individual study and pooled across Studies 0017 and 0018. The pathogens presented are those the Applicant is pursuing in their label. In the pooled analyses, clinical response rates are similar across treatment groups for patients with either MRSA or MSSA isolated at baseline in the MAT and ME populations. These two pathogens, MRSA and MSSA, are the most common pathogens isolated at baseline. The small sample sizes for the other pathogens make meaningful interpretation difficult.

Table 6: Clinical response at TOC in the Microbiological All-treated Population (Post-Amendment) by Baseline Pathogen

Pathogen	Study 0017		Study 0018 [1]		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	92/135 (68.2)	110/151 (72.8)	134/166 (80.7)	132/172 (76.7)	226/301 (75.1)	242/323 (74.9)
Staphylococcus aureus, MSSA	77/96 (80.2)	67/89 (75.3)	66/89 (74.2)	76/111 (68.5)	143/185 (77.3)	143/200 (71.5)
Enterococcus faecalis	14/15 (93.3)	12/17 (70.6)	11/14 (78.6)	18/25 (72.0)	25/29 (86.2)	30/42 (71.4)
Streptococcus pyogenes	9/10 (90.0)	9/11 (81.8)	7/11 (63.6)	12/17 (70.6)	16/21 (76.2)	21/28 (75.0)
Streptococcus agalactiae	8/10 (80.0)	4/6 (66.7)	7/11 (63.6)	12/14 (85.7)	15/21 (71.4)	16/20 (80.0)
Streptococcus anginosus group	8/10 (80.0)	5/6 (83.3)	6/10 (60.0)	7/9 (77.8)	14/20 (70.0)	12/15 (80.0)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

Table 7: Clinical response at TOC in the Microbiological Evaluable Population (Post-Amendment) by Baseline Pathogen

Pathogen	Study 0017		Study 0018 [1]		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)	208/239 (87.0)	225/262 (85.9)
Staphylococcus aureus, MSSA	71/82 (86.6)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)	132/161 (82.0)	131/154 (85.1)
Enterococcus faecalis	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81.0)	22/23 (95.6)	28/35 (80.0)
Streptococcus pyogenes	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)	16/19 (84.2)	19/21 (90.5)
Streptococcus agalactiae	8/9 (88.9)	3/3 (100.0)	6/10 (60.0)	10/12 (83.3)	14/19 (73.7)	13/15 (86.7)
Streptococcus anginosus group	7/8 (87.5)	5/5 (100.0)	6/9 (66.7)	4/4 (100.0)	13/17 (76.5)	9/9 (100.0)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

5 SIGNATURES/DISTRIBUTION LIST (Optional)

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Concurring Reviewer(s): Thamban Valappil, PhD

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OB/ Lillian Patrician

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22110	ORIG 1		TELAVANCIN
NDA 22110	ORIG 1		TELAVANCIN

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/s/

SCOTT S KOMO
6/17/2009
Signing for Dr. Thamban Valappil and myself

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

Clinical Studies

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Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products (DAIOP)
Clinical Team:	Janice Pohlman, MD MPH
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Table of Contents

1 Conclusions and Recommendations

The Applicant provided evidence of the effectiveness of telavancin in the treatment of complicated skin and skin structure infections (cSSSI). Based on a 10% noninferiority (NI) margin, telavancin was noninferior to vancomycin in the two Phase 3 studies (Studies 0017 and 0018) for clinical response at Test-of-Cure (TOC) in both of the co-primary analysis populations, All-Treated (AT) and Clinically Evaluable (CE). However, it is noted that the Applicant did not provide evidence that telavancin is more effective than vancomycin in the treatment of cSSSI for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pathogens isolated at baseline.

An NI margin of 10% for cSSSI was deemed reasonable by the Anti-Infective Drugs Advisory Committee (AIDAC) at their 11/18/08 meeting on this topic. There were concerns raised at the meeting about the inclusion of patients with major abscesses in NI studies of cSSSI with the thought that patients with this type of wound infection should be excluded from studies. Historical studies have shown no quantifiable treatment effect with antibacterial agents following primary incision and drainage in patients with superficial or simple abscesses — a type of uncomplicated skin and skin structure infection. Similarly, quantification of a treatment effect in patients with major abscesses — a type of cSSSI — is also uncertain.

A sensitivity analysis removing patients with major abscesses (~40% of the data), found that telavancin was noninferior to vancomycin in both co-primary populations for Study 0017 and for the AT population in Study 0018 using a 10% NI margin. In the other co-primary population for Study 0018, the CE population, there was a -5% difference in success rates between telavancin and vancomycin with a 95% CI of (-12.3, 2.3) and thus did not demonstrate noninferiority of telavancin to vancomycin using a 10% NI margin. Further details can be found in Table 3.

Finally, there are concerns that the relative effect of telavancin compared to vancomycin decreases as the level of baseline renal impairment increases. Both the Applicant and the reviewer agree that the cause of this observation is unclear and appears to be multifactorial and the attributable factors are unknown. Given that this is an exploratory subgroup finding, the significance of the finding is not clear. Note, there was a similar decrease in relative efficacy of telavancin compared to vancomycin in older patients, ≥65 years, compared to younger patients, <65 years. This is likely due to the fact that age and baseline renal impairment are highly correlated, as would be expected.

2 Submission Overview

This submission contains the Applicant's complete response to the approvable letter that was issued on 10/19/07 (submission date 12/06/06). The Applicant submitted an original new drug application (NDA) for telavancin on 12/06/06. Subsequently, an approvable letter was issued on 10/19/07 to the Applicant listing the deficiencies requiring response prior to approval. The deficiencies were 1) significant deviations from Current Good Manufacturing Practice regulations at the proposed manufacturing facility, 2) benefit to risk ratio of the drug product is in question because of the following: a) decreased efficacy in clinical cure rates were noted to occur in patients with decreased baseline creatinine clearance, b) relative to vancomycin,

decreased efficacy in clinical cure rates was noted to occur in patients with increasing age, c) relative to vancomycin, there is an imbalance in the reported rate of serious renal disorders and vascular disorders, d) thorough QT/QTc study demonstrated that the baseline and placebo corrected QTcF interval was lengthened greater than 10 milliseconds, e) drug product appears to be a teratogen in at least one and possibly three species, and f) there is insufficient information to recommend a dosing regimen for patients with a creatinine clearance of less than 10 mL/min including patients on hemodialysis.

In my review of the original submission, (submitted: 12/06/06), data from Site 38091 were excluded because of data integrity issues raised during site inspection by the Division of Scientific Investigations (DSI). Based on this finding and a subsequent inspection of the clinical research organization (CRO), there was a question of the adequacy of study monitoring. DSI conducted additional site inspections and determined that the study monitoring was adequate. In addition, the Applicant conducted an internal audit which was consistent with DSI's findings. During the audit, two additional sites, 37004 and 38020, were identified and it was determined that data from these sites should also be excluded. The revised analyses in this review exclude the data from all three sites (38091, 37004, and 38020) in Study 0018. Note, only selected analyses will be presented in this review. Please see my earlier review of the 12/06/06 submission for additional analyses.

3 Brief Overview of Clinical Studies

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains, (

b(4)

), *Streptococcus* pyogenes, *Streptococcus* agalactiae, *Streptococcus* anginosus grp. (including *S.* anginosus, *S.* intermedius and *S.* constellatus), and *Enterococcus* faecalis (vancomycin-susceptible isolates only). The proposed dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous (IV) infusion once every 24 hours for 7 to 14 days.

The two Phase 3 studies (Studies 0017 and 0018) were randomized, double blind, double-dummy, active-controlled, parallel group, multicenter, multinational trials. Patients with complicated Gram-positive skin and skin structure infections (primarily due to MRSA) were randomized to receive either telavancin 10 mg/kg IV once daily or vancomycin 1 g q 12 hours. Treatment duration was to be from 7 to 14 days. Investigators were encouraged to administer aztreonam and/or metronidazole in patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. In the Phase 3 studies, 862 (429 telavancin and 433 vancomycin) and 1035 (517 telavancin and 518 vancomycin) patients were enrolled in Studies 0017 and 0018 respectively. Study 0017 was conducted in 29 countries with approximately 73% of the patients enrolled in the United States, while Study 0018 was conducted in 17 countries with a slightly lower percentage (66%) of the patients enrolled from the United States.

The primary efficacy variable in the studies was the Clinical Response at Test-of-Cure. The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary and a 10% noninferiority margin was used. For the superiority analysis, the AT analysis population was the population of interest.

If the two studies were able to demonstrate the noninferiority of telavancin to vancomycin, an additional goal was to demonstrate the superiority of telavancin 10 mg/kg over vancomycin in patients infected with MRSA pathogens at baseline. This analysis was to be performed pooled across Studies 0017 and 0018 in the AT population.

If telavancin is shown to have superior efficacy in patients infected with MRSA at baseline, then the efficacy and safety of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) will be examined to demonstrate that the advantages in the MRSA subpopulation do not occur to the detriment of the complementary subpopulation.

4 Statistical Issues and Findings

In this section, revised results, excluding the three sites, will be presented. In addition, the following statistical issues will discussed in this review– the 10% noninferiority margin used in the studies and the inconsistency of the treatment effect across levels of baseline renal impairment. These issues will be discussed and their impact assessed.

The baseline demographics in the AT Population (Post-Amendment) are presented in Table 1. Note data from the three sites (38091, 37004, and 38020) with data integrity issues have been excluded. The baseline demographics are similar between treatment groups.

Table 1: Baseline Demographics in the AT Population (Post-Amendment)

	Study 0017		Study 0018	
	Telavancin N=426	Vancomycin N=429	Telavancin N=458	Vancomycin N=481
Age (years)				
Mean (range)	48.9 (18-96)	47.7 (17-90)	49.2 (18-95)	49.9 (18-91)
Age Distribution				
<65 years	337 (79%)	357 (83%)	377 (82%)	379 (79%)
≥65 years	89 (21%)	72 (17%)	81 (18%)	102 (21%)
Sex				
Male	230 (54%)	248 (58%)	258 (56%)	294 (61%)
Female	196 (46%)	181 (42%)	200 (44%)	187 (39%)
Race				
Black, of African heritage	59 (14%)	52 (12%)	69 (15%)	74 (15%)
White	349 (82%)	353 (82%)	336 (73%)	343 (71%)
Other	18 (4%)	24(6%)	53 (12%)	64 (13%)
US vs. International				
US	306 (72%)	316 (74%)	287 (63%)	310 (64%)
Non-US	120 (28%)	113 (26%)	171 (37%)	171 (36%)
Medical/Surgical Conditions Directly Associated with cSSSI [1]				
Recent trauma	115 (27%)	125 (29%)	59 (13%)	65 (14%)
Diabetes mellitus	109 (26%)	109 (25%)	113 (25%)	118 (25%)
Bite	33 (8%)	50 (12%)	34 (7%)	34 (7%)
Recent surgical procedure	37 (9%)	42 (10%)	58 (13%)	48 (10%)
Peripheral vascular disease	42 (10%)	28 (7%)	33 (7%)	49 (10%)
Chronic skin disease	34 (8%)	25 (6%)	25 (5%)	44 (9%)
Chronic edema	21 (5%)	20 (5%	21 (5%)	32 (7%)
Other	74 (17%)	66 (15%)	61(13%)	73 (15%)
Description of cSSSI				
Major Abscess	179 (42%)	193 (45%)	196 (43%)	204 (42%)
Deep/Extensive Cellulitis	156 (37%)	161 (38%)	153 (33%)	176 (37%)
Wound Infection	72 (17%)	60 (14%)	67 (15%)	61 (13%)
Infected Ulcer	16 (4%)	12 (3%)	29 (6%)	36 (7%)
Infected Burn	3 (<1%)	3 (<1%)	13(3%)	6 (1%)
Baseline Creatinine Clearance (ml/min)				
>80	274 (64%)	291 (68%)	279 (61%)	286 (60%)
>50-80	85 (20%)	85 (20%)	112 (24%)	118 (25%)
30-15	41 (10%)	35 (8%)	32 (7%)	45 (9%)
<30	21 (5%)	12 (3%)	17 (4%)	16 (3%)
Missing	5 (1%)	6 (1%)	18 (4%)	16 (3%)

[1] Counts (and percentages) represent the number (percentage) of patients with each medical condition.
Source: CSR, Tables 8-3, 8-4, 8-5, 8-7, and 8-8 excluding Sites 38091, 37004, and 38020 from Study 0018

Noninferiority Margin

A major statistical issue was the size of the noninferiority margin used in the two Phase 3 studies. This topic was discussed at the November 18, 2008 meeting of the AIDAC. The AIDAC members felt that a 10% margin was a reasonable compromise as long as major abscesses are excluded and there are safety, cost, and/or antimicrobial benefits associated with the test product. The Agency also found that a 10% noninferiority margin for cSSSI was justifiable (see Appendix A-1) but did not exclude major abscesses.

Primary Analyses

Table 2: Clinical Success Rates at TOC in Post-Amendment Patients

	Applicant Analyses			FDA Analyses		
Population	**Telavancin n/N % **	**Vancomycin n/N % **	**Difference[2] % (95% CI[3])**	**Telavancin n/N % **	**Vancomycin n/N % **	**Difference[2] % (95% CI[3])**
All Treated						
Study 0017	323/426 (75.8)	321/429 (74.8)	1.0 (-4.8, 6.8)	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)
Study 0018 [1]	358/458 (78.2)	364/481 (75.7)	2.5 (-2.9, 7.9)	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
Clinically Evaluable						
Study 0017	304/346 (87.9)	302/349 (86.5)	1.3 (-3.6, 6.3)	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)
Study 0018 [1]	327/368 (88.9)	334/371 (90.0)	-1.2 (-5.6, 3.3)	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)

[1] Excluded patients from Sites 38091, 37004, and 38020
[2] Difference is (telavancin – vancomycin)
[3] 95% CI calculated using a continuity correction

For Study 0017, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 1.0% with a corresponding 95% CI of (-4.8%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 1.0% with a corresponding 95% CI of (-5.3%, 7.2%) for the AT population. In the other co-primary analysis of the CE population, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 1.3% with a corresponding 95% CI of (-3.6%, 6.3%) while the Agency analysis found a similar result with a treatment difference of 1.5% with a corresponding 95% CI of (-4.3%, 7.3%).

For Study 0018, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of 2.5% with a corresponding 95% CI of (-2.9%, 7.9%) while the Agency analysis found a similar result with a treatment difference of 0.7% with a corresponding 95% CI of (-5.1%, 6.5%) for the AT population. In the other co-primary analysis of the CE population, the Applicant's analysis found a treatment difference (Telavancin – Vancomycin) of -1.2% with a corresponding 95% CI of (-5.6%, 3.3%) while the Agency analysis found a similar result with a treatment difference of -3.8% with a corresponding 95% CI of (-9.2%, 1.5%).

Thus, using a noninferiority margin of 10%, the Applicant was able to demonstrate the noninferiority of telavancin to vancomycin in both co-primary analysis populations for the two

Phase 3 studies. This was consistent for both the Applicant's analyses and the Agency's analyses.

As a sensitivity analysis, major abscesses were removed from the analysis as AIDAC had suggested. Major abscesses constituted 43.5% (372/458) of the AT patients in Study 0017 and 42.6% (400/939) of the AT patients in Study 0018. The results of these analyses are provided in Table 3.

Table 3: Clinical Success at TOC in Post-Amendment Patients Excluding Major Abscesses

	FDA Analyses			FDA Analyses Excluding Patients w/Major Abscesses		
Population	**Telavancin Success n/N %**	**Vancomycin Success n/N %**	**Difference (telavancin – vancomycin) % (95% CI[2])**	**Telavancin Success n/N %**	**Vancomycin Success n/N %**	**Difference (telavancin – vancomycin) % (95% CI[2])**
All Treated						
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)	176/247 (71.3)	166/236 (70.3)	0.9 (-7.6, 9.4)
Study 0018 [1]	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)	159/195 (81.5)	153/192 (79.7)	1.8 (-6.5, 10.2)
CE						
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)	196/262 (74.8)	208/277 (75.1)	-0.3 (-7.8, 7.4)
Study 0018 [1]	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)	169/205 (82.4)	188/215 (87.4)	-5.0 (-12.3, 2.3)

[1] Excluded patients from Sites 38091, 37004, and 38020
[2] 95% CI calculated using a continuity correction

When major abscesses are excluded, telavancin was noninferior to vancomycin in both co-primary populations for Study 0017 and for the AT population in Study 0018 using a 10% NI margin. In the other co-primary population for Study 0018, the CE population, the difference (telavancin – vancomycin) in success rates was -5.0% with a 95% CI of (-12.3, 2.3) and thus did not demonstrate noninferiority of telavancin to vancomycin using a 10% NI margin. In this analysis, the exclusion of patients with major abscesses increased the point estimate of the difference between the two groups from -3.8% to -5.0%. This was similar to the effect on the point estimate for the CE population in Study 0017 as well. However, because the two rates were more similar in Study 0017, this did not result in the lower confidence bound being lower than -10% for CE population as it did in Study 0018.

It should be noted that CE population in Study 0018 had low power to demonstrate noninferiority assuming the observed rates are the actual rates, this study had only 29% power to demonstrate noninferiority of telavancin to vancomycin using a 10% noninferiority margin. Alternatively, if one assumes that the response rates for both groups are those observed for vancomycin, i.e. 87.4%, then the study has 86% power to demonstrate noninferiority using a 10% margin

Efficacy in Patients with MRSA Isolated at Baseline

Table 4: Clinical Success at TOC in All-treated patients with MRSA at baseline (Post-Amendment)

Population	Telavancin Success n/N (%)	Vancomycin Success n/N (%)	Difference[2] (telavancin – vancomycin) % (95% CI)
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018 [1]	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
Pooled [1] (0017 + 0018)	227/301 (75.4)	242/323 (74.9)	0.9 (-5.8, 7.6) p-value 0.18

[1] Excluded patients from Sites 38091, 37004, and 38020
[2] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights.
p-value is a two-sided Mantel-Haenszel test based on a stratified analysis by study.

As it was the Applicant's objective to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population has been demonstrated, the discussion of these results will follow. The analysis plan was to pool data across Studies 0017 and 0018 to perform the analyses. The results of the two studies were not found to be substantially dissimilar (FDA Analysis: Breslow-Day statistic=1.81, p=0.18) so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses.

In AT patients with MRSA isolated as a pathogen at baseline, the Applicant failed to demonstrate that telavancin was superior to vancomycin (p=0.18) in clinical response at TOC (see Table 4).

The analysis of the efficacy of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) was examined to demonstrate that the potential advantages in the MRSA subpopulation are not observed at the detriment of the complementary subpopulation. In this subpopulation, the response rates in the two treatment groups were similar. However, since there was no evidence of the superiority of telavancin to vancomycin, the analysis of the MRSA-complement is less critical.

Decreased relative efficacy of telavancin compared to vancomycin for patients with renal impairement

This finding was noted in the review of the initial submission and was one of the issues included in the approvable letter.

To address this issue, the Applicant investigated the data and found no consistent, persuasive statistical evidence that treatment with telavancin is inferior to vancomycin in the patient subgroups identified above (Studies 0017 and 0018). Further analysis of the clinical data suggested that imbalances in baseline characteristics and medical conditions were more influential than the factors identified in the simple logistic regression subgroup analyses."

We have also looked at the patients who were clinical failures stratified by baseline renal function and could not find a consistent pattern as to why there was a higher proportion of clinical failures in the telavancin group compared to the vancomycin group.

Table 5: Subgroup Analyses in the CE Population (Post-Amendment)

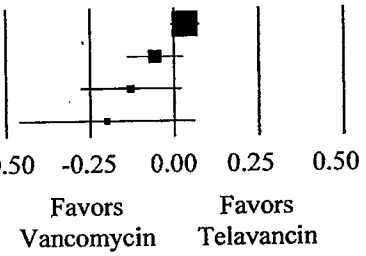
	Telavancin[1] % (n/N)	Vancomycin[1] % (n/N)	Difference [2] (TLV-Comparator) (95% CI)
US/Non-US			
US	394/472 (83.5)	403/486 (82.9)	0.6 (-4.2, 5.3)
Non-US	197/231 (85.3)	200/221 (90.5)	-5.3 (-11.2, 0.7)
Age			
<65 years	503/581 (86.6)	492/570 (86.3)	0.2 (-3.8, 4,1)
≥65 years	88/122 (72.1)	111/137 (81.0)	-8.6 (-19.1, 1.8)
History of Diabetes			
Diabetes	128/167 (76.5)	146/183 (79.8)	-3.2 (-11.8, 5.4)
No diabetes	462/535 (86.4)	457/524 (87.2)	-0.8 (-4.9, 3.2)
Baseline Creatinine Clearance			
> 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
> 50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
< 30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)
Wound type			
Major Abscess	263/303 (86.8)	262/300 (87.3)	-0.5 (-5.9, 4.8)
Wound Infection	87/108 (80.6)	83/96 (86.5)	-5.8 (-15.9, 4.4)
Deep/Extensive Cellulitis	199/240 (82.9)	227/273 (83.2)	-0.2 (-6.7, 6.3)
Infected Ulcer	30/40 (75.0)	25/31 (80.6)	-6.2 (-25.8, 13.5)
Infected Burn	12/12 (100)	6/7 (85.7)	9.8 (-5.9, 25.6)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018
[2] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights

There was a significant difference (decrease) in clinical response rates between patients with baseline renal impairment treated with telavancin compared to those treated with vancomycin. Patients with progressive degrees of baseline renal impairment had a greater decline in clinical response rate when treated with telavancin (see Figure 1). This decline in clinical response rate seen with telavancin treatment in patients with progressive levels of baseline renal impairment is of some concern. However, conclusions regarding this finding are limited by the exploratory nature of the post hoc analyses of subgroups and small numbers. A similar pattern of decrease in clinical response rates was seen in older patients treated with telavancin while clinical response rates in patients treated with vancomycin did not decrease. The decline in response rates may be related to decreased efficacy in older patients, since aging is correlated with a decline in creatinine clearance. The decrease in apparent response rates may be related to the failure to adjust (increase) the telavancin dose in response to improving renal function.

