Pre-Treatment Baseline Evaluation

The baseline evaluation was to be performed in the 24 hours before study treatment was initiated. Procedures included:

- obtaining informed consent and medical history
- assessment of clinical signs and symptoms of cSSSI (Clinical Signs and Symptom Score) including body temperature, length and width of the primary infection site
- appropriate specimen from skin infection site for Gram stain and culture
- two independent blood specimens for culture
- X-ray to rule out osteomyelitis if clinically indicated
- blood and urine samples for hematology, serum chemistry, and urinalysis
- serum for β-HCG testing if patient was female of child-bearing age
- three 12-lead ECGs at 5-10 minute intervals (if any QTc > 500 msec the patient was not to be admitted to the study).

Clinical Signs and Symptoms Score

The clinical signs and symptom score proposed measured six parameters which were assessed according to the chart shown in Table 16 below. The presence of a factor was scored as 1 and the absence of the factor 0. For wound drainage, if non-purulent the score was 1 and purulent 2. The maximum score that a patient could have was 7.

Table 16: Clinical Signs and Symptoms Score

Parameter	Assessment		
Wound drainage	Absent	Non-purulent	Purulent
Erythema	Absent	Present	Not applicable
Fluctuance	Absent	Present	Not applicable
Localized warmth	Absent	Present	Not applicable
Pain/tenderness	Absent	Present	Not applicable
Edema/Induration	Absent	Present	Not applicable

From Clinical Study Report 0017, Table 6-3, pg 59. [also CSR 0018, Table 6-3, pg 56]

MO Comment: The clinical signs and symptoms score proposed in the Original Protocol contained eight parameters. In addition to those shown in the table above, the original score also incorporated measurement of WBC count and body temperature. The maximum score that a patient could have was 11.

Relationship of the symptom score to severity of infection has not been established. Additionally, it is not clear that all factors should be weighted equally in the score (i.e., should fluctuance or induration count the same as erythema or localized warmth).

Microbiology Procedures

The protocol specified that a specimen from the primary infection site was necessary for entry into the study. Pathogens isolated from subculture at the local lab were to be sent to a central microbiology laboratory for identification of genus and species and MIC testing. The protocol

indicated that swab cultures were not acceptable and contamination with superficial colonizing bacterial flora was to be avoided. Deep cultures (needle aspiration, biopsy, surgically obtained specimens) from an area contiguous to the infection site were to be obtained. Sterile cultures of pus or drainage fluid were acceptable.

For visits occurring after the baseline (entry) visit, an appropriate specimen from the primary infection site was to be sent for culture only if a clinically significant lesion and/or purulent drainage was present.

β-HCG testing
Female patients were to have a serum sample tested for β-hCG at the local site, with confirmation by the central laboratory site. A negative β-hCG test was to be documented prior to administration of study medication.

Daily Procedures during Treatment
The following procedures were to be performed daily regardless of whether the patient was an inpatient or outpatient: study medication administration, assessment of clinical signs and symptoms score of primary infection site, length and width of the primary infection site, body temperature, assessment of adverse events, two independent blood specimens for culture if baseline blood cultures were positive or patient's condition deteriorated, any significant wound procedures such as incision and drainage, debridement, amputation, suture removal, etc. were to be recorded, and all concomitant medications were to be reported.

Every-Third-Day Procedures During Study Treatment
In addition to daily procedures listed previously, blood and urine samples for safety laboratories (hematology, serum chemistry, and urinalysis). Day 4, 7, 10, and 13 tests could have been collected within a ± 1 day window. Safety laboratories were to be obtained and sent to the central laboratory for testing.

Safety laboratory results were to be forwarded to investigators as rapidly as possible (expedited reports for any significantly abnormal results), but these results were not meant to be used for daily patient management since results may not have been available for 24-48 hours.

On Day 4 only (± 1 day), 3 12-lead ECGs were to be obtained at 5-10 minute intervals immediately following the active dose of study medication. If any QTc > 500 msec was observed, an ECG was to be repeated in 15 minutes; if the second QTc measurement was also >500 msec, the patient was to be discontinued, an EOT visit performed, and a follow-up visit scheduled. Also on Day 4 (per Protocol Amendment 1) PK sampling was to be performed at selected sites at the following designated timepoints: just prior to infusion, 0.25-0.5 hours following the start of infusion, and at 1-1.5 and 2-3.5 hours following the start of infusion.

End-of-Therapy Evaluation
All patients were to have an EOT evaluation as soon as possible after the last dose of study medication and no later than 3 days after last dose (Day 3P). During this visit, the investigator was to provide the reason for discontinuation of study medication, along with assessment of

clinical response at EOT (see Efficacy Endpoints in the Statistical Analysis Section of this review). The following procedures were to be performed: assessment of clinical signs and symptom scores, length and width of the primary infection site, assessment of clinical response by comparing a patient's signs and symptoms at EOT to baseline, body temperature, appropriate specimen from the primary infection site for microbiology culture (if clinically indicated), blood and urine samples for hematology, serum chemistry, urinalysis, and β-HCG (in females of child-bearing potential) unless obtained in previous 24 hrs, three 12-lead ECGs at 5-10 minute intervals, any significant wound procedures, all concomitant medications received, and adverse event assessment.

Test-of-Cure Evaluation

The original protocol stated that the investigator was to make every effort to conduct the TOC visit 7-14 days after the patient's EOT visit. Protocol Amendment 1 specified that the visit was to occur within 7-14 days after the last dose of study medication (between Day 7P and 14P). For patients who had been assessed as "cured" or "indeterminate" at EOT, the investigator was to record the clinical outcome at the TOC visit, based on the efficacy endpoint definitions of cure, failure, and indeterminate (see Statistical Analysis section). The following procedures were to be performed on all patients: assessment of adverse events, any significant wound procedures recorded, all concomitant medications recorded, and specimens for safety laboratories (hematology, serum chemistry, and urinalysis). Only patients with outcome of clinical "cure" or "indeterminate" at EOT were to have a clinical assessment of the primary infection site at TOC and to have the following procedures performed: assessment of clinical signs and symptoms, assessment of clinical response by comparing a patient's EOT signs and symptoms with those at baseline, length and width of the primary infection site, body temperature, and appropriate microbiologic specimen for culture (if clinically indicated).

Safety Monitoring

Adverse events (AEs) were to be monitored throughout the study period. An AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have a causal relationship with the treatment. AEs could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product. Pre-existing events which increased in frequency or severity or changed in nature during or as a consequence of use of a drug were also considered to be AEs. Laboratory abnormalities were usually not recorded as AEs, however abnormal laboratory findings associated with signs and/or symptoms were to be recorded as AEs or SAEs if meeting the definition of an event.

Any AE with onset date after study drug administration and up to the last day of the study (Follow-Up/TOC visit) was to be recorded as an AE on the CRF. A patient experiencing an AE was to be followed until resolution or stabilization or until the study was completed.

All AEs were to be assessed by the investigator and recorded on the appropriate CRF page including date of onset and resolution, severity relationship to study drug, outcome, and action taken with the study drug.

Severity was to be graded as follows:
- mild – aware of sign or symptom, but easily tolerated
- moderate – discomfort enough to cause interference with usual activities
- severe – incapacitating with inability to work or perform usual activities

Relationship was to be assessed as follows:
- Not related – evidence existed that the AE had an etiology other than study drug
- Possibly/probably related – a temporal relationship existed between the event onset and administration of the study drug. It could not be readily explained by the patient's clinical state or concomitant therapies and appeared with some degree of certainty to be related based on known therapeutic and pharmacologic actions of the drug. In the case of cessation or reduction of dose, the event abated or resolved and reappeared upon re-challenge.

Serious Adverse Events (SAEs)
An SAE was defined as follows: any AE that occurred at any dose and resulted in any of the following outcomes:
- Death
- Life-threatening situation
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received study drug
- Other important medical events may have been considered a SAE based upon appropriate medical judgement, that the event may have jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed.

All deaths regardless of cause were to be reported for patients on study and for deaths occurring within 30 days of the last study drug dose or within 30 days of the last study evaluation whichever was longer.

All SAEs were to be reported to the Sponsor within 24 hours of the investigator's awareness of the occurrence. For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents were to be faxed when requested and applicable. All SAEs were to be followed until the event resolved, stabilized, or for 30 days after the last dose of study drug, whichever was longer.

Clinical and Microbiological Outcome Assessment

Clinical Response
The primary efficacy endpoint was the Clinical Response assessed by the investigator at the TOC visit.

A Clinical Response was to be performed by the investigator at EOT and TOC visits according to the following definitions:

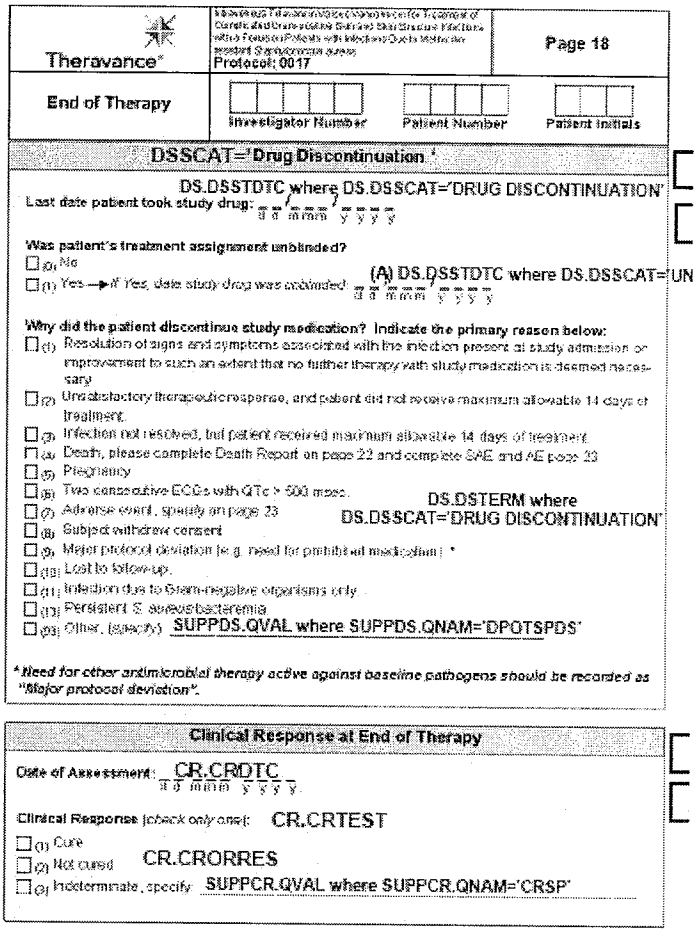
Cure: resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibiotic therapy is necessary.
Not Cured: inadequate response to study therapy.
Indeterminate: inability to determine outcome.
Missing: no determination reported (added per final SAP).

If a patient was withdrawn prematurely, the Clinical Response was to represent the status of infection at that time and was considered to be the Clinical Response at EOT. Patients with a Clinical Response of "Cured" or "Indeterminate" at EOT were to have efficacy and safety assessments performed at the TOC visit, while patients who were "Not Cured" at EOT were to have safety assessments only (i.e, failures carried forward).

MO Comment: The format of the CRF EOT and TOC Evaluation pages and application of clinical response definitions were closely examined after an investigator in Study 0018 (Site #38091) was noted during a DSI site inspection to be providing primary efficacy endpoint data that was discrepant from these definitions at TOC. This problem was noted for patients prematurely discontinued from study medication and treated with additional antimicrobials. The EOT and TOC pages of the CRF are reproduced from the Annotated CRF submitted with the Applicant's datasets and shown below (CRFs from Study 0017 and Study 0018 were the same).

Figure 1 below contains a copy of the annotated EOT CRF page.

Figure 1: EOT Assessment



MO Comment: As noted previously, "drug discontinuation" could occur if:

- *Patients had satisfactory resolution of infection (i.e. the assessment was "cure")* OR
- *Unsatisfactory therapeutic response (failure)* OR
- *Patients required termination of study medication for "other reason", such as meeting ECG withdrawal criteria, AE occurrence, or withdrawal of consent.*

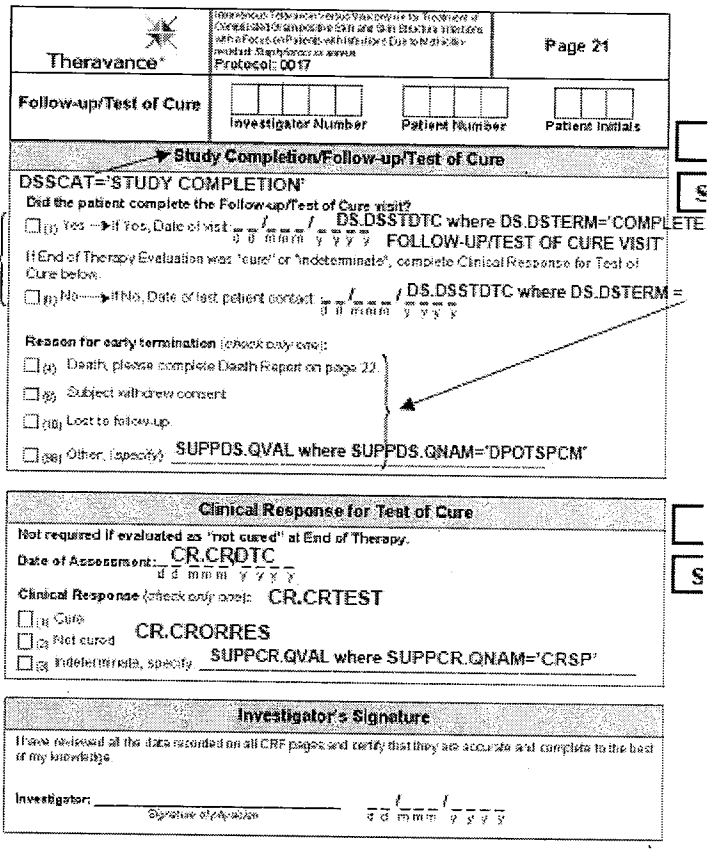
In general, patients who have resolution of infection and completed a course of study therapy should not be included in a listing of "discontinuations".

For patients in whom termination of study medication was for "other" reason, it is not clear that investigators consistently used the clinical response definitions as contained in the protocol. If strictly followed, a patient who terminated due to an AE and required additional non-study antibiotics could be assessed as "Not Cured" in the Clinical Response at EOT section. Another investigator could assess a patient discontinued due to occurrence of an AE to have a clinical response of "Indeterminate" at EOT. The patient who was "Not Cured" at EOT would have

that outcome carried forward and be assessed as a clinically evaluable failure, while the patient who was "Indeterminate" at EOT could be assessed at TOC as cured.

Figure 2 below is a copy of the TOC assessment page of the CRF.

Figure 2 TOC Assessment



MO Comment: As noted on this page, assessment of Clinical Response at TOC was not required if the patient was evaluated as "not cured" at EOT.

Microbiological Response

Although microbiological outcomes were included in the list of secondary endpoints, the protocol did not define how these would be determined.

The formal SAP included the definitions for microbiological response and determination of pathogen status of a given isolate.

All pathogens isolated from deep culture specimens at the local laboratory were to be sent to the central laboratory for re-identification of organism (genus and species) and antibiotic

susceptibility. However, the SAP indicates that information from both sites could be used to determine microbiological response.

The microbiological responses were determined directly from culture data (if available) or in the absence of culture data extrapolated from the clinical response. Pathogen status was determined by the study medical monitors and approved by the Principal Investigator. Organisms were considered to be pathogens if they were generally accepted as causing SSSI or if published literature documenting the organism as a cause of cSSSI was available. For patients with post-surgical wounds, coagulase negative staphylococci were accepted as pathogens.

By-Pathogen Microbiologic Response (determined only for Gram positive pathogens isolated at the baseline evaluation from an appropriate source, evaluated at EOT and TOC)
Eradicated: either the pathogen was absent, or "No Growth" was recorded on the CRF
Presumed Eradicated: no culture data were available, but the patient had a Clinical Response of "Cure"
Not Eradicated: the pathogen was documented as present
Presumed Not Eradicated: no culture data were available, but the patient had a clinical response of "Not Cured"
Indeterminate: no culture data were available, and the patient had a clinical response of "Indeterminate"
Missing: no culture data were available and the Clinical Response was missing.

For purposes of analysis, a Clinical Response of "Not Cured" at EOT was carried forward to TOC. If multiple cultures occurred in the evaluation window, the By-Pathogen Microbiologic Response was to be determined from the culture closest in time to the evaluation of Clinical Response.

By-Patient Microbiologic Response (patients with one or more pathogens at Baseline were to be assigned a By-Patient Microbiologic Response at the specified evaluation, evaluated at EOT and TOC)
Eradicated: the absence of all Baseline pathogens from the culture or "No Growth" was recorded on CRF
Presumed Eradicated: no culture data were available, but the patient had a Clinical Response of "Cured"
Not Eradicated: at least one Baseline pathogen was documented as present
Presumed Not Eradicated: no culture data were available, but the patient had a Clinical Response of "Not Cured"
Indeterminate: no culture data were available and the patient had a Clinical Response of "Indeterminate"
Missing: no culture data were available and the Clinical Response was missing.

For the purposes of analysis, the categories for By-Pathogen and By-Patient Microbiological Response were collapsed as follows:

- Eradicated = eradicated or presumed eradicated
- Not Eradicated = not eradicated, presumed not eradicated, indeterminate, missing

MO Comment: Microbiological responses were assessed by the Applicant based on either culture data at follow-up (TOC) or extrapolated from clinical response at TOC.

Overall Therapeutic Response (combination of clinical and microbiological responses) was analyzed by the Applicant. Because the majority of microbiological responses were extrapolated from clinical responses and propensity of follow-up cultures to contain colonizing organisms, the overall therapeutic response was not included in the FDA analysis.

Similarly, the Clinical signs and symptoms of Infection Score (CIS) has not been validated, was not helpful in determining severity of infection, and was also not included in the FDA analysis.

Statistical Analysis

Original Protocol

The original protocol and Protocol Amendment 1 provided a framework for the statistical analysis of the studies. Information included identification of primary, secondary, tertiary and safety endpoints, and definitions of the analysis populations. The primary efficacy analysis was designed to test for the clinical non-inferiority of telavancin to vancomycin, using a non-inferiority margin of 10%.

A sample size of 375 patients per treatment arm was projected to provide 300 clinically evaluable patients per arm, assuming 80% of enrolled patients would be clinically evaluable. If the clinical cure rates for telavancin and vancomycin were 80%, a one-sided 0.025 level test of non-inferiority of telavancin relative to vancomycin using a non-inferiority margin of 10% would have 86% power.

A prespecified secondary analysis was to be performed by pooling the results of the two independent studies, 0017 and 0018, in order to assess whether telavancin was superior to vancomycin in the treatment of infections caused by MRSA. The pooled enrollment of 750 patients per arm was expected to provide approximately 208 analyzable patients per arm; assuming two-thirds of the population would have *Staph aureus* and that one-half of those would be MRSA and that five-sixths of the MRSA-infected patients would be evaluable. Assuming the clinical cure rates for telavancin and vancomycin were 90% and 80% respectively, then a one-sided 0.025 level test would have 81% power to detect telavancin's superiority.

A more detailed statistical analysis plan (SAP Version 1, November 16, 2005) was submitted in the pre-NDA meeting package (IND 60,237, N-127) and discussed at the pre-NDA meeting on December, 15, 2005. Additional FDA comments were communicated to the Applicant in writing. The final SAP (SAP Version 2.0, August 8, 2006) was submitted to the FDA on August 8, 2006 and comments provided to the Applicant on September 1 and September 8, 2006. FDA comments were received by the Applicant after database lock and the Applicant was unblinded, although FDA was not.

The following presentation and discussion relates to the definitions from the final SAP, as well as FDA comments and concerns.

Analysis Populations

Efficacy Populations:

All-Treated (AT): All patients who received any amount of study medication analyzed according to their randomized treatment group.

Modified All-Treated (MAT): Patients in the all-treated population who also have a pathogen recovered from pretreatment cultures of the primary infection site and/or blood cultures.

Clinically Evaluable: Those patients in the all-treated population whose adherence to the protocol makes it reasonable to infer that their clinical response reflects the effect of the study drug. The specific criteria are:

- No baseline Gram positive pathogens resistant to vancomycin
- No baseline Gram negative pathogens resistant to aztreonam
- Received the study medication as assigned by the randomization code
- Received at least 4 days (8 doses) of study medication for a Clinical Response of Cure or 3 days (6 doses) of study medication for a Clinical Response of Not Cured
- Study medication compliance of 80-120%
- Diagnosis of one of the following cSSSI with MRSA either suspected or confirmed as the major cause of infection: major abscess requiring surgical incision or drainage, infected burn, deep/extensive cellulitis, infected ulcer, wound infection
- Purulent drainage or collection, OR at least 3 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
- Did not violate the following exclusion criteria:
  - #1 pertaining to prior therapy or need for non-study antibiotics
  - #4 pertaining to uncomplicated infection
  - #5 pertaining to self-limited infection
  - #6 pertaining to superinfected eczema, hidradenitis suppurativa, or other chronic medical conditions
  - #7 pertaining to concurrent infections of unremovable prosthetic materials
  - #8 pertaining to concurrent presence of osteomyelitis, endocarditis, or other deep site tissue infection
  - #9 pertaining to infection due to resistant Gram positive organisms based on susceptibility of baseline pathogens
  - #10 pertaining to burns, diabetic foot ulcers, ischemic ulcers/wounds, etc.

  Criteria 4-8 and 10 were based on investigator judgement and if enrollment approval was obtained, the patient was not excluded from the CE based on violation of exclusion criteria
- Had a TOC Clinical Response of "Cure" or "Not Cured", or had an EOT Clinical Response of "Not Cured"
- The TOC evaluation, if made, was made between D6P and D28P inclusive. If no TOC evaluation was made, then an EOT evaluation was made between D0P and D5P
- Did not receive a concomitant antibiotic at any time before the TOC assessment that was potentially effective against the condition under study if the concomitant antibiotic was given for any reason other than lack of efficacy

Microbiologically Evalauble (ME): Those patients in the Clinically Evalauble analysis population who had a Gram positive pathogen recovered from pretreatment cultures of the primary infection site and/or blood.

Safety Population: All patients who received at least one dose of study medication analyzed by drug exposure group:

- Drug exposure group for telavancin is all patients who received one or more doses of telavancin regardless of randomization
- Vancomycin drug exposure group is all patients who received only vancomycin regardless of randomization

Endpoints

The Applicant listed a primary endpoint, along with 3 secondary endpoints, and multiple tertiary endpoints. The study endpoints of interest and presented in the FDA analysis are:

Co-Primary

- Clinical response in the AT and CE populations

Secondary

- By-Patient clinical response at TOC in the MAT and ME populations
- By-Pathogen clinical response at TOC for MRSA
- By-Pathogen clinical response at TOC for Gram positive pathogens other than MRSA

Safety

- Adverse events
- Clinical laboratory tests: hematology, serum chemistry, and urinalysis
- Electrocardiogram QT and QTc intervals

The Original Protocol called for a Clinical Events Committee organized to adjudicate cases that did not meet protocol-specified criteria for evaluability or clinical outcome determinations. However, since Studies 0017 and 0018 were blinded, the decision was made to use investigator assessment of outcome rather than a central adjudicated outcome and this was stated in the SAP. Exceptions for strict use of investigator-determined outcome referred to the following Sponsor determinations while blinded:

- Organism classification as pathogen/non-pathogen
- Classification of non-study antibiotics as "potentially effective" against the cSSSI infection/organisms
- Surgical procedure classification
- Evaluation/Assessment Window Classification

MO Comment: Shown in Table 17 below are the changes to the Applicant's analyses requested by FDA after receipt of the final SAP.

Table 17

COMPARISON OF SAP AND ADDITIONAL ANALYSES PER US FDA SUGGESTED CHANGES TO CRITERIA FOR CLINICAL AND MICROBIOLOGIC EVALUABILITY

Criterion	SAP	Additional Analyses
Test-of-Cure/Follow-up window	Day 6P[a] to Day 28P	Day 7P to Day 21P
Duration of Study Medication for CE Cure	At least 4 days (8 doses) of study medication, and compliance of 80% to 120% of intended doses	At least 5 days (10 doses) of study medication
Specimens for Culture of Baseline Pathogens	All specimens considered acceptable since non-acceptable specimen types were prohibited by protocol	If the specimen type was non-missing, the method was adjudicated by study medical monitors and the Principal Investigator as "acceptable". If specimen type was missing, it was considered acceptable.
Baseline Pathogens	Coagulase-negative staphylococci (e.g. *S. epidermidis*) accepted as baseline pathogens if the cSSSI type was wound infection	Coagulase-negative staphylococci accepted as baseline pathogens if the cSSSI type was wound infection, **and** that Gram-stain results must be consistent (i.e. contain Gram-positive cocci)
Baseline Pathogen window	Day -3 to Day 2	Day -1 to Day 1, unless patient was treatment failure, then Day -3 to Day 1
ME population	Patients with pathogens[b] identified by the Central Laboratory, unless specimen lost or not viable, then local lab results could be used	Only pathogens identified by the Central Laboratory

[a] Post day of last dose of study medication

[b] as identified by the study medical monitors and approved by the Principal Investigator

From Clinical Study Report 0017, Appendix 26, pg 9721 (of electronic submission).

Study Review Methods

A 10% random sample of patients randomized to study treatment was generated by the FDA statistician for each Phase 3 study. Case report forms for these patients were submitted to the FDA by the Applicant. One half of the random sample CRFs from each study were reviewed (i.e., 5% of random CRFs from each of the 2 studies) in a treatment-blinded fashion by the FDA medical reviewer for assessment of adherence to inclusion/exclusion criteria, study procedures, and outcome assessment. Results of the FDA's assessment of the patient's assignment to a given analysis population, outcome based on events recorded in the CRF, and pathogen status of isolated organisms were compared to the Applicant's assessment. Discrepancies were noted and categorized into areas for further examination.

The following issues were identified in review of Study 0017 CRFs:

1) Patients 0017-38101-0272 had a major abscess from which a needle aspirate Gram stain was positive for numerous WBCs and Gram positive cocci and culture was positive for *Staph*

epidermidis. Similarly, patient 0017-38101-0850 had an abscess which was aspirated and had the same Gram stain and culture results.

MO Comment: The Applicant excluded these patients from the microbiological populations (MAT and ME) because the Staph epidermidis was not isolated from a post-surgical wound. The FDA reviewer thought that based on the contained process and positive findings on Gram stain and culture, that Staph epidermidis was a pathogen in this instance. The patients were included in the MAT and ME populations; patient 0017-38101-0272 had microbiological response of presumed persistence (due to clinical response of failure and no culture performed at EOT) and patient 0017-38101-0850 had microbiological response of presumed eradication based on clinical response of "cure" at TOC

2) Patient 0017-38101-0396 had an abscess, with "wound drainage" Gram stain showing numerous WBCs and culture positive for viridans streptococci (specimen not sent to central laboratory). A single blood culture on 2 separate days was positive for coagulase negative Staph (one isolate identified as *Staph hominis*).

