HEPATOBILIARY

The following Table, Table 53, shows the hepatic parameter assessed, the number of patients evaluated for that parameter, the baseline mean, standard deviation, median, and maximum values. The same parameters are shown for the worst change from baseline in each of the Phase 3 cSSSI studies separately and combined.

Table 53: Hepatic 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
ALT (U/L) – high												
• N	319	319	352	352	384	384	402	402	703	703	754	754
• Mean	19.03	15.72	19.88	23.31	19.5	14.63	18.60	17.53	19.29	15.12	20.23	20.2
• Std dev	8.24	36.64	8.63	35.83	8.12	37.64	7.70	28.46	8.17	37.17	8.17	32.22
• Median	17.0	8.0	18.0	11.0	18.0	6.0	17.0	9.0	18.0	7.0	17.0	10.0
• Max												
AST (U/L) – high												
• N	312	312	337	337	374	374	389	389	686	686	726	726
• Mean	20.75	12.32	20.32	19.87	20.33	12.51	19.41	13.68	20.52	12.42	19.83	16.55
• Std dev	6.41	27.41	6.03	28.60	6.10	45.79	5.86	21.19	6.24	38.51	5.95	25.08
• Median	20.0	7.0	20.0	11.0	19.0	5.0	18.0	7.0	19.0	6.0	19.0	8.0
• Max												
Alkaline phosphatase (U/L) – high												
• N	338	338	350	350	390	390	415	415	728	728	765	765
• Mean	82.51	8.87	81.38	10.27	80.88	7.92	82.55	9.95	81.64	8.36	82.02	10.10
• Std dev	19.85	23.21	19.70	23.60	19.52	25.41	19.65	20.26	19.68	24.40	19.67	21.83
• Median	81.00	3.00	79.0	6.0	78.50	4.0	82.0	5.00	80.0	4.00	81.0	6.00
• Max												
Total bilirubin (μmol/L) – high												
• N	352	352	349	349	411	411	419	419	763	763	768	768
• Mean	8.61	0.98	8.07	0.28	8.23	0.95	8.34	0.02	8.40	0.97	8.21	0.14
• Std dev	4.32	5.23	4.16	4.45	4.17	5.03	4.11	3.97	4.24	5.12	4.13	4.2
• Median	7.0	0	7.0	0	7.0	0	7.0	0	7.00	0	7.0	0
• Max												

From ISS, Supporting Table 129, pgs 67-76.

b(4)

MO Comment:

• Vancomycin demonstrates a greater mean increase in transaminases (ALT and AST) and alkaline phosphatase than telavancin. However, the maximum change from baseline for transaminases is seen in the tealavancin-treated groups, while the maximum change in alkaline phosphatase is similar between treatment groups.

• The mean increase of 0.97 μmol/L in total bilirubin is greater for the telavancin treatment group compared to the mean increase of 0.12 μmol/L (0.85 or 0.05 mg/dL in conventional units) greater than that for the vancomycin treatment group from Studies 0017 and 0018 combined. This increase may or may not be clinically significant.

The following Table, Table 54, shows similar parameters for the 7.5 mg/kg telavancin dose studies compared to the 10 mg/kg dose studies.

Table 54: Hepatic 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
ALT (U/L) - high								
• N	144	144	146	146	783	783	827	827
• Mean	20.14	23.50	19.86	32.92	19.49	14.80	19.33	21.44
• Std dev	9.30	34.01	9.11	82.03	8.43	35.71	8.27	36.23
• Median	82.0	9.50	18.0	14.50	18.0	7.0	18.0	10.0
• High								
AST (U/L) - high								
• N	135	135	145	145	763	763	801	801
• Mean	20.93	20.95	20.47	33.25	20.53	12.33	19.91	17.33
• Std dev	6.87	25.51	6.71	126.93	6.47	36.97	6.18	26.60
• Median	20.0	13.0	19.0	12.0	19.0	6.0	19.0	9.0
• High								
Alkaline Phosphatase (U/L) - high								
• N	150	150	165	165	811	811	848	848
• Mean	84.99	7.49	86.03	9.05	81.90	8.11	82.47	9.84
• Std dev	19.09	23.86	19.67	20.43	19.74	23.83	19.83	21.84
• Median	82.0	3.0	84.0	4.0	80.0	3.00	81.50	5.0
• High								
Total bilirubun (μmol/L)								
• N	160	160	169	169	849	849	854	854
• Mean	7.32	1.99	7.40	1.42	8.36	1.07	8.18	0.23
• Std dev	3.73	7.70	3.86	4.06	4.19	5.01	4.11	4.16
• Median	6.84	1.71	6.84	1.71	7.0	0	7.0	0
• High								
From ISS, Supporting Table 128, pgs 62-66.								

b(4)

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 large difference in sample sizes.

- *The higher dose of telavancin does not appear to have a greater mean increase in transaminases relative to the lower telavancin dose.*
- *The mean increase in alkaline phosphatase appears slightly greater for the higher dose of telavancin treatment, although a similar change is seen for vancomycin in the low versus high telavancin studies making interpretation of dose-related effect difficult.*
- *The mean increase in the total bilirubin concentration is less for the higher dose of telavancin although a similar change is seen for vancomycin in the low versus high telavancin studies making interpretation of dose-related effect difficult.*
- *Except for the change in total bilirubin, the mean worst change for paramters was seen in the vancomycin treatment group in Study 0017.*

RENAL

Tables 55 and 56 show the number, mean and standard deviation, median, and maximum values for baseline serum creatinine and blood urea nitrogen. The same parameters are shown for the mean changes of the highest changes from baseline through EOT.

b(4)

Tabel 55: Renal 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
Serum Creatinine (μmol/L) - high												
• N	372	372	401	401	444	444	453	453	816	816	854	854
• Mean	69.62	18.35	71.32	8.06	73.56	18.97	74.03	8.85	71.76	18.69	72.76	8.48
• Std dev	17.03	31.75	16.51	19.04	17.26	38.95	17.20	19.06	17.26	35.83	16.92	19.04
• Median	71.0	9.00	71.0	8.0	71.0	9.00	71.0	9.00	71.0	9.0	71.0	9.0
• Max												
Urea Nitrogen (mmol/L) - high												
• N	372	372	390	390	439	439	437	437	811	811	827	827
• Mean	4.84	1.77	4.74	1.32	4.80	1.75	4.92	1.16	4.82	1.76	4.84	1.24
• Std dev	1.72	2.74	1.64	1.95	1.66	2.81	1.62	1.76	1.69	2.78	1.63	1.86
• Median	4.60	1.48	4.30	1.10	4.60	1.40	4.60	1.0	4.60	1.40	4.60	1.10
• Max												

From ISS, Supporting Table 129, pgs 67-76.

MO Comment:

• *The mean maximum increase in serum creatinine is 19 μmol/L for telavancin-treated patients compared to 8 μmol/L for vancomcycin-treated patients. However, the higher mean and standard deviation for the telavancin treatment groups, along with similar median values for change from baseline in both telavancin and vancomycin treatment groups, may be due to more outliers in the high category in the telavancin treatment groups.*

• *The mean maximum increase from baseline for BUN is 1.76 mmol/L for telavancin compared to 1.24mmol/L for vancomcyin in the 2 Phase 3 studies.*

Table 56: Renal 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
Serum Creatinine (µmol/L) - high								
• N	168	168	173	173	905	905	939	939
• Mean	70.02	19.91	69.73	8.57	72.10	18.39	72.91	8.14
• Std dev	17.89	35.10	17.0	15.27	17.31	35.12	16.84	18.45
• Median	70.72	9.00	70.72	8.84	71.0	9.00	71.0	8.84
• High								
Urea Nitrogen (mmol/L) - high								
• N	156	156	168	168	891	891	901	901
• Mean	4.60	1.85	4.51	1.39	4.79	1.70	4.82	1.21
• Std dev	1.65	2.17	1.42	2.01	1.66	2.71	1.60	1.83
• Median	4.30	1.64	4.29	1.10	4.60	1.40	4.60	1.10
• High								

From ISS, Supporting Table 128, pgs 62-66.

b(4)

MO Comment:

• *There is no apparent dose-related effect on the mean maximum increase in serum creatinine between the two telavancin dose groups. The maximum change from baseline is 2 times higher in the telavancin 10 mg/kg treatment, however this could reflect a single outlier patient and cannot be used alone to conclude there is a dose effect.*

The Applicant also included mean change summary tables for potentially clinically significant magnesium, potassium, and LDH concentrations. Urine microalbumin was the only urinalysis parameter evaluated.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The Applicant provided a table in the ISS that shows the number of patients in each of the Post-Amendment 1 Phase 3 studies (0017 and 0018 separately and combined) who had a PCS (potentially clinically significant) hematology laboratory parameter.

HEMATOLOGY
The following table, Table 57, shows the number of patients with PCS laboratory values for hematology parameters.

Table 57: Potentially Clinically Significant Hematology Values (Phase 3 cSSSI: 0017 and 0018 10 mg/kg Telavancin versus Comparator)

| | Study 0017 | | | | Study 0018 | | | | 0017 + 0018 | | | |
| | Telavancin | | Vancomycin | | Telavancin | | Vancomycin | | Telavancin | | Vancomycin | |
	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)
Hematocrit												
• Male ≤ 0.3	166	3 (2)	165	3 (2)	203	2 (<1)	226	1 (<1)	369	5 (1)	391	4 (1)
• Female ≤ 0.28	149	6 (4)	145	2 (1)	154	6 (4)	145	4 (3)	303	12 (4)	290	6 (2)
Hemoglobin												
• Male ≤ 90 g/L	144	1 (<1)	159	1 (<1)	197	0	218	1 (<1)	341	1 (<1)	377	2 (<1)
• Female ≤ 85 g/L	124	1 (<1)	122	0	133	1 (<1)	128	0	257	2 (<1)	250	0
Hemoglobin												
• Male ≤ 90 g/L AND ≥ 10 g/L below BL	144	1 (<1)	159	1 (<1)	197	0	218	1 (<1)	341	1 (<1)	377	2 (<1)
• Female ≤ 85 g/L AND ≥ 10 g/L below BL	124	1 (<1)	122	0	133	1 (<1)	128	0	257	2 (<1)	250	0
WBC ≤ 2.8 × 10^9/L	273	3 (1)	275	7 (3)	298	5 (2)	293	3 (1)	571	8 (1)	568	10 (2)
WBC ≥ 16 × 10^9/L	273	6 (2)	275	4 (1)	298	7 (2)	293	1 (<1)	571	13 (2)	568	5 (<1)
Eosinophils ≥ 0.10 (≥ 10%)	386	10 (3)	401	7 (2)	451	6 (1)	444	8 (2)	837	16 (2)	845	15 (2)
Neutrophils ≤ 0.10 (≤ 10%)	232	3 (1)	237	1 (<1)	257	2 (<1)	260	0	489	5 (1)	497	1 (<1)
Platelet Count ≥ 700 × 10^9/L	330	3 (<1)	340	1 (1)	364	4 (1)	367	7 (2)	694	7 (1)	707	11 (2)
Platelet Count ≤ 75 × 10^9/L	330	2 (<1)	340	0	364	0	367	0	694	2 (<1)	707	0
Platelet Count ≤ 75 × 10^9/L AND ≥ 50 × 10^9/L	330	2 (<1)	340	0	364	0	367	0	694	2 (<1)	707	0

From ISS, Supporting Table 120, pgs 3-9.

MO Comment:

- *There are twice as many females with PCS low hematocrit values in the telavancin treatment group compared to the vancomycin group for the Phase 3 studies combined, however this difference is not apparent in the hemoglobin values. The PCS eosinophil counts are balanced between the two treatment groups. The number of patients with PCS leukopenia or neutropenia does not differ between the telavancin and vancomycin treatment groups; this is important to note because vancomycin therapy has been associated with these events. There are two subjects with PCS low platelet values in the telavancin treatment group in Study 0017, with no similar events in the telavancin treatment group in Study 0018 or vancomycin treatment group in either study. These subjects will be discussed in Section 7.1.7.3.3 below.*

Table 58 below shows the number of patients with PCS hematology values for the SSSI studies using a 7.5 mg/kg dose of telavancin compared to those using a 10 mg/kg dose of telavancin.