Figure 1: Clinical Response at TOC in the FDA CE Population for Studies 0017 + 0018 -- By Baseline Renal Impairment

Baseline Creatinine Clearance (ml/min)	Cures / Total (%)	
	Telavancin	Vancomycin
>80	403/451 (89)	394/458 (86)
>50-80	130/164 (79)	142/167 (85)
30-50	43/62 (69)	51/62 (82)
<30	15/25 (60)	16/20 (80)



Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

In the 10/19/07 approvable letter, the following deficiencies that are related to subgroup analyses were identified: benefit to risk ratio of the drug product is in question because of the following: a) decreased efficacy in clinical cure rates were noted to occur in patients with decreased baseline creatinine clearance, b) relative to vancomycin, decreased efficacy in clinical cure rates was noted to occur in patients with increasing age.

To address this issue, the investigated the data further and found "no consistent, persuasive statistical evidence that treatment with telavancin is inferior to vancomycin in the patient subgroups identified above (Studies 0017 and 0018). Further analysis of the clinical data suggested that imbalances in baseline characteristics and medical conditions were more influential than the factors identified in the simple logistic regression subgroup analyses."

We also looked at the patients who were clinical failures stratified by baseline renal function and could not a consistent pattern as to why there was a higher proportion of clinical failures in the telavancin group compared to the vancomycin group.

Efficacy by Baseline Pathogen

Clinical response at TOC in the MAT and ME populations broken down by baseline pathogen are presented for both treatment arms in Table 6and Table 7 respectively. The results are presented by individual study and pooled across Studies 0017 and 0018. The pathogens presented are those the Applicant is pursuing in their label. In the pooled analyses, clinical response rates are similar across treatment groups for patients with either MRSA or MSSA isolated at baseline in the MAT and ME populations. These two pathogens, MRSA and MSSA, are the most common pathogens isolated at baseline. The small sample sizes for the other pathogens makes it difficult to make a meaningful interpretations.

Table 6: Clinical response at TOC in the Microbiological All-treated Population (Post-Amendment) by Baseline Pathogen

Pathogen	Study 0017		Study 0018 [1]		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	92/135 (68.2)	110/151 (72.8)	134/166 (80.7)	132/172 (76.7)	226/301 (75.1)	242/323 (74.9)
Staphylococcus aureus, MSSA	77/96 (80.2)	67/89 (75.3)	66/89 (74.2)	76/111 (68.5)	143/185 (77.3)	143/200 (71.5)
Enterococcus faecalis	14/15 (93.3)	12/17 (70.6)	11/14 (78.6)	18/25 (72.0)	25/29 (86.2)	30/42 (71.4)
Streptococcus pyogenes	9/10 (90.0)	9/11 (81.8)	7/11 (63.6)	12/17 (70.6)	16/21 (76.2)	21/28 (75.0)
Streptococcus agalactiae	8/10 (80.0)	4/6 (66.7)	7/11 (63.6)	12/14 (85.7)	15/21 (71.4)	16/20 (80.0)
Streptococcus anginosus group	8/10 (80.0)	5/6 (83.3)	6/10 (60.0)	7/9 (77.8)	14/20 (70.0)	12/15 (80.0)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

Table 7: Clinical response at TOC in the Microbiological All-treated Population (Post-Amendment) by Baseline Pathogen

Pathogen	Study 0017		Study 0018 [1]		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)	208/239 (87.0)	225/262 (85.9)
Staphylococcus aureus, MSSA	71/82 (86.6)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)	132/161 (82.0)	131/154 (85.1)
Enterococcus faecalis	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81.0)	22/23 (95.6)	28/35 (80.0)
Streptococcus pyogenes	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)	16/19 (84.2)	19/21 (90.5)
Streptococcus agalactiae	8/9 (88.9)	3/3 (100.0)	6/10 (60.0)	10/12 (83.3)	14/19 (73.7)	13/15 (86.7)
Streptococcus anginosus group	7/8 (87.5)	5/5 (100.0)	6/9 (66.7)	4/4 (100.0)	13/17 (76.5)	9/9 (100.0)

[1] Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

APPENDICES

A-1: Agency Approach to the Justification of Non-Inferiority Margin for the Treatment of Complicated Skin and Skin Structure Infections

Background

Skin and skin structure infections are common and encompass a wide variety of disease presentations and severity. Complicated skin and skin structure infections (cSSSI) include infected ulcers, burns, and major abscesses and infections of deeper soft tissues. Infections such as necrotizing fasciitis, secondarily infected atopic dermatitis or eczema, ecthyma gangrenosum in neutropenic patients or infections involving prosthetic materials (e.g., catheter tunnel infections) are usually not included in the primary clinical studies supporting the approval of a new agent.[1] The majority of skin infections are caused by Gram positive organisms such as *Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus agalactiae.* All recent registrational trials for the indication of cSSSI have been non-inferiority trials with a non-inferiority margin of 10-15%. Treatment guidelines recommend antibacterial agents for the treatment of skin and soft-tissue infections, the choice of antibacterials is based on the nature and severity of infection and susceptibility patterns.[2]

FDA issued draft guidance on the use of active-controlled non-inferiority studies for approval of anti-bacterial agents in October, 2007, to articulate FDA's thinking regarding appropriate clinical study designs to evaluate antibacterial drugs (Appendix). This document outlines the steps taken by the Agency to estimate the treatment effect of antibacterials in the treatment of cSSSI and to justify an appropriate non-inferiority (NI) margin.

The first step in determining an appropriate NI margin is reliable estimation of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M1, based on placebo-controlled studies). In the absence of data from placebo-controlled studies, this determination is often based on data available from treated versus untreated disease. To protect from drawing false conclusions from an NI study, it is important to discount (or reduce) the magnitude of the treatment effect based on previous data to account for trial-to-trial variability, untestable constancy assumptions, and for other uncertainties. The second step involves clinical judgment regarding how much of the estimated treatment effect (M1) should be preserved in determining a clinically acceptable NI margin, referred to as M2.

As no data from placebo-controlled studies in cSSSI are available, results from comparative clinical trials of treated versus standard-of-care, and from observational studies in patients treated with antibacterial agents or with no specific therapy were reviewed to estimate the treatment effect of antibacterials in cSSSI. Direct extrapolation of treatment effect from historical studies to contemporary cSSSI trials is problematic. The historical studies do not meet the standards of present clinical trials in terms of randomization and blinding. Additionally, differences in patient populations and microbiologic characteristics of the causative micro-organisms make direct comparisons difficult. Several of the historical studies specifically addressed patients with bacteremia or severe streptococcal infections often in the setting of war

wounds. Such patients are generally excluded from clinical trials and hence direct applicability of those data to determining an NI margin is limited.

Based on review of the data discussed in the following sections, the Agency believes that non-inferiority trials are acceptable for the indication of cSSSI, provided that appropriate patient populations are enrolled and acceptable endpoints are assessed.

Approach in determining the NI margin

The following steps were followed by the Agency in justifying an appropriate non-inferiority margin for cSSSI:

1. Estimate historical evidence for sensitivity to drug effect in cSSSI
2. Evaluate constancy of the treatment effect: Validity of the assumption that current treatment effect of the active control is similar to the effect seen in historical studies
3. Review other supportive evidence for antibacterial treatment effect in skin and skin structure infections
    - Treatment effect in uncomplicated skin and skin structure infections (uSSSI) such as impetigo and skin abscesses
    - Dose-ranging studies
    - Use of prophylactic antibacterials to prevent wound infections
    - Outcomes in patients who received discordant therapy based on *in vitro* susceptibility results
4. Review of contemporary cSSSI trials
5. Review of contemporary uSSSI trials
6. Estimation of NI margin

Historical evidence for sensitivity to drug effect (HESDE) in cSSSI

1. Placebo-controlled trials in cSSSI:

No placebo controlled studies were identified, likely due to the reduction in mortality observed since the introduction of sulfonamides and penicillins compared to observed mortality in natural history studies from the pre-antibiotic era.

2. Treated vs. standard of care

Two studies were identified that compared outcomes in patients treated with sulfonamides to those treated with ultra-violet (UV) light. Both studies were conducted by the same authors under very similar conditions. These studies are summarized below:

1. Snodgrass WR and Anderson T (BMJ 1937)[3]: Cases of erysipelas were studied from middle of May 1936-middle February 1937 in Ruchill Hospital Glasgow. All groups were treated under similar conditions. The wards and nursing staff were common to both groups. Each case was reviewed daily. Duration of disease before admission to hospital, age of the patient, severity of the infection, and associated diseases were similar in the two groups. The authors report that these factors were evaluated by a statistician who felt that weighting either line of treatment by any of these factors was not needed. The

authors note that 49 cases were "severe" and that in 5 cases in the prontosil group, the condition was so severe that a fatal result would not have been unexpected. One patient in the UV group showed uncontrolled spread with high fever for 6 days and was in a typhoid state when prontosil was used and the patient's recovery was completely unexpected.

Methods: The first 161 cases were allocated to 3 groups in order of admission: Group 1- UV light only, Group 2 Prontosil only and Group 3 UV light plus prontosil. The second 151 cases were divided into 3 groups, the first two were same as above and the third was treated with scarlet fever antitoxin. Six cases were removed from the series as the diagnosis was questionable. The number of cases per group was as follows: UV light alone-104, Prontosil alone-106, UV light+Prontosil-54, and antitoxin alone-48.

Treatments: Treatments were given during the acute stage only, and was not maintained after the subsidence of the local lesion and cessation of fever and toxemia. No other local treatment was given to any case. UV light was administered at a distance of 12" and was given for 8 minutes in females and 10 minutes in males, once daily. Treatment was repeated at 24 hr intervals if considered necessary. Average number of exposures was 2.6. Prontosil was administered orally as 1, 2, or 3 tablets of 0.3 g each every 4 hours; 10 patients received intramuscular (IM) prontosil, six of whom also received oral therapy. The average dose was 5 g (range 1.2-15 grams).

Results: Patients who died [n=15, 5 each in the UV group and prontosil group (1 had failed UV light), 1 in UV+Prontosil group and the 4 in anti-toxin group] were excluded, so the total number of cases in the series was 297.The fatal cases were not directly related to worsening erysipelas. However, some were bacteremic/ had other foci of streptococcal infection such as meningitis and empyema. In some there was no clear cause of death as post-mortem was not performed.

The following two tables summarize the results of this study for two endpoints, cessation of spread of lesion and resolution of fever. The authors had also provided results for resolution of toxemia. As the definition of toxemia (prostration, headache, state of the tongue, insomnia, vomiting, abdominal distension, and delirium) was subjective, the results are not included here.

The proportion of cases that showed no spread of the lesion after the end of the first day was 58/98 (59%) in the UV group and 84/102 (82%) in the prontosil group. After two days in the hospital, the lesion continued to spread in only 2% (2/102) of all prontosil cases compared to 23/98 (23%) for the UV group. The number and percentage of patients who had resolution of the spread of the lesion by day of treatment in the UV light and prontosil groups are summarized in the following table:

Table 1: Cessation of spread of lesion

Treatment	0 days N (%)	1 day N (%)	2 days N (%)	3 days N (%)	4 days N (%)	5 days and more N (%)	Total
UV light	32 (32.7)	26 (26.5)	17 (17.3)	11 (11.2)	5 (5.1)	7 (7.1)	98
Prontosil	48 (47)	36 (35.3)	16 (15.7)	1 (1)	1 (1)	0	102

After 48 hrs of treatment, 43/89 (48%) of patients in the UV group were afebrile compared to 70/72 (76%) in the prontosil group. As some patients did not have pyrexia at admission they were excluded from the denominators. The number and percentage of patients who had resolution of fever by day of treatment in the UV light and prontosil groups are summarized in the table 2:

Table 2: Resolution of primary pyrexia

Treatment	1 day N (%)	2 days N (%)	3 days N (%)	4 days N (%)	5 days and more N (%)	Total with Fever
UV light	16 (18)	27 (30.3)	12 (13.5)	11 (12.4)	23 (25.8)	89
Prontosil	37 (40.2)	33 (35.9)	14 (15.2)	2 (2.2)	6 (6.5)	92

Treatment difference between the prontosil group and the UV group for the endpoints of cessation of spread of lesion and resolution of pyrexia 48 hours after institution of treatment are provided in the following table:

Table 3: Assessment at 48 hrs

Endpoint	Prontosil	Ultra-violet	Treatment difference (95% CI)
Cessation of spread of lesion	100/102 (98.0%)	75/98 (76.5%)	21.5% (11.7%, 31.3%)
Resolution of pyrexia	70/92 (76.1%)	43/89 (48.3%)	27.8% (13.1%, 42.4%)

2. Snodgrass and Anderson (BMJ 1937)[4]: As the previous study had demonstrated benefit of prontosil in the treatment of erysipelas and there was evidence that prontosil was converted in the body to sulphanilamide, Snodgrass and Anderson conducted the second study with the following objectives: To evaluate the benefits of sulphanilamide in the treatment of erysipelas, to investigate the effects of a larger and more prolonged dosage and to investigate the effect of varying dosage of sulphanilamide during the first 12 hours.

Methods: All cases from middle of February to middle of August 1937 were included. The cases were assigned to two treatment groups in the order of their admission. There was a total of 270 cases, 135 in each group; 12 cases originally in the UV light group were subsequently treated with sulphanilamide. Other than the specific treatments assigned, the two groups were comparable. The wards to which they were admitted and the nursing staff was common to all

cases. No other local treatment was given. Duration of illness before admission to hospital, age of the patient, severity of infection, and associated diseases were similar in the two groups.

Treatments: UV light was administered at a distance of 12" and was given for 8 minutes in females and 10 minutes in males, once daily. Treatment was repeated at 24 hr intervals if considered necessary. Average number of exposures was 1.4.

Sulphanilamide was given orally in a powder form as 1, 2, or 3 gram doses at 4 hourly intervals and was continued until temperature became normal. The average duration of this treatment was 2. 5 days and the average dose was 14.64 grams. Thereafter 0.75 grams was given three times a day until patient left the hospital. The average stay in the hospital was 14.4 days.

Results: Five deaths in the sulphanilamide group and one death in the UV light group were excluded from the analyses. In addition 12 patients who failed UV light and were switched to sulphanilamide (9 of whom recovered) were also excluded from the analyses. So, the total number of cases in the sulphanilamide group was 130 and in the UV light group was 122. In the sulphanilamide group 11 patients (8.1%) developed septic complications directly attributable to erysipelas compared to 28 patients (20.7%) in the UV light group.

The following two tables summarize the results of this study for two endpoints, cessation of spread of lesion and resolution of fever. The authors have also provided results for resolution of toxemia. As the assessment of toxemia was subjective, the results are not included here.

The proportion of cases which showed no spread of lesion after the end of the first day was 126/130 (96.9%) in the sulphanilamide group and 72/122 (59%) in the UV light group. After two days in the hospital, the lesions continued to spread in 1/130 (0.8%) of sulphanilamide treated cases and in 33/122 (27%) of the UV light treated patients.

The number and percentage of patients who had resolution of the spread of the lesion by day of treatment are summarized in the following table:

Table 4: Cessation of spread of lesion

Treatment	0 days N (%)	1 day N (%)	2 days N (%)	3 days N (%)	4 days N (%)	5 days and more N (%)	Total
Sulphanilamide	78 (60)	48 (36.9)	3 (2.3)	1 (0.8)	-	-	130
UV light	48 (39.3)	24 (19.7)	17 (14)	12 (10)	14 (11.5)	7 (5.7)	122

After 48 hrs of treatment, 53/112 (47.3%) patients in the UV light group were afebrile compared to 94/125 (75.2%) in the sulphanilamide group. Pyrexia continued for more than three days in 12/125 (9.6%) sulphanilamide treated cases compared to 45/112 (40%) in the UV light treated group. As some patients did not have pyrexia at admission they were excluded from the denominators. The number and percentage of patients who had resolution of fever by day of treatment are summarized in the following table:

Table 5: Duration of primary pyrexia

Treatment	0 days N (%)	1 day N (%)	2 days N (%)	3 days N (%)	4 days N (%)	5 days and more N (%)
Sulphanilamide	5	48 (38.4)	46 (36.8)	19 (15.2)	9 (7.2)	3 (2.4)
UV light	10	28 (25)	25 (22.3)	14 (12.5)	10 (8.9)	35 (28.7)

Treatment difference between the sulphanilamide group and the UV group for the endpoints of cessation of spread of lesion and resolution of pyrexia 48 hours after institution of treatment are provided in the following table:

Table 6: Assessment at 48 hrs

Endpoint	Sulphanilamide	Ultra-violet	Treatment difference (95% CI)
Cessation of spread of lesion	129/130 (99.2%)	89/122 (73.0%)	26.3% (17.5%, 35.1%)
Resolution of pyrexia	94/125 (75.2%)	53/112 (47.3%)	27.9% (15.1%, 40.7%)

For the two endpoints of cessation of spread of lesion and proportion with apyrexia, a meta-analysis using a random-effects model was performed. The results are shown below:

Meta-analysis for cessation of spread of lesion

Figure 1 shows the results of a DerSimonian and Laird random effects meta-analysis for the endpoint of cessation of spread of lesion at 48 hours for the two studies described above. The meta-analysis reveals that the overall antibacterial treatment effect with sulfonamides for the clinical endpoints of cessation of spread of lesion was 24.1% (95% CI, 18.2%, 30.0%).

Figure 1: Meta-analysis for cessation of spread of lesion at 48 hours

Study name	Risk difference	Standard error	Lower limit	Upper limit
Prontosil	0.215	0.045	0.127	0.303
Sulphanilamide	0.263	0.041	0.183	0.343
Overall	0.241	0.030	0.182	0.300

-0.35 -0.18 0.00 0.18 0.35

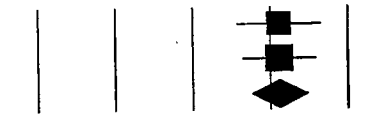
Favors UV Favors S/P

Meta-analysis for resolution of pyrexia

Figure 2 shows the results of a DerSimonian and Laird random effects meta-analysis for resolution of fever at 48 hours as an endpoint in the two studies described above. The meta-analysis reveals that the antibacterial treatment effect for sulfonamides for the clinical endpoint of resolution of fever was 27.8% (95% CI, 18.9%, 36.8%).

Figure 2: Meta-analysis for resolution of pyrexia at 48 hours

Study name	Risk difference	Standard error	Lower limit	Upper limit
Prontosil	0.278	0.069	0.142	0.413
Sulphanilamide	0.279	0.061	0.159	0.398
Overall	0.278	0.046	0.189	0.368



-0.50 -0.25 0.00 0.25 0.50

Favors UV Favors S/P

The results of the two random effects meta-analyses in patients with erysipelas demonstrate that there is a statistically significant difference for the clinical endpoints of cessation of lesion spread and resolution of fever at 48 hours with the use of sulfonamides compared to UV light. The treatment effect of sulfonamides compared to UV light in erysipelas for the endpoints of cessation of spread of lesion and/or the resolution of pyrexia was estimated to be 18% based on the lower bound of the 95% confidence intervals for the two meta-analyses discussed above. Using the lower bound of the 95% confidence interval is a conservative estimate of the

antibacterial treatment effect and discounts for some of the uncertainties and the associated variability in the estimate of treatment effect.

Other studies in erysipelas

Several historical studies were identified that compared UV light therapy to other topical therapies. [5-9] Most of these studies showed that patients treated with UV light had better outcomes in terms of resolution of local signs and fever. It was not possible to quantify the treatment effect of UV light over other local therapies from these studies because the proportion of patients who had complete resolution of signs and symptoms at a fixed time point was not reported. Only the average time to resolution was reported, which can be influenced by outliers. Results of some of the larger series are summarized here. These data support the assumption that the placebo cure rate estimated from patients with erysipelas who were treated with UV light is likely to be an overestimate of the true placebo effect.

1. Ude WH and Platou ES [7]. JAMA July 5, 1930: Four hundred and two cases of erysipelas treated in the department of contagious diseases at the Minneapolis General Hospital during the years 1922-1929 were summarized in this report. Data from a follow up publication with 68 additional cases of erysipelas treated with UV light are included in the last column[8]. Mortality, average time to resolution of symptoms and to resolution of fever was lower in UV light treated patients.

Table 7: Outcomes for different modalities of treatment in erysipelas

* The year 1924 was omitted due to the smallpox epidemic ¶ includes data from the follow up publication

2. Sutherland DS and Fay FM. The Medical Officer November 2, 1935[9].

A series of 90 cases of varying age and severity who were treated with UV light are described in this report. The majority of cases were elderly and debilitated and several were complicated by

other conditions. All cases were treated in one ward reserved for acute cases of erysipelas. In 60% of cases, only one treatment was given. The authors note that 6-12 hrs after exposure, the erysipelas lesion was surrounded by erythema and usually in 48 hrs both the erythema and erythematous swelling subsided and usually pain was also completely relieved. The irradiated area desquamated later. Patients treated with UV light had better outcomes compared to those treated with other local therapies as summarized in the following table:

Table 8: Comparison of outcomes in erysipelas patients treated with UV light

	UV light (n=90)	Other methods (n=90)
Average age of patients	40 years	38 years
Deaths	6 (6.6%)	9 (10%)
Average duration of pyrexia	60 hrs	108 hrs
Average stay in hospital	18 days	28 days
No. of relapses	12	10

Others: ichthyol, glycerine, iodine, magnesium sulfate, anti-streptococcal serum

3. Natural history studies

Most of these studies describe patients with various types of skin infections, several of whom were bacteremic or had severe disease such as necrotizing gangrene. In clinical trials, the proportion of patents with bacteremia is usually very low and patients with necrotizing gangrene are usually excluded. So, these studies are not directly relevant to the majority of patients enrolled in present day clinical trials. Also, most of these studies used mortality as an endpoint, while in contemporary clinical trials clinical outcome is the primary endpoint. However, these studies still provide evidence that untreated disease is often fatal and that in survivors is associated with significant morbidity. In the following section, these studies will be described briefly.

1. Meleney FL, Archives of Surgery, 1924[10]: This case series of 20 patients with hemolytic streptococcus gangrene provides one of the earliest descriptions of the clinical outcomes in untreated streptococcal gangrene. Seven patients were bacteremic. Four patients (20%) died (three were bacteremic) and the remainder had a very prolonged recovery. Most were preceded by a minor trauma, while in a few there was no obvious portal of entry. The author notes that within 24 hours, the local lesion enlarged significantly and was often accompanied by systemic symptoms and prostration. By the 4^{th}-5^{th} day, the area became frankly gangrenous and by day 7-10, the line of demarcation became sharply defined, dead skin separated and eventually healing set in. However, in the more severe cases, the process continued to advance and the patient became progressively more ill. Wound care consisted of incision and drainage, use of soaks and Dakins solution. Re-epithelialization took much longer and often grafting was done on an average by the fiftieth day.

