Medical Team Leader Memo

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Application:	NDA 22-110, Telavancin for Injection
Date of Submission:	December 19, 2006
PDUFA Goal Date:	October 19, 2007
Applicant:	Theravance
Drug Class:	Lipoglycopeptide
Trade Name:	VIBATIV
Indications:	Complicated Skin and Skin Structure Infections
Dosing Regimen:	10 mg/kg every 24 hours intravenously

Recommended Regulatory Action:
Based on the data submitted in NDA 22-110, I would recommend an approvable action for telavancin for the treatment of complicated skin and skin structure infections (cSSSI) for the following reasons:

1. Renal adverse events associated with telavancin use need to be further delineated by the Applicant. Renal adverse events (serious and non-serious) were more common in patients treated with telavancin. Abnormalities in renal laboratory parameters (urea nitrogen and creatinine) were also more common in telavancin-treated patients. Clinical cure rates in telavancin-treated patients with reduced creatinine clearance were significantly lower compared to vancomycin-treated patients. The specific populations at greater risk of renal adverse events based on factors such as threshold creatinine clearance or specific co-morbidities need to be identified.

2. A product label that adequately conveys the risks associated with telavancin use, including higher frequency of renal adverse events, potential for prolongation of the QT interval and teratogenicity noted in animal toxicology studies needs to be provided by the Applicant.

3. Telavancin was non-inferior to vancomycin in two adequate and well controlled trials. Though superiority of telavancin over vancomycin in the treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) was not demonstrated in clinical studies, telavancin demonstrated activity similar to vancomycin. MRSA is an ongoing public health issue and treatment options are limited. Though other therapeutic options are available for treatment of MRSA skin and skin structure infections, the safety profile of some of those drugs precludes their use in certain patient populations. Though telavancin has demonstrated activity against vancomycin non-susceptible *S. aureus* isolates in *in vitro* studies, no vancomycin non-susceptible *S. aureus* isolates (MIC exceeding 2 ug/ml) were identified in the clinical studies.

4. Issues with the Ben Venue facility in Bedford, Ohio where an FDA inspection revealed significant deviations from the Current Good Manufacturing Practice regulations need to be resolved.

Background:
Telavancin is a lipoglycopepetide antibiotic produced by chemical modification of vancomycin. The drug product is a sterilized powder for injection and contains hydroxypropyl-β-cyclodextrin (HP-β-CD) as a solubilizing agent. Telavancin acts by interruption of late-stage glycopeptide synthesis with concomitant cell wall disruption followed by cell death. A proposed additional mechanism of action is disruption of the microbial cell membrane. It is unclear if this mechanism is significant at obtainable free concentrations of the drug. For additional information, please see microbiology review by Kerry Snow, MS.

The proposed indication is for treatment of complicated skin and skin structure infections (cSSSIs) caused by *Staphylococcus aureus* (including methicillin-resistant and susceptible strains), [redacted] *Streptococcus* b(4)

pyogenes, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

The proposed dosing regimen is 10 mg/kg infused intravenously over 60 minutes once every 24 hours for 7-14 days with modified dosing regimen for patients with renal impairment.

In support of this indication, the Applicant has performed two phase 2 and two phase 3 studies comparing telavancin with vancomycin or semi-synthetic penicillins. The Applicant had initiated Studies 0017 and 0018 using a telavancin dose of 7.5 mg/kg IV q 24 hours and then amended the studies to increase the dose to 10 mg/kg q 24 hours. The increase was based on the results of a Phase 2 cSSSI study (202b) which was ongoing during planning of the Phase 3 trials. Use of the higher dose was based on higher microbiologic eradication rates in patients treated with the higher dose. Additionally, PK/PD modeling had suggested that doses of 750 mg (or approximately 10 mg/kg) would result in greater than 95% probability of target attainment for organisms with MICs as high as 2 μg/mL.

Two phase 3 studies (Studies 0017 and 0018) of identical design comparing telavancin to vancomycin were performed to assess the efficacy and safety of telavancin for the treatment of patients with cSSSI. Only patients enrolled post-amendment were included in the efficacy analysis. Each study was a randomized, double-blind, active-controlled, parallel group, multicenter, and multinational trial. Patients with cSSSIs were randomized to receive either telavancin 10 mg/kg IV q 24 hr or vancomycin 1 gm IV q 12 hr for 7-14 days. Adjunctive aztreonam or metronidazole could be used to treat patients with infections due to suspected or culture positive Gram negative and/or anaerobic organisms.

The primary objective of both studies was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with complicated Gram positive cSSSIs with emphasis on patients with infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). A key secondary objective was to pool the efficacy data from each of these studies to assess the superiority of telavancin to vancomycin in patients with MRSA infections. The co-primary efficacy endpoint analyses for Studies 0017 and 0018 were the Clinical Response at the test of cure (TOC) visit in the All Treated (AT) and Clinically Evaluable (CE) populations.

The Applicant had also conducted two Phase 2 studies (telavancin 7.5 mg/kg in 202a and primarily 10 mg/kg in 202b) compared to standard therapy (vancomycin or anti-staphylococcal penicillin such as nafcillin, oxacillin, or cloxacillin) in the treatment of patients with cSSSI. These studies were not included in the overall efficacy determination and were reviewed for safety.

Results:
A total of 862 patients were randomized in study 0017 (429 patients to telavancin and 433 patients to the vancomycin). A total of 1035 patients were randomized in study 0018 (517 patients randomized to telavancin and 518 patients to vancomycin).

The two treatment groups were similar with respect to demographic characteristics of age, race, and gender. The proportion of patients enrolled from US sites was 72-74% in study 0017 and 63-66% in study 0018. The two treatment groups in each study were similar for type of cSSSI, and hospitalization status at study entry. Approximately 25% of the population had diabetes. Approximately 65% of patients had a baseline creatinine clearance of > 80 ml/min. Abscesses were the most common type of infection (42-45%) followed by cellulitis (33-38%). Only a limited number of patients with infected ulcers were enrolled. A smaller proportion of patients in study 0018 was hospitalized at study entry (61-62%) compared to study 0017 (83%). Approximately 70% of patients were treated for 7-14 days; the maximum number of days of exposure was 18 days.

Analysis populations as defined by the Applicant and the FDA differed for the following criteria:
Test-of-Cure/Follow-up window
Study medication compliance
Relevance of bacteria identified (e.g. coagulase negative Staphylococci from swab specimen)
Baseline pathogen window
Central vs. local laboratory results
Dr. Pohlman's assessment of evaluablity and outcomes after review of case report forms
Exclusion of data from site 38091 due to issues identified during DSI inspections

The following tables represent the number of patients in each of the analysis populations for studies 0017 and 0018.

Table 1: Analysis Populations (Study 0017)

	Sponsor		FDA	
Number (%) of Patients	**Telavancin n(%)**	**Vancomycin n (%)**	**Telavancin n (%)**	**Vancomycin n (%)**
All-Treated (AT)	426 (100)	429 (100)	426 (100)	429 (100)
Modified All-Treated (MAT)	307 (72)	322 (75)	260 (61)	274 (64)
Clinically Evaluable (CE)	346 (81)	349 (81)	343 (81)	348 (81)
Microbiologically Evaluable (ME)	237 (56)	255 (59)	219 (51)	234 (55)

Table 2: Analysis Populations (Study 0018)

	Sponsor		FDA	
Number (%) of Patients	**Telavancin n(%)**	**Vancomycin n (%)**	**Telavancin n (%)**	**Vancomycin n (%)**
All-Treated (AT)	502 (100)	510 (100)	472 (100)	489 (100)
Modified All-Treated (MAT)	373 (74)	381 (75)	303 (64)	322 (66)
Clinically Evaluable (CE)	399 (79)	395 (77)	365 (77)	363 (74)
Microbiologically Evaluable (ME)	290 (58)	281 (55)	240 (51)	239 (49)

The following table summarizes the clinical cure rates in the co-primary AT and CE populations. In both studies the pre-defined non-inferiority margin of -10% was met. Cure rates in the FDA analyses were lower than that in the Applicant's analyses. In study 0017 the drop in cure rates

was noted in both treatment arms, however in study 0018, the effect was more pronounced in the telavancin arm in both the AT and CE populations.

Table 3: Clinical Cure Rate at TOC in AT and CE Populations

	Applicant Assessment			FDA Assessment		
Population	Telavancin n/N %	Vancomycin n/N %	Treatment Difference (95% CI)	Telavancin n/N %	Vancomycin n/N %	Treatment Difference (95% CI)
AT						
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 (-5.0, 7.0)
Study 0018	387/502 (77.1)	376/510 (73.7)	3.4 (-1.9, 8.8)	348/472 (72.5)	360/489 (73.6)	0.1 (-5.5, 5.7)
Pooled 0017 + 0018	710/928 (76.5)	697/939 (74.2)	2.3 (-1.6, 6.2)	657/898 (73.2)	667/918 (72.7)	0.5 (-3.6, 4.6)
CE						
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 (-4.0, 7.0)
Study 0018	354/399 (88.7)	346/395 (87.6)	1.1 (-3.4, 5.6)	306/365 (83.8)	318/363 (87.6)	-3.8 (-8.8, 1.3)
Pooled 0017 + 0018	658/745 (88.3)	648/744 (87.1)	1.2 (-2.1, 4.6)	595/708 (84.0)	606/711 (85.2)	-1.2 (-4.9, 2.6)

Clinical success rates by pathogen for some of the more commonly isolated organisms in the ME population were as follows:

Table 4: Clinical Response by pathogen (ME Population), Study 0017

Pathogen	Applicant Assessment		FDA Assessment	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Staphylococcus aureus, MRSA	101/116 (87.1)	118/138 (85.5)	90/109 (82.6)	107/126 (84.9)
Staphylococcus aureus, MSSA	80/90 (88.9)	77/91 (84.6)	70/81 (86.4)	66/79 (83.5)
Enterococcus faecalis	13/13 (100.0)	11/14 (78.6)	12/12 (100)	11/14 (78.60
Streptococcus pyogenes	11/12 (91.7)	12/13 (92.3)	9/10 (90)	9/10 (90)
Streptococcus agalactiae	9/10 (90)	4/5 (80)	8/9 (88.9)	3/3 (100)
Streptococcus anginosus	5/5 (100)	3/3 (100)	5/5 (100)	3/3 (100)

Table 5: Clinical Response by pathogen (ME Population), Study 0018

Pathogen	Applicant Assessment		FDA Assessment	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Staphylococcus aureus, MRSA	151/162 (93.2)	142/163 (87.1)	119/131 (90.8)	118/137 (86.1)
Staphylococcus aureus, MSSA	80/91 (87.9)	77/85 (90.6)	62/80 (77.5)	64/74 (86.5)
Enterococcus faecalis	12/14 (85.7)	17/20 (85.0)	10/11 (90.9)	17/21 (81)
Streptococcus pyogenes	10/11 (90.9)	11/12 (91.7)	7/9 (77.8)	11/12 (91.7)
Streptococcus agalactiae	6/9 (96.7)	13/14 (92.9)	6/10 (60)	10/12 (83.3)
Streptococcus anginosus	6/6 (100)	5/5 (100)	4/5 (80)	3/3 (100)

MRSA Analysis: It was the Applicant's objective to demonstrate superiority of telavancin in patients with baseline MRSA infections once non-inferiority of telavancin to vancomycin in the overall population had been demonstrated. Superiority was not demonstrated in either the Applicant or FDA analyses. In the Applicant's analysis, the treatment difference was 0.4% (95% CI -5.9, 6.8) and in the FDA analysis the treatment difference was 0.1% (95% CI -6.7. 6.8).

Table 6 shows the number of patients treated with telavancin versus comparator in the drug development program as of September 21, 2006 (for patients enrolled prior to May 15, 2006).

Table 6: Number of Subjects Evaluated for Safety – All Telavancin Studies

	Number of Subjects Exposed	
Study Group	Telavancin	Comparator
Clinical Pharmacology Studies		
Single Dose Studies[1] (0.25 – 15 mg/kg)	124	47
Multiple Dose Studies (7.5 – 15 mg/kg)	144	103
Total Clinical Pharmacology Studies	268	150
Efficacy and Safety Studies in cSSSI		
Studies 0017, 0018, and 202b (Post Amendment) 10 mg/kg telavancin dose	1029	1033
Study 202a and Studies 0017, 0018, 202b (Original Protocol) 7.5 mg/kg telavancin	192	189
Total Efficacy and Safety Studies	1221	1222[2]
Total Completed Studies	1489	1372
Ongoing Treatment-Blinded Studies[3]	208	208
Grand Total	1697	1580

From Summary of Clinical Safety, Table 2, pg 16.
[1] Of the telavancin-treated patients, 79 subjects received a single dose and 45 received single doses on more than one occasion separated by one week or more.
[2] 1195 received vancomycin and 27 received anti-staphylococcal penicillins
[3] Treatment blinded: number per group estimated at 50% of total (studies with 1:1 randomization).

For the purpose of the safety review patients from Phase 2 Study 202a, and Original Protocol 202b, 0017, and 0018 where the dose of telavancin used was 7.5 mg/kg were compared to those in the Post Amendment populations from 202b, 0017, and 0018 where the dose of telavancin used was 10 mg/kg.

The Four Month Safety Update (4MSU) submitted to the NDA on April 17, 2007 contained unblinded safety information from an additional 29 telavancin-treated patients in Study 203a

(uncomplicated *Staphylococcus aureus* bacteremia) and from the on-going treatment blinded HAP studies (0015and 0019). A Phase 1 Japanese PK study has enrolled 37 subjects, of whom it is assumed 67% (25) were randomized to and received telavancin treatment.

Deaths: There were 18 deaths reported in the Phase 2 and Phase 3 studies combined, one death occurred in a patient treated with telavancin 7.5 mg/kg, eight deaths occurred in patients treated with telavancin 10 mg/kg, and nine deaths occurred in patients treated with the comparator, vancomycin. An additional 5 deaths in telavancin patients and 2 deaths in vancomycin patients occurred outside of study death reporting window. For narratives of patients who died and their relatedness to study drugs, please see Dr. Pohlman's review.

Serious Adverse Events (SAE): In the 10 mg/kg telavancin studies, SAEs occurred in 76 (7%) of telavancin-treated patients and 45 (4%) of vancomycin-treated patients. Renal failure acute was the most common individual SAE in the telavancin 10 mg/kg group. Five patients (0.5%) in the telavancin 10 mg/kg group reported renal failure acute as an SAE compared to one patient (0.09%) in the vancomycin arm. Respiratory failure was the most frequently reported individual SAE in the vancomycin arm, occurring in four patients (0.4 %) compared to one patient (0.09%) in the telavancin 10 mg/kg dose group. Renal SAEs are discussed in some detail here, for other SAEs, please see Dr. Pohlman's review.

Treatment-Emergent Adverse Events (TEAE):

- Dysgeusia was the most commonly reported TEAE. It occurred in 325/1029 (32%) telavancin-treated patients compared to 62/1033 (6%) vancomycin-treated patients.
- Nausea occurred in 265/1029 (26%) telavancin-treated patients compared to 148/1033 (14%) vancomycin-treated patients.
- Foamy urine (coded as urine abnormality) was reported in 125/1029 (12%) telavancin-treated patients compared to 27/1033 (3%) vancomycin-treated patients.
- TEAEs which occurred more commonly in vancomycin-treated patients were pruritus [128/1033 (12%)] and generalized pruritus [60/1033 (6%)] compared to 60/1029 (6%) and 28/1029 (3%) in telavancin-treated patients respectively.

Renal Adverse Events

Overall renal adverse events occurred in 28/1221 (2.3%) telavancin-treated patients and 6/1222 (0.5%) comparator-treated patients. Of the 28 telavancin-treated patients, 15 were classified as SAEs and the other 13 were non-SAEs. Among the telavancin-treated patients, 22 received a dose of 10 mg/kg and 6 received 7.5 mg/kg. The two treatment groups were similar with respect to baseline serum creatinine and creatinine clearance. The following table summarizes the baseline renal status in the two treatment groups:

Table 7: Baseline renal status

Characteristic	Telavancin 7.5 mg/kg (n=192)	Vancomycin (n=189)	Telavancin 10 mg/kg (n=1029)	Vancomycin (n=1033)
Baseline creatinine				
Mean	74.2	71.5	81.7	81.5
SD	30.2	24.7	48.3	61.8
Median	70.7	70.7	71.0	71.0
Range	35, 274	27, 256	27, 645.3	27, 1291
Baseline Creatinine Clearance				
Mean	104	107.9	94.8	95.9
SD	37.8	35.4	37.3	37.2
Median	104.4	106.1	95.6	94.9
Range	16.1, 248.8	20.4, 202.3	5.7, 297.6	6.9, 228.0
Baseline Creatinine Clearance categories				
>80 ml/min	141 (77%)	140 (76%)	655 (65%)	667 (66%)
>50-80 ml/min	27 (15%)	35 (19%)	230 (23%)	228 (23%)
30-50 ml/min	10 (5%)	8 (4%)	78 (8%)	84 (8%)
< 30 ml/min	6 (3%)	2 (1%)	40 (4%)	29 (3%)

Most patients treated with telavancin showed improvement in serum creatinine over time. Although, three patients were reported as improved they had a final serum creatinine twice that seen at baseline.

Among patients who developed renal adverse events a greater proportion of telavancin-treated patients had baseline creatinine clearance of < 80 ml/min. The baseline creatinine clearance in patients who developed renal adverse events is summarized in Table 8.

Table 8: Baseline Creatinine clearance in patients who developed renal adverse events

Baseline Creatinine clearance	Telavancin N=27*	Comparator N=6
<30 ml/min	6	2
30-50 ml/min	6	0
50-80 ml/min	9	1
> 80 ml/min	6	3

*Creatinine clearance value for one patient was missing

Renal adverse events are summarized below:

Common AEs: In the renal and urinary disorders SOC, there were 10 (<1%) cases of renal insufficiency in the telavancin arm compared to 2 (<1%) in the vancomycin arm in the 10 mg/kg dose group. In the 7.5 mg/kg group, there were 3 cases of renal insufficiency in the telavancin arm compared to none in the vancomycin arm.

SAEs: Preferred terms indicating renal impairment were renal tubular necrosis, renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and increased blood creatinine.

Overall fifteen patients in the telavancin arm and four in the comparator arm had renal SAEs. Of the telavancin-treated patients, three received 7.5 mg/kg and 12 received 10 mg/kg. The 15 telavancin-treated patients had 21 SAEs while the four comparator-treated patients had four SAEs. The renal SAEs included five patients each with renal insufficiency and renal failure acute, two patients with renal impairment, one patient each with acute prerenal failure and renal tubular necrosis. Four patients had blood creatinine increased and three patients had blood urea increased. In 11/15 patients, the renal SAE was considered possibly/probably related to study medication and 7/15 discontinued study medication because of the renal SAE. In the vancomycin-treated patients, two had blood creatinine increased and one each had renal failure acute and renal failure chronic. Three telavancin-treated patients needed dialysis, two refused dialysis and both died subsequently. One vancomycin-treated patient required hemodialysis. Of the 15 telavancin-treated patients with SAEs, one patient had no underlying co-morbidities that could have contributed to renal AEs. A brief narrative of this patient and of the one patient who developed acute tubular necrosis is provided below.