Table 58: Potentially Clinically Significant Hematology Values (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		Vancomycin		Telavancin		Vancomycin	
	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)
Hematocrit								
• Male ≤ 0.3	78	0	72	1 (1)	400	6 (2)	418	4 (<1)
• Female ≤ 0.28	48	0	51	1 (2)	327	13 (4)	307	6 (2)
Hemoglobin								
• Male ≤ 90 g/L	71	0	65 (1)	1 (2)	365	2 (<1)	402	2 (<1)
• Female ≤ 85 g/L	32	0	49 (1)	1 (2)	280	5 (2)	268	0
Hemoglobin								
• Male ≤ 90 g/L AND ≥ 10 g/L below BL	71	0	65	1 (2)	365	1 (<1)	402	2 (<1)
• Female ≤ 85 g/L AND ≥ 10 g/L below BL	32	0	49	1 (2)	280	2 (<1)	268	0
WBC ≤ 2.8 x 10^9/L	111	5 (5)	113	1 (<1)	621	9 (1)	616	12 (2)
WBC ≥ 16 x 10^9/L	111	0	113	2 (2)	621	14 (2)	616	8 (1)
Eosinophils ≥ 0.10 (≥ 10%)	171	7 (4)	174	3 (2)	926	18 (2)	930	18 (2)
Neutrophils ≤ 0.10 (≥ 10%)	92	1 (1)	97	3 (3)	530	7 (1)	537	1 (<1)
Platelet Count ≥ 700 x 10^9/L	152	4 (3)	150	2 (1)	769	8 (1)	779	13 (2)
Platelet Count ≤ 75 x 10^9/L	152	2 (1)	150	0	769	2 (<1)	779	0
Platelet Count ≤ 75 x 10^9/L AND ≥ 50 x 10^9/L	152	2 (1)	150	0	769	2 (<1)	779	0
From ISS, Table 6-3, pg252-253.								

MO Comment: There is no apparent dose-related effect for telavancin on PCS values for WBC count, neutrophils, or eosinophils. There does appear to be a possible dose-related effect on the number of PCS values for hematocrit in females, however the number of patients is small and must be interpreted carefully due to difference in sample size.

There are two patients who were treated with the 7.5 mg/kg dose and two treated with the 10 mg/kg dose of telavancin and none treated with vancomycin who had PCS decrease in platelet count. The telavancin patients with low platelets will be discussed in Section 7.1.7.3.3 below.

HEPATIC

Tne next table shown below, Table 59, provides some perspective on dose-related effects on occurrence (observation) of PCS hepatic parameters.

Table 59: Hepatic PCS (Phase 3 Studies: telavancin 10 mg vs comparator)

	Study 0017				Study 0018				0017 + 0018			
	Telavancin		Vancomycin		Telavancin		Vancomycin		Telavancin		Vancomycin	
	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)
ALT (max post BL), N=319												
• ≥3 x ULN	319	9 (3)	352	17 (5)	402	7 (2)	384	11 (3)	703	16 (2)	754	28 (4)
• ≥5 x ULN	319	3 (<1)	352	3 (<1)	402	5 (1)	384	2 (<1)	703	8 (1)	754	5 (<1)
• ≥10 x ULN	319	1 (<1)	352	0	402	1 (<1)	384	0	703	2 (<1)	754	0
• ≥20 x ULN	319	0	352	0	402	0	384	0	703	0	754	0
• ≥3 x ULN and at least 50 U > BL	319	9 (3)	352	17 (5)	402	7 (2)	384	11 (3)	703	16 (2)	754	28 (4)
AST (max post BL)												
• ≥3 x ULN	312	6 (2)	337	13 (4)	389	7 (2)	374	9 (2)	686	13 (2)	728	22 (3)
• ≥5 x ULN	312	2 (<1)	337	4 (1)	389	3 (<1)	374	2 (<1)	686	5 (<1)	728	6 (<1)
• ≥10 x ULN	312	1 (<1)	337	0	389	2 (<1)	374	1 (<1)	686	3 (<1)	728	1 (<1)
• ≥20 x ULN	312	0	337	0	389	1 (<1)	374	0	686	1 (<1)	728	0
• ≥3 x ULN and at least 50 U > BL	312	6 (2)	337	13 (4)	389	7 (2)	374	9 (2)	686	13 (2)	728	22 (3)
Alkaline Phosphatase (max post BL)												
• ≥1.5 x ULN	338	8 (2)	350	4 (1)	390	7 (2)	415	4 (<1)	728	15 (2)	765	8 (1)
Total Bilirubin (max post BL)												
• ≥1.5 x ULN	352	3 (<1)	349	2 (<1)	411	4 (<1)	419	0	763	7 (<1)	768	2 (<1)
• ≥1.5 x ULN and at least 9 μmol/L > BL	352	2 (<1)	349	2 (<1)	411	4 (<1)	419	0	763	6 (<1)	768	2 (<1)
Composite Endpoints												
• ALT/AST ≥3 x ULN and Bilirubin ≥1.5 x ULN	297	0	303	0	373	0	378	0	670	0	681	0
• ALT/AST ≥5 x ULN and Bilirubin ≥1.5 x ULN	297	0	303	0	373	0	378	0	670	0	681	0
• ALT/AST ≥10 x ULN and Bilirubin ≥1.5 x ULN	297	0	303	0	373	0	378	0	670	0	681	0
• ALT/AST ≥20 x ULN and Bilirubin ≥1.5 x ULN	297	0	303	0	373	0	378	0	670	0	681	0

From ISS, Supporting Table 117, pgs 371-374.

MO Comment:

- *Low level PCS elevations in transaminases (ALT and AST) occurred more frequently in vancomycin-treated patients than in telavancin-treated patients. High level PCS ALT elevation (i.e. ≥ 10) occurred in only two telavancin-treated patients and no vancomycin-treated patients. High level PCS AST elevation, although infrequent, also occurred in a greater number of telavancin-treated patients.*

- *Alkaline phosphatase elevations that were PCS were twice as frequent in telavancin-treated patients compared to vancomycin-treated patients.*

- *PCS elevations in total bilirubin elevations were infrequent, but did occur in greater than twice as many patients treated with telavancin.*

- *No patients in either group met the "Hy's Rule" criteria for possible drug-induced liver injury.*[8]

Tne next table shown below, Table 60, provides some perspective on dose-related effects on occurrence (observation) of PCS hepatic parameters.

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8 Lewis, JL. "Hy's Law," the "Rezulin Rule" and other predictors of severe drug-induced hepatotoxicity: putting risk-benefit into perspective. Pharmacoepidemiology and Drug Safety 2006;15:221-229.

Table 60: PCS Hepatic (Telavancin 7.5 vs 10 mg/kg)

	Original Protocol 202a+202b+0017+0018				Post Amendment 202b+0017+0018			
	Telavancin		Vancomycin		Telavancin		Vancomycin	
	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)	# pts	Abnl (%)
ALT (max post BL) N=319								
• ≥ 3 x ULN	144	7 (5)	146	7 (5)	783	16 (2)	827	32 (4)
• ≥ 5 x ULN	144	0	146	2 (1)	783	8 (1)	827	6 (<1)
• ≥ 10 x ULN	144	0	146	1 (<1)	783	2 (<1)	827	1 (<1)
• ≥ 20 x ULN	144	0	146	1 (<1)	783	0	827	0
• ≥ 3 x ULN and at least 50 U > BL	144	7 (5)	146	7 (5)	783	16 (2)	827	32 (4)
AST (max post BL)								
• ≥ 3 x ULN	135	4 (3)	145	4 (3)	763	14 (2)	801	24 (3)
• ≥ 5 x ULN	135	0	145	2 (1)	763	5 (<1)	801	7 (<1)
• ≥ 10 x ULN	135	0	145	1 (<1)	763	3 (<1)	801	0
• ≥ 20 x ULN	135	0	145	1 (<1)	763	1 (<1)	801	0
• ≥ 3 x ULN and at least 50 U > BL	135	4 (3)	145	4 (3)	763	14 (2)	801	24 (3)
Alkaline Phosphatase (max post BL)								
• ≥ 1.5 x ULN	150	1 (<1)	165	2 (1)	811	15 (2)	848	9 (1)
Total Bilirubin (max post BL)								
• ≥ 1.5 x ULN	160	2 (1)	169	1 (<1)	849	8 (<1)	854	2 (<1)
• ≥ 1.5 x ULN and at least 9 µmol/L > BL	160	2 (1)	169	1 (<1)	849	7 (<1)	854	2 (<1)
Composite Endpoints								
• ALT/AST ≥ 3 x ULN and Bilirubin ≥ 1.5 x ULN	138	0	142	0	748	0	758	0
• ALT/ AST ≥ 5 x ULN and Bilirubin ≥ 1.5 x ULN	138	0	142	0	748	0	758	0
• ALT/AST ≥ 10 x ULN and Bilirubin ≥ 1.5 x ULN	138	0	142	0	748	0	758	0
• ALT/ AST ≥ 20 x ULN and Bilirubin ≥ 1.5 x ULN	138	0	142	0	748	0	758	0
From ISS, Table 5-18, pgs 235-236.								

MO Comment:

- *Low level transaminase elevations that are PCS are seen with the same frequency in both telavancin dose groups. Higher level PCS transmainase elevations occur only in the higher (10 mg/kg) telavancin dose group.*
- *PCS elevations in alkaline phosphatase and total bilirubin do not appear to be dose-related.*
- *There were no patients in either telavancin dose group or in the comparator group who met Hy's Rule criteria.*

Brief narratives for patients with higher level transaminase levels that are PCS and for patients with PCS elevations in total bilirubin can be found in Section 7.1.7.3.3 below.

RENAL

Table 61 below shows the patients who developed PCS elevation in renal function laboratory studies (serum Cr and blood urea nitrogen). Patients included in assessment of each parameter had to have a normal baseline and at least one post-baseline measurement.

Table 61: Potentially Clinically Significant Renal Values (Phase 3 cSSSI: 0017 and 0018 10 mg/kg Telavancin versus Comparator)

| | Study 0017 | | | | Study 0018 | | | | 0017 + 0018 | | | |
| | Telavancin | | Vancomycin | | Telavancin | | Vancomycin | | Telavancin | | Vancomycin | |
	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)
Serum Creatinine												
Maximum Change from BL												
Increase to 1.25 x BL	374	143 (38)	402	84 (21)	448	162 (36)	454	93 (20)	822	305 (37)	856	177 (21)
Any Post-BL Cr ≥ 133 µmol/L and at least 44 µmol/L > BL	374	21 (6)	402	8 (2)	448	31 (7)	454	11 (2)	822	52 (6)	856	19 (2)
Any Post-BL Cr ≥ 133 µmol/L and at least 50% > BL	374	21 (6)	402	7 (2)	448	27 (6)	452	10 (2)	822	48 (6)	856	17 (2)
Highest Post-BL Result												
133 µmol/L to < 177 µmol/L and at least 44 µmol/L > BL	374	10 (3)	402	6 (1)	448	18 (4)	454	9 (2)	822	28 (3)	856	15 (2)
177 µmol/L to < 265 µmol/L and at least 44 µmol/L > BL	374	8 (2)	402	1 (<1)	448	9 (2)	454	1 (<1)	822	17 (2)	856	2 (<1)
265 µmol/L to < 442 µmol/L and at least 44 µmol/L > BL	374	3 (<1)	402	1 (<1)	448	2 (<1)	454	1 (<1)	822	5 (<1)	856	2 (<1)
≥ 442 µmol/L and at least 44 µmol/L > BL	374	0	402	0	448	2 (<1)	454	0	822	2 (<1)	856	0
BUN Post-BL Result												
> 11 mmol/L	372	23 (6)	390	10 (3)	439	24 (5)	437	14 (3)	811	47 (6)	827	24 (3)

From ISS, Supporting Table 108, pgs 247-249.