MO Comment: The Applicant included this patient in the MAT population, the patient was lost to follow up and had an indeterminate response. FDA excluded this patient from the MAT population because alpha Strep from wound drainage was considered to be a contaminant as was coagulase negative Staph from a single blood culture on two separate days and agree with indeterminate outcome assessment.

3) Patient 0017-38271-0736 had a needle aspirate from an area of cellulitis which had a negative Gram stain and culture positive for *Enterococcus faecalis*, *Enterococcus faecium*, *Corynebacterium* spp., and coagulase negative *Staph*.

MO Comment: The Applicant included this patient in the MAT and ME populations and the patient had a clinical response of "cure" and no cultures, so microbiological response was presumed eradication. The FDA reviewer excluded this patient from the MAT and ME populations due to the polymicrobic nature of the culture and suspected contamination from colonizing skin.

4) Patients 0017-38101-0972, 0017-38271-0429, and 0017-38271-0966 were included in the Applicant's MAT analysis population despite having only Gram negative bacilli isolated from baseline cultures. Note: patient 0017-38101-0972 received 11 days of study treatment compared to aztreonam for 5 days, patient 0017-38271-0429 received study treatment for 5 days and aztreonam for 3 days, and patient 0017-38271-0966 received study treatment for 11 days and did not receive aztreonam.

MO Comment: Telavancin and vancomycin have no activity against Gram negative bacilli. Adjunctive aztreonam therapy for patients with suspected or proven Gram negative pathogens was recommended, but not required. In Study 0017, aztreonam was used as concomitant therapy in 55% of patients and metronidazole in 40%. Therefore,

since use of antimicrobial therapy active against Gram negative bacteria was not consistent, the FDA reviewer excluded patients with Gram negative organisms only (i.e. no Gram positive bacteria isolated in baseline culture) from the MAT analysis population. This is consistent with the FDA definition used for the microbiological all-treated populations in other applications of Gram positive spectrum antimicrobial agents for this indication.

5) Patient 0017-38271-0948 was assessed by the investigator as "Indeterminate" at the TOC visit due to the remaining erythema (42 X 30 cm) and the investigator being unable to mark the patient as "Cured".

MO Comment: The FDA assessed this patient as being "Not Cured" given the investigator's opportunity to assess wound and inability to assess patient as "Cured". The patient was not given any further antimicrobial therapy, but there was no subsequent follow-up required by the study and it is unknown whether the patient may have required further treatment.

6) Patient 0017-09004-0705 was assessed by the investigator as "Cure" at TOC.

MO Comment: The FDA assessed this patient as "Not Cured" since the patient was discontinued due to an adverse event of exanthem and required subsequent non-study antimicrobial therapy for the primary cSSSI site. (After FDA review systematic changes based on EOT indeterminate / < 72 hours of study medication due to AE / additional non-study antibiotics administered for primary infections this patient was classified as not CE and with "Indeterminate" outcome. See discussion below about systematic review of study datasets.)

The following issues were identified in CRFs from Study 0018:

1) Patient 0018-01024-2608 had only Gram negative organisms isolated from baseline microbiologic cultures. Note: this patient received study treatment for 5 days and no aztreonam.

MO Comment: The Applicant included this patient in the MAT population, the FDA reviewer did not. See discussion above for CRFs from 0017. For Study 0018, aztreonam was used in 14% of patients and metronidazole in 7%.

2) Patient 0018-38240-2886 had MRSA isolated at the local laboratory only and the isolate was not sent to the central microbiology laboratory for identification and susceptibility testing.

MO Comment: Local microbiology culture isolates were to be sent to a central laboratory for confirmation of organism identification and antimicrobial susceptibility testing.

3) Patient 0018-06007-2609 had a right foot infected ulcer (no further localization) with MSSA (12/2), treated until 12/15 [wound healed at EOT] and required amputation of the right great

toe on the same foot (12/17) for necrosis and received cefazolin after amputation (qualified as a protocol deviation).

MO Comment: The Sponsor excluded the patient from the CE population (major protocol deviation and discontinued study medication early) and stated the patient was cured and MSSA eradicated (AT and MAT cure). The FDA reviewer included patient in the CE population and assessed clinical response as "Not Cured". Localization of the presenting ulcer to the right leg/foot is ambiguous given the measured size of the infection site (35 cm x 9 cm). The assumption by the FDA reviewer was that the necrotic toe was related to the cSSSI infection process and if the site has been amputated, one can't assess the wound (at a minimum should be "Indeterminate").

4) Patient 0018-38008-2945 had MRSA isolated (local lab identification only) from a wound infection of a left BKA site and required revision of the amputation site on D8, no culture was sent from the OR, and on D9 discontinued from study therapy, although a wound drain was in place. The investigator assessed the outcome as "cure" with resolution of signs and symptoms of infection.

MO Comment: The Applicant included the patient in the CE and ME populations with clinical response of cure and microbiological assessment indicating eradication. The FDA reviewer included the patient in the CE population, excluded the patient from the ME population due to lack of central microbiology lab result, and assessed clinical response as failure due to late surgery (D8). Revision of the amputation site in this case at D8 is indicative of ongoing problems at the site and has major impact on the outcome.

5) Patient 0018-38315-2493 had MRSA, was mistakenly continued on cefazolin while receiving study medication, and required a second debridement to "drain wound" and treated with linezolid.

MO Comment: The Applicant excludes the patient from the CE population (and therefore ME population), due to protocol violation and receiving a non-study antimicrobial. However, the FDA reviewer notes that the patient required a late drainage procedure (D8) despite receiving study medication and an antibiotic that wouldn't have been considered "effective" (cefazolin for MRSA). The patient was subsequently treated with linezolid after EOT. The FDA reviewer assessed this patient as a CE and ME failure. The CRF for the EOT visit is confusing as the initial investigator response at EOT was "Indeterminate", along with a notation about linezolid treatment and the reason for discontinuation as AE is crossed out. The outcome is finally assessed as "Cure" and reasoning for "discontinuing" therapy as resolution of signs and symptoms of infection.

Based on review of blinded CRFs it was noted by the FDA reviewer that some patients who prematurely discontinued study medication and were assessed as having "Indeterminate" Clinical Response at EOT, and then requiring additional non-study antibiotics were subsequently assessed by the investigator as "Cured" at TOC. The assessment of the following 2 patients demonstrates this inconsistency.

- Patient #0018-6005-2801: the patient was treated for culture negative abdominal cellulitis (1/24), treatment was discontinued after 5 days due to AE (rash) and the patient was assessed as "Cure" by the investigator at EOT (1/28). At the TOC visit (2/7), despite receiving treatment with non-study antibiotic (cefazolin) the patient had an outcome assessment by the investigator of "Cure". Although this patient was not clinically evaluable, the patient was "cured" in the AT population.
- Patient #0018-06003-2353: the patient was treated for a culture negative ulcer of the right foot (10/6), treatment was discontinued after 5 days due to AE (acute renal failure) and the patient was assessed by the investigator as "Not Cured". The patient was subsequently treated with non-study antibiotics. At the TOC visit, an outcome assessment was not made (as directed on the TOC page) and the outcome assessment for this patient was based on the EOT assessment of "Not Cured". This patient was assessed as an AT and CE failure.

This prompted a systematic review of the study datasets for patients who received concomitant antibiotics for the primary cSSSI after initiation of study medication and prior to the TOC assessment. FDA adjudication of Clinical Response assessment was performed according to the following algorithm.

- Patients who were discontinued from study therapy due to an AE occurring before 72 hours of treatment with study medication were excluded from the CE population and assigned clinical response of "Indeterminate" (or Not Cured).
- Patients who were discontinued from study therapy due to an AE occurring after 72 hours of treatment with study medication and treated with a non-study antibiotic for the cSSSI were assessed as CE "Not Cured" unless there was another protocol-defined reason for being non-evaluable.
- Patients who were discontinued due to withdrawal of consent or due to QTcF > 500 msec were excluded from the CE population and assessed as indeterminate.
- Patients with infection due to Gram negative organisms only were excluded from the CE population and assigned an outcome of indeterminate (this recommendation was also included as an FDA comment to the Applicant's SAP and should have already been applied in the FDA analysis).
- Patients who received potentially effective non-study antibiotics for the cSSSI after > 72 hours of study therapy and excluded from the Applicant's CE due to "major protocol violation" were included as in the FDA CE population and assessed as failures.

6.1.4 Efficacy Findings

Disposition

A total of 862 patients at 40 sites were randomized into Study 0017, Protocol Amendment 1. There were 429 patients randomized to the telavancin (10 mg/kg) treatment group and 433 patients to the vancomycin treatment group. An additional 143 patients had been randomized into the Original Protocol Study 0017, with 73 patients randomized to telavancin (7.5 mg/kg) and 70 patients to vancomycin. Patients receiving study medication per the Original Protocol (either

telavancin or vancomycin) are not included in this review of efficacy, but are included in safety analyses in Section 7.0 Integrated Review of Safety.

A total of 1035 patients at 89 sites were randomized into Study 0018 after Protocol Amendment 1 was incorporated. There were 517 patients randomized to the telavancin (10 mg/kg) treatment group and 518 patients to the vancomycin treatment group. An additional 39 patients had been randomized into the Original Protocol Study 0018, with 20 patients randomized to telavancin (7.5 mg/kg) and 19 patients to vancomycin treatment groups. Patients receiving study medication per the Original Protocol (either telavancin or vancomycin) are not included in this review of efficacy, but are included in safety analyses in Section 7.0 Integrated Review of Safety.

Randomization was stratified by geographic region and diabetic status and is shown in Table 18 below.

Table 18: Randomization Stratification

Breakdown of Randomization Stratification				
	Study 0017[1]		Study 0018[2]	
	Telavancin N=429	Vancomycin N=433	Telavancin N=517	Vancomycin N=518
Randomized (total)	429	433	517	518
Randomized (not treated)	3	4	15	8
Randomized (treated)	426	430	502	510[3]
	Number (%) of Patients Treated			
Country Group 1 o US	326 (77%) 306 (72%)	331 (77%) 316 (74%)	372 (74%) 328 (65%)	378 (74%) 336 (66%)
Country Group 2	11(3%)	12 (3%)	66 (13%)	67 (13%)
Country Group 3	89 (21%)	86 (20%)	64 (13%)	65 (13%)
Diabetes	94 (22%)	98 (23%)	118 (24%)	120 (24%)
No Diabetes	332 (78%)	331 (77%)	384 (76%)	390 (76%)

[1] From Clinical Study Report 0017, Table 7.2, pg 94.
Group 1: United States, Australia, Belgium
Group 2: South Africa
Group 3: Croatia, Israel, Malaysia, Russia.
[2] From Clinical Study Report 0018, Table 7.2, pg 95.
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
[3] One patient (0018-33005-2552) randomized to vancomycin received telavancin; the patient was included in the vancomycin AT (and MAT) for efficacy analyses (excluded from CE/ME) and included in the vancomycin group in the table above. For safety analyses, this patient is included in the telavancin group.

MO Comment: The rationale for including countries within their respective groups is not provided. The majority of patients, >70% in Study 0017 and > 65% in Study 0018 were from the United States. The incidence of diabetes was approximately 23%, although based on review of enrolled patient CRFs, particularly concomitant medications, there was actually a slightly higher incidence of diabetes mellitus identified.

In Study 0017, two sites randomized 465 of the 862 study patients (54%); 234 of these patients were randomized to the telavancin treatment arm and 231 to the vancomycin treatment arm.

There were no formal limitations on the number of patients a site could enroll included in the protocol. The two sites, Site #38101 and Site #38271 were inspected by DSI and results from both sites were certified for use in the FDA analysis by DSI. Efficacy analyses were performed by the FDA including and excluding these 2 sites from the co-primary efficacy analyses to rule out a center effect on overall results.

The reason for patients being randomized and subsequently not treated is not explained for all patients. In Study 0018, there were a slightly higher number of patients randomized and not treated, with twice as many patients randomized to the telavancin treatment arm. The overall number of patients was small and would not be likely to impact the overall analysis of the study.

Patients were to receive treatment with study medication for a minimum of 7 days and a maximum of 14 days. Patients could discontinue treatment for a variety of safety and administrative reasons. Patients were clinically evaluable if they received at least 3 days of study medication for those who were "Not Cured" and at least 4 days for those who were "Cured".

Table 19 shows the reasons for premature discontinuation of study medications.

Table 19: Discontinuation of Study Drug – AT Population

	Study 0017[1]		Study 0018[2]	
	Telavancin (N=426)	**Vancomycin (N=429)**	**Telavancin N=502**	**Vancomycin[3] N=510**
Completed Course of Study Drug	350 (82%)	355 (83%)	396 (79%)	411 (81%)
• Resolution in ≤ 14 days • Infection not resolved with 14 days of treatment	341 (80%) 9 (2%)	342 (80%) 13 (3%)	384 (76%) 12 (2%)	398 (78%) 13 (3%)
Premature Discontinuation of Study Drug	76 (18%)	74 (17%)	106 (21%)	99 (19%)
• Unsatisfactory therapeutic response	14 (3%)	13 (3%)	10 (2%)	15 (3%)
• Death	2 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)
• Two consecutive ECGs with QTc > 500	0	1 (<1%)	1 (<1%)	1 (<1%)
• Adverse event	29 (7%)	22 (5%)	43 (9%)	28 (5%)
• Patient withdrew consent	11 (3%)	14 (3%)	16 (3%)	18 (4%)
• Major protocol deviation	1 (<1%)	2 (<1%)	8 (2%)	1 (<1%)
• Lost to follow-up	6 (1%)	6 (1%)	7 (1%)	9 (2%)
• Infection due to Gram negative organisms only	2 (<1%)	4 (<1%)	5 (<1%)	6 (1%)
• Persistent SA bacteremia			1 (<1%)	0
• Other	11 (3%)[4]	10 (2%)[5]	13 (3%)[6]	18 (4%)[7]

[1] Based on data from Clinical Study Report 0017, Table 7-3, Pg 97.
[2] Based on data from Clinical Study Report 0018, Table 7-3, Pg 99.
[3] One patient (0018-33005-2552) randomized to vancomycin received telavancin; the patient was included in the vancomycin AT (and MAT) for efficacy analyses (excluded from CE/ME) and included in telavancin safety analyses.
[4] Telavancin: non-compliance or drug administration problems (7), infections met exclusion criteria (3), treatment stopped after only 5 minutes of drug infusion (1).
[5] Vancomycin: non-compliance or drug administration problems (6), infections met exclusion criteria (4).
[6] Telavancin: non-compliance or drug administration problems (5), infections met exclusion criteria (3), site ran out of study medication (2), therapy stopped due to protocol amendment not yet approved by country regulatory authorities (1), Gram negative superinfection (1), threatening behavior (1).
[7] Vancomycin: non-compliance or drug administration problems (10), infections met exclusion criteria (3), withdrawn by physician (1 for security reasons, 1 for unclear reasons but not AE, 1 for mild facial flushing that resolved the same day), unsatisfactory response (2).

MO Comment: The frequency and reason for premature termination of study drug therapy was similar across treatment arms and studies. Adverse events leading to discontinuation were slightly more frequent in Study 0018 and for the telavancin treatment group (9%) compared to 5% for the vancomycin treatment group in that study. AEs will be more fully discussed in Section 7 Safety Review.

Study completion was based on whether a patient had a follow-up (Test-of-Cure; TOC) evaluation. Reasons for early termination included death, withdrawal of consent, loss to follow-up and other reasons. The TOC visit was to occur within 7-14 days after the last dose of study medication per protocol, but the window in which this visit could occur was extended by the Applicant to 6-28 days after the last dose. The reasons for patients discontinuing from the Study are shown in Table 20 below.

Table 20: Study Completion – AT Population

	Study 0017[1]		Study 0018[2]	
	Telavancin (N=426)	**Vancomycin (N=429)**	**Telavancin (N=502)**	**Vancomycin[3] (N=510)**
Completed End-of-Therapy Visit	423 (99.3%)	424 (98.8%)	500 (99.7%)	506 (99.2%)
Completed Follow-Up Visit	387 (91%)	387 (90%)	463 (92%)	456 (89%)
Number of days after last study drug				
• ≤ 6 days	6 (1%)	8 (2%)	21 (4%)	16 (3%)
• 7-14 days	365 (86%)	357 (83%)	415 (83%)	418 (82%)
• ≥ 15 days	16 (4%)	22 (5%)	27 (5%)	22 (4%)
Patients who terminated early	39 (9%)	42 (10%)	39 (8%)	54 (11%)
(Reasons for early termination)				
• Death	4 (<1%)	5 (1%)	3 (<1%)	3 (<1%)
• Patient withdrew consent	5 (1%)	8 (2%)	4 (<1%)	9 (2%)
• Lost to follow-up	26 (6%)	23 (5%)	22 (4%)	32 (6%)
• Adverse event	1 (<1%)	1 (<1%)	3 (<1%)	5 (<1%)
• Major protocol deviation	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
• Other	2 (<1%)[4]	3 (<1%)[4]	5 (<1%)[5]	4 (<1%)[6]

[1] Based on data from Clinical Study Report 0017, Table 7-4, Pg 100.
[2] Based on data from Clinical Study Report 0018, Table 7-4, Pg 101.
[3] One patient (0018-33005-2552) randomized to vancomycin received telavancin; the patient was included in the vancomycin AT (and MAT) for efficacy analyses (excluded from CE/ME) and included in telavancin safety analyses.
[4] Baseline pathogens were due to Gram negative pathogens only.
[5] "Other" reason for termination telavancin: lost to follow-up due to Hurricane Katrina (2), patient rehospitalized (1), regulatory "hold" pending approval of protocol amendment (1), threatening behavior (1).
[6] "Other" reason for termination vancomycin: lost to follow-up due to Hurricane Katrina (3), problem with home nursing (1).

MO Comment: The number of patients completing EOT and TOC visits was similar across studies and for the two treatment groups. Reasons for early termination were also similar.

The number (percent) of patients in the vancomycin treatment group who failed to complete the study (i.e., were lost to follow-up) was slightly higher than in the telavancin group (6% versus 4%, respectively). Withdrawal of consent was also slightly higher in the vancomycin treatment group compared to the telavancin group (9 patients versus 4 patients, respectively), but this number was relatively small.

For Study 0017, twenty of the twenty six patients in the telavancin treatment group were lost to follow-up and could not be contacted after the study; three of these twenty six patients had significant adverse events (serious AE OR severe AE OR AE leading to discontinuation of study drug). Similarly for the vancomycin treatment group, sixteen of the twenty three patients were lost to follow-up and could not be contacted after the study; two of these sixteen patients had significant adverse events (serious AE or severe AE or AE leading to discontinuation of study drug). The following is a list of patients with such events during the study, with a brief description of the event.

- 0017-09003-0603 (T): mild reaction on D7 related to new topical therapy (Aquacel) applied to ulcer with new wounds noted in the surrounding soft tissue on the same day, assessed by the investigator as unrelated to study treatment.
- 0017-38001-0693 (T): DVT/PE, with death secondary to PE, underlying ovarian cancer (death occurred after CRFs completed/after study completed), assessed by the investigator as unrelated to study medication (FDA review: SAE unlikely related to study medication, see discussion in review of safety).
- 0017-38101-0277 (T): PE, study medication discontinued the same day as diagnosis, investigator assessed as unrelated to study medication (FDA review: temporally related to study medication, see discussion in review of safety).
- 0017-09003-0326 (V): severe chest pain on Day 2, assessed by the investigator as unrelated to study medication (no narrative), and the patient continued study treatment after event.
- 0017-30003-0594 (V): psychotic disorder and delirium, study medication discontinued the same day, investigator assessed as unrelated to study medication (FDA: unlikely related to study medication, confounded by administration of anesthetic agents and sedatives).

For Study 0018, twenty one of the twenty two patients in the telavancin treatment group were lost to follow-up and could not be contacted after the study: two of these twenty one had significant adverse events (serious AE or severe AE or AE leading to discontinuation of study drug). Twenty nine of the thirty two patients in the vancomycin treatment group were lost to follow-up and could not be contacted after the study; two of these patients had significant adverse events (serious AE or severe AE or AE leading to discontinuation of study drug). The following is a list of patients with such events during the study, with a brief description of the event.

- 0018-38074-3015 (T): osteomyelitis after 14 days treatment with study medication, investigator assessed event as unrelated to study medication, stated the patient was non-compliant and the recurrence of abscess (underlying osteomyelitis) was unrelated to study medication. (FDA review: patient had multiple irrigation and drainage procedures after study medication discontinued due to osteomyelitis and patient subsequently had finger amputated; this likely represents primary treatment failure at EOT with failure carried forward)
- 0018-38112-2234 (T): 57 year old female with diabetes mellitus, neuropathy, iron deficiency anemia, hypertension, and hyperlipidemia treated with study medication for 6 days, concomitant medications included glucophage, insulin, amitriptyline, atorvastatin, metoprolol, and nadolol. Mild elevation of alk phos at baseline, with further increase (2X) and >10 increase in ALT and AST on D4 (normal total bilirubin), by D8 (2 days after

discontinuing study medication), alk phos remains elevated (stable), ALT and AST improving (now <10 x normal), and normal total bilirubin. The patient was lost to follow up due to Hurrican Katrina. The investigator assessed increased liver function tests (LFTs) as unrelated to study medication, and noted improvement. (FDA review: AE that is possibly/probably related to study medication although comorbid condition or medication may contribute.)

- 0018-38260-2213 (V): The patient developed non-cardiac chest pain on Day 3 and was discontinued from study medication (on Day 2, AEs of nausea, vomiting, and diarrhea possibly/probably related to study medication were also noted). The investigator assessed AE as possibly/probably related to study medication.
- 0018-38260-2236 (V): The patient was discontinued from study medication due to a rash. The investigator assessed this event as possibly/probably related to study medication.

Duration of Study Therapy

The duration of therapy was determined by the investigator based on clinical assessment of the cSSSI site. The minimum duration of therapy was to be 7 days and the maximum 14 days. Table 21 shows the actual duration of study treatment for the FDA AT population by study.

Table 21: Duration of Study Therapy

	Study 0017		Study 0018	
#Day on Treatment	Telavancin	Vancomycin	Telavancin	Vancomycin
1	8 (1.9)	6 (1.4)	6 (1.3)	14 (2.9)
2	6 (1.4)	9 (2.1)	13 (2.8)	12 (2.5)
3	12 (2.8)	7 (1.6)	13 (2.8)	15 (3.1)
4	9 (2.1)	11 (2.6)	9 (1.9)	7 (1.4)
5	6 (1.4)	13 (3)	14 (3)	7 (1.4)
6	12 (2.8)	7 (1.6)	15 (3.2)	13 (2.7)
7	37 (8.7)	31 (7.2)	69 (14.6)	64 (13.1)
Subtotal @ 7 Days	**90 (21.1)**	**84 (19.6)**	**139 (29.4)**	**132 (27.0)**
8	78 (18.3)	59 (13.8)	110 (23.3)	110 (22.5)
9	30 (7)	25 (5.8)	28 (5.9)	31 (6.3)
10	32 (7.5)	39 (9.1)	56 (11.9)	37 (7.6)
11	33 (7.8)	28 (6.5)	28 (5.9)	38 (7.8)
12	19 (4.5)	35 (8.2)	17 (3.6)	22 (4.5)
13	20 (4.7)	17 (4)	19 (4)	17 (3.5)
14	34 (8)	34 (7.9)	51 (10.8)	68 (13.9)
15	90 (21.1)	108 (25.2)	23 (4.9)	32 (6.5)
16			0 (0)	1 (0.2)
17			0 (0)	0 (0)
18			1 (0.2)	1 (0.2)
Total	**426**	**429**	**472**	**489**

MO Comment: The Applicant notes in the clinical study reports that patients who received "15 days" of treatment actually received fourteen 24-hr intervals of study medication over fifteen calendar days. The duration of study therapy appears to be shorter for patients treated in Study 0018 compared to Study 0017. In Study 0017, over 20% of patients received the maximum of 14-days of therapy compared to less than 10% of Study 0018 patients. Even if duration of 14 and 15 days is combined to take into account the "extra" calendar day (as noted above), there still

appears to be a discrepancy between the two studies with approximately 30% in Study 0017 and 15-20% in Study 0018 receiving 14-15 days of therapy. While duration of therapy was to be based on the investigator assessment of the primary infection site, it is not clear whether all investigators understood that therapy was not required for the full 14-day period. This statement is based on review of some CRFs where investigator TOC comments indicate that patients had clinical response assessed as "Indeterminate" because they did not receive the "full 14 days" of therapy.

Reconciliation of Applicant and FDA Analysis Populations

Prior to submission of the NDA, the FDA provided comments to the Applicant regarding concerns about some of the criteria established for inclusion of patients into analysis populations. These comments were received by the Applicant after database lock and unblinding, but occurred while the FDA was blinded. The CSR for Study 0017 and 0018 contain an Appendix in which the results of the analyses as recommended by FDA are contained. The Applicant states that overall, the results are similar to their analysis.

Additional changes were made by the FDA reviewer to the composition of the analysis populations and outcome determinations based on blinded review of CRFs, DSI inspection report from an investigative site, and systematic review of patients who received non-study antibiotics for cSSSI after prematurely discontinuing study medication. The explanation for these changes has been previously presented.

Table 22 and 23 outline the changes made for FDA analysis in Study 0017 and Study 0018 respectively.

Table 22: Number of Patients in Each Analysis Population (Study 0017)

	Sponsor[1]			FDA		
Number (%) of Patients	Telavancin	Vanco	Total	Telavancin	Vanco	Total
All-Treated (AT)	426 (100)	429 (100)	855 (100)	426 (100)	429 (100)	855 (100)
Modified All-Treated (MAT)	307 (72)[2]	322 (75)[2]	629 (74)	260 (61)	274 (64)	534 (62)
Clinically Evaluable (CE)	346 (81)	349 (81)	695 (81)	343 (81)	348 (81)	691 (81)
Microbiologically Evaluable (ME)	237 (56)[2]	255 (59)[2]	492 (58)	219 (51)	234 (55)	453 (53)
ME as % of CE	68%	73%	71%	64%	67%	66%

[1] From Clinical Study Report 0017, Table 8-1, pg 104.
[2] For the MAT populations, there were 6 telavancin-treated patients and 1 vancomycin-treated patient with blood pathogens only. For the ME populations, there were 3 telavancin-treated patients and no vancomycin-treated patients with blood pathogens only.