202b-00910-9058: A 28-year old patient with no co morbidities developed acute renal failure on day 2 and about a month later serum creatinine had returned to normal. The only potential confounders were anti-inflammatory medications (diclofenac and ibuprofen) that he had received for three weeks prior to study entry. As his baseline creatinine was normal the renal failure is more likely related to telavancin rather than the anti-inflammatory medications. It is also possible that telavancin had an additive effect on the underlying damage from the anti-inflammatory drugs.

0018-38160-2007: This telavancin-treated patient had acute tubular necrosis (ATN) and had received the 7.5 mg/kg dose. He had underlying alcoholic liver disease, cirrhosis, and ascites. His creatinine increased from a baseline value of 0.7 to 2.6 mg/dl on study day 3, which peaked at 3.4 on study day 7. Telavancin was continued and on day 10 his creatinine was 2.6 mg/dl which decreased to 1.9 mg/dl on day 14. The patient died 85 days after the last dose of telavancin due to liver failure. Despite continuing on telavancin his creatinine levels decreased, so it is difficult to attribute the ATN solely to telavancin administration and may in part be related to his underlying illnesses.

One of the four vancomycin-treated patients was receiving hemodialysis prior to entry and was continued and the other three showed resolution of the renal SAE. Narratives of patients with renal SAEs are summarized in Dr. Pohlman's review.

Renal AEs leading to discontinuation: Thirteen telavancin-treated (9 SAEs and 4 non-SAES) and two vancomycin-treated (1 SAE and 1 non-SAE) patients discontinued study or study medication due to renal treatment-emergent adverse events that were assessed as possibly/probably related to study medication.

Deaths: Four telavancin-treated patients with renal failure died, two had refused dialysis. Two of these patients died during the study reporting period (through the follow-up/Test-of-Cure visit or for 28 days after the End-of-Therapy visit for patients who did not have a TOC visit) and two

died outside the reporting period. There were no deaths in vancomycin-treated patients with renal AEs.

Renal Laboratory Parameters:
Following is a summary of the renal laboratory parameters in telavancin-treated patients who received 10 mg/kg. Table 7 provide information on change in serum creatinine and blood urea from baseline to worst value and Table 8 provides information on change in creatinine and urea nitrogen using different clinically significant definitions. In all analyses abnormal values were more common in telavancin treated patients. Though the mean change in creatinine was 2x that in vancomycin treated patients, the median was similar suggesting that there were more outliers in the telavancin group.

Table 9: Renal laboratory Parameters

Post Amendment 202b+0017+0018 (Telavancin 10 mg/kg)						
	Telavancin			Vancomycin		
	Baseline	Worst value	Change	Baseline	Worst value	Change
Serum Creatinine (µmol/L)						
N	905	905	905	939	939	939
Mean	72.10	90.49	18.39	72.91	81.05	8.14
Std dev	17.31	38.90	35.12	16.84	21.84	18.45
Median	71.0	80.00	9.00	71.0	80.00	8.84
Maximum	136.0	530	450.0	133.0	309.0	203.0
Urea Nitrogen (mmol/L)						
N	891	891	891	901	901	901
Mean	4.79	6.49	1.70	4.82	6.03	1.21
Std dev	1.66	3.08	2.71	1.60	2.04	1.83
Median	4.60	6.00	1.40	4.60	5.70	1.10
Maximum	11.4	49.3	40.4	11.1	21.8	12.3

Table 10: Potentially clinically significant renal laboratory changes

Characteristic	Post Amendment 202b+0017+0018			
	Telavancin		Vancomycin[1]	
	Patients	Abnormal (%)	Patients	Abnormal (%)
Serum Creatinine				
Increase to 1.25 x BL	917	330 (36)	945	190 (20)
Any Post-BL Cr ≥ 133 µmol/L and at least 44 µmol/L > BL	917	57 (6)	945	19 (2)
Any Post-BL Cr ≥ 133 µmol/L and at least 50% > BL	917	52 (6)	945	17 (2)
Highest Post-BL Result				
133 µmol/L to < 177 µmol/L and at least 44 µmol/L > BL	917	32 (3)	945	15 (2)
177 µmol/L to < 265 µmol/L and at least 44 µmol/L > BL	917	17 (2)	945	2 (0.2)
265 µmol/L to < 442 µmol/L and at least 44 µmol/L > BL	917	6 (0.6)	945	2 (0.2)
≥ 442 µmol/L and at least 44 µmol/L > BL	917	2 (<1)	945	0
BUN Post-BL Result				
> 11 mmol/L	891	49 (5)	901	25 (3)

From ISS, Table 5-17, pgs 229-230. BL= Baseline
[1] Includes 27 patients (20 in 202a and 7 in 202b Post-Amendment) who received an antistaphylococcal penicillin instead of vancomycin.

Shifts in renal parameters: In study 0017, 22/333 (6.6%) telavancin-treated patients and 9/338 (2.7%) vancomycin-treated patients who had normal values at baseline had high creatinine values at the test of cure (TOC) visit. This difference is also noted in study 0018 (43/399 (10.8%) telavancin-treated and 15/398 (3.8%) vancomycin-treated patients.

Clinical outcomes based on renal function: Clinical cure rates in patients with reduced creatinine clearance, especially in those < 50 ml/min was lower than that seen in patients with creatinine clearance > 80 ml/min. The reduction in clinical cures was much more pronounced in telavancin-treated patients. The following table summarizes the cure rates in the FDA pooled CE population based on creatinine clearance:

Table 11: Clinical Cure Rates Based on Baseline Renal Function – Pooled FDA-CE Population

	Telavancin (n/N) %	Vancomycin (n/N) %	Difference (TLV-Comparator) (95% CI)[1]	p-value[2]
Baseline Creatinine Clearance				
• > 80 mL/min	406/455 (89.2)	397/461 (86.1)	3.1 (-1.2, 7.3)	0.02
• > 50-80 mL/min	131/165 (79.4)	142/168 (84.5)	-5.2 (-13.5, 3)	
• 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 (-47.4, 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, diabetes, and subgroup variable.

ECG changes: The non-GLP hERG assay showed some inhibition of hERG potassium ion channel currents. This finding was confirmed in a GLP assay; however 50% inhibition was not reached at concentrations up to 600 μg/mL (approximately 80-fold higher than observed free plasma concentrations in humans treated with 10 mg/kg per day). No effects on cardiac repolarization were seen with telavancin in studies conducted in anesthetized and conscious telemeterized dogs even at free plasma concentration levels approximately 4-5 times higher than achieved with doses of 10 mg/kg/day in humans.

Phase 1 Clinical Pharmacology Studies: The Sponsor conducted a "thorough ECG trial" as defined by the November 2002 FDA – Health Canada concept paper which was being developed at that time. Full details regarding the study design, ECG monitoring, and analysis of results can be found in the IRT QT Study review. The study showed that at both the 7.5 mg/kg and 15 mg/kg dose, telavancin has an effect on the QT interval. At both doses the baseline and placebo-corrected QTcF interval (ΔΔQTcF) was lengthened greater than 10 msec, the threshold for regulatory concern. There were no subjects with QTcF ≥ 500 msec or torsades de pointes. Based on a step-wise linear mixed-effects model describing the relationship between telavancin concentrations and the ΔΔQTcF interval, the expected ΔΔQTcF of telavancin 10 mg/kg was estimated to be 12-15 msec. The mean ΔΔQTcF for moxifloxacin was 24 msec, however in this study moxifloxacin was administered intravenously daily for three days rather than as a single oral dose used for assay sensitivity.

Clinical Studies: The on-drug average and on-drug maximum change compared to baseline are shown in Table 10 reproduced from the Applicant's ISS.

Table 12: Summary of Post-Drug Changes from Baseline in QTcF Interval

	Original Protocol 0017, 0018, 202b and 202a		Post-Amendment 1 0017, 0018, and 202b	
	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033
Post-Drug Average[2] Change, msec				
• N	189	183	971	979
• Mean	11.6	3.8	9.4	2.8
• Standard Deviation	15.6	14.8	17.4	15.9
• Minimum	-27.8	-34.3	-98.8	-52.5
• Median	12.0	5.0	9.0	2.7
• Maximum	66.3	46.8	93.5	66.3
Post-Drug Maximum[3] Change, msec				
• N	189	183	971	979
• Mean	20.6	12.4	15.9	8.4
• Standard Deviation	17.2	18.0	18.7	16.7
• Minimum	-23.7	-32.7	-89.0	-49.7
• Median	19.3	12.0	15.3	7.7
• Maximum	79.3	124.7	103.7	94.7

From ISS, Table 7-3, pgs 279-80.
Note: In 202a and 202b, post-drug ECGs were to be obtained on every third day of study drug and at EOT. In 0017, 0018, and post-amendment 202b, ECGs were to be obtained once on Day 3, 4, or 5 and at EOT.
[1] Includes 27 patients (20 in 202a and 7 in 202b) who received an antistaphylococcal penicillin instead of vancomycin.
[2] Based on all QT measurements from Day 1 on patients with a baseline and at least one post-baseline value.
[3] Based on maximum value of all QT measures (triplicate averages) from Day 1 on patients with a baseline and at least one post-baseline value.

The results show that both mean and median post-drug average change and maximum change from baseline in QTcF were greater for the telavancin treatment groups at both the 7.5 and 10 mg/kg dose than those for the vancomycin treatment groups. The average and maximum change appear to be higher in the 7.5 mg/kg dose group suggesting lack of a dose-response. However the higher values noted may also be influenced by the more frequent ECG testing in the Phase 2 202a and 202b studies than in the Phase 3 studies with greater opportunity for measurement of outlier values.

Analyses focused on outliers or shifts from normal to abnormal

QTcF > 500 msec was seen in one telavancin treated patients and three vancomycin patients and 16 telavancin-treated patients had change> 60 msecs compared to 6 in vancomycin-treated patients. Several of these patients had underlying co-morbidities that may contribute to the ECG changes.

The maximum post-drug QTcF and maximum post-drug change in QTcF are outlined in the following table:

Table 13: Summary of Post-Drug Changes from Baseline in QTcF Interval

	Original Protocol 0017, 0018, 202b and 202a		Post-Amendment 1 0017, 0018, and 202b	
	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033
Maximum Post-Drug Value, number (%) by category				
• ≤450 msec	171 (90)	178 (96)	874 (88)	934 (95)
• >450 and ≤480 msec	16 (8)	7 (4)	106 (11)	41 (4)
• >480 and ≤500 msec	2 (1)	0	8 (<1)	9 (<1)
• >500 msec	0	1 (<1)	1 (<1)	2 (<1)
• Total	189 (100)	186[2] (100)	989[2] (100)	986[2] (100)
Maximum Post-Drug Change, number (%) by category				
• ≤30 msec	141 (75)	161 (88)	789 (81)	885 (90)
• >30 and ≤60 msec	46 (24)	21 (11)	168 (17)	89 (9)
• >60 msec	2 (1)	1 (<1)	14 (1)	5 (<1)
• Total	189 (100)	183 (100)	971 (100)	979 (100)

From ISS, Table 7-3, pgs 279-80.
Note: In 202a and 202b, post-drug ECGs were to be obtained on every third day of study drug and at EOT. In 0017, 0018, and post-amendment 202b, ECGs were to be obtained once on Day 3, 4, or 5 and at EOT.
[1] Includes 27 patients (20 in 202a and 7 in 202b) who received an antistaphylococcal penicillin instead of vancomycin.
[2] The total number of patients with maximum post-drug values differs from the number with the measurement that incorporates baseline readings since these patients did not have baseline ECGs.

The important issues identified based on the Pharmacology/Toxicology review by Zhou Chen, MD, PhD and Terry Peters, DVM are discussed briefly below. For a more detailed review, see Dr. Chen's review.

Toxicology
The major organs of toxicity in rats and dogs were the kidney and liver. A finding of undetermined significance with prolonged (> 4 week) administration of the drug was macrophage hypertrophy, hyperplasia, and accumulation in various organs.

Renal toxicity: Renal toxicity in rats was manifested by diffuse tubular vacuolation following 2 week administration (≥ 25 mg/kg/day), minimal mutlifocal tubular degeneration with mild increase in BUN and creatinine after 4 weeks administration (≥ 50 mg/kg/day), increased incidence/severity of proximal tubular degeneration, inflammatory cell infiltrates and tubular casts, with increased BUN and creatinine and hematuria after 13 and 26 weeks administration (≥ 50 mg/kg/day). These changes were generally reversible after a 4 week recovery period, but in the 13- and 26-week studies, only partially reversible. Renal toxicity in dogs was manifested by tubular vacuolation and necrosis with increase in BUN and creatinine after 4 and 13 weeks administration (≥ 25 mg/kg/day) which generally decreased after a 4 week recovery period.

Some of the renal changes were noted in animals treated with placebo containing HP-β-CD, but changes were generally more pronounced in those receiving telavancin (containing HP-β-CD as an inactive ingredient).

Hepatotoxicity: In rats this was manifested by hepatocellular degeneration along with elevated alkaline phosphatase, ALT, and AST in the 13 week study and macrophage accumulation and elevated ALT and AST in the 26 week study. Partial reversibility of elevated laboratory values after the 4-week recovery was noted in the 13-week study. In dogs this was manifested by an increase in reactive sinusoidal lining cells, centrolobular macrophages, and hepatocellular degeneration present in high dose (100 mg/kg/day) animals along with elevations in alkaline phosphatase, ALT, and AST in the 13 week study. The laboratory changes were partially reversed at recovery. As with the renal changes, similar but less pronounced findings were noted in animals treated with HP-β-CD placebo.

Others: Macrophage hypertrophy, hyperplasia, and accumulation were seen primarily with more prolonged administration (13 and 26 week studies) and were noted in the reticulo-endothelial cell system (lymph nodes, bone marrow, liver, and spleen) as well as in the kidney and lungs. These changes persisted throughout the 4 week recovery period. The changes were also referred to as eosinophilic and histiocytic. As with the previous changes, similar findings were noted in animals treated with HP-β-CD. The clinical significance of these changes is unknown.

Teratogenicity: This is a summary of findings from Dr. Zhou Chen's review. For details, please refer to reviews by Dr. Chen and Dr. Pohlman and also consults from The Reproductive and Developmental Toxicity Pharmacology Toxicology Coordinating Committee (PTCC) Subcommittee and The Pediatric and Maternal Health Team.

1. Intravenous Injection Rat Developmental Toxicity Study with AMI-6424: This study included a diluent control (5% dextrose), placebo (containing HP-β-CD), and 50, 100, and 150 mg/kg/day AMI-6424 doses.
    - Fetal weight decreases were noted at doses of ≥ 100 mg/kg/day.
    - Brachymelia (left hind limb) in one fetus from one litter (out of 332 fetuses and 24 litters examined) in the 100 mg/kg/day group was associated with other findings including protruding tongue, syndactyly (left hind limb, middle three digits), and anophthalmia.
    - One fetus from one litter (out of 322 fetuses and 25 litters examined) in the 150 mg/kg/day group had isolated brachymelia.
    - Brachymelia was thought to be drug-related by the FDA reviewer and Applicant. Syndactyly was thought to be drug-related by the FDA reviewer.
    - Neither skeletal abnormality was noted in the historical database.
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Rats:

	Diluent	*Placebo*	*50 mg/kg/day*	*100 mg/kg/day*	*150 mg/kg/day*
Litters Evaluated:	25	24	25	24	25
Fetuses evaluated:	319	322	312	332	322
Brachymelia	0	0	0	1 (1) 4.2%	1 (1) 4.0%
Syndactyly	0	0	0	1 (1) 4.2%	0
Total Litter Incidence*	**0**	**0**	**0**	**4.2%**	**4.0%**

*** Incidence for Brachymelia, micromelia or syndactyly were not in the historical data base submitted.**

2. Intravenous Injection Rabbit Developmental Toxicity Study with AMI-6424": This study included a diluent control (5% dextrose), placebo (containing HP-β-CD), and 60 and75 mg/kg/day doses of AMI-6424.
    - Multiple abnormalities were noted in one fetus from the 75 mg/kg/day dose group including flexed front paw, brachymelia (including absent ulna), adactyly (absence of a digit), gastroschisis.
    - One fetus was noted to have an umbilical hernia.
    - Also noted in the high dose group were malformations including fusion of sternebrae and vertebral anomalies in single animals from different litters and were not appreciated in the 60 mg/kg/day group.
    - The skeletal defects were felt to be treatment related by the FDA reviewer. The limb abnormalities (brachymelia, absent ulna, and adactyly) were also thought to be treatment related by the laboratory (Covance) performing the test. This was the same laboratory which had performed the rat studies. b(4)
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Rabbits:

	Placebo	*60 mg/kg/day*	*75 mg/kg/day*
Litters Evaluated:	18	20	19
Fetuses evaluated:	138	172	156
Flexed Front Paws, brachymelia, and adactyly	0	0	1 (1) 5.3%
Absent ulna	0	0	1 (1) (5.3%)
Total Litter Incidence	**0**	**0**	**10.6%**

*** Historical Control Incidence for Malrotated Hindlimbs = 0.8%; Flexed front paws – 0.8%; adactyly – 0.3%; no incidence rate given for brachymelia or absent ulna.**

On the basis of findings in two animal species, FDA requested that the Applicant conduct a study in a third species and recommended the minipig.

3. Telavancin: Study for effects on embryo-fetal development in the minipig": This study included a diluent, "placebo for telavancin injection" and doses of 25, 50, and 75 mg/kg/day of telavancin.
    - Findings included increased preimplantation loss at all doses (but within historical control range) and post-implantation loss in all dose groups.
    - Increase in late resorptions occurred in the high dose group.
    - Increased external malformations evidenced by polydactyly, syndactyly, and deformed foreleg were seen in the low and mid dose groups. Polydactyly was also noted in a placebo group fetus. No limb abnormalities were observed in the high dose group.
    - Many animals in this study required treatment with other antimicrobial agents noted as an unusual finding.
    - Skeletal abnormalities observed were greater than the historical control rates reported by the producer of the minipigs (Ellegaard Minipigs
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Gottingen Minipigs:

	Diluent	*Placebo*	*25 mg/kg/day*	*50 mg/kg/day*	75 mg/kg/day
Litters Evaluated:	7	5	9	8	5
Fetuses evaluated:	34	24	31	36	17
Syndactyly	0	0	0	1 (1) 12.5%	0
Polydactyly: Single Limb	0	1 (1) 20%	2 (2) 22.2%	2 (4) 25%	0
Polydactyly: Multiple limbs	0	0	2 (2) 22.2%	1 (1) 12.5%	0
Misshapen digits & deformed leg	0	0	0	1 (1) 12.5%	0
Total Litter Incidence*	**0%**	**20%**	**33.3%**	**50%**	**0%**

*** Historical Control Incidence for Polydactyly = 5.71%; Syndactyly = 2.86%**

- The Pharmacology/Toxicology reviewers, along with the Maternal Health consultant and Reproductive and Developmental Toxicity PTCC Subcommittee have determined that telavancin is a multi-species teratogen with drug-related limb defects in all species tested (including rat, rabbit, and minipig).
- The Reproductive and Developmental Toxicity PTCC Subcommittee did not recommend a specific pregnancy category and recommended that the following factors be considered in assignment of pregnancy category including:
    - Seriousness of the indication and potential for serious complications in pregnancy associated with the indication
    - Availability of alternative treatments
    - Teratogenic effect occurring at or near proposed human dose

    - "Potential benefit" of the treatment should exceed the risk
- The Maternal Health Team recommended classification of the drug as pregnancy category X based on no perceived benefit over existing therapy with an increase in risk based on teratogenicity potential. They also recommended a boxed warning and restricted distribution at the pharmacy level to include documentation of age, gender, and evidence of non-childbearing potential for females.