MO Comment:

- *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. Although the "increase to 1.25 x baseline" parameter is probably too sensitive in hospitalized patients with many comorbid conditions, the other two paramters assessing change from baseline ("Any Post-BL Cr ≥ 133 µmol/L and at least 44 µmol/L > BL" or "Any Post-BL Cr ≥ 133 µmol/L and at least 50% > BL") indicate that 6% of telavancin-treated patients met the criteria compared to 2% of vancomycin-treated patients.*

- *High-level elevations of serum Cr were observed in more telavancin-treated patients compared to vancomycin-treated patients.*

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- *The number of patients was somewhat higher in Study 0018, although the study population was larger, so there is not a major difference in % of patients with PCS values.*

Table 62 below shows the number of patients who maintained normal serum creatinine values from baseline to the EOT and TOC visits. It also shows the number of patients in a given baseline category who change from baseline by follow-up measurements at EOT and TOC.

Table 62: Shift Table – Serum Cr for Study 0017

Supporting Table 95 (Cont'd): Serum Chemistry Values – Shift Table – Safety Population, Study 0017

Lab test name: CREATININE (UMOL/L)	Telavancin 10 mg/kg Baseline				Vancomycin Baseline			
	High	Norm	Low	Total	High	Norm	Low	Total
END OF THERAPY								
High	27	24	0	51	15	11	0	26
Normal	12	339	1	352	8	383	1	392
Low	0	2	0	2	0	2	0	2
FOLLOW-UP/TEST OF CURE								
High	30	22	0	52	12	9	0	21
Normal	10	311	0	321	7	338	1	346
Low	0	0	1	1	0	0	0	0

Source: Dataset(s): ADSL ADLABS Program: \vol\sasunix\td-6424\0017\hardlock\programs\t_labshift.sas Run Date: 02NOV06/18:56 by djansen on NET_ASRV SASv9.1

From 0017 Clinical Study Report, Supporting Table 95, pg 108.

MO Comment: There are twice as many patients in the telavancin treatment arm who have a change from a normal baseline serum creatinine to a high serum creatinine at EOT compared to vancomycin-treated patients (24/365 or 6.6% for telavancin and 11/396 or 2.8% for vancomycin). At the TOC visit (designated in the protocol to occur at 7-14 days after the last dose of study medication), this difference was maintained between the two treatment groups (22/333 or 6.6% and 9/338 or 2.7%, respectively.

Table 63 below shows similar results for Study 0018.

Table 63: Shift Table – Serum Cr for Study 0018

Supporting Table 95 (Cont'd):Serum Chemistry Values – Shift Table – Safety Population, Study 0018

Lab test name: CREATININE (UMOL/L)	Telavancin 10 mg/kg Baseline				Vancomycin Baseline			
	High	Norm	Low	Total	High	Norm	Low	Total
END OF THERAPY								
High	31	41	0	72	19	16	0	35
Normal	8	393	3	404	23	426	1	450
Low	0	2	1	3	0	2	0	2
FOLLOW-UP/TEST OF CURE								
High	28	43	0	71	20	15	0	35
Normal	7	356	1	364	19	382	1	402
Low	0	0	1	1	0	1	0	1

Source: Dataset(s): ADSL ADLABS Program: \vol\sasunix\td-6424\0018\hardlock\programs\t_labshift.sas Run Date: 02NOV06/22:30 by djansen on NET_ASRV SASv9.1

From 0018 Clinical Study Report, Supporting Table 95, pg 109.

MO Comment: In Study 0018, this difference was slightly greater with 41/436 (9.4%) of telavancin-treated patients having a change from a normal baseline creatinine to a high creatinine by EOT compared to 16/440 (3.6%) of vancomycin-treated patients. This difference was still noted at the TOC visit with 43/399 (10.8%) telavancin-treated patients shifted from normal to high creatinine compared to 15/398 (3.8%) vancomycin-treated patients.

Table 64 below shows the number of patients developing PCS elevations in renal function parameters in patients who participated in the telavancin 7.5 mg/kg studies and the telavancin 10 mg/kg studies.

Table 64: PCS Renal (Telavancin 7.5 vs 10 mg/kg)

	Original Protocol 202a+202b+0017+0018				Post Amendment 202b+0017+0018			
	Telavancin		Vancomycin[1]		Telavancin		Vancomycin[1]	
	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)	Patients	Abnormal (%)
Serum Creatinine								
Maximum Change from BL								
Increase to 1.25 x BL	173	64 (37)	180	44 (24)	917	330 (36)	945	190 (20)
Any Post-BL Cr ≥ 133 µmol/L and at least 44 µmol/L > BL	173	9 (5)	180	2 (1)	917	57 (6)	945	19 (2)
Any Post-BL Cr ≥ 133 µmol/L and at least 50% > BL	173	9 (5)	180	2 (1)	917	52 (6)	945	17 (2)
Highest Post-BL Result								
133 µmol/L to < 177 µmol/L and at least 44 µmol/L > BL	173	2 (1)	180	1 (<1)	917	32 (3)	945	15 (2)
177 µmol/L to < 265 µmol/L and at least 44 µmol/L > BL	173	4 (2)	180	1 (<1)	917	17 (2)	945	2 (<1)
265 µmol/L to < 442 µmol/L and at least 44 µmol/L > BL	173	3 (2)	180	0	917	6 (<1)	945	2 (<1)
≥ 442 µmol/L and at least 44 µmol/L > BL	173	0	180	0	917	2 (<1)	945	0
BUN Post-BL Result								
> 11 mmol/L	156	10 (6)	168	4 (2)	891	49 (5)	901	25 (3)
From ISS, Table 5-17, pgs 229-230. [1] Includes 27 patients (20 in 202a and 7 in 202b Post-Amendment) who received an antistaphylococcal penicllin instead of vancomycin.								

MO Comment:
- *The frequency (number/percent) of patients with each specified category of PCS serum Cr measurements appears to be relatively similar in the 7.5 mg/kg telavancin treatment group compared to the 10 mg/kg telavancin treatment group. However, frequency in the low dose telavancin group may be artificially elevated due to the small population size at that dose (i.e. the addition of a single patient to a category increases the frequency by 1%).*

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities
From the PCS tables, the following patients were identified for closer review.

HEMATOLOGY

Patients with platelet counts $\leq 75 \times 10^9/L$ AND $\geq 50 \times 10^9/L$ below baseline:
Phase 3 Telavancin:
0017-04004-0680 – The patient's medical history included a recent craniotomy for meningioma. The patient received a single dose of telavancin for a wound infection and was changed to vancomycin and rifampin. The CRF notes that the patient only received 5 minutes of study medication. Platelets counts are as follows: baseline 236,000, 6 days after study medication was discontinued at TOC 55,000. Other intervening medications included fraxiparine, valproic acid, and amiodarone. It is unlikely that the study medication caused the thrombocytopenia and is more likely related to other interim medications particularly valproic acid and fraxiparine.
0017-38271-0896 – The patient's medical history included chronic renal failure with AV fistula for hemodialysis, coronary artery disease with a history of congestive heart failure and cardiomyopathy, hypertension, peripheral vascular disease, and peptic ulcer disease. The patient had the following platelet counts: Baseline 150,000, Day 5 84,000, Day 8 38,000, Day 10 113,000, Day 13 160,000 and EOT 202,000. The patient's thrombocytopenia resolved while continuing study medication which makes a relationship with study medication unlikely.
Phase 2 Telavancin:
202a-00901-3022 – The patient had a thigh abscess. Baseline platelet count was 234,000 and 3 hours later was 59,000 (the same time indicated for study medication administration in the CRF). On Day 4 of study medication, the platelet count was 386,000. The patient was discontinued from study medication on Day 6 due to the diagnosis of necrotizing fasciitis (noted as an AE in the CRF).
202a-00907-3005 – The patient was treated with a 2 week course of telavancin for cellulitis. No medical history is included in the CRF. The patient's baseline platelet count was 208,000, Day 2 168,000, Day 6 64,000 with clumping noted, Day 9 739,000, and Day 13 780,000. All platelet counts were obtained while the patient was on study medication. The patient was also receiving paracetamol and ibuprofen. Given the description of clumping in connection with the low platelet count (no indication that a manual platelet count was performed) suggests this may be an inaccurate assessment. The increase in platelet count as study therapy continued also suggests that the transient thrombocytopenia was not related to study medication.

No vancomycin-treated patients had PCS low platelet counts during the SSSI studies.

HEPATIC

Patients with AST $\geq 10 \times$ ULN:
- 0017-38111-0380 (telavancin): 78 yo male with recent hospitalization for treatment of injuries sustained in an ATV accident including closed head injury, right hemianopsia, and multiple fractures. The patient had a history of coronary artery disease with bypass in the past, atrial fibrillation, pacemaker, COPD, bilateral carotid endarterectomy, myelodysplastic syndrome, prostate and bladder cancer. On D10 of study medication, the patient had a

myocardial infarction and CHF, and 2 days later developed renal insufficiency. He developed RUQ pain, along with transaminase elevation (which had been 2-3 x ULN at baseline), with AST 152 U/L, ALT 216 U/L, and normal alkaline phosphatase and total bilirubin on the last day of a 13-day treatment course. Lab measurement of transaminases peaked 1 week post-MI with AST 366 U/L, ALT 416 U/L, LDH 851 U/L (3-4 x ULN), and continuing normal alkaline phosphatase and total bilirubin. Approximately 1 week later, transaminases had decreased to AST 44 U/L, ALT 93 U/L, and LDH of 381 U/L. The investigator assessed the SAE of MI as possibly/probably related to study medication, although noting comorbidities. FDA reviewer concurs.

- 0018-38112-2234 (telavancin): 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 alkaline phosphatase at baseline, with further increase (2X) and >10X increase in transaminases on D4 (normal total bilirubin), by D8 (2 days after discontinuing study medication), alkaline phosphatase remained elevated (stable), transaminases were improving (now <10 x normal), and total bilirubin was normal. The patient was lost to follow up due to Hurricane Katrina. The investigator assessed increased 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. The changes are cholestatic in nature and may represent fatty liver associated with diabetes.)

Patients with AST ≥ 20 x ULN:

- 0018-33002-2409 (telavancin): 66 yo with chronic renal failure who was discontinued from study medication due to development of acute renal failure and hyperkalemia (4 days into treatment). One week after study medication was discontinued the patient had a brainstem infarction. The patient had an elevated alkaline phosphatase (197 U/L with normal range of 35-125 U/L) and normal transaminases (AST and ALT normal at 26 U/L and total bilirubin normal at 6 µmol/L) at baseline. The patient was noted to have increasing renal insufficiency with increase in serum Cr from baseline of 184 µmol/L (2.1 mg/dL) to 551 µmol/L (6.2 mg/dL) along with increasing transaminases (AST 761 U/L and ALT 510 U/L), stable alkaline phosphatase and normal bilirubin of 13 µmol/L. Study medication was discontinued and 1 week later, total bilirubin, alkaline phosphatase, and AST had normalized, with residual mild elevation of ALT. Serum creatinine had also decreased to 256 µmol/L (3.0 mg/dl). The patient was readmitted to the hospital with a brainstem infarction and was discharged and died at home the next day. The LFT abnormalities were not included in AE reporting by the investigator.

- 202a-00901-2026 (standard / comparator therapy in Phase 2): 22 yo with a gunshot wound cellulitis secondary to Group A Strep (Strep pyogenes), who had normal LFTs at baseline. Ten days after the start of treatment had AST 1549 U/L, ALT 921 U/L, LDH 1330 U/L, and normal alkaline phosphatase and total bilirubin. There is no narrative for this patient and it is not known whether the patient received vancomycin or semi-synthetic penicillin which was allowed if MRSA was not isolated (although this wouldn't make sense from a clinical standpoint for S. pyogenes). No AEs were reported and no additional lab studies were available.