Table 23: Number of Patients in Each Analysis Population (Study 0018)

	Sponsor[1]			FDA		
Number (%) of Patients	Telavancin	Vanco	Total	Telavancin	Vanco	Total
All-Treated (AT)	502 (100)	510 (100)	1012	472 (100)	489 (100)	961
Modified All-Treated (MAT)	373[2] (74)	381[2] (75)	654 (65)	303 (64)	322 (66)	625 (65)
Clinically Evaluable (CE)	399 (79)	395 (77)	794 (78)	365 (77)	363 (74)	728 (76)
Microbiologically Evaluable (ME)	290[2] (58)	281[2] (55)	571 (56)	240 (51)	239 (49)	479 (50)
ME as % of CE	73%	71%	72%	66%	66%	66%

[1] From Clinical Study Report 0018, Table 8-1, pg 105.
[2] For the MAT populations, there was 1 telavancin-treated patient and 4 vancomycin-treated patients with blood pathogens only. For the ME populations, there were no telavancin-treated patients and 4 vancomycin-treated patients with blood pathogens only.

MO Comment: The number of patients in each treatment group is evenly balanced for both the Applicant and FDA analyses. The explanations for the differences are listed below and are based on FDA comments to the Applicant about the SAP, and review-related concerns about the consistency of clinical response determination in patients receiving non-study antibiotics following premature discontinuation of study medication (based on FDA blinded review of CRFs and DSI inspection findings).

The Applicant and FDA AT populations are the same for Study 0017. The FDA AT population excludes patients enrolled at Site #38091 (Note: these patients are excluded from the efficacy analyses, but not the safety analyses) based on results of the DSI inspection of that site.

The decrease in the number of patients in the FDA MAT population was primarily due to the exclusion of patients in whom only Gram negative pathogens were isolated from microbiological culture. In Study 0017, 22 patients in the telavancin treatment arm and 15 in the vancomycin treatment arm had only Gram negative organisms cultured at baseline. Similarly for Study 0018, 12 patients were in the telavancin treatment arm and 17 were in the vancomycin treatment arm. Additional changes are based on the difference in pathogen status classification of coagulase negative staphylococci between Applicant and FDA.

Changes in the number of patients who met criteria for the Clinically Evaluable population were based on FDA comments sent to the Applicant on September 1, 2005 regarding the final SAP for the ATLAS studies (Studies 0017 and 0018) submitted to FDA on August 8, 2005 (noted above). Additional changes resulted from the systematic (algorithmic) review of patients who discontinued study drug for reasons other than resolution and who subsequently received a post-baseline systemic antibiotic for the cSSSI. This review was precipitated by the review of the random sample CRFs and report from the DSI inspection of Site #38091 where the investigator did not seem to be consistently following the protocol definitions for outcome. Specifically, it was noted that patients who prematurely discontinued study antibiotic and received additional antibiotics for the cSSSI under study and who were not specified as clinical failures at the EOT visit could be considered clinical cures at TOC despite receipt of non-study antimicrobials.

The FDA and Applicant assessment of whether a patient was CE and outcome assessment were also discrepant in terms of the adjudication of significance of surgical procedures performed and timing of the procedure related to administration of study medication. The protocol specified that at the time of study assessments, the investigator was to record performance of any significant wound procedure such as incision and drainage, debridement, amputation, suture removal, etc. The Study Design section of the protocol had stated that surgical management of the infection was permissible and considered standard of care. However, significant surgical intervention on more than two occasions during the study was to constitute evidence of failure, although this was not stated anywhere in the definition of failure (i.e., outcome of "Not cured") in either the protocol or SAP. One of the Sponsor determinations while blinded was to determine which surgical procedures might significantly affect outcome (e.g., amputation, drainage, or en bloc excision) and which represented ancillary treatment (e.g., debridement). The Applicant evaluation was based on number of procedures performed without taking into account timing of procedure relative to the start of study medication. While recognizing that surgical drainage is important in resolution of infection, the FDA reviewer believes that the requirement for a significant procedure >96 hours after primary drainage and initiation of study medication constitutes evidence of clinical failure. Additionally, amputation of the primary site has a major impact on outcome assessment and patients having amputation of that site after being on study therapy (even if prospectively planned) were considered to be CE failures.

Finally the change in number of Microbiologically Evaluable patients is due to a decrease in the number of patients considered to have pathogens based on lack of central laboratory confirmation of identification and susceptibility, as well as the changes impacting the CE population.

Table 24 shows the baseline demographic information for patients randomized and treated in Study 0017 and Study 0018.

Table 24: Demographics of Study Population (AT Population)

	Study 0017[1]		Study 0018[2]	
	Telavancin N=426	Vancomycin N=429	Telavancin N=472	Vancomycin N=489
Age (years)				
• Mean	48.9	47.7	48.9	49.8
• Min, max	18, 96	17, 90	18, 95	18, 91
Age Distribution				
• <65 years	337 (79%)	357 (83%)	391 (83%)	386 (79%)
• ≥65 years	89 (21%)	72 (17%)	81 (17%)	103 (21%)
• <75 years	381 (89%)	398 (93%)	431 (91%)	442 (90%)
• ≥75 years	45 (11%)	31 (7%)	41 (9%)	47 (10%)
Sex				
• Male	230 (54%)	248 (58%)	268 (57%)	299 (61%)
• Female	196 (46%)	181 (42%)	204 (43%)	190 (39%)
Race				
• American Indian / Alaska Native	3 (<1%)	2 (<1%)	7 (1%)	9 (2%)
• Asian	7 (2%)	9 (2%)	38 (8%)	44 (9%)
• Black, of African heritage	59 (14%)	52 (12%)	71 (15%)	74 (15%)
• Hawaiian/Pacific Islander	3 (<1%)	9 (2%)	4 (<1%)	8 (2%)
• White	349 (82%)	353 (82%)	348 (74%)	351 (72%)
• Aborigine	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
• Multi-racial	4 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)

[1] From CSR 0017, Table 8-3, pgs 108-109.
[2] Based on FDA demographic analysis (minus site #38091).

MO Comment: The two treatment groups were relatively well balanced in regard to age, gender, and race. There was a slight male predominance in the overall study populations and the majority of patients were white. Approximately 20% of the study population was over the age of 65 years, with approximately 10% of the overall population 75 years of age or older. The percent of the population ≥ 65% years old is similar to that studied for other recent cSSSI NDAs.

Table 25 below shows some of the baseline characteristics of the randomized and treated population for Study 0017 and Study 0018.

Table 25: Baseline Characteristics of the Study Population (AT)

	Study 0017[1]		Study 0018[2]	
Baseline Characteristics	**Telavancin N=426**	**Vancomycin N=429**	**Telavancin N=472**	**Vancomycin N=489**
Body Mass Index Distribution				
• Underweight (< 18.5 kg/m²)	7 (2%)	10 (2%)	8 (2%)	7 (1%)
• Normal Weight (18.5 - < 25 kg/m²)	138 (32%)	128 (30%)	142 (30%)	143 (29%)
• Overweight (25 - < 30 kg/m²)	133 (31%)	137 (32%)	138 (29%)	149 (31%)
• Obese (30 - < 40 kg/m²)	104 (24%)	120 (28%)	127 (27%)	132 (27%)
• Morbidly Obese (≤ 40 kg/m²)	44 (10%)	34 (8%)	57 (12%)	57 (12%)
• Missing			0	1
Medical/Surgical Conditions Directly Associated with cSSSI				
• Recent trauma	115 (27%)	125 (29%)	59 (13%)	66 (13%)
• Diabetes mellitus	109 (26%)	109 (25%)	119 (25%)	119 (24%)
• Bite	33 (8%)	50 (12%)	34 (7%)	34 (7%)
• Recent surgical procedure	37 (9%)	42 (10%)	59 (13%)	50 (10%)
• Peripheral vascular disease	42 (10%)	28 (7%)	33 (7%)	49 (10%)
• Chronic skin disease	34 (8%)	25 (6%)	26 (6%)	44 (9%)
• Chronic edema	21 (5%)	20 (5%)	21 (4%)	44 (9%)
Description of cSSSI				
• Major Abscess	179 (42%)	193 (45%)	207 (44%)	208 (43%)
• Deep/Extensive Cellulitis	156 (37%)	161 (38%)	155 (33%)	177 (36%)
• Wound Infection	72 (17%)	60 (14%)	68 (14%)	62 (13%)
• Infected Ulcer	16 (4%)	12 (3%)	29 (6%)	36 (7%)
• Infected Burn	3 (<1%)	3 (<1%)	13(3%)	6 (1%)
Hospitalized at Study Entry[3]	354 (83%)	358 (83%)	289 (61%)	302 (62%)

[1] From Clinical Study Report 0017, Table 8-4, pgs 110-1, Table 8-7, pg 119, Table 8-8, pg 121.
[2] Based on FDA demographic analysis (minus site #38091).
[3] FDA reviewer analysis [Hosp sequence 1, with comment in relatedness (or not) to cSSSI].

MO Comment: The treatment groups for each study were well matched for BMI, type of cSSSI, and hospitalization status at study entry. For both studies, approximately 35-40% of the population was obese or morbidly obese and 25% had diabetes (diabetes was a randomization stratification factor). Abscesses were the most common type of infection studied, with cellulitis the second most common type. There were a limited number of patients studied with infected ulcer since patients with chronic ulcers were excluded from the studies. The hospitalization rate at study entry in Study 0018 (61-62%) is much less than that for Study 0017 (83%); this may represent a difference in the severity of illness in patients across the two studies.

In Table 26, the baseline renal function of patients enrolled and treated in the study is shown.

Table 26: Baseline Renal Function (AT Population)

Renal Parameter	Study 0017[1]		Study 0018[2]	
	Telavancin N=426	Vancomycin N=429	Telavancin N=472	Vancomycin N=489
Baseline Serum Creatinine (umol/L)				
• Mean, SD	83, 60.1	81, 79.5	82.5, 41.7	82.5, 46.8
• Median	71	71	76	73.5
• Min, Max				
Baseline Serum Creatinine (mg/dL)				
• Mean [mg/dL=mmol/l÷88.4]	0.9, 0.7	0.9, 0.9	0.93, 0.47	0.93, 0.53
• Median	0.8	0.8	0.86	0.83
• Min, Max				
Categories (CrCL), n/N (%)				
• >80 mL/min	274 (65)	291 (69)	289 (64)	291 (62)
• >50-80 mL/min	85 (20)	85 (20)	116 (26)	119 (25)
• 30-50 mL/min	41 (10)	35 (8)	32 (7)	46 (10)
• <30 mL/min	21 (5)	12 (3)	17 (4)	16 (4)
• Missing	5	6	18	17
Hemodialysis, n/N (%)				
• On hemodialysis	6 (1)	4 (<1)	3 (<1)	1 (<1)
• No hemodialysis	420 (99)	425 (99)	468 (99)	488 (100)
• Missing	0	0	1	0

[1] From Clinical Study Report 0017, Table 8-5, pgs113-4.
[2] FDA baseline analysis (minus site #38091).

b(4)

MO Comment: The treatment groups were well matched with respect to renal function. In Study 0017, 35% of the telavancin treated patients had some degree of renal impairment at baseline compared to 31% of the vancomycin treated patients. In Study 0018, 37% of the telavancin treated patients had some degree of renal impairment at baseline compared to 39% of the vancomycin treated patients. Less than 1% of patients were on hemodialysis at baseline.

Clinical Efficacy Results

The co-primary efficacy endpoint analyses for Studies 0017 and 0018 were the Clinical Response at TOC in the AT and CE populations. Table 27 shows the results of the Applicant and FDA co-primary efficacy analyses for Study 0017 and Study 0018.

Table 27: Clinical Response (Cure) Rate at TOC in AT and CE Populations: Applicant and FDA Co-Primary Efficacy Analyses

	Applicant Assessment[1]			FDA Assessment		
	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
Population	n/N %	n/N %	% (95% CI)	n/N %	n/N %	% (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)
0017 + 0018 Combined	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)
0017 + 0018 Combined	658/745 (88.3)	648/744 (87.1)	1.2 (-21., 4.6)	595/708 (84.0)	606/711 (85.2)	-1.2 (-4.9, 2.6)

[1] From the ISE, Table 5-33, pg 173.

MO Comment: The FDA and Applicant analyses for Study 0017 and Study 0018 support the conclusion that telavancin demonstrated clinical non-inferiority to vancomycin using the prespecified non-inferiority margin of 10% for the co-primary analysis populations for efficacy. Similarly, the result for the pooled analysis supports the same conclusion. The FDA and Applicant analysis results for Study 0017 AT and CE populations are similar. However, for Study 0018, the point estimates for clinical response rates in the FDA analyses are lower than those of the Applicant. For the FDA-AT population, the point estimate is 0.1 compared to 3.4 for the Applicant. For the FDA-CE population the point estimate is -3.8 compared to 1.1 for the Applicant. Likewise, the lower bound of the 95% CI(s) for the FDA analyses are lower than that of the Applicant. The results of the pooled analyses also show a decrease in the point estimates for both the AT and CE populations, with decrease in the lower bound of the 95% CI(s). Although the results of both FDA and Applicant analyses for Studies 0017 and 0018, both singly and combined, support the conclusion of non-inferiority, it is of some concern that the response rates for the FDA analyses for Study 0018 are considerably lower.

Some of the explanation for this difference comes from the exclusion of Site #38091 from the FDA analysis based on DSI inspection report. The site had been chosen for inspection based on much higher clinical cure rates for telavancin relative to other sites and also for being one of the higher enrolling sites (approximately 5% of the study population). However, this only explains about half of the difference. The other major factor likely influencing the difference is based on the FDA systematic readjudication of clinical outcomes in patients who received concomitant antimicrobials for cSSSI during the study or had major surgical procedures after receiving at least 4 days of study medication. Based on this analysis, patients who may have been excluded

from the Applicant's CE analysis due to receipt of non-study antibiotics, were included in the FDA analysis as CE failures.

There were two high enrolling investigative sites for Study 0017, accounting for 54% of the study population. These two centers, #38101 and #38271, were inspected by DSI and the data from the sites was found to be acceptable for use in analysis. However, since the effect these two sites might have on the results of analyses is substantial, a sensitivity analysis was performed to assess the effect on overall efficacy of Study 0017. The results are shown in Table 28 below.

Table 28: Clinical Response at TOC Sensitivity Analysis (FDA Analysis Population)

	Study 0017			Study 0017 Excluding Sites 38101 and 38271		
Population	Telavancin Success N (%)	Vancomycin Success N (%)	Difference in Success Percents (telavancin – vancomycin) (95% CI)	Telavancin Success N (%)	Vancomycin Success N (%)	Difference in Success Percents (telavancin – vancomycin) (95% CI)
All-Treated	309/426 (72.5)	307/429 (71.6)	1.0 (-5.0, 7.0)	140/195 (71.8)	140/199 (70.4)	1.4 (-7.5, 10.4)
Clinically Evaluable	289/343 (84.3)	288/348 (82.8)	1.5 (-4.0, 7.0)	124/150 (82.7)	126/150 (84.0)	-1.3 (-9.8, 7.1)

The point estimates for each treatment group (i.e., telavancin, vancomycin) and between the treatment differences in the original analysis and the analysis excluding the two sites are similar. The width of the 95% CI is wider due to the smaller sample size with the sites excluded. The lower bound of the 95% CI is still greater than -10% in both analyses, satisfying the predefined non-inferiority margin. Therefore, including these two centers in the analysis did not alter the overall results.

The results of the analyses for one of the major secondary endpoints, clinical response in the MAT and ME populations (ie., patients who had an identified pathogen at baseline), for the FDA and Applicant analysis populations are shown in Table 29 below.

Table 29: Clinical Response (Cure) Rate at TOC in MAT and ME Populations: Applicant and FDA Secondary Endpoint Analyses

	Applicant Assessment[1]			FDA Assessment		
	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
Population	n/N %	n/N %	% (95% CI)	n/N %	n/N %	% (95% CI)
MAT						
Study 0017	235/307 (76.5)	241/322 (74.8)	1.7 (-5.0, 8.4)	196/260 (75.4)	204/274 (74.5)	0.9 (-6.4, 8.3)
Study 0018	284/373 (76.1)	282/381 (74.0)	2.1 (-4.0, 8.3)	225/303 (74.3)	239/322 (74.2)	0 (-6.8, 6.9)
0017 + 0018 Combined				421/563 (74.8)	443/596 (74.3)	0.4 (-4.6, 5.5)
ME						
Study 0017	210/237 (88.6)	220/255 (86.3)	2.3 (-3.5, 8.2)	187/219 (85.4)	196/234 (83.8)	1.6 (-5, 8.3)
Study 0018	260/290 (89.7)	250/281 (89.0)	0.7 (-4.4, 5.8)	201/240 (83.8)	208/239 (87)	-3.3 (-9.6, 6.3)
0017 + 0018 Combined				388/459 (84.5)	404/473 (85.4)	-0.9 (-5.5, 3.7)

[1] Study 0017: Clinical Study Report 0017, Table 8-27, pg 164, for Study 0018: Clinical Study Report 0018, Supporting Table 38, pg 260.

MO Comment: As for the AT and CE populations, both the FDA and Applicant analyses for Studies 0017 and 0018 MAT and ME populations demonstrate the clinical non-inferiority of telavancin compared to vancomycin using the prespecified non-inferiority margin of 10%. Lower response rates are seen in the FDA analyses for both the MAT and ME populations relative to the Applicant's. The results for the pooled analyses of the difference in clinical response rates in the FDA MAT and ME populations are shown above. The Applicant did not include this particular analysis in the ISE, but instead included the microbiological response in the MAT and ME populations. FDA did not use the microbiological response for this population, since the majority of microbiological responses are extrapolated from clinical responses and there is a high likelihood that cultures of residual skin lesions could be colonized and not truly infected.

Secondary Pooling of Results for Studies 0017 and 0018 to Test for Superiority of Telavancin Compared to Vancomycin for Treatment of cSSSI in Patients with Infection Caused by MRSA

If telavancin was non-inferior to vancomycin in the treatment of patients with cSSSI in both clinical studies, the Applicant proposed pooling the results of the studies to test for superiority of telavancin compared to vancomycin in the treatment of patients with cSSSI caused by MRSA. The FDA informed the Applicant that the AT population should be used for analysis for superiority. (See the Statistical Review and Evalaution by Scott Komo, Dr.P.H. for more complete discussion of the statistical analysis for superiority.)

Table 30 below shows the results of the FDA and Applicant analyses of clinical response rates for patients in the AT population who had MRSA isolated from baseline cultures.

Table 30: Clinical Response Rates for the AT Population with MRSA Isolated

	Applicant Assessment[1]			FDA Assessment		
	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
Population	n/N %	n/N %	% (95% CI)	n/N %	n/N %	% (95% CI)
MRSA						
Study 0017	104/146 (71.2)	122/167 (73.1)	-1.8 (-11.8, 8.1)	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	161/204 (78.9)	155/202 (76.7)	2.2 (-5.9, 10.3)	136/170 (80)	133/175 (76)	4 (-4.7, 12.7)
Pooled 0017 + 0018	262/350 (75.7)	277/369 (75.1)	0.4 (-5.9, 6.8) p-value 0.889	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.
[1] ISE, Table 5-34, pg 176.

MO Comment: Both the FDA and Applicant analyses failed to demonstrate the superiority of telavancin to vancomycin at TOC in patients with cSSSI caused by MRSA.

The Applicant was also advised by the FDA that if superiority of telavancin was demonstrated, it would also be necessary to demonstrate that the potential advantages in patients with MRSA did not cause disadvantages in patients without MRSA (MRSA Complement). Table 31 below shows the response rates in both the FDA and Applicant analyses for the AT population of patients who did not have MRSA isolated from baseline cultures.

Table 31: Clinical Response Rates for the AT Population MRSA Complement

	Applicant Assessment[1]			FDA Assessment		
	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
Population	n/N %	n/N %	% (95% CI)	n/N %	n/N %	% (95% CI)
MRSA Complement						
Study 0017	219/280 (78.2)	199/262 (76)	2.3 (-4.8, 9.3)	217/291 (74.6)	212/302 (70.2)	3.7 (-3.6, 11)
Study 0018	226/298 (75.8)	221/308 (71.8)	4.1 (-2.9, 11.1)	197/278 (70.9)	227/314 (72.3)	-2.1 (-9.2, 5.1)
Pooled 0017 + 0018	445/578 (77)	420/570 (73.7)	3.2 (-1.8, 8.2)	429/593 (72.3)	424/592 (71.6)	0.7 (-4.4, 5.8)

Difference and 95% CI are computed using a stratified analysis by study.
[1] ISE, Table 5-35, pg 179.

MO Comment: The results of the analysis shown above demonstrate that the 0017 and 0018 pooled AT population of patients who did not have MRSA isolated at baseline were not disadvantaged, however the analysis is not essential since superiority was not demonstrated.

Clinical Efficacy Results by Subgroup

The effect of subgroup variables such as baseline demographic factors, comorbid medical conditions, and infection type on clinical response at TOC was analyzed for the pooled (Study 0017 and0018) FDA-adjudicated CE population. Table 32 below shows the subgroup analysis for effects related to age, gender, and race.

Table 32: Clinical Response Rates in Demographic Subgroups - CE Population (Age, Gender, Race)

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

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

MO Comment: The clinical response rates differed depending on the age of the patient, with response rates significantly decreasing for those ≥ 65 yrs. The decrease in clinical response rate was also much larger for telavancin (91% in those < 65 compared to 78% in those ≥ 65 years) than for vancomycin (88% in those < 65 compared to 84% in those ≥ 65 yrs). The decrease in clinical response rates related to age is not unexpected due to the increased likelihood of comorbid conditions associated with age. The clinical response rates were similar for males and females. The clinical response rates were also similar across racial groups.

Table 33 shows the effect of region (US/non-US), history of diabetes, baseline renal function (calculated CLcr), and cSSSI type.

Table 33: Clinical Response Rates in Subgroups - CE Population

	Telavancin % (n/N)	Vancomycin % (n/N)	Difference (TLV-Comparator) (95% CI)[1]	p-value[2]
US/Non-US				
• US	398/477 (83.4)	405/489 (82.8)	0.6 (-4.1, 5.3)	0.32
• Non-US	197/231 (85.3)	201/222 (90.5)	-5.3 (-11.3, 0.7)	
History of Diabetes				
• Diabetes	131/171 (76.6)	146/183 (79.8)	-3.3 (-11.9, 5.3)	0.08
• No diabetes	463/536 (86.4)	460/528 (87.1)	-0.7 (-4.8, 3.3)	
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)	
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 except for the US/ex-US analysis where region was excluded from the model because it is collinear to the subgroup variable and similarly diabetes was excluded when history of diabetes was in the model.

MO Comment: The clinical response rates were similar across geographic region (US/non-US). Response rates were lower in patients with a history of diabetes. Clinical response rates did not differ significantly across cSSSI type, although some of the groups (i.e., infected ulcer and infected burn) are small.

There was a significant difference (decrease) in clinical response rates between patients with renal impairment treated with telavancin compared to those treated with vancomycin. Patients with progressive degrees of renal impairment have a greater decline in clinical response rate when treated with telavancin. This decline in clinical response rate seen with telavacin treatment in patients with progressive levels of renal impairment is of some concern, since patients with compromised renal function (i.e., ESRD on hemodialysis) are at increased risk for infection with MRSA. It is not clear whether the decrease in apparent response rates may be related to failure to adjust (increase) the telavancin dose in response to improving renal function that may accompany treatment of an acute illness (i.e. infection).

6.1.5 Clinical Microbiology

Table 34 shows the baseline microbiological characteristics of the MAT population for patients in Study 0017 and Study 0018.

Table 34: Baseline Microbiological Characteristics of the MAT population

	Study 0017[1]		Study 0018[2]	
Baseline Characteristics	Telavancin N=260	Vancomycin N=274	Telavancin N=303	Vancomycin N=322
Baseline Pathogen				
• Gram positive pathogens only	224 (86)	248 (91)	260 (86)	280 (87)
• Mixed Gram positive and Gram negative	30 (12)	25 (9)	37 (12)	38 (12)
Gram positive bacteremia	18 (7)	7 (3)	13 (4)	11 (3)
Presence or Absence of PVL in SA BL				
• Staph aureus (all)				
○ PVL +	N=230	N=240	N=262	N=285
○ PVL –	143 (62)	163 (68)	173 (66)	188 (66)
• MRSA	87 (38)	77 (32)	89 (34)	97 (34)
○ PVL +	N=135	N=151	N=171	N=175
○ PVL -	112 (83)	132 (87)	143 (84)	153 (87)
• MSSA	23 (17)	19 (13)	28 (16)	22 (13)
○ PVL +	N=95	N=89	N=91	N=110
○ PVL -	31 (33)	31 (35)	30 (33)	35 (32)
	64 (67)	58 (65)	61 (67)	75 (68)

[1] From FDA Baseline Analysis
[2] From FDA Baseline Analysis (minus site #38091).

MO Comment: Across the 2 studies, approximately 86% of the patients in the telavancin treatment groups and 89% of the patients in the vancomycin treatment groups had only Gram positive pathogens isolated from the primary cSSSI site.

The number of patients with Gram positive bacteremia across the studies was rare, with the highest rate of bacteremia (7%) occurring in the Study 0017 telavancin treatment group. Among patients treated with telavancin, there were 14 patients with MRSA, 9 patients with MSSA, 3 patients with Strep agalactiae, and 2 patients with Strep pyogenes bacteremia. Among patients treated with vancomycin, there were 4 patients with MRSA, 6 patients with MSSA, 1 patient with Strep agalactiae, and 3 patients with Strep pyogenes bacteremia.

Staphylococcus aureus *was the most common pathogen isolated, with approximately two-thirds of those isolates being MRSA. The MRSA isolates were PVL positive in 85-86%, while MSSA isolates were PVL positive in 33%.*

Microbiological Efficacy Results By Subgroup (By Pathogen)

In addition to the clinical response rates reported by patient in the microbiological populations, clinical response rates by pathogen present at baseline were assessed for both Study 0017 and Study 0018. Table 35 shows the clinical response rates for the MAT population and Table 36 shows the rates for the ME population in Study 0017. [Note: #s in purple are off by 1 – stats trying to isolate – problem appears to be related to patients having more than 1 baseline culture with MRSA]

Table 35: Clinical Response at TOC in the MAT Population (0017)

Pathogen	Applicant Assessment[1]		FDA Assessment	
	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	104/146 (71.2)	122/167 (73.1)	92/135 (68.2)	110/151 (72.9)
Staphylococcus aureus, MSSA	84/104 (80.8)	79/106 (74.5)	77/96 (80.2)	67/89 (75.3)
Enterococcus faecalis	15/16 (93.8)	12/18 (66.7)	14/15 (93.3)	12/17 (70.6)
Streptococcus pyogenes	11/13 (84.6)	12/14 (85.7)	9/10 (90)	9/11 (81.8)
Streptococcus agalactiae	9/12 (75)	4/7 (57.1)	8/10 (80)	4/6 (66.7)
Streptococcus anginosus	6/7 (85.7)	3/3 (100)	6/7 (85.7)	3/3 (100)
Streptococcus constellatus	0/2	2/3 (66.7)	0/1 (0)	2/2 (100)
Streptococcus intermedius	2/2 (100)	0/1	2/2 (100)	0/1

[1] CSR 0017, Supporting Table 41, pg 237.