The Applicant had been informed of the FDA concerns regarding teratogenicity in the NDA Filing communication on February 20, 2007. The Applicant requested and was granted a meeting with the FDA on July 11, 2007 to discuss the preclinical teratogencity findings.

The Applicant acknowledged that telavancin produced limb abnormalities in both rat and rabbit, although their consultant, Dr. Scialli was of the opinion that the rat teratogenicity was based on low litter weights rather than limb findings which were not confirmed by the skeletal examination (skeletal exam only done in one of the two rats with brachymelia and finding not noted on that exam). He also noted that there was difficulty in interpreting the minipig study due to poor reproductive performance (small number of litters to examine); one of the control groups had a pregnancy rate to term of only 36%.

Conclusions:

Efficacy: The Applicant has provided sufficient evidence for the efficacy of telavancin the treatment of cSSSI. In two adequate and well-controlled Phase 3 studies, telavancin was demonstrated to be non-inferior to vancomycin. Telavancin was not superior to vancomycin in the treatment of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). In *in vitro* studies, telavancin has demonstrated activity against vancomycin non-susceptible isolates. However, no vancomycin non-susceptible *S. aureus* isolates (MIC exceeding 2 ug/ml) were identified in the clinical studies.

Safety:

- Renal Adverse Events: Overall there was a higher frequency of renal adverse events including elevation in renal laboratory parameters (BUN/creatinine) in telavancin-treated patients. Though the frequency of renal adverse events in telavancin-treated patients was low (2.3%), there was a consistent difference between telavancin and vancomycin in the frequency of renal adverse events (SAE and non-SAE) and also in renal laboratory parameters. As this difference was seen in both studies it is less likely that it was a chance finding. Also, the two treatment groups were similar in terms of baseline creatinine and creatinine clearance. So, it is unlikely that the increased renal adverse events could be attributed to differences in baseline renal function. Furthermore, animal studies had identified kidney as a target organ of toxicity. Most of the renal SAEs occurred in patients with underlying co-morbidities that could compromise renal function. The potential for renal AEs with telavancin use should be clearly communicated in the product label with possible restriction of its use in patients with renal impairment or significant risk factors for compromised renal function till further data are available regarding the risk of nephrotoxicity.

- Potential for prolongation of QT interval and teratogenicity in at least two animal species were two other safety concerns identified and should also be addressed in the product label.

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/s/

Sumathi Nambiar
10/19/2007 12:55:03 PM
MEDICAL OFFICER

Division Director Summary Review

Date	October 18, 2007
From	Wiley A. Chambers, MD, Acting Director, DAIOP
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-110
Proprietary / Established Names	Vibativ (telavancin powder)
Dosage Forms / Strength	Powder for reconstitution
Proposed Indication(s)	Complicated Skin and Skin Structure Infections
Recommended Action:	*Approvable*

1. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status
This is the first action on this new molecular entity. Telavancin is a lipoglycopepetide antibiotic produced by a chemical modification of vancomycin. The proposed drug product contains hydroxypropyl-β-cyclodextrin as a solubilizing agent, in addition to mannitol. Telavancin is not approved or marketed anywhere in the world.

2. CMC
As noted in the CMC reviews, the chemistry/manufacturing issues have been resolved with the exception of the manufacturing inspection at Ben Venue. This facility was issued a 483 for deficiencies which include problems with the quality assurance department and repeated instances in which written procedures were not followed. These issues are of sufficient magnitude to preclude approval of the application at this time.

3. Nonclinical Pharmacology/Toxicology
From the Pharmacology Toxicology Review, "In safety pharmacology studies, televancin (TD-6424) inhibited *hERG* channels and elicited a prolongation of action potential in isolated canine cardiac Purkinje fibers. No treatment-related cardiovascular effects were seen in *in vivo* studies in dogs. No drug-induced respiratory or neurological effects were noted.

In tissue distribution studies conducted in dogs, rats and mice, high concentrations of radioactivity were seen in the bone, liver and kidney. TD-6424 is highly protein bound (approximately 90%) in mouse, rat, dog, bovine, rabbit and human plasma as well as human skin blister fluids. The hydroxylated metabolites are the major metabolites in rat, dog and monkey urine. Urine excretion is the major route in dogs, mice, rats.

Several toxicological studies were conducted with durations of up to 6-months in rats and 3 months in dogs. The organs of toxicity identified in these studies include the kidney and liver in both species. Multiple organ macrophage accumulation/hypertrophy/hyperplasia was also noted. The drug is a multi-species teratogen.

Although some of the findings (e.g., increased BUN, creatinine, AST, and ALT levels) were seen in the placebo (hydroxypropyl-β-cyclodextrin) control animals, the findings were more significant

and more frequent in the drug-treated animals, leading to the conclusion that the active compound contributed significantly to the alterations.

After several intensive discussions between the sponsor and the Agency, and among different disciplines within the Agency, the following recommendations to the labeling are proposed by the reviewing pharmacologist.

Warnings and Precautions

b(4)

Pregnancy

b(4)

Carcinogenesis, Mutagenesis, Impairment of Fertility

b(4)

b(4)

Maternal Health Consultation Conclusions
For the proposed indication of cSSSI, televancin, if approved, should be assigned pregnancy category X because of a consistent teratogenic signal in three animal species combined with a lack of evidence of clinical benefit over eight other approved therapies for this indication. It is possible that data submitted for a different clinical indication in the future could support pregnancy category C if some direct benefit to mother or fetus was demonstrated. However, for the indication of cSSSI, there is no increase in benefit to offset the increase in risk for a pregnant patient.

A RiskMAP that includes education and reminders alone will not adequately safeguard against televancin use in pregnant women, and a RiskMAP with a performance-linked access system is probably not feasible in acute care situations to treat acute infections.

I agree with the conclusions of the Pharm/Tox group and disagree with the conclusions listed in the Maternal Health Consultation. As identified in this review, there are microorganisms which are sensitive to Televancin and resistant to vancomycin. This is likely to lead to bacterial infections which may be appropriately treated with telavancin and for which no other therapy is appropriate. It would be helpful if the applicant can clearly identify some of these cases.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review concluded:

a. 10mg/kg dose, as proposed by the sponsor, is acceptable.
   i. The clinical cure rate is similar between 7.5 mg/kg and 10 mg/kg groups. The exposures seem to be at the plateau region of the exposure-response curve.
   ii. Microbiological eradication rate is higher for the 10 mg/kg dose versus 7.5 mg/kg. The expected microbiological response rate for a patient with the exposure of 1239 mg*hr/mL (median exposure at the dose of 7.5 mg/kg) is 72.8%, whereas the response rate increased to 81.6% for a patient with the exposure of 1739 mg*hr/mL (median exposure at the dose of 10 mg/kg) under the treatment duration of 7 days.
   iii. 10 mg /kg yields only marginally (and numerically) higher risk of renal function reduction (defined as at least 20% reduction in creatinine clearance from baseline at any time during the trial) compared to 7.5 mg/kg (14% vs. 17.6%).
b. Treatment duration of 7-14 days is acceptable.
c. The clinical cure and microbiological eradication rates seem to have achieved the maximum between 7-14 days. Patients treated for less than 7 days have lower probability of treatment success.

I concur with the conclusions and recommendations from the clinical pharmacology group.

5. Clinical Microbiology

From a Clinical Microbiology prospective, the Microbiology team has recommended approval with labeling revisions and breakpoint revisions identified in their review. I concur with that review and the breakpoints identified in the table below.

Susceptibility Breakpoints Proposed by the Agency

Pathogen	Susceptibility Interpretive Criteria					
	MIC (µg/ml)			Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus including methicillin-resistant isolates)	≤1	--	--		--	--
Streptococcus pyogenes, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, *S. constellatus*)	≤0.012	--	--		--	--
Enterococcus faecalis (vancomycin-susceptible only)	≤1	--	--		--	--

6. Clinical/Statistical

6.1. Efficacy

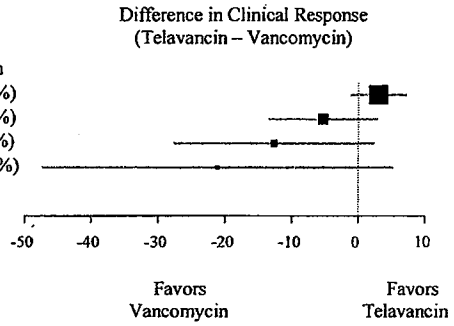
	Sponsor's Analysis				FDA Analysis			
	Study 0017		Study 0018		Study 0017		Study 0018	
	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)	Telavancin 10 mg/kg N (%)	Vancomycin N (%)
All-Treated								
Cure	323 (75.8)	321 (74.8)	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)	

Based on the controlled clinical studies, there was no significant difference between Telavancin and vancomycin in treatment response and the differences are within the supported non-inferiority limit. This conclusion remains regardless of the various sensitivity analyses that have been performed.

Differences due to renal impairment and age are significant, although as noted in the primary reviews, age and renal function are inversely correlated. See below.

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%)



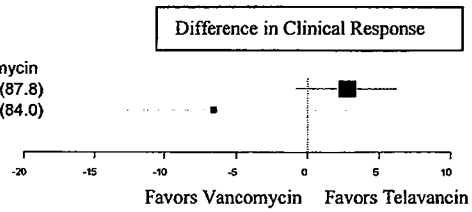
Clinical Response Rate at TOC in the CE Population (Studies 0017 + 0018) -- FDA Analyses

	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.

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

Age	Telavancin	Vancomycin
<65 Yrs	558/616 (90.6)	527/600 (87.8)
>=65 Yrs	100/129 (77.5)	121/144 (84.0)



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.

There is some merit for differentiating telavancin from vancomycin because there is a population of patients that are more sensitive to telavancin than to vancomycin, but this population is small.

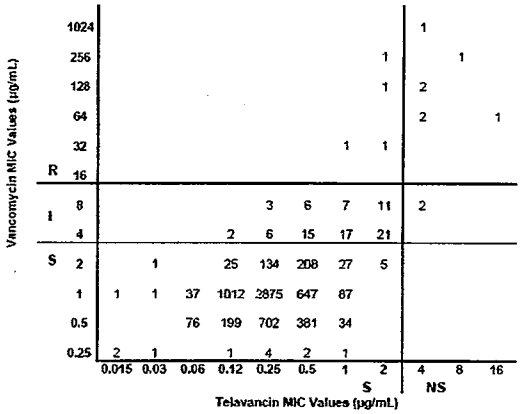
Clinical Response at TOC in the MAT Population (Post-Amendment)
-- By Baseline Pathogen in FDA Adjudicated Data

	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)

There are also organisms for which the cure rate with vancomycin is considerably better than telavancin.

There may be organisms for which there may be cases of a microorganism being sensitive to telavancin and not to vancomycin.

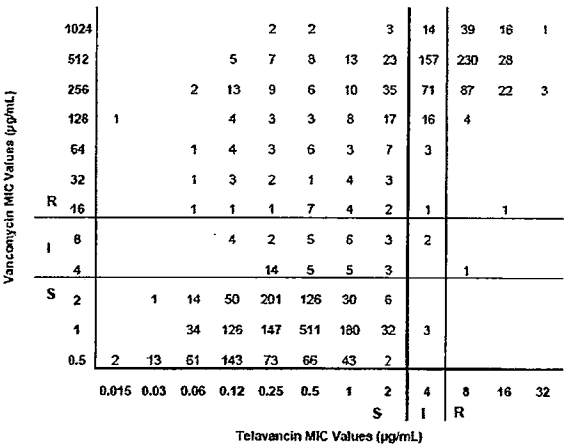
Telavancin and Vancomycin MIC Values of *S. aureus* (n=6,564) from Clinical and Surveillance Studies



Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies

Source: 5.3.5.4.1.6 Figure 8, December 6, 2006, submission

Telavancin and Vancomycin MIC Values of Enterococcal spp. (n=2,835) from Clinical and Surveillance Studies



Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies.

Source: 5.3.5.4.1.6 Figure 9, December 6, 2006, submission

In these tables, it is noted that there are organisms which are sensitive to telavancin and resistant to vancomycin, although the number of these organisms is small and the breakpoints for sensitivity and resistence will need to be modified as described in the microbiology review. It is important to note that the organisms identified in the tables above are from both Clinical Study sources and Surveillance studies which may include indications other than cSSSI.

6.2. Safety

6.2.1. Renal Safety

There is an imbalance in the reported renal and vascular events, although the numbers are small.

Serious Adverse Events	Study 0017		Study 0018		Studies 0017 + 0018	
MedDRA SOC/Preferred Term	TLV N=426	Vanc N=429	TLV N=503	Vanc N=509	TLV N=929	Vanc N=938
Renal and Urinary Disorders						
Any serious event	5 (1%)	1 (0.2%)	6 (1%)	1 (0.2%)	11 (1%)	2 (0.2%)
Calculus bladder	1 (0.2%)	0	0	0	1 (0.1%)	0
Nephrolithiasis	0	0	1 (0.2%)	0	1 (0.1%)	0
Renal failure acute	1 (0.2%)	0	3 (0.6%)	0	4 (0.4%)	0
Renal failure chronic	0	0	0	1 (0.2%)	0	1 (0.1%)
Renal impairment	2 (0.5%)	0	0	0	2 (0.2%)	0
Renal insufficiency	1 (0.2%)	0	2 (04%)	0	3 (0.3%)	0
Renal vessel disorder	0	1 (0.2%)	0	0	0	1 (0.1%)
Vascular Disorders						
Any serious event	5 (1)	1 (0.2%)	4 (0.8%)	1 (0.2%)	9 (1%)	2 (0.2%)
Deep vein thrombosis	2 (0.5%)	0	0	0	2 (0.2%)	0
Gangrene	0	0	1 (0.2%)	0	1 (0.1%)	0
Hypotension	1 (0.2%)	1 (0.2%)	1 (0.2%)	0	2 (0.2%)	1 (0.1%)
Orthostatic hypotension	0	0	1 (0.2%)	0	1 (0.1%)	0
Peripheral ischemia	0	0	0	1 (0.2%)	0	1 (0.1%)
Peripheral occlusive disease	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0
Varicose vein ruptured	1 (0.2%)	0	0	0	1 (0.1%)	0

Discontinued Patients	202a and Original Protocol 0017 + 0018 + 202b		Post-Amendment 1 0017 + 0018 + 202b		All Efficacy and Safety Studies	
	TLV 7.5 N=192	VANC N=189	TLV 10 N=1029	VANC N=1033	TLV N=1221	VANC N=1222
Renal and Urinary Disorders	2 (1)	0	9 (<1)	1 (<1)	11 (<1)	1 (<1)
Vascular Disorders	2 (1)	0	2 (<1)	2 (<1)	4 (<1)	2 (<1)

Treatment emergent adverse events	Study 202a + Original Protocol 202b + 0017 + 0018		Post Amendment 202b + 0017 + 0018		ALL Telavancin SSSI Studies	
MedDRA SOC	TLV 7.5 N=192	Vanc N=189	TLV 10 N=1029	Vanc N=1033	TLV N=1221	Vanc N=1222
Renal and Urinary Disorders	3 (2%)	0	12 (1%)	3 (0.3%)	15 (1%)	3 (0.2%)
Vascular Disorders	1 (0.5%)	2 (1%)	10 (1%)	2 (0.2%)	11 (1%)	4 (0.3%)

Additional adverse events that deserve mention include:

Serious Adverse Events	Study 0017		Study 0018		Studies 0017 + 0018	
MedDRA SOC/Preferred Term	TLV N=426	Vanc N=429	TLV N=503	Vanc N=509	TLV N=929	Vanc N=938
Nervous System						
Dysgeusia	156 (37)	31 (7)	155 (31)	31 (6)	311 (33)	62 (7)
GI						
Nausea	128 (30)	95 (22)	121 (24)	47 (9)	249 (27)	142 (15)
Vomiting	78 (18)	50 (12)	49 (10)	19 (4)	127 (14)	69 (7)
Skin and Subcutaneous Tissue Disorders						
Any event	90 (21)	139 (32)	75 (15)	114 (22)	165 (18)	253 (27)
Erythema	6 (1)	11 (3)	2 (<1)	0	9 (<1)	19 (2)
Hyperhidrosis	10 (2)	9 (2)	5 (<1)	4 (<1)	15 (2)	13 (1)
Pruritus	25 (6)	58 (14)	29 (6)	62 (12)	54 (6)	120 (13)
Pruritus generalized	19 (4)	40 (9)	9 (2)	20 (4)	28 (3)	60 (6)
Rash	17 (4)	23 (5)	18 (4)	20 (4)	35 (4)	43 (5)

There were more GI related events and taste disturbances in the Televancin groups and more rash related events in the vancomycin groups.

6.2.2. **QT**

As described in the Cardiology consultation: In this 'thorough QT/QTc study' the effects of administering two doses (7.5 mg/kg and 15 mg/kg infused intravenously over 60 minutes) of telavancin were assessed at steady state after three days of once daily dosing. At both doses, the baseline- and placebo corrected QTcF interval was lengthened greater than 10 msec, the threshold of regulatory concern (Table). The mean Cmax of the supratherapeutic dose (15 mg/kg) represents a 50% increase in exposure over the highest clinical dose of 10 mg/kg (expected mean Cmax of 122 µg/ml based on linear pharmacokinetics).

Dosing Regimen	Mean Cmax, µg/ml	Time of maximum ΔΔQTcF	Mean ΔΔQTcF, msec	90 % Confidence Interval, msec
7.5 mg/kg	88	Immediately post infusion	14	8, 20
15 mg/kg	186	Immediately post infusion	18	11, 25
400 mg Moxifloxacin	Not applicable	Immediately post infusion	24	18, 30

Telavancin undergoes very little metabolism and is predominantly excreted unchanged in the urine. Therefore, subjects with impaired renal function are expected to have the highest exposure to telavancin.

The increase in QT is not as high as that seen with Moxifloxacin, but is increased. The clinical implications are not known.

7. Advisory Committee Meeting

An advisory committee meeting has not been convened, however, during the review of the application, a number of issues have been raised which might benefit from additional advice. These issues include: language associated with the risk of fetal abnormalities if telavancin is administered to a pregnant women, differences in efficacy related to renal function, effect of the drug product on the QTC.

8. Other Regulatory Issues

8.1. Application Integrity Policy (AIP) – *not invoked*

8.2. Exclusivity/patent issues – *none identified*

9. Financial Disclosure – *Although no issues have been identified based on the information submitted to date, complete information has not been submitted. Information is lacking on 3 investigators.*

10. Labeling

The review of the labeling has been deferred until the issues listed below are resolved.

11. DSI Audits

The DSI inspections have been completed. The data from the inspected sites were considered acceptable for review although there were minor deviations from best practices.

12. Conclusions and Recommendations

12.1. It is recommended that NDA 22-110, be considered approvable with a request to submit information which addresses the following deficiencies:

12.1.1. FDA inspection of the Ben Venue facility in Bedford, Ohio revealed significant deviations from the Current Good Manufacturing Practice regulations.