2. Skinner and Keefer, Archives of Internal Medicine 1941[11] : This report described 122 cases of *S. aureus* bacteremia at Boston city Hospital. Only 22 patients recovered (fatality rate 82%). The portal of entry was skin (57), respiratory tract (30), bone (11), genitourinary tract (11), other/unknown (13). Of the 57 cases of skin infections, 30 had boils and carbuncles, 14 had infected wounds, and 14 had other lesions.

Of the 75 patients who received only general care, 63 (84%) died, while 33/42 (78.5%) who received general care plus sulfonamides died. In all 22 cases that recovered, the infection was localized into superficial abscesses with no deep infections. It is unclear as to how many of these patients were treated with sulfonamides. In 31 patients, the infection localized and an abscess formed that was amenable to surgical treatment. In this group, mortality was 29%.

3. Keefer CS, Ingelfinger FJ, Spink WW 1937[12]: This is a series of 246 cases of hemolytic streptococcal bacteremia; 61 had cellulitis/erysipelas. The overall mortality was 72%, with the highest (49/61, 80%) mortality in those with cellulitis and erysipelas irrespective of age.

4. Uncontrolled studies

A series of articles have been published describing the clinical response seen in patients with various types of surgical infections, including skin and soft tissue infections who were treated with penicillins or sulfonamides. Most of these studies were uncontrolled and are only discussed briefly. The study by Florey conducted in patients with hand infections is described in greater detail as the types infections studied are fairly representative of the types of infections seen in patients enrolled in current cSSSI trials. Also, as the surgical procedures were standardized between the two groups, it is likely that treatment effect seen with penicillin represents an antibacterial effect beyond that achieved by the surgical procedure alone.

Studies that evaluated use of penicillin

1. Florey et al. Lancet 1944[13]

This was a study of local application of penicillin driven primarily by the limited availability of penicillin. Hand infections were chosen as they were common, caused permanent disability and considerable loss of working time. In this comparative study of 212 cases of acute hand infections, half were treated with current methods and the other half by local penicillin application in addition to the usual surgical procedures. The authors state that "*the great majority of control cases remained septic for over a week and nearly 3/4^{ths} were infected till their wounds healed. In penicillin treated cases, sepsis by clinical and bacteriologic criteria was eliminated within a week, pus was scanty, and relief of pain and improvement in general condition was striking.*"

Alternate cases were treated with penicillin. Observations were made at operation and daily in the acute phase and twice a week after that. Patients were followed for up to 6 months after surgery. The same team operated on both the penicillin treated and control patients. Post-operative care of outpatients in both series was provided by one investigator. Control patients received various local applications and some received sulfonamides by mouth.

Treatments

Controls: Wounds were packed with paraffin gauze at operation and later with eusol preparations. As wounds became superficial, topical sulfonamide or gentian violet was sometimes applied.

Penicillin: At operation, the wounds were powdered with the calcium salt of penicillin and packed with gauze soaked in penicillin paste. Treatment was usually given for a week.

Other treatments: Oral sulfonamides were used in the more severe control cases and in 3 of the penicillin cases.

Table 9: Summary of cases based on site of infection

Site of infection	Control	Penicillin-treated
Paronychia	26	26
Pulp infection	27	28
Web-space infection	9	9
Tendon sheath infection	11	11
Miscellaneous abscesses	12	12
Septic lacerations	5	6
Miscellaneous lesions	12	18
Total	102	110

These reflect numbers treated, follow up was not available for all patients so numbers in the descriptions may differ

Group A Streptococci and *S. aureus* were the most common organisms identified. Others included micrococci, other hemolytic streptococci, and coliforms. The initial infecting organisms were as follows:

Table 10: Initial infecting organisms

Group	*S. aureus*	*S. pyogenes*	Both	Other hem strep	Micrococci	Coliforms	Total
Controls	74	6	21	0	1	0	102
Penicillin	66	13	27	1	2	1	110

Following is a summary of the cases by infection type:

Paronychia

There were 21 controls and 22 cases of paronychia. Duration of symptoms was 1 day- 6 weeks. Infections were due to *S. aureus* or *S. pyogenes*. There was little evidence of pus in both groups, hence drying was considered an adequate criterion to assess efficacy. The mean days to drying in the penicillin group was 15.5 ± 8.2 days and in the control group was 7.7 ±3.2 days (difference 7.8±2.6).

Simple pulp infections

This group was confined to deep infections of the soft tissues of the pulp, all subcutaneous abscesses were excluded. Six penicillin cases and 4 controls had osteitis and were excluded from the analysis.

Table 11: Outcomes in patients with simple pulp infections

	Days to disappearance of pus (21 controls, 22 cases) Mean±SD	Dry (23 controls, 22 controls) Mean±SD	Epithelialised (19 controls, 20 cases) Mean±SD	Full movement (22 controls, 19 cases) Mean±SD
Control	14.2 ± 12.8	20.7 ± 13.0	29.7 ± 13.5	25.7 ± 19.5
Penicillin mean±SD	1.4 ± 2.7	10.8 ± 4.8	21.7 ± 8.7	11.7 ± 4.3
Difference mean±SD	12.8 ± 2.9	9.9 ± 2.9	8.0 ± 3.7	14.0 ± 4.3

In addition to the difference in days to resolution of signs and symptoms noted above, there was difference in between the two groups in duration of pain and throbbing.

Web-space infections

One control case received oral sulphathiazole after surgery. There was one case of thenar infection in each group and one control and 3 penicillin cases had two spaces affected. As shown in table 12, penicillin-treated patients had better outcomes.

Table 12: Outcomes in patients with web-space infections

	Days to disappearance of pus (9 controls, 9 cases) Mean±SD	Full movement (9 controls, 9 cases) Mean±SD	Healed (9 controls, 9 cases) Mean±SD
Control	15.7 ± 16.0	24.7 ± 17.3	34.2 ± 20.3
Penicillin	3.6 ± 3.3	10.4 ± 8.3	18.8 ± 6.5
Difference	12.1 ± 5.3	14.3 ± 2.1	15.4 ± 7.1

Tendon-sheath infection

Patients with tenosynovitis that occurred as a complication in other groups and cases of suspected tendon-sheath infection that did not have evidence at operation of increased fluid or perforation of sheath by a septic sinus were excluded. Severity was judged based on type of fluid in sheath (clear, turbid, or frankly purulent), condition of tendons and extension into other spaces. Six penicillin cases and 4 controls were severe. Five controls received oral sulphonamide, 4 post operatively and one pre-operatively. One penicillin treated patient who had lymphangiitis and lymphadenitis received sulphanilamide for two days before surgery.

The authors note that pus was copious in all controls and slough was a prominent feature while in the penicillin group it was always scanty. They also note that these patients were ill, had fever, loss of appetite, pain and often sleeplessness and if sepsis persisted, pallor and weight loss were obvious. Penicillin patients were fit enough to be asking to go home in the second week and apart from the painful dressings they appeared to recover rapidly and to suffer little pain. Clinical outcomes in the two groups are summarized in the following table:

Table 13: Outcomes in patients with tendon-sheath infections

	Disappearance of pus (10 controls, 11 cases) Mean±SD	Disappearance of fever (10 controls, 11 cases) Mean±SD	Healing (11 controls, 10 cases) Mean±SD
Control	40.4 ± 21.4	12.0 ± 8.8	58.9 ± 30.3
Penicillin	5.9 ± 5.8	3.7 ± 2.6	34.1 ± 18.6
Difference	34.8 ± 7.0	8.3 ± 4.0	24.8 ± 10.9

Abscesses

This series included well formed circumscribed abscesses, in various parts such as hand, forearm, axilla, groin, back of neck. Three-quarters of each series had received expectant treatment and in some resolution was already taking place. The authors stated that the value of drug was not likely to be great in this group of patients. Three patients received penicillin injection into abscess cavity. Healing time and, in some cases, cessation of pus was similar in the two groups. However, the amount of pus formed was much less in the penicillin group.

Table 14: Outcomes in patients with abscesses

	Days to disappearance of pus (12 controls, 12 cases) Mean±SD	Dry (12 controls, 12 cases) Mean±SD
Control	9.6 ± 7.8	23.6 ± 10.3
Penicillin	3.4 ± 1.8	20.8 ± 10.9
Difference	6.2 ± 2.8	2.8 ±0.17

Septic lacerations of hand

As clinically, the cases and controls were different, the authors did not compare clinical outcomes and only compared microbiologic outcomes. All cases were open suppurating wounds which involved more than one tissue.

2. Lyons C. JAMA 1943 [14]. In this series, both intravenous and intramuscular penicillin were used. Limited local treatment was also used. Overall, 49/57 (86%) of patients were improved. It appears that patients with abscesses had a higher cure rate compared to those with wound infections. The numbers of patients with the different types of skin infections were however very small. The following table summarizes the results seen in patients with skin and skin structure infections:

Table 15: Outcomes in patients with skin and skin structure infections

Diagnosis	Number	Improved	Died	No effect
Abscesses	12	11	0	1
Burns	2	1	1	0
Skin and subcutaneous tissue	12	11	0	1
Wound infections	21	17	0	4
Cellulitis	5	5	0	0
Erysipelas	1	1	0	0
Wound infections	2	1	0	1
Pyoderma	1	1	0	0
Cellulitis	1	1	0	0
Total	57	49	1	7

3. Garrod LP. BMJ 1943 [15]: This is an abstract of a report published by the War Office entitled "A preliminary report to the war office and the medical research council on investigations concerning the use of penicillin in war wounds carried out under the direction of Prof HW Florey and Brig. Hugh Cairns".

A total of 171 cases of recent soft- tissue wounds treated with penicillin were described. Most wounds were 3-12 days old, majority were infected, some were purulent and most were clinically dirty. All underwent immediate closure and penicillin was administered through tubes inserted at operation twice daily for 4 days. In some cases, penicillin powder was used. Results were as follows: 104/171 (60.8%) had complete union, 60/171 (35%) had subtotal union, i.e. healing by granulation and 7/171 (4%) failed.

4. Keefer CS et al. JAMA 1943 [16]: This report summarizes 500 cases of various types of infections treated with penicillin. Penicillin was administered IV, IM or locally. The amount of penicillin and frequency of administration varied. There were 91 patients with *S. aureus* bacteremia; 34/91 (37%) died. Of the patients with bacteremia, 10 had infections of the skin and subcutaneous tissues and all recovered. Of the 137 cases with local staphylococcal infections without bacteremia, 109 (80%) recovered or improved, 11 (8%) died, and in 17 (12%) there was no effect. Among the 23 patients with cSSSI in the non-bacteremic group, 19 greatly improved or recovered completely and 4 failed (1 had an abscess of the thigh, treated locally, 1 had extensive psoriasis with local staphylococcal infection, and one each had chronic sinus/ulcer).

5. Lockwood JS et al. Annals of Surgery 1944[17]: This is a summary of 440 medical and surgical cases treated with penicillin. Of the 57 cases of staphylococcic bacteremia, two thirds survived. The source of bacteremia was not specified in the cases. Only a few cases of boils/carbuncles were treated because of the likelihood of spontaneous recovery and shortage of penicillin supply. The author noted that checking the spread of cellulitis and localization of the suppurative focus usually occurred 2-3 days after commencing systemic therapy.

6. Meleney FL. Annals of Surgery 1946[18]: This report summarizes 744 cases of surgical infections including cases of skin infections treated with systemic or topical penicillin (438 systemic alone, 142 local alone, 164 both systemic and local). Outcomes were classified as follows:

Excellent- Cases responding abruptly/ definitely within first 72 hours of treatment
Good- Cases clearly showing the benefit of the drug but over a longer period of time, perhaps a week or ten days.
Questionable- Cases which might have done just as well without the drug as a result of the surgical procedure or some other associated treatment.
No effect- Cases in which infection was not altered in any way but ran its natural course.

Overall results were favorable in ~65% of penicillin treated cases and unfavorable in 35% as shown in the following table:

Table 16: Outcomes in patients with all types of surgical infections

Total number	Favorable			Unfavorable		
	Excellent	Good	Combined	Questionable	No effect	Combined
744	14.8 %	49.9 %	64.7 %	17.8 %	17.6 %	35.4 %

In the following table, the outcomes by diagnosis for 340 patients with skin and skin structure infections are presented. Cure rates varied by the infection type with the highest cure rates in patients with cellulitis and furuncles and the lowest rates in those with ulcers/ infected burn.

Table 17: Outcomes in patients by type of skin and skin structure infection

Diagnosis	Total cases (n)	Favorable %	Unfavorable %
Furuncle	26	92.3	7.7
Cellulitis	36	91.7	8.3
Carbuncle	28	82.2	17.9
Superficial abscess	32	81.3	18.8
Deep abscess	58	68.9	31.0
Infected soft part wound	37	64.8	35.1
Infected operative wound	70	61.3	38.6
Ulcer of the skin	22	50.0	50.0
Infected burn	31	45.2	54.8

Studies that evaluated use of other antibacterials

1. Long and Bliss. JAMA 1937 [19]: This is a summary of 19 cases treated with para-amino-benzene-sulfonamide and its derivatives. Cases were treated with parenteral (iv/sc) and oral therapy. Of the 7 cases of SSSI, all 5 with erysipelas recovered. Fever returned to normal in 24-60 hours and lesions disappeared rapidly. One patient was bacteremic with beta hemolytic streptococcus. In the one patient with chronic impetigo (3.5 months) who had resisted all therapy lesions improved after drug administration and culture was negative for beta hemolytic streptococcus in 4 days. The seventh patient had cellulitis, bacteremia due to beta hemolytic streptococcus and septicemia and died 9 hrs after first injection.

2. Keefer CS. NEJM 1938 [20]. In this report, nine cases of hemolytic streptococcal infection with bacteremia and 8 cases of localized infection without bacteremia were described. Of the 9 patients with bacteremia three had SSTI (2 cellulitis, one post-operative wound infection) and all of them survived. Of the eight cases of localized infection without bacteremia, 7 with puerperal sepsis and 1 with cellulitis were described; there were no deaths.

3. Kirby WMM. NEJM 1960[21]. In the 1950s, the role of vancomycin in the treatment of staphylococcal infections was evaluated. Several of these patients were bacteremic and some of them had localized staphylococcal infections. Kirby et al. evaluated vancomycin in 33 patients from 1957-1959. All patients except one had bacteremia. Overall, 20/33 (61%) patients were cured, 6 improved but died of underlying diseases and 7 were failures. Of the 20 patients with skin infections, 11 were cured and 4 had improved.

5. Historical evidence for sensitivity to drug effect (HESDE) in uSSSI

The placebo cure rates in impetigo were estimated from studies that compared topical/systemic therapy to placebo. Placebo success rates in simple cutaneous abscesses were assessed from studies that compared incision and drainage plus systemic antibacterials to incision and drainage alone.

Impetigo
Studies assessing topical therapy

1. Phase 3 clinical trial of Altabax (retapamulin ointment, 1%)[22]: Retapamulin is a topical antimicrobial, approved for the treatment of impetigo. This study was used to estimate the placebo success rate because it was conducted in a contemporary patient population. This was a randomized, double-blind, multi-center, placebo-controlled Phase 3 study in adult and pediatric subjects $\geq$ 9 months of age with impetigo. Topical retapamulin 1% BID was compared to placebo BID for 5 days in 210 (139 retapamulin and 71 placebo) adult and pediatric patients with a clinical diagnosis of primary bullous or non-bullous impetigo. Patients with a bacterial skin infection that due to depth or severity could not be treated by a topical antibiotic were excluded.

The primary endpoint was clinical response at the end of therapy (EOT) visit on Day 7. Clinical success was defined as the absence of lesions that had been treated, or if the treated lesions were dry, without crusts, and with or without erythema compared to baseline, or there was improvement (defined as a decline in the size of the affected area, number of lesions or both)

such that no further antimicrobial therapy was required. Success rates in the ITT population at the EOT visit were 119/139 (85.6%) for retapamulin and 37/71 (52.1%) for placebo. The treatment difference between the retapamulin and placebo group was 33.5% (95% CI, 20.5%-46.5%).

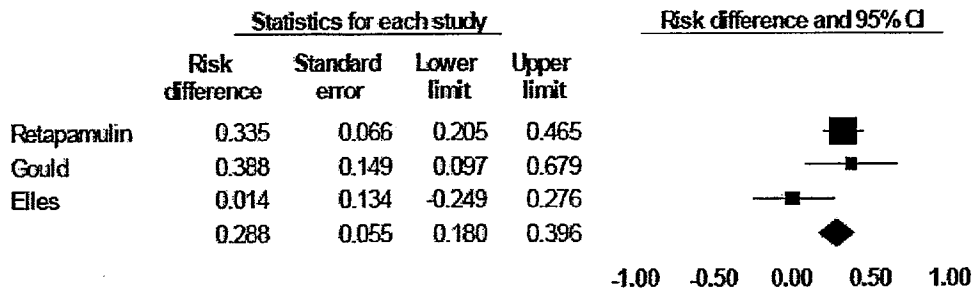
2. Eells LD. Arch Dermatol 1986 [23]: This was a randomized, double-blind, vehicle-controlled study comparing 2% mupirocin to vehicle (polyethylene glycol) in the treatment of impetigo/ecthyma. Fifty-two patients were enrolled and 27% of patients were subsequently not evaluable. Treatment was administered three times per day for 8±1 days. One patient in the vehicle group who had ecthyma was excluded from the ITT analysis. The ITT results for clinical success (Cure + Improvement) at the EOT visit were 17/26 (65.4%) in the mupirocin group and 16/25 (64.0%) in the vehicle group. It should be noted that 27% of the patients were unevaluable. The treatment difference between the mupirocin and vehicle group was 1.4% (-28.8%, 31.6%).

3. Gould PW. N Z Med J 1986 [24]: This was a randomized, double-blind, placebo-controlled study comparing mupirocin and placebo. One hundred seven (107) patients (54 mupirocin and 53 placebo) with acute primary skin infections, infected dermatoses, or infected traumatic lesions who had not received topical or systemic antibiotics during the preceding 3 days were enrolled in the study. The clinical success (Cure + Improvement) in the subgroup of patients with impetigo in the ITT population at the EOT visit were 12/17 (70.6%) in the mupirocin group and 7/22 (31.8%) in the placebo group. The treatment difference between the mupirocin and placebo group was 38.8% (4.4%, 73.1%).

4. Koning 2004 [25]: In a Cochrane review of interventions for impetigo, topical antibiotics showed better cure rates than placebo (pooled odds ratio (OR) 6.49, 95% CI, 3.93 to 10.73), and neither of the two topical antibiotic was superior to the other (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI 0.69 to 2.16).

Meta-analysis of topical studies
Using a fixed effects meta-analysis of the three topical antibacterial studies in impetigo described above, the antibacterial treatment difference compared to placebo in the ITT population was 28.8% (95% CI, 18.0%, 39.6%).

Figure 3: Meta-analysis of topical studies for uSSSI



Studies assessing systemic therapy

1. Burnett JW. NEJM 1962[26]: Eighty-nine outpatients with yellowish crusted skin lesions were studied from Jan-June 1961. They were randomly assigned to one of four groups- erythromycin propionate and wet dressings, erythromycin without wet dressings, placebo, or wet dressings. Of the 89 cases, 60 had impetigo and 29 had other skin infections (all had very purulent edematous, yellow exudates and had antecedent dermatologic conditions that had become secondarily infected). Patients were seen 3-4 days after starting therapy and at intervals of 3-4 days. There were no dropouts. When continual treatment did not occur, treatment was declared a failure and patients were given an alternate antibiotic. The gram stain was positive in 97.8% of patients, 75 (84.2%) had a positive culture for *S. aureus, S. pyogenes*, or both.

In the erythromycin group, the cure rate was 86.4% (38/44) and in the no-antibiotic group the cure rate was 24.4% (11/45). The treatment difference between the two groups was 61.9% (95% CI 43.5%, 80.3%). The average time to healing in the antibiotic group was 10 days and in the controls was 25 days.

2. Eaglstein WH. Arch Dermatol 1977[27]: Hospitalized patients with dermatitis considered secondarily infected based on wet, oozing, weeping appearance and crusts were included in this study. They were afebrile, had normal WBC and negative blood cultures. Patients were randomly assigned to cloxacillin 250 mg qid or placebo capsules for 7 days. All patients received tap water compresses. Each clinical feature was graded on a scale of 0-3.

Twenty-eight patients were studied over the three year period, 14 in each treatment group. The mean pre-treatment values for the clinical characteristics were similar in the two groups. The groups were also similar with respect to age, sex, race, and type of dermatitis. On the 6th day, the cloxacillin-treated group had significantly less redness, weeping, and crusting and by the 7th day, there was more re-epithelialization in the antibiotic-treated group.

Bower M. Med J Aust 1984 [28]: Children > 4 months of age attending an outpatient clinic were enrolled in the trial if they presented for treatment of sores only, had a skin lesion which had surrounding cellulitis, or was exuding pus, or was greater than 3 cm in diameter, or had more than 5 sores greater than 2 cm in size, and had no medical treatment for six days. Children were randomly assigned to receive either penicillin or placebo. In the penicillin group they received

i.m. procaine penicillin on day 0 and day 2. In the placebo group, they received one dose of pigbel vaccine on day 0 and a dose of triple antigen on day 2.

There were a total of 227 children in the study, 114 in the penicillin group and 113 in the placebo group. Of the 227 children, 70 (30%) had infected sores, 58 (26%) had infected scabies, 44 (19%) had infected cuts, 30 (13%) had tropical ulcers and the remainder had boils, burns or a bite. Effect of treatment was only assessed in the 68 children who had three visits (30 in the penicillin group and 38 in the placebo group). A scoring system was used to assess response and the overall cure rates were significantly higher in those treated with penicillin.

The following table summarizes the treatment effect seen in studies of uSSSI:

Table 18: Clinical Success in the ITT Population for Impetigo Studies

Study	Administration Route	Antibacterial Agent	Success Rate n/N (%)		Treatment Difference (Antibacterial – Vehicle) (95% CI)
			Antibacterial	Vehicle	
Retapamulin	topical	retapamulin	119/139 (85.6%)	37/71 (52.1%)	33.5% (20.5%, 46.5%)
Gould	topical	mupirocin	12/17 (70.6%)	7/22 (31.8%)	38.8% (4.4%, 73.1%)
Eells	Topical	mupirocin	17/26 (65.4%)	16/25 (64.0%)	1.4% (-28.8%, 31.6%)
Burnett	PO	erythromycin	38/44 (86.4%)	11/45 (24.4%)	61.9% (43.5%, 80.3%)

Abscesses

The utility and clinical benefit of adjunctive antimicrobial therapy following primary incision and drainage of abscesses has been questioned. Based on the following randomized, double-blind, placebo-controlled studies there is evidence to suggest that antimicrobial therapy following primary incision and drainage of abscess provides no additional benefit, over incision and drainage alone.