Patients with ALT ≥ 10 x ULN:
- 0017-38111-0380 T (see AST narrative)
- 0018-33002-2409 T (see AST narrative)
- 202b-00903-9037 V: SAE "liver failure" (see SAE narrative)

Patients with ALT ≥ 20 x ULN:
- 202a-00901-2026 V (see AST narrative)

Table 65: Patients with Total Bilirubin ≥ 1.5 x ULN and at least 9 μmol/L above BL
(Note: Hy's Rule uses total bilirubin ≥ 3 x ULN = 36 μmol/L)

Dose / Patient ID T bili in μmol/L [μmol/L÷17.1= mg/dL]	Baseline	PCS value (time relative to study treatment)	Comments [Normal SI 3-21 μmol/L, Normal conventional 0.2-1.2 mg/dL]
Telavancin 7.5 mg/kg			
0017-38163-0122	9 (0.5 mg/dL)	TOC 36 (2.1 mg/dL)	T bili (EOT) 5 μmol/L, isolated elevation in bilirubin History of hepatitis C
202a-00905-3018	11 (0.6 mg/dL)	TOC 91 (5.3 mg/dL)	EOT 4 μmol/L, TOC lab 3 weeks post-treatment Patient had mild ↑alk phos, normal ALT and AST
Telavancin 10 mg/kg			
0017-38271-0391	19 (1.1 mg/dL)	TOC 44 (2.6 mg/dL)	Last value TOC: sample hemolyzed, no AST reported, EOT 17 μmol/L Mild increase in AST noted (even at baseline) Patient with history of COPD, CHF, morbid obesity
0017-38271-0981	7 (0.4 mg/dL)	EOT 38 (2.2 mg/dL)	TOC 10 μmol/L ALT, AST baseline 1.5-2 x ULN, ALT mild inc throughout Treated with ciprofloxacin prior to study
0018-38074-2944	14 (0.8 mg/dL)	(D4) 36 (2.1 mg/dL)	EOTand TOC 7 μmol/L Alk phos 2 x ULN, mild inc ALT, AST Residual mild inc alk phos Patient with diabetes, required IV labetolol for hypertension, concomitant medications included acetominohen
0018-38110-3006	21 (1.2 mg/dL)	EOT 34 (2.0 mg/dL)	TOC 19 μmol/L, mild inc ALT at TOC D5 mild inc ALT, AST Concomitant treatment with acetominophen
0018-38304-2190	7 (0.4 mg/dL)	(D10) 32 (1.9 mg/dL)	EOT and TOC (3 weeks later) 5 μmol/L Isolated bilirubin increase Concomitant medications included diclofenac
0018-38322-2676	15 (0.9 mg/dL)	55 EOT (3.2 mg/dL)	TOC 26 μmol/L Mild baseline inc alk phos, otherwise isolated bilirubin increase Diabetes mellitus, on simvastatin
202b-00901-9044	19 (1.1 mg/dL)	(later same day) 30 (1.7 mg/dL)	EOT 11 μmol/L, last (1 day after EOT) 5 μmol/L (?) Post-operative increase
Vancomycin			
0017-23002-0324	6 (0.4 mg/dL)	32 Days 3-5 (1.9 mg/dL)	Baseline: Alk Phos 4-5 x ULN, ALT, AST > 10-20 x ULN (D 7) 22 μmol/L, decreasing ALP, AST, ALT (D 11) 15 μmol/L, ALP and ALT dec, AST nl Treated 14 days, EOT 16 μmol/L , TOC 13 μmol/L Concomitant medications included diclofenac at study entry
0017-38101-0729	21 (1.2 mg/dL)	34 TOC (2.0 mg/dL)	EOT 14 μmol/L , 1 month later 24 μmol/L Baseline ALT, AST 3-5 xULN, Alk Phos 1.5 xULN, elevated along with t bili Polysubstance abuse, hepatitis C antibody positive
202a-00110-1100	15 (0.9 mg/dL)	(D4) 31 (1.8 mg/dL)	EOT 27 μmol/L, TOC 24 μmol/L (1 week post EOT) Baseline ALT 54 U/L, D4 63, EOT 36, TOC 41 Baseline AST 114 U/L, D4 71, EOT 52, TOC 55 Alkaline Phosphatase normal Diabetes: Glucovance new med / no other medical history in CRF
Patient IDs from ISS, Supporting Table 119, pg 403. Laboratory values, medical history, and concomitant meds from patient CRFs.			

MO Comment: Nine telavancin-treated patients (two at the 7.5 mg/kg dose and seven at the 10 mg/kg dose) developed an increase in total bilirubin of ≥ 1.5 x ULN and at least 9 μmol/L compared to three patients treated with vancomycin. The majority of patients had elevations in other hepatic parameters and had decreases in total bilirubin after therapy was discontinued.

Many had confounding comorbid conditions such as hepatitis C and/or medications (e.g., diclofenac or acetaminophen) which may have contributed to the abnormalities. All of the patients had increases in total bilirubin < 3 x ULN except for one telavancin-treated patient, #202a-00905-3018, enrolled in the Phase 2 telavancin 7.5 mg/kg study. This patient (905-3018) is not highlighted in the study report for Study 202a, nor is there a narrative available. Review of the CRF indicates that patient was a 21 yo male with normal total bilirubin of 11 μmol/L and mild elevation in alkaline phosphatase at study entry at 177 U/L (normal 40-120 U/L) who was treated for a left hand/arm abscess. Concomitant medication included diclofenac. On D4 total bilirubin was normal 2 μmol/L and alkaline phosphatase had decreased to 137 U/L. The patient was treated for 7 days and at EOT, total bilirubin was 4 μmol/L and alkaline phosphatase stable. The patient was seen back in follow-up 2-1/2 weeks later and was noted to have bilirubin of 91μmol/L and alkaline phosphatase of 153 U/L. No other information is available.

Patients were identified from the ISS AE dataset with safety laboratory related AEs in the Investigations SOC that were classified as severe and/or serious and/or who discontinued from study medication due to the adverse event. In the Phase 3 cSSSI studies there were 10 patients in the telavancin treatment group (10 mg/kg) and 6 patients in the vancomycin treatment group who met these criteria. These Phase 3 patients, along with patients with severe and/or serious and/or who discontinued study medication in any SSSI infection are listed below in Table 66.

Table 66: Laboratory Abnormalities Assessed as AEs in Investigations SOC (medDRA)

Patient ID	Phase / Dose	AE	Comment
TELAVANCIN			
0018-19006-2894 Severe	3 / 10	ALT ↑ / AST ↑	Patient with history of diabetes mellitus and rheumatoid arthritis No baseline central lab, study medication discontinued D4 for "hypertransaminasemia" / ALT 26 (nl), AST 31 (nl), sl ↑ alk phos, nl t bili D8, (4 days after D/C), D8 ALT 47, AST 48, alk phos 270 ↑↑ (2xULN), total bilirubin < 3 μmol/L Treated 8 days with study medication, no follow-up
0018-38112-2234 Discontinued / PCS	3 / 10	ALT ↑ / AST ↑ Alk Phos ↑, LDH ↑	Previous narrative
0017-18004-0768 Discontinued / SAE	3 / 10	INR ↑	Coumadin for a fib (D4) INR increased from 1.22 to 5.92 (PT test ≈ 2 hrs after dose)
0018-38164-2900 Severe	3 / 10	INR ↑	Coumadin for DVT No coagulation lab reported
0018-38110-2568 Discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 2.0 mg/dL (Study drug D/C D2) D3 Cr 5.9, D10 9.1 mg/dL (last)
0018-38148-2359 Severe, SAE, discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 0.9 mg/dL D4 Cr 2.1 mg/dL (study drug D/C) D13 1.0 mg/dL
0018-38148-2498 Severe, SAE, and discontinued	3 / 10	Cr ↑ / BUN ↑	Previous narrative Baseline Cr no central D4 Cr 2.7 mg/dL (study drug D/C D3) D12 Cr 1.5 mg/dL
0018-38260-2099 Severe, SAE, and discontinued	3 / 10	Cr ↑ / BUN ↑	Previous narrative Baseline Cr 0.9 mg/dL D5 Cr 2.2 mg/dL (Study drug D/C D6) D8 Cr 4.6 mg/dL, D10 Cr 6.0 mg/dL, D15 Cr 2.8 mg/dL, D 17 2.0 mg/dL

Patient ID	Phase / Dose	AE	Comment
0018-38304-2233 Severe and discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 0.8 mg/dL D4 Cr 3.1 mg/dL (Study Drug D/C D6) D12 Cr 2.3 mg/dL (last)
0018-38304-2670 Severe and discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 1.2 mg/dL D4 Cr 4.5 mg/dL (D/C med) D7 Cr 5.0 mg/dL, D9 Cr 5.1 mg/dL, D23 Cr 2.3 mg/dL (last)
202b-00107-6002 Discontinued	2 / 10	Cr ↑	Previous narrative Baseline Cr 1.1 mg/dL D4 and D8 Cr 1.2 mg/dL, D 11 Cr 1.8 mg/dL (CRF indicates study med D/C, but medication log continues to have administration times listed for 3 days) D14 (EOT) Cr 1.6 mg/dL, D21 (TOC) Cr 1.6 mg/dL
202a-00112-1055 Therapy interrupted, not discontinued	2 / 7.5	Cr ↑	Baseline Cr 0.9 mg/dL D3 1.5 mg/dL, D5 2.3 mg/dL, D7 2.2 mg/dL (last) Discontinued D7 for treatment failure (dataset indicates treatment interruption, unable to confirm in CRF)
202b-00101-7008 Severe, SAE, and discontinued	2 / 7.5	Cr ↑ BUN ↑	Previous narrative Baseline Cr 0.6 mg/dL D4 Cr 1.1 mg/dL D7 Cr 3.1 mg/dL, AE noted on D10 and study medication D/C D11 (EOT) Cr 3.2 mg/dL, D12 (EOT+1 day) Cr 2.4 mg/dL D20 (TOC) Cr 1.2 mg/dL
VANCOMYCIN			
0017-09004-0862 Severe	3 / 10	ALT ↑	ALT ↑ (baseline) 70 U/L D4 237, D7 123, D10 65, D13 34, study med x 12 days Nl Alk Phos and T Bili
0018-38099-2222 SAE and discontinued	3 / 10	ALT ↑ AST ↑	Previous narrative Baseline ALT 88, AST 60 D5 ALT 261, AST 201 D18 ALT 172, AST 83 T bili and alk phos normal throughout
202b-00101-7060 Severe	2 / 10	Alk Phos↑ GGT ↑	BL ALP 469 U/L, GGT 386 D4 ALP 462, GGT 333 D7 ALP 295, GGT 215 D9 ALP 274, GGT 171 D11 ALP 185, GGT 162 D26 ALP 832, GGT 443
0018-38297-2786 Severe	3 / 10	K ↓	D5 2.3 D11 3.3, D12 3.9, D19 3.6
0017-38005-0180 SAE	3 / 10	WBC ↑ Cr ↑	Previous narrative WBC 18.7 (osteo) Baseline Cr 1.3 mg/dL D4 Cr 3.4 mg/dL D11 (1 wk off) Cr 1.0 mg/dL
0017-38024-0697 Severe, SAE, and discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 0.7 mg/dL D3 Cr 0.7 mg/dL (D/C D6) D7 Cr 3.0 mg/dL(EOT) D12 1.6 mg/dL (TOC), D25 1.0 mg/dL
0018-38025-2330 Discontinued	3 / 10	Cr ↑	Previous narrative Baseline Cr 1.2 mg/dL (D/C med D3) D4 Cr 3.5 mg/dL (EOT) D15 Cr 2.7 mg/dL (TOC)
Previous Narratives available in SAE and Discontinuations Section of this review.			

MO Comment: Most of the patients listed in the table above have been previously discussed in the SAE and/or discontinuation due to AE sections of this review.