12.1.2. Financial disclosure information for three (3) sub-investigators was not included in the application.

12.1.3. The 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. This imbalance in reported events extends to patients discontinued due to Renal and Urinary Disorders, laboratory values for serum creatinine changes and is present in the treatment emergent adverse events for Renal and Urinary Disorders, and in Vascular Disorders.

(d) The thorough QT/QTc study demonstrated that the baseline and placebo corrected QTcF interval was lengthened greater than 10 milliseconds.

(e) The drug product appears to be a teratogen in at least one and possibly three species.

Additional clinical data or re-analyses of previously conducted clinical trials is needed to provide a justification of why the risks associated with the issues identified above do not outweigh the potential benefit observed as a result of the treatment of complicated skin and skin structure infections (cSSSI) with telavancin. Alternatively, revised labeling should be submitted which may minimize the intended population according to their identified increased risks.

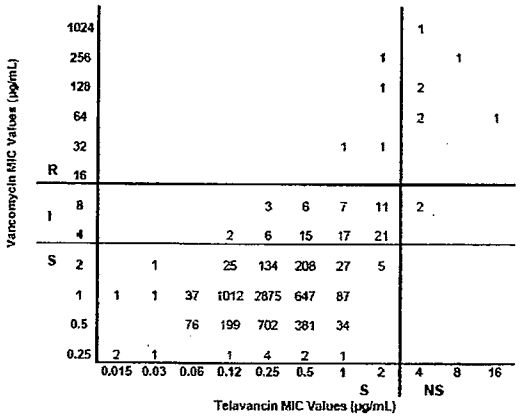
12.1.4. Figure 8 from 5.3.5.4.1 of the December 6, 2006, submission displayed below identifies 4 S. aureus isolates which are sensitive to telavancin and resistant to vancomycin. There appear to be no S. aureus isolates that are sensitive to vancomycin and resistant to telavancin. Figure 9 from 5.3.5.4.1 of the December 6, 2006, submission displayed below identifies 227 Enterococcal spp. isolates which are sensitive to telavancin and resistant to vancomycin. There appear to be no Enterococcal spp. isolates that are sensitive to vancomycin and resistant to telavancin.

(a) Please confirm whether you have identified any *S. aureus* or Enterococcal spp. isolates (particularly *Enterococcus faecium* and *Enterococcus faecalis)* which are sensitive to vancomycin and resistant to telavancin.

(b) Please identify the clinical disease from which there were vancomycin resistant (MIC of >16 mcg/mL)/telavancin sensitive *S. aureus* or Enterococcal spp. (particularly *Enterococcus faecium* and *Enterococcus faecalis)* isolates.

(c) If there are clinically relevant isolates (any bacterial organism) which are sensitive to telavancin (MIC ≤1 mcg/mL) and resistant to vancomycin, please identify them along with the clinical condition from which they were isolated.

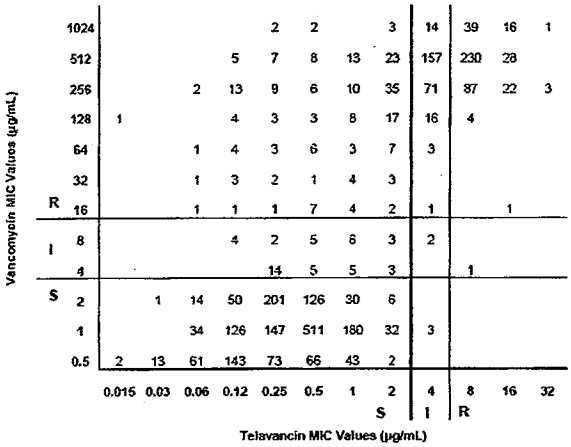
Telavancin and vancomycin MIC Values of S. aureus (n=6,564) from Clinical and Surveillance Studies



Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies

Source: 5.3.5.4.1.6 Figure 8, December 6, 2006, submission

Telavancin and vancomycin MIC Values of Enterococcal spp. (n=2,835) from Clinical and Surveillance Studies



Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0016, ME population and MIC values from all surveillance studies.

Source: 5.3.5.4.1.6 Figure 9, December 6, 2006, submission

12.1.5 Pregnancy Category C is appropriate if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in human, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. The submitted application presents theoretical reasons why it may be appropriate for a pregnant women to take telavancin, but it does not appear to identify clinical cases of cSSSI where clinical isolates have been demonstrated to be sensitive to telavancin and resistant to other anti-infectives such as vancomycin. Isolates such as the ones identified in item 4 above may be such cases if the clinical source is from a cSSSI clinical case. Please identify specific clinical cSSSI cases, not necessarily pregnant women, in which the clinical circumstances would suggest that if the case had been a pregnant women, it may have been appropriate for her to take telavancin.

12.1.6 Labeling review will be deferred until all other deficiencies in the application have been submitted and reviewed.

12.1.7 The nature of the issues involved in this application suggests that we may seek advice from the Anti-Infective Advisory Committee following a response by the applicant to the deficiencies identified. Discussion with the Advisory Committee may include, but not necessarily be limited to, the overall benefit/risk profile of telavancin in light of its benefits in treating cSSSI, teratogenic potential, decreased efficacy in patients with impaired renal function, renal adverse events, and potential for QT prolongation.

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/s/

Wiley Chambers
10/19/2007 04:25:16 PM
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CLINICAL REVIEW

Application Type	NDA 22-110
Submission Number	000
Submission Code	N
Letter Date	12/06/06
Stamp Date	12/19/06
PDUFA Goal Date	10/19/07
Reviewer Name	Janice K. Pohlman, MD, MPH
Review Completion Date	10/18/07
Established Name	Telavancin
(Proposed) Trade Name	(Vibativ)
Therapeutic Class	Glycopeptide Antibacterial
Applicant	Theravance, Inc.
Priority Designation	S
Formulation	Powder for Reconsitution and IV Administration
Dosing Regimen	10 mg/kg
Indication	cSSSI
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Not Approvable based on an unfavorable risk to benefit assessment for the complicated skin and skin structure infection (cSSSI) indication.

- Patients treated with telavancin had a higher number of renal serious adverse events (SAEs) and discontinuations from therapy associated with renal adverse events (AEs), along with a greater number of patients with potentially clinically significant (PCS) laboratory evidence of renal impairment by a variety of prespecified measurements than did patients treated with vancomycin. Three patients treated with telavancin required hemodialysis (one of whom had rising serum creatinine documented prior to study participation); two of these patients refused dialysis based on comorbid conditions and died. There were a few patients identified who were noted to have improving renal function at test of cure (TOC) or last study laboratory who had serum creatinine values that were still two times the baseline value.
- In addition to nephrotoxicity, there are concerns about teratogenicity based on findings in embryo-fetal development studies in rats, rabbits, and minipigs. Limb abnormalities were noted in all species, although it is not clear whether they were the same in all species and related to appendicular skeletal abnormalities and/or related to soft tissue differentiation. Interpretation of the minipig study was compromised by the small number of fetuses available for examination, as well as limb findings in one control group fetus.
- Telavancin has demonstrated an effect on the QT interval, although based on the FDA clinical reviewer interpretation of the data, the effect appears to be less than that seen for moxifloxacin, an antibiotic which has an oral formulation and is administered to outpatients.
- There was no clinical evidence provided that telavancin provides an additional treatment benefit over vancomycin in patients with cSSSI, including infections caused by MRSA and causes more renal toxicity than vancomycin.

Telavancin did demonstrate non-inferiority to vancomycin in two independent Phase 3 studies in the treatment of patients with complicated SSSIs (cSSSI) thought to be due to Gram positive bacteria. Both Phase 3 studies demonstrated non-inferiority based upon a prespecified margin of 10% with valid justification provided by the Applicant for use of this margin.

- Telavancin did not demonstrate superiority relative to vancomycin in the treatment of patients who had methicillin-resistant *Staph aureus* (MRSA) identified from baseline microbiological cultures.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The recommendation for this NDA is not approvable, therefore no risk management plans have been recommended.

1.2.2 Required Phase 4 Commitments

The recommendation for this NDA is not approvable, therefore no Phase 4 commitments have been established.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Applicant conducted four studies evaluating the safety and efficacy of telavancin compared to vancomycin in the treatment of adults (≥ 18 yrs of age) with cSSSI suspected to be caused by Gram positive bacteria, including MRSA. The Phase 2 studies (I6424-202a and I6424-202b) and the Phase 3 studies (0017 and 0018) were of similar design and were randomized, double-blind, active-controlled studies comparing telavancin IV q 24 hrs to standard therapy. The primary objective was to demonstrate non-inferiority of telavancin compared to standard therapy for the primary efficacy endpoint of clinical response at TOC using a non-inferiority margin of 10%.

The Phase 2 studies evaluated both a 7.5 mg/kg dose of telavancin (202a) and a 10 mg/kg dose of telavancin (202b) compared to investigator determined standard therapy. Standard therapy was vancomycin or antistaphylococcal penicillin (nafcillin, oxacillin, or cloxacillin). The choice of standard therapy was determined by the investigator prior to randomization. Patients could be treated for a minimum of 4 days and maximum of 14 days.

The Phase 3 studies were initiated using a telavancin dose of 7.5 mg/kg, but were amended after 182 patients were enrolled, to a 10 mg/kg dose of telavancin IV q 24 hr compared to vancomycin IV q 12 hr. Treatment duration was 7 to 14 days. Aztreonam and/or metronidazole could be used as adjunctive therapy for Gram negative and/or anaerobic bacteria, respectively, but were not required. An appropriate baseline specimen was to be obtained for Gram stain and microbiological culture at the local laboratory, with any pathogens isolated sent to a central microbiology laboratory for confirmation of identification and antimicrobial susceptibility.

The co-primary efficacy endpoint was the clinical response at the TOC visit in the All-Treated (AT) and Clinically Evaluable (CE) populations. Secondary efficacy endpoints included clinical response in the Microbiological All-Treated (MAT) and Microbiological Evaluable (ME) population, as well by-pathogen and by-patient response in the microbiological analysis populations.

The FDA analysis populations differed from the Applicant's for Study 0017 and 0018 in the following way:

- Study 0018 populations excluded patients from site #38091.
- Clinical evaluability status and outcome in Study 0017 and 0018 populations for patients who received effective non-study antibiotic(s) for the cSSSI from the time of initiation of study therapy to TOC were re-adjudicated.
- Clinical evaluability status and outcome in the same studies for patients having surgical/wound-related procedures with impact on outcome after 96 hours of study treatment were re-adjudicated.
- Patients with Gram negative bacteria only isolated from the baseline microbiological culture of the cSSSI site were excluded from the MAT and ME analysis populations.
- FDA recommended changes to the Applicant's final statistical analysis plan: Test-of-Cure (TOC) window of 7-21 days after End-of-Therapy (EOT), at least 5 days (or 10 doses) of study medication for 80% compliance, coagulase-negative staphylococci accepted as pathogens if the Gram stain was consistent with infection for cultures of wounds, baseline pathogen window of Day -1 to Day 1, and only pathogens identified at the central microbiology laboratory were included in microbiological analysis.

The primary statistical analysis was to determine the non-inferiority of telavancin compared to vancomycin in adult patients with cSSSI caused by suspected Gram positive bacteria, using a pre-specified non-inferiority margin for difference in success (telavancin – vancomycin) of -10%. Study 0017 and 0018 were of identical design but conducted independently and the Applicant proposed pooling the results of the two studies in order to assess superiority of telavancin compared to vancomycin in the treatment of patients with MRSA isolated from baseline cultures.

The Phase 2 studies allowed two different comparators (vancomycin or antistaphylococcal penicillin) and shorter duration of therapy compared to the Phase 3 studies. The Phase 2 studies were also performed sequentially and used by the Applicant to determine the dose to be used in the pivotal Phase 3 studies. For these reasons, the data from the Phase 3 studies, after the increase in dose of telavancin to 10 mg/kg (proposed to-be-marketed dose), were used for primary evaluation of safety and efficacy. The data from the Phase 2 studies and Original Protocol Phase 3 studies were used to evaluate safety only and allowed for a limited dose-effect comparison of telavancin 7.5 mg/kg and 10 mg/kg in relation to AEs.

1.3.2 Efficacy

The results of the two Phase 3 studies, Study 0017 and Study 0018, for the co-primary efficacy analysis populations support the conclusion that telavancin demonstrates non-inferiority to vancomycin using the prespecified non-inferiority margin of 10%. The results of the efficacy analysis for the co-primary FDA All-Treated (FDA-AT) and FDA Clinically Evaluable (FDA-CE) populations are shown in Table 1.

Table 1: Clinical Response Rates (FDA-AT and FDA-CE, Studies 0017 and 0018)

	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
FDA Population	n/N %	n/N %	% (95% CI)
AT			
Study 0017	309/426 (72.5)	307/429 (71.6)	0.9 (-6.4, 8.3)
Study 0018	348/472 (72.5)	360/489 (73.6)	0 (-6.8, 6.9)
0017 + 0018 Combined	657/898 (73.2)	667/918 (72.7)	0.4 (-4.6, 5.5)
CE			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.6 (-5, 8.3)
Study 0018	306/365 (83.8)	318/363 (87.6)	-3.3 (-9.6, 6.3)
0017 + 0018 Combined	595/708 (84.0)	606/711 (85.2)	-0.9 (-5.5, 3.7)

The results of Study 0017 and Study 0018 demonstrate the non-inferiority of telavancin to vancomycin in the treatment of patients with cSSSI caused by suspected Gram positive bacteria, including MRSA. Although the point estimate for the difference in success rates favors telavancin in Study 0017 and vancomcyin in Study 0018 (or no difference in Study 0018 depending on the population of interest), the lower bound of the 95% confidence interval is greater than -10%, the prespecified non-inferiority margin.

Table 2 shows the Study 0017 and Study 0018 pooled clinical response rates in patients in the FDA-AT analysis population with MRSA isolated from baseline microbiological culture. The AT population was used to test for superiority of telavancin compared to vancomycin.

Table 2: Clinical Response Rate in FDA-AT Population with MRSA at Baseline

	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin
Population	n/N %	n/N %	% (95% CI)
MRSA			
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	136/170 (80)	133/175 (76)	4 (-4.7, 12.7)
Pooled 0017 + 0018	228/305 (74.8)	243/326 (74.5)	0.1 (-6.7, 6.8) p-value 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.			

Telavancin failed to demonstrate superiority compared to vancomycin in the treatment of patients with cSSSI caused by MRSA.

Subgroup analyses of clinical response rates were performed based on demographic and baseline characteristics of the study populations.

Table 3 shows the pooled FDA-CE clinical response rates for each type of cSSSI studied. The clinical response rates were similar for telavancin and vancomycin based on type of cSSSI studied.

Table 3: Clinical Response Rates Based on cSSSI Type – FDA-CE Population

	Telavancin (n/N) %	**Vancomycin (n/N) %**	**Difference (TLV-Comparator) (95% CI)[1]**	**p-value[2]**
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)	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, diabetes, and subgroup variable.				

Clinical response rates for patients were analyzed according to baseline renal function and results are shown in Table 4 for the pooled FDA-CE population. There was a decrease in clinical response rates noted for patients treated with telavancin as the degree of renal impairment increased. This difference was not seen in patients treated with vancomycin.

Table 4: Clinical Response Rates Based on Baseline Renal Function – FDA-CE Population

	Telavancin (n/N) %	Vancomycin (n/N) %	Difference (TLV-Comparator) (95% CI)[1]	p-value[2]
Baseline Creatinine Clearance				
• > 80 mL/min	406/455 (89.2)	397/461 (86.1)	3.1 (-1.2, 7.3)	0.02
• > 50-80 mL/min	131/165 (79.4)	142/168 (84.5)	-5.2 (-13.5, 3)	
• 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 (-47.4, 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, diabetes, and subgroup variable.

The clinical response rates by baseline pathogen in the FDA-ME population are shown in Table 5. The clinical response rates for *Staph aureus* (MRSA and MSSA) are relatively similar for both treatment groups.

Table 5: Clinical Response Rates by Pathogen – FDA-ME Population (Pooled 0017 and 0018)

Pathogen	Telavancin (n/N) %	Vancomycin (n/N) %	Difference (TLV-Comparator) (95% CI)[1]
Staphylococcus aureus, MRSA	209/240 (87.1)	226/264 (85.6)	1.4 (-4.6, 7.4)
Staphylococcus aureus, MSSA	133/162 (82.1)	131/154 (85.1)	-2.9 (-11.1, 5.2)
Enterococcus faecalis	22/23 (95.7)	28/35 (80)	15.4 (-0.8, 31.6)
Streptococcus pyogenes	16/19 (84.2)	20/22 (90.9)	-7.0 (-27.6, 13.5)
Streptococcus agalactiae	14/19 (73.7)	13/15 (86.7)	-19.8 (-46.6, 7.1)
Streptococcus anginosus	9/10 (90)	6/6 (100)	-10.0 (-27.5, 7.5)
Streptococcus constellatus	3/5 (60)	4/4 (100)	-50.0 (-78.3, -21.7)
Streptococcus intermedius	2/3 (66.7)	0	-7.0 (-27.6, 13.5)

1.3.3 Safety

Table 6 shows the number of patients treated with telavancin versus comparator in the telavancin development program as of September 21, 2006 (for patients enrolled prior to May 15, 2006).

Table 6: Number of Subjects Evaluated for Safety – All Telavancin Studies

	Number of Subjects Exposed	
Study Group	**Telavancin**	**Comparator**
Clinical Pharmacology Studies		
Single Dose Studies[1] (0.25 – 15 mg/kg)	124	47
Multiple Dose Studies (7.5 – 15 mg/kg)	144	103
Total Clinical Pharmacology Studies	**268**	**150**
Efficacy and Safety Studies in cSSSI		
Studies 0017, 0018, and 202b (Post Amendment) 10 mg/kg telavancin dose	1029	1033
Study 202a and Studies 0017, 0018, 202b (Original Protocol) 7.5 mg/kg telavancin	192	189
Total Efficacy and Safety Studies	**1221**	**1222**
Total Completed Studies	1489	1372
Ongoing Treatment-Blinded Studies[2]	208	208
Grand Total	**1697**	**1580**

From NDA 22-110, Module 2.7.4, Summary of Clinical Safety, Table 2, pg 16.
[1] Of the telavancin-treated patients, 79 subjects received a single dose and 45 received single doses on more than one occasion separated by one week or more.
[2] Treatment blinded: number per group estimated at 50% of total (studies with 1:1 randomization).

The post amendment Phase 3 studies included 929 patients treated with telavancin 10 mg/kg dose and 938 patients treated with comparator. There were an additional 100 patients treated with telavancin 10 mg/kg and 95 treated with comparator in a Phase 2 study of similar design. There were also 192 patients treated with telavancin 7.5 mg/kg (99 in 2 Phase 2 studies and 93 in Phase 3 studies) and 189 patients treated with comparator in these studies. Protocol-specified duration of treatment in these studies was 7-14 days for Phase 3 and 4-14 days for Phase 2.