1. Llera JL. Annals of Emergency Medicine 1985[29]: Adults with cutaneous abscesses treated in a single ER with primary incision and drainage were randomized to receive cephradine or placebo QID for 7 days. Although 81 patients were randomized, follow-up and results were reported for 50 (62%) patients; 27 treated with cephradine and 23 with placebo. Follow-up results at 7 days (either in person or by telephone) indicated clinical improvement in 26/27 patients receiving cephadrine and 22/23 patients receiving placebo (both 96%).

2. Rajendran PM. Antimicrob Agents Chemother 2007[30]: A randomized, double-blind study of 166 subjects with surgically drainable, non-recurrent abscesses was conducted in an outpatient clinic where patients were at high risk for MRSA infection. Approximately 80% of abscesses were < 5 cm in size. After primary incision and drainage, patients were randomized to receive cephalexin 500 mg or placebo QID for 7 days. There was no difference in clinical cure rate between patients receiving cephalexin 69/82 (84.1%) versus placebo 76/84 (90.5%); 42/82 patients treated with cephalexin had MRSA with 2 failures and 43/84 patients treated with placebo had MRSA with 4 treatment failures.

3. Lee MC. Pediatr Infect Dis J 2004[31]: This was a prospective observational study in which children presenting to a single ER or acute care center with a skin abscess caused by MRSA were identified by microbiological culture results. Information regarding patient characteristics and nature of infection, along with initial and subsequent antimicrobial therapy following incision and drainage was obtained. Clinical improvement was noted in most instances despite ineffective antimicrobial therapy. However, patients with infection site of > 5 cm were more likely to fail management with incision and drainage if given inappropriate antimicrobial therapy.

Supportive evidence for treatment effect in cSSSI

1. **Dose ranging studies:**

Dose-ranging studies for the treatment of cSSSI were reviewed to assess if clinical cure rates with the lower dose could be used as an estimate of the placebo cure rates in patients with cSSSI.[32, 33]

Both studies were open-label randomized controlled studies. The placebo cure rates could not be estimated from these two dose-ranging studies for the following reasons:

- In one study there was a difference in the assessment time between the two groups
- In the other study, a small difference (<10%) in clinical success rates between the high (approved dose) and low dose groups suggests that the low dose may have been effective and therefore does not provide a reasonable estimate for the placebo success rate. The following table summarizes these two studies:

Table 19: Dose-ranging studies in cSSSI

Author/Year	n	Treatments	Response	Comments
Seltzer et al. CID 2003	62	2 doses of dalbavancin 1100 mg or 1 gram followed by 500 mg 1 week later vs. standard of care	ITT: 60% in single dose group, 91% in 2-dose group, 76% in comparator CE: 64% in single dose group, 92% in 2-dose group, 76% in comparator	Small number of patients/group. Follow up period in the 1 –dose group occurred sooner (day 24) than that in 2-dose group (day 34)
Postier et al. Clin Therap 2004	160	Tigecycline 25 mg BID vs. 50 mg BID	?CE: 67% (53.3-79.3) in the low dose and 74% (60.3-85) in the high dose	Likely low dose was also effective

2. **Studies of prophylaxis:**

Prophylactic administration of antimicrobial therapy has demonstrated the ability to reduce the rate of infections in certain circumstances and provide supportive evidence for treatment effect with antibacterials in SSTI. However, since infection rates were low and the studies were of limited size, it was difficult to quantify the magnitude of the treatment benefit.

1. Maddox JS. J Am Acad Dermatol 1985 [34]: Use of prophylactic topical therapy for skin infections was assessed at a day care center during the known seasonal peak for streptococcal

pyoderma. Fifty nine children 2-5 years of age were treated with either an antibiotic or placebo ointment (treatment was blinded to observers, but randomization process not stated). Children were observed daily, with ointment applied to minor breaks in the skin or bites. Skin infections developed in 4/27 (15%) treated with bacitracin and 15/32 (47%) of patients receiving placebo.

2. Dire DJ. Acad Emerg Med1995 [35]: This was a single center, randomized, double-blind, placebo-controlled study of topical antimicrobial therapy in prevention of infection in patients with uncomplicated soft-tissue wounds presenting to the ER within 12 hours of injury and necessitating suturing. Patients with puncture wounds, immunosuppression, underlying fractures, neurovascular compromise, or who had used antibiotics within the past 7 days were excluded. Patients were randomized to one of four topical treatments; antibiotic-free carrier ointment (petrolatum control - PTR), bacitracin zinc ointment (BAC), neomycin sulfate, bacitracin zinc, and polymixin B sulfate combination (NEO), or silver sulfadiazine (SIL). Use of BAC, NEO, or SIL for uncomplicated, repaired lacerations resulted in lower infection rates compared to the control group that received petrolatum.

Four hundred sixty five patients were enrolled. Data for 39 patients was excluded due to protocol violations (primarily no follow-up). Infection prevention rates (per protocol) were reported for those patients who followed up. The overall wound infection rate was 9.9% (42/426). The infection rates for each treatment group were as follows: BAC 6/109 (5.5%), NEO 5/110 (4.5%), SIL 12/99 (12.1%), and PTR 19/108 (17.6%).

3. Discordant therapy:

Studies in which administered antimicrobial therapy is shown to be inactive against the pathogen isolated have served as surrogates for placebo-controlled studies or untreated infection. These studies are retrospective in nature and have limited utility in establishing treatment effect due to inclusion of a variety of bacterial organisms, small sample size, inadequate endpoint definition, failure to include co-morbidities, and consideration of spontaneous resolution of minor infections. However, they provide indirect evidence for treatment effect with antibacterials in skin infections.

Contemporary cSSSI trials

In most contemporary cSSSI trials, entry criteria include lesions that involve deeper soft tissue or require surgical intervention such as surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers. Severity is often defined based on the presence of the following: fever, presence of purulent drainage, localized warmth, tenderness, elevated WBC etc. Often patients in these studies have underlying comorbidities such as diabetes mellitus and peripheral vascular disease. Most recent clinical trials have evaluated parenteral antibacterial therapy, most often administered in an inpatient setting, though some patients have been treated as outpatients provided they meet certain pre-specified criteria. Patients with uSSSI such as simple abscesses, impetigo, furuncles, folliculitis, and secondarily infected dermatoses are excluded from these studies.

Concomitant therapy in the form of surgical interventions and local wound care measures are usually permitted. The exact number and nature of surgical procedures allowed has varied among

the studies. Some studies have differentiated bedside surgical interventions from those performed in the operating room. Similarly, the nature and extent of local therapies allowed has also varied among studies. Patients who undergo amputation such that the focus of infection is removed are usually considered failures.

Outcome is typically assessed at a fixed time point relative to completion of study therapy. The test of cure visit generally occurs 7-14 days after end of therapy. Patients are classified as either cure or failure based on resolution or improvement of signs and symptoms and the need for further antibacterial therapy.

All recent registrational trials have been non-inferiority trials and have used an NI margin of 10-15%. The active comparators in these studies have included vancomycin, linezolid, and semi-synthetic penicillins. Some studies have allowed for initiation of therapy with vancomycin with an option to switch to semi-synthetic penicillins if MSSA was identified. Similarly some studies have allowed for oral switch after a period of parenteral therapy. Additionally, some studies have allowed for concomitant aztreonam for gram-negative coverage and metronidazole for anaerobic coverage.

Active comparator success rates in cSSSI

To examine the effect of antibacterials that could be used as active comparators, studies from recent NDA submissions were identified. Recent studies were used because of concerns about constancy of the treatment effect related to potential differences in baseline patient and pathogen characteristics. Table 20 displays the results for clinical studies from recent NDA submissions.

Table 20: Clinical Success Rates at TOC for Contemporary cSSSI Studies (ITT)

Drug / Study	Comparator	Test Drug Clinical Success Rate n/N (%)	Comparator Clinical Success Rate n/N (%)
Tigecycline Study 300	vancomycin + aztreonam	217/295 (73.6)	217/288 (75.4)
Tigecycline Study 305	vancomycin + aztreonam	231/275 (84.0)	235/271(86.7)
Daptomycin Study 9801	vancomycin or SSP	165/264 (62.5)	162/266 (60.9)
Daptomycin Study 9901	vancomycin or SSP	217/270 (80.4)	235/292 (80.5)
Linezolid Study 55	SSP	278/400 (65.5)	274/419 (65.4)
Meropenem Study 3591IL/009	imipenem-cilastatin	295/510 (57.8)	321/527 (60.9)
Moxifloxacin Study 100273	piperacillin / tazobactam	148/273 (54.2)	157/274 (57.3)
Moxifloxacin Study 10279	amoxicillin/clavulanate	295/406 (72.6)	297/397 (74.8)

SSP: semi-synthetic penicillin

As shown in the above table, the cure rates varied between studies. The relatively low clinical success rates seen in moxifloxacin Study 100273, may be explained by the large proportion of patients who had inconclusive results at the TOC assessment (moxifloxacin: 30%; piperacillin/tazobactam: 26%). Most of these patients were missing a TOC assessment (moxifloxacin: 22%; pipercillin/tazobactam: 20%). Note, this level of inconclusive data was not

seen in the other moxifloxacin study, Study 10279, where the proportion of indeterminate findings was small (moxifloxacin 1%; amoxicillin /clavulanate 1%). For meropenem Study 3591IL/0079, the relatively low rates for clinical success may be explained by the large number of patients who discontinued study treatment due to failing enrollment criteria [meropenem: 79/510 (16%); imipenem-cilastatin: 60/527 (11%)].

Treatment Efficacy of Linezolid versus Vancomycin

To examine whether there is evidence that linezolid is more effective than vancomycin for the treatment of cSSSI, the following studies were identified that compared linezolid to vancomycin in the treatment of cSSSI.

Weigelt J. Antimicrob Agents Chemother 2005[36]: Study 128 was a Phase IV randomized, open-label, multi-center trial comparing linezolid to vancomycin in the treatment of cSSSI; 1180 patients were randomized and received either IV or oral linezolid 600 mg every 12 hours or IV vancomycin 1 gm every 12 hours. Vancomycin patients with documented MSSA were to be switched to a semi-synthetic penicillin (oxacillin, nafcillin, flucloxacillin, or dicloxacillin). The minimal treatment period was 4 days, and the treatment duration was intended to be 7 to 14 days but not longer than 21 days.

The primary endpoint was clinical response at the Test-of Cure visit (7 days after End-of-Therapy) in the ITT population. The ITT results presented in the paper excluded 226 (107 linezolid, 119 vancomycin) patients who had indeterminate outcomes. Because this analysis is not protected by randomization and is susceptible to selection bias, we present the authors' sensitivity analysis where all indeterminates were considered failures. In this analysis, the clinical response rates were 75.3% (439/583) for the linezolid group and 70.2% (402/573) for the vancomycin group. The observed treatment difference was 5.1% with a corresponding 95% CI of (0%, 10.3%). As this was an open label study it has the potential to seriously bias the results. Thus, it can be inferred that linezolid is at worst similar to vancomycin. This study does not however provide evidence that a larger NI margin can be justified when linezolid is used as a comparator rather than vancomycin.

Stevens DL. Clin Infect Dis 2002[37]: This was a randomized, open-label, multicenter trial that compared linezolid IV/PO to vancomycin IV for the treatment of methicillin-resistant *Staphylococcus* species (MRSS) infections; 468 patients, thirteen years or older, were randomized with 460 patients receiving study medication. Patients enrolled had the following primary sources of MRSS infections: skin and soft tissue infections, pneumonia, urinary tract infections, right sided endocarditis, and bacteremia. Patients with skin and soft tissue infections made up 50% (230/460) of the population. In this subgroup, the cure rates in the ITT population were 52.4% (64/122) for the linezolid group and 50.0% (54/108) for the vancomycin group. The estimated treatment difference (linezolid – vancomycin) was 2.5% with a 95% CI of (-11.4%, 16.3%). These results should be interpreted with caution as they represent subgroup analyses and are prone to multiplicity issues.

Sharpe JN. Am J Surg. 2005 [38]: This was a randomized, open-label, single-center study that compared oral linezolid (600 mg every 12 h) with vancomycin IV (1 g every 12 h) in patients

with lower-extremity cSSSI caused by MRSA. Treatment was administered for 7-21 days and assessment of clinical response was performed ten days after end of therapy.

One hundred seventeen patients were enrolled and sixty were randomized in 1:1 ratio to study drug (30 linezolid, 30 vancomycin). Fifty-seven patients were excluded if they had known penicillin allergies that would prevent the use of cefazolin, were hypersensitive to linezolid or vancomycin formulations, or had received other investigational medications. Some of the exclusion criteria included: secondary skin infection; recurrent infection at the same site within 2 months; an infected, irremovable device; osteomyelitis; endocarditis; meningitis; septic arthritis; necrotizing fasciitis; gas gangrene; uSSSI; medical conditions causing prolonged inflammation; acute infections not caused by MRSA or caused by a gram-negative pathogen; long-term hospitalization resulting from concomitant morbidities; pregnancy; or lactation.

Reported clinical response (cure + improvement) rates were 97% in the linezolid group and 43% in the vancomycin group. The statistical test for the difference in cure rates between groups has a reported p-value of 0.015. However, neither the population nor the denominator was reported in the calculation of these percentage rates. If we assume all randomized patients were in the analysis population the reported p-value cannot be reproduced. This study had several limitations: it was a small, open-label, single-center study, patients could have received upto 48 hours of effective therapy prior to enrollment, the study report does not provide any information on the frequency of such antibiotic use or the types of prior therapies used in the two treatment groups, and finally, a large proportion of enrolled patients were not randomized.

The following table summarizes results from two studies that compared linezolid with vancomycin:

Table 21: Clinical Response in cSSSI Studies comparing Linezolid and Vancomycin (ITT population)

Study	Linezolid n/N (%)	Vancomycin n/N (%)
Weigelt	439/583 (75.3)	402/573 (70.2)
Stevens (cSSSI subgroup)	64/122 (52.4)	54/108 (50.0)

Active comparator rates in uSSSI

Four recent studies that were used to support the indication of uSSSI were reviewed. All four studies were randomized, active controlled, non-inferiority studies. The types of infections seen in these studies included cellulitis, folliculitis, impetigo, simple abscesses, and furunculosis. About 10-20% of patients enrolled had abscesses. The timing of the test of cure visits varied between studies (7-14, 10-21 days after end of therapy). The primary analysis populations also varied between studies. The following table summarizes cure rates in the ITT population seen in these studies:

Table 22: Clinical Success Rates at TOC for Contemporary uSSSI Studies (ITT)

Test Drug	Comparator	Test Drug Clinical Success Rate n/N (%)	Comparator Clinical Success Rate n/N (%)
Cefditoren	Cefadroxil	215/278 (77%)	207/273 (76%)
Cefditoren	Cefuroxime	215/291 (74%)	225/283 (80%)
Linezolid	Clarithromycin	293/341 (85.9%)	269/322 (83.5%)
Linezolid[#]	Cefadroxil	205/248 (82.7)	193/251 (76.9)

[#]Pediatric patients

Constancy of treatment effect

The conclusion that HESDE can be used to choose an M1 can be reached based on the assumption that the current clinical trials are sufficiently similar to the historical studies with respect to all important study design and conduct features that might influence the effect size of the active control. The design features of interest include the characteristics of the patient population, disease definition, disease severity, definitions and ascertainment of study endpoints, dose of active control, entry criteria, age, comorbidities, and analytic approaches.

From the historical studies, it is evident that antibacterial therapy, primarily sulfonamides or penicillins had a remarkable effect on the resolution of signs and symptoms of skin infections. In the comparative studies of sulfonamides and ultra-violet light (Snodgrass 1937, 1938) there was a clear benefit of treatment with sulfonamides for both resolution of fever and cessation of spread of lesion. Data from uncontrolled studies of penicillins and sulfonamides have shown that patients treated with antibacterials appeared to have quicker resolution of pus and faster return to normal function (Florey 1944, Meleney 1946). Additional supportive evidence is provided by natural history studies of untreated *S. aureus* and *S. pyogenes* bacteremia where the mortality was ~70% (Keefer 1937, Skinner and Keefer 1941). Although several of these patients had severe skin and soft tissue infections, the antibacterial treatment effect derived from these studies is likely to be higher than that seen in cSSSI trials, as very few patients in cSSSI trials are bacteremic. Also, in these natural history studies, the endpoint reported was mortality and not clinical outcome as assessed in clinical trials.

In the absence of placebo-controlled studies in patients with cSSSI, evidence of antibacterial treatment effect was indirectly derived from these historical data. In cSSSI, as currently defined, it is safe to assume that the treatment effect will at least be the same if not greater than that seen in the studies of erysipelas.

Although erysipelas is not always a severe disease, it can nevertheless be associated with mortality in the more severe cases especially at the extremes of age. In a paper by Hosford in 1938 [39], he states "*since the introduction of sulphanilamide as a remedy in streptococcal infections, we have a drug of utmost value in the general treatment of erysipelas*". He also states that " *In most cases it has a profound, sometimes dramatic effect: the temperature drops to normal in 48 hrs or less, the rash fades, and the patient feels better. Although left untreated, it will run its own course and disappear, the treatment is planned to shorten the course of the*

disease and add to the comfort of the patient". So, there seems to be no uncertainty in a treatment effect with sulfonamides in erysipelas with respect to resolution of signs and symptoms.

There are some limitations to these historical data. The assessments for treatment effect in the Snodgrass studies were made 48 hours after instituting treatment, while in clinical trials, assessment of cure is usually made 7-14 days after completing therapy. However, the endpoint assessed was cessation of spread of lesion and not resolution the lesion. Hence the treatment effect seen at 48 hours for cessation of spread is still applicable to an endpoint evaluating resolution of signs and symptoms at a later time point. Secondly, the very high success rate in terms of cessation of spread of lesion may not be directly applicable to all types of cSSSI. As erysipelas is a superficial cellulitis with prominent lymphatic involvement, it has a characteristic raised border that is very well demarcated. The lack of spread of the lesion is thus easier to define. In other forms of cSSSI, such as deep abscesses, wound infections or cellulitis this may be harder to discern. In the series of patients describing the effects of penicillin therapy in surgical infections (Lyons 1943, Meleney 1946), the cure rates certainly differed depending on the type of infection with higher cure rates in patients with cellulitis and lower rates in those with wound infections, ulcers or other types of infections. As no untreated controls were used in these studies, it is not possible to directly estimate a treatment effect compared to placebo by infection type.

S. aureus and *S. pyogenes* were the main microorganisms isolated from patients with skin infections in historical studies and they continue to be the most common microorganisms identified in present trials. However, there are differences in the microbiological characteristics of organisms when comparing studies from the earlier part of the 20th century to the present especially with regard to antimicrobial susceptibility. There has been an increasing prevalence of MRSA, especially community-acquired MRSA in skin and soft tissue infections in recent years.

One other area of difference between patient populations in historical studies and contemporary trials is the presence of co-morbidities and availability of supportive care. Patients in contemporary trials tend to often have co-morbidities such as obesity, diabetes mellitus and renal impairment which can impact on the nature of cSSSI and also on the cure rates. However, ancillary care including wound management and other supportive care is more advanced in the present day trials compared to historical studies.

The only contemporary placebo-controlled studies identified in patients with skin and soft tissue infections were the studies conducted in patients with impetigo or superficial skin abscesses. A clear treatment effect over placebo was seen in the study comparing retapamulin to placebo in the treatment of impetigo. Although there are differences in the clinical characteristics, need for surgical intervention(s) and outcomes in patients with cSSSI compared to patients with impetigo there are similarities in that both types of infections involve the skin and the most common micro-organisms in these two infections are *S. aureus* and *S. pyogenes*. It is thus reasonable to assume that in patients with cSSSI, the treatment effect should at least be the same if not greater than that seen in studies of impetigo.

Despite these uncertainties, it is still reasonable to assume that there is a significant treatment effect with antibacterials in cSSSI and that the treatment effect seen in historical studies is applicable to contemporary clinical trials. Some of the uncertainties can be addressed by discounting the treatment effect (M1).

Estimate of Treatment Effect

Based on a meta-analysis of the studies of sulfonamides in the treatment of erysipelas, the treatment effect of sulfonamides over UV light for cessation of lesion spread at 48 hours was 24.1% (95% CI, 18.2%, 30.0%) and for resolution of pyrexia at 48 hours was 27.8% (95% CI, 18.9%, 36.8%). The treatment effect for impetigo from a meta-analysis of placebo-controlled trials of topical therapies was 28.8% with a corresponding 95% CI of (18.0%, 39.6%). Based on a single study of systemic erythromycin for treatment of impetigo and other uncomplicated skin and skin structure infections, the treatment effect was 61.9% (95% CI, 43.5%, 80.3%). Randomized, double-blind, placebo-controlled studies in patients with superficial skin abscesses have shown no treatment effect with antibacterials beyond the benefit of incision and drainage. The direct applicability of this information to larger/deeper abscesses seen in cSSSI trials is unclear. Hence, there is greater uncertainty in treatment effect for this type of infection included under the indication of cSSSI.

There are concerns about the internal consistency of the treatment effect and the fact that evidence came from studies based on very limited data. It is possible that these estimates and conclusions could change based on the availability of more information on the placebo and/or control effect in the future. It is important that the magnitude of the estimated treatment effect based on HESDE accounts for all possible sources of uncertainties. One of the strategies employed in choosing an M1 for an NI trial is by way of 'discounting ' or reducing the effect of the active control to account for these uncertainties. The treatment effect (M1) of 18% using the lower bound of the 95% CI discounts for uncertainties and the associated variability in the estimate and should be considered keeping the following points in mind:

- No placebo controlled studies were identified in patients with cSSSI
- The two erysipelas studies (Snodgrass 1937, 1938), used to estimate treatment effect (M1) showed that patients treated with sulfonamides had better outcomes for cessation of spread of lesion and resolution of fever than those treated with UV light. Further evidence for a treatment effect is provided by the fact that in the sulphanilamide group 11 patients (8.1%) developed septic complications directly attributable to erysipelas compared to 28 patients (20.7%) in the UV light group.
- In studies of UV light therapy, it appears that there was a treatment effect for UV light over other local therapies. Hence, the treatment effect of sulfonamides over placebo is likely to be higher.
- Although some cases of erysipelas can be considered as being in the spectrum of uncomplicated skin infections, in historical studies the mortality in untreated erysipelas was 15%, with higher mortality at the extremes of age; patients who were

bacteremic had a mortality of 70-90%. In the study of prontosil versus UV light, the authors state that *"in 5 cases in the prontosil group, the condition was so severe that a fatal result would not have been unexpected. One patient in the UV group showed uncontrolled spread with high fever for 6 days and was in the typhoid state when prontosil was used and patient's recovery was completely unexpected"*, providing evidence that some of these cases were in fact severe.