Table 36: Clinical Response at TOC in the ME Population (0017)

Pathogen	Applicant Assessment[1]		FDA Assessment	
	TLV	VANC	TLV	VANC
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)
Streptococcus constellatus	0/2 (0)	2/3 (66.7)	0/1 (0)	2/2 (100)
Streptococcus intermedius	2/2 (100)	0/0 (0)	2/2 (100)	0/0 (0)

[1] CSR 0017, Table 8-28, pg 187.

MO Comment: As noted previously in the Microbiological Outcome Assessment discussion, microbiological endpoints can be based on results of follow-up cultures if clinically significant signs of a skin infection are noted or can be "presumed" based on clinical response observed. Since the majority of patients had clinical response rates of "Cured" and the likelihood of identifying colonizing organisms is high in patients with healing wounds, the clinical response rates are being reported for assessment of microbiological outcome.

Staphylococcus aureus *was the most common pathogen isolated. The FDA assessment of the clinical response rate in the ME population for patients with MRSA infection is 84.9% for the vancomycin treatment group compared to 82.6% for the telavancin treatment group; the Applicant's assessment for patients with MRSA infection shows a slightly higher clinical response rate for telavanicn at 87.1% compared to 85.5% for vancomycin in the same population. The clinical response rates for the MAT population with MRSA-related infection appear to be slightly higher for vancomycin compared to telavancin in both the FDA and Applicant analysis. The difference between FDA and Applicant assessment in the ME population for MRSA may reflect exclusion of patients with local only microbiologic culture results from the FDA-ME population and addition of evaluable failures to this same population in patients receiving concomitant nonstudy antibiotics for the cSSSI. This does not explain the higher response rate for telavancin relative to vancomycin for MRSA in the Applicant's ME population compared to the lower response rate seen in the Applicant's MAT population for MRSA.*

Response rates for MSSA appear similar and are slightly higher for telavancin compared to vancomycin in both the FDA and Applicant analyses. Response rates for other Gram positive organisms are difficult to interpret due to the small number of isolates.

Similarly, clinical response rates by pathogen in the MAT and ME populations for Study 0018 are shown in Table 37 and 38, respectively.

Table 37: Clinical Response at TOC in the MAT Population (0018)

Pathogen	Applicant Assessment[1]		FDA Assessment	
	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	161/204 (78.9)	155/202 (76.7)	135/170 (79.4)	133/175 (76)
Staphylococcus aureus, MSSA	86/107 (80.4)	85/120 (70.8)	67/91 (73.6)	76/111 (68.5)
Enterococcus faecalis	13/17 (76.5)	19/25 (76)	12/15 (80)	18/25 (72)
Streptococcus pyogenes	10/15 (66.7)	13/20 (65)	7/12 (58.3)	13/19 (68.4)
Streptococcus agalactiae	8/11 (72.7)	14/16 (87.5)	7/11 (63.6)	13/15 (86.7)
Streptococcus anginosus	6/7 (85.7)	5/5 (100)	4/6 (66.7)	5/5 (100)
Streptococcus constellatus	4/5 (80)	4/5 (80)	4/6 (66.7)	4/5 (80)
Streptococcus intermedius	0/1	1/2 (50)	0/1 (0)	0/1 (0)

[1] CSR 0018, Supporting Table 41, pg 263-264.

Table 38: Clinical Response at TOC in the ME Population (0018)

Pathogen	Applicant Assessment[1]		FDA Assessment	
	TLV	VANC	TLV	VANC
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)
Streptococcus constellatus	4/4 (100)	3/3 (100)	2/3 (66.7)	2/2 (100)
Streptococcus intermedius	0/1 (0)	1/1 (100)	0/1 (0)	0/0 (0)

[1] CSR 0018, Table 8-28, pg 172-173.

MO Comment: As for Study 0017, Staph aureus *was the most common pathogen isolated. The FDA assessment of the clinical response rate in the ME population for patients with MRSA infection is 90.8% for the telavancin treatment group compared to 86.1% for the vancomycin treatment group; the Applicant's assessment for patients with MRSA infection also appears higher for telavanicn at 93.2% compared to 87.1% for vancomycin in the same population. Consistent results, although with lower cure rates overall, are seen in the MAT population for telavancin compared to vancomycin in patients with MRSA.*

Response rates for MSSA appear to be higher for the vancomycin treatment groups in both the FDA and Applicant analyses. The FDA response rate for telavancin versus MSSA is 77.5% compared to the Applicant's response rate of 87.9%. Response rates for other Gram positive organisms are difficult to interpret due to the small number of isolates, although response rates for telavancin versus Streppyogenes *and* Strep agalactiae *in the FDA analysis are lower.*

6.1.6 Efficacy Conclusions

- The results of two independent studies of identical design, Study 0017 and Study 0018, support the conclusion that telavancin demonstrates clinical non-inferiority to vancomycin using a prespecified non-inferiority margin of 10% for the co-primary analysis populations for efficacy. Superiority of telavancin to vancomycin in treatment of patients with cSSSI and in whom MRSA was isolated from baseline microbiological culture was not demonstrated in the prespecified pooled analysis of Study 0017 and 0018.
- The Applicant provided an adequate justification for use of the non-inferiority design and margin used in this study. Review of the justification will be in an Appendix to this review.
- Although the results of both FDA and Applicant analyses support the conclusion of non-inferiority, it is concerning that the point estimates for the clinical response rates for the FDA analyses for Study 0018 differ from those of the Applicant and from those of Study 0017. The FDA response rate for telavancin is considerably lower than that of the Applicant for clinical response in the CE population and the point estimate favors treatment with vancomycin.
- The apparent decrease in clinical response rates for patients with renal impairment treated with telavancin is not explained and may be of clinical concern.
- Investigator assessment of clinical outcome in patients who prematurely discontinued study medication and were subsequently treated with non-study antibiotics may have been inconsistent based on strict application of outcome definitions and assessment as "Not cured" or looser interpretation and assessment as "Indeterminate". These assessments impacted whether a patient was a CE failure or a nonevaluable cure. Investigator assessment may have been "Not Cured" if the definition was strictly interpreted and the patient would have been assessed as a clinically evaluable failure (if otherwise not excluded from the CE population).
- The FDA and Applicant differed in the adjudication of pathogen status for microbiological isolates and outcome assessment for patients undergoing significant wound care procedures after a minimum duration (96 hours) of study therapy.
- Blinding of the study may have been impacted by the observation of taste disturbance and foamy urine in recipients of telavancin.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All safety information available in the Applicant's database from September 21, 2006 for patients enrolled as of May 15, 2006 was included in the NDA submission. The safety database for telavancin at the time of NDA submission included information from:

- 11 clinical pharmacology studies
- 10 mg/kg telavancin dose studies including two Phase 3 cSSSI studies (0017 and 0018) and a Phase 2 SSSI study (202b) evaluating use of a 10 mg/kg dose of telavancin (primarily)
- 7.5 mg/kg telavancin dose studies including a Phase 2 SSSI study (202a) and additional subjects from the original protocol 202b, 0017, and 0018 studies in cSSSI evaluating use of a 7.5 mg/kg dose of telavancin
- Additional treatment-blinded safety information on approximately 208 additional patients exposed to telavancin in two ongoing Phase 3 studies in hospital-acquired pneumonia (HAP) and an ongoing Phase 2 study in uncomplicated *Staph aureus* bacteremia was also included
- A total of 1489 patients and subjects had been exposed to at least one dose of telavancin.

Table 39 below 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 39: Number of Subjects Evaluated for Safety – All Telavancin Studies

	Number of Subjects Exposed	
Study Group	**Telavancin**	**Comparator**
Cinical 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 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).

For the purpose of the safety review, adverse events are grouped according to the dose of telavancin used in a particular study (i.e. 7.5 mg/kg or 10 mg/kg) and also based on whether the study was used in the primary determination of efficacy for the indication studied. Therefore, event analyses are provided separately and combined for Studies 0017 and 0018 patients who were enrolled in the Post Amendment or 10 mg/kg Phase 3 studies. The many shared design elements of the Phase 2 and 3 cSSSI studies (i.e, randomized, investigator blinded, active control with the vast majority of patients receiving vancomycin as the comparator) with variation in dose of telavancin (either 7.5 mg/kg or 10 mg/kg) allowed some examination of telavancin dose-related effects on safety. For that reason, the patients from Phase 2 Study 202a and Original Protocol 202b, 0017, and 0018 (where the dose of telavancin used was 7.5 mg/kg) are 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 SA bacteremia). Additional information from the on-going treatment blinded HAP studies (0015and 0019) includes patients enrolled as of November 15, 2006, with a data cutoff of February 22, 2007. It is assumed that 50% of patients (388) enrolled were in the telavancin treatment arms. A Phase 1 Japanese PK study has enrolled 37 subjects, of whom it is assumed 67% (25) were randomized to and received telavancin treatment.

7.1.1 Deaths

The Applicant provided a listing and narratives for deaths that occurred in clinical studies 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. Additional deaths reported to the Applicant that

occurred outside the delineated reporting period were noted in text with a brief summary, but were not included in line-listings of death in the individual clinical study reports or ISS.

The ISS submitted with the NDA states that there were 98 deaths known to have occurred during the telavancin clinical development program.

- There were no deaths in the Phase 1 clinical pharmacology studies.
- There were 18 deaths reported in the SSSI studies (Phase 2 202a and 202b, Phase 3 0017 and 0018); 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.
- Eighty deaths blinded to treatment assignment were reported in the ongoing uncomplicated SA bacteremia trial (Phase 2 203a) and two HAP studies (Phase 3 0015 and 0019).

Four patients treated with telavancin experienced at least one possible/probable related AE with death as an outcome as assessed by the investigator compared to no patients treated with comparator (vancomycin).

Table 40 lists the 18 patients who died during the cSSSI studies, along with investigator and FDA assessment of relatedness of study medication to the AE causing death. In some instances, the assessment of relatedness was different for the investigator and FDA reviewer. The FDA reviewer's rationale is explained at the bottom of the table. FDA narratives of deaths can be found in Appendix A. A list of the 7 patients who died outside of the reporting period follows the table and brief narratives of those deaths can also be found in Appendix A.

Table 40: Deaths in the Telavancin Clinical Development Program

Drug /Dose Patient ID	Age (yrs)	Sex	Days of Treatment	Day Event Occurred	Day of Death	Adverse Event with Outcome of Death	Investigator Assessment of AE Relatedness to Study Medication	FDA Assessment of AE Relatedness to Study Medication
Telavancin 7.5 mg								
0017-02008-0120	82	F	10	8 8 10 10 11	16	Respiratory distress Pulmonary edema Renal insufficiency Respiratory failure Sepsis	Possibly / Probably Not related Possibly / Probably Possibly / Probably Not related	Possibly related
Telavancin 10 mg								
0017-02010-0546	65	M	2	3	3	Ventricular arrhythmia	Possibly / Probably	Possibly related
0017-04004-0677	49	F	4	- 8 (prior)	5	Systemic inflammatory response syndrome (SIRS)	Not related	Not related (unlikely) / SIRS preceded rx
0017-27010-0474	65	F	15	24	24	Cerebrovascular accident	Not related	Not related
0017-38001-0693	96	F	8	12	33	Ovarian cancer	Not related	Not related
0017-38002-0428	70	M	6		10	Renal insufficiency	Possibly / Probably	Possibly related / DNR, no HD
0018-01002-2474	75	F	6	7	7	Cardiac arrest (unwitnessed)	Possibly / Probably	Possibly related
0018-19006-2894	84	M	9	11	11	Cardio-respiratory arrest	Not related	**Possibly related**
0018-38160-2501	77	M	5	5	5	Acute respiratory failure Acute MI	Not related	**Possibly related**
Vancomycin								
0017-02001-0257	46	M	5	5	5	Pulmonary embolism	Not related	**Possibly / can't R/O (blinded)**
0017-38016-0824	49	F	2	2	2	Cardio-respiratory arrest Pulmonary embolism	Not related Not related	Not related
0017-38024-0695	53	M	14	17	17	Cardiac failure Respiratory failure	Not related Not related	Not related
0017-38271-0659	47	M	6	13 9 11	13	Cardio-respiratory arrest Coma hepatic Respiratory failure	Not related Not related Not related	Not related

Table 40 Deaths (con't)

Drug /Dose Patient ID	Age (yrs)	Sex	Days of Treatment	Day Event Occurred	Day of Death	Adverse Event with Outcome of Death	Investigator Assessment of AE Relatedness to Study Medication	FDA Assessment of AE Relatedness to Study Medication
0017-38271-1010	90	M	14	21	21	Respiratory distress	Not related	**Possibly related**
0018-22000-2742	55	M	2	2	3	Cardiac failure	Not related	**Possibly related**
0018-30907-2323	66	F	3	2	3	Cardiogenic shock Pulmonary edema Septic shock	Not related Not related Not related	Not related
0018-38260-2555	53	M	1	8	9	Cardiac arrest	Not related	Not related
Comparator 202b								
202b-00903-9037	41	F	6	6	11	Multi-organ failure Sepsis Hepatic failure Renal failure acute Respiratory failure	Not related Not related Not related Not related Not related	Not related

FDA Review Rationale

Telavancin

Patient 0018-19006-2894: The patient died 2 days after completing a course of study therapy from cardio-respiratory arrest. The patient had multiple comorbidities and was noted to have RBBB on ECG and elevated LFTs after completing study therapy. The exact reason for cardiac arrest is not apparent and LFT elevations were explained retrospectively. It is not possible to exclude a possible relationship to study medication in this case.

Patient 0018-38160-2501: The patient had multiple cardiac and pulmonary comorbidities that were the most likely factors leading to acute MI and respiratory failure, but the patient was on study therapy which can not be excluded as possibly related to the event.

Vancomycin

Patient 0017-02001-0257: The patient died on day 5 of study treatment due to a saddle pulmonary embolus (by autopsy); in a blinded trial, role of study medication cannot be ruled out.

Patient 0017-38271-1010: The patient died as a result of progressive respiratory failure and an episode of ventricular tachycardia. Although the investigator attributed the patient's respiratory failure to aspiration pneumonia, CHF, and/or worsening renal insufficiency, study medication may have contributed to the renal insufficiency and fluid overload.

Patient 0018-22000-2742: The patient died on day 3 of study treatment due to cardiac insufficiency and atrial fibrillation (and had developed anuria before death). It is not possible to exclude study medication in this instance since there is limited prior cardiac history.

In addition to the 18 deaths previously reported in the table, there were 5 deaths in telavancin patients [2 in Study 0017, 3 in Study 0018 (including 1 in the 7.5 mg/kg telavancin dose group original protocol and 2 in the 10 mg/kg telavancin dose group post-amendment)] and 2 deaths in vancomycin patients (Study 0017) that occurred outside of study death "reporting window". The following is a list with a brief narrative. More complete narratives can be found in Appendix A.
Telavancin

- 0017-18015-0802 (10 mg/kg): The cause of death 27 days after discontinuing study therapy was respiratory failure secondary to ventilator-associated pneumonia (VAP) and assessed by the investigator as unrelated to study medication. [Concur]
- 0017-38271-0517 (10 mg/kg): The patient developed respiratory distress and hypotension after 8 days of study therapy and was discontinued from therapy. The patient had a follow-up (TOC) assessment 8 days after discontinuation. Despite mechanical ventilation, the patient developed acute respiratory distress syndrome (ARDS) and multi-system organ failure (MSOF) and died 12 days after study therapy was discontinued The patient had underlying comorbidities (including hypertension, diabetes, congestive heart failure (CHF), and renal failure requiring hemodialysis) with telavancin appropriately adjusted (per CRF and 0017 study report narrative / ISS narrative says "inappropriate" dose). The investigator assessed the event of respiratory distress as unrelated to study medication, however it is not possible to exclude study medication as related to clinical decline (progressive respiratory failure). The event did occur outside the designated reporting period for study-related deaths (i.e. after the TOC assessment).
- 0018-33002-2409 (10 mg/kg): This patient had a baseline history of renal insufficiency, with noted increase in serum Cr (from 2.1 to 6.2 mg/dL). Seven days after discontinuation of study medication, serum Cr had decreased to 2.9 mg/dL. However, following the TOC visit, the patient had a brainstem infarction. The investigator assessed the event of brainstem infarction as unrelated to study medication. [Concur]
- 0018-38160-3068 (10 mg/kg): This patient had an underlying history of severe heart failure and chronic renal insufficiency. He received an inappropriate (high) dose of study medication based on baseline renal function. The patient's serum Cr rose from baseline of 4.1 mg/dL throughout study treatment to a maximum of 10.3 mg/dL one week after study medication discontinuation (TOC visit). The patient died seven days after the TOC visit from progressive renal failure and refusal of dialysis and was outside of the study death reporting period. The investigator assessed the event of acute renal failure as possibly/probably relating to study medication, although noting comorbidities. [Concur and although outside the reporting period (i.e. after TOC) it would be reasonable to include with study deaths due to the progressive rise in Cr through and after study]
- 0018-38160-2007 (original protocol, 7.5 mg/kg): The patient had a history of cirrhosis due to alcohol-related liver disease. Although the patient developed elevated serum Cr during the study (which showed signs of resolution after discontinuing study medication), the patient died over 2 months after discontinuing study medication from liver failure related to ongoing alcohol abuse. The investigator assessed the event of liver failure as unrelated to study medication. [Concur]

Vancomycin

- 0017-38111-0646 (vancomycin): The patient was discontinued from study therapy at D3 for QTc > 500 msec which was not confirmed by central ECG readings. The patient died from complications of HAP approximately 3 weeks after study medication discontinuation. The investigator assessed the event as unrelated to study medication. [Concur]
- 0017-38271-0856 (vancomycin): The patient died of unknown causes while on vacation approximately 1 month after completing a successful course of therapy for cellulitis. The death was assessed as being unrelated to study medication. [Concur]

MO Comment: Based on an unblinded FDA review of Applicant narratives (and secondary review of CRFs or datasets), 6/9 deaths that occurred in the telavancin treatment groups during clinical studies were considered to be possibly/probably related to study medication and 3/9 deaths were considered to be unrelated. FDA review of the 9 deaths that occurred in the vancomycin treatment groups indicates that 3/9 deaths were considered to be possibly/probably related to study treatment and unrelated in 6/9. [This is compared to investigator assessment in which 4/9 telavancin-treated patients who died had AEs assessed as possibly/probably related to study medication compared to 0/9 comparator-treated patients.]

FDA review of deaths that occurred outside of the Applicant reporting period indicated that 2/5 deaths in the telavancin-treated patients had possible/probable relationship to study medication compared to 0/2 deaths reported for patients treated with vancomycin.

The overall rate of death in both telavancin and comparator-treated patients was small and the patients who died had other comorbidities that may have been responsible or contributed to the outcome of death.

Ongoing Treatment Blinded Trials (NDA Submission)

As of the cutoff date for the NDA submission (database cutoff of September 21, 2006 includes data for patients enrolled prior to May 15, 2006) there had been 80 deaths known to have occurred in the ongoing, treatment assignment blinded studies.

Bacteremia:

- Five of 58 patients in the uncomplicated SA bacteremia study (Study 203 a) had died. Eleven AEs with death as an outcome were reported in the five patients who had died. The AE preferred terms were: neuroleptic malignant syndrome, schizoaffective disorder, intestinal ischemia, sepsis, bacterial endocarditis, renal failure acute, death, renal failure chronic, and pneumonia. Brief summaries for these deaths can be found in Appendix B. (Unblinded safety data has subsequently been submitted; see 4MSU discussion below)

HAP:

- Seventy five of 357 (21%) of patients in the HAP studies (Studies 0015 and 0019) have died; 44 deaths/213 enrolled (21%) occurred in Study 0015 and 31 deaths/144 enrolled (22%) occurred in Study 0019. This incidence is similar to that reported for similarly designed Phase 3 studies reported in the literature. A similar mortality rate has been observed in a study of linezolid versus vancomycin in the treatment of HAP; Rubenstein, et al reported a

mortality rate of 17.7% for linezolid and for vancomycin.[7] AEs resulting in death were reported most frequently in the Infections and Infestations System Organ Class [(SOC), 24 patients, 7%]. The next most frequently reported were in the Respiratory, Thoracic, and Mediastinal Disorders SOC and Cardiac Disorders SOC [22 (6%) and 18 (5%), respectively]. TEAEs resulting in death reported at an incidence greater than 1% include: septic shock (13 patients, 4%), multi-organ failure (10 patients, 3%), cardiac arrest (8 patients, 2%), respiratory failure (7 patients, 2%), sepsis (6 patients, 2%), respiratory failure (7 patients, 2%), sepsis (6 patients, 2%), cardio-respiratory arrest (5 patients 1%), and renal failure acute (4 patients, 1%).

- None of the deaths have been assessed as related to study drug administration by the investigator. Patients may have had multiple listed AEs associated with death. The primary area(s) of concern for study medication toxicity identified from completed (unblinded) Phase 2 and Phase 3 studies is the kidney, with other potential areas of concern being cardiovascular (related to potential for QT prolongation), hepatic (related to preclinical, animal study findings), and dermatologic (related to history of glycopeptide drug class) systems.
- The Applicant has identified patients in whom renal treatment-emergent AEs (TEAEs) had death as an outcome, as well as patients with AEs in other SOC in whom renal involvement was apparent from the narrative describing the event.
  - There were eight patients (8/357, 2.2%) with renal TEAEs with death as an outcome: renal failure acute (4; 0015-38049-4143, 0015-38049-4187, 0019-05003-6084, 0019-38069-6174), renal insufficiency (2; 0015-38148-4218, 0019-18004-6107), oliguria (1; 0015-38049-4192), and anuria (1; 0019-18005-6035). Brief summaries for these events with outcome of death can be found in Appendix B.
  - An additional twelve patients with a preferred term for a terminal event in a System Organ Class other than Renal Disorders, but in whom renal involvement was apparent in the narrative describing the event: multi-organ failure (2; 0015-01014-4081, 0015-01014-4082), sepsis or septic shock (4; 00155-38024-4268, 0015-30905-4234, 0015-12016-4158), respiratory distress (1; 0015-38271-4115), hypovolemic shock (1;0015-01014-4233), ventricular fibrillation, ventricular tachycardia (1; 0015-3801-4141), pneumonia aspiration (1; 0019-38106-6074), lung infection Pseudomonal (1; 0019-01019-6029), and pneumonia, COPD (1; 0019-02019-6007).
- Ten patients in Study 0015 have had 15 preferred term TEAEs with death as an outcome; the only event occurring in more than one patient is cardiac arrest in 8/213 patients (4%) and two patients with ventricular arrhythmias (one fibrillation and one tachycardia). Eight patients in Study 0019 have had 8 preferred term TEAEs with death as an outcome: the only event occurring in more than one patient is cardio-respiratory arrest in 5/144 patients (3%).
- There was one patient with hepatic failure associated with death as an outcome in Study 0019.

Additional information related to deaths reported for the ongoing telavancin clinical studies in the 4MSU can be found in Section 7.2.9.

7 Rubenstein E, et al. Linezolid (PNU-100766) versus Vancomycin in the Treatment of Hospitalized Patients with Nosocomial Pneumonia: A Randomized, Double-Blind, Multicenter Study. CID 2001;32:402-412.

7.1.2 Other Serious Adverse Events

At least one SAE was reported in 288 patients (93 telavancin, 60 vancomycin, 135 treatment blinded) during the telavancin clinical development program as of the time of NDA submission.

Clinical Pharmacology Studies

Two SAEs occurred in patients participating in the clinical pharmacology studies (0.7% of subjects); both occurred in telavancin-treated patients, with 1 SAE of abdominal pain and 1 SAE of gastric ulcer perforation. The events were considered to be unrelated to study medication. Brief narratives for these 2 events are as follows:

- **103A-00001-00025** (gastric ulcer perforation): The patient was a 52 yo male with ESRD who received 1 dose of telavancin (7.5 mg/kg) and was hospitalized 1 week after administration of telavancin for GI bleeding attributed to NSAID administration. The patient was discharged 5 days later with resolution of the bleeding.
- **104A-00001-00555** (abdominal pain): The patient was a 21 yo female in the 15 mg/kg treatment group who was hospitalized for severe abdominal pain and fever 16 days following completion of the study, with event subsequently determined to be related to a kidney infection.

SSSI Studies

In the Phase 2 and Phase 3 cSSSI studies, there were 121 SAEs that occurred in 91/1221 (7%) of telavancin-treated patients; 76 patients were enrolled in telavancin 10 mg/kg studies and 15 in telavancin 7.5 mg/kg studies. In the comparator treatment arm, there were 100 SAEs that occurred in 60/1222 (5%) patients; 45 patients enrolled in telavancin 10 mg/kg studies and 15 in telavancin 7.5 mg/kg studies.