Table 7 shows the number of patients in the Phase 3 telavancin 10 mg/kg studies (0017, 0018), all telavancin 10 mg/kg studies (0017, 0018, 202b post amendment), all telavancin 7.5 mg/kg studies (0017, 0018, 202b original protocol and 202a), and total number of patients by treatment group who experienced at least one AE, death, SAE, or discontinuation due to AE.

Table 7: Overview of Treatment-Emergent AEs – AT Population, all cSSSI Studies

	Telavancin				COMPARATOR[1]			
	Phase 3 10 mg/kg N=929	ALL 10 mg/kg N=1029	ALL 7.5 mg/kg N=192	Total TLV N=1221	Phase 3 [T 10 mg/kg] N=938	ALL [T 10 mg/kg] N=1033	ALL [T 7.5 mg/kg] N=189	Total [ALL T] N=1222
Patients with at least one AE	735	791	144	935	676	730	138	868
Patient Deaths	8	8	2	10	8	9	0	9
Patients with SAEs	69	76	15	91	42	45	15	60
Patients who discontinued due to AEs	73	79	9	88	53	56	6	62

Adapted from CSRs: I6424-202a:Table 9-2, I6424-202b:Table 9-2, Original Protocol Table 4-2, 0017: Table 9-3, Original Protocol. Table 4-3, 0018: Table 9-3, Original Protocol
1 Column headings for comparator studies indicate the dose of telavancin used in the telavancin treatment arm / events indicated are for comparator treatment group.

SAEs indicative of renal impairment were higher in the telavancin treatment groups compared to the vancomcyin treatment groups for Study 0017 and Study 0018; 11/929 (1.2%) of telavancin-treated patients and 3/938 (0.3%) of vancomycin-treated patients had renal SAEs (Preferred terms: blood creatinine increased, blood urea increased, renal insufficiency, renal impairment, renal failure acute, renal tubular necrosis). There were a greater number of patients who discontinued treatment due to renal AEs in the telavancin treatment group compared to the vancomycin treatment group; 13/929 (1.4%) of telavancin-treated patients and 2/938 (0.2%) of vancomycin-treated patients discontinued treatment due to renal AEs.

Results of safety laboratory testing for serum creatinine (Cr) show that for patients with normal baseline serum Cr who had elevations of Cr to ≥ 133 µmol/L (1.5 mg/dL) and either a change to at least a 44 µmol/L (0.5 mg/dL) greater than baseline or at least 50% greater than baseline were 3-5 times more likely to occur in telavancin-treated patients. The number (percent) of telavancin-treated patients meeting these definitions were 52/929 (5.6%) and 48/929 (5.2%), compared to 19/939 (0.2%) and 17/939 (1.8%) for vancomycin-treated patients, respectively.

Based on interpolation of the data from the "Thorough QT study" with telavancin doses of 7.5 mg/kg and 15 mg/kg, the mean baseline-corrected, placebo-corrected QT prolongation on Day 3 was estimated to be 12-15 msec for telavancin 10 mg/kg and 24 msec for positive control.

Common adverse drug reactions observed in Phase 3 studies are shown in Table 8. The list of reactions is derived from the treatment-emergent AEs (TEAEs) observed during the study. The following criteria have been applied to the observed events in order to limit ADRs to those events for which there is some basis to believe there is a causal relationship between the occurrence of the AE and the use of the drug:

- Adverse events occurring at an incidence of at least 10% PLUS
- Adverse events that occurred at a rate at least 5% higher in one treatment group compared to the other PLUS
- Any adverse event that showed a dose response in placebo-controlled normal volunteer studies or during any Phase 2 or 3 clinical studies.

Table 8: Common Treatment Emergent Adverse Events – Studies 0017 and 0018, Combined

System / Reaction	Telavancin N=929	Vancomycin N=938
Body as a Whole		
• Infusion-related reactions[a]	11%	20%
Digestive System		
• Nausea	27%	15%
• Vomiting	14%	7%
Nervous System		
• Taste disturbance[b]	33%	7%
Renal System		
• Foamy urine[c]	13%	3%

Adapted from NDA 22-110, September 13, 2007 Applicant Submission, Table 3.
[a] Infusion-related reactions are defined as flushing of the upper body and face, urticaria, rash, and/or pruritus.
[b] Usually described as metallic or soapy taste and coded as dysgeusia
[c] Coded as urine abnormality

1.3.4 Dosing Regimen and Administration

The recommended dose of telavancin for treatment of cSSSI in adult patients (≥ 18 yrs) is 10 mg/kg IV q 24 hrs, with treatment duration of 7-14 days. This dose/duration was demonstrated to be non-inferior to vancomycin with a non-inferiority margin of 10% in the treatment of patients with cSSSI caused by Gram positive organisms.

Based on pharmacometric review, the 7.5 mg/kg dose and the 10 mg/kg dose of telavancin appeared to have similar clinical response rates. However, the microbiological eradication rate appeared to be higher in patients treated with the 10 mg/kg dose of telavancin. There was a slightly higher risk of nephrotoxicity associated with the 10 mg/kg dose (4-5%).

Dose adjustments for patients with renal impairment are shown below.

Creatinine Clearance[1] (mL/min)	Recommended Dose Of Telavancin
>50	10 mg/kg every 24 hrs
>30-50	7.5 mg/kg every 24 hrs
10-30	10 mg/kg every 48 hrs
[1] As measured by the Cockroft-Gault formula	

1.3.5 Drug-Drug Interactions

To date, there has been minimal demonstration of direct drug-drug interactions with telavancin. Although it appears to be a weak inhibitor for CYP450 enzymes *in vitro*, in a Phase 1 trial telavancin did not significantly alter the PK of midazolam when a single dose of telavancin was administered concomitantly.

The Applicant provided an analysis of the effect of concomitant administration of medications associated with renal dysfunction ("nephrotoxic drugs") on development of PCS increases in serum Cr on patients treated with study medication. Approximately one-third of the patients in both telavancin and vancomycin treatment groups were taking concomitant medications which have been associated with renal dysfunction ("renal concomitant medication"). The list of nephrotoxic medications included non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, diuretics, antiviral, and immunosuppressive medications. There were no patients listed for the Phase 3 study who received concomitant aminoglycosides. Patients treated with telavancin who had normal baseline serum Cr and were taking renal concomitant medications had an increased risk of a PCS serum Cr increase (34/320 or 11%) compared to those who were not taking renal concomitant medications (14/502 or 3%); the risk also increased for patients treated with vancomycin, but the overall risk for vancomycin patients, even those taking renal concomitant medications was less (for those taking concomitant medications, 12/333 or 4% compared to 5/523 or 1% not taking concomitant medications developed PCS increases in serum Cr).

The potential for telavancin interaction with agents likely to cause torsades de pointes is discussed in Section 7.1.7.3.3.

1.3.6 Special Populations

There are no special dosing considerations based on demographics that have been identified to date, specifically in regard to age, gender, and race. The use of telavancin has only been studied in adults (≥ 18 years), therefore there are no specific recommendations for dosing in the pediatric population.

Based on the clinical pharmacology review, the Applicant's recommendations for dosing in moderate and severe renal impairment are acceptable.

b(4)

In the Phase 1 PK study patients were dialyzed immediately following administration of telavancin; this is the opposite of usual clinical practice in which drug is typically administered following hemodialysis. The mean plasma clearance of telavancin was also noted to be greater for dialysis patients than for those with severe renal impairment, despite only 5.9% of the dose being measured in the dialysate fluid. Therefore, the recommendations for dosing in hemodialysis patients cannot be made at this time.

There are no specific dosage adjustments recommended for patients with hepatic impairment.

The Applicant requested a deferral for pediatric studies at the time of NDA submission. FDA agreed to this request and deferred pediatric studies until December 31, 2012, pending evaluation of the initial safety and efficacy data for approvability in the treatment of adults. Applicant has subsequently submitted a pediatric study request on June 19, 2007. Review of this pediatric proposal has been deferred until a decision on approvability of the pending application has been made.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Telavancin is a lipoglycopepetide antibiotic produced by chemical modification of vancomycin. The drug product is a sterilized powder for injection and contains hydroxypropyl-β-cyclodextrin [(HP-β-CD) as a solubilizing agent], mannitol, and sodium hydroxide and hydrochloric acid for pH adjustment.

- The established name is telavancin.
- The proposed trade name is VIBATIV.
- Previous names include AMI-6424, TD-6424.
- The drug is a new molecular entity (NME).
- The pharmacologic class is antibacterial.
- The proposed indication is for treatment of cSSSIs caused by *Staphylococcus aureus* (including methicillin-resistant and –susceptible strains), (*Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). b(4)
- The proposed dosing regimen is 10 mg/kg infused intravenously over 60 minutes once every 24 hours for 7-14 days. For patients with renal impairment, the following doses were proposed by the Applicant.

  Modifications for Renal Impairment ( ) b(4)

Creatinine Clearance (mL/min)	Telavancin Dosage And Dosage Interval
30-50 (moderate impairment)	7.5 mg/kg q 24 hr
< 30 (severe impairment)	10 mg/kg q 48 hr
( )	

- The proposed treatment population is adults (≥ 18 years of age) with cSSSI.

2.2 Currently Available Treatment for Indications

The following antibiotics are approved for use in the treatment of adults with cSSSI caused by Gram positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA): vancomycin [treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci], linezolid, daptomycin, and tigecycline.

2.3 Availability of Proposed Active Ingredient in the United States

Telavancin is a NME that is not currently marketed in the US. Since telavancin is produced by chemical modification of vancomycin, availability of an adequate vancomycin source is important. During the telavancin development program a single source of vancomycin ( ) DMF ( ) has been used. The Applicant has established impurity/degradant thresholds for telavancin as required by FDA; these thresholds will be important to telavancin product quality should an alternate source of vancomycin become necessary. (See Section 3.1 CMC below) b(4)

No other major problems are anticipated in the availability of the proposed active ingredient.

2.4 Important Issues With Pharmacologically Related Products

Vancomcyin has been used extensively for treatment of serious Gram positive infections (including infections caused by MRSA) since the late 1950's. Adverse drug reactions associated with vancomycin include[1,2]:

- Red-Man Syndrome: histamine-like reaction generally associated with the first dose of vancomycin and/or rapid infusion rates and characterized by pruritus and flushing of the head, neck, face, and torso.
- Nephrotoxicity: rates vary widely in the literature (from 0-15% or higher) and depend upon the definition used to define nephrotoxicity. Higher rates often occur with concomitant administration of aminoglycosides or other comorbid conditions.
- Infusion-site phlebitis
- Dermatologic manifestations: linear bullous IgA dermatosis, Stevens-Johnson syndrome, rash
- Neutropenia: 2%-12%[3]
- Thrombocytopenia: rare
- Drug fever

Teicoplanin is a glycopeptide that is not approved for use in the US. A meta-analysis of 11 clinical studies compared the efficacy and safety of teicoplanin in 651 patients treated with teicoplanin and 625 treated with vancomycin. The analysis showed significantly fewer reports of AEs in patients treated with teicoplanin compared to vancomycin (13.9% compared to 21.9%), including nephrotoxicity and Red-Man syndrome[4].

1 Monroe SG, Polk R. Vancomycin. In: Yu, MeriGn, Barriere, ed. Antimicrobial Therapy and Vaccines. Williams and Wilkins. Baltimore, MD, 1999:1012-1014.
2 Finch RG, Eliopoulis GM. Safety and Efficacy of glycopeptides antibiotics. Journal of Antimicrobial Chemotherapy,2 005;55,SuppS2:ii5-ii13.
3 Pai MP, Mercier R-C, Koster SA. Epidemiology of Vancomycin-Induced Neutropenia in Patients Receiving Home Intravenous Infusion Therapy. The Annals of Pharmacotherapy, 2006;40:224-228.
4 Wood MJ. The comparative efficacy and safety of teicoplanin and vancomycin. Journal of Antimicrobial Chemotherapy 1996;37:209-222.

2.5 Presubmission Regulatory Activity

The Applicant submitted the IND for telavancin (IND 60,237) on May 25, 2002. The IND submission contained clinical data from a two-part Phase 1 study in healthy male subjects conducted in the UK. Part 1 of the study assessed safety and tolerability of single, ascending doses and Part 2 multiple (7) daily infusions of three different doses of telavancin. The IND contained the protocol for a Phase 2 Skin and Skin Structure Infection (SSSI) study.

An IND safety teleconference between the FDA and Applicant was held on June 25, 2002. At that time, the FDA expressed concern about some preclinical aspects of the submission including limited animal exposures, lack of ADME data, and positive findings in a non-GLP hERG assay. From a clinical perspective, there was concern about lack of pharmacokinetic (PK) and safety data in female subjects and the potential effects of telavancin on cardiac repolarization. At the time of this conference, the Applicant had completed a GLP hERG and Purkinje fiber assay as well as a conscious telemeterized dog study, and although study reports were pending, preliminary results in the hERG and Purkinje assay were reported as positive. The Applicant agreed to provide data from the first 30 patients enrolled in the Phase 2 SSSI study prior to proceeding with additional enrollment. Additionally, the Applicant agreed to perform a Phase 1 ECG or "thorough QT" study as defined in the 2002 FDA – Health Canada Concept paper.[5]

An End-of-Phase 2 meeting was held between the FDA and the Applicant on July 12, 2004. At this meeting, the proposed protocols for the Phase 3 cSSSI and hospital-acquired pneumonia (HAP) studies were discussed. The Applicant proposed performing two independent studies of identical design for each indication. They planned to pool the efficacy results from the results of the two studies within a given indication to test for superiority of telavancin versus comparator in patients with infections caused by MRSA. Definitive agreement between FDA and the Applicant on pooling of results to test for superiority was deferred until protocol design issues and the statistical analysis proposal were more fully developed. The FDA informed the Applicant that efficacy in a superiority analysis should be determined in the intent-to-treat (ITT) population and any superiority claims would take into account the risk versus benefit analysis. The Applicant proposed that the safety database for the NDA would have approximately 1,375 telavancin-treated patients (625 in the 10 mg/kg dose HAP studies and 750 in the 7.5 mg/kg dose cSSSI studies). The FDA stated that the safety database should contain adequate information to support the to-be-marketed dose and that absent a safety signal the proposed safety database would be sufficient. The Agency queried the Applicant about initiating the Phase 3 studies with a telavancin dose of 7.5 mg/kg while a second Phase 2 study in treatment of SSSI using a telavancin dose of 10 mg/kg was ongoing. The Applicant stated that although they had sufficient information from the Phase 2 study using the 7.5 mg/kg dose to proceed with that dose, they had pharmacokinetic/pharmacodynamic (PK/PD) data indicating that a higher dose might be better. They thought the second Phase 2 study would be completed early enough in the course of the Phase 3 studies to make a transition if needed to the higher 10 mg/kg dose.

[5] http://www.fda.gov/ohrms/dockets/ac/03/briefing/pubs%5Cprelim.pdf

A pre-NDA meeting was held between the FDA and Applicant on December 15, 2005. The FDA confirmed that the clinical program in cSSSI (Studies 0017 and 0018) might be adequate to support the use of the proposed 10 mg/kg dose of telavancin if efficacy was demonstrated and there was no safety signal. The Agency was asked by the Applicant whether it was acceptable to seek approval for the cSSSI indication in an initial NDA and HAP in a supplemental NDA. The FDA indicated that given demonstration of apparent toxicity in the preclinical program, the NDA would be strengthened by the demonstration of efficacy in cSSSI and an additional indication, such as HAP. The FDA deferred specific comments about the statistical analysis plan (SAP) to a later date. Discussion continued about the SAP for the superiority analysis in patients with infections caused by MRSA. The FDA indicated that the proposed safety database of 750 to 800 patients dosed at the 10 mg/kg dose was sufficient to determine AEs in at least 1% of patients and absent a safety signal would be sufficient to support use of 10 mg/kg dose for 7-14 days for this indication. However, the Applicant was reminded that the FDA had not yet received a study report on safety of the 10 mg/kg dose with a particular concern noted about nephrotoxicity.

2.6 Other Relevant Background Information

The drug product contains HP-β-CD as an excipient and solubilizing agent for telavancin. Hydroxypropyl-β-cyclodextrin is also contained in the intravenous and oral formulations of itraconazole. Noted in the itraconazole label is that chronic oral administration of HP-β-CD to rats at doses of 500, 2000, or 5000 mg/kg/day (human equivalent dose is 1.7 x 500 mg/kg/day dose) for 25 months produced pancreatic exocrine hyperplasia and neoplasia in carcinogenicity testing. Adenocarcinoma was observed in treated animals, but not in controls. Development of tumors is thought to be possibly related to cholecystokinin.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Telavancin is formulated as a sterile, preservative-free lyophilized powder containing either 250 mg or 750 mg of telavancin free base for intravenous use after reconstitution and dilution with 5% dextrose injection or 0.9% sodium chloride injection. The inactive ingredients are HP-β-CD (at a concentration 10 mg per mg of telavancin), mannitol, and hydrochloric acid and sodium hydroxide for pH adjustment. The Applicant states that the HP-β-CD was added as a solubilizing agent.

The drug product is produced by chemical modification of vancomycin. Many of the impurities and degradants in telavancin come from the vancomycin derivative. The vancomcycin thus far has been supplied by ( ) who holds DMF ( ) for vancomycin hydrochloride. DMF ( ) has been reviewed multiple times and was last found adequate in February 2006. The Applicant has established quality attributes for the drug product manufactured from this vancomycin source as requested by FDA. These are important should need for another source of vancomycin be required. b(4)

No issues related to product sterility were noted in the Product Quality Microbiology Review by John Metcalfe, Ph.D. See also the CMC review by Balajee Shanmugam, Ph.D. for a full discussion of CMC issues.

3.2 Animal Pharmacology/Toxicology

The important issues identified based on the Pharmacology/Toxicology review by Zhou Chen, MD, PhD, and Terry Peters, DVM, are discussed briefly below. For a more detailed review, see Dr. Chen's review.

Toxicology

The major organs of toxicity in rats and dogs were the kidney and liver. A finding of undetermined significance with prolonged (> 4 week) administration of the drug was macrophage hypertrophy, hyperplasia, and accumulation in various organs.

- Renal toxicity in rats was manifested by diffuse tubular vacuolation following 2 week administration (≥ 25 mg/kg/day), minimal mutlifocal tubular degeneration with mild increase in blood urea nitrogen (BUN) and creatinine (Cr) after 4 weeks administration (≥ 50 mg/kg/day), increased incidence/severity of proximal tubular degeneration, inflammatory cell infiltrates and tubular casts, with increased BUN and Cr and hematuria after 13 and 26 weeks administration (≥ 50 mg/kg/day). These changes were generally reversible after a 4 week recovery period, but in the 13- and 26-week studies, only partially reversible. Renal toxicity in dogs was manifested by tubular vacuolation and necrosis with increase in BUN and Cr after 4 and 13 weeks administration (≥ 25 mg/kg/day) which generally decreased after a 4 week recovery period [note that one female treated with 50 mg/kg/day (high dose) for 4 weeks had an exacerbation of tubular degeneration/necrosis after 4 week recovery]. Some of the renal changes were noted in animals treated with placebo containing HP-β-CD, but changes were generally more pronounced in those receiving telavancin (containing HP-β-CD as an inactive ingredient).
- Liver toxicity in rats was manifested by hepatocellular degeneration along with elevated alkaline phosphatase (alk phos), alanine transaminase (ALT), and aspartate aminotransferase (AST) in the 13-week study and macrophage accumulation and elevated ALT and AST in the 26-week study. Partial reversibility of elevated laboratory values after the 4-week recovery was noted in the 13-week study. Liver toxicity in dogs was manifested by an increase in reactive sinusoidal lining cells, centrolobular macrophages, and hepatocellular degeneration present in high dose (100 mg/kg/day) animals along with elevations in alk phos, ALT, and AST in the 13 week study. The laboratory changes were partially reversed at recovery. As with the renal changes, similar but less pronounced findings were noted in animals treated with HP-β-CD placebo.
- Macrophage hypertrophy, hyperplasia, and accumulation were seen primarily with more prolonged administration (13- and 26-week studies) and were noted in the reticulo-endothelial cell system (lymph nodes, bone marrow, liver, and spleen) as well as in the kidney and lungs. These changes persisted throughout the 4-week recovery period. The changes were also referred to as eosinophilic and histiocytic. As with the previous changes,

similar findings were noted in animals treated with HP-β-CD. The clinical significance of these changes is unknown.