- Patients in the erysipelas studies were treated with various dosing regimens of sulfonamides, some of which were inadequate. Treatment effect with current antibacterials is likely to be higher than that seen with Prontosil or other sulfonamides; patients enrolled in current cSSSI trials are generally treated with parenteral antibacterials.

- It is likely that for other forms of cSSSI such as cellulitis and wound infections, the treatment effect is at least the same or greater than that seen with erysipelas or impetigo.

- It is difficult to compare the patient populations from the 1930s with those enrolled in contemporary trials. It is however possible that patients in present studies have more comorbidities that can have an impact on the type and severity of the cSSSI and the outcomes. On the other hand, ancillary care such as wound management is likely to be far superior in current trials and its contribution to overall cure is difficult to discern from that of the treatment effect due to antibacterials.

- The uncontrolled study of topical penicillin by Florey (1944) showed a clear treatment effect for reduction of pus and resolution of signs and symptoms in severe hand infections. Further evidence is provided by the authors' statement that *"the great majority of control cases remained septic for over a week and nearly 3/4^{ths} were infected till their wounds healed. In penicillin treated cases, sepsis by clinical and bacteriologic criteria was eliminated within a week, pus was scanty, and relief of pain and improvement in general condition was striking."* As most of these patients were treated with topical penicillin, the treatment effect with systemic penicillin or with present day antibacterials is only likely to be higher.
- Natural history studies showed that mortality in untreated staphylococcal and streptococcal bacteremia was very high (70-80%).

- Uncontrolled studies of treatment with penicillin or sulfonamide (Lockwood 1944, Keefer 1938) in patients with staphylococcal or streptococcal bacteremia showed reduction in mortality and improvement in signs and symptoms.

- Randomized, double-blind, placebo-controlled studies suggest that antimicrobial therapy following primary incision and drainage of superficial abscess provides no additional benefit. Patients enrolled in studies of cSSSI have deeper/larger abscesses that often require hospitalization. So, whether or not the lack of treatment effect in superficial/small abscesses is applicable to abscesses classified as cSSSI is unknown.

In the study by Florey (1944), it does appear that some patients with abscesses were improving with expectant treatment. The treatment effect was also small in these cases compared to other types of infections. Hence, the greatest uncertainty in treatment effect for cSSSI exists for this subgroup of patients.

Non-inferiority Margin

With the limitations discussed above, the treatment effect (M1) of antibacterial drugs in cSSSI for a clinical response endpoint of resolution/improvement in signs and symptoms is estimated to be at least 18%, based on studies in erysipelas and impetigo. The timing of assessment in the erysipelas studies was at 48 hours after starting therapy while in the impetigo study it was at the end of 7-10 days of therapy. A fraction of this treatment effect should be preserved in determining a clinically acceptable NI margin. For cSSSI, the magnitude of treatment effect will be at least the same or greater than that seen in the studies of impetigo or erysipelas from which the M1 was derived. Additionally, data from other historical studies have shown a clear benefit of antibacterial treatment for skin infections that were more severe than impetigo and erysipelas. Hence, a 10% NI margin that preserves 44% of M1 can be justified for a clinical response endpoint in cSSSI trials, provided appropriate patient populations are enrolled and appropriate endpoints are evaluated. It will also be important that confounders such as surgical interventions be minimized and balanced across treatment arms.

However, in a uSSSI study, there are more uncertainties in the treatment effect especially if patients with infections such as minor skin abscesses, folliculitis, and furunculosis are enrolled. It will thus be important to enroll patients in an uSSSI study with disease conditions such as erysipelas (cellulitis) or impetigo wherein a treatment effect has been demonstrated and to exclude patients with minor skin abscesses where there is no demonstrable treatment effect for antibacterials beyond that achieved by the incision and drainage procedure alone. Given these uncertainties in treatment effect for uSSSI, a larger fraction of the treatment effect should be preserved compared to that used for a cSSSI study.

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5 SIGNATURES/DISTRIBUTION LIST (Optional)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-110 / N000
Drug Name:	Telavancin for Injection (10 mg/kg IV q24h)
Indication(s):	Complicated skin and skin structure infection
Applicant:	Theravance Inc.
Date(s):	12/6/06 (letter)
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, Dr.P.H.
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Keywords: active control/non-inferiority, pooling

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Sponsor provided evidence that telavancin is effective in the treatment of complicated skin and skin structure infections (cSSSI). Based on a 10% noninferiority margin, telavancin was noninferior to vancomycin in the two Phase III studies (Studies 0017 and 0018) for clinical response at Test-of-Cure (TOC) in both of the co-primary analysis populations, All-Treated (AT) and Clinically Evaluable (CE). However, the Sponsor did not provide evidence that telavancin is more effective than vancomycin in the treatment of cSSSI for patients with methicillin-resistant *Staphylococcus* aureus (MRSA) pathogens isolated at baseline. Finally, there are concerns that the relative effect of telavancin compared to vancomycin decreases as the level of baseline renal impairment increases. Similarly, the relative efficacy of telavancin compared to vancomycin is decreased in older patients, ≥65 years, compared to younger patients, <65 years. Note that age and baseline renal impairment are highly correlated.

1.2 Brief Overview of Clinical Studies

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains.) *Streptococcus* pyogenes, *Streptococcus* agalactiae, *Streptococcus* anginosus grp. (including *S.* anginosus, *S.* intermedius and *S.* constellatus), and *Enterococcus* faecalis (vancomycin-susceptible isolates only). The proposed dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous (IV) infusion once every 24 hours for 7 to 14 days. b(4)

The two Phase III studies (Studies 0017 and 0018) were randomized, double blind, double-dummy, active-controlled, parallel group, multicenter, multinational trials. Patients with complicated Gram-positive skin and skin structure infections (primarily due to MRSA) were randomized to receive either telavancin 10 mg/kg IV once daily or vancomycin 1 g q 12 hours. Treatment duration was to be from 7 to 14 days. Investigators were encouraged to administer aztreonam and/or metronidazole in patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. In the Phase III studies, 862 (429 telavancin and 433 vancomycin) and 1035 (517 telavancin and 518 vancomycin) patients were enrolled in Studies 0017 and 0018 respectively. Study 0017 was conducted in 29 countries with approximately 73% of the patients enrolled in the United States, while Study 0018 was conducted in 17 countries with a slightly lower percentage (66%) of the patients enrolled from the United States.

The primary efficacy variable in the studies was the Clinical Response at Test-of-Cure. The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary and a 10% noninferiority

margin was used. For the superiority analysis, the AT analysis population was the population of interest.

1.3 Statistical Issues and Findings

The following statistical issues were found during the review of this submission – the adequacy of the justification of the 10% noninferiority margin, the sample size modification, and the large proportion of patients from two sites in Study 0017. These issues had the potential to affect the assessment of efficacy of telavancin, however further review suggested that these three issues were not felt to affect the overall determination of efficacy of telavancin in the treatment of cSSSI with details discussed in this section. There were two issues that involved the inconsistency of the treatment effect across both levels of renal impairment and age that still remain an outstanding issue. The issues will be discussed below and their impact assessed.

Noninferiority margin justification

A 10% noninferiority margin was used for both Study 0017 and 0018.

Reviewer's Comments

Based on data submitted by the Sponsor and the Agency's review of the literature and other supportive evidence, the 10% noninferiority margin is acceptable for the treatment of cSSSI using vancomycin as the comparator. Details can be found in the Appendix.

Sample size increase in Study 0018

In study 0018, the sample size was increased during the trial in an attempt to demonstrate the superiority of telavancin relative to vancomycin in the subgroup of patients with a baseline MRSA pathogen isolated. It was agreed by the Division that the analysis would performed pooled across Studies 0017 and 0018 and that the sample size increase would be based on a blinded (pooled) MRSA evaluability rate in order to have adequate statistical power for the pooled MRSA superiority analysis. The number of patients enrolled after the sample size increase was approximately 1/4 of the total for Study 0018. In a sensitivity analysis to assess the effect of the sample size increase (see Table 1), it was found that the results of the pre- and post-sample size increase were similar although it appears that the vancomycin response rate increased slightly (AT population -- Pre: 72.6% vs. Post: 77.3%) subsequent to the sample size increase while the telavancin response rate was relatively constant. Thus the point estimate of the difference decreased slightly subsequent to the sample size increase. Based on these sensitivity analyses, no evidence was found that the sample size increase introduced bias into study.

Table 1: Sensitivity analysis of Clinical Response at TOC examing effect of sample size increase

	Study 0018 enrolled prior to sample size increase		Study 0018 enrolled subsequent to sample size increase	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated				
Cure	263/358 (73.5)	275/379 (72.6)	85/114 (74.6)	85/110 (77.3)
Difference (95% CI)[1]	0.9 (-5.5, 7.3)		-2.7 (-13.9, 8.5)	
Clinically Evaluable				
Cure	231/275 (84)	243/278 (87.4)	75/90 (83.3)	75/85 (88.2)
Difference (95% CI)[1]	-3.4 (-9.2, 2.4)		-4.9 (-15.2, 5.4)	

Effect of two large centers in Study 0017

In Study 0017, the top two highest enrolling sites, Site 38101 and Site 38271 enrolled 260 (30%) and 201 (24%) of the patients. The next highest enrolling site enrolled 61 (7%) of the patients. A sensitivity analysis was performed to assess the effect of these two sites on the overall results (see Table 2). The exclusion of the two sites did not change the results substantially. Both the point estimates of the response rates for the individual treatment groups and treatment difference between groups were similar. In addition, the confidence interval widened as expected due to the smaller sample size but the intervals were still centered on similar point estimates. Also, both analyses still met the noninferiority margin even with both sites excluded. Thus, it is felt that results for Study 0017 were not unduly affected by the two large centers.

Table 2: Clinical Response at TOC Sensitivity Analysis (Post-Amendment) -- FDA Adjudicated Data

	Study 0017		Study 0017 excluding Sites 38101 and 38271	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated				
Cure	309/426 (72.5)	307/429 (71.6)	140/195 (71.8)	140/199 (70.4)
Difference (95% CI)[1]	1.0 (-5.0, 7.0)		1.4 (-7.5, 10.4)	
Clinically Evaluable				
Cure	289/343 (84.3)	288/348 (82.8)	124/150 (82.7)	126/150 (84.0)
Difference (95% CI)[1]	1.5 (-4.0, 7.0)		-1.3 (-9.8, 7.1)	

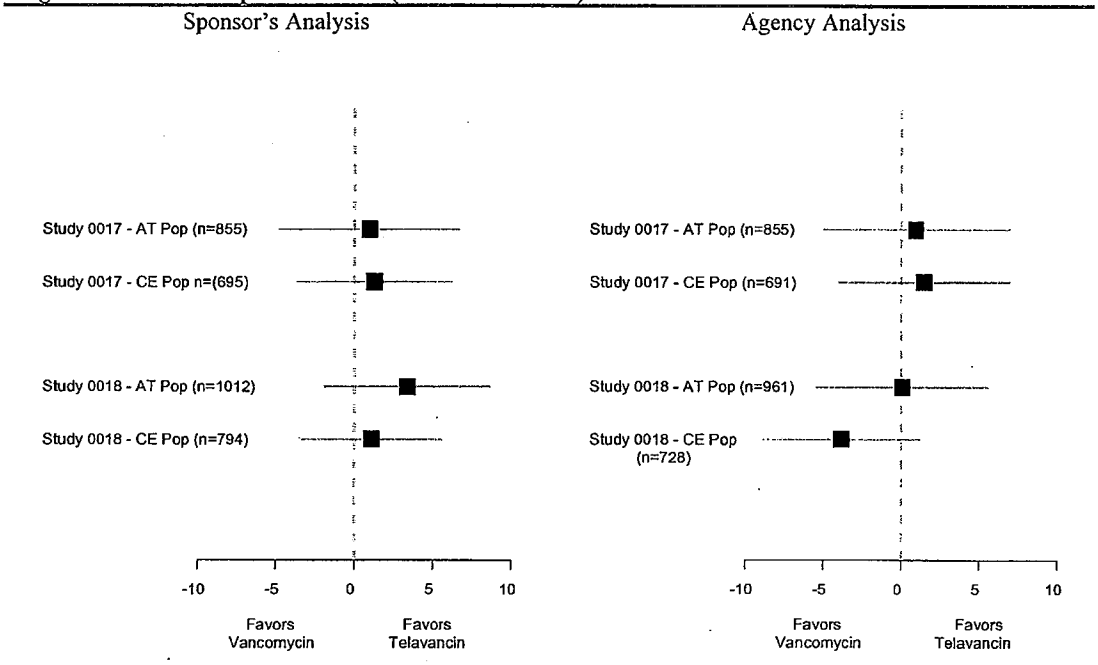
It was not felt that the preceding statistical issues had a meaningful impact on the on the overall determination of efficacy, with the exception of the heterogeneity of treatment effects across levels of renal impairment and age, which will be discussed later. The overall efficacy findings will be presented below.

In both of the Phase III studies (Studies 0017 and 0018), efficacy was demonstrated based on the noninferiority of telavancin to vancomycin for the primary endpoint of clinical response at TOC in both the AT and CE populations. Noninferiority was assessed in the treatment difference in clinical response rates using a 10%. noninferiority margin (see Table 3). The finding was consistent in both the Sponsor's analyses and the Agency analyses of the primary endpoint (see Figure 1). However, it is noted for Study 0018 that the Agency analyses resulted in a ~3% decrease in the treatment difference for both the AT and CE population compared to the Sponsor's analyses. As the Sponsor's analysis plan proposed testing for superiority if noninferiority was demonstrated, it is noted that the studies did not provide evidence that telavancin was statistically superior to vancomycin in either of the studies.

Table 3: Clinical Response at TOC (Post-Amendment)

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated								
Cure	323 (75.8)	321 (74.8)	387 (77.1)	376 (73.7)	309 (72.5)	307 (71.6)	348 (73.7)	360 (73.6)
Total	426	429	502	510	426	429	472	489
Difference (95% CI)[1]	1.0 (-4.8 , 6.8)		3.4 (-1.9 , 8.7)		1.0 (-5.0, 7.0)		0.1 (-5.5, 5.7)	
Clinically Evaluable								
Cure	304 (87.9)	302 (86.5)	354 (88.7)	346 (87.6)	289 (84.3)	288 (82.8)	306 (83.8)	318 (87.6)
Total	346	349	399	395	343	348	365	363
Difference (95% CI)[1]	1.3 (-3.6 , 6.3)		1.1 (-3.4 , 5.6)		1.5 (-4.0, 7.0)		-3.8 (-8.8, 1.3)	

Figure 1: Clinical Response at TOC (Post-Amendment)



For Study 0017, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.0% with a corresponding 95% CI of (-4.8%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 1.0% with a corresponding 95% CI of (-5.0%, 7.0%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.3% with a corresponding 95% CI of (-3.6%, 6.3%) while the Agency analysis found a similar result with a treatment difference of 1.5% with a corresponding 95% CI of (-4.0%, 7.0%).

For Study 0018, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 3.4% with a corresponding 95% CI of (-1.9%, 8.7%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-5.5%, 5.7%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.1% with a corresponding 95% CI of (-3.4%, 5.6%) while the Agency analysis found a similar result with a treatment difference of -3.8% with a corresponding 95% CI of (-8.8%, 1.3%). There was noticeable decrease (~3%) in the treatment difference between telavancin and vancomycin in both the AT and CE populations that was caused by a decrease in the telavancin response rates in both the populations. A large portion of the difference is due to the removal of Site 38091 that was excluded because of issues raised by DSI during the site inspection. The results from that site heavily favored telavancin for both the AT population (Telavancin: 22/30 (73.3%); Vancomycin: 8/21 (38.1%)) and the CE population (Telavancin: 21/24 (87.5%); Vancomycin: 8/19 (42.1%)).

As it was the Sponsor's objective to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population has been demonstrated, the discussion of these results will follow. The analysis plan was to pool data across Studies 0017 and 0018 to perform the analyses. The results of the two studies were not found to be substantially dissimilar (FDA Analysis: Breslow-Day statistic=1.562, p=0.21) so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses. However, it should be noted that in the FDA analysis, there was a noticeable difference in the estimates for the treatment difference (telavancin – vancomycin) in response rates for the MRSA subgroup between Studies 0017 and 0018 (Study 0017: -4.7%; Study 0018: 4.0%).

In patients with a MRSA pathogen isolated at baseline, the Sponsor failed to demonstrate the superiority of telavancin to vancomycin in clinical response at TOC (see Table 13). This was consistent in both the analyses performed by the Sponsor and the Agency. In the pooled analysis of the MRSA patients, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 0.4% with a corresponding 95% CI of (-5.9%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-6.7%, 6.8%) for the AT population. The test of the difference in clinical response at TOC between telavancin and vancomycin yielded clearly non-statistically significant finding with 2-sided p-values of 0.889 and 0.985 in the Sponsor's and Agency analyses.

Although, it was felt that the Sponsor demonstrated that telavancin was noninferior to vancomycin in the treatment cSSSI, there is a concern about the inconsistency of treatment effect across both baseline renal impairment levels and age that will be discussed below.

Effect of Baseline Renal Impairment

Subgroup analyses that examined the effect of baseline renal impairment on clinical response at TOC were performed. The treatment difference in response rates between telavancin and vancomycin was not constant across levels of renal impairment (p=0.02) in the pooled CE population of Studies 0017 and 0018. In order to assess the effect of the level of baseline renal impairment on the treatment difference, we examined the interaction of the treatment group and the baseline renal impairment in a logistic regression that modeled clinical response at TOC with study, treatment, region, diabetes, baseline renal impairment, the treatment by baseline renal impairment as predictors in the model. Further evidence of this issue is that the magnitude of relative difference between treatment arms increased as the level of baseline renal impairment increased. A graphical representation is presented in Figure 2. The increase in the treatment difference as renal impairment increases occurs because the telavancin response rates decreases as renal impairment increases [Normal: 406/455 (89.2%); mild: 131/165 (79.4%); moderate: 43/62 (69.4%); severe: 15/25 (60%)], while the vancomycin response rates are relatively constant across renal impairment level [Normal: 397/461 (86.1%); mild: 142/168 (84.5%); moderate: 51/62 (82.3%); severe: 16/20 (80%)] (see Table 4).

Figure 2: Clinical Response at TOC in the CE Population for Studies 0017 + 0018 (Post-Amendment) -- By Baseline Renal Impairment (FDA Analysis)

Baseline Creatinine Clearance	Telavancin	Vancomycin
>80 mL/min	406/455 (89.2%)	397/461 (86.1%)
>50-80 mL/min	131/165 (79.4%)	142/168 (84.5%)
30-50 mL/min	43/62 (69.4%)	51/62 (82.3%)
<30 mL/min	15/25 (60.0%)	16/20 (80.0%)

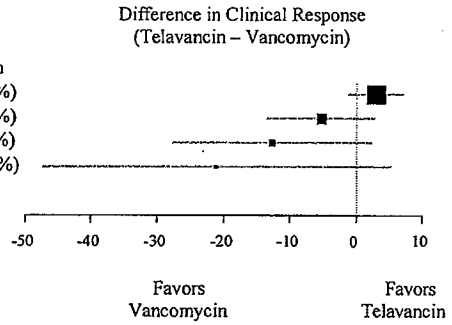


Table 4: Clinical Response Rate at TOC in the CE Population (Studies 0017 + 0018) – FDA Analyses

	Telavancin % (n/N)	Vancomycin % (n/N)	Difference (TLV – Comp) (95% CI)[1]	p-value[2]
Baseline Creatinine Clearance				
>80 mL/min (Normal)	406/455 (89.2)	397/461 (86.1)	3.1 (-1.2, 7.3)	0.02
>50-80 mL/min (mild)	131/165 (79.4)	142/168 (84.5)	-5.2 (-13.5, 3)	
30-50 mL/min (moderate)	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)	
<30 mL/min (severe)	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.4, 5.3)	

[1] Difference and 95% CI are based on analyses stratified by study
[2] p-value based on the interaction of treatment and subgroup variable controlling for study, treatment, region, diabetes, and baseline creatinine clearance.

Effect of Age

For age, the clinical response rates for both treatment groups decreased in the ≥65 year old stratum as compared to the <65 year old stratum. This is not unexpected as older patients often represent a sicker population with more comorbidities. However, the drop in response rate was much larger for telavancin [<65: 558/616 (90.6%); ≥65: 100/129 (77.5%)] than for vancomycin [<65: 527/600 (87.8%); ≥65: 121/144 (84.0%)], see Figure 3. The treatment difference (telavancin – vancomycin) differed significantly depending on the baseline age of the patient (p-value=0.04). In order to assess the effect of age on the treatment difference, we examined the interaction of the treatment group and the age (<65, ≥65) in a logistic regression that modeled clinical response at TOC with study, treatment, region, diabetes, age (<65, ≥65), and treatment by age as predictors in the model. In patients <65 years old at baseline, the difference was 2.7% with a 95% CI of (-0.8, 6.2) while in the ≥65 old stratum, the difference was -6.6% with a 95% CI of (-16.2%, 3.0) (see Table 5). Note that age is strongly correlated with baseline renal impairment, see Figure 4. As expected, the proportion of older patients, ≥65 years old, increased as the level of baseline renal impairment increased.