Table 41 lists the SAEs that occurred in the Phase 3 Studies 0017 and 0018 (telavancin 10 mg/kg) dose studies singly and combine

Table 41: SAEs in cSSSI (Phase 3 Studies 0017 and 0018: Telavancin 10 mg/kg versus Comparator)

	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
Any serious event: # patients (%)	**31 (7)**	**27 (6)**	**38 (8)**	**15 (3)**	**69 (7)**	**42 (4)**
Blood and Lymphatic System						
Any serious event	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Anemia	0	0	3 (<1)	0	3 (<1)	0
Leukopenia	0	1 (<1)	0	0	0	1 (<1)
Thrombocytopenia	0	1 (<1)	0	0	0	1 (<1)
Cardiac Disorders						
Any serious event	6 (1)	6 (1)	4 (<1)	5 (<1)	10 (1)	11 (1)
Acute myocardial infarction	0	0	0	1 (<1)	0	1 (<1)
Angina pectoris	1 (<1)	0	0	0	1 (<1)	0
Atrial fibrillation	0	2 (<1)	0	1 (<1)	0	3 (<1)
Bradycardia	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Cardiac arrest	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Cardiac failure	0	1 (<1)	0	1 (<1)	0	2 (<1)
Cardiac failure congestive	0	1 (<1)	0	0	0	1 (<1)
Cardio-respiratory arrest	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Cardiogenic shock	0	0	0	1 (<1)	0	1 (<1)
Myocardial infarction	2 (<1)	0	2 (<1)	1 (<1)	4 (<1)	1 (<1)
Myocardial ischemia	1 (<1)	0	0	0	1 (<1)	0
Ventricular arrhythmia	1 (<1)	0	0	0	1 (<1)	0
Gastrointestinal Disorders						
Any serious event	0	3 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (<1)
Abdominal pain	0	2 (<1)	0	0	0	2 (<1)
Ascites	0	0	0	1 (<1)	0	1 (<1)
Diarrhea	0	0	1 (<1)	0	1 (<1)	0
Upper gastrointestinal hemorrhage	0	1 (<1)	0	0	0	1 (<1)
General Disorders and Administration Site						
Any serious event	3 (<1)	2 (<1)	1 (<1)	2 (<1)	4 (<1)	4 (<1)
Chest discomfort	1 (<1)	0	0	0	1 (<1)	0
Infusion site reaction	0	0	0	1 (<1)	0	1 (<1)
Injection site cellulitis	1 (<1)	0	0	0	1 (<1)	0
Malaise	0	0	1 (<1)	0	1 (<1)	0
Non-cardiac chest pain	0	1 (<1)	0	0	0	1 (<1)
Pyrexia	0	1 (<1)	0	1 (<1)	0	2 (<1)
Rigors	0	0	0	1 (<1)	0	1 (<1)
Systemic inflammatory response syndrome	1 (<1)	0	0	0	1 (<1)	0
Hepatobiliary Disorders						
Any serious event	0	0	2 (<1)	0	2 (<1)	0
Cholecystitis	0	0	1 (<1)	0	1 (<1)	0
Hepatic cirrhosis	0	0	1 (<1)	0	1 (<1)	0
Immune System Disorders						
Any serious event	1 (<1)	2 (<1)	4 (<1)	1 (<1)	5 (<1)	3 (<1)
Anaphylactic reaction	0	0	1 (<1)	0	1 (<1)	0
Drug hypersensitivity	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)	2 (<1)
Hypersensitivity	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Infections and Infestations						
Any serious event	1 (<1)	5 (1)	6 (1)	3 (<1)	7 (<1)	8 (<1)
Abscess soft tissue	0	0	1 (<1)	0	1 (<1)	0
Bacteremia	0	1 (<1)	0	0	0	1 (<1)
Bronchitis	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	0	1 (<1)	0	0	0	1 (<1)
Gastroenteritis	0	1 (<1)	0	0	0	1 (<1)
Gastrointestinal infection	0	0	0	1 (<1)	0	1 (<1)
Osteomyelitis	1 (<1)	0	1 (<1)	0	2 (<1)	0
Pelvic infection	0	1 (<1)	0	0	0	1 (<1)
Pneumonia	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)
Sepsis	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Septic shock	0	0	0	1 (<1)	0	1 (<1)

Table 41 SAEs (con't)	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
Infections and Infestations (con't)						
Urinary tract infection	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Injury, Poisoning and Procedural Complications						
Any serious event	1 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (<1)
Ankle fracture	1 (<1)	0	0	0	1 (<1)	0
Hip fracture	0	0	0	1 (<1)	0	1 (<1)
Non-accidental overdose	0	0	1 (<1)	0	1 (<1)	0
Post-procedural hemorrhage	0	1 (<1)	0	0	0	1 (<1)
Procedural hypotension	0	1 (<1)	0	0	0	1 (<1)
Soft tissue injury	0	0	0	1 (<1)	0	1 (<1)
Investigations						
Any serious event	1 (<1)	2 (<1)	3 (<1)	1 (<1)	4 (<1)	3 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	1 (<1)
Blood creatinine increased	0	2 (<1)	3 (<1)	0	3 (<1)	2 (<1)
Blood urea increased	0	0	2 (<1)	0	2 (<1)	0
International normalized ratio increased	1 (<1)	0	0	0	1 (<1)	0
White blood cell count increased	0	1 (<1)	0	0	0	1 (<1)
Metabolism and Nutrition Disorders						
Any serious event	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Dehydration	0	0	2 (<1)	0	2 (<1)	0
Hyperglycemia	0	1 (<1)	0	0	0	1 (<1)
Hypoglycemia	0	0	1 (<1)	0	1 (<1)	0
Musculoskeletal and Connective Tissue Disorders						
Any serious event	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Intervertebral discitis	0	0	1 (<1)	0	1 (<1)	0
Pain in extremity	0	0	0	1 (<1)	0	1 (<1)
Neoplasms benign, malignant, and unspecified						
Any serious event	1 (<1)	0	0	0	1 (<1)	0
Overian cancer	1 (<1)	0	0	0	1 (<1)	0
Nervous system Disorders						
Any serious event	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
Brain stem infarction	0	0	1 (<1)	0	1 (<1)	0
Cerebrovascular accident	1 (<1)	0	0	0	1 (<1)	0
Coma hepatic	0	1 (<1)	0	0	0	1 (<1)
Psychiatric Disorders						
Any serious event	2 (<1)	0	2 (<1)	0	4 (<1)	0
Mental status changes	1 (<1)	0	2 (<1)	0	3 (<1)	0
Schizophrenia, paranoid type	1 (<1)	0	0	0	1 (<1)	0
Renal and Urinary Disorders						
Any serious event	5 (1)	1 (<1)	6 (1)	1 (<1)	11 (1)	2 (<1)
Calculus bladder	1 (<1)	0	0	0	1 (<1)	0
Nephrolithiasis	0	0	1 (<1)	0	1 (<1)	0
Renal failure acute	1 (<1)	0	3 (<1)	0	4 (<1)	0
Renal failure chronic	0	0	0	1 (<1)	0	1 (<1)
Renal impairment	2 (<1)	0	0	0	2 (<1)	0
Renal insufficiency	1 (<1)	0	2 (<1)	0	3 (<1)	0
Renal vessel disorder	0	1 (<1)	0	0	0	1 (<1)
Reproductive System and Breast Disorders						
Any serious event	0	1 (<1)	0	0	0	1 (<1)
Ovarian cyst	0	1 (<1)	0	0	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders						
Any serious event	7 (2)	8 (2)	4 (<1)	1 (<1)	11 (1)	9 (<1)
Acute respiratory failure	0	0	2 (<1)	0	2 (<1)	0
Alveolitis allergic	0	0	1 (<1)	0	1 (<1)	0
Chronic obstructive airways disease exac	1 (<1)	0	0	0	1 (<1)	0

Table 41 SAEs (con't)	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
Respiratory, Thoracic and Mediastinal Disorders (con't)						
Dyspnea	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Lung infiltration	0	0	0	0	0	1 (<1)
Pulmonary congestion	1 (<1)	0	0	0	1 (<1)	0
Pulmonary embolism	2 (<1)	2 (<1)	0	0	2 (<1)	2 (<1)
Pulmonary edema	0	0	0	1 (<1)	0	1 (<1)
Respiratory distress	2 (<1)	2 (<1)	0	0	2 (<1)	2 (<1)
Respiratory failure	1 (<1)	3 (<1)	0	0	1 (<1)	3 (<1)
Skin and Subcutaneous Tissue Disorders						
Any serious event	1 (<1)	0	2 (<1)	0	3 (<1)	0
Erythema multiforme	0	0	1 (<1)	0	1 (<1)	0
Rash	1 (<1)	0	1 (<1)	0	2 (<1)	0
Vascular Disorders						
Any serious event	5 (1)	1 (<1)	4 (<1)	1 (<1)	9 (<1)	2 (<1)
Deep vein thrombosis	2 (<1)	0	0	0	2 (<1)	0
Gangrene	0	0	1 (<1)	0	1 (<1)	0
Hypotension	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
Orthostatic hypotension	0	0	1 (<1)	0	1 (<1)	0
Peripheral ischemia	0	0	0	1 (<1)	0	1 (<1)
Peripheral occlusive disease	1 (<1)	0	1 (<1)	0	2 (<1)	0
Varicose vein ruptured	1 (<1)	0	0	0	1 (<1)	0
From ISS, Supporting Table 64, pgs 95-104.						

MO Comment: For the Phase 3 cSSSI, renal failure acute was the most frequently reported individual SAE in patients treated with telavancin 10 mg/kg and was reported in four patients (0.5%) compared to no patients in the comparator treatment group (vancomycin). Respiratory failure was the most frequently reported individual SAE in the comparator treatment group, occurring in three patients (0.3%) compared to one patient (0.1%) in the telavancin 10 mg/kg dose group.

The following table, Table 42, shows the most frequently reported SAEs by SOC for patients in all telavancin 7.5 mg/kg studies compared to all telavancin 10 mg/kg studies as well as for all cSSSI efficacy and safety studies for telavancin.

Table 42: SAEs in cSSSI (Telavancin 7.5 mg/kg and 10 mg/kg Studies and Total)

	Study 202a + Original Protocol 202b + 0017 + 0018		Post Amendment 202b + 0017 + 0018		ALL Telavancin SSSI Studies	
MedDRA SOC	TLV 7.5 N=192	Vanc[1] N=189	TLV 10 N=1029	Vanc[1] N=1033	TLV N=1221	Vanc[1] N=1222
Any serious event (# patients, %)	**15 (8)**	**15 (8)**	**76 (7)**	**45 (4)**	**91 (7)**	**60 (5)**
Blood and Lymphatic System	2 (1)	0	4 (<1)	1 (<1)	6 (<1)	1 (<1)
Cardiac Disorders	2 (1)	1 (<1)	11 (1)	11 (1)	13 (1)	12 (<1)
Gastrointestinal Disorders	0	0	2 (<1)	4 (<1)	2 (<1)	4 (<1)
General Disorders and Administration Site	1 (<1)	0	4 (<1)	5 (<1)	5 (<1)	5 (<1)
Hepatobiliary Disorders	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Immune System Disorders	0	0	5 (<1)	3 (<1)	5 (<1)	3 (<1)
Infections and Infestations	4 (2)	7 (4)	10 (<1)	10 (<1)	14 (1)	17 (1)
Injury, Poisoning and Procedural Complications	0	2 (1)	2 (<1)	4 (<1)	2 (<1)	6 (<1)
Investigations	1 (<1)	0	4(<1)	3 (<1)	5 (<1)	3 (<1)
Metabolism and Nutrition Disorders	0	0	3 (<1)	1 (<1)	3 (<1)	1 (<1)
Musculoskeletal and Connective Tissue Disorders	0	2 (1)	2 (<1)	1 (<1)	2 (<1)	3 (<1)
Neoplasms benign, malignant, and unspecified	1 (<1)	0	1 (<1)	0	2 (<1)	0
Nervous System Disorders	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Psychiatric Disorders	1 (<1)	2 (1)	5 (<1)	0	6 (<1)	2 (<1)
Renal and Urinary Disorders	3 (2)	0	12 (1)	3 (<1)	15 (1)	3 (<1)
Reproductive System and Breast Disorders	0	1 (<1)	0	1 (<1)	0	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders	3 (2)	1 (<1)	11 (1)	11 (1)	14 (1)	12 (<1)
Skin and Subcutaneous Tissue Disorders	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Surgical and Medical Procedures	0	0	1 (<1)	0	1 (<1)	0
Vascular Disorders	1 (<1)	2 (1)	10 (<1)	2 (<1)	11 (<1)	4 (<1)

From ISS, Table 5-9, pgs.159-168.
[1] Includes 27 patients (20 in 202a and 7 in 202b Post-Amendment 1 who received an antistaphylococcal penicillin instead of vancomycin.

The Applicant concluded that based on the overall number of SAEs in the cSSSI studies (i.e., all telavancin studies), a dose response effect between the 7.5 mg/kg and 10 mg/kg dose was not suggested.

MO Comment: The number of patients participating in the 7.5 mg/kg telavancin studies is much smaller (< 20%) than that of the 10 mg/kg studies and therefore any observations made on number of events must be interpreted cautiously. The number (percent) of patients with SAEs was similar for the patients in the telavancin 7.5 mg/kg and telavancin 10 mg/kg studies. However, the rate of SAEs observed was higher in telavancin 10 mg/kg studies relative to comparator [rates of 76/1029 (7%) and 45/1033 (4%), respectively] than in the telavancin 7.5 mg/kg studies relative to comparator [rates of 15/192 (8%) and 15/189 (8%), respectively]. The

number of adverse events occurring in each SOC is small and AEs occur in ≤1% of patients in a given SOC.

In the telavancin treatment groups (7.5 mg/kg and 10 mg/kg studies combined), all individual (preferred term) SAEs occurred at an incidence of <1%. Anemia, acute renal failure, and renal insufficiency were reported in 5 patients each, and myocardial infarction and blood creatinine increased in 4 patients each (2 of the "blood creatinine increased" patients overlap with 2 in the "renal insufficiency" coded term). In patients treated with comparator in the cSSSI studies (vancomycin for 1195 patients and antistaphylococcal penicillin in 27 patients) the most common SAEs were respiratory failure and cellulitis in 4 patients each, and atrial fibrillation, pneumonia, and pulmonary embolism in 3 patients each.

Based on FDA review of the ISS data set for AEs, twenty seven (ISS report: 26) of the patients in the telavancin-treated group (2.1%; 3 in telavancin 7.5 mg/kg and 24 in telavancin 10 mg/kg) and fourteen (ISS Report: 13) patients in the vancomycin-treated group (1.1%; 2 in telavancin 7.5 mg/kg and 12 in telavancin 10 mg/kg studies) had SAEs that were assessed by the investigator as associated with study medication. SAEs assessed by the investigator as possibly/probably related to study medication and occurring in more than one patient included: renal insufficiency (5 patients), blood creatinine increased (4 patients / 2 overlap with renal insufficiency), renal failure acute (3 patients), blood urea increased (3 patients), and drug hypersensitivity (3 patients). SAEs that occurred in more than one vancomycin-treated patient and assessed as possibly/probably related to study drug administration included: blood creatinine increased (2 patients), drug hypersensitivity (2 patients), and atrial fibrillation (2 patients).

Renal SAEs

Based on the number of renal SAEs reported and imbalance in investigator assessment of possible relatedness for telavancin versus vancomycin, these patients are described below, along with FDA aasessment of relatedness of event to study medication. There were 19 patients identified in the Renal and Urinary Disorders and Investigations System Organ Classes with reported SAEs indicating evidence of renal impairment; the preferred terms include renal tubular necrosis, renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and increased blood creatinine. Fifteen of the patients were treated with telavancin and four with vancomycin. Table 43 lists those patients who had renal SAEs and provides information regarding confounding factors and course of abnormalities, along with assessment of relationship to study medication by the investigator and FDA Medical Reviewer.

Table 43: Renal SAEs (Telavancin cSSSI Studies)

Patient ID	Age / Gender	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	High Cr	Last Cr	Investigator Relatedness	FDA Relatedness
Telavancin 7.5 mg										
0017-02008-0120	82 / F	Yes	Yes	Renal insufficiency (death)	Yes	1.0 mg/dL	3.2 mg/dL	3.2 mg/dL	Yes	Yes
0018-38160-2007	51 / M	No	Yes	ATN (resolution)	Yes	0.7 mg/dL	3.4 mg/dL	1.9 Mg/dL	No	Yes
202b-00101-7008	76 / F	Yes	Yes	Acute renal insufficiency Prerenal azotemia Elevated BUN Elevated Cr	Yes	0.9 mg/dL	3.4 mg/dL	1.2 mg/dL	Yes	Yes
Telavancin 10 mg										
0017-38117-0240	51 / F	Yes	Yes	Acute renal failure	Yes	1.0 mg/dL	3.1 mg/dL	1.1 mg/dL	No	Yes
0017-38271-0953	93 / M	Yes	Yes	Renal impairment (worsening of)	Yes	1.4 mg/dL	2.3 mg/dL	1.8 mg/dL	No	Yes
0017-38002-0428	70 / M	Yes	Yes	Renal insufficiency (death – refused dialysis)	Yes	1.0 mg/dL	2.7 mg/dL	N/A	Yes	Yes
0017-18001-0721	46 / M	Yes	Yes	Renal impairment (hemodialysis initiated)	Increasing prior to study	5.5 mg/dL	10.8 mg/dL	7.3 mg/dL	Yes	Yes
0018-06003-2353	84 /F	Yes	Yes	Acute renal failure	Yes	1.7 mg/dL	3.0 mg/dL	1.2 mg/dL	No (changed)	Yes
0018-06003-2721	56 / F	Yes	Yes	Acute renal failure	?*	0.9 mg/dL	1.7 mg/dL	0.7 mg/dL	Yes	Yes
0018-38160-3068	95 / M	Yes	Yes	Acute renal failure (death – refused dialysis)	Yes	4.1 mg/dL	10.3 mg/dL	N/A	Yes	Yes
0018-38148-2498	47 / F	Yes	Yes	Elevated blood creatinine Elevated blood urea	Yes	0.7 mg/dL	2.7 mg/dL	1.5 mg/dL	Yes	Yes
0018-38260-2099	50 / F	Yes	Yes	Renal insufficiency (interstitial nephritis)	Yes	0.9 mg/dL	6.0 mg/dL	2.0 mg/dL	Yes	Yes
0018-38148-2359	57 / F	Yes	Yes	Elevated creatinine	Yes	0.9 mg/dL	2.1 mg/dL	1.0 mg/dL	Yes	Yes
0018-38322-2757	66 / F	Yes	Yes	Acute renal failure	Yes	0.6 mg/dL	3.7 mg/dL	0.9 mg/dL	Yes	Yes

Patient ID	Age / Gender	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	High Cr	Last Cr	Investigator Relatedness	FDA Relatedness
Telavancin 10 mg (Continued)										
202b-00910-9058	28 / M	No	Yes	Acute renal failure	Yes	1.0 mg/dL	3.5 mg/dL	1.1 mg/dL	Yes	Yes
Vancomycin										
0017-38005-0180	77 / F	Yes	Yes	Increased Cr	Yes	1.4 mg/dL	3.4 mg/dL	1.0 mg/dL	Yes	Yes
0017-38024-0697	62 / M	Yes	Yes	Increased Cr	Yes	0.7 mg/dL	3.0 mg/dL	1.0 mg/dL	Yes	Yes
0018-38260-2555	53 / M	Yes	Yes	Renal failure chronic	Yes (?)	HD	HD	HD	No	? blinding
202b-00903-9037	41 / F	No	?	Renal failure acute	Yes	0.6 mg/dL	2.3 mg/dL (?)	(?)	No	No
202b-00903-9037 information from death narrative (CRF of limited utility – only abnormal Cr is D3 of 1.4 mg/dL or 125µmol/L)										

Fifteen patients treated with telavancin had renal SAEs reported as shown above; eleven of these events were assessed by the investigator as possibly/probably related to study medication. The FDA medical reviewer was unable to exclude study medication as possible/probable cause in any of these cases. Four patients treated with vancomycin had renal SAEs reported; two were assessed by the investigator as having renal SAEs possibly/probably related to study medication compared to three patients with events possibly/probably related to study medication as assessed by the FDA reviewer.

Four telavancin-treated patients with renal failure died (two after the study death reporting period); two had other comorbid illnesses, refused dialysis, and died. One of the patients refusing dialysis had increasing creatinine prior to study entry, as did another patient who had dialysis initiated. The other patients treated with telavancin showed improvement in serum creatinine, although three patients reported as improved (0018-38160-2007, 0018-38148-2498, 0018-38260-2099) were still at 2 times their baseline serum Cr. One of the four vancomycin-treated patients was receiving hemodialysis prior to entry and was continued. The other three vancomycin-treated patients showed resolution of the renal SAE.

Narratives for these events can be found in Appendix C.

Cardiac SAEs

Twenty six patients experienced at least one SAE in the Cardiac Disorders System SOC; thirteen patients were in the telavancin treatment groups (11 treated with 10 mg/kg and 2 with 7.5 mg/kg) and thirteen in the comparator treatment group. Four of thirteen of the telavancin-treated patients had a fatal outcome, however the cardiac events in two of these deaths were not considered to be related to study medication by the investigator. FDA assessment of the deaths was that study medication could not be excluded in any of the four. Six of the thirteen vancomycin-treated patients had a fatal outcome, however none of the cardiac events were considered to be related to study medication by the investigator.

The following list contains patient IDs, SAE terms, and investigator and FDA assessment of causality. Narratives can be found in Appendix C.

Deaths in patients with cardiac SAEs treated with telavancin

0017-02010-0546: ventricular arrhythmia [assessed by the investigator as possibly/probably related to study medication, although event occurred at least 24-36 hrs after a single dose of study medication and patient was found dead in bed / FDA reviewer concurs]

0018-01002-2474: cardiac arrest [assessed by the investigator as possibly related, patient found dead from unknown cause / FDA reviewer concurs]

0018-19006-2894: cardio-respiratory arrest [investigator assessed the event as unrelated to study medication, had developed, new onset atrial fibrillation 1 day after and death 2 days after study medication was discontinued / FDA reviewer disagrees since the cause of death is not well explained by the history and cardiac events developed shortly after treatment was discontinued.]

0018-38160-2501: myocardial infarction, acute respiratory failure [post-operative myocardial infarction (MI) assessed by the investigator as unrelated to study medication / FDA reviewer disagrees and although comorbidities are present, temporally the event and clinical deterioration coincides with study drug administration.]

Possibly/probably related cardiac SAEs in patients treated with telavancin (Four of the thirteen SAEs, including the 2 patients who died discussed previously)

0017-02010-0546: ventricular arrhythmia [see deaths above]

0018-01008-2474: cardiac arrest [see deaths above]

0017-38101-0436: bradycardia [the investigator assessed the event as possibly related to study medication / FDA reviewer unsure whether bradycardia was truly symptomatic or if exaggerated physiologic response in 30 yo male and therefore not related to study medication, but would not dispute investigator assessment]

0017-38111-0380: myocardial infarction [the investigator assessed the event of MI as possibly related to study medication, although patient continued on study medication / FDA reviewer agrees temporally related, although with patient continuing on study medication relationship less likely]

Unrelated cardiac SAEs in patients treated with telavancin

0017-18004-0768: myocardial ischemia [assessed by investigator as unrelated / FDA reviewer does not disagree with investigator, confounded case]

0017-38101-0059 (7.5 mg/kg dose): atrial fibrillation [investigator assessed as unrelated to study medication in patient with reported "arrhythmia" prior to study therapy / FDA reviewer concurs]

0017-38101-0069 (7.5 mg/kg): congestive cardiac failure [the investigator assessed the event of CHF as unrelated to study medication in this patient with a history of CHF and who had been discontinued from study medication 2 days prior to the event / FDA reviewer concurs]
0017-18001-0722: myocardial infarction [the investigator assessed the event as unrelated to study medication / FDA reviewer disagrees]
0017-38271-0402: angina pectoris [investigator assessed as unrelated to study medication / FDA reviewer concurs, not certain if truly cardiac chest pain or exacerbation of gastroesophageal reflux disease (GERD)]
0018-06005-2728: myocardial infarction [investigator assessed the SAE on non-Q wave MI on the second day of study treatment as unrelated to study medication / FDA reviewer disagrees]
202b-00111-7055: atrial fibrillation [the investigator assessed this event as unrelated to study medication]

The following is a list of patients treated with vancomycin who had SAEs in the Cardiac SOC. There were 14 events in 13 patients, with 6 deaths, 2 patients with SAEs possibly related to study medication, and 3 discontinuations. Brief narratives can be found in Appendix C.

Deaths in patients with cardiac SAEs treated with vancomycin:

- 0018-22000-2742 (atrial fibrillation, cardiac failure - possibly/probably related to study medication by investigator, FDA reviewer disagrees since relationship of anuria and cardiac failure cannot be excluded)
- 0017-38024-0695 (cardiac failure congestive – not related to study medication by investigator, FDA reviewer concurs)
- 0018-30907-2323 (cardiogenic shock – not related to study medication by investigator, FDA reviewer concurs)
- 0018-38260-2555 (cardiac arrest – not related to study medication by investigator in ISS dataset / conflicts with narrative that states possibly related, FDA reviewer concurs with possible relationship with study medication)
- 0017-38271-0659 (bradycardia, cardio-pulmonary arrest - not related to study medication by investigator, FDA reviewer concurs)
- 0017-38016-0824 (cardio-respiratory arrest, pulmonary embolus – not related to study medication by investigator, FDA reviewer concurs given PE diagnosed at 24 hours of study treatment) [not listed with cardiac deaths in ISS "other SAE section"]

Discontinuations in patients with cardiac SAEs treated with vancomycin:

- 0017-38101-0873 (bradycardia – not related to study medication by investigator, FDA reviewer concurs)
- 0017-09002-0765 (cardiac failure, also pneumonia, bronchitis – unrelated to study medication by investigator, FDA reviewer disagrees since the decompensation is temporally related to study medication)
- 0018-33002-2605 (acute myocardial infarction – unrelated to study medication by investigator, FDA review disagrees since event temporally related)

Possibly/Probably related cardiac SAEs in patients treated with vancomycin:

- 0017-38101-0247: atrial fibrillation (possibly/probably related to study medication by investigator, FDA reviewer concurs)

- 0017-38271-0434: atrial fibrillation (possibly/probably related to study medication by investigator, FDA reviewer concurs)

Other Cardiac SAEs in patients treated with vancomycin (not death, discontinuation or related):

- 0018-38025-2330: myocardial infarction – not related to study medication by investigator, FDA reviewer concurs
- 0017-38111-0098: cyanosis – not related to study medication by the investigator, FDA reviewer disagrees and although other factors likely, relationship cannot be excluded.

Hypersensitivity or Histamine-Release SAEs

Treatment-emergent SAEs that potentially represented hypersensitivity or histamine-release reactions were seen in 13 patients; nine of these patients were treated with telavancin and four were treated with vancomycin.

Seven of the nine patients treated with telavancin had hypersensitivity or histamine-release reactions that were assessed by the investigator as SAEs **possibly/probably related** to study medication. These events include: drug hypersensitivity (three patients), rash (two patients), pneumonia (one patient), alveolitis allergic (one patient), hypersensitivity (one patient), and anaphylactic reaction (one patient). The following is a list of these patients, along with reaction, study day of occurrence, confounding events/medications, as well as treatment administered for the reaction.

- 0017-38271-0391 (rash on torso and legs): The patient had been treated with antibiotics (levofloxacin, cefazolin, clindamycin) for 6 days prior to entering study and had a rash in her mouth and on arms and torso at entry. On D2 she developed severe generalized pruritus and D3 progressive worsening of the rash. Telavancin and aztreonam were discontinued and the patient was treated with methylprednisolone. The patient was recovered 5 days after discontinuing study medication.
- 0017-38271-0406: (drug hypersensitivity): The patient developed mild generalized pruritus on D4 which was treated with diphenhydramine. On D11, during infusion of the morning dose of study medication, the patient experienced shakiness, chills, and abdominal pain which lasted 20-25 minutes and was treated with Vicodin. Similar episodes on D12 and D13 were accompanied by mild tachycardia and low grade fever (temperature 99.4°F on D12 and 101.7°F on D13). The patient received no specific treatment [except Vicodin].
- 0018-25003-2196 (drug hypersensitivity): Following the first dose of study medication, the patient developed a fever (temperature 38.5°C), chills, red rash on the upper body and extremities, and vomiting. The patient was treated with hydrocortisone and was considered to be recovered the following day, but was discontinued from the study at his request.
- 0018-38160-2540 (drug hypersensitivity): The patient was treated for 10 days with telavancin and on D10, presented to the ER with wheezing, morbilliform rash on the trunk and extremities that spread to palms and soles, and moderate nausea. Telavancin was discontinued and the patient was treated with prednisone and was considered recovered the next day.
- 0018-38091-2132 (hypersensitivity): The patient was premedicated with diphenhydramine and began the D4 infusion without difficulty. Twenty minutes after infusion, the patient developed a sensation of not being able to clear his throat, along with shortness of breath and

dry heaves. He developed tachycardia (HR 120) and tachypnea (RR 20-25) and the patient was given an epinephrine injection (0.3 mg SQ) by the home health nurse and was transported to the ER. He was improved within 15 minutes of arrival, was observed, and sent home. Telavancin was discontinued.