- Also commented upon in results of laboratory testing were: marked decreases in platelet counts (45% of baseline) in the 2-week dog study (including controls) attributed to complications associated with chronic catheterization and anemia [decreased red blood cell count (RBC) count, hemoglobin, and hematocrit in 13-week and 26-week rat studies (including controls)].

Safety Pharmacology

The Applicant was required to perform a thorough QT study (as defined in the 2002 FDA – Health Canada Concept paper) at the time of the IND submission.

- hERG effect in HEK293 cells showed inhibition of the tail current at all doses ≥ 15 μg/mL, although when corrections were made for placebo effect, an IC_{50} could not be calculated as it would be greater than the maximal 600 μg/mL tested.
- Purkinje fiber (canine) effect was noted as prolongation of the action potential duration (APD) at 0.5 and 1 Hz at concentrations ≥ 50 μg/mL. AMI-6424 demonstrated no effect in the Purkinje fiber (sheep) assay.
- An *in vivo* conscious telemeterized dog study showed no evidence of treatment-related effects on blood pressure, heart rate, or EKG parameters. The study did demonstrate evidence of a histaminergic reaction at high doses (100 mg/kg/day as a single or repeat dose).

Teratogenicity

For a complete review of teratogenicity issues, particularly the animal studies and pregnancy-related issues, refer to the Pharmacology/Toxicology Review by Zhou Chen, MD, PhD.

A brief summary of the Pharmacology/Toxicology review findings related to embryo-fetal development included in the Pharmacology /Toxicology review is presented below:

- "Intravenous Injection Rat Developmental Toxicity Study with AMI-6424": This study included a diluent control (5% dextrose), placebo (containing HP-β-CD), and 50, 100, and 150 mg/kg/day AMI-6424 doses.
    - Fetal weight decreases were noted at doses of ≥ 100 mg/kg/day.
    - Brachymelia (left hind limb) in one fetus from one litter (out of 332 fetuses and 24 litters examined) in the 100 mg/kg/day group was associated with other findings including protruding tongue, syndactyly (left hind limb, middle three digits), and anophthalmia.
    - One fetus from one litter (out of 322 fetuses and 25 litters examined) in the 150 mg/kg/day group had isolated brachymelia.
    - Brachymelia was thought to be drug-related by the FDA reviewer and Applicant. Syndactyly was thought to be drug-related by the FDA reviewer.
    - Neither skeletal abnormality was noted in the historical database.
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Rats:

	Diluent	*Placebo*	*50 mg/kg/day*	*100 mg/kg/day*	*150 mg/kg/day*
Litters Evaluated:	25	24	25	24	25
Fetuses evaluated:	319	322	312	332	322
Brachymelia	0	0	0	1 (1) 4.2%	1 (1) 4.0%
Syndactyly	0	0	0	1 (1) 4.2%	0
Total Litter Incidence*	**0**	**0**	**0**	**4.2%**	**4.0%**

*** Incidence for Brachymelia, micromelia or syndactyly were not in the historical data base submitted.**

From Reproductive and Developmental Toxicity PTCC Subcommittee Consult

- "Intravenous Injection Rabbit Developmental Toxicity Study with AMI-6424": This study included a diluent control (5% dextrose), placebo (containing HP-β-CD), and 60 and 75 mg/kg/day doses of AMI-6424.
    - Multiple abnormalities were noted in one fetus from the 75 mg/kg/day dose group including flexed front paw, brachymelia (including absent ulna), adactyly (absence of a digit), gastroschisis.
    - One fetus was noted to have an umbilical hernia.
    - Also noted in the high dose group were malformations including fusion of sternebrae and vertebral anomalies in single animals from different litters which were not appreciated in the 60 mg/kg/day group.
    - The skeletal defects were felt to be treatment-related by the FDA reviewer. The limb abnormalities (brachymelia, absent ulna, and adactyly) were also thought to be treatment related by the laboratory (Covance) performing the test. This was the same laboratory which had performed the rat studies.
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Rabbits:

	Placebo	*60 mg/kg/day*	*75 mg/kg/day*
Litters Evaluated:	18	20	19
Fetuses evaluated:	138	172	156
Flexed Front Paws, brachymelia, and adactyly	0	0	1 (1) 5.3%
Absent ulna	0	0	1 (1) (5.3%)
Total Litter Incidence	**0**	**0**	**10.6%**

*** Historical Control Incidence for Malrotated Hindlimbs = 0.8%; Flexed front paws – 0.8%; adactyly – 0.3%; no incidence rate given for brachymelia or absent ulna.**

From Reproductive and Developmental Toxicity PTCC Subcommittee Consult

On the basis of findings in two animal species, FDA requested that the Applicant conduct a study in a third species and recommended the minipig.

- "Telavancin: Study for effects on embryo-fetal development in the minipig": This study included a diluent, "placebo for telavancin injection" [Lot #2213-99-731674, protocol does not specify constituents] and doses of 25, 50, and 75 mg/kg/day of telavancin.
    - Findings included increased preimplantation loss at all doses (but within historical control range) and post-implantation loss in all dose groups.
    - Increase in late resorptions occurred in the high dose group.
    - Increased external malformations evidenced by polydactyly, syndactyly, and deformed foreleg were seen in the low and mid dose groups. Polydactyly was also noted in a placebo group fetus. No limb abnormalities were observed in the high dose group.
    - Many animals in this study required treatment with other antimicrobial agents which was noted as an unusual finding.
    - Skeletal abnormalities observed were greater than the historical control rates reported by the producer of the minipigs (Ellegaard Minipigs in [redacted] b(4)
    - The following table shows the number of litters and number of fetuses examined and number (frequency) of events observed.

Gottingen Minipigs:

	Diluent	*Placebo*	*25 mg/kg/day*	*50 mg/kg/day*	75 mg/kg/day
Litters Evaluated:	7	5	9	8	5
Fetuses evaluated:	34	24	31	36	17
Syndactyly	0	0	0	1 (1) 12.5%	0
Polydactyly: Single Limb	0	1 (1) 20%	2 (2) 22.2%	2 (4) 25%	0
Polydactyly: Multiple limbs	0	0	2 (2) 22.2%	1 (1) 12.5%	0
Misshapen digits & deformed leg	0	0	0	1 (1) 12.5%	0
Total Litter Incidence*	**0%**	**20%**	**33.3%**	**50%**	**0%**

*** Historical Control Incidence for Polydactyly = 5.71%; Syndactyly = 2.86%**

From Reproductive and Developmental Toxicity PTCC Subcommittee Consult

- The Pharmacology/Toxicology reviewers, along with the Maternal Health consultant and Reproductive and Developmental Toxicity PTCC Subcommittee have determined that telavancin is a multi-species teratogen with drug-related limb defects in all species tested (including rat, rabbit, and minipig).
- The Reproductive and Developmental Toxicity PTCC Subcommittee recommended factors to be considered in labeling (assignment of pregnancy category) including:

  - Seriousness of the indication and potential for serious complications in pregnancy associated with the indication
  - Availability of alternative treatments
  - Teratogenic effect occurring at or near the proposed human dose
  - "Potential benefit" of the treatment should exceed the risk
- The Maternal Health Team recommended classification of the drug as pregnancy category X based on lack of perceived benefit over existing therapy with an increase in risk based on teratogenicity potential. They also recommended a boxed warning and restricted distribution at the pharmacy level to include documentation of age, gender, and evidence of non-childbearing potential for females.

The Applicant had been informed of the FDA concerns regarding teratogenicity in the NDA Filing communication on February 20, 2007. The Applicant requested and was granted a meeting with the FDA on July 11, 2007, to discuss the preclinical teratogencity findings.

The Applicant's external consultant, Anthony Scialli, MD, an obstetrician-gynecologist with subspecialty training in reproductive and developmental toxicology, provided an overview of the preclinical findings. The Applicant acknowledged that telavancin produced limb abnormalities in both rat and rabbit, although Dr. Scialli expressed his opinion that the rat teratogenicity (or no observed effect level) was based on low litter weights rather than the limb findings which were not confirmed by the skeletal examination (skeletal exam was only done in one of the two rats with brachymelia and finding was not noted on that exam). There was difficulty in interpreting the minipig study due to poor reproductive performance (small number of litters to examine); one of the control groups had a pregnancy rate to term of only 36%. This made it difficult to draw any conclusions from the study.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of clinical data reviewed was the NDA submission containing clinical study reports from SSSI studies (Phase 2 and Phase 3) and a synopsis of safety information from ongoing clinical studies.

4.2 Tables of Clinical Studies

Tables 9-11 show the clinical and clinical pharmacology studies performed in the telavancin development program.

Table 9: Completed Clinical Studies in Patients with cSSSI

Study Number	Title	Objective	Design / Type of Control	Treatments / Dose / Route of Administration	Number of Patients	Duration of Treatment	# Centers / Location
0017	A Phase 3, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram positive SSSI with a Focus on Patients with Infections Due to MRSA	Efficacy and Safety	Randomized Double-Blind Active-Controlled [Placebo Dummy Infusion at 12 hrs for patients receiving telavancin]	Telavancin 10 mg/kg IV q 24 hr [Original Protocol: Telavancin 7.5 mg/kg IV q 24 hr] Versus Vancomycin 1 g IV q 12 hr	Telavancin (10) N=426 Vancomycin N=429 Original Protocol T (7.5)=73 V=70	7-14 days	58 centers Multi-national
0018	A Phase 3, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram positive SSSI with a Focus on Patients with Infections Due to MRSA	Efficacy and Safety	Randomized Double-Blind Active-Controlled [Placebo Dummy Infusion at 12 hrs for patients receiving telavancin]	Telavancin 10 mg/kg IV q 24 hr [Original Protocol: Telavancin 7.5 mg/kg IV q 24 hr] Versus Vancomycin 1 gm IV q 12 hr	Telavancin (10) N=502[1] Vancomycin N=510[1] Original Protocol T (7.5)=20 V=19	7-14 days	131 centers Multi-national
I6424-202a	A Phase 2, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Standard Therapy for Treatment of Complicated Gram positive SSSI	Efficacy and Safety	Randomized Double-Blind Active-Controlled	Telavancin 7.5 mg/kg IV q 24 hr Versus Standard Therapy [Vancomycin 1 g IV q 12 or anti-staphylococcal penicillin q 6 hr]	Telavancin (7.5) N=84 Standard[2] N=83	4-14 days	20 centers US and South Africa
I6424-202b	A Phase 2, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Standard Therapy for Treatment of Complicated Gram positive SSSI	Efficacy and Safety	Randomized Double-Blind Active-Controlled	Telavancin 10 mg/kg IV q 24 hr [Original Protocol: Telavancin 7.5 mg/kg IV q 24 hr] Versus Standard Therapy [Vancomycin 1 g IV q 12 or anti-staphylococcal penicillin q 6 hr]	Telavancin (10) N=100 Standard[3] N=95 Original Protocol T (7.5)=15 V=17	4-14 days	18 centers US and South Africa

Adapted from ISE, Table 4-1, pgs 28-29.

[1] One patient was randomized to treatment with vancomycin and received telavancin instead; for safety analyses this patient is included in the telavancin treatment group and for efficacy analyses this patient is included with the vancomycin treatment group. The numbers in the table above include that patient in the vancomycin treatment group.

[2] 20 patients received antistaphylococcal penicillin and 83 received vancomycin.

[3] 7 patients received antistaphylococcal penicillin and 88 patients received vancomycin.

Table 10: Ongoing Clinical Studies

Study Number	Title	Objective	Design / Type of Control	Treatments / Dose / Route of Administration	Number of Patients	Duration of Treatment	# Centers / Location
I6424-203a	A Phase 2, Randomized, Double-Blind, Parallel Group, Multinational Trial of Intravenous Telavancin (TD-6424) for the Treatment of Uncomplicated *Staph aureus* Bacteremia	Efficacy and Safety	Randomized Double-Blind Active-Controlled	Telavancin Standard Therapy (Vancomycin or antistaphylococcal penicllin if prespeciified for patients with MSSA)	Up to 60	Up to 14 days	
0015	A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to MRSA	Efficacy and Safety	Randomized Double-Blind Active-Controlled	Telavancin Vancomycin	[750 patients planned]	Up to 14 days	Multinational
0019	A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to MRSA	Efficacy and Safety	Randomized Double-Blind Active-Controlled	Telavancin Vancomycin	[750 patients planned]	Up to 14 days	Multinational
0029	Emergency IND	Treatment SA bacteremia	Open-label	Telavancin 10 mg/kg IV q 24 hr	1		1
Source: IND 60,237, N-210							

Table 11: Clinical Pharmacology Studies

Study Number	Title	Design / Type of Control	Treatments / Dose / Route of Administration Number of Patients	Location
I6424a-101a	Tolerability of Ascending Doses of Intravenous TD-6424 in Healthy Volunteers	Randomized, double-blind, placebo-controlled	Single doses: 0.25, 1, 2.5, 5, 10 , 12.5, 15 mg/kg IV (9 dose periods) N=27 Multiple doses: 7.5, 12.5, 15 mg/kg IV X 7 days, N=27	UK (pre-IND) Single center
I6424a-102a	Pharmacokinetics of Intravenous TD6424 in Elderly Male and Female Subjects	Randomized, double-blind, placebo-controlled	Single dose 12.5 mg/kg IV Elderly N=3 Young N=4 [Terminated early due to aPTT finding]	UK (pre-IND) Single center
I6424a-103a	Safety and Pharmacokinetics of Intravenous ARBELIC™ (TD-6424 for Injection) in Subjects with Varying Degrees of Renal Function	Open label	Single dose, 7.5 mg/kg IV Healthy (CL_{cr}>80 mL/min) N=6 Mild renal impair (CL_{cr}=51-80 mL/min) N=7 Mod renal impair (CL_{cr}=30-50 mL/min) N=6 Severe renal impair (CL_{cr} <30 mL/min) N=4 Hemodialysis N=6	US and UK Two centers
I6424a-104a	Safety and Pharmacokinetics of Intravenous TD-6424 in Healthy Subjects	Randomized, double blind, placebo and positive control (moxifloxacin) ECG / QT Study	Daily dose x 3 days: telavancin 7.5 or 15 mg/kg, placebo, or moxifloxacin 400 mg IV Telavancin 7.5 mg/kg N=40 Telavancin 10 mg/kg N=39 Placebo N=40 Moxifloxacin N=40	US Single center
I6424a-105a	Safety and Pharmacokinetics of Intravenous ARBELIC™ (TD-6424 for Injection) in Elderly Male and Female Subjects	Open label	Single dose, 10mg/kg IV Female N=8 Male N=8	UK Single center
I6424a-107a	Pharmacokinetics and Tissue Penetration of Telavancin in Healthy Subjects	Open label Skin blister study	Daily dose of telavancin 7.5 mg/kg IV x 3 days Males N=9 (8 completed)	US Single center
I6424a-108a	Bronchopulmonary Concentrations of TD-6424 After Intravenous Administration of TD-6424 to Healthy Subjects	Open label Bronchoscopy for lung tissue/endothelial lining fluid concentration	Daily dose of telavancin 10 mg/kg IV x 3 days	US Single center

Study Number	Title	Design / Type of Control	Treatments / Dose / Route of Administration Number of Patients	Location
0016	Safety and Pharmacokinetics of Intravenous Telavancin in Subjects with Varying Degrees of Hepatic Function	Open label	Single dose of telavancin 10 mg/kg IV Normal subjects N=8 Hepatic Impairment (Child-Pugh B) N=8	US Single center
0027	A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]telavancin Following Single Intravenous Administration to Healthy Male Volunteers	Open label	Single dose of [^{14}C]telavancin IV N=6	UK Single center
0032	A Phase 1, Double Blind, Crossover Study to Evaluate the Interaction of Telavancin and Midazolam in Healthy Subjects	Randomized, double-blind, placebo-controlled, crossover	Telavancin 10 mg/kg or placebo IV x 7 days On Study Day 7 each subject received a single dose of 1 mg IV midazolam After a 7-day washout, the subject received the alternate treatment x 7 days, followed by midazolam N=16 (2 groups of 8 subjects)	US Single center
0035	An Open, Randomized, 3-Period Crosover Study to Investigate the Potential for Drug Interactions Between Telavancin and Aztreonam or Telavancin and Piperacillin/tazobactam in Healthy Subjects	Two part, 3-period/sequence, randomized, crossover study	Part 1: subjects received, in randomized fashion, telavancin 10 mg/kg alone, aztreonam 2 gm alone, and the combination of telavancin 10 mg/kg + aztreonam 2 gm, with a dose on Day 1, 8, and 15 N=12 Part 2: subjects received telavancin 10 mg/kg alone, piperacillin/tazobactam 4.5 gm alone, and the combination of telavancin 10 mg/kg and piperacillin/tazobactam 4.5 gm on Day 1, 8, 15 N=12	US Single center

Adapted from NDA 22-110, Module 2, Section 2.7.6, Synopses of Individual Studies, pg1.

4.3 Review Strategy

The two Phase 3 studies (Study 0017 and Study 0018), after Protocol Amendment 1 increased the dose of telavancin to 10 mg/kg, were used in assessment of efficacy for this application. Information from the SSSI Phase 2 studies, Study 202a (telavancin dose of 7.5 mg/kg) and Study 202b (primarily a telavancin dose of 10 mg/kg), along with the original protocol Phase 3 studies (Study 0017 and 0018 with a telavancin dose of 7.5 mg/kg) was used in evaluating safety only. Additional clinical information from the Phase 1 studies, the Phase 2 uncomplicated *Staph aureus* (SA) bacteremia study 203a (study completed during the course of this review, but results not yet submitted to the FDA), and ongoing Phase 3 hospital-acquired pneumonia studies (Study 0015 and Study 0019) was used to evaluate the safety of telavancin.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to inspect four of the Applicant's investigative sites, with two sites selected from each of the two studies being used to determine efficacy (Study 0017 and Study 0018).

The two Study 0017 sites were selected for audit based on the high enrollment numbers (> 50% of the study population).