Figure 3: Clinical Response at TOC in the CE Population (Studies 0017 + 0018 Post-Amendment) -- FDA Adjudicated Data By Age Category

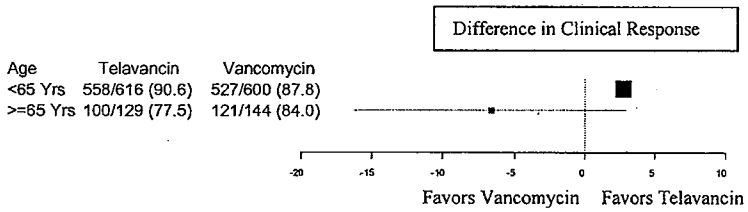
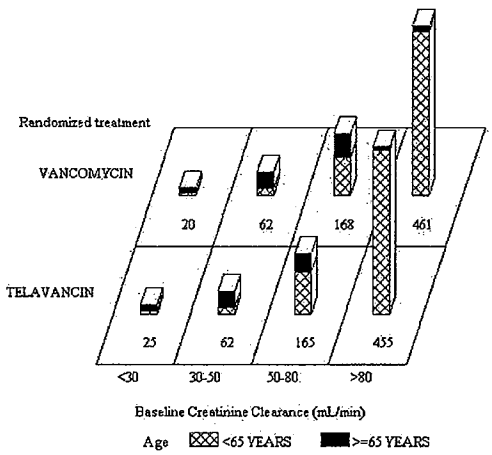


Table 5: Clinical Response at TOC by Age in the CE Population (Post-Amendment) -- FDA Adjudicated Data (Pooled Studies 0017 and 0018)

	Telavancin % (n/N)	Comparator % (n/N)	Difference (TLV – Comp) (95% CI)[1]	p-value[2]
Age				
< 65 Yrs.	90.6 (558/616)	87.8 (527/600)	2.7 (-0.8 , 6.2)	0.04
>= 65 Yrs.	77.5 (100/129)	84.0 (121/144)	-6.6 (-16.2 , 3.0)	

[1] Difference and 95% CI are based on analyses stratified by study
[2] p-value based on the interaction of treatment and subgroup variable controlling for study, treatment, region, diabetes, and subgroup variable.

Figure 4: Relationship of Age and Baseline Creatinine Clearance in the CE Population (Studies 0017+0018) – FDA Adjudicated Data



2. INTRODUCTION

2.1 Overview

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms:

Staphylococcus aureus (including methicillin-resistant strains, [redacted] *Streptococcus* pyogenes, *Streptococcus* agalactiae, *Streptococcus* anginosus grp. (including *S.* anginosus, *S.* intermedius and *S.* constellatus), and *Enterococcus* faecalis (vancomycin-susceptible isolates only). b(4)

The recommended dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous (IV) infusion once every 24 hours for 7 to 14 days. Because telavancin is eliminated primarily by the kidney, a dosage adjustment is recommended for patients with creatinine clearance ≤ 50 mL/min.

This submission contains three clinical studies conducted at the proposed dose of 10 mg/kg, one Phase II study (202b) and two Phase III studies (0017 and 0018). Note, that the dose was increased from 7.5 mg/kg to 10 mg/kg (Amendment 1) during the Phase III studies based on the results of the results of Study 202b. The Division agreed with the Sponsor's proposal that the results of the data prior to Amendment 1 will be used for the safety assessment only and not for the efficacy assessment. In addition to the data in studies 0017 and 0018 prior to Amendment 1, study 202a was also performed at the 7.5 mg/kg dose.

Each study was a double blind, double-dummy, randomized and active-controlled, comparing telavancin IV q 24 hr with standard therapy. The minimum duration of study therapy was 4 days in the Phase 2 studies and 7 days in the Phase 3 studies. The maximum allowable duration of study therapy was 14 days in all four studies. In the Phase 2 studies, which were conducted in the United States (U.S.) and South Africa, standard therapy was the investigator's prerandomization choice of an antistaphylococcal penicillin (nafcillin or oxacillin 2 g q 6 hours, or in South Africa, cloxacillin 0.5-1.0 g q 6 hours) or vancomycin (1 g IV q 12 hr). In the U.S., nafcillin, oxacillin and vancomycin are approved for use in treating cSSSI, the latter for infections due to Methicillin-resistant *Staphylococcus* aureus (MRSA). Cloxacillin is approved for use in South Africa but not in the U.S.; however, it is essentially the same as oxacillin and nafcillin in its spectrum of activity and pharmacokinetics, and hence was considered an acceptable comparator. In order to maintain the blind, dummy infusions were used.

The telavancin development program consists of a comprehensive set of clinical pharmacology studies, three studies evaluating telavancin 10 mg/kg in cSSSI, additional controlled studies evaluating telavancin 7.5 mg/kg in cSSSI, two ongoing Phase 3 controlled studies of telavancin 10 mg/kg in the treatment of hospital-acquired pneumonia (HAP), [redacted] Approximately 1697 patients and subjects have been exposed to telavancin and 1580 to comparator in these studies as of the data cutoff. For purposes of this application, the term "data cutoff" means all data in the sponsor's database as of 21 September 2006 for patients enrolled as of 15 May 2006. b(4)

2.2 Data Sources

The clinical study reports and datasets are located at the following location: \\Cdsesub1\nonectd\N22110\N_000\2006-12-06\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The two Phase III studies (Studies 0017 and 0018) were randomized, double blind, active-controlled, parallel group, multicenter, multinational trials. Patients with complicated Gram-positive skin and skin structure infections (primarily due to MRSA) were randomized to receive either telavancin 10 mg/kg IV once daily or vancomycin 1 g q 12 hours. Treatment duration was to be from 7 to 14 days. Investigators were encouraged to administer aztreonam and/or metronidazole in patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. In the Phase III studies, 862 (429 telavancin and 433 vancomycin) and 1035 (517 telavancin and 518 vancomycin) patients were enrolled in Studies 0017 and 0018 respectively. Study 0017 was conducted in 29 countries with approximately 73% of the patients enrolled in the United States, while Study 0018 was conducted in 17 countries with a slightly lower percentage (66%) of the patients enrolled from the United States.

Patients were randomized in a 1:1 ratio with randomization stratified on the combination of a pre-specified country grouping (see Table 6 for the pre-specified country groupings) and diabetic status (present or absent).

Table 6: Pre-specified Country Grouping used in Stratified Randomization

Country Grouping	Study 0017	Study 0018
Grouping 1	United States, Australia, and Belgium	United States, Canada, France, Germany, Italy, Spain, and United Kingdom
Grouping 2	South Africa	South Africa, Argentina, Chile, Peru, Singapore, Taiwan
Grouping 3	Croatia, Israel, Malaysia, and Russia	Korea, Lithuania, and Poland

Source: SCE, Table 16

Baseline evaluations were performed within 24 hours prior to treatment start and included pertinent medical history, an assessment of the signs and symptoms of the infection, measurement of the primary infection site, Gram's stain and culture of the primary infection site, blood culture, clinical laboratory tests, an X-ray to rule out osteomyelitis (if clinically indicated), and three 12-lead electrocardiograms (ECGs).

All patients were to have an End-of-Therapy (EOT) visit within 3 days following the last dose of study medication and a Follow-Up visit within 7 to 14 days after the EOT visit. A Test-of-Cure (TOC) assessment (assessment of signs/symptoms, measurement of infection site, assessment of clinical response) was conducted at the Follow-Up visit for patients who were a clinical cure or had an indeterminate outcome at the EOT visit. Both the EOT and TOC evaluations included an assessment of the clinical signs and symptoms of the infection, measurement of the primary infection site, an assessment of the clinical response by comparing a patient's signs and symptoms at the EOT or Follow-Up Visit, respectively, to those recorded at study admission,

Endpoints

Primary

The primary efficacy variable was the Clinical Response at Test-of-Cure. The Clinical Response was based on the following criteria: (1) Cured: resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibiotic therapy was necessary; (2) Not Cured: inadequate response to study therapy; and (3) Indeterminate: inability to determine outcome. For purposes of analysis, a Clinical Response of "Not Cured" at EOT was carried forward to TOC. Other efficacy parameters included By Patient Microbiologic Response, By Pathogen Microbiologic Response, Overall Therapeutic Response, clinical signs and symptoms of infection, duration of treatment with study medication, time to resolution of fever, and size of primary infection site.

Secondary

- By-Pathogen Microbiologic Response at Test-of-Cure for MRSA.
- By-Patient Microbiologic Response at Test-of-Cure.
- Overall Therapeutic Response at Test-of-Cure.

Sample size

A planned enrollment of 750 patients, under Protocol Amendment 1, of 375 patients per arm was expected to provide 300 clinically evaluable patients per arm, with the assumption that at least 80% of enrolled patients were to be clinically evaluable. Patients enrolled under the Original Protocol were not counted towards the planned enrollment under Protocol Amendment 1. If the population clinical cure rates for telavancin and vancomycin were both 80%, then a one-sided, 0.025 level test of the non-inferiority of telavancin relative to vancomycin, and employing a non-inferiority margin of 10%, was to have 86% power.

The protocol also included sample size and power calculations for the pooled analysis of Studies 0017 and 0018 in which the superiority of telavancin relative to vancomycin in MRSA infections was to be tested. The pooled enrollment of 750 patients per arm was expected to provide approximately 208 analyzable patients per arm; this assumed that two thirds of enrolled patients would have S. aureus, one half of the S. aureus would be MRSA, and five sixths of the MRSA infected patients would be evaluable. If the population clinical cure rates for telavancin and vancomycin were 90% and 80%, respectively, then a one sided, 0.025 test level had approximately 81% power to detect the superiority of telavancin over vancomycin.

Using the revised estimates, a pooled enrollment of approximately 850 MRSA patients is required in Studies 0017 and 0018 to ensure a statistically significant and clinically meaningful difference in clinical cure rates. While it was anticipated that Studies 0017 and 0018 would enroll at the same pace and contribute equally to the population of patients with MRSA, Study 0018 is enrolling at a rate that is ~1.2x faster than Study 0017. Therefore, the total enrollment for Study 0018 has been increased to approximately 1200 patients.

Statistical Analysis

Analysis Populations

1. All-Treated: The "All-Treated" (AT) analysis population was to be comprised of patients who received any amount of study medication. Patients were to be analyzed according to the treatment group assigned by randomization;
2. Modified All-Treated: The "Modified All-Treated" (MAT) analysis population was to be comprised of patients in the All-Treated population who also had a pathogen isolated at Baseline from the primary infection site and/or from blood cultures;
3. Clinically Evaluable: The "Clinically Evaluable" (CE) analysis population was to be comprised of patients in the All-Treated population who received the study medication assigned by the randomization schedule, and
    a. had no Baseline Gram-positive pathogens that were resistant to vancomycin;
    b. had no Baseline Gram-negative organisms known to be resistant to aztreonam;
    c. received at least 4 days (8 doses) of study medication for a Clinical Response of Cured or 3 days (6 doses) of study medication treatment for a Clinical Response of Not Cured;
    d. had study medication compliance of 80% to 120%;
    e. had a diagnosis of cSSSI with MRSA either suspected or confirmed;
    f. had a TOC Clinical Response of "Cured" or "Not Cured" or an EOT clinical response of "Not Cured";
    g. had a TOC evaluation made between Day 6P (where "Day xP" denotes "x" days after end of study medication) and Day 28P inclusive;
    h. did not receive a concomitant antibiotic at any time before the Test-of-Cure assessment that was potentially effective against the condition under study if the concomitant antibiotic was given for any reason other than lack-of-efficacy;
    i. complied with the selected exclusion and inclusion criteria outlined in the SAP
4. Microbiologically Evaluable: The "Microbiologically Evaluable" (ME) analysis population was to be comprised of patients in the CE population who had a Gram-positive pathogen recovered from pre-treatment cultures of the primary infection site and/or from blood cultures.

The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary. For the superiority analysis, the AT population served as the primary population.

The primary efficacy analysis was to initially test for the clinical non-inferiority of telavancin relative to vancomycin using a difference in the rate of clinical response at TOC and employing a non-inferiority margin of 10%. The testing was to be performed by using a 95% confidence interval for the difference in clinical response rates based on the normal approximation to the binomial distribution. If noninferiority was established, then statistical superiority would be examined using the confidence interval approach to determine whether the lower bound of 95% confidence interval was greater than zero.

Reviewer Comment:
The Sponsor has provided a justification for the 10% noninferiority margin, which is discussed in the Appendix.

If the two studies were able to demonstrate the noninferiority of telavancin to vancomycin, an additional goal was to demonstrate the superiority of telavancin 10 mg/kg over vancomycin in patients infected with MRSA pathogens at baseline. This analysis was to be performed pooled across Studies 0017 and 0018 in the AT population.

If telavancin is shown to have superior efficacy in patients infected with MRSA at baseline, then the efficacy and safety of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) will be examined to demonstrate that the advantages in the MRSA subpopulation do not occur to the detriment of the complementary subpopulation.

The Division had requested that the analyses be conducted differently in response to the Sponsor's Statistical Analysis Plan (SAP); however, these changes were not included in the Sponsor's primary analyses because the blind for the database had been broken. The differences in the analyses were in the timing of the TOC visit window, duration of study medication to be considered a CE cure, specimens for culture of the baseline pathogen, specific baseline pathogens that would qualify one to be part of the MAT and ME populations, window to collect the baseline pathogen, and laboratory to determine ME eligibility. Details can be found in Table 7.

Table 7: Differences between Sponsor Analyses and Agency Recommended Analyses

Criterion	SAP	Additional Analyses
Test-of-Cure/Follow-up window	Day 6P to Day 28P	Day 7P to Day 21P
Duration of Study Medication for CE Cure	At least 4 days (8 doses) of study medication, and compliance of 80% to 120% of intended doses	At least 5 days (10 doses) of study medication
Specimens for Culture of Baseline Pathogens	All specimens considered acceptable since non-acceptable specimen types were prohibited by protocol	If the specimen type was non-missing, the method was adjudicated by study medical monitors and the Principal Investigator as "acceptable". If specimen type was missing, it was considered acceptable.
Baseline Pathogens	Coagulase-negative staphylococci (e.g. S. epidermidis) accepted as baseline pathogens if the cSSSI type was wound infection	Coagulase-negative staphylococci accepted as baseline pathogens if the cSSSI type was wound infection, and that Gram-stain results must be consistent (i.e. contain Gram-positive cocci)
Baseline Pathogen window	Day -3 to Day 2	Day -1 to Day 1, unless patient was treatment failure, then Day -3 to Day 1

ME population	Patients with pathogens identified by the Central Laboratory, unless specimen lost or not viable, then local lab results could be used	Only pathogens identified by the Central Laboratory

Day xP represents the x^{th} day after randomization
Source: CSR, Appendix 26

The analyses that are presented below contain both the Sponsor's Analyses and also analyses based on Agency adjudicated results. The Agency analysis contains the changes outlined in Table 7 as well as the exclusion of Site 38091 and changes to evaluability and outcome, both clinical and microbiological, due to late surgical procedures that were performed and discontinuations and subsequent antibiotic use. These changes were made because of issues identified by Dr. Janice Pohlman, the clinical reviewer. For further details, please see the review of Dr. Janice Pohlman. Site 38091 was excluded because of issues identified during the DSI inspection.

The disposition of patients was similar between the two treatment arms for both studies and can be found in Table 8.

Table 8: Disposition of Patients for Studies 0017 and 0018 (Post-Amendment)

	Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
Randomized	429	433	517	518
Randomized by Not Treated	3	4	15	8
Received Study Drug [1]	426	429	502	510
Completed The Intended Course Of Study Therapy	350 (82)	355 (83)	396 (79)	411 (81)
Resolution of Signs and Symptoms in ≤ 14 days	341 (80)	342 (80)	384 (76)	398 (78)
Infection not resolved but patient received maximum allowable 14 days of treatment	9 (2)	13 (3)	12 (2)	13 (3)
Did not complete the intended course of study therapy	76 (18)	74 (17)	106 (21)	99 (19)
Unsatisfactory Therapeutic Response	14 (3)	13 (3)	10 (2)	15 (3)
Death	2 (<1)	2 (<1)	2 (<1)	3 (<1)
Two Consecutive ECG's With QTC > 500 msec	0 (0)	1 (<1)	1 (<1)	1 (<1)
Adverse Event	29 (7)	22 (5)	43 (9)	28 (5)
Patient Withdrew Consent	11 (3)	14 (3)	16 (3)	18 (4)
Major Protocol Deviation	1 (<1)	2 (<1)	8 (2)	1 (<1)
Lost To Follow-Up	6 (1)	6 (1)	7 (1)	9 (2)
Infection due to Gram-negative organism only	2 (<1)	4 (<1)	5 (1)	6 (1)
Persistent *S. aureus* bacteremia	0	0	1 (<1)	0
Other	11 (3)	10 (3)	13 (3)	18 (4)

[1] Percentages in the lower half of the table are based on the % of patients who received study drug, (In Study 0017, 426 for telavancin and 429 for vancomycin; and in Study 0018, 502 for telavancin and 510 for vancomycin)
Source: ISE, Table 5-2

The number of patients in each treatment group was evenly balanced for both the Sponsor's and Agency analyses in the AT, CE, MAT, and ME population, see Table 9. In Study 0017, the all-treated population contained 426 telavancin and 429 vancomycin treated patients for both the Sponsor's and Agency analyses. In Study 0018, the all-treated population contained 502 telavancin and 510 vancomycin treated patients in the Sponsor's analyses, while there are 472 telavancin and 489 vancomycin treated patients in the Agency analyses. The examination of the other co-primary analysis population, CE, showed similar balance between treatment groups -- in study 0017, there were 346 telavancin and 349 vancomycin treated patients in the Sponsor's analyses and 343 telavancin and 348 vancomycin treated patients in the Agency analyses. In Study 0018, there were 399 telavancin and 395 vancomycin treated patients in the Sponsor's analyses and 365 telavancin and 363 vancomycin treated patients in the Agency analyses.

Table 9: Analysis Populations (Post-Amendment)

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018)		Study 0017		Study 0018	
Population	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
AT	426 (100)	429 (100)	502 (100)	510 (100)	426 (100)	429 (100)	472 (100)	489 (100)
MAT	307 (72)	322 (75)	373 (74)	381 (75)	260 (61)	274 (64)	303 (64)	322 (66)
CE	346 (81)	349 (81)	399 (79)	395 (77)	343 (81)	348 (81)	365 (77)	363 (74)
ME	237 (56)	255 (59)	290 (58)	281 (55)	219 (51)	234 (55)	240 (51)	239 (49)

Source: SCE, Table 20

The demographics of the AT population are summarized in Table 10 for both the Sponsor's and Agency analyses. The two treatment groups appeared similar with respect to demographic baseline characteristics of age, race and gender in both the Sponsor's and Agency analyses. For both studies, the proportion of patients from US sites was similar across treatment arms, with ~70-75% of the patients from US sites in Study 0017 and ~60-65% in Study 0018. Very few patients were on hemodialysis in either study (FDA analysis: 10/855 in Study 0017 and 4/961 in Study 0018).

Other baseline microbiological characteristics in the MAT population are provided in Table 11. The two treatment arms are similar for gram stain type for the baseline pathogens, the number of baseline pathogens, and the incidence of baseline *S.* aureus pathogens with the PVL gene.

Table 10: Patient Demographics in the AT Population for Studies 0017 and 0018 (Post-Amendment)

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	TLV (N=426)	VANC (N=429)	TLV (N=502)	VANC (N=510)	TLV (N=426)	VANC (N=429)	TLV (N=472)	VANC (N=489)
US vs. Non-US								
US	306 (72)	316 (74)	328 (65)	336 (66)	306 (72)	316 (74)	298 (63)	315 (64)
Non-US	120 (28)	113 (26)	174 (35)	174 (34)	120 (28)	113 (26)	174 (37)	174 (36)
Age								
Mean	48.9	47.7	48.7	49.6	48.9	47.7	49.0	49.8
Min, Max	18.0, 96.0	17.0, 90.0	18.0, 95.0	18.0, 91.0	18.0, 96.0	17.0, 90.0	18.0, 95.0	18.0, 91.0
Age Distribution								
<65 years	337 (79)	357 (83)	417 (83)	403 (79)	337 (79)	357 (83)	391 (83)	386 (79)
≥65 years	89 (21)	72 (17)	85 (17)	107 (21)	89 (21)	72 (17)	81 (17)	103 (21)
Age Distribution								
<75 years	381 (89)	398 (93)	460 (92)	463 (91)	381 (89)	398 (93)	431 (91)	442 (90)
≥75 years	45 (11)	31 (7)	42 (8)	47 (9)	45 (11)	31 (7)	41 (9)	47 (10
Sex								
Male	230 (54)	248 (58)	287 (57)	311 (61)	230 (54)	248 (58)	268 (57)	299 (61)
Female	196 (46)	181 (42)	215 (43)	199 (39)	196 (46)	181 (42)	204 (43)	190 (39)
Race								
American Indian / Alaska Native	3 (<1)	2 (<1)	8 (2)	9 (2)	3 (<1)	2 (<1)	7 (1)	9 (2)
Asian	7 (2)	9 (2)	38 (8)	44 (9)	7 (2)	9 (2)	38 (8)	44 (9)
Black, of African heritage	59 (14)	52 (12)	73 (15)	76 (15)	59 (14)	52 (12)	71 (15)	74 (15)
Hawaiian / Pacific Islander	3 (<1)	9 (2)	4 (<1)	8 (2)	3 (<1)	9 (2)	4 (<1)	8 (2)
White	349 (82)	353 (82)	375 (75)	370 (73)	349 (82)	353 (82)	348 (74)	351 (72)
Aborigine	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)
Mixed Race	4 (<1)	3 (<1)	4 (<1)	3 (<1)	4 (<1)	3 (<1)	4 (<1)	3 (<1)
Body Mass Index (kg/m^2)								
Underweight < 18.5 (kg/m^2)	7 (2)	10 (2)	8 (2)	7 (1)	7 (2)	10 (2)	8 (2)	7 (1)
Normal Wt 18.5 - < 25 (kg/m^2)	138 (32)	128 (30)	149 (30)	147 (29)	138 (32)	128 (30)	142 (30)	143 (29)
Overweight 25 - < 30 (kg/m^2)	133 (31)	137 (32)	144 (29)	157 (31)	133 (31)	137 (32)	138 (29)	149 (31)
Obese 30 - < 40 (kg/m^2)	104 (24)	120 (28)	141 (28)	137 (27)	104 (24)	120 (28)	127 (27)	132 (27)
Morbidly Obese ≥40 (kg/m^2)	44 (10)	34 (8)	60 (12)	61 (12)	44 (10)	34 (8)	57 (12)	57 (12)
Missing	0	0	0	1	0	0	0	1
Baseline Serum Creatinine Clear Clearance								
>80 mL/min	274 (65)	291 (69)	311 (64)	308 (62)	274 (65)	291 (69)	289 (64)	291 (62)
>50-80 mL/min	85 (20)	85 (20)	120 (25)	121 (25)	85 (20)	85 (20)	116 (26)	119 (25)
30-50 mL/min	41 (10)	35 (8)	34 (7)	47 (10)	41 (10)	35 (8)	32 (7)	46 (10)
<30 mL/min	21 (5)	12 (3)	18 (4)	17 (3)	21 (5)	12 (3)	17 (4)	16 (4)
Missing	5	6	19	17	5	6	18	17
Hemodialysis								
Patient on hemodialysis	6 (1)	4 (<1)	3 (<1)	1 (<1)	6 (1)	4 (<1)	3 (<1)	1 (<1)
Patient not on hemodialysis	420 (99)	425 (99)	498 (99)	509 (99)	420 (99)	425 (99)	468 (99)	488 (100)
Missing	0	0	1	0	0	0	1	0