- *The four telavancin treated patiens not previously noted include:*
    - *#0018-19006-2894: AE of increased ALT and AST noted, but lab reports indicate that the primary hepatic laboratory abnormality was elevation in alkaline phosphatase to 2xULN 4 days after discontinuation. The cause of this elevation is not clear based on patient's medical history and listed concomitant medications.*
    - *#0017-18004-0768: AE of increased INR in a patient on warfarin for atrial fibrillation. The abnormal PT/INR was noted on D4 in a sample drawn two hour after telavancin administration. The chromogenic factor X assay was not performed.*
    - *#00178-38164-2900: AE of increased INR in a patient on warafrin for deep vein thrombosis (DVT). There are no details on the anticoagulation history or coagulation testing in the CRF.*
    - *#202a-00112-1055: AE of increased creatinine for which treatment was interrupted. CRF indicated treatment was administered for 7 days and the patient was discontinued due to treatment failure.*
- *The three vancomycin treated patients not previously discussed include:*
    - *#0017-09004-0862: AE of increased ALT (>AST elevation) which was classified as severe. Mild elevation of approximately 1.5x ULN increased to approximately 6xULN on D4, decreasde on D7 to 3xULN while continuing on medication. Study treatment continued for 12 days and ALT continued to decline. Concomitant paracetamol administration was noted.*
    - *#202b-00101-7060: AE of increased alkaline phosphatase and GGT in a patient with marked elevations of unknown etiology at baseline (no medical history in CRF) and normal total bilirubin and transaminases. Alkaline phosphatase and GGT decreased for a time on therapy, but increased to higher levels 2 weeks after study medication was discontinued.*
    - *#0018-38297-2786: AE of severe hypokalemia noted on D5 of study treatment in a patient on antiretroviral medications.*

7.1.7.4 Additional analyses and explorations

The dose effect of telavancin on deaths, SAEs, discontinuations, common AEs, and renal function has been discussed previously (see specific sections for review).

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured in the clinical pharmacology studies, with the QT study (study 104a) providing the most systematic review of vital signs in these studies.

Study 104a was performed in healthy adult subjects. It was a randomized, double-blind, parallel group study with 40 patients randomized to each of 4 treatment groups; subjects received either telavancin 7.5 mg/kg, telavancin 15 mg/kg, placebo (negative control), or moxifloxacin 400 mg IV for 3 days. Vital signs were evaluated at screening, Day 0 (all subjects received an infusion of D5W as a baseline "dose/infusion"), Day 1, Day 2, Day 3, and Day 5. Specifically, blood pressure and heart rate were measured prior to and at the end of infusion of study medication. No clinically significant individual abnormalities were noted, but there was evidence of a modest but statistically significant increase in blood pressure and slight decrease in heart rate.

The least square mean changes in blood pressure and heart rate on Day 3 were:
Telavancin (7.5 mg/kg): 1/4* mmHg and -8 bpm
Telavancin (10 mg/kg): 3*/6* mmHg and -7 bpm
Placebo: -1/1 mmHg and -4 bpm

In considering the intended use of telavancin in patients with cSSSI, these effects were not considered to be clinically meaningful by the Applicant.

Among the efficacy and safety studies, vital signs were assessed as safety parameters in the Phase 2 study in which they were performed at baseline, daily, and at EOT and TOC. No formal assessment of vital signs was included in the Phase 3 studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The Phase 2 study report data was reviewed for information regarding changes in vital signs during the study. Since the indication for medication use is treatment of infection, temperature was not examined in detail. The focus of assessment was placed on heart rate and blood pressure.

Study 1624-202b was a Phase 2 SSSI study in which 100 patients were treated with telavancin and 95 patients with standard therapy.

7.1.8.3 Standard analyses and explorations of vital signs data

The study report included a table containing the mean, median, and range of recorded tempertature, heart rate, and systolic and diastolic blood pressure. These values were also reported for change from pre-treatment value relative to study day, EOT, and TOC.

Baseline mean heart rate was similar for patients treated with telavancin and standard therapy at 84.5 and 94.9 beats per minute. Mean change from baseline at EOT was slighty greater in the standard therapy group at -7.6 bpm compared to -5.4 for the telavancin group, however by TOC the mean change was similar for the groups at -5.9 for standard therapy and -5.8 for telavancin.

Baseline mean systolic blood pressure was similar for the two treatment groups at 130 mmHg for telavancin compared to 129.5 mmHg for the standard therapy group. Mean change from baseline at EOT and TOC was slightly greater in the telavancin treatment group at -4.1 mmHg compared to -3.1 mmHg for the standard therapy group at EOT and -2.1 mmHg compared to 1.1 mmHg for the groups respectively at TOC.

Baseline diastolic blood pressure was slightly higher in the standard therapy group at baseline compared to the telavancin group at 75.2 mmHg and 73.5 mmHg, respectively. Mean change from baseline at EOT was less for telavancin at -0.4 mm Hg compared to -2.5 mmHg for standard therapy and higher for telavancin at TOC at +2.5 mmHg compared to +1.6 mmHg for standard therapy.

The mean changes in vital signs were not clinically significant.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations of vital signs were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical Testing
The effects of telavancin on cardiac repolarization included non-GLP and GLP hERG potassium ion channel current assays, canine and ovine Purkinje fiber assays, and anesthetized and conscious telemeterized dog studies. For a full review of these studies, please refer to the Pharmacology/Toxicology review by Zhou Chen, MD, PhD.

The non-GLP hERG assay showed some inhibition of hERG potassium ion channel currents. This finding was confirmed in a GLP assay, however 50% inhibition was not reached at concentrations up to 600 μg/mL (approximately 80-fold higher than observed free plasma concentrations in humans treated with 10 mg/kg per day). The effects of

telavancin on action potential duration (APD) were studied in canine and ovine Purkinje fibers. The canine study demonstrated a modest increase (≤11%) in the duration required to reach 60% and 90% repolarization at concentrations of 50 and 150 µg/mL and stimulation frequency of 1 Hz. The increases were not dose dependent or seen at other frequencies and were not observed in ovine Purkinje fibers.

No effects on cardiac repolarization were seen with telavancin in studies conducted in anesthetized and conscious telemeterized dogs. The studies included qualitative and quantitative assessments of ECGs and did not demonstrate an effect on QTc interval even at free plasma concentration levels approximately 4-5 times higher than achieved with doses of 10 mg/kg/day in humans.

Phase 1 Clinical Pharmacology Studies
Based on results of the non-GLP hERG, the Applicant was advised by the Division to conduct a "thorough ECG trial" as defined by the November 2002 FDA – Health Canada concept paper which was being developed at that time. Full details regarding the study design, ECG monitoring, and analysis of results can be found in the IRT QT Study review done by the QT Study Review Team.

Briefly, the study was a randomized, double-blind study of the effects of two doses of telavancin, 7.5 mg/kg (planned treatment dose) and 10 mg/kg (supratherapeutic dose). The study included positive (400 mg of moxifloxacin) and negative (placebo, which was D5W with telavancin vehicle containing HP-β-CD) controls. Forty subjects were randomized to one of the four treatment regimens; each subject received a placebo infusion of D5W on Day 0 and received a single intravenous dose of randomized treatment for three days. Single 12-lead ECGs were obtained at screening and multiple timepoints around the Day 0 dose (placebo for all 4 treatment groups) and Day 3 dose (assigned study treatment) to address intrinsic variability in subjects. The multiple ECGs at numerous timepoints obtained around the third dose of assigned study treatment were used to characterize the effect of telavancin on the QT/QTc interval at steady state following a 60 minute infusion. Telavancin concentrations in plasma were also determined during these ECG assessments to assure that concentrations achieved were representative or higher than the anticipated therapeutic dose would achieve.

One hundred forty nine of the 160 patients enrolled completed the study. Nine subjects discontinued from the study due to AE; one subject in the placebo group, two subjects from the moxifloxacin group, one subject from the telavancin 7.5 mg/kg group, and five subjects from the telavancin 10 mg/kg group. AEs were all hypersensitivity reactions with dermatologic manifestations. Two subjects discontinued for "other" reasons; one subject was discontinued before receiving study drug after experiencing premature ventricular contractions following the Day 0 D5W dose and a second due to a family emergency.

The post-dose changes in QTcF interval (unadjusted for changes with placebo) are shown in the table below which was copied from the Applicant's ISS.

Table 67: Post-dose Changes in QTcF Interval

Table 7-1   Summary of Post-Dose Changes in QTc Interval (Corrected Using Fridericia's Correction Formula; from Study 104a)

	Placebo N=39	Moxifloxacin 400 mg N=39	Telavancin 7.5 mg/kg N=39	Telavancin 15 mg/kg N=34
Mean Change from Baseline to Day 3, msec:				
Least-squares Mean, ± standard error	-1.1 ±1.36	8.1 ±1.39	3.0 ±1.37	3.4 ±1.51
Median	-0.8	9.0	2.4	3.7
Min, Max				
Categorical Changes, number (%) of subjects:				
<30 msec	39 (100)	39 (100)	39 (100)	34 (100)
≥30 msec	0	0	0	0
Maximum Change from Baseline to Day 3, msec:				
Least-squares Mean, ± standard error	17.7 ±1.86	27.5 ±1.69	23.0 ±1.87	22.2 ±2.06
Median	18.5	24.8	23.6	21.4
Min, Max				
Categorical Changes, number (%) of subjects:				
<10	6 (15.4)	1 (2.6)	4 (10.3)	4 (11.8)
10 to <20	15 (38.5)	10 (25.6)	12 (30.8)	12 (35.3)
20 to <30	13 (33.3)	13 (33.3)	13 (33.3)	11 (32.4)
30 to <60	5 (12.8)	15 (38.5)	10 (25.6)	6 (17.6)
≥60	0	0	0	1 (2.9)
Outliers,* number (%) of subjects	5 (12.8)	15 (38.5)	10 (25.6)	7 (20.6)
QTcF ≥500 msec	0	0	0	0
QTcF increase from baseline ≥30 msec	5	15	10	7
New abnormal U-wave	0	0	0	0

Source: Supporting Table 5 through 10 in 104a CSR
* Outliers were defined as subjects with QTcF > 500 msec, QTcF increase > 30 msec, and/or new abnormal U-wave.

From ISS, pg 263.

The results show that telavancin does have an effect on the QT interval. The 15 mg/kg telavancin dose has a slightly greater effect on the mean change from baseline than does the 7.5 mg/kg dose, while the 7.5 mg/kg dose has a slightly greater effect on the mean maximum change from baseline than does the 10 mg/kg dose. Both telavancin doses appear to have less effect on the mean and maximum change from baseline than does moxifloxacin in this study. There were no subjects with QTcF ≥ 500 msec. A single subject who received 15 mg/kg of telavancin had a QTcF increase from baseline ≥ 60 msec (63 msec), although this occurred at 17 hours after the dose at a time when the telavancin concentration was close to trough. There were a greater number of telavancin-treated patients (relative to placebo) that had QTcF increases ≥ 30 msec, but the number of subjects for each dose group was less than that for moxifloxacin.

Additional Clinical Pharmacology studies with QTc interval data included Phase 1 study 101a (single, ascending doses in healthy subjects), 103a (renal impairment), and 105a (elderly). The evaluations of QTc interval data in the studies of patients with renal impairment and the elderly were primarily for outliers as opposed to measurement of mean change from baseline. In the renal impairment study (103a), a maximum mean increase in QTcF of 17.5 msec at 1 hr 30 minutes post-infusion was observed in patients with ESRD. No patient demonstrated a QTcF > 500 msec or a change > 60 msec from baseline. In Study 105a performed in elderly subjects, a maximum mean increase in QTcF interval of 14.0 msec at 1 hr 15 minutes post-infusion was observed. No subject had a QTcF or QTcB interval of > 500 msec or change in QTcF or QTcB of > 60 msec.

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Clinical Studies

The Phase 2 SSSI (primarily cSSSI) studies, 202a and 202b, were of identical study design except for the dose of telavancin administered. In 202a, the dose of telavancin was 7.5 mg/kg and 202b the dose was 10 mg/kg (predominantly, although the study was initiated with 7.5 mg/kg); the active comparator in both studies was vancomycin, which could be changed to an anti-staphylococcal penicillin (oxacillin, nafcillin, cloxacillin) if MSSA was isolated (or suspected). Baseline, following infusion every third day (Day 4, 7, 10, 13 ± 1 day), and EOT ECGs (in triplicate at 5-10 minute intervals) were obtained. ECGs were transmitted to the central ECG lab for analysis of ECG intervals and morphology, including the QT/QTc interval. QT, QTc Bazett-corrected (QTcB) and QTc Fredericia-corrected (QTcF) were to be reported, with QTcF planned prospectively as the "primary" endpoint (result reported in the body of the report).