- Site #38101 randomized 385 patients (122 under the original protocol and 263 under Protocol Amendment 1); the 263 patients enrolled under Protocol Amendment 1 made up 31% of the Study 0017 population analyzed for efficacy. Sixty five patient records were audited. There were some discrepancies noted between source document and the case report form (CRF) log for study dose infusion starting times, concomitant medications, and laboratory AE reports were not completely filled out for a few patients (<5 in each category). However, the data generated at this site for Study 0017 was thought to be acceptable for use in analysis.
- Site #38271 randomized 202 subjects (all patients under Protocol Amendment 1); the 202 patients enrolled under Protocol Amendment 1 made up 24% of the Study 0017 population analyzed for efficacy. Fifty patient records were audited. There were no significant deviations noted and the data generated by the site was thought to be acceptable for use in analysis.

The two Study 0018 sites were selected for audit based on site enrollment numbers (two of the higher enrolling sites for this study). Additionally, Site #38091 was selected because the rate of success of study medication relative to comparator was out of proportion to other sites enrolling similar numbers of patients. Site #38112 was selected as a major enrollment site, and also due to previous notification by the Applicant of some source data that was lost in the aftermath of Hurricane Katrina.

- Site #38091 randomized 51 patients. All fifty one patient records were audited. The inspection noted that the investigator had problems with primary efficacy endpoint determination in six patients, source documents (specifically, sheets with information regarding hospitalization for the cSSSI used to transfer information to the outpatient center) were discarded, records of disposition of the drug were not adequate, and the IRB was not

promptly notified in the event of an SAE occurrence. The data generated at the site were inadequate for use in the primary efficacy analysis. The investigator responded to the Form FDA 483 issued at the end of inspection with a written letter on April 30, 2007. The responses to and remedies for the issues raised were adequate with the exception of two issues for which DSI has requested additional written responses from the investigator.

- Site #38112 randomized 75 patients (1 under the Original Protocol and 74 under Protocol Amendment 1). All seventy five patient records were examined for informed consent and the primary efficacy endpoint assessment. All patient files were examined for hospital medical records, labs, EKGs, and progress notes and all were found be organized and legible. The inspection was conducted over 6 days, so in depth review of records for accuracy and drug accountability were not performed due to time constraints. The data generated was assessed as being acceptable to use in assessment of efficacy for this indication.

Telavancin is a NME. The Applicant underwent inspection by the FDA from May 31, 2007 until June 6, 2007 to review their conduct as sponsor of the clinical studies for telavancin treatment of cSSSI. The Applicant was found to have adhered to applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

As many of the study responsibilities were contracted out, an FDA inspection of the Applicant's primary contract research organization (CRO), Covance Inc, Princeton, NJ, is planned (Insepction and report are pending at the time of this review).

4.5 Compliance with Good Clinical Practices

As noted previously, many of the clinical study reponsibilities were contracted out. The Applicant noted in the Phase 3 cSSSI study reports that several strategies were utilized to ensure consistency in conduct of the study across investigative sites. Site research personnel received training in protocol-specific procedures, as well as good clinical practices at regional investigator meetings. A global monitoring plan was used to guide consistent review and audit of the CRFs and clinical site activities. Periodic site visits were performed by the Medical Monitor, Principal Investigator, and other staff of the Applicant to assess site understanding of the protocol. The Applicant had independent Quality Assurance personnel audit study sites to verify compliance with study procedures and GCP.

4.6 Financial Disclosures

The Applicant has included Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators for all but three subinvestigators whom their CRO is still trying to locate.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology program included 11 pharmacokientic studies to characterize the pharmacokinetic profile in healthy young and elderly adult subjects and subjects with renal and hepatic impairment. Studies were also conducted to examine the effect of telavancin on cardiac repolarization, the degree of penetration of telavancin into skin blister and lung tissue, and the

potential for interaction of telavancin with other medications, including aztreonam, piperacillin/tazobactam, and midazolam. Presented below is a brief summary of findings. For a complete discussion see the Clincial Pharmacology review by Jeff Tworanzyanski, Pharm.D.

5.1 Pharmacokinetics

The pharmacokinetics of telavancin are linear and increase relatively proportionately to dose as dose increases from 5 mg/kg to 12.5 mg/kg. Multiple dose infusion with doses ranging from 7.5 mg/kg/day to 15 mg/kg/day demonstrated a half-life of approximately 7-8 hours on Day 1 and 9 hours on Day 7 of dosing. The drug is approximately 90% protein bound and distributes primarily to extracellular water.

The primary metabolite of telavancin is a hydroxylated metabolite, AMI-11352, which has about 10% of the activity of telavancin. The primary route of elimination is through renal excretion (76% of dose).

In vitro assays in human microsomes demonstrated that CYP450 isoforms including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11 did not metabolize telavancin. Telavancin did demonstrate weak inhibitory effects on the major CYP450 enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. An *in vivo* drug interaction study performed with midazolam (substrate for CYP3A4) showed that telavancin has no significant effect on the PK of midazolam. The clinical studies of telavancin allow the concomitant use of aztreonam (in cSSSI studies and ongoing HAP studies) and piperacillin/tazobactam (ongoing HAP studies). Therefore interaction studies were conducted for each of these drugs with telavancin and the studies did not show evidence of interaction.

An analysis using calculated multiple dosing mean concentration-time profiles for elderly subjects indicated profiles similar to those for young healthy subjects. Plasma clearance may decrease along with decreased renal clearance in the elderly. Mean concentration-time profiles did not differ among male and female subjects. Therefore, there are no specific dose adjustments recommended on the basis of advanced age or gender.

The study of PK parameters in subjects with renal impairment was evaluated in a single 7.5 mg/kg study in subjects with normal renal function (CL_{cr} > 80 mL/min), mild renal impairment (CL_{cr} 51-80 mL/min), moderate renal impairment (CL_{cr} 30-50 mL/min), severe renal impairment (CL_{cr} < 30 mL/min) and patients with end-stage renal disease (ESRD) on hemodialysis. The mean C_{max} was similar among subjects with normal renal function and mild, moderate, and severe renal impairment and lowest in patients with ESRD following hemodialysis. The mean clearance was decreased 11% in those with mild and 19% in those with moderate renal impairment, with a decrease of 55% in those with severe renal impairment. ESRD patients who received hemodialysis after telavancin dosing demonstrated clearance 40% less than patients with normal renal function (greater than that in patients with severe disease). The mean $AUC_{0-\infty}$ increased 13%, 29%, 119%, and 79% in subjects with mild, moderate, severe, and ESRD, respectively, compared to subjects with normal renal function. An average of 5.9% of the telavancin dose was present in the dialysate. Therefore, a dosage adjustment recommended by

the Applicant for patients with moderate renal impairment (7.5 mg/kg q 24 hrs) and severe renal impairment (10 mg/kg q 48 hrs) is acceptable. The PK of telavancin has not been evaluated in ESRD subjects who are dosed with telavancin following dialysis.

b(4)

In general, the mean PK parameters were similar in normal subjects and subjects with hepatic impairment, therefore no dosage adjustment is recommended for patients with hepatic impairment.

5.2 Pharmacodynamics

Telavancin is a lipoglycopeptide antimicrobial agent with activity against Gram positive bacteria and has two proposed mechanisms of action. Telavancin inhibits peptidoglycan synthesis by cross-linking of peptidoglycan strands in the cell membrane as does vancomycin. The second proposed mechanism of action is disruption of the microbial cell membrane, but this mechanism may not be functional until higher drug concentrations are reached and may not be achievable with free concentrations of this drug. The Applicant also provided data from *in vivo* animal models that support the use of $AUC_{(0-24)}$/MIC as the best PK/PD predictor of antimicrobial efficacy. For a more complete discussion of the antimicrobial activity and PK/PD modeling refer to the Microbiology Review by Kerry Snow, MS, MT(ASCP), Pharmacometric Review by Hao Zhu, Ph.D., and the Clinical Pharmacology Review by Jeff Tworzyanski, PharmD.

For drug effects on cardiac conduction, see Section 7.1.9 Electrocardiograms (ECGs) review and QT team review.

Based on the Pharmacometrics Review of modeling of the relationship of telavancin exposure to renal function over the course of the study (using both the worst CL_{cr} and the last measured CL_{cr}), the conclusion was reached that there was a minimal increase in risk using the 10 mg/kg dose rather than the 7.5 mg/kg dose (4-5% increase).

5.3 Exposure-Response Relationships

Dose selection for the Phase 3 cSSSI studies was discussed at the End-of-Phase 2 meeting. The Applicant proposed that the Phase 3 cSSSI studies be initiated using a telavancin dose of 7.5 mg/kg based on demonstration of acceptable efficacy and safety data from a Phase 2 SSSI study. However, at that time a second Phase 2 study in SSSI was being conducted using a dose of telavancin 10 mg/kg which had been suggested to be more efficacious based on PK/PD data. This PK/PD data was not submitted to the Agency. The Agency queried the Applicant about the rationale for intiating the Phase 3 trials with the lower dose, however the Applicant anticipated completion of the study early enough in the course of the Phase 3 trials to adjust the dose if necessary. The Applicant subsequently amended the Phase 3 protocols to increase the dose of telavancin to 10 mg/kg.

Based on the Pharmacometrics Review, the 10 mg/kg dose did not provide additional benefit over the 7.5 mg/kg dose in terms of clinical efficacy. Microbiological eradication however was driven by both exposure (dose) and treatment duration demonstrating higher eradication rates for the 10 mg/kg dose relative to the 7.5 mg/kg dose for the same duration.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Complicated Skin and Skin Structure Infections (cSSSIs)

Complicated skin and skin structure infections include infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses or a significant underlying disease state that complicates the response to treatment. Superficial infections or abscesses in an anatomical site, such as the rectal area, where the risk of anaerobic or Gram negative pathogen involvement is higher, should be considered complicated infections.[6]

6.1.1 Methods

The Applicant performed four efficacy and safety studies that met specifications outlined in the 1998 FDA guidance document; each study was double-blind, randomized, and active-controlled, comparing telavancin IV with standard therapy for the indication.

The two Phase 3 studies, Study 0017 and Study 0018 (Post-Amendment 1, with telvancin dose of 10 mg/kg IV q 24 hrs), were of identical design and constitute the primary studies used to demonstrate the efficacy of telavancin compared to vancomycin for the treatment of patients with infections due to Gram positive pathogens. Eight hundred sixty two patients were enrolled in Study 0017 and one thousand thirty five in Study 0018. The Applicant had initated Studies 0017 and 0018 using a telavancin dose of 7.5 mg/kg and enrolled 143 and 39 patients to each study, respectively, but these patients are not included in the efficacy determination.

The Applicant in the course of clinicial development also performed two Phase 2 studies (202a and 202b) which were used to determine the efficacy and safety of two doses of telavancin [7.5 mg/kg in 202a and (primarily) 10 mg/kg in 202b] compared to standard therapy (vancomycin or anti-staphylococcal penicillin such as nafcillin, oxacillin, or cloxacillin) in the treatment of patients with cSSSI due to Gram positive pathogens. These studies, although providing some information on dose-response, are not included in the overall efficacy determination.

6.1.2 General Discussion of Endpoints

The primary endpoint for the study was the Clinical Response at the Test-of-Cure Visit (TOC) which was to occur at 7-14 days after the last dose of study medication was administered. Clinical Response was defined according to the following definitions:

- Cure – resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibiotic therapy was necessary

[6] Draft Guidance for Industry: Uncomplicated and Complicated Skin and Skin Structure Infections – Developing Antimicrobial Drugs for Treatment. FDA/CDER/July 1998.

- Not Cured – inadequate response to study therapy
- Indeterminate – inability to determine outcome

As was stated in the Statistical Analysis Plan (SAP), the End-of-Therapy (EOT) and TOC Clinical Response was determined by the blinded investigator based on consideration of a patient's signs and symptoms at the specified evaluation compared with the signs and symptoms present at baseline. If a patient was withdrawn prematurely, the Clinical Response was to represent the status of infection at the time of that evaluation.

As stated in the study protocol, in the event that Clinical Response was rated as "Not Cured" at EOT, Clinical Response would not be evaluated at TOC. The patient's Clinical Response of "Not Cured" would be carried forward from TOC, however the patient would be evaluated for safety at the TOC visit.

While there was no clinical events committee utilized to adjudicate Clinical Response as planned for in the protocol, the Applicant (study medical monitors with review and approval of the Principal Investigator) determined the following before breaking the study blind:

- Classification of organisms isolated from microbiological cultures at baseline as to pathogen / non-pathogen status
- Determination of whether non-study antimicrobial agents were considered to be "potentially effective" for the indication being studied
- Determination of whether surgical procedures performed might significantly affect the clinical outcome or represented ancillary treatment.

6.1.3 Study Design

Title
Study 0017, Study 0018: A Phase 3, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-positive Skin and Skin Structure Infections with a Focus on Patients with Infections Due to Methicillin-resistant *Staphylococcus aureus*

MO Comment: Study 0017 and 0018 were of identical study design, but were conducted and analyzed independently.

Study Objectives
The primary objective was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with complicated Gram positive skin and skin structure infections (cSSSIs) with emphasis on patients with infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) at a follow-up or test-of-cure (TOC) visit.

A key secondary objective was to pool the efficacy data from each of these studies to assess the superiority of telavancin to vancomycin in patients with MRSA infections. Other secondary objectives of each study were to analyze the clinical and microbiological efficacy of telavancin

compared to vancomycin in patients with baseline bacterial pathogens at TOC and efficacy in infections caused by Gram positive pathogens (By-Pathogen Response).

Study Design
Each study was a randomized, double-blind, active-controlled, parallel group, multicenter, multinational trial. Patients with cSSSIs (primarily due to MRSA) were randomized to receive either telavancin 10 mg/kg IV q 24 hr or vancomycin 1 gm IV q 12 hr. Adjunctive aztreonam or metronidazole could be used to treat patients with infections due to suspected or culture positive Gram negative and/or anaerobic organisms.

Patients had a baseline clinical and microbiological evaluation within 24 hours of study enrollment. Patients were to be treated for 7-14 days with study medication. Patients had daily assessment of the primary infection site, along with recording of concomitant medications, adjunctive surgical or significant wound procedures, and occurrence of adverse events (AEs). After completing therapy, patients had an EOT assessment and TOC assessment 7-14 days after the EOT assessment. Efficacy assessment included clinical evaluation of the infection site and microbiological assessment (culture) only if a significant wound and/or drainage persisted at the infection site.

Approximately 750 patients were to be enrolled in each study in order to obtain 600 clinically evaluable patients (300 per treatment arm). Patients were stratified at randomization by diabetes status and country group (3 country groups per study).

Changes in Study Conduct (Protocol Amendments)
The Original Protocol for Study 0017 and 0018 was issued July 22, 2004.

Protocol Amendment 1 for Study 0017 and 0018 was submitted on December 21, 2004.
The most important change related to an increase in the telavancin dose from 7.5 to 10 mg/kg IV q 24 hr (with dose adjustment for renal impairment). The increase was based on the results of a Phase 2 cSSSI infection study (Study I6424-202b, FAST 2) which was ongoing during planning of the Phase 3 trials. This study compared telavancin at a dose of 10 mg/kg q 24 hr with standard therapy (vancomycin or penicillinase-resistant penicillin). Numerically higher clinical response rates and microbiologic eradication rates were reported for patients with infections due to MRSA treated with the higher dose. Additionally, per the Applicant, PK/PD modeling had suggested that doses of 750 mg (or approximately 10 mg/kg) would result in > 95% probability of target attainment for organisms with MICs as high as 2 μg/mL. The safety profile of the higher dose regimen was assessed by the Applicant as being similar to that of the 7.5 mg/kg dose. An additional (approximate) 750 patients were randomized to each study after the telavancin dose was increased.

Additional changes included:

- Investigators were encouraged to use aztreonam and/or metronidazole if polymicrobic infections due to Gram negative and/or anaerobic organisms were suspected.

- The dose of telavancin to be administered to patients with moderate and severe renal impairment and hemodialysis populations was modified. Changes made are shown in table 12.

Table 12: Modifications for Renal Impairment and Hemodialysis

Creatinine Clearance (mL/min)	Telavancin Dosage Original Protocol	Telavancin Dosage Post-Amendment 1
30-50 (moderate impairment)	5.6 mg/kg q 24 hr	7.5 mg/kg q 24 hr
< 30 (severe impairment)	7.5 mg/kg q 48 hr	10 mg/kg q 48 hr
Hemodialysis	7.5 mg/kg q 48 hr (no supplement required following hemodialysis)	10 mg/kg q 48 hr (no supplement required following hemodialysis)

- Allowing investigators to estimate creatinine clearance based on local laboratory serum creatinine values while awaiting central laboratory data. The amendment also stated that if renal function changed over the course of the study creatinine clearance should be reassessed and the dose of study medication adjusted accordingly.
- Changed the volume of D5W used for reconstituting telvancin from 24 mL to 23 mL.
- Clarified that infusions of telavancin and placebo or vancomycin were to be administered at 12 hr intervals ± 4 hrs to allow flexibility for sites to administer study medications within a reasonable time window.
- Included procedure to obtain body temperature at pre-treatment Baseline, daily, at EOT, and TOC.
- Clarified that assessment of signs and symptoms of infection site was not required on Day 1 following study drug administration since this was performed prior to the first dose on Day 1 (duplicative assessments).
- Included in the Day 4 procedures section that PK sampling was to be conducted at selected sites at prespecified timepoints.
- Clarification in the TOC evaluation section that a Follow-up visit was to be conducted for all patients randomized into the study for safety purposes and only those patients who were evaluated as clinical "Cure" or "Indeterminate" at EOT were to have a TOC evaluation of clinical response during the Follow-up visit.
- The clinical response of "Indeterminate" was added as an option for the TOC evaluation.
- The addition of two criteria that would constitute a need for patient removal from the study. These criteria were infection due to Gram negative organism(s) only and persistent *Staph aureus* (SA) bacteremia. Patients who discontinued study treatment and were evaluated as "Cure" or "Indeterminate" at the end of study were to have a TOC evaluation for Clinical Response at the Follow-up visit.
- Reprioritized the secondary and tertiary variables. Clarified that signs and symptoms score and size of primary infection site were to be summarized through Day 7, the minimum duration of treatment specified by the protocol.
- The telavancin stability information was updated and indicated that telavancin reconstituted vials and infusion bags are stable for 48 hrs under refrigeration (2-8°C).

- Removed the requirement for use of cover sleeves for the study medication infusion.
- The addition of the requirement for a Gram stain to be performed on each specimen obtained for culture.
- Clarification that a swab from skin surrounding the infection site was unacceptable (rather than swabs of infection site).
- Removed the requirement for Day 1 laboratory tests since pretreatment tests were to have been performed in the previous 24 hours.
- Clarified that the only medications required to be reported on the CRF from EOT to TOC visit were antibiotics.
- The addition that the TOC visit should be conducted 7-14 days after the last dose of study medication, rather than EOT (if EOT and last dose date were not the same).
- Deleted the section pertaining to the requirement for digital photographs of the primary infection site.
- Clarified that investigative sites were to use local laboratories for patient study eligibility and acute patient management decisions.
- Specified that patients enrolled prior to Amendment 1 were to be analyzed separately from those enrolled after Amendment 1.
- The definition of the CE population was edited to correct inadvertent omissions from the original protocol. The following details were added:
    - If a patient appeared to comply with the specified inclusion/exclusion criteria at study admission, but subsequent findings indicated otherwise, the patient would be excluded from the analysis population.
    - The patient received at least 72 hours of study medication (for failures). If the patient is a clinical cure, the patient received at least 96 hours of study medication.
    - Patient received at least 80% of intended doses.
    - Patient either had a TOC evaluation or was previously evaluated as clinically "not cured'.
    - Patient did not receive a potentially effective non-study antibacterial medication during the study, unless the patient was previously evaluated as clinically, "not cured".
- Removed body temperature and white blood cell (WBC) count as parameters to be assessed in determining the clinical signs and symptoms of infection score.