Source: SCE, Table 24, CSR Table 7-2

Table 11: Demographics in the Micro AT Population

Subgroup	Sponsor Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	TLV (N=307)	VANC (N=322)	TLV (N=373)	VANC (N=381)	TLV (N=260)	VANC (N=274)	TLV (N=303)	VANC (N=322)
Baseline Pathogen								
Gram + Pathogens Only	244 (81)	274 (85)	315 (85)	314 (83)	224 (88)	248 (91)	260 (88)	280 (88)
Gram - Pathogens Only	22 (7)	15 (5)	12 (3)	17 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Mixed Gram + / Gram - Infection	35 (12)	32 (10)	45 (12)	46 (12)	30 (12)	25 (9)	37 (12)	38 (12)
No Primary Site Infections	6	1	1	4	6	1	6	4
#Patients (%) w/any primary infection site pathogens								
1 Pathogen	234 (78)	264 (82)	300 (81)	288 (76)	204 (80)	232 (85)	240 (81)	245 (77)
2 Pathogens	50 (17)	41 (13)	45 (12)	53 (14)	35 (14)	29 (11)	34 (12)	44 (14)
3 Pathogens	11 (4)	14 (4)	16 (4)	20 (5)	9 (4)	10 (4)	12 (4)	16 (5)
4+ Pathogens	6 (2)	2 (<1)	11 (3)	16 (4)	6 (2)	2 (<1)	11 (4)	13 (4)
No Primary Site Infections	6	1	1	4	6	1	6	4
Presence/Absence of PVL Gene								
MRSA	146	167	204	202	135	151	171	175
PVL +	115 (79)	134 (80)	155 (76)	162 (80)	112 (83)	132 (87)	143 (84)	153 (87)
PVL -	26 (18)	23 (14)	31 (15)	24 (12)	23 (17)	19 (13)	28 (16)	22 (13)
MSSA	104	106	107	120	95	89	91	110
PVL+	32 (31)	31 (29)	31 (29)	35 (29)	31 (33)	31 (35)	30 (33)	35 (32)
PVL-	70 (67)	63 (59)	68 (64)	78 (65)	64 (67)	58 (65)	61 (67)	75 (68)

Source: CSR Table 8-10

Efficacy Results

Primary Analyses

In both of the Phase III studies (Studies 0017 and 0018), telavancin was noninferior to vancomycin for the primary endpoint of clinical response at TOC in both the AT and CE populations based on the treatment difference in clinical response rates using a 10% noninferiority margin (see Table 12). The finding was consistent in both the Sponsor's analyses and the Agency analyses of the primary endpoint. However, it is noted for Study 0018 that the Agency analyses resulted in a ~3% decrease in the treatment difference for both the AT and CE population compared to the Sponsor's analyses. As the Sponsor's analysis plan proposed testing for superiority if noninferiority was demonstrated, it is noted that the studies did not provide evidence that telavancin was statistically superior to vancomycin in either of the studies.

For Study 0017, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.0% with a corresponding 95% CI of (-4.8%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 1.0% with a corresponding 95% CI of (-5.0%, 7.0%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.3% with a corresponding

95% CI of (-3.6%, 6.3%) while the Agency analysis found a similar result with a treatment difference of 1.5% with a corresponding 95% CI of (-4.0%, 7.0%).

For Study 0018, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 3.4% with a corresponding 95% CI of (-1.9%, 8.7%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-5.5%, 5.7%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.1% with a corresponding 95% CI of (-3.4%, 5.6%) while the Agency analysis found a similar result with a treatment difference of -3.8% with a corresponding 95% CI of (-8.8%, 1.3%). There was noticeable decrease (~3%) in the treatment difference between telavancin and vancomycin in both the AT and CE populations that was caused by a decrease in the telavancin response rates in both the populations.

Table 12: Clinical Response at TOC (Post-Amendment Patients)

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated								
Cure	323 (75.8)	321 (74.8)	387 (77.1)	376 (73.7)	309 (72.5)	307 (71.6)	348 (73.7)	360 (73.6)
Total	426	429	502	510	426	429	472	489
Difference (95% CI)[1]	1.0 (-4.8 , 6.8)		3.4 (-1.9 , 8.7)		1.0 (-5.0, 7.0)		0.1 (-5.5, 5.7)	
Clinically Evaluable								
Cure	304 (87.9)	302 (86.5)	354 (88.7)	346 (87.6)	289 (84.3)	288 (82.8)	306 (83.8)	318 (87.6)
Total	346	349	399	395	343	348	365	363
Difference (95% CI)[1]	1.3 (-3.6 , 6.3)		1.1 (-3.4 , 5.6)		1.5 (-4.0, 7.0)		-3.8 (-8.8, 1.3)	

[1] Difference in Cure rates (telavancin – vancomycin) and the two-sided 95% CI was stratified by study.
Source: ISE, Table 5-33

As it was the Sponsor's objective to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population has been demonstrated, the discussion of these results will follow. The analysis plan was to pool data across Studies 0017 and 0018 to perform the analyses. The results of the two studies were not found to be substantially dissimilar (FDA Analysis: Breslow-Day statistic=1.562, p=0.21) so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses. However, it should be noted that in the FDA analysis, there was a noticeable difference in the estimates for the treatment difference (telavancin – vancomycin) in response rates for the MRSA subgroup between Studies 0017 and 0018 (Study 0017: -4.7%; Study 0018: 4.0%).

In patients with a MRSA pathogen isolated at baseline, the Sponsor failed to demonstrate the superiority of telavancin to vancomycin in clinical response at TOC (see Table 13). This was consistent in both the analyses performed by the Sponsor and the Agency. In the pooled analysis

of the MRSA patients, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 0.4% with a corresponding 95% CI of (-5.9%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-6.7%, 6.8%) for the AT population. The test of the difference in clinical response at TOC between telavancin and vancomycin yielded clearly non-statistically significant findings with 2-sided p-values of 0.889 and 0.985 in the Sponsor's and Agency analyses.

Table 13: Clinical Response at TOC in All-treated patients with MRSA at baseline (Post-Amendment)

	Sponsor's Analysis						FDA Analysis					
	Study 0017		Study 0018		Studies 0017 + 0018		Study 0017		Study 0018		Studies 0017 + 0018	
	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)
Cure	104 /146 (71.2)	122/167 (73.1)	161 /204 (78.9)	155/202 (76.7)	265/350 (75.7)	277/369 (75.1)	92/135 (68.1)	110/151 (72.8)	136/170 (80)	133/175 (76)	228/305 (74.8)	243/326 (74.5)
Diff (95% CI)	-1.8 (-11.8 , 8.1)		2.2 (-5.9 , 10.3)		0.4 (-5.9, 6.8)		-4.7 (-15.3, 5.9)		4 (-4.7, 12.7)		0.1 (-6.7, 6.8)	
p-value					0.889						0.985	

Difference and 95% CI are computed using a stratified analysis by study.
p-value is a two-sided test based on a stratified analysis
Source: ISE, Table 5-34

The analysis of the efficacy of telavancin in the complement of the MRSA subpopulation, (i.e. in patients that are not known to be infected with MRSA at baseline) was examined to demonstrate that the potential advantages in the MRSA subpopulation are not observed at the detriment of the complementary subpopulation. However, since there was no evidence of the superiority of telavancin to vancomycin, the analysis of the MRSA-complement is less critical. However, a summary of the results is found in Table 14.

Table 14: Clinical Response at TOC in the All-Treated MRSA Complement (Post-Amendment)

	Sponsor's Analysis						FDA Analysis					
	Study 0017		Study 0018		Studies 0017 + 0018		Study 0017		Study 0018		Studies 0017 + 0018	
	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)	TLV N (%)	VANC N (%)
Cure	219/280 (78.2)	199/262 (76.0)	226/298 (75.8)	221/308 (71.8)	445/578 (77.0)	420/570 (73.7)	217/291 (74.6)	212/302 (70.2)	197/278 (70.9)	227/314 (72.3)	429/593 (72.3)	424/592 (71.6)
Diff (95% CI)	2.3 (-4.8 , 9.3)		4.1 (-2.9 , 11.1)		3.2 (-1.8 , 8.2)		3.7 (-3.6, 11)		-2.1 (-9.2, 5.1)		0.7 (-4.4, 5.8)	

Difference and 95% CI are computed using a stratified analysis by study.
Source: ISE, Table 5-35

Secondary endpoint

For the secondary endpoint clinical response at TOC in the microbiological populations (MAT and ME), similar results to the primary analyses were found (see Table 15).

Table 15: Clinical Response in the Microbiological Populations

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
Micro All-Treated								
Cure	235 (76.5)	241 (74.8)	284 (76.1)	282 (74.0)	196 (75.4)	204 (74.5)	225 (74.3)	239 (74.2)
Total	307	322	373	381	260	274	303	322
Difference (95% CI)[1]	1.7 (-5.0, 8.4)		2.1 (-4.0, 8.3)		0.9 (-6.4, 8.3)		0 (-6.8, 6.9)	
Microbiological Evaluable								
Cure	210 (88.6)	220 (86.3)	260 (89.7)	250 (89.0)	187 (85.4)	196 (83.8)	201 (83.8)	208 (87)
Total	237	255	290	281	219	234	240	239
Difference (95% CI)[1]	2.3 (-3.5, 8.2)		0.7 (-4.4, 5.8)		1.6 (-5, 8.3)		-3.3 (-9.6, 3)	

Source: CSR, Supporting Table 38

Efficacy by Baseline Pathogens

Clinical response at TOC in the MAT and ME populations broken down by baseline pathogen are presented for both treatment arms in Table 16 and Table 17 respectively. The results are presented by individual study and pooled across Studies 0017 and 0018. The pathogen subgroups that are presented are those that the Sponsor is pursuing in their label.

Table 16: Clinical Response at TOC in the MAT Population (Post-Amendment) -- By Baseline Pathogen in FDA Adjudicated Data

	Study 0017		Study 0018		Pooled		Difference
Pathogen	TLV	VANC	TLV	VANC	TLV	VANC	(TLV-VANC)
STAPHYLOCOCCUS AUREUS, MRSA	92/135 (68.2)	110/151 (72.9)	135/170 (79.4)	133/175 (76)	227/305 (74.4)	243/326 (74.5)	-0.3 (-7, 6.5)
STAPHYLOCOCCUS AUREUS, MSSA	77/96 (80.2)	67/89 (75.3)	67/91 (73.6)	76/111 (68.5)	144/187 (77)	143/200 (71.5)	5 (-3.6, 13.7)
ENTEROCOCCUS FAECALIS	14/15 (93.3)	12/17 (70.6)	12/15 (80)	18/25 (72)	26/30 (86.7)	30/42 (71.4)	14.8 (-3.7, 33.3)
STREPTOCOCCUS PYOGENES	9/10 (90)	9/11 (81.8)	7/12 (58.3)	13/19 (68.4)	16/22 (72.7)	22/30 (73.3)	-2.5 (-26.2, 21.3)
STREPTOCOCCUS AGALACTIAE	8/10 (80)	4/6 (66.7)	7/11 (63.6)	13/15 (86.7)	15/21 (71.4)	17/21 (81)	-9.5 (-36.3, 17.3)
STREPTOCOCCUS ANGINOSUS	6/7 (85.7)	3/3 (100)	4/6 (66.7)	5/5 (100)	10/13 (76.9)	8/8 (100)	-25 (-49.2, -0.9)
STREPTOCOCCUS CONSTELLATUS	0/1 (0)	2/2 (100)	4/6 (66.7)	4/5 (80)	4/7 (57.1)	6/7 (85.7)	-30.4 (-71.7, 11.0)
STREPTOCOCCUS INTERMEDIUS	2/2 (100)	0/1 (0)	0/1 (0)	0/1 (0)	2/3 (66.7)	0/2 (0)	57.1 (57.1, 57.1)

Table 17: Clinical Response at TOC in the ME population (Post-Amendment) -- By Pathogen in FDA Adjudicated Data

Pathogen	Study 0017		Study 18		Pooled		Difference (TLV-VANC) (95% CI)
	TLV	VANC	TLV	VANC	TLV	VANC	
STAPHYLOCOCCUS AUREUS, MRSA	90/109 (82.6)	107/126 (84.9)	119/131 (90.8)	118/137 (86.1)	209/240 (87.1)	226/264 (85.6)	1.4 (-4.6, 7.4)
STAPHYLOCOCCUS AUREUS, MSSA	70/81 (86.4)	66/79 (83.5)	62/80 (77.5)	64/74 (86.5)	133/162 (82.1)	131/154 (85.1)	-2.9 (-11.1, 5.2)
ENTEROCOCCUS FAECALIS	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81)	22/23 (95.7)	28/35 (80)	15.4 (-0.8, 31.6)
STREPTOCOCCUS PYOGENES	9/10 (90)	9/10 (90)	7/9 (77.8)	11/12 (91.7)	16/19 (84.2)	20/22 (90.9)	-7 (-27.6, 13.5)
STREPTOCOCCUS AGALACTIAE	8/9 (88.9)	3/3 (100)	6/10 (60)	10/12 (83.3)	14/19 (73.7)	13/15 (86.7)	-19.8 (-46.6, 7.1)
STREPTOCOCCUS ANGINOSUS	5/5 (100)	3/3 (100)	4/5 (80)	3/3 (100)	9/10 (90)	6/6 (100)	-10 (-27.5, 7.5)
STREPTOCOCCUS CONSTELLATUS	0/1 (0)	2/2 (100)	2/3 (66.7)	2/2 (100)	3/5 (60)	4/4 (100)	-50 (-78.3, -21.7)
STREPTOCOCCUS INTERMEDIUS	2/2 (100)	0/0 (0)	0/1 (0)	0/0 (0)	2/3 (66.7)	0/0 (0)	-7 (-27.6, 13.5)

Difference and 95% CI are based on analyses stratified by study

Treatment Duration

The dosing in the study was designed to be for 7-14 days in length. As can be seen in Table 18, the distribution of the day on treatment for telavancin is pretty evenly spread across the 7-14 day period with modes at 7-8 days and 14-15 days, which represent the recommended minimum and maximum duration lengths for these trials.

Table 18: Number of Days on Treatment in the AT Population (Post-Amendment) -- FDA Analysis

#Day on Treatment	Study 17		Study 18	
	TELAVANCIN	VANCOMYCIN	TELAVANCIN	VANCOMYCIN
1	8 (1.9)	6 (1.4)	6 (1.3)	14 (2.9)
2	6 (1.4)	9 (2.1)	13 (2.8)	12 (2.5)
3	12 (2.8)	7 (1.6)	13 (2.8)	15 (3.1)
4	9 (2.1)	11 (2.6)	9 (1.9)	7 (1.4)
5	6 (1.4)	13 (3)	14 (3)	7 (1.4)
6	12 (2.8)	7 (1.6)	15 (3.2)	13 (2.7)
7	37 (8.7)	31 (7.2)	69 (14.6)	64 (13.1)
8	78 (18.3)	59 (13.8)	110 (23.3)	110 (22.5)
9	30 (7)	25 (5.8)	28 (5.9)	31 (6.3)
10	32 (7.5)	39 (9.1)	56 (11.9)	37 (7.6)
11	33 (7.8)	28 (6.5)	28 (5.9)	38 (7.8)
12	19 (4.5)	35 (8.2)	17 (3.6)	22 (4.5)
13	20 (4.7)	17 (4)	19 (4)	17 (3.5)
14	34 (8)	34 (7.9)	51 (10.8)	68 (13.9)
15	90 (21.1)	108 (25.2)	23 (4.9)	32 (6.5)
16			0 (0)	1 (0.2)
17			0 (0)	0 (0)
18			1 (0.2)	1 (0.2)
Total	426	429	472	489

3.2 Evaluation of Safety

Please refer to the clinical review of the reviewing medical officer, Dr. Janice Pohlman.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

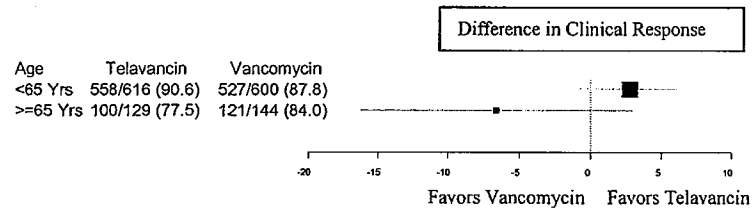
4.1 Gender, Race and Age

To look for subgroup differences by gender, race, or age, subgroup analyses for the primary endpoint, clinical response at TOC, in the CE population using the FDA adjudicated data were conducted. In order to assess the effect of the subgroup variable on the treatment difference, we examined the interaction of the treatment group and the subgroup variable in a logistic regression that modeled clinical response at TOC with study, treatment, region, diabetes, the subgroup variable, the treatment by subgroup variable as predictors in the model. The results are presented below in Table 19.

For gender, the clinical response rates were similar for telavancin and vancomycin across gender. In addition, treatment differences were also similar for males and females (p=0.785).

For age, the clinical response rates for both treatment groups decreased in the ≥65 year old stratum as compared to the <65 year old stratum. This is not unexpected as older patients often represent a sicker population with more comorbidities. However, the drop in response rate was much larger for telavancin (<65: 558/616 (90.6%); ≥65: 100/129 (77.5%)) than for vancomycin (<65: 527/600 (87.8%); ≥65: 121/144 (84.0%)). The treatment difference (telavancin – vancomycin) differed significantly depending on the baseline age of patient (p-value=0.04). In patients <65 years old at baseline, the difference was 2.7% with a 95% CI of (-0.8, 6.2) while in the ≥65 old stratum, the difference was -6.6% with a 95% CI of (-16.2%, 3.0) (see Figure 5)

Figure 5: Clinical Response at TOC in the CE Population (Studies 0017 + 0018 Post-Amendment) -- By Age Category



For race, the response rates across racial subgroups were similar between the treatment groups; thus the treatment differences were similar across races (p=0.283). The Black subgroup had a slightly higher response rate for both treatment groups than for in the White subgroup which contained the majority of the patients. However, almost all of the Black patients were younger than 65 years of age (telavancin: 103/104 (99.0%); vancomycin: 95/95 (95.8%) which was not

the case for the White subgroup. This is depicted in Figure 6. Thus, the negative age effect found above could explain the higher response rates in the black subgroup.

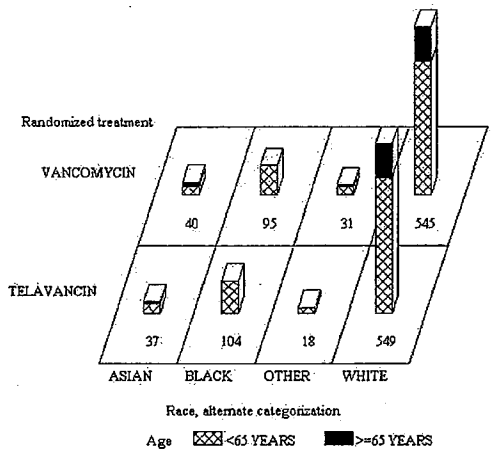
Table 19: Subgroup Analyses of Clinical Response at TOC by Gender, Race and Age in the CE Population (Post-Amendment) -- FDA Adjudicated Data (Pooled Studies 0017 and 0018)

	Telavancin % (n/N)	Comparator % (n/N)	Difference (TLV – Comp) (95% CI)[1]	p-value[2]
Age				
< 65 Yrs.	90.6 (558/616)	87.8 (527/600)	2.7 (-0.8 , 6.2)	0.04
≥ 65 Yrs.	77.5 (100/129)	84.0 (121/144)	-6.6 (-16.2 , 3.0)	
Sex				
Male	88.8 (366 /412)	87.3 (378 /433)	1.5 (-2.8 , 5.9)	0.785
Female	87.7 (292 /333)	86.8 (270 /311)	0.9 (-4.3 , 6.0)	
Race				
Asian	88.6 (31 /35)	90.5 (38 /42)	-2.0 (-17.6 , 13.2)^	0.283
Black	94.4 (102 /108)	86.9 (86 /99)	7.7 (-0.8 , 15.8)^	
White	87.8 (510 /581)	87.4 (501 /573)	0.3 (-3.5 , 4.1)	
Other	71.4 (15 /21)	76.7 (23 /30)	-3.0 (-26.5 , 18.4)^	

[1] Difference and 95% CI are based on analyses stratified by study

[2] p-value based on the interaction of treatment and subgroup variable controlling for study, treatment, region, diabetes, and subgroup variable.

Figure 6: Distribution of Age and Race in the CE Population (Studies 0017 + 0018)



4.2 Other Special/Subgroup Populations

To examine subgroup differences by US vs. ex-US, history of diabetes, baseline renal function, and wound type, subgroup analyses for clinical response at TOC, in the CE population using the FDA adjudicated data were conducted. In order to assess the effect of the subgroup variable on the treatment difference, we examined the interaction of the treatment group and the subgroup variable in a logistic regression that modeled clinical response at TOC with study, treatment,

region, diabetes, the subgroup variable, the treatment by subgroup variable as predictors in the model. The results are presented below in Table 20.

US and ex-US patients performed similarly for the telavancin group (US: 398/477 (83.4%); ex-US: 197/231 (85.3%)). In the vancomycin group, for ex-US patients the response rate was slightly higher than for US patients (405/489 (82.85)). However, the treatment difference did not differ statistically between US and ex-US patients (p=0.32).

In looking at wound type, both telavancin and vancomycin had similar response rates for most for the wound types. The rates differed slightly for the Infected Ulcer and Infected Burn subgroups in the telavancin arm but the number of patients in these two subgroups was small their with the resulting lower precision in these estimates.