- 0018-38126-2316 (bilateral pneumonia): The patient was admitted to the hospital with cellulitis of the abdomen following an insect bite. He also complained of myalgias, malaise, intermittent anxiety, generalized pain, and nausea and vomiting for a week prior to admission. On D3 of treatment, the patient developed hypoxia with pulse oximetry of 86% on room air. A chest CT confirmed chest X-ray (CXR) findings of bilateral infiltrates. Azithromycin was added without effect. By D6 the patient was receiving 50% vent mask with pulse oximetry above 90%. The patient rapidly recovered after D6 when telavancin was discontinued and linezolid administered. The pulmonologist and pathologist concluded the patient most likely had drug-induced lung disease.
- 0018-38333-2796 (alveolitis allergic): The patient developed chills and a "flushing" or "burning" sensation in the chest beginning with the D10 infusion and fever was also noted that day. On D11, severe non-cardiac chest pain was reported. On D12, moderate nausea and vomiting were reported and the patient was hospitalized with hypersensitivity pneumonitis. CXR showed a diffuse interstitial process and oxygen saturation was 83% on room air. Study drug was discontinued and the patient was treated with methylprednisolone, paracetamol, and diphenhydramine. The event was considered to be resolved the next day with O2 sat on room air of 96%.

The **two telavancin-treated patients in whom the SAE was assessed** by the investigator as being **unrelated** to study medication are:

- 0018-38091-2087 (anaphylactic reaction, rash): The patient was treated with cefazolin, clindamycin, and levofloxacin for cellulitis on the day of study entry. After the first dose of telavancin, the patient had nausea, vomiting, and a rash noted on the arms. She was treated with diphenhydramine and triamcinolone cream. Telavancin was discontinued, but the patient was then treated with a series of antibiotics including clindamycin and levofloxacin, then doxycycline and rifampin, then clindamycin, ceftriaxone, and prednisone. Ceftriaxone was replaced by linezolid and aztreonam as the rash worsened. The patient was transferred to the ICU and prednisone changed to methylprednisolone. The patient was discharged 6 days later.
- 0018-25001-2576 (erythema multiforme): On D8 of study treatment, the patient had a CT with contrast (iopromide). Following the procedure, the patient complained of flushing of the head and anterior torso and generalized pruritus. The patient was treated with hydrocortisone. On D11, the patient developed a severe rash with itching and the rash was localized to the head, torso, and both arms. The patient was diagnosed with erythema multiforme, telavancin discontinued, and prednisone, clemastine, fluticasone, and clobetasol. The patient improved, but had some persistent rash at discharge 2 weeks later. The event was initially assessed as possibly related to study medication, but was subsequently attributed to IV contrast.

Three of the four patients treated with vancomycin (or comparator) had hypersensitivity or histamine-related reactions assessed by the investigator as SAEs **possibly/probably related** to

study medication. The following is a list of patients, along with reaction and treatment administered:

- 0017-38005-0720 (drug hypersensitivity): On study D11, developed a raised, "welt-like" rash, had fever (T 99.3°F), and complained of headache and back pain. The patient was sent to the ER, received diphenhydramine and prednisone, and sent home. Vancomycin was discontinued and the patient was recovered by the next day.
- 0018-01014-2784 (drug hypersensitivity): Forty minutes after the first dose of study medication, the patient developed facial edema and full body flushing without respiratory involvement. The patient was treated with hydrocortisone, diphenhydramine, and dexamethasone.
- 202a-00902-2016 (angioneurotic edema): The patient received an antistaphylococcal penicillin (not vancomycin) and developed a SAE of lobar pneumonia, thrombocytopenia, and disseminated intravascular coagulation (DIC).

The patient and event in the **one vancomycin-treated patient that was assessed** by the investigator as **unrelated** to study medication is:

- 0017-38101-0523 (hypersensitivity related to tegretol): Four days after completing a 14 day course of study medication, the patient developed a generalized maculopapular rash, pruritus, and fever, and the patient was hospitalized. Work-up included blood cultures, CXR, and lumbar puncture (LP). The patient was treated with diphenhydramine and acetaminophen and discharged 3 days later. This SAE of allergic reaction was attributed to tegretol therapy.

Uncomplicated *Staphylococcus aureus* Bacteremia

The Phase 2 uncomplicated SA bacteremia study was blinded to treatment assignment at the time of the NDA submission. As of submission (data cutoff), there were 19/58 patients (33%) with reported SAEs, with 3 patients having SAEs that were assessed by the investigator as possibly/probably associated with study medication. The following is a list of those patients, along with event:

- 203a-305-5009: hypersensitivity
- 203a-111-4002: adverse drug reaction
- 203a-148-4030: blood creatinine increased [assessed by investigator as possibly/probably related to study medication, however patient's serum Cr remained within normal range during hospitalization]

Unblinded safety data has been submitted to the NDA with the 4MSU on April 17, 2007. See Section 7.2.9 for additional information.

Ongoing Hospital-Acquired Pneumonia Studies

The Phase 3 HAP studies (0015 and 0019) are ongoing and remain blinded to treatment assignment. In the original NDA submission, based on enrollment of 357 patients, there were 116 (32%) of patients with SAEs.

SAEs that were reported in > 2% of patients enrolled included: septic shock (16 patients, 4%), renal failure acute (13 patients, 4%), cardiac arrest and multi-organ failure (11 patients each, 3%), sepsis and respiratory failure (7 patients each, 2%), and atrial fibrillation (6 patients, 2%).

Sixteen of the 116 patients with SAEs (4.5%) had events that the investigator assessed as possibly/probably related to study medication. These events were renal failure acute (seven patients), atrial fibrillation (three patients), renal insufficiency (two patients), myocardial ischemia, polyneuropathy, rash maculopapular, ventricular tachycardia, and hepatocellular damage (one patient each). SAEs indicating renal insufficiency were reported for 19 patients, of whom 9 patients were assessed by investigator as having SAEs possibly/probably related to study medication.

Related (nine):

- Renal failure acute: 0015-01014-4233, 0015-04008-4091, 0019-05003-6031, 0015-05007-4231, 0015-12016-4158, 0019-38055-6175, and 0015-38102-4060
- Renal insufficiency: 0015-12006-4126, 0025-18010-4139

Unrelated (ten):

- Renal failure acute: 0015-02012-4209, 0015-38049-4143, 0015-38049-4187, 0019-05003-6084, 0019-18004-6111, 0019-38069-6174
- Renal insufficiency: 0015-38148-4218, 0019-18004-6107
- Oliguria: 0015-38049-4192
- Anuria: 0019-18005-6035

The rate of renal SAEs is greater than that seen in the cSSSI studies (5% versus 1%). However given the serious nature of the condition under study (HAP), along with comorbidities of patients being studied it is not unexpected. It is somewhat higher than that noted in the FDA review of the linezolid versus vancomycin study in HAP where there were 6 kidney failure acute AEs in the linezolid arm (6/203 or 3.0%) versus 4 kidney failure AEs in the vancomycin arm (4/193 or 2.1%).

Additional safety data has been submitted to the NDA with the 4MSU on April 17, 2007. See Section 7.2.9 for updated information.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The protocol-specified treatment duration for the Phase 3 cSSSI was 7 to 14 days, while patients in the Phase 2 SSSI could be treated for 4 to 14 days. Satisfactory/sufficient treatment was determined by the investigator based on resolution of signs and symptoms at the primary infection site. Table 44 below shows the number of patients who completed or did not complete a course of study therapy (completion defined as the investigator assessment of resolution of the infection or receipt of the maximum 14-day course of therapy). Reasons for premature discontinuation of treatment are also shown.

Table 44: Discontinuation of Study Drug – Studies 0017 and 0018 Individually and Combined (Telavancin 10 mg/kg versus Vancomycin)

	Study 0017		Study 0018[1]		Studies 0017 + 0018	
	TLV N=426	VANC N=429	TLV N=502	VANC N=510	TLV N=928	VANC N=939
Completed Study Therapy	350 (82)	355 (83)	396 (79)	411 (81)	746 (80)	766 (82)
Did Not Complete Course of Study Therapy	76 (18)	74 (17)	106 (21)	99 (19)	182 (20)	173 (18)
• Unsatisfactory Response	14 (3)	13 (3)	10 (2)	15 (3)	24 (3)	28 (3)
• Death	2 (<1)	2 (<1)	2 (<1)	3 (<1)	4 (<1)	5 (<1)
• Two consecutive ECGs with QTc>500	0 (0)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
• Adverse Event	29 (7)	22 (5)	43 (9)	28 (5)	72 (8)	50 (5)
• Patient Withdrew Consent	11 (3)	14 (3)	16 (3)	18 (4)	27 (3)	32 (3)
• Major Protocol Deviation	1 (<1)	2 (<1)	8 (2)	1 (<1)	9 (<1)	3 (<1)
• Lost to Follow-Up	6 (1)	6 (1)	7 (1)	9 (2)	13 (1)	15 (2)
• Infection due to Gram Negatives Only	2 (<1)	4 (<1)	5 (<1)	6 (<1)	7 (<1)	10 (1)
• Persistent SA bacteremia	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)
• Other	11 (3)	10 (2)	13 (3)	18 (4)	24 (3)	28 (3.0)

From ISE, Table 5-4, pg 87 and ISE, Supporting Table 1, pgs 303-304.
[1] One patient randomized to vancomycin (included in the vancomycin treatment group in this table) was treated with telavancin.

The rate of premature discontinuation of study medication was similar across treatment arms (telavancin and comparator) and for each of the telavancin Phase 3 studies. Overall, for patients treated with telavancin 10 mg/kg, 182/928 (20%) discontinued treatment prematurely versus 173/939 (18%) for vancomycin. The reasons for early discontinuation occurred with similar frequency across treatment arms, except for the number (percent) of patients who discontinued study treatment due to adverse events which is slightly higher in the telavancin group (particularly in Study 0018).

The patients who discontinued study therapy early for reasons categorized as "other" were balanced across treatment arms and studies. Based on a review of patients in this category (from the subject analysis datasets), none of these patients discontinued for safety reasons (i.e. AEs).

In the ISE, the Applicant notes that for the Phase 3 cSSSI studies (0017 and 0018, 10 mg/kg dose of telavancin) there were a total of 103 patients who did not complete the study because they were lost to follow-up (LTFU); 48/928 (5.2%) patients were in the telavancin treatment arm and 55/939 (5.9%) in the vancomycin treatment arm. The number (percent) of patients LTFU was similar across treatment groups. The Applicant states that a review of all available information for these patients did not reveal any known AEs that were not otherwise reported for the clinical studies.

Table 45 shows the number of patients who completed or did not complete study therapy in the active comparator studies of telavancin 7.5 mg/kg versus telavancin 10 mg/kg. Reasons for early discontinuation are also provided.

Table 45: Discontinuation of Study Drug – Studies 202a and Original Protocol 202b, 0017 and 0018 (telavancin 7.5 mg/kg) and Post-Amendment 202b, 0017 and 0018 (telavancin 10 mg/kg)

	Study 202a and Original Protocol 202b, 0017, 0018		Studies 0017 + 0018 + 202b	
	TLV 7.5 N=192	VANC N=189	TLV 10 N=1028	VANC N=1034
Completed Study Therapy	169 (88)	169 (89)	833 (81)	853 (82)
Did Not Complete Course of Study Therapy	23 (12)	20 (11)	195 (19)	181 (18)
• Unsatisfactory Response	2 (1)	4 (2)	26 (3)	30 (3)
• Death	0	0	4 (<1)	5 (<1)
• Two consecutive ECGs with QTc>500	0	0	1 (<1)	2 (<1)
• Adverse Event	9 (5)	6 (3)	78 (8)	53 (5)
• Patient Withdrew Consent	3 (2)	3 (2)	29 (3)	32 (3)
• Major Protocol Deviation	1 (1)	1 (1)	10 (<1)	3 (<1)
• Lost to Follow-Up	4 (2)	4 (2)	13 (1)	15 (1)
• Infection due to Gram Negatives Only	0	0	7 (<1)	10 (1)
• Persistent SA bacteremia	0	1 (1)	1 (<1)	0 (0)
• Other	3 (2)	1 (1)	26 (3)	31 (3)

From CSR 0017 Appendix 23, pg 17-18, 0018 Appendix 23, pg 17-18, I6424 202a, pg 66-67, I6424 202b, Appendix 47, pg 12-14.

The rate of premature discontinuation of study therapy and comparator is higher in the 10 mg/kg telavancin studies than in the telavancin 7.5 mg/kg studies, but similar across treatment arms for the each designated dose group of studies. Based on these data, the Applicant concluded that there does not appear to be a dose-related factor in premature discontinuations. However, the number of patients enrolled in the 7.5 mg/kg studies is much smaller than in the 10 mg/kg studies, so no definite conclusions can be drawn about effect of dose based on these data.

The patients in the telavancin 7.5 mg/kg dose studies who discontinued study therapy early for reasons categorized as "other" were balanced across treatment arms (study medication and comparator. Based on a review of patients in this category (from the Sponsor's study reports), none of these patients discontinued for safety reasons (i.e. AEs).

The number of patients LTFU for the study in the telavancin 7.5 mg/kg studies was 12/383 (3.1%) patients; 5/192 (2.6%) were in the telavancin treatment arm and 7/191 (3.6%) were in the vancomycin/standard treatment group. For the telavancin 10 mg/kg studies there were 112/2026 (5.5%) patients LTFU; 54/1028 (5.3%) were in the telavancin treatment arm and 58/1034 (5.6%) were in the vancomycin treatment arm. Although the number (percent) of patients who discontinued from the telavancin 10 mg/kg studies is higher than the number of patients who discontinued from the telavancin 7.5 mg/kg studies, it appears to be similar for telavancin versus comparator at each dose. The Applicant concludes that this suggests that there were no issues related to blinding or conduct and analyses that would present difficulty in interpreting the effectiveness of the drug. The relatively small number of patients enrolled and subsequently LTFU in the telavancin 7.5 mg/kg studies is much less than that in the telavancin 10 mg/kg studies and does not allow for direct comparison of dose effect on the rates. The Applicant states in the ISE that patients who were LTFU and did not complete the study had no AEs that were not reported elsewhere.

7.1.3.2 Adverse events associated with dropouts

One hundred ninety seven patients discontinued study medication or study due to an adverse event in the telavancin clinical development program. Seventeen patients (13 telavancin and 4 comparator) discontinued from clinical pharmacology studies, 150 patients (9 telavancin 7.5 mg/kg, 79 telavancin 10 mg/kg, and 62 vancomycin) discontinued from cSSSI studies, and 30 have discontinued from the ongoing treatment-blinded studies.

Clinical Pharmacology Studies

Early discontinuation of subjects in the clinical pharmacology studies occurred in 13/268 (5%) of those treated with telavancin and 4/150 (3%) of those treated with comparator (included placebo containing hydroxypropyl-β-cyclodextrin or moxifloxacin used in the ECG study). All but 3 of the listed events can be related to drug hypersensitivity/allergy or histamine-related AEs, manifested primarily as dermatologic findings. There was only one AE preferred term "red man syndrome" reported for telavancin. To better characterize the dermatologic events in one of the clinical pharmacology studies (104a), an external consultant familiar with glycopeptide infusion reactions reviewed masked subject records for six subjects; four had events recorded as Type 1 hypersensitivity reactions (one treated with telavancin 7.5 mg/kg, two treated with telavancin 15 mg/kg, and one treated with moxifloxacin) and two subjects who experienced infusion-related reactions (both treated with telavancin 10 mg/kg). The consultant concluded that all but one event (that which was reported for the moxifloxacin patient) were variants of "Red-man Syndrome" commonly seen in persons receiving glycopeptides.

The three events unrelated to hypersensitivity or histamine-related reactions occurred in patients in the telavancin treatment arm and included two reports of tinnitus and one report of dizziness (presyncope).

- 101APT1-00001-00013 (tinnitus) – 19 yo male developed tinnitus 9 hours and 10 minutes after receiving a first dose of telavancin (1 mg); the episode lasted for 3 hours. Tinnitus was reported again 23 hours later at which time the subject terminated. Information that the event had resolved was received by the Sponsor, but not recorded in the CRF.
- 101APT2-00001-00031 (tinnitus) – 29 yo male in the multiple dose phase discontinued after experiencing mild tinnitus prior to dosing on Day 3 (7.5 mg/kg). The tinnitus resolved in 48 hours.
- 101APT1 -00001-00002 (dizziness) – 25 yo male terminated due to pre-syncope beginning immediately after the start of treatment in period 3 (2.5 mg/kg) which lasted until the infusion was stopped 2 minutes later.

No similar complaints were recorded in subsequent clinical pharmacology testing.

Completed Phase 2 and Phase 3 SSSI studies

TEAEs resulting in early discontinuation of study medication in the cSSSI studies occurred in 88 (7%) of the telavancin-treated patients and 62 (5%) of the vancomycin-treated patients; in the telavancin 10 mg/kg studies, 8% of telavancin-treated and 5% of vancomycin-treated patients discontinued and in the telavancin 7.5 mg/kg studies, the rates of discontinuation were 5% for telavancin and 3% for vancomycin.

Table 46 shows the number (percent) of patients who discontinued study medication due to an AE by SOC.

Table 46: Discontinuation of Study Therapy Due to AE

	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
Any Discontinuation AE	9 (5)	6 (3)	79 (8)	56 (5)	88 (7)	62 (5)
Blood and Lymphatic System Disorders	1 (<1)	0	2 (<1)	0	3 (<1)	0
Cardiac Disorders	0	0	4 (<1)	5 (<1)	4 (<1)	5 (<1)
Ear and Labyrinth Disorders	0	0	0	2 (<1)	0	2 (<1)
Gastrointestinal Disorders	1 (<1)	0	13 (1)	6 (<1)	14 (1)	6 (<1)
General Disorders and Administration Site	1 (<1)	1 (<1)	8 (<1)	8 (<1)	9 (<1)	9 (<1)
Hepatobiliary Disorders	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Immune System Disorders	0	0	6 (<1)	5 (<1)	6 (<1)	5 (<1)
Infections and Infestations	2 (1)	3 (2)	15 (1)	7 (<1)	17 (1)	10 (<1)
Injury, Poisoning, and Procedural Complications	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Investigations	1 (<1)	0	11 (1)	5 (<1)	12 (<1)	5 (<1)
Metabolism and Nutrition Disorders	0	0	2 (<1)	0	2 (<1)	0
Musculoskeletal and Connective Tissue Disorders	0	1 (<1)	2 (<1)	0	2 (<1)	1 (<1)
Nervous System Disorders	1 (<1)	0	5 (<1)	2 (<1)	6 (<1)	2 (<1)
Psychiatric Disorders	0	0	3 (<1)	1 (<1)	3 (<1)	1 (<1)
Renal and Urinary Disorders	2 (1)	0	9 (<1)	1 (<1)	11 (<1)	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	2 (1)	0	8 (<1)	6 (<1)	10 (<1)	6 (<1)
Skin and Subcutaneous Tissue Disorders	3 (2)	1 (<1)	20 (2)	21 (2)	23 (2)	22 (2)
Surgical and Medical Procedures	0	0	1 (<1)	0	1 (<1)	0
Vascular Disorders	2 (1)	0	2 (<1)	2 (<1)	4 (<1)	2 (<1)

Adapted From ISS, Table 5-13, pgs 198-206.

Nausea (10 patients, 1%), rash (9 patients, 0.9%), blood creatinine increased (7 patients, 0.7%), vomiting (7 patients, 0.7%), renal failure acute (6 patients, 0.6%), and osteomyelitis (6 patients, 0.6%) were the most frequently reported events leading to discontinuation in patients treated with the telavancin 10 mg/kg dose. The most frequent TEAEs leading to discontinuation of study medication in the comparator treated group (vancomycin) for the 10 mg studies were pruritus (7 patients, 0.7%), drug hypersensitivity (5 patients, 0.5%), and rash (5 patients, 0.5%). Renal insufficiency (2 patients, 1%) was the only TEAE resulting in discontinuation of study medication in more than 1 patient in the telavancin 7.5 mg/kg group, while the comparator group for the 7.5 mg studies had no single TEAE resulting in discontinuation in more than one patient.

Renal TEAEs (and Investigations SOC Cr) resulting in discontinuation of study medication:
Thirteen telavancin-treated patients discontinued study medication due to renal TEAEs that were possibly/probably associated with study medication versus two vancomycin-treated patients. Nine patients who discontinued telavancin prematurely had renal SAEs previously outlined in Section 7.1.2 Serious Adverse Events and are listed below, along with preferred terms.

- 202b-00101-7008: acute prerenal failure, blood creatinine increased, blood urea increased, renal insufficiency
- 0017-38002-0408: renal insufficiency
- 0017-18015-0802: renal insufficiency

- 0018-33002-2409: renal failure acute, hyperkalemia
- 0018-38148-2498: blood creatinine increased, blood urea increased
- 0018-38260-2099: blood creatinine increased, blood urea increased, renal insufficiency
- 0018-38148-2359: blood creatinine increased
- 0018-38322-2757: renal failure acute

There were four additional telavancin-treated patients who had renal AEs which resulted in early discontinuation of study medication that were possibly/probably related, but were not considered to be SAEs. These patients are listed below:

- 0018-38110-2568 (renal failure acute, blood creatinine increased): The patient is a 76 yo male treated with a history of chronic renal insufficiency, diabetes mellitus, CHF, hypertension, and chronic obstructive pulmonary disease (COPD) who received telavancin for 2 days. Concomitant medications included insulin, metformin, captopril, and furosemide added on D2. Baseline serum Cr was 2.0 mg/dL, which increased to 5.9 mg/dL by D3 and study medication was discontinued. On D10 (8 days after stopping study medication) serum Cr remained elevated at 9.1 mg/dL.
- 0018-38304-2233 (blood creatinine increased): The patient is a 51 yo male who was treated with telavancin for 5 days. The patient developed nausea and vomiting on D3 and on D4 was noted to have elevated serum Cr of 3.1 mg/dL (baseline serum Cr of 0.8 mg/dL). Telavancin was discontinued on D5 due to elevated Cr, dysgeusia, nausea, and vomiting. At the follow-up visit (TOC) on D12 (7 days after discontinuing study medication), the dysgeusia, nausea, and vomiting had resolved, and the serum Cr was decreased ("improved" at 2.3 mg/dL, but still abnormal).
- 0018-38304-2670 (blood creatinine increased): The patient is a 54 yo male treated with telavancin for 4 days. He was also receiving dyazide and clopidogrel. Baseline serum Cr was 1.4 mg/dL and on D4 was 4.5 mg/dL at which time the patient was also complaining of nausea. Telavancin was discontinued and nausea resolved the next day. On D7, 3 days after discontinuing medication, serum Cr was 5.0 mg/dL. Twenty days after discontinuing, serum Cr had decreased to 2.3 mg/dL, which showed improvement, but was still not resolved.
- 202b00107-6002 (blood creatinine increased): The patient is a 44 yo male with a history of hypertension and venous stasis dermatitis who was treated with 14 days of telavancin. Concomitant medications included lisinopril, furosemide, ibuprofen, verapamil, and aspirin. Baseline serum Cr was 1.1 mg/dL and was noted to be mildly elevated at 1.8 mg/dL on D11. Approximately three weeks later, the serum Cr had "normalized" to 1.3 mg/dL. FDA reviewer agrees this was a mild increase and appears to have resolved.

There were two vancomycin-treated patients who had renal AEs assessed as possibly/probably related to study medication by investigators and these are listed below:

- 0017-38024-0697 (blood creatinine increased): SAE previously assessed
- 0018-38025-2330 (blood creatinine increased, myocardial infarction): The patient is a 67 yo male with a history of MI, hypertension, diabetes mellitus, hepatitis C, common bile duct stricture with stent, peripheral neuropathy, and HIV infection who was treated with vancomycin for 2 days. Concomitant medications included lopinavir/ritonavir, tenofivir, trizivir, atovaquone, enalopril, and insulin. Hypotension unrelated to study drug was noted on D2, and on D3 serum Cr was noted to be elevated from baseline 1.2 mg/dL to 3.5 g/dL. On D9 the patient developed severe chest pain, required treatment for hypertensive crisis and

pulmonary edema and was diagnosed with MI in the setting of profound anemia (hematocrit of 19%) on D11. The patient also had *Klebsiella pneumoniae* septicemia. On D12 (10 days after discontinuation, serum Cr was 2.7 mg/dL. The investigator assessed the elevated Cr to be possibly/probably related to study medication initially.

Hypersensitivity or histamine-release TEAEs resulting in discontinuation:
Potential study medication-related hypersensitivity or histamine-release TEAEs that resulted in discontinuation of study medication occurred in 61 patients; 31 patients were treated with telavancin (3%) and 30 with vancomycin (3%). Six of the televancin patients with these TEAEs were reported as SAEs and previously discussed in Section 7.1.2 SAEs. These patients along with reaction are listed below:

- 0017-38271-0391 (rash)
- 0018-25003-2196 (drug hypersensitivity)
- 0018-38091-2132 (hypersensitivity)
- 0018-38160-2540 (drug hypersensitivity)
- 0018-38126-2316 (pneumonia)
- 0018-38333-2796 (allergic alveolitis)

There were an additional 25 patients treated with telavancin who had TEAEs associated with hypersensitivity/histamine-related reactions who discontinued medication early, but were not considered to have SAEs:

- 0017-09004-0321: allergic dermatitis after 11 days of treatment treated with diphenhydramine
- 0017-09004-0498: exanthem (mild) after first dose of study medication (discontinued for other reasons from telavancin)
- 0017-09004-0755: exanthem (moderate) treated with dexamthasone, diphenhydramine, and chloropyramine
- 0017-09004-0937: exanthema (moderate) treated with methylprednisolone and chloropyramine
- 0017-18014-0845: pruritus on D2 of treatment, treated with promethazine and metamizole
- 0017-38002-0839: "Red-man Syndrome" after the first dose, resolved spontaneously without treatment
- 0017-38005-0781: drug hypersensitivity characterized as rigors, headache, elevated blood pressure, and sensation of feeling cold – symptoms resolved without specific treatment
- 0017-38016-0543: rash with nausea and vomiting on D4 and treated with promethazine
- 0017-38101-0160: pruritus, urticaria on D10 (had received cefazolin treatment prior to study) with resolution of symptoms on diphenhydramine
- 0017-38271-0643: pyrexia (drug fever) on D12 which resolved after treatment with diphenhydramine, methylprednisolone, and promethazine
- 0018-38160-2665: rash on D10 followed by "mild" angioedema (swelling of lip and lower right face) on D11 that resolved with methylprednisolone, diphenhydramine, and loratidine
- 0018-38025-2823: swollen tongue along with nausea, vomiting, dry mouth, and confusion which resolved after treatment with diphenhydramine and promethazine

- 0018-38074-2516: drug hypersensitivity (acute allergic reaction) on D12 characterized as shortness of breath, feeling of panic, and hypertension that was treated with diphenhydramine, methylprednisolone, paracetamol, and ondansetron
- 0018-38110-2014: pruritus, along with shortness of breath, itching, stomach upset, and nausea after the first dose that was treated with ondansetron, diphenhydramine, and famotidine
- 0018-33002-2369: rash pruritic on D10 treated with cyproheptadine, diphenhydramine, hydrocortisone, and betamethasone
- 0018-33002-2713: rash generalized treated with betamethasone, diphenhydramine, and prednisolone
- 0018-38110-2905: pruritus generalized on D10 that resolved with prednisone
- 0028-38282-2881: pruritus on D2-3 and treated with diphenhydramine and cetirizine
- 0018-38091-3033: pruritus generalized, rash generalized
- 0018-2006-2150: pruritus and rash began on D3 and on D5 developed bullous dermatitis on his wrist and was treated with prednisolone, phennniramine, and dexamethasone
- 0018-06005-2801: pruritus, rash on D6 with no specific treatment administered
- 0018-38107-2114: rash after a single dose with no specific treatment administered
- 202a-00115-1021: rash on D13 with no specific treatment administered
- 202b-00112-7101: rash (scrotum) D2 treated with diphenhydramine
- 202b-00115-6005: rash with fever (temperature of 38.2°C) on D9

Additional two "serious" SAEs in telavancin-treated patients which were assessed as NOT RELATED to study medication (and were discussed previously in the SAE section)

- 0018-25001-2576: erythema multiforme
- 0018-38091-2987: anaphylactic reaction, rash

Three of the thirty vancomycin-treated (or comparator) patients had SAEs associated with hypersensitivity or histamine-release TEAEs leading to discontinuation; two patients had drug hypersensitivity (0017-38005-0720, 0018-01014-2784) and one had angioneurotic edema (202a-00902-2016). The additional 27 patients with TEAEs resulting in discontinuation of study medication had the following: exanthem (4), pruritus (7), scratch (1), drug hypersensitivity (3), Red-Man Syndrome (2), rash (10), erythema (2), urticaria (3), and dermatitis allergic (1).