The Phase 3 cSSSI studies, 0017 and 0018, were of identical study design. The Post-Amendment 1 dose of telavancin was 10 mg/kg (patients with normal to mild renal impairment), although both studies had been initiated using a 7.5 mg/kg dose of telavancin. The active comparator for both studies was vancomycin. Baseline, Day 4 ± 1 (post-infusion), and EOT ECG testing was performed in triplicate, with results transmitted to a central ECG laboratory for analysis. QT, QTcB, and QTcF were to be reported, with QTcF planned prospectively as "primary" endpoint (result reported in the body of the report).

Three ECGs at a given time point were averaged to obtain a single analysis value. The baseline value was defined as the mean of the three pretreatment values. On-drug average was the arithmetic average of all interval values at all time points after initiation of therapy through EOT. On-drug maximum was defined as the ECG showing the maximum of all ECG interval values after initiation of therapy through EOT.

7.1.9.2   Selection of studies and analyses for overall drug-control comparisons

The Post-Amendment 1 Phase 3 cSSSI patients (0017, 0018) and Phase 2 SSSI study 202b patients were analyzed together since patients were treated with the 10 mg/kg dose of telavancin or the comparator vancomycin (> 99% comparator-treated patients). Similarly, patients enrolled under the original protocol for studies 0017, 0018, and 202b, and patients from the Phase 2 SSSI 202a were analyzed together since patients in these studies were treated with either a 7.5 mg/kg dose of telavancin or vancomycin (utilized as comparator in approximately 90%).

7.1.9.3   Standard analyses and explorations of ECG data

7.1.9.3.1   Analyses focused on measures of central tendency

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The on-drug average and on-drug maximum change compared to baseline were analyzed for both groups of study patients previously outlined and results are shown in Table 68 reproduced from the Applicant's ISS.

Table 68: Summary of Post-Drug Changes from Baseline in QTcF Interval

	Original Protocol 0017, 0018, 202b and 202a		Post-Amendment 1 0017, 0018, and 202b	
	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033
Post-Drug Average[2] Change, msec				
• N	189	183	971	979
• Mean	11.6	3.8	9.4	2.8
• Standard Deviation	15.6	14.8	17.4	15.9
• Minimum	(			)
• Median	12.0	5.0	9.0	2.7
• Maximum	(			)
Post-Drug Maximum[3] Change, msec				
• N	189	183	971	979
• Mean	20.6	12.4	15.9	8.4
• Standard Deviation	17.2	18.0	18.7	16.7
• Minimum	(			)
• Median	19.3	12.0	15.3	7.7
• Maximum	(			)

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

b(4)

The results show that both mean and median post-drug average change and maximum change from baseline in QTcF were greater for the telavancin treatment groups at both the 7.5 and 10 mg/kg dose than those for the vancomycin treatment groups. The average and maximum change appear to be higher in the Original Protocol 0017, 0018, 202b and 202a, where telavancin was administered at a dose of 7.5 mg/kg indicating that the higher, proposed therapeutic dose did not have any greater effect than the lower dose (i.e., threshold effect reached). However the higher values noted may also be influenced by the more frequent ECG testing in the Phase 2 202a and 202b studies than in the Phase 3 studies with greater opportunity for measurement of outlier values.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The maximum post-drug QTcF and maximum post-drug change in QTcF were also examined to identify patients who may be more affected by drug administration than others. The results are reproduced from the Applicant's ISS and shown in Table 69.

Table 69: Summary of Post-Drug Changes from Baseline in QTcF Interval

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

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

The maximum QTcF change from baseline is greater for patients treated with telavancin (both doses) than patients treated with vancomycin, however the observed maximum post-baseline QTcF interval for patients treated with telavancin is not markedly increased relative to those treated with vancomycin overall (i.e, QTcF > 500 msec) seen in one telavancin treated patient and three vancomycin patients.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

The Applicant provided narrative summaries for patients with QTcF > 500 msec, change in QTcF > 60 msec, and treatment discontinuation due to these changes. Table 70 shows the patients who experienced one of these changes, along with study medication (and dose) received, risk factors for torsades de pointes, and cardiac adverse events experienced. Risk factors included hypokalemia, presence of congestive heart failure, other cardiac AEs, and concomitant medications (www.torsades.org) including diuretic therapy.

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Table 70: Outlier QTcF Intervals

	Treatment	Risk Factors for Possible QT Effect and Cardiac AEs	Cardiac AE
QTcF >500 msec			
0017-09004-0608 QTcF 505 msec	Telavancin (10 mg/kg)	Cardiomyopathy, amiodarone, hypokalemia	None
0018-38110-2918 QTcF 512 msec	Vancomycin	Congestive cardiomyopathy, history of VT with AICD, cardiac arrest, HTN (waiver for enrollment), hypokalemia	None
0018-38312-2358 QTcF 515 msec	Vancomycin	Sick sinus with a fib, hypocalcemia, hypokalemia, sotalol	None
202a-115-1036 QTcF 532 msec	Vancomycin	DM, hypokalemia, CAD	None
QTcF >500 msec (repeat x2) D/C from study medication			
0018-01006-2292[1]	Telavancin (10 mg/kg)	HTN, supraventricular arrhythmia with history of AV node ablation and pacemaker. sotalol	Mild worsening of palpitations
0017-38111-0646[1]	Vancomycin	Sertraline	None
0018-20006-2737[1]	Vancomycin	HTN, hypokalemia, risperidone	None
Maximum Increase QTcF of > 60 msec			
0017-38101-0284	Telavancin (10 mg/kg)	Methadone	None
0017-38101-0362	Telavancin (10 mg/kg)	Risperidone, hypomagnesemia	None
0017-38101-0437	Telavancin (10 mg/kg)	Hypokalemia, hypomagnesemia	None
0017-38101-0538	Telavancin (10 mg/kg)	Hypomagnesemia	Poss-related: (non-cardiac) chest pain
0017-38101-1020	Telavancin (10 mg/kg)	HTN, methadone, quetiapine	None
0017-38111-0380	Telavancin (10 mg/kg)	Coronary artery disease, prior MI, amiodarone, quetiapine	MI, CHF / SAE
0017-38271-0556	Telavancin (10 mg/kg)	History of MI, CHF, methadone	None (chest pain)
0017-38271-0736	Telavancin (10 mg/kg)	HTN	None
0018-20006-2399	Telavancin (10 mg/kg)	DM	None
0018-33002-2411	Telavancin (10 mg/kg)	HTN, DM, hypokalemia, nicardipine	None
0018-38074-2538	Telavancin (10 mg/kg)	HTN	None
202b-901-9055	Telavancin (10 mg/kg)	Promethazine, prochlorperazine, hypokalemia	None
202b-905-9006	Telavancin (10 mg/kg)	DM, HTN, asthma, indapamide	None
202b-907-8003	Telavancin (10 mg/kg)	DM, haloperidol	Cardiac failure (with septic shock) / discontinued
0017-38101-0026	Telavancin (7.5 mg/kg)	Methadone	None
202a-00115-1029	Telavancin (7.5 mg/kg)	DM	None
0017-38001-0432	Vancomycin	DM, hypokalemia, hypomagnesemia, tolterodine, fluoxetine	None
0017-38271-0307	Vancomycin	DM, hypokalemia, hypomagnesemia	None
0018-25006-2151	Vancomycin	DM	None
0018-38247-2776	Vancomycin	HTN, DM, hypokalemia, hypomagnesemia, amitriptyline	None
0018-38321-2358 (also QTcF >500 msec)	Vancomycin	Sick sinus with a fib, hypocalcemia, hypokalemia, sotalol	None
202a-00115-1036	Vancomycin	DM, hypokalemia, CAD	None
[1] Based on local ECG, not confirmed on core lab reading of ECG			

The table shows that in patients with QTcF interval > 500 msec or maximum change in QTcF of > 60 msec, other factors may have contributed to ECG findings. These factors include comorbid medical conditions (such as coronary artery disease, hypertension, or diabetes) that

put patients at risk for ischemia and congestive heart failure, and concomitant medications and electrolyte disturbances that may affect the QT interval. The cardiac AEs that occurred in these patients can be explained by these underlying factors.

There were more telavancin-treated patients then comparator-treated patients who had a maximum increase in the QTcF interval of > 30 msec (approximately twice as many). In the telavancin 7.5 mg/kg studies, there were 48/192 patients (25%) in the telavancin group compared to 22/189 patients (11.6%) in the vancomycin group who had a maximum increase of > 30 msec. In the telavancin 10 mg/kg studies, there were 182/1029 patients (17.7%) in the telavancin group compared to 94/1033 (9.1%) in the vancomycin group who had maximum increase in QTcF of > 30 msec. Since the frequency of occurrence of QTcF change > 30 msec was higher for the telavancin 7.5 mg/kg treatment group, the Applicant concluded that there was no suggestion that an increased dose (i.e., the 10 mg/kg dose) resulted in more patients with change in QTcF > 30 msec.

The Applicant provided a summary of patients who were considered to be outliers in terms of ECG measurements (either QTcF > 500 msec or change in QTcF > 30 msec) and in whom a cardiac AE occurred. There were 10 telavancin-treated patients (one treated with 7.5 mg/kg and nine with 10 mg/kg) and 5 vancomycin-treated patients with the defined QTcF changes who also had a **cardiac adverse event**.

- No patients had absolute maximum QTcF of > 500 msec
- Two patients in the telavancin treatment group had AEs categorized as serious or resulting in discontinuation and QTcF of > 60 msec:
  - 0017-38111-0380*: SAE of myocardial infarction, congestive heart failure, also history of CABG and risk factors for congestive cardiomyopathy [possibly/probably related to study medication]
  - 202b-907-8003: heart failure associated with septic shock, AE resulted in discontinuation [assessed by the investigator as unrelated to study medication]
- The other seven telavancin 10 mg/kg patients with QTcF of > 30 msec who had AEs which were not classified as serious and did not result in discontinuation were:
  - 0017-38024-0385*: worsening congestive heart failure, hx of CHF, risk factors for congestive cardiomyopathy [investigator assessed as not related to medication]
  - 0017-38024-0817*: congestive heart failure, risk factors for congestive cardiomyopathy [investigator assessed as not related to medication]
  - 0017-38101-1006: bradycardia, asymptomatic [possibly, probably related to study medication]
  - 0017-38101-1009: sinus tachycardia [possibly, probably related to study medication]
  - 0017-38271-0897: mild mitral/tricuspid regurgitation with diastolic dysfunction [investigator assessed as not related to study medication]
  - 0017-38271-0978: congestive (dilated) cardiomyopathy (prior history of CHF, MI, HTN, DM), angina pectoris, atrial fibrillation [investigator assessed as not related to study medication]
  - 202b-00101-7128: palpitations, DM on multiple medications including promethazine, hydrochlorothiazide, potassium, and magnesium replacement [investigator assessed as not related to study medication]

- Three (*) of the nine patients above treated with telavancin 10 mg/kg had risk factors for CHF (CAD, DM, HTN).
- One patient treated with telavancin 7.5 mg/kg had <u>QTcF > 30 msec</u> and had a cardiac AE:
  - o 202a-00110-1017: arrhythmia (not drug-related), on multiple concomitant medications including digoxin, salbutamol, cyclobenzaprine, furosemide, and carvedilol, ECG with atrial fibrillation, left anterior hemiblock, and RBBB at baseline and end-of-infusion D4 [investigator assessed as not related to study medication]

For the <u>vancomycin</u> treatment group:
- Five patients treated with vancomycin had <u>QTcF outliers (QTcF > 500 msec or change in QTcF > 30 msec) and a cardiac AE</u> reported:
  - o 0018-38025-2330: SAE myocardial infarction, also angina pectoris [investigator assessed as unrelated to study medication]
  - o 0017-38101-0461: angina pectoris [possibly/probably related to study medication]
  - o 0017-38271-0999: mixed aortic and cardiac valve disease (mild aortic stenosis) [investigator assessed as not related to study medication]
  - o 0018-33002-2633: angina pectoris [investigator assessed as not related to study medication]
  - o 0018-38012-2177: first degree AV block and sinus bradycardia [investigator assessed as not related to study medication]

There were 3 patients with QTcF outliers (QTcF > 500 msec or change in QTcF > 30 msec) who had QT related, non-cardiac SOC Events in the Investigations SOC (prolongation of QTcF). These patients were:
<u>Telavancin (10 mg/kg)</u>
- 0018-38211-2650: 75 yo female with pre-existing hypocalcemia, had QTcF > 500 msec reported as AE on D10 (last day of rx, 1 ECG of 3 showed QTcF of 503 msec)
<u>Vancomycin</u>
- 0017-38111-0646: met QTcF criteria for discontinuation with local ECG reading, but not confirmed centrally (see previous table)
- 0017-38271-0830: no confirmation of either QTcF > 500 msec or increased QTcF interval of > 60 msec

The ISS dataset of AEs was searched for AEs (both investigator reported and MedDRA preferred terms) that might be indicative of a problem with QT prolongation and/or ventricular arrhythmia such as Torsades de pointes. The following terms were searched: bradycardia, arrhythmia, palpitations, ventricular arrhythmias, ventricular tachycardia, ventricular extrassystoles, ventricular bigeminy, cardio-respiratory arrest, cardiac arrest, sudden death, fall, syncope, and light headedness. There were no patients treated with telavancin who had AEs that were preceded by CRF evidence of ventricular arrhythmia due to torsades de pointes.