For renal impairment (baseline creatinine clearance), the clinical response rates for the vancomycin group was relatively constant across the renal impairment categories. However, in the telavancin group, the response rate decreased markedly as the level of renal impairment increased (Normal: 406/455 (89.2%); mild: 131/165 (79.4%); moderate: 43/62 (69.4%); severe: 15/25 (60%)). The treatment difference between telavancin and vancomycin decreased significantly (p=0.02) as the level of renal impairment increased.

For history of diabetes, the response rate was higher for non-diabetics relative to diabetics for both groups. However, there was treatment difference differed significantly (p=0.08) depending on whether one had a history of diabetes or not. Patients who had a history of diabetes performed worse on telavancin relative to vancomycin than those without a history of diabetes.

Table 20: Subgroup Analyses of Clinical Response at TOC in Other Subgroup Populations the CE Population (Post-Amendment) -- FDA Adjudicated Data (Pooled Studies 0017 and 0018)

	Telavancin % (n/N)	Vancomycin % (n/N)	Difference (TLV – Comp) (95% CI)[1]	p-value[2]
US/Non-US				
US	398/477 (83.4)	405/489 (82.8)	0.6 (-4.1, 5.3)	0.32
Non-US	197/231 (85.3)	201/222 (90.5)	-5.3 (-11.3; 0.7)	
History of Diabetes				
Diabetic	131/171 (76.61)	146/183 (79.8)	-3.3 (-11.9, 5.3)	0.08
Non-diabetic	463/536 (86.4)	460/528 (87.1)	-0.7 (-4.8, 3.3)	
Baseline Creatinine Clearance				
>80 mL/min (Normal)	406/455 (89.2)	397/461 (86.1)	3.1 (-1.2, 7.3)	0.02
>50-80 mL/min (mild)	131/165 (79.4)	142/168 (84.5)	-5.2 (-13.5, 3)	
30-50 mL/min (moderate)	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)	
<30 mL/min (severe)	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.4, 5.3)	
Wound Type				
Major Abscess	266/307 (86.6)	262/301 (87.0)	-0.4 (-5.7, 5)	0.99
Wound Infection	88/109 (80.7)	84/97 (86.6)	-5.7 (-15.8, 4.4)	
Deep/Extensive Cellulitis	199/240 (82.9)	228/274 (83.2)	-0.2 (-6.7, 6.2)	
Infected Ulcer	30/40 (75.0)	26/32 (81.2)	-6.8 (-26.2, 12.6)	
Infected Burn	12/12 (100.0)	6/7 (85.7)	9.9 (-5.9, 25.6)	

[1] Difference and 95% CI are based on analyses stratified by study

[2] p-value based on the interaction of treatment and subgroup variable controlling for study, treatment, region, diabetes, and subgroup variable except for the US/ex-US analysis where region was excluded from the model because it is collinear to the subgroup variable and similarly diabetes was excluded when history of diabetes was in the model.

Note that both the history of diabetes and age are strongly correlated with baseline renal impairment, Figure 7 and Figure 8 respectively. As expected, the proportion of older patients, ≥65 years old, increased as the level of baseline renal impairment increased. Similarly, the proportion of patients with a history of diabetes increased as the level of baseline renal impairment increased.

Figure 7: Relationship of Age and Baseline Creatinine Clearance (CE Population: Studies 0017+0018 Post-Amendment)

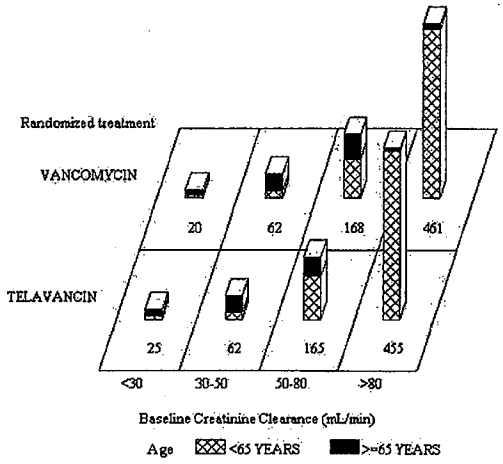
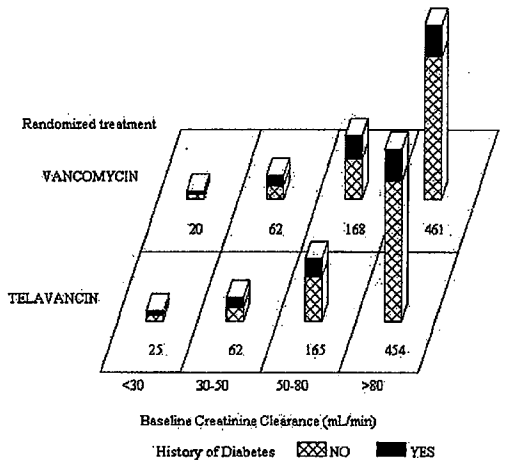


Figure 8: Relationship of History of Diabetes and Baseline Creatinine Clearance (CE Population: Studies 0017+0018 Post-Amendment)



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following statistical issues were found during the review of this submission – the adequacy of the justification of the 10% noninferiority margin, the sample size modification, and the large proportion of patients from two sites in Study 0017. These issues had the potential to affect the assessment of efficacy of telavancin, however further review suggested that the first three issues were not felt to affect the overall determination of efficacy of telavancin in the treatment of cSSSI with details discussed in this section. There was a last issue that involved the inconsistency of the treatment effect across levels of renal impairment that still remains an outstanding issue. The issues will be discussed below and their impact assessed.

Noninferiority margin justification

A 10% noninferiority margin was used in both Studies 0017 and 0018.

Reviewer's Comments
Based on data submitted by the Sponsor and the Agency's review of the literature and other supportive evidence, the 10% noninferiority margin is acceptable for the treatment of cSSSI using vancomycin as the comparator. Details can be found in the appendix.

Sample size increase in Study 0018

In study 0018, the sample size was increased during the trial in an attempt to demonstrate the superiority of telavancin relative to vancomycin in the subgroup of patients with a baseline MRSA pathogen isolated. It was agreed by the Division that the analysis would performed pooled across Studies 0017 and 0018 and that the sample size increase would be based on a blinded (pooled) MRSA evaluability rate in order to have adequate statistical power for the pooled MRSA superiority analysis. The number of patients enrolled after the sample size increase was approximately 1/4 of the total for Study 0018. In a sensitivity analysis to assess the effect of the sample size increase (see Table 21, it was found that the results of the pre- and post-sample size increase were similar although it appears that the vancomycin response rate increased slightly (AT population -- Pre: 72.6% vs. Post: 77.3%) subsequent to the sample size increase while the telavancin response rate was relatively constant. Thus the point estimate of the difference decreased slightly subsequent to the sample size increase. Based on these sensitivity analyses, no evidence was found that the sample size increase introduced bias into study.

Table 21: Sensitivity analysis of Clinical Response at TOC examing effect of sample size increase

	Study 0018 enrolled prior to sample size increase		Study 0018 enrolled subsequent to sample size increase	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated				
Cure	263/358 (73.5)	275/379 (72.6)	85/114 (74.6)	85/110 (77.3)
Difference (95% CI)[1]	0.9 (-5.5, 7.3)		-2.7 (-13.9, 8.5)	
Clinically Evaluable				
Cure	231/275 (84)	243/278 (87.4)	75/90 (83.3)	75/85 (88.2)
Difference (95% CI)[1]	-3.4 (-9.2, 2.4)		-4.9 (-15.2, 5.4)	

Effect of two large centers in Study 0017

In Study 0017, the top two highest enrolling sites, Site 38101 and Site 38271 enrolled 260 (30%) and 201 (24%) of the patients. The next highest enrolling site enrolled 61 (7%) of the patients. A sensitivity analysis was performed to assess the effect of these two sites on the overall results (see Table 22. The exclusion of the two sites did change the results substantially. Both the point estimates of the response rates for the individual treatment groups and treatment difference between groups was similar. In addition, the confidence interval widened as expected due to the smaller sample size but the intervals were still centered on similar point estimates. Also, both analyses still met the noninferiority margin even with both sites excluded. Thus, it is felt that results for Study 0017 were not unduly affected by the two large centers.

Table 22: Clinical Response at TOC Sensitivity Analysis (Post-Amendment) -- FDA Adjudicated Data

	Study 0017		Study 0017 excluding Sites 38101 and 38271	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated				
Cure	309/426 (72.5)	307/429 (71.6)	140/195 (71.8)	140/199 (70.4)
Difference (95% CI)[1]	1.0 (-5.0, 7.0)		1.4 (-7.5, 10.4)	
Clinically Evaluable				
Cure	289/343 (84.3)	288/348 (82.8)	124/150 (82.7)	126/150 (84.0)
Difference (95% CI)[1]	1.5 (-4.0, 7.0)		-1.3 (-9.8, 7.1)	

It was not felt that the preceding statistical issues had a meaningful impact on the on the overall determination of efficacy, with the exception of the renal impairment subgroups, the efficacy finding will be presented below.

In both of the Phase III studies (Studies 0017 and 0018), efficacy was demonstrated by telavancin was noninferior to vancomycin for the primary endpoint of clinical response at TOC

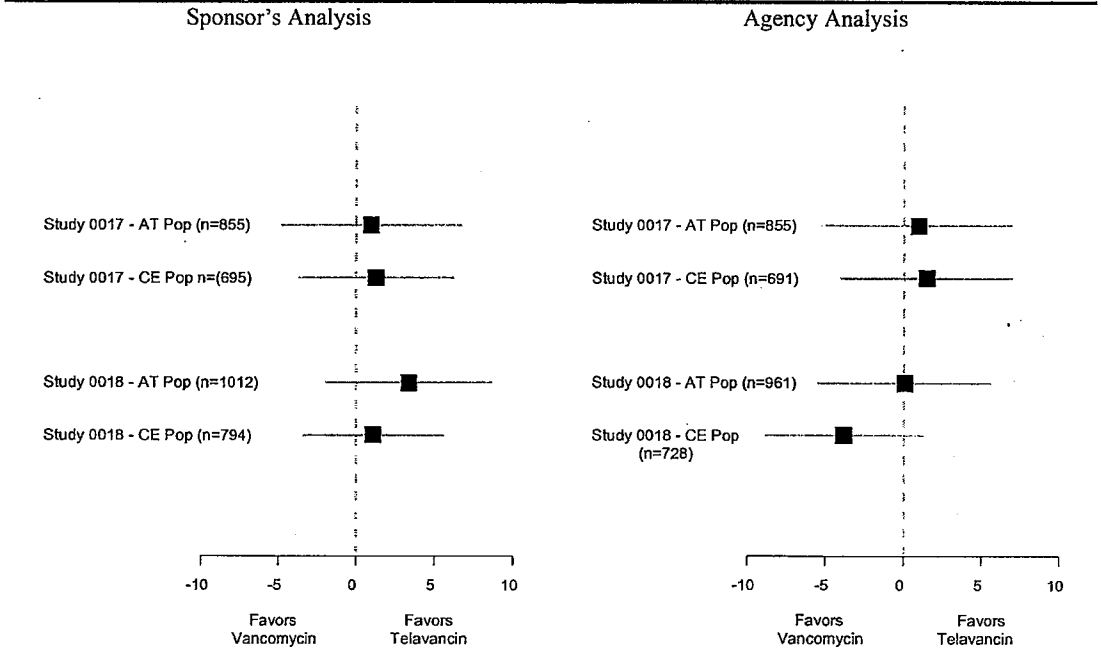
in both the AT and CE populations based on the treatment difference in clinical response rates using a 10%. noninferiority margin (see Table 23). The finding was consistent in both the Sponsor's analyses and the Agency analyses of the primary endpoint (see Figure 9). However, it is noted for Study 0018 that the Agency analyses resulted in a ~3% decrease in the treatment difference for both the AT and CE population compared to the Sponsor's analyses. As the Sponsor's analysis plan proposed testing for superiority if noninferiority was demonstrated, it is noted that the studies did not provide evidence that telavancin was statistically superior to vancomycin in either of the studies.

Table 23: Clinical Response at TOC (Post-Amendment Patients)

	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study Q018		Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated								
Cure	323 (75.8)	321 (74.8)	387 (77.1)	376 (73.7)	309 (72.5)	307 (71.6)	348 (73.7)	360 (73.6)
Total	426	429	502	510	426	429	472	489
Difference (95% CI)[1]	1.0 (-4.8 , 6.8)		3.4 (-1.9 , 8.7)		1.0 (-5.0, 7.0)		0.1 (-5.5, 5.7)	
Clinically Evaluable								
Cure	304 (87.9)	302 (86.5)	354 (88.7)	346 (87.6)	289 (84.3)	288 (82.8)	306 (83.8)	318 (87.6)
Total	346	349	399	395	343	348	365	363
Difference (95% CI)[1]	1.3 (-3.6 , 6.3)		1.1 (-3.4 , 5.6)		1.5 (-4.0, 7.0)		-3.8 (-8.8, 1.3)	

[1] Difference in Cure rates (telavancin – vancomycin) and the two-sided 95% CI was stratified by study.
Source: ISE, Table 5-33

Figure 9: Clinical Response at TOC (Post-Amendment)



For Study 0017, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.0% with a corresponding 95% CI of (-4.8%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 1.0% with a corresponding 95% CI of (-5.0%, 7.0%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.3% with a corresponding 95% CI of (-3.6%, 6.3%) while the Agency analysis found a similar result with a treatment difference of 1.5% with a corresponding 95% CI of (-4.0%, 7.0%).

For Study 0018, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 3.4% with a corresponding 95% CI of (-1.9%, 8.7%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-5.5%, 5.7%) for the AT population. In the other co-primary analysis of the CE population, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 1.1% with a corresponding 95% CI of (-3.4%, 5.6%) while the Agency analysis found a similar result with a treatment difference of -3.8% with a corresponding 95% CI of (-8.8%, 1.3%). There was noticeable decrease (~3%) in the treatment difference between telavancin and vancomycin in both the AT and CE populations that was caused by a decrease in the telavancin response rates in both the populations. A large portion of the difference is due to the removal of Site 38091 that was excluded because of issues raised by DSI during the site inspection. The results from that site heavily favored telavancin for both the AT population (Telavancin: 22/30 (73.3%); Vancomycin: 8/21 (38.1%)) and the CE population (Telavancin: 21/24 (87.5%); Vancomycin: 8/19 (42.1%)).

As it was the Sponsor's objective to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population has been demonstrated, the discussion of these results will follow. The analysis plan was to pool data across Studies 0017 and 0018 to perform the analyses. The results of the two studies were not found to be substantially dissimilar so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses.

In patients with a MRSA pathogen isolated at baseline, the Sponsor failed to demonstrate the superiority of telavancin to vancomycin in clinical response at TOC (see Table 13). This was consistent in both the analyses performed by the Sponsor and the Agency. In the pooled analysis of the MRSA patients, the Sponsor's analysis found a treatment difference (Telavancin – Vancomycin) of 0.4% with a corresponding 95% CI of (-5.9%, 6.8%) while the Agency analysis found a similar result with a treatment difference of 0.1% with a corresponding 95% CI of (-6.7%, 6.8%) for the AT population. The test of the difference in clinical response at TOC between telavancin and vancomycin yielded clearly non-statistically significant finding with 2-sided p-values of 0.889 and 0.985 in the Sponsor's and Agency analyses.

Although, it was felt that the Sponsor demonstrated that telavancin was noninferior to vancomycin in the treatment cSSSI, there is a concern about the inconsistency of treatment effect across both baseline renal impairment levels and age that will be discussed below.

Effect of Baseline Renal Impairment

Subgroup analyses that examined the effect of baseline renal impairment on clinical response at TOC were performed. The treatment difference in response rates between telavancin and vancomycin was not constant across levels of renal impairment ($p=0.02$) in the pooled CE population of Studies 0017 and 0018. In order to assess the effect of the level of baseline renal impairment on the treatment difference, we examined the interaction of the treatment group and the baseline renal impairment in a logistic regression that modeled clinical response at TOC with study, treatment, region, diabetes, baseline renal impairment, the treatment by baseline renal impairment as predictors in the model. Further evidence of this issue is that the magnitude of relative difference between treatment arms increased as the level of baseline renal impairment increased. A graphical representation is presented in Figure 2. The increase in the treatment difference as renal impairment increases occurs because the telavancin response rates decreases as renal impairment increases [Normal: 406/455 (89.2%); mild: 131/165 (79.4%); moderate: 43/62 (69.4%); severe: 15/25 (60%)], while the vancomycin response rates are relatively constant across renal impairment level [Normal: 397/461 (86.1%); mild: 142/168 (84.5%); moderate: 51/62 (82.3%); severe: 16/20 (80%)] (see Table 24).

In the two other subgroups which were thought to be correlated with baseline renal impairment, age and history of diabetes, a statistically significant differential effect of telavancin relative to vancomycin across stratum levels also existed, p-value of 0.04 for age dichotomized into <65 and ≥ 65 years of age and also for history of diabetes where the p-value was 0.08. By looking at

Figure 11, it appears that effects of age and history of diabetes are collinear to the effect of baseline renal impairment. For age, there is a strong association of age with renal impairment where majority of the patients younger than 65 years old have normal renal function and the majority of patients with moderate or severe renal impairment are greater than 65 years of age. Similarly for history of diabetes, most of the patients with normal renal function did not have a history of diabetes while a much larger proportion of the patients with moderate or severe diabetes had a history of diabetes.

Table 24: Clinical Response Rate at TOC in the CE Population (Studies 0017 + 0018) – FDA Analyses

	Telavancin % (n/N)	Vancomycin % (n/N)	Difference (TLV – Comp) (95% CI)[1]	p-value[2]
Baseline Creatinine Clearance				
>80 mL/min (Normal)	406/455 (89.2)	397/461 (86.1)	3.1 (-1.2, 7.3)	0.02
>50-80 mL/min (mild)	131/165 (79.4)	142/168 (84.5)	-5.2 (-13.5, 3)	
30-50 mL/min (moderate)	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)	
<30 mL/min (severe)	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.4, 5.3)	
Age				
< 65 Yrs.	90.6 (558/616)	87.8 (527/600)	2.7 (-0.8 , 6.2)	0.04
>= 65 Yrs.	77.5 (100/129)	84.0 (121/144)	-6.6 (-16.2 , 3.0)	
History of Diabetes				
Diabetic	131/171 (76.61)	146/183 (79.8)	-3.3 (-11.9, 5.3)	0.08
Non-diabetic	463/536 (86.4)	460/528 (87.1)	-0.7 (-4.8, 3.3)	

[1] Difference and 95% CI are based on analyses stratified by study

[2] p-value based on the interaction of treatment and subgroup variable controlling for study, treatment, region, diabetes, and subgroup variable except for the US/ex-US analysis where region was excluded from the model because it is collinear to the subgroup variable and similarly diabetes was excluded when history of diabetes was in the model.

Figure 10: Clinical Response at TOC in the CE Population (Studies 0017 + 0018) – By Baseline Renal Impairment (FDA Analyses)

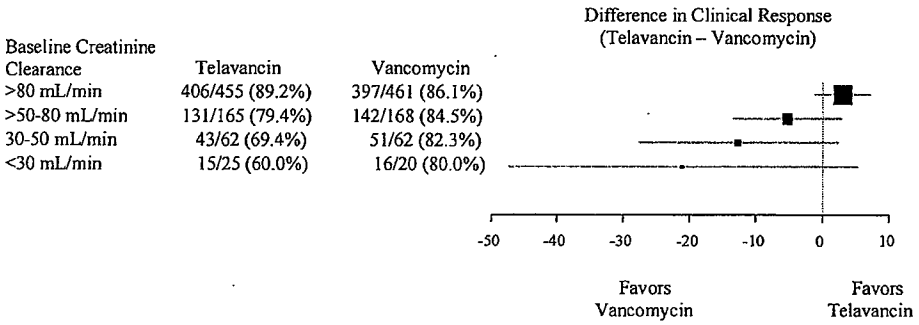
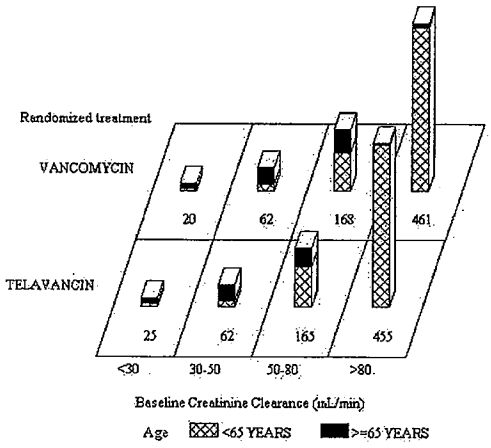
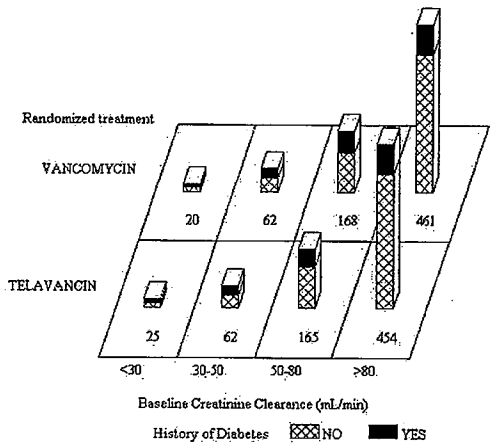


Figure 11: Distribution of CE Patients in Studies 0017 + 0018 By Baseline Creatinine Clearance, Age, and History of Diabetes

Distribution of Baseline Creatinine Clearance and Age



Distribution of Baseline Creatinine Clearance and History of Diabetes



5.2 Conclusions and Recommendations

The Sponsor provided evidence that telavancin is effective in the treatment of complicated skin and skin structure infections (cSSSI). Based on a 10% noninferiority margin, telavancin was noninferior to vancomycin in the two Phase III studies (Studies 0017 and 0018) for clinical response at Test-of-Cure (TOC) in both of the co-primary analysis populations, All-Treated (AT) and Clinically Evaluable (CE). However, the Sponsor did not provide evidence that telavancin is more effective than vancomycin in the treatment of cSSSI for patients with methicillin-resistant *Staphylococcus* aureus (MRSA) pathogens isolated at baseline. Finally, there are concerns that the relative effect of telavancin compared to vancomycin decreases as the level of baseline renal impairment increases. Similarly, the relative efficacy of telavancin compared to vancomycin is decreased in older patients, ≥65 years, compared to younger patients, <65 years. Note that age and baseline renal impairment are highly correlated.

APPENDIX

SIGNATURES/DISTRIBUTION LIST

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