Gastrointestinal TEAEs resulting in discontinuation of study medication:
Gastrointestinal TEAEs resulted in discontinuation of study medication occurred in 14/1221 (1.1%) of telavancin patients (13 at the 10 mg/kg dose and 1 at the 7.5 mg/kg dose) compared to 6/1222 (0.4%) of vancomycin-treated patients.

Nausea and/or vomiting was the reason for premature discontinuation in 12 patients (1%) treated with telavancin (1 at the 7.5 mg/kg dose and 11 at the 10 mg dose) compared to 5 patients (0.4%) treated with comparator.

Bacteremia 203a
As of data cutoff for the NDA submission, two patients were reported to have discontinued study medication prematurely due to TEAEs. One event, adverse drug reaction (vasovagal syncope),

was considered to be possibly/probably related to study medication and the other, multi-organ failure, to be unrelated. See Section 7.2.9 for additional information presented in the 4MSU.

Ongoing HAP Studies (0015 and 0019)
As of the cutoff for the NDA submission, there were 28 patients in HAP studies (0015 and 0019) who were reported to have discontinued prematurely due to TEAEs. Renal failure acute (five patients, 1%) and mutli-organ failure, meningitis, septic shock, and renal insufficiency (two patients each, 0.6%) were the most frequently reported TEAEs. Adverse events related to potential renal impairment (renal failure acute, renal insufficiency, renal impairment, and blood creatinine increased) occurred in nine patients (3%).

See Section 7.2.9 for additional information presented in the 4MSU.

7.1.3.3 Other significant adverse events

The Applicant provided a written analysis of adverse events reviewed by organ system for renal, cardiovascular, and hepatic systems. This analysis included both nonclinical and clinical information.

Renal Adverse Event Summary
Preclinical studies indicated that administration of telavancin to rats and dogs at 1-2 times the human equivalent dose (HED) caused small increases in BUN and Cr along with the finding of renal tubular degeneration. Changes in blood chemistry and urinalysis were generally reversible with shorter term exposures and partially reversible after a 4-week recovery period in animals treated for 13 weeks and 6 months.

The FDA reviewer has examined narratives, CRFs, and pertinent laboratory data for patients in the telavancin clinical development program who have had renal-related SAEs resulting in death or discontinuation from therapy, as well as other SAEs.

The summary of the findings include:

- Deaths: Two patients treated with telavancin had renal insufficiency listed as a SAE with death as an outcome that were assessed by the investigator as possibly/probably related to study medication. One patient treated with vancomycin had acute renal failure listed as an SAE resulting in death, however the investigator assessed the AE as not related to study medication. The FDA reviewer agrees with the assessments. Of patients in whom death occurred outside the study death-reporting period (i.e., until the TOC visit or 28 days following EOT if no TOC visit) and were reported to the Applicant, four of five patients who received telavancin had renal insufficiency or renal failure during the course of study, with one patient reported to have ongoing renal insufficiency at the time of death.
- Other SAEs: Nienteen patients had renal SAEs reported during the cSSSI studies (see Table 43). Fifteen of the nineteen were in the telavancin treatment group and four in the comparator treatment group. Three of the telavancin patients required hemodialysis; two (one of whom had rising Cr prior to study), refused dialysis (and further care due to

age/comorbidities), and died. Three patients treated with telavancin showed incomplete resolution of Cr with values still 2 times their baseline Cr.

- Discontinuation of study medication due to renal TEAEs: Fourteen patients discontinued study medication prematurely due to renal SAEs; thirteen of the patients were treated with telavancin compared to one treated with vancomycin.

Laboratory values indicative of renal function are examined in Section 7.1.7.3. Of note, two to three times as many patients treated with telavacin in Studies 0017 and 0018 combined developed clinically significant elevations in serum Cr and BUN compared to patients treated with vancomycin, regardless of which particular functional definition of renal impairment was used.

Cardiac Adverse Event Summary

Based on the results from Study I6424-104a, the Phase 1 Thorough ECG Study, it has been demonstrated that telavancin prolongs the QT interval. Information about the results of that study can be found in Section 7.1.6.1 Overview of ECG Testing in this review and in the QT Study Review by the Interdisciplinary Review Team for QT Studies.

Review of the data from clinical studies can be found in Section 7.1.6.3 Standard Analyses and Explorations of ECG Data.

The FDA reviewer has examined narratives, CRFs, and pertinent laboratory data for patients in the telavancin clinical development program who have had cardiac-related SAEs resulting in death or discontinuation from therapy, as well as other SAEs.

The summary of the findings include:

- Deaths: Four patients treated with telavancin had cardiac events resulting in death, with two of the patient's events assessed as possibly or probably related to study medication by the investigator. The FDA reviewer could not exclude relationship to study medication in any of the four deaths, although noting multiple confounders for each patient. Six patients treated with vancomycin had cardiac events resulting in death, with none of the cardiac events assessed as related to study medication by the investigator. The FDA reviewer assessed one of the six patients treated with vancomycin as having cardiac events leading to death possibly/probably related to study medication.
- Other SAEs: Twenty six patients experienced at least one SAE in the Cardiac Disorders System SOC; thirteen patients were in the telavancin treatment groups (11 treated with 10 mg/kg and 2 with 7.5 mg/kg) and thirteen (ISS database 12 / there is one patient with cardio-respiratory arrest listed that didn't get included in the "serious" category) in the comparator treatment group. The investigator assessed the relationship of study medication to cardiac event as possible/probable in four telavancin-treated patients (4/13) compared to eight patients assessed as having events possibly/probably related to study medication by the FDA reviewer. For vancomycin, the investigator assessed two patients (2/13) as having cardiac SAEs possibly/probably related to study medication compared to six patients assessed by the FDA reviewer as having events possibly/probably related to study medication.

- Discontinuation of study medication due to cardiac TEAEs: Four patients treated with telavancin discontinued study medication due to cardiac events compared to three patients treated with vancomycin. These patients are listed below along with the investigator assessment of relationship to study medication.

  Telavancin:
  - 0017-09004-0479; angina, not related
  - 0018-38107-2421: atrial fibrillation, possibly/probably related
  - 0018-38110-2037: angina, possibly/probably related
  - 202b-00907-8003: cardiac failure, not related

  Vancomycin:
  - 0017-09002-0765; cardiac failure, not related
  - 0018-33002-2605: acute MI, possibly/probably related
  - 0018-33002-2622: angina pectoris, possibly/probably related

Hepatic Adverse Event Summary

Preclinical studies of 6-13 week duration were associated with elevated transaminase levels (AST, ALT) in rats and dogs. These changes were associated with hepatocellular injury (hepataocellular degeneration and necrosis) that showed evidence of reversibility. In dogs, elevations were also noted in alkaline phosphatase in dogs treated with telavancin 100 mg/kg/day (13 weeks).

Hepatobiliary SAEs: In the ISS database, there are three patients with hepatobiliary-related SAEs; two patients received telavancin and one patient comparator. These patients, along with a brief narrative are listed below.

Telavancin

- 0018-19006-2775: The patient had hepatic carcinoma and had received chemoembolization approximately 2 weeks prior to being treated with study medication. The patient was discharged with home IV study medication administered. The patient was then admitted to a different hospital with worsening of hepatic cirrhosis after 8 days of study therapy and study medication was discontinued with resolution of MRSA infected ulcer noted. The investigator assessed the event as unrelated to study medication.
- 0018-25001-2395: The patient was an 80 yo female with diabetes, peripheral vascular disease (PVD), and history of cholelithiasis treated with 14 days of telavancin for an infected femoral artery thrombectomy wound. On Day 14 of treatment, she developed acute cholecystitis and pneumonia and had a cholecystectomy. The investigator assessed the event as unrelated to study medication.

Comparator

- 202b-00903-9037: The patient was a 41 yo randomized to vancomycin therapy and was treated for five days for an enlarging foot ulcer. The patient was noted to be anemic and had elevated LFTs after enrollment and admitted to chronic alcohol use. The patient had further elevation in total bilirubin (with moderation of elevated alkaline phosphatase and AST) and developed respiratory distress and circulatory failure 5 days after study medication was discontinued. The AE of multi-system organ failure was assessed as unrelated to study medication.

Discontinuations due to hepatobiliary-related AEs: The only patients who discontinued from study medication are two of the patients previously described (0018-19006-2775 and 202b-00903-9037).

Liver function laboratory studies are discussed in detail in Section 7.1.7.3. Briefly, low level (≥ 3 x ULN) elevation in transaminases were more common in patients treated with vancomycin and seen in approximately 2% of patients. Elevation in total bilirubin and alkaline phosphatase were slightly more common in patients treated with telavancin, but were seen in approximately 1% of patients. No patients treated with telavancin or vancomycin met Hy's Rule criteria for drug-induced liver injury.

7.1.4 Other Search Strategies

The Applicant had a comprehensive screen of the AE database for drug-induced AE syndromes performed by [redacted] The AE database was screened for preferred terms suggesting the possible presence of AE syndromes including: acute liver failure, acute renal failure, acute respiratory failure, agranulocytosis, anaphylaxis, aplastic anemia, confirmed/suspected endotoxin shock, idiopathic thrombocytopenic purpura, intussusception, malignant hypertension, pulmonary fibrosis, rhabdomyolysis, sclerosing syndromes, seizure, significant hemolytic anemia, thrombocytopenia, Torsades de pointes, toxic epidermal necrolysis, and ventricular fibrillation. b(4)

Patients positive in the screening test were then categorized into one of three levels based on coded preferred term AEs. These levels were:

- Probable (specific): preferred term indicated the patient probably had the AE syndrome
- Level 1 (broader): preferred terms include those with less specificity, with medium suspicion of the AE syndrome
- Level 2 (broadest): least specific preferred term, lower suspicion of event of interest

The following is an example of an algorithm used to identifiy an event of interest reproduced from the Applicant's ISS. The example is "acute liver failure".

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Supporting Table 174: Algorithms to Identify Patients Most Likely to Have Experienced Special Syndromes

ACUTE LIVER FAILURE

PROBABLE		
COMA HEPATIC	HEPATIC FAILURE	HEPATOTOXICITY
LEVEL 1		
ALANINE AMINOTRANSFERASE INCREASED ANASARCA	ASPARTATE AMINOTRANSFERASE INCREASED BLOOD ALBUMIN DECREASED	BLOOD ALKALINE PHOSPHATASE INCREASED BLOOD BILIRUBIN INCREASED HEPATIC ENZYME INCREASED
LEVEL 2		
ALANINE AMINOTRANSFERASE ABNORMAL ASPARTATE AMINOTRANSFERASE ABNORMAL ASCITES BLOOD ALKALINE PHOSPHATASE ABNORMAL COAGULATION FACTOR DECREASED	COAGULATION TIME PROLONGED HEPATIC FUNCTION ABNORMAL HYPOALBUMINEMIA LIVER FUNCTION TEST ABNORMAL MULTIORGAN FAILURE	OEDEMA PERIPHERAL PITTING EDEMA PROTHROMBIN TIME PROLONGED

From ISS, Supporting Table 174, pg 12.

In the example above, preferred terms indicating "probable level" included: coma hepatic, hepatic failure, and hepatotoxicity. Level 1 terms are: ALT increase, anasarca, AST increase, blood albumin decreased, blood alkaline phosphatase increased, blood bilirubin increased, and hepatic enzyme increased. Level 2 terms are at the bottom of the Table. Patients identified in either the "Probable" or "Level 1" categories were reviewed case by case to determine if they had the designated syndrome and what role the study medication may have played. Patients identified to Level 2 were only reviewed if the results at the higher levels indicated a possible connection with the study medication.

The Applicant's Drug-Induced Analysis Report was reviewed. Patient numbers were not provided for all patients who were categorized as "probable" or "Level 1". The following specific AE discussions were noted:

- Thrombocytopenia: The initial screen identified 55 telavancin-treated and 43 vancomycin-treated patients. Five telavancin- and four vancomycin-treated patients had AEs coded to preferred terms of thrombocytopenia and platelet count increased [ISS reads this way, but algorithm reported in ISS, Supporting Table 174 reads "platelet count decreased"] and were classified as "probable". All of these patients had documented low post-treatment platelets counts except for one vancomycin-treated patient noted to have platelet clumping. One telavancin-treated patient (202b-00101-7120) had epistaxis associated with a single low platelet count of 13,000 (BL was 271,000 and 7 days after study treatment was discontinued was 136,000). One telavancin- and one vancomycin-treated patient were identified as having probable thrombocytopenia based on presence of a rash; neither had a low platelet count associated. The Level 2 screen was also performed with 35 (3%) of telavancin- and 18 (1%) of vancomycin-treated patients were identified. Most of these patients had bleeding events [e.g., epistaxis, gastrointestinal (GI) bleeding, hematuria, and gingival bleeding]. One telvancin patient (0017-38001-0693) had severe intra-abdominal bleeding related to undiagnosed ovarian cancer. Another telavancin-treated patient was noted to have thrombocytopenia that was clinically significant and may have contributed to epistaxis (0017-38271-0896). One vancomycin-treated patient (0017-18004-0767) had a severe GI bleed.

  MO Comment: Review of the CRF indicates that patient # 202b-00101-7120 had a baseline complete blood count (CBC) in which a platelet count was not reported due to clumping. The platelet count of 271,000 noted above was obtained after a dose of study medication was administered. The patient was noted to have right lower lobe pneumonia and the next day had a platelet count of 13,000 (Day 7 of study therapy). Data clarification pages appended to the CRF indicate that the patient had "low grade DIC" on the same day as the low platelet count was recorded, although no additional coagulation parameters were provided. Ten days after study medication was discontinued the patient's platelet count was 136,000. The CRF does not contain information regarding other pertinent medical history for the patient.

  The other telavancin-treated patient identified with thrombocytopenia (#0017-38271-0896) had a history of chronic renal failure with AV fistula, coronary artery disease with a history of congestive heart failure and cardiomyopathy, hypertension, peripheral vascular disease,

and peptic ulcer disease. The patient had a baseline platelet count of 150,000, Day 5 platelet count of 84,000, Day 8 platelet count of 38,000, Day 10 platelet count of 113,000, Day 13 platlet count of 160,000 and EOT platelet count of 202,000. The patient's thrombocytopenia resolved while continuing study medication which makes a relationship with study medication unlikely.

- Rhabdomyolysis: The initial screen identified 111 telavancin- and 99 vancomycin-treated patients. None of these patients experienced an AE of rhabdomyolysis categorized as "probable". Twenty telavancin- and 9-vancomycin treated patients were categorized as Level 1; most patients experienced an episode of renal insufficiency or myalgias. One telavancin-treated patient (0018-38322-2757) experienced both renal insufficiency and myalgias noted 2 days later. A second telavancin-treated patient (202b-00101-7130) developed a localized myositis in the left thigh with elevated transmainase levels and the myositis remitted despite continuation of study medication. One vancomycin-treated patient (202b-00903-9037) experienced localized deltoid muscle pain with elevated transaminases. No cases of rhabdomyolysis related to study medication were found in this screen of the database.
- Torsades de pointes: The initial screen identified 46 telavancin- and 31 vancomycin-treated patients. None of these patients had an AE classified as "probable". Seven telavancin- and 7 vancomycin-treated patients were identified in the Level 1 screen. Level 1 screening terms included: cardiac arrest, cardio-respiratory arrest, ECG QT interval prolonged, ventricular arrhythmia, ventricular fibrillation, and ventricular tachycardia. A review of the cases indicated that none of these patients were documented to have Torsades de pointes.
- Ventricular fibrillation: The initial screen identified 67 telavancin-treated and 40 vancomycin-treated patients. There were no patients classified as "probable" for having experienced this AE (i.e. coded as "ventricular fibrillation"). Three telavancin- and four vancomycin-treated patients were identified in the Level 1 screen. Level 1 screening terms included cardiac arrest, cardiac flutter, ventricular arrhythmia, cardiopulmonary failure, cardio-respiratory arrest, and cardioversion. All of the telavancin-treated patients died (Patients #0017-02010-0546 coded as "ventricular arrhythmia", #0018-01002-2472 as "cardiac arrest", and #0018-19006-2894 as "cardio-respiratory arrest") and three vancomycin-treated patients died (hepatic coma, pulmonary embolus, and cardiac pump failure). The fourth vancomycin-treated patient had a brief mild episode of "heart flutter" unlikely to have represented ventricular fibrillation.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were monitored throughout the study period of all clinical studies. Adverse events (or experiences) were defined as any untoward medical occurrence in a patient administered the pharmaceutical product and which did not necessarily have a causal relationship with the treatment. An AE could be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the drug. Pre-existing conditions which increased in

frequency or severity or changed in nature during or as a consequence of use of the drug were also considered to be adverse events. Laboratory abnormalities were usually not recorded as an AE. However, abnormal laboratory findings or other abnormal assessments (e.g., ECG, vital signs) were to be recorded as AEs if they met the definition (i.e. signs or symptoms of a disease).

An adverse event was not to include worsening of the primary infection treated in the protocol.

All adverse events were assessed by the investigator responsible for reporting on the clinical assessment of the patient. There were no specific methods outlined for eliciting adverse event complaints from patients other than clinical observation and standard medical care of a patient.

Follow-up of AEs was to continue through the last day of the study (TOC visit), until the investigator/Applicant determined that the subject's condition was stable, or up to 28 days after the last dose of study drug, whichever was longer. The Applicant could request that certain events be followed until resolution.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The investigator was to assess the relationship to study medication using the following definitions:

- Not related: evidence existed that the AE had an etiology other than study medication (e.g, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Possibly/probably related: a temporal relationship existed between the event onset and administration of the study medication. It could not be readily explained by the patient's clinical state or concomitant therapies and appeared with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abated or resolved and reappeared upon rechallenge.

These criteria in addition to good clinical judgement were to be used as a guide for determining the causal assessment. If the event was thought to be unrelated to study therapy, an alternative explanation was to be provided.

MO Comment: Causality assessment according to the above definitions may have resulted in some under-reporting of AEs since the precise effects of the study drug are unknown and observations may have been attributed more readily to underlying comorbid medical conditions or medications with known AE profiles.

Adverse event severity was graded according to the following definitions:

- Mild: aware of signs and symptoms, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activities
- Severe: incapacitating with inability to work or perform usual activities

Verbatim AE terms were coded using the MedDRA dictionary, version 6.1. The following medical encoding software systems were used; Oracle Clinical Thesaurus Management System (Phase 1 and 3) and Clintrial version 4.3 (Phase 2). For all studies, verbatim terms were first run

through an auto-encoder in the respective software systems using MedDRA version 6.1. The auto-encoder directly matched verbatim terms to a lower level term in the MedDRA dictionary. In Phase 1, the Pharmaceutical Clinical Data Manager reviewed all terms not coded by the auto-encoder and manually coded them by searching through the dictionaries for acceptable descriptions of the verbatim term. In Phase 2, the Duke Clinical Research Institute Clinical Trial Coordinator reviewed and manually coded all terms not coded by the auto-encoder based on rules specified in the Medical Coding Process Guideline for the studies. In Phase 3, the ( ) Dictionary Coding Specialist reviewed and manually coded all terms not encoded by the autoencoders using the MedDRA Term Selection: Points to Consider: Release 3.2 as a guideline for splitting and coding AEs as well as pre-determined rules approved by Theravance. For all studies, coding was reviewed by Theravance's medical monitor.

MO Comment: Comparison of the verbatim (investigator) AE term and coded AE terms appeared to be satisfactory as the AEs were being reviewed.

7.1.5.3 Incidence of common adverse events

The overall incidence of treatment-emergent AEs in the Post-Amendment cSSSI efficacy and safety studies (Studies 0017 and 0018) was 79% in the telavancin treatment group and 72% in the vancomycin treatment group. Most of the AEs were mild or moderate in intensity; there were 105 events in 71/929 (7.6%) telavancin-treated patients and 99 events in 63/938 (6.7%) vancomycin-treated patiets that were considered to be severe. [18 vs 4 renal events]

7.1.5.4 Common adverse event tables

Table 47 below shows the TEAEs that occurred at a rate of ≥ 2% in the Post Amendment (10 mg/kg) Phase 3 cSSSI Studies 0017 and 0018 individually and combined.

TABLE 47 : TEAEs Incidence ≥ 2% in Phase 3 Studies 0017, 0018, and 0017/0018 combined (Telavancin 10 mg/kg versus Comparator)

	Study 0017		Study 0018		Post-Amendment 0017 + 0018	
MedDRA SOC/Preferred Term	TLV N=426	Vanc N=429	TLV N=503	Vanc N=509	TLV N=929	Vanc[1] N=938
Any event (# patients, %)	358 (84)	335 (78)	377 (75)	341 (67)	735 (79)	676 (72)
Blood and Lymphatic System						
Any event	16 (4)	19 (4)	15 (3)	12 (2)	31 (3)	31 (3)
Anemia	12 (3)	8 (2)	11 (2)	10 (2)	23 (2)	18 (2)
Gastrointestinal Disorders						
Any event	214 (50)	188 (44)	182 (36)	120 (24)	396 (43)	308 (33)
Abdominal pain	11 (3)	17 (4)	6 (1)	9 (2)	17 (2)	26 (3)
Constipation	61 (14)	37 (9)	35 (7)	5 (<1)	96 (10)	61 (7)
Diarrhea	31 (7)	41 (10)	36 (7)	35 (7)	67 (7)	76 (8)
Dry mouth	11 (3)	15 (3)	9 (2)	7 (1)	20 (2)	22 (2)
Dyspepsia	14 (3)	16 (4)	7 (1)	7 (1)	21 (2)	23 (2)
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)
General Disorders and Administration Site						
Any event	122 (29)	112 (26)	112 (22)	100 (20)	234 (25)	212 (23)
Asthenia	8 (2)	9 (2)	5 (<1)	7 (1)	13 (1)	16 (2)
Fatigue	19 (4)	21 (5)	22 (4)	10 (2)	41 (4)	31 (3)
Infusion site erythema	7 (2)	9 (2)	17 (3)	15 (3)	24 (3)	24 (3)
Infusion site pain	21 (5)	21 (5)	20 (4)	19 (4)	41 (4)	40 (4)
Infusion site phlebitis	6 (1)	7 (2)	12 (2)	14 (3)	18 (2)	21 (2)
Infusion site pruritus	5 (1)	9 (2)	4 (<1)	9 (2)	9 (<1)	18 (2)
Infusion site reaction	7 (2)	7 (2)	7 (1)	7 (1)	14 (2)	14 (1)
Non-cardiac chest pain	12 (3)	7 (2)	4 (<1)	5 (<1)	16 (2)	12 (1)
Pyrexia	9 (2)	10 (2)	6 (1)	2 (<1)	15 (2)	12 (1)
Rigors	22 (5)	14 (3)	19 (4)	7 (1)	41 (4)	21 (2)
Infections and Infestations						
Any event	70 (16)	42 (10)	55 (11)	48 (9)	125 (13)	90 (10)
Urinary tract infection	6 (1)	4 (<1)	13 (3)	3 (<1)	19 (2)	7 (<1)
Investigations						
Any event	19 (4)	33 (8)	44 (9)	38 (7)	63 (7)	71 (8)
ALT increased	2 (<1)	3 (<1)	6 (1)	13 (3)	8 (<1)	16 (2)
Metabolism and Nutrition Disorders						
Any event	40 (9)	45 (10)	45 (9)	39 (8)	85 (9)	84 (9)
Anorexia	10 (2)	10 (2)	7 (1)	1 (<1)	17 (2)	11 (1)
Decreased appetitie	13 (3)	17 (4)	12 (2)	2 (<1)	23 (3)	19 (2)
Hypoglycemia	11 (3)	8 (2)	7 (1)	3 (<1)	18 (2)	11 (1)
Hypokalemia	1 (<1)	7 (2)	9 (2)	12 (2)	10 (1)	19 (2)
Musculoskeletal and Connective Tissue Disorders						
Any event	51 (12)	40 (9)	22 (4)	30 (6)	73 (8)	70 (7)
Arthralgia	12 (3)	8 (2)	7 (1)	5 (<1)	19 (2)	13 (1)
Back pain	14 (3)	8 (2)	6 (1)	9 (2)	20 (2)	17 (2)
Nervous System Disorders						
Any event	212 (50)	126 (29)	207 (41)	106 (21)	419 (45)	232 (25)
Dizziness	27 (6)	35 (8)	28 (6)	18 (4)	55 (6)	53 (6)
Dysgeusia	156 (37)	31 (7)	155 (31)	31 (6)	311 (33)	62 (7)
Headache	82 (19)	69 (16)	48 (10)	51 (10)	130 (14)	120 (13)
Psychiatric Disorders						
Any event	97 (23)	84 (20)	38 (8)	48 (9)	135 (15)	132 (14)
Anxiety	18 (4)	14 (3)	8 (2)	8 (2)	26 (3)	22 (2)
Insomnia	71 (17)	53 (12)	19 (4)	33 (6)	90 (10)	86 (9)
Renal and Urinary Disorders						
Any event	98 (23)	29 (7)	71 (14)	28 (6)	169 (18)	57 (6)
Urine abnormality	69 (16)	8 (2)	53 (11)	19 (4)	122 (13)	27 (3)

TABLE 47 : TEAEs Incidence ≥ 2% in Phase 3 cSSSI Studies (con't)	Study 0017		Study 0018		Post-Amendment 0017 + 0018	
MedDRA SOC/Preferred Term	TLV N=426	Vanc N=429	TLV N=503	Vanc N=509	TLV N=929	Vanc N=938
Respiratory, Thoracic, and Mediastinal Disorders						
Any event	67 (16)	57 (13)	37 (7)	27 (5)	104 (11)	84 (9)
Cough	12 (3)	13 93)	5 (<1)	7 (1)	17 (2)	20 (2)
Dyspnea	10 (2)	7 (2)	5 (<1)	5 (<1)	15 (2)	12 (1)
Pharyngolaryngeal Pain	15 (4)	13 (3)	7 (1)	5 (<1)	22 (2)	18 (2)
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)
Vascular Disorders						
Any event	31 (7)	32 (7)	27 (5)	33 (6)	58 (6)	65 (7)
Flushing	4 (<1)	1 (<1)	6 (1)	14 (3)	10 (1)	15 (2)
Hypotension	12 (3)	7 (2)	5 (<1)	6 (1)	17 (2)	13 (1)
From ISS, Supporting Table 28, pgs 11-16.						