Study 0018, Protocol Amendment 2 (for Study 0018 only) was submitted to the FDA on February 22, 2006 (IND 60,237, N-168). The primary purpose of this amendment was to allow for an increase in sample size to obtain approximately 850 patients.

This change was made in Study 0018 only, and increased the planned enrollment from 375 to 600 patients per arm to account for changes in the initial assumptions used by the Applicant to estimate power and sample size for the pooled analysis in patients with MRSA. The FDA had advised the Applicant that assessment of superiority of telavancin to vancomycin in patients with MRSA infections was to be conducted in the ITT (All-Treated) population wherein the clinical cure rates were expected to be lower. Using the revised estimates, enrollment of approximately

850 patients with MRSA would be required to ensure a statistically significant and clinically meaningful difference in clinical cure rates. While it had been anticipated that both studies would enroll at the same rate, Study 0018 was enrolling at a rate that was 1.2 times faster than Study 0017. Therefore the enrollment for Study 0018 was increased to approximately 1200 patients (600 per arm).

Other changes included:

- Updated information that telavancin and vancomycin could be reconstituted with normal saline or 5% Glucose Injection (G5W) in addition to D5W.
- Provided additional telavancin stability data indicating that telavancin in reconstituted vials and infusion bags is stable for 72 hours under refrigeration. Once removed from refrigeration, the reconstituted telavancin should be used within 72 hours.
- Clarified the instructions regarding the 12-hour duration between study medication infusions and if necessary that two active doses of telavancin could be administered in less than 24 hours if necessary. All active doses were to be separated by at least 8 hours.
- Provided additional information about infusion times for patients who might not tolerate the 60 minute infusions. Infusions of either medication could be infused over 120 minutes with adjustment in PK sampling times to just prior to infusion, 0.5-1 hour, 2-2.5 hours, and 3-4.5 hours after the infusion was started.
- Clarified instruction for collection and reporting of events related to worsening of infection. If the primary infection worsened, whether or not it met the criteria for serious adverse event (SAE, except in cases of death) it was not to be recorded in the CRF as an AE or SAE. This was to be captured in the clinical assessment section of the CRF binder.
- Stated that a Clinical Events Committee (CEC) was not to be used in this study.
- Clarified that the primary efficacy endpoint was the clinical response determined by the investigator at the TOC assessment.

MO Comment: FDA requested that the Applicant provide analyses for Protocol Amendment 1 patient data compared to that of patients added after Protocol Amendment 2 was instituted to confirm that the study population overall was not altered.

The Applicant also instituted "Administrative Changes" as follows:

- Clarified that certain lots of telavancin intended for use in Phase 2 could be used for patients enrolled in thr current study if patients were randomized prior to receipt of Phase 3 study drug.
- Provided additional instructions for the timing of doses in patients with $CL_{cr} < 30$ mL/min. Doses of telavancin were to be administered 48 hours apart (either AM or PM dose). However, if consistent with hospital policy and required for performance of study procedures, the dose could be changed from PM to AM (telavancin administered less than 36 hours after the original dose).
- Instructed that if the need arose for temporary unblinding, the investigator was to contact the ATLAS Study Physician before unblinding the patient to discuss the need for unblinding.

- Clarified the exclusion criterion regarding diabetic foot ulcer and allowed enrollment of the patient after discussion with the study physician if not a chronic problem and there was some perfusion of the infected foot.

Study Population

Although patients with cSSSI due to any suspected Gram positive pathogen could be enrolled, the primary focus of the study was on patients with infection caused by MRSA. The following criteria were used in attempt to enrich the population for patients likely to be infected with MRSA:

- Hospitalization within the previous 6 months
- Antibiotic treatment (especially fluoroquinolones) within the prior 3 months
- Chronic illness (especially diabetes)
- Prior infection with MRSA
- Admission from a nursing home
- Surgical procedure during current hospital stay
- Residing in an area known to have a high prevalence of community-acquired MRSA

Inclusion criteria:

- Males and females ≥ 18 years of age
- Diagnosis of one of the following cSSSIs with MRSA either suspected or confirmed as the major cause of the infection:
  - Major abscess requiring surgical incision and drainage
  - Infected burn
  - Deep/extensive cellulitis
  - Infected ulcer
  - Wound infections
- Expected to require at least 7 days of intravenous antibiotic treatment
- Presence of purulent drainage or collection, OR at least three of the following:
  - Erythema
  - Fluctuance
  - Heat and/or localized warmth
  - Pain and/or tenderness to palpation
  - Swelling and/or induration
  - Fever (defined as > 38°C/100.4°F orally, rectally or tympanically)
  - WBC count > 10,000/mm^3
  - 15% immature neutrophils (bands) irrespective of WBC count
- Accessible site for culture
- Informed consent as defined by the local IRB or Ethics Committee

Exclusion criteria:

- Received > 24 hours of potentially effective systemic antibiotic therapy prior to randomization, unless the pathogen was resistant to prior treatment or the patient was a treatment failure (no clinical improvement after 3 days) and/or required a non-study systemic antibacterial regimen to which the target organism was susceptible

- Requirement for concomitant administration of agents containing a cyclodextrin solubilizer such as intravenous Sporanox® (itraconazole) or Vfend® (voriconazole)
- Patients with baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure, uncorrected abnormal K+ or Mg++ blood levels, or severe left ventricular hypertrophy
- Uncomplicated skin and superficial skin structure infection (e.g., simple abscess, impetiginous lesion, furuncle, or superficial cellulitis)
- Self-limited infection (e.g., isolated folliculitis or other infection that had a high surgical incision cure rate, or furunculosis or carbunculosis that was not associated with a cellulitis at least 2 cm in radius)
- Superinfected eczema, hidradenitis suppurativa, or other chronic medical conditions (e.g., atopic dermatitis) where inflammation may have been prominent for an extended period even after successful bacterial eradication
- Concurrent infections of unremovable prosthetic material (e.g., permanent cardiac pacemaker battery packs, or joint replacement prostheses)
- Concurrent presence of osteomyelitis, endocarditis, or other deep site tissue infection other than skin and skin structure infection
- Infections due to a Gram positive organism known to be resistant to vancomycin (e.g., vancomycin-resistant enterococcus) or Gram negative organisms known to be resistant to aztreonam
- Burns involving > 20% of body surface area or third degree/full thickness in nature, diabetic foot ulcers, ischemic ulcers/wounds, necrotizing fasciitis, gas gangrene, or mediastinitis. An administrative change on July 25, 2005, allowed enrollment of patients with diabetic foot ulcers if they were not chronic and there was some perfusion of the foot, after discussion with study physician.
- Severely neutropenic (absolute neutrophil count < 500 cells/mm^3), or anticipated to develop severe neutropenia during study treatment period due to prior or planned chemotherapy or HIV positive with known CD4 count < 100 cells/mm^3 during the last 6 months
- Known hypersensitivity to, or intolerance of, study medications or their formulation excipients
- Female patients of childbearing potential if pregnant, nursing, or unable to use a highly effective method of birth control during the study and for at least one month following the last dose of study medication. A negative serum pregnancy test was to be documented prior to treatment. A highly effective method of birth control was defined as one that results in a low failure rate (i.e., < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or vasectomized partner. Male patients were to agree to use medically acceptable birth control for at least three months following the last dose of study medication. A vasectomy or condom used with spermicide was a medically acceptable birth control method for males.
- Prior enrollment in a clinical trial of telavancin
- Treatment with another investigational medication/device within 30 days of study entry
- In shock or unlikely to survive through the treatment and evaluation procedures
- Unable to comply with study procedures

- Any other condition which, in the opinion of an investigator, would confound or interfere with the evaluation of safety or efficacy of the investigational drug, or prevent compliance with the study protocol.

Discontinuations from Study Drug Therapy:
Patients could be discontinued from study therapy early for the following reasons:

- AE requiring discontinuation
- Clinical failure
- Patient choice
- Identification of a resistant pathogen (defined as vancomycin-resistant Gram positive pathogen or aztreonam-resistant Gram negative pathogen)
- Major violation of the protocol (e.g., clinical diagnosis of the infection other than cSSSI)
- Pregnancy
- QTc > 500 msec on 2 consecutive ECGs
- Need for prohibited medication
- Infection due to Gram negative organisms only
- Persistent SA bacteremia
- Other

All patients were to undergo an EOT visit. If withdrawn prior to completing the study, the reason for discontinuation was to be documented on the CRF and follow-up and test-of-cure evaluation, if applicable, were to be conducted.

MO Comment: The EOT page of the CRF contained a section which required the investigator to indicate the reason study medication was discontinued. In addition to the responses which may have indicated premature discontinuation of study medication, responses for resolution of infection and failure were also included in the list. The next section of the EOT page was for investigator assessment of clinical response at EOT (i.e., Cure, Not Cured, or Indeterminate) or the time of discontinuation. Only patients who were assessed as "Cure" or "Indeterminate" at EOT were to have clinical response for efficacy as well as a safety assessment at TOC; patients who were "Not Cured" at EOT were to be assessed for safety only at TOC. No specific instructions were given to investigators regarding clinical response assessment for patients prematurely withdrawn from study therapy for reasons other than resolution or clinical failure. According to the protocol definitions, patients who required alternate, non-study antibiotics for treatment of the cSSSI under study should have been clinical failures at EOT and outcome carried forward to TOC (strictly based on protocol definitions). However, some investigators assessed the clinical response as being "Indeterminate" at EOT. These patients were to have outcome assessments at TOC and despite receiving alternate non-study antibiotic could have been assessed as cures.

The EOT discontinuation section also contained a notation indicating that the need for antimicrobial therapy active against baseline pathogens be recorded as "major protocol deviation". This allowed some patients who were given other antimicrobial therapy for reason of clinical failure to be excluded from the clinically evaluable analysis population because of deviation from the protocol.

Additional discussion about the impact of premature discontinuation of study medication and subsequent assessment of clinical response for efficacy at TOC can be found in later sections of this review. [Efficacy endpoint, CRF and systematic data review, and DSI inspection of Site #38091]

Study Treatments

Study medications were to be administered intravenously as 60-minute infusions of 100 to 250 mL. To maintain the blind between vancomycin (q 12 hr) and telavancin (q 24 hr), placebo dummy infusions of 5% Dextrose Injection USP [D5W, 5% Glucose Injection (G5W), or normal saline], were to be administered to patients randomized to the telavancin treatment group, so that all patients would be receiving a dose of study medication (one active dose and then active or placebo dose 12 hr later).

Telavancin was supplied as a sterile, , lyophilized powder for IV injection. Each vial contained 250 mg of telavancin, 2.5 g HP-β-CD to aid solubility, 312.5 mg mannitol, and sodium hydroxide and/or hydrochloric acid for pH adjustment. Each vial of telavancin was to be reconstituted with 23 mL of D5W, G5W, or saline. After reconstitution, each mL of formulated solution contained 10 mg of telavancin, 100 mg HP-β-CD, and 12.5 mg of mannitol. The reconstituted solution was to be diluted using D5W (or G5W or normal saline) to total 100 to 250 mL prior to administration. b(4)

Prescribing information for vancomycin was to be obtained from the manufacturer's package insert. To maintain the study blind, vancomycin was to be administered in a volume of 100 to 250 mL D5W (or G5W or normal saline). Vancomycin was to be supplied by the investigative site, but if unavailable, the Applicant would provide sites with a supply.

In all cases, the first dose of study medication on Day 1 was to be active (i.e., telavancin or vancomycin). Beginning on Day 2, and throughout the period of IV medication, the time of the dose that was to be active was pre-specified by the study staff and communicated with the pharmacist. This was to ensure that ECG and pharmacokinetic sampling were performed around the active dose. Per Administrative Change, July 25, 2005, for patients with renal insufficiency, doses were to remain on a time based schedule, i.e., patients receiving active dose on the evening of Day 1 were to receive active dose on the subsequent evenings of Days 3, 5, 7, etc, except in situations where hospital policy or performance of study procedures, required shifting the active dose to the morning.

The total duration of study medication was to be determined by the investigator as clinically indicated and was to continue until resolution of signs and symptoms associated with the infection present at study admission improved to such an extent that no further therapy with study medication was deemed necessary. The minimum duration of therapy was to be 7 days and maximum 14 days.

The dose of telavancin was to be adjusted in patients with moderate to severe renal insufficiency based on Cockcroft-Gault equation estimation of creatinine clearance, as follows in Table 13:

Table 13: Dose Adjustment for Patients with Renal Impairment (Post Amendment)

Creatinine Clearance[1,2] (mL/min)	Telavancin Dosage Original Protocol (7.5 mg/kg)*	Telavancin Dosage Protocol Amendment 1 (10 mg/kg)*
30-50	5.6 mg/kg q 24 hr	7.5 mg/kg q 24 hr
< 30	7.5 mg/kg q 48 hr	10 mg/kg q 48 hr
Hemodialysis	7.5 mg/kg q 48 hr (no supplement for dialysis)	10 mg/kg q 48 hr (no supplement for dialysis)

[1]Cockcroft-Gault estimation of creatinine clearance

- Cl_{Cr} = [(140-age) X ideal body weight (IBW)*] ÷ serum creatinine X 72 OR
- (per Protocol Amendment 1) Cl_{Cr} = [(140-age) X ideal body weight (IBW)*] ÷ serum creatinine (µmol/L) X 0.814

[2] For females, multiply the result by 0.85

* Use actual body weight if < IBW

- IBW (male) = 50 kg + 0.9 kg/cm over 152 cm in height
- IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

If renal function changed (i.e., serum creatinine increased above normal range or decreased from elevated levels) during the course of study medication treatment, creatinine clearance was to be re-estimated and dosage of study medication adjusted as appropriate.

The vancomycin regimen could be monitored and dosage adjusted according to the standard procedure of each institution by unblinded study personnel.

During the course of the NDA preparation, the Applicant appointed an Independent Dosing Regimen Adjudicator (IDRA) who was an outside consultant responsible for evaluating the appropriateness of initial and subsequent dosage regimens of telavancin and vancomycin. The assessment was retrospective and no interaction between the study investigators or IDRA occurred. The Applicant's primary charge to the IDRA was to assess whether an individual patient's dosage of study medication treatment at the outset and during the course of study were appropriate based on the protocol-specified dosage of telavancin and general guidelines for vancomycin dosage. The following guidelines were developed for the IDRA assessment of the vancomycin dosage regimen and dosing was considered appropriate if their regimens fell within +/- 20% of the following recommendations in Table 14:

Table 14: DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance	**Vancomycin Dose**
mL/min	**mg/24 hr**
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

Clinical Study Report 0017, Page 44 Table adapted from Moellering et al). Moellering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. Ann Inter Med 1981;94:343.

For functionally anephric patients, an initial vancomycin dose of 15 mg/kg of body weight was to be given. In patients with marked renal impairment, maintenance doses of 250 to 1000 mg once every several days may be more convenient, rather than administering on a daily basis. In anuria, a dose of 1,000 mg every 7 to 10 days has been recommended and was considered to be appropriate.

Randomization and Blinding
Patients were randomized to either telavancin or vancomycin in a 1:1 ratio, using a permuted blocks algorithm. The randomization was stratified by geographic region (3 groups of countries) and the presence or absence of diabetes. The treatment assignment was to be blinded to the investigator and study staff and patients. An unblinded site pharmacist accessed a central interactive voice response system to obtain patient number and treatment. Each site was to prepare a Blinding Plan that was to be approved by the Sponsor. The unblinded individual was not to be involved in any observation. CRF entry, monitoring or reporting required by study protocol other than for dispensing records, vancomycin concentrations, and study medication dosage adjustments. Any dosage adjustments were to be evaluated and performed in the pharmacy.

MO Comment: The geographic regions clustered in a group were not prespecified to the Agency. No rationale for the clustering of countries within a group has been provided.

0017
Group 1: United States, Australia, Belgium
Group 2: South Africa
Group 3: Croatia, Israel, Malaysia, Russia

0018
Group 1: Canada, France, Germany, Italy, Spain, the United Kingdom, the United States
Group 2: Argentina, Chile, Peru, South Africa, Taiwan
Group 3: Korea, Lithuania, Poland

Prior and Concomitant Therapy
For patients with polymicrobic infections involving Gram negative and/or anaerobic bacteria in addition to Gram positive organisms for which study medication was administered, ONLY aztreonam and/or metronidazole administered in accordance with manufacturers package insert could have been added.

Treatment Compliance
All treatments administered were to be recorded in the CRF including start and stop times of infusion, elapsed time of infusion, and volume of infusion were to be recorded.

Study Evaluations
The Applicant states that for the purpose of this study report, study days were numbered relative to the first dose of study medication which was designated as Day 1. Accordingly, the day

preceding the first dose was Day 0 and the day prior to that Day -1. The last day of study medication was designated as Day 0P, with subsequent increase in number for each day off study medication.

Table 15 is the flow sheet reproduced from the 0017/0018 Clinical Study Report which provides an outline of study efficacy and safety assessments:

Table 15: Study Evaluations

	Treatment Period					
Event	**Pretreatment**	**Daily**	**Every Third Day[a]**	**Day 3, 4, or 5**	**End of Therapy Visit**	**Follow-Up Visit[d]**
Informed Consent	X					
Medical History	X					
Assess clinical signs and symptoms of infection	X	X[i]			X	X[e]
Body temperature[h]	X	X			X	X
Measurement of primary infection site	X	X[i]			X	X[e]
Infection site specimen for Gram stain and culture	X				X[e]	X[e, f]
Response assessment					X	X[e]
12-lead ECG	X			X	X	
X-ray[b]	X					
Blood culture X 2	X	X[c]				
Hematology	X		X		X	X
Serum chemistry	X		X		X	X
Urinalysis	X		X		X	X
Pregnancy test	X				X	
Dosing		X				
Assess AEs		X			X	X
Concomitant medications		X			X	X[g]

Clinical Study Report 0017, Table 6-2, pgs 47-48, Clinical Study Report 0018, Table 6-2, pgs 45-46.
[a] Every third day was defined as Study Day 4, 7, 10, and 13
[b] X-ray was to be obtained to rule out osteomyelitis, if clinically indicated
[c] If the admission blood culture was positive OR the admission blood culture was negative but the patient's condition deteriorated leading the investigator to suspect bacteremia, two independent blood cultures were to be obtained until daily specimens were negative and the bacteremia was believed to be resolved
[d] A follow-up visit was required for all patients. Test-of-Cure evaluations (assessment of signs/symptoms, measurement of infection site, assessment of clinical response) were to be conducted for those patients who were evaluated as "cure" or "indeterminate" at the EOT visit
[e] Test-of-Cure evaluations
[f] Only if a clinically significant lesion and/or drainage was present
[g] Antibiotics were only to be collected at this visit
[h] Added per Protocol Amendment 1
[i] Per Protocol Amendment 1, not required on Day 1, following study drug administration