7.1.9.4   Additional analyses and explorations

7.1.9.4.1 Effect of telavancin concentration on QTcF

The Applicant also provided analyses of plasma telavancin concentrations in relation to average and maximal changes in the QTcF interval in patients in Studies 0017 and 0018. Three hundred eighty three subjects had PK profiles in Studies 0017 and 0018.

The following two figures were included in the Applicant's analysis and are reproduced here; figure 7-4 shows the scatter plot for average change in QTcF versus plasma concentration and figure 7-5 shows the scatter plot for maximum change in QTcF interval versus plasma concentration. The Applicant states that the plots are truncated at C_{max} values no greater than 300 µg/mL, to better show the distribution of plasma concentrations.

Figure 7-4:   Mean Post-Dose Change in QTcF versus Maximum Plasma Telavancin
Concentration (Protocols 0017 and 0018)
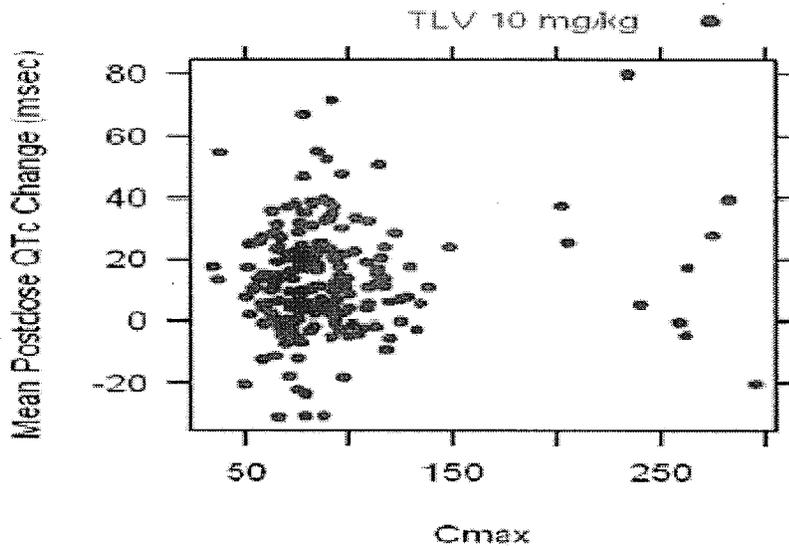
From ISS, Figure 7-4, pg 286.

Figure 7-5:   Maximum Post-Dose Change in QTcF versus Maximum Plasma Telavancin
Concentration (Protocols 0017 and 0018)
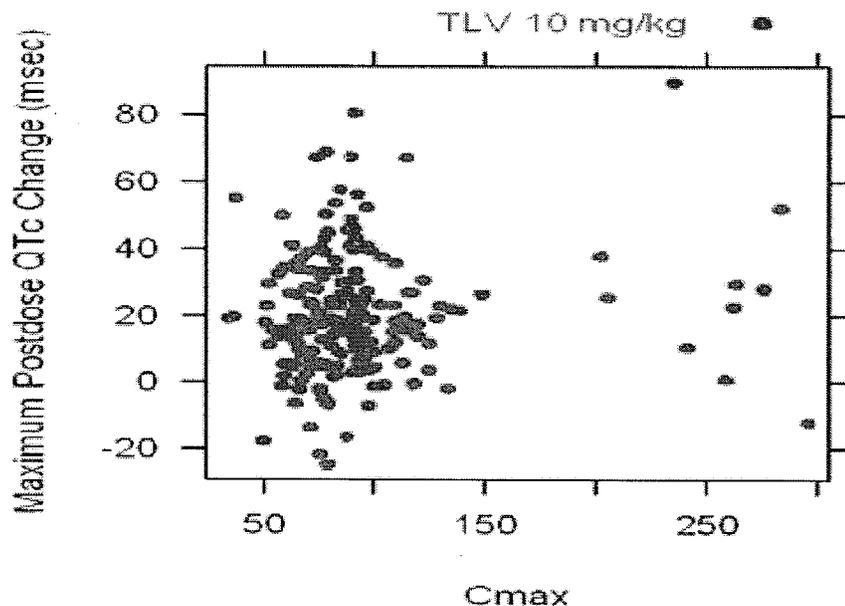
From Integrated Summary of Safety, Figure 7-5, pgs 287.

The Applicant stated that C_{max} plasma concentrations cluster around 100 µg/mL for the plasma concentration and 10-20 msec for the average and maximum change. From these plots, the Applicant concluded there is no apparent relationship between the change in the QTcF interval and maximum measured telavancin concentrations.

MO Comment: The majority of C_{max} plasma concentrations appear to cluster around 90-100 µg/mL, while the average change in QTcF clusters around 10-20 msec and maximum change in QTcF around 15-25 msec. Although changes of QTcF > 30 msec appear to occur with no greater frequency at higher concentrations, it is not possible to rule out a concentration effect since patients may have other risk factors or conditions associated with the increase in QTcF.

The Applicant also used plasma concentration data from the Phase 3 cSSSI studies and noncompartmental pharmacokinetic analysis to assess whether patients with outlying QTcF values (QTcF change ≥ 30 msec or QTcF > 500 msec) were more likely to have high plasma concentrations of telavancin than those without those changes. The analysis results which are shown in Table 71 indicate that patients with outlier QTcF values were not more likely to have higher plasma concentrations.

Table 71: PK Parameters for Phase 3 cSSSI Patients With/Without OTcF Outliers

Table 7-5:   Pharmacokinetic Parameters for Patients from Phase 3 studies in cSSSI with
               and without Outlying QTcF Values[1]

PK Parameter	Patients without Outlying QTcF			Patients with Outlying QTcF			
	N	Mean (SEM)	95% CI2	N	Mean (SEM)	95% CI2	P value
Cmin (µg/mL)	302	8.6 (0.4)	7.8, 9.4	68	7.5 (0.7)	6.1, 8.9	0.177
Cmax (µg/mL)	302	89.7 (2.9)	84.0, 95.5	68	86.1 (5.4)	75.4, 96.8	0.555
AUC (µg·hr/mL)	299	878 (16)	847, 910	68	833 (29)	776, 891	0.175

[1] QTcF prolongation > 30 msec prolongation or > 500 msec
[2] CI=confidence interval
Source: Supporting Table 176

From ISS, Table 7-5, pg 288.

7.1.9.4.2 Effect of telavancin on QTcF in patients with other risk factors for torsades de pointes

Although the Phase 3 cSSSI studies excluded patients with some of the known risk factors for Torsades de pointes (such as congenital long QT syndrome, QTc > 500 msec, uncompensated heart failure, and severe left ventricular hypertrophy), there were patients included who had other potential risk factors. This afforded an opportunity to assess the interaction of telavancin with these other potential factors, such as use of medications associated with definite or possible risk of Torsades, patients with a history of or current compensated CHF, hypokalemia, and/or diuretic therapy. The Applicant analyzed all telavancin-treated patients (both 7.5 mg/kg and 10 mg/kg doses) as a group compared to vancomycin therapy, since the effect on QTcF was apparent and similar at both doses of telavancin.

Risk of Torsades in patients with risk factors was determined by identifying patients with hypokalemia, CHF, and/or furosemide-treatment, along with ECG abnormalities (QTcF outliers of ≥ 30 msec increase or ≥ 500 msec interval) from the Phase 2 and 3 study databases ("other" risk factors). Overall, 37% of the telavancin group and 30% of the vancomycin group had "other" risk factors. A greater number of patients with "other" risk factors showed outlying QTcF values in the telavancin treatment groups than in the vancomycin patients with "other" risk factors (22% versus 12%), driven primarily by those taking concomitant medications or those with hypokalemia. Additonally, among telavancin treated patients, patients with "other" risk factors were more likely to have an outlying QTcF value than those without "other" risk factors (22% versus 17%); the vancomycin group with "other" risk factors similarly had a greater risk of outlying QTcF values (12% versus 9%), but the rate of events in either vancomycin group (with or without other risk factors) was not as high as telavancin. More extreme values [i.e., threshold of QTcF change of > 60 msec (rather than ≥ 30 msec) and/or the same QTcF interval outlier > 500 msec] were seen in telavancin-treated patients taking concomitant medications with known or possible risk of Torsades (10/253 or 4%) than in telavancin-treated patients not taking those concomitant medications (7/968 or 0.7%). The risk of more extreme outliers in the vancomycin-

treated patients was low whether or not concomitant medications with Torsades risk were being taken (1/199 or 0.5% for those taking versus 6/1023 or 0.6%).

7.1.10 Immunogenicity

Telavancin is a low molecular weight compound and was not tested for immunogenicity.

7.1.11 Human Carcinogenicity

Telavancin is being assessed for short-term treatment (7-14 days) of an acute infectious process. Therefore, carcinogenicity testing is not indicated at this time.

7.1.12 Special Safety Studies

There were no special safety studies, other than the "Thorough QT Study" previously described in Section 7.1.9.1, that were requested.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Glycopeptides such as vancomycin and teicoplanin do not have a history of abuse and withdrawal symptoms have not been observed. Therefore, telavancin was not specifically studied for withdrawal phenomenon or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

Female patients of childbearing potential were to be excluded from clinical studies if they were pregnant, nursing, or unable to use a highly effective method of birth control during and for one month after the last dose of study medication. Therefore, there are no adequate and well-controlled studies in pregnant women. Patients were screened with serum β-hCG at baseline and EOT.

If a female patient or a partner of a male patient became pregnant during a study, the medical monitor was to be notified and followup information regarding the outcome of pregnancy and postnatal sequelae was required. The Applicant was notified about two female patients who became pregnant during participation in a telavancin clinical study.

0018-38148-2928: 22 yo female was treated with telavancin (10 mg/kg) for a MRSA facial abscess for 14 days. Baseline pregnancy test was negative. The patient was on oral contraceptives. The EOT pregnancy test was negative and the patient returned six days later for a TOC visit at which time the infection was resolved. The patient's physician was notified by the patient's obstetrician approximately one month later that the patient was pregnant and estimated date of conception was the day of the TOC visit. The patient's delivery date was estimated for mid-( ) A May 4, 2007 response by the Applicant to an FDA request for follow-up information regarding Patient #0018-38148-2928 stated that she delivered on

b(6)

(*} There were no complications reported and no abnormalities or health problems have been noted in her baby girl. **b(6)**

0017-38271-0734: 23 yo female was treated with study medication (vancomycin) for nine days for an MSSA suprapubic abscess. She also received aztreonam and metronidazole for five days. Baseline and EOT pregnancy tests were negative. She returned for a TOC visit 1 week later and infection was resolved. Two weeks later she reported a positive pregnancy test. She noted some "spotting" that day and had a miscarriage later that day.