MO comment:

- *The most commonly reported TEAE occurred in telavancin-treated patients and was included in the nervous system SOC; dysgeusia or altered taste was observed in 311/929 (33%) of telavancn-treated patients compared to 62/938 (7%) of vancomycin-treated patients.*
- *The next most commonly reported TEAEs in the telavancin-treated patients were in the gastrointestinal SOC; nausea occurred in 249/929 (27%) of telavancin-treated patients compared to 142/938 (15%) of vancomycin-treated patients. Similarly, vomiting was twice as common in telavancin-treated patients with 127/929 (14%) patients experiencing an episode of vomiting compared to 69 (7%) of vancomycin-treated patients.*
- *Also more commonly reported in telavancin-treated patients was foamy urine (coded as urine abnormality) which was observed in 122/929 (13%) of telavancin-treated patients compared to 27/938 (3%) of vancomycin-treated patients.*
- *The only TEAEs which occurred with increased frequency in the vancomycin-treated group were pruritus in 120/938 (13%) and generalized pruritus 60/938 (6%) and seen in the telavancin-treated groups in 54/929 (6%) and 28/929 (3%), respectively.* (Pruritus and generalized pruritus have not been combined since they may not have been mutually exclusive.)

In order to look for a dose response effect, the Original Protocol patients from Studies 202a, 202b, 0017, and 0018 who received telavancin 7.5 mg/kg dose were assessed in relation to those from the Post Amendment 1 Studies 202b, 0017, and 0018 who received 10 mg/kg for occurrence of TEAEs.

Table 48 shows the TEAEs that occurred at a rate of ≥ 2% in the Original Protocol (7.5 mg/kg) Phase 2 & 3 cSSSI studies (202a, 202b, 0017, and 0018) compared to the Post Amendment (10 mg/kg) Phase 2 & 3 cSSSI studies (202b, 0017, and 0018).

Table 48: TEAEs Incidence ≥ 2% in Original Protocol Phase 2 & 3 Studies Compared to Post Amendment 1 Phase 2 & 3 Studies

	Original Protocol 202a+202b+0017+0018		Post-Amendment 0017 + 0018 + 202b	
MedDRA SOC/Preferred Term	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033
Any event (# patients, %)	144 (75)	138 (73)	791 (77)	730 (71)
Blood and Lymphatic System				
Any event	10 (5)	6 (3)	37 (4)	37 (4)
Anemia	6 (3)	4 (2)	26 (3)	22 (2)
Gastrointestinal Disorders				
Any event	73 (38)	70 (37)	422 (41)	328 (32)
Abdominal pain	5 (3)	5 (3)	17 (2)	26 (3)
Abdominal pain upper	0	2 (1)	8 (<1)	16 (2)
Constipation	14 (7)	11 (6)	101 (10)	68 (7)
Diarrhea	9 (5)	12 (6)	73 (7)	81 (8)
Dry mouth	4 (2)	2 (1)	21 (2)	22 (2)
Dyspepsia	6 (3)	5 (3)	21 (2)	25 (2)
Nausea	48 (25)	40 (21)	265 (26)	148 (14)
Vomiting	21 (11)	17 (9)	135 (13)	75 (7)
General Disorders and Administration Site				
Any event	42 (22)	39 (21)	250 (24)	226 (22)
Asthenia	1 (<1)	2 (1)	13 (1)	16 (2)
Edema peripheral	5 (3)	2 (1)	13 (1)	14 (1)
Fatigue	5 (3)	3 (2)	42 (4)	31 (3)
Infusion site erythema	3 (2)	4 (2)	26 (3)	27 (3)
Infusion site pain	6 (3)	6 (3)	42 (4)	40 (4)
Infusion site phlebitis	0	0	19 (2)	21 (2)
Infusion site pruritus	1 (<1)	0	9 (<1)	18 (2)
Non-cardiac chest pain	2 (1)	1 (<1)	16 (2)	12 (1)
Pyrexia	4 (2)	2 (1)	17 (2)	16 (2)
Rigors	7 (4)	4 (2)	47 (5)	23 (2)
Infections and Infestations				
Any event	27 (14)	23 (12)	138 (13)	101 (10)
Urinary tract infection	6 (3)	5 (3)	20 (2)	9 (<1)
Vaginal mycosis	3 (2)	0	10 (<1)	13 (1)
Investigations				
Any event	30 (16)	29 (15)	74 (7)	93 (9)
ALT increased	7 (4)	14 (7)	11 (1)	17 (2)
AST increased	9 (5)	16 (8)	11 (1)	13 (1)
Blood creatinine increased	4 (2)	2 (1)	14 (1)	6 (<1)
Metabolism and Nutrition Disorders				
Any event	25 (13)	15 (8)	96 (9)	92 (9)
Anorexia	4 (2)	3 (2)	17 (2)	11 (1)
Decreased appetitie	1 (<1)	0	27 (3)	19 (2)
Hypoglycemia	2 (1)	1 (<1)	18 (2)	11 (1)
Hypokalemia	8 (4)	1 (<1)	11 (1)	23 (2)
Hypomagnesemia	3 (2)	6 (3)	8 (<1)	16 (2)
Musculoskeletal and Connective Tissue Disorders				
Any event	12 (6)	18 (10)	77 (7)	75 (7)
Arthralgia	5 (3)	0	20 (2)	17 (2)
Back pain	4 (2)	3 (2)	20 (2)	17 (2)
Pain in extremity	1 (<1)	6 (3)	13 (1)	12 (1)
Nervous System Disorders				
Any event	61 (32)	38 (20)	441 (43)	240 (23)
Dizziness	15 (8)	6 (3)	58 (6)	55 (5)
Dysgeusia	21 (11)	5 (3)	325 (32)	62 (6)
Headache	26 (14)	20 (11)	138 (13)	124 (12)
Hypoaesthesia	3 (2)	6 (3)	6 (<1)	12 (1)
Paraesthesia	3 (2)	4 (2)	6 (<1)	12 (1)
Somnolence	3 (2)	3 (2)	11 (1)	6 (<1)

Table 48: TEAEs Incidence ≥ 2% in Original Protocol (con't)	Original Protocol 202a+202b+0017+0018		Post-Amendment 0017 + 0018 + 202b	
MedDRA SOC/Preferred Term	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033
Psychiatric Disorders				
Any event	38 (20)	30 (16)	151 (15)	137 (13)
Agitation	5 (3)	8 (4)		
Anxiety	11 (6)	10 (5)	27 (3)	22 (2)
Insomnia	23 (12)	17 (9)	103 (10)	89 (9)
Renal and Urinary Disorders				
Any event	19 (10)	13 (7)	181 (18)	66 (6)
Hematuria	3 (2)	2 (1)	12 (1)	3 (<1)
Renal insufficiency	3 (2)	0	10 (<1)	2 (<1)
Urine abnormality	6 (3)	4 (2)	125 (12)	27 (3)
Respiratory, Thoracic, and Mediastinal Disorders				
Any event	29 (15)	13 (7)	112 (11)	88 (9)
Cough	5 (3)	3 (2)	19 (2)	21 (2)
Dyspnea	8 (4)	3 (2)	17 (2)	12 (1)
Pharyngolaryngeal Pain	2 (1)	1 (<1)	23 (2)	18 (2)
Skin and Subcutaneous Tissue Disorders				
Any event	34 (18)	40 (21)	175 (17)	262 (25)
Dry skin	0	5 (3)	8 (<1)	11 (1)
Erythema	2 (1)	3 (2)	8 (<1)	11 (1)
Hyperhidrosis	4 (2)	5 (3)	16 (2)	13 (1)
Pruritus	14 (7)	14 (7)	60 (8)	128 (12)
Pruritus generalized	4 (2)	4 (2)	37 (4)	43 (4)
Rash	6 (3)	4 (2)	37 (4)	43 94)
Vascular Disorders				
Any event	13 (7)	18 (10)	64 (6)	72 (7)
Flushing	1 (<1)	3 (2)	10 (<1)	16 (2)
Hypertension	4 (2)	5 (3)	16 (2)	14 (1)
Hypotension	7 (4)	4 (2)	19 (2)	13 (1)

ISS, Table 5-3, pgs 93-97.
[1] Includes 27 patients (20 in 202a and 7 in Post-Amendment 1) who received an antistaphylococcal penicillin instead of vancomycin.

MO Comment: The frequencies of the most common TEAEs observed were compared for the 7.5 mg/kg and 10 mg/kg telavancin dose studies (Post-Amendment 202b events are included in the 10 mg/kg column). Although direct comparison should be interpreted carefully due to difference in sample sizes, some general observations are noted.

- *Dysgeusia appears to have a definite dose relationship, occurring in 325/1029 (32%) of those treated with telavancin 10 mg/kg compared to 21/192 (11%) of those treated with telavancin 7.5 mg/kg.*
- *The frequency of gastrointestinal TEAEs (nausea and vomiting) appear to be relatively similar across the two doses with rates of nasusea and vomiting of 265/1029 (26%) and 135/1029 (13%) for the telavancin 10 mg/kg group and 48/192 (25%) and 21/192 (11%) for the telavancin 7.5 mg/kg group. However, the difference between the telavancin-treated groups and vancomycin-treated groups is much greater for those receiving telavancin at 10 mg/kg doses than 7.5 mg/kg doses (for nausea 12% versus 4% and vomiting 6% versus 2%, respectively) and suggest a dose effect for these TEAEs.*
- *Urine abnormality is more frequent in the telavancin 10 mg/kg treatment group compared to the telavancin 7.5 mg/kg group, with the finding noted in 125/1029 (12%) compared to 6/192 (3%), respectively, and appears to have a relationship to dose.*
- *There is no apparent telavancin dose-related effect on pruritus.*

In the Phase 1 clinical pharmacology studies, dysgeusia, foamy urine, headache, and nausea were noted in >10% of subjects. In Study 104a (QT study), with placebo, 7.5 mg/kg, and 10 mg/kg telavancin dose arms, a dose relationship was noted for the following AEs:

AE	Placebo	7.5 mg/kg telavancin	10 mg/kg telavancin
Dysgeusia	2.5%	45%	64.1%
Nausea	2.5%	12.5%	33.3%
Vomiting	0	2.5%	20.5%

7.1.5.5 Identifying common and drug-related adverse events

The NDA submission and Applicant-proposed labeling included a table listing TEAEs. A request was sent to the Applicant from the FDA on August 30, 2007 to submit an alternate table (if necessary) listing adverse drug reactions as defined in the FDA guidance document on selecting and characterizing data in the adverse reactions section of the label. The Applicant was also asked to submit the algorithm or rationale for determining whether an event met the definition for adverse drug reaction.

The Applicant submitted the requested information to the NDA on September 13, 2007. The algorithm used to identify ADRs proposed is as follows:

-
-
-

b(4

b(4)

An alternate proposal was to use a table listing Treatment-Emergent Adverse Reactions with number / percent of patients included based on investigator assessment of causality.

Table 49 is reproduced from the ISS in the original NDA submission and is based strictly on event occurrence in > 2% of either treatment group.

Table 49: Treatment-Emergent Adverse Events with an Incidence > 2% in Telavancin or Vancomycin – Studies 0017 and 0018 AT Populations Combined

Table 5-1: Treatment-Emergent Adverse Events with an Incidence of > 2% in Telavancin or Vancomycin – Studies 0017 and 0018 Combined - Safety Population

	Telavancin 10 mg/kg (N=929)	Vancomycin (N=938)
BODY AS A WHOLE		
Rigors	4%	2%
Generalized Pruritus	3%	6%
DIGESTIVE SYSTEM		
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
Abdominal pain	2%	3%
METABOLIC AND NUTRITIONAL		
Decreased Appetite	3%	2%
NERVOUS SYSTEM		
Taste Disturbance[a]	33%	7%
Dizziness	6%	6%
RENAL SYSTEM		
Foamy Urine[b]	13%	3%
SKIN AND APPENDAGES		
Pruritus	6%	13%
Rash	4%	5%
OTHER		
Infusion Site Pain	4%	4%
Infusion Site Erythema	3%	3%

[a] Usually described as metallic or soapy taste

b(4)

MO Comment: The first of the Applicant's newly proposed approaches to determining ADRs is preferred.

b(4)

The FDA medical reviewer would recommend use of the Applicant's criteria if all 3 of the criteria listed are required. Additionally, AEs that occur at a rate at least 5% higher in the vancomycin group should also be considered for inclusion.

7.1.6 Less Common Adverse Events

Based on the size of the safety database (total telavancin treated population of N=1221 in clinical trials) an event occurring in 1/400 patients would be detectable.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory tests including hematology, chemistry, urinalysis, and tests of coagulation were incorporated into Clinical Pharmacology protocols to monitor the general safety of subjects.

During the initial Phase 1 studies, subjects with unexplained prolongation of the prothrombin time were observed. Evaluations conducted in conjunction with this finding in the elderly subject study (102a) suggested that prolongation of the prothrombin time and partial thromboplastin time associated with the administration of telavancin did not indicate a drug effect on coagulation. Results from a series of *in vitro* and *in vivo* studies confirmed that telavancin interferes with common laboratory tests used to monitor coagulation (prothrombin time, international normalized ratio, activated partial thromboplastin time, and in high concentrations, activated clotting time) but does not interfere with coagulation.

Table 50 from the Applicant's ISS shows which coagulation studies have been determined to be affected by telavancin.

Table 50

Table 6-1: Coagulation Tests Affected and Unaffected by Telavancin

Affected by Telavancin	Unaffected by Telavancin
Prothrombin time	Thrombin time
International normalized ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic Factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) Factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

From ISS, Table 6-1, pg 244.

For patients receiving unfractionated heparin where monitoring is required within 18 hours of a dose of telavancin, the Applicant recommended use of the chromogenic Factor Xa-based assay instead of an aPTT, activated clotting time, or coagulation-based Factor Xa assay. The Applicant recommended use of the functional Factor X assay for monitoring of warfarin in patients receiving telavancin. Anticoagulation tests should be performed at the end of a dosing interval or at least 18 hours after the last dose.

Preclinical and early Phase 1 human studies indicated the potential for telavancin to interfere with the semi-quantitative reagent strips for measuring urine protein. Interference was also demonstrated with a quantitative colorimetric test with pyrogallol red-molybdate. Assessment of telavancin effect on urinary excretion was studied by three methods in the 4-arm ECG study (I6424-104a). Measurement of urinary total protein by colorimetric assay and urinary microalbumin by nephelometry was performed on a 6-hr collection of urine commencing at the intiation of Day 3 infusion of telavancin (7.5 mg/kg and 15 mg/kg), placebo, and moxifloxacin. A standard reagent strip test of urine was also performed 24 hours after the last dose of the study medication. Dose-dependent increases in urine protein were detected with the colorimetric method, with increases in the telavancin groups also statistically significantly different from the placebo and moxifloxacin groups. When microalbumin was assayed there was a slight difference in the 15 mg/kg telavancin group (0.4 mg/dL versus 0.2 mg/dL for placebo and 7.5 mg/kg telavancin versus 0.1 mg/dL for moxifloxacin); this difference between the 10 mg/kg telavancin dose group and the other groups was statistically significant. The Applicant notes that the colorimetric assay is most likely artifactually elevated compared to the more sensitive microalbumn nephelometric test which may be exhibiting true dose-related effects on the kidney, causing a real increase in microalbumin, although most elevations remained in the normal range.

Therefore, the Applicant recommends use of urine dipstick testing as a screening measure. However, if the sample tests positive for protein, the test should be followed up with measurement of urine microalbumin.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

In the cSSSI studies, hematology, serum chemistry, and urinalysis were performed at baseline, after infusion every third day (Days 1, 4, 7, 10, 13 with ±1 day window), at EOT, and TOC evaluations. All laboratory tests were to be performed in a central laboratory. The focus of the Applicant's assessment of laboratory results was on potentially significant changes and mean change in baseline for hematology, serum chemistry, and urine microalbumin.

The focus of the clinical laboratory assessments in the Applicant's ISS focus on mean change from baseline and potentially clinically significant changes for hematology, serum chemistry, and urinalysis.

The specific laboratory tests reported and analyzed within each category include:

- Hematology: hematocrit, hemoglobin, WBC count with microscopy differential (% immature/band neutrophils, mature neutrophils, eosinophils), and platelet count.

- Serum chemistry: potassium, magnesium, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT, and AST.
- Urinalysis: presence of blood, bilirubin, urobilinoge, nitrite, leukocytes, microscopic examination of sediment (if dipstick positive) and microalbumin.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The Applicant assessed the designated laboratory parameter for the mean change from the baseline value to the worst value through the end of therapy. The number of patients evaluated for each parameter was dependent both on the number of patients who had a baseline value with at least one follow-up value before EOT and for whom the baseline assessment was normal.

HEMATOLOGY

Tables 51 and 52shows the hematology parameter assessed, the number of patients evaluated for that parameter, the baseline mean value, and the mean change of the worst value mean prior to EOT. Extreme values for a parameter will be addressed in the discussion of potentially clinically significant laboratories.

Table 51: Hematology Parameters (Phase 3 cSSSI: 0017 and 0018 10 mg/kg Telavancin versus Comparator)

	Study 0017				Study 0018				0017 + 0018			
	Telavancin		Vancomycin		Telavancin		Vancomycin		Telavancin		Vancomycin	
	BL	Change	BL	Change	BL	Change	BL	Change	BL	Change	BL	Change
Hematocrit – low												
• N	315	315	310	310	357	357	371	371	672	672	681	681
• Mean	0.42	-0.04	0.41	-0.03	0.42	-0.03	0.42	-0.03	0.42	-0.03	0.42	-0.03
• Std dev	0.04	0.03	0.04	0.03	0.04	0.03	0.04	0.03	0.04	0.03	0.04	0.03
Hemoglobin (g/L) – low												
• N	268	268	281	281	330	330	346	346	598	598	627	627
• Mean	136.27	-11.00	136.64	-9.83	137.52	-8.61	138.28	-7.95	136.96	-9.68	137.55	-8.79
• Std dev	12.18	9.83	12.09	10.20	11.8	9.64	12.79	10.17	11.98	9.79	12.5	-8.0
WBC (10^9/L) – high												
• N	273	273	275	275	298	298	293	293	571	571	568	568
• Mean	7.54	1.05	7.57	0.49	7.53	0.98	7.67	0.27	7.53	1.02	7.62	0.38
• Std dev	1.66	2.79	1.74	2.39	1.80	3.18	1.64	2.1	1.73	3.0	1.69	2.24
WBC (10^9/L) – low												
• N	273	273	275	275	298	298	293	293	571	571	568	568
• Mean	7.54	-1.91	7.57	-2.03	7.53	-1.43	7.67	-1.82	7.53	-1.66	7.62	-1.92
• Std dev	1.66	2.05	1.74	1.91	1.80	2.03	1.64	1.71	1.73	2.05	1.69	1.81
Eosinophils (%) – high												
• N	386	386	401	401	451	451	444	444	837	837	845	845
• Mean	1.55	2.36	1.6	2.39	1.6	1.67	1.65	1.92	1.58	1.99	1.63	2.14
• Std dev	1.13	2.89	1.2	2.32	1.25	1.78	1.18	2.00	1.2	2.38	1.19	2.17
Neutrophils (%) – low												
• N	232	232	237	237	257	257	260	260	489	489	497	497
• Mean	4.91	-1.56	4.8	-1.7	4.79	-1.18	4.9	-1.48	4.85	-1.36	4.85	-1.58
• Std dev	1.37	1.73	1.32	1.43	1.43	1.63	1.29	1.42	1.4	1.69	1.31	1.43
Platelet Count (10^9/L) – high												
• N	330	330	340	340	364	364	367	367	694	694	707	707
• Mean	260.70	83.10	269.61	93.96	264.9	75.41	267.41	77.54	262.9	79.07	268.47	85.44
• Std dev	63.23	94.99	69.87	91.40	66.32	92.45	62.49	94.40	64.86	93.68	66.1	93.26
Platelet Count (10^9/L) – low												
• N	330	330	340	340	364	364	367	367	694	694	707	707
• Mean	260.70	-17.85	269.61	-7.24	264.9	-11.41	267.41	-6.66	262.9	-14.47	268.47	-6.94
• Std dev	63.23	72.6	69.87	59.17	66.32	65.14	62.49	58.47	64.86	68.81	66.1	58.77

From ISS, Supporting Table 123, pgs 21-28.

MO Comment:

- *The mean decrease in platelet count from baseline to lowest post-baseline value was greater for the telavancin-treated patients compared to vancomycin-treated patients; the difference for telavancin was a 14.5 x 10^9/L decrease compared to 7.0 x 10^9/L for vancomycin. This finding is of interest in light of patients who developed a PCS decrease in platelets while on telavancin treatment (see below in discussion of PCS platelet counts). Conversely, there was a greater mean increase in platelet counts in vancomycin-treated patients compared to telavancin-treated patients, although the increase is of less clinical concern than the decrease.*
- *The mean hemoglobin decrease was slightly greater in the telavancin treated patients when Studies 0017 and 0018 are combined, however the change of 0.89 g/dL (0.09 mg/dL in conventional units) does not appreciably affect the mean change in hematocrit and is not clinically significant.*
- *There was a slight greater decrease in WBC count and % neutrophils for vancomycin relative to telavancin when the studies are combined; the decrease for vancomycin is 1.9 x 10^9/L compared to the decrease for telavancin of 1.7 x 10^9/L (difference of 0.2 x 10^9/L or 0.22 x 10^3/μL in conventional units) WBC count and 1.6% compared to 1.4% for neutrophils, respectively. The number of patients with normal WBC count at baseline who had low values at EOT was also slightly greater for vancomycin when examining the shift tables, with 30/544 (5.5%) of vancomycin-treated patients and 24/534(4.5%) of telavancin-treated patients having this finding.*
- *There was a slightly greater increase in mean change in % eosinophils in vancomycin-treated patients relative to telavancin; the increase was 2.1% compared to 2.0% for vancomycin and telavancin, respectively. This change was also noted in the number (percent) of patients with normal % eosinophils at baseline who had a high value at the end of therapy; 44/811(5.4%) treated with vancomycin had high % eosinophils at EOT compared to 24/777 (3.1%) for telavancin in Studies 0017 and 0018 combined.*

Table 52: Hematology Parameters (original protocol telavancin 7.5 mg/kg versus comparator and post amendment 10 mg/kg telavancin versus comparator)

	Original Protocol 202a+202b+0017+0018				Post Amendment 202b+0017+0018			
	Telavancin 7.5		Vancomycin		Telavancin 10		Vancomycin	
	BL	Change	BL	Change	BL	Change	BL	Change
Hematocrit – low								
• N	126	126	123	123	727	727	725	725
• Mean	0.42	-0.04	0.42	-0.04	0.42	-0.03	0.42	-0.03
• Std dev	0.03	0.03	0.04	0.03	0.04	0.03	0.04	0.03
Hemoglobin (g/L) – low								
• N	103	103	114	114	645	645	670	670
• Mean	136.23	-9.88	137.03	-10.82	137.12	-9.97	137.69	-9.08
• Std dev	9.26	9.20	11.79	11.15	12.04	10.16	12.48	10.27
WBC (10^9/L) – high								
• N	111	111	113	113	621	621	616	616
• Mean	8.03	0.59	7.79	0.49	7.58	1.04	7.65	0.44
• Std dev	1.66	2.20	1.81	2.29	1.75	2.97	1.72	2.34
WBC (10^9/L) – low								
• N	111	111	113	113	621	621	616	616
• Mean	8.03	-2.39	7.79	-2.25	7.58	-1.67	7.65	-1.93
• Std dev	1.66	1.86	1.81	1.72	1.75	2.04	1.72	1.81
Eosinophils (%) – high								
• N	171	171	174	174	926	926	930	930
• Mean	1.5	2.39	1.65	2.15	1.56	2.02	1.61	2.20
• Std dev	1.05	2.30	1.19	1.98	1.19	2.34	1.19	2.23
Neutrophils (%) – low								
• N	92	92	97	97	530	530	537	537
• Mean	5.04	-1.85	4.89	-1.87	4.83	-1.35	4.84	-1.59
• Std dev	1.2	1.37	1.36	1.44	1.4	1.67	1.32	1.41
Platelet Count (10^9/L) – high								
• N	152	152	150	150	769	769	779	779
• Mean	263.88	99.68	266.99	95.48	263.72	80.72	268.74	88.18
• Std dev	60.2	112.56	57.25	90.15	64.47	94.73	65.72	97.34
Platelet Count (10^9/L) – low								
• N	152	152	150	150	769	769	779	779
• Mean	263.88	-25.74	266.99	-16.15	263.72	-15.17	268.74	-8.86
• Std dev	60.20	61.91	57.25	50.95	64.47	66.61	65.72	58.36
From ISS, Supporting Table 122, pgs 17-20.								

MO Comment: The comparison of laboratory parameters between populations enrolled under the Original Protocol and Post Amendment 1 may demonstrate some telavancin dose-related laboratory changes, however, the results should be interpreted cautiously due to the difference in sample sizes.

- *The 10 mg/kg dose of telavancin appears to have no greater effect on hemoglobin and hematocrit than the 7.5 mg/kg dose of telavancin.*
- *The higher dose of telavancin does not appear to detrimentally affect the WBC count or % neutrophils.*
- *The higher dose of telavancin also doesn't appear to have a greater mean increase in % eosinophils than the lower dose.*
- *The decrease in mean change in platelet count is greater in the 7.5 mg/kg telavacin dose group than the 10 mg/kg telavancin group, although the mean change relative to vancomycin is consistent for each of the dose groups.*