7.1.15 Assessment of Effect on Growth

Telavancin is being assessed at this time for treatment of cSSSI in adults and therefore no formal assessment of telavancin effect on growth has been done.

7.1.16 Overdose Experience

There were no AEs associated with overdose of telavancin during the clinical studies.

Based on PK data from Study 103a the amount of telavancin removed by hemodialysis represented approximately 5.9% of the dose administered just prior to hemodialysis.

Exploration of dose-related effects on AEs was performed by the Applicant by examining AE profiles of patients participating in the four-arm ECG study 104a. This study included a telavancin 7.5 mg/kg and 10 mg/kg dose, placebo with HP-β-CD, and moxifloxacin. Evidence of dose-related effect was noted in association with dysgeusia, nausea, injection site erythema, headache, rash, and "Red-Man Syndrome".

Overall in the cSSSI studies, dose-related effects on AEs were noted between telavancin 7.5 mg/kg and telavancin 10 mg/kg for the AEs of dysgeusia (11% compared to 32%) and foamy urine (3% compared to 12%).

The Applicant examined the AE profiles in Studies 0017 and 0018 for patients who received an initial dose of telavancn 1.25 times greater than the protocol-recommended dose. The ISS did not state whether these patients included patients from the initial telavancin 7.5 mg/kg dose studies or only from the post amendment 10 mg/kg dose studies.

There were a total of 39 patients identified who received an initial dose of telavancin that was higher than that specified in the protocol based on calculated baseline creatinine clearance and recorded weight. Fifteen patients received > 1.25 to 1.5X protocol-specified dose, 11 received >1.5 to 2X the specified dose, and 13 received > 2X the protocol-specified dose. These 39 patients were not identified by the Applicant.

The Applicant notes that of the 39 patients, 32 (82%) had creatinine clearance values of < 50 mL/min. The Applicant noted that this population is significantly different from those with normal renal function receiving an appropriate dose and therefore an AE dose-response

comparison could not be made since it would reflect characteristics of a population with renal insufficiency.

The Applicant's recommendation of adherence to the recommended dose of telavancin was based largely on the observed dose-related effects noted in the ECG study and the cSSSI studies.

7.1.17 Postmarketing Experience

Telavancin is not licensed in any country and is not available for commercial use. Therefore, there is no postmarketing data.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Table 72 below shows the number of patients treated with telavancin versus comparator in the telavancin development program as of September 21, 2006 (for patients enrolled prior to May 15, 2006).

Table 72: Number of Subjects Evaluated for Safety – All Telavancin Studies

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

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

Clinical pharmacology studies were performed in healthy subjects and also in subjects with a desired demographic or medical condition of interest (e.g. elderly, renal impairment, hepatic impairment patients). Patients in the Efficacy and Safety studies had the condition which was being studied (i.e. skin infection, bacteremia, or hospital-acquired pneumonia).

7.2.1.1 Study type and design/patient enumeration

See Section 4.2, Tables of Clinical Studies.

7.2.1.2 Demographics

Table 73 below shows the demographic characteristics of the clinical pharmacology subjects.

Table 73: Demographics of Clinical Pharmacology Population

	Healthy Subject[1] (N=163)	Intrinsic Factor[2] (N=63)	Extrinsic Factor[3] (N=42)	Total (N=268)
Age (years)				
• Mean	27.7	60.7	32.9	36.3
• Min, max	18.0, 52.0	36.0, 83.0	18.0, 50.0	18.0, 83.0
Age Distribution				
• <65 years	163 (100)	35 (56)	42 (100)	240 (90)
• ≥65 years	0	28 (44)	0	28 (10)
• ≥75 years	0	8 (13)	0	8 (3)
Sex				
• Male	117 (72)	41 (65)	30 (71)	188 (70)
• Female	46 (28)	22 (35)	12 (29)	80 (30)
Race				
• Asian	4 (4)	0	0	4 (2)
• Black	8 (7)	14 (23)	8 (19)	30 (14)
• White	101 (89)	47 (77)	34 (81)	182 (84)
• Other	1 (<1)	0	0	1 (<1)
• Missing	49	2	0	51
Body Mass Index Distribution (kg/m²)				
• Mean	24.7	26.4	26.7	25.4
• Min, max	17.2, 33.2	16.9, 35.8	18.9, 35.1	16.9, 35.8

From ISS, Table 4-14, pgs 57-59.
[1] Studies 0027, 101a (single and multiple dose), 102a (Amended, 4 healthy subjects), 104a, 107a, and 108a
[2] Studies 105a, 102a (Original, 3 elderly subjects), 103a, 0016
[3] Studies 0032 and 0035

MO Comment: With the exception of the studies of PK in the elderly and those with comorbid medical conditions, the clinical pharmacology population was predominantly young, white males. For the studies in the elderly and patients with renal and hepatic impairment, the population was older (44% of subjects were over age 65 yrs) and predominantly white, with 65% males.

Table 74 below shows the demographic characteristics of the study populations for the clinical studies of telavancin in the treatment of cSSSIs.

Table 74: Demographics of Phase 2 and Phase 3 cSSSI Study Populations

	All 7.5 mg/kg Studies 202a and Original Protocol 202b + 0017 + 0018		All 10 mg/kg Studies 202b + 0017 + 0018 Post-amendment		Phase 3 cSSSI Studies 0017+0018 (10 mg/kg)	
	TLV 7.5 mg/kg N=192	Vanc[1] N=189	TLV 10 mg/kg N=1029	Vanc[1] N=1033	TLV 10 mg/kg N=929	Vanc N=938
Age (years)						
• Mean	46.4	44.0	48.4	48.2	48.8	48.7
• Min, max	18.9, 89.5	18.4, 86.0	18.0, 96.0	17.0, 91.0	18.0, 96.0	17.0, 91.0
Age Distribution						
• <65 years	175 (91)	175 (95)	847 (82)	850 (82)	755 (81)	759 (81)
• ≥65 years	17 (9)	10 (5)	182 (18)	183 (18)	174 (19)	179 (19)
• ≥75 years	11 (60)	7 (4)	91 (9)	78 (8)	87 (9)	78 (8)
Sex						
• Male	122 (64)	111 (59)	572 (56)	621 (60)	517 (56)	559 (60)
• Female	70 (36)	78 (41)	457 (44)	412 (40)	412 (44)	379 (40)
Race						
• Aborigine	0	0	1 (<1)	1 (<1)	1(<1)	1 (<1)
• American Indian/Alaskan Native	0	2 (1)	12 (1)	11 (1)	11 (1)	11 (1)
• Asian	7 (4)	3 (2)	48 (5)	54 (5)	46 (5)	52 (6)
• Black, of African heritage	38 (20)	51 (27)	161 (16)	158 (15)	132 (14)	128 (14)
• Hawaiian/Pacific Islander	11 (6)	9 (5)	10 (<1)	18 (2)	7 (<1)	17 (2)
• White	121 (64)	109 (58)	765 (74)	766 (74)	724 (78)	723 (77)
• Multi-racial	13 (7)	14 (7)	32 (3)	25 (2)	8 (<1)	6 (<1)
Body Mass Index Distribution (kg/m²)						
• Mean	29.2	29.1	29.7	29.3	29.9	29.4
• Min, max	15.1, 69.6	14.5, 83.4	13.3, 93.9	14.4, 87.5	13.3, 93.9	15.8, 87.5

From ISS, Tables 4-16 and 4-17, pgs 62-66, Supporting Table 13, pgs 21-23, Supporting Table 15, pgs 27-28.
[1] Includes 27 patients (20 in 202a and 7 in Post-Amendment 202b) who received an antistaphylococcal penicillin instead of vancomycin.

MO Comment: The primary clinical studies designed to assess the efficacy and safety of telavancin in treatment of cSSSI were characterized by patients with a mean age of 49 years and approximately 20% of patients over the age of 65 years. There was a slight male predominance. The majority of patients were white, followed by about 15% of the study population who were black and 5-6% Asian. The mean BMI was around 30 kg/m² and approximately 25% of the population was obese or morbidly obese (BMI 30-<40 or ≥40 kg/m², respectively).

7.2.1.3   Extent of exposure (dose/duration)

Table 75 below, reproduced from the ISS, shows the duration of exposure to telavancin in each of the clinical pharmacology studies.

Table 75: Duration of Telavancin Exposure – Clinical Pharmacology Studies

Table 4-3:   Number (%) of Subjects by Duration of Exposure to Telavancin - Clinical Pharmacology Studies – Safety Population

Study Group	Any Exposure	One Day		Number of Days Exposure 2-6 days		7-14 days	
Healthy Subject PK							
Study 0027	6	6	(100%)	0		0	
Study 101a[3]	45	11	(24%)	18	(40%)	16	(36%)
Study 102a[1]	4	4	(100%)	0		0	
Study 104a	79	6	(8%)	73	(92%)	0	
Study 107a	9	1	(11%)	8	(89%)	0	
Study 108a	20	0		20	(100%)	0	
Intrinsic Factor PK							
Study 105a	16	16	(100%)	0		0	
Study 102a[2]	2	2	(100%)	0		0	
Study 103a	29	29	(100%)	0		0	
Study 0018	16	11	(69%)	5	(31%)	0	
Extrinsic Factor PK							
Study 0032	16	0		0		16	(100%)
Study 0035	26	2	(8%)	24	(92%)	0	
Total	268	88	(33%)	148	(55%)	32	(12%)

[1] The data in this row are from Amended Protocol 102a which included 4 healthy subjects

[2] The data in this row are from Original Protocol 102a which included 3 elderly subjects

[3] Includes single- and multiple-dose phase

Source: Data Set: ADAE, Program: PhaseIDuration, Run Date: 30OCT2006

From ISS, Table 4-3, pg 37.

Table 76, reproduced from the ISS, shows the number of patients exposed to a designated dose in the clinical pharmacology studies.

Table 76: Number of Subjects By Dose of Telavancin – Clinical Pharmacology Studies

Table 4-4:   Number (%) of Subjects by Dose of Telavancin - Clinical Pharmacology
Studies – Safety Population

Study Group	Any Exposure	<7.5 mg/kg		7.5 mg/kg		10 mg/kg		>10 mg/kg	
Healthy Subject PK									
Study 0027	6	0		0		6	(100)	0	
Study 101a[3]	45	17	(38)	7	(16)	6	(13)	33	(73)
Study 102a[1]	4	0		2	(50)	0		2	(50)
Study 104a	79	0		40	(51)	0		39	(49)
Study 107a	9	0		9	(100)	0		0	
Study 108a	20	0		0		20	(100)	0	
Intrinsic Factor PK									
Study 105a	16	0		0		16	(100)	0	
Study 102a[2]	2	0		0		0		2	(100)
Study 103a	29	0		29	(100)	0		0	
Study 0016	16	0		0		16	(100)	5	(31)
Extrinsic Factor PK									
Study 0032	16	0		0		16	(100)	0	
Study 0035	26	0		0		26	(100)	0	
Total	268	17	(6)	87	(32)	106	(40)	81	(30)

[1] The data in this row are from Amended Protocol 102a which included 4 healthy subjects

[2] The data in this row are from Original Protocol 102a which included 3 elderly subjects

[3] Includes single- and multiple-dose phases

Source: Data Set: ADAE, Program: PhaselDose, Run Date: 31JUL2006

From ISS, Table 4-4, pg 38.

The exposure to "comparator drugs" in the clinical pharmacology studies was confined to four studies (Study 101a, Study 104a, Study 0032, and Study 0035), each with limited durations of treatment. These included parallel exposures to placebo and moxifloxacin in Study 104a, parallel exposures to aztreonam and piperacillin-tazobactam in Study 0035, and crossover exposures to placebo and telavancin in Study 101a, Study 0032, and Study 0035. Therefore, most direct comparisons of telavancin to comparator are of limited utility, with the exception of the QT Study (Study 104a) in which one-quarter of the subjects received moxifloxacin.

Table 77 below, reproduced from the ISS, shows the extent (dose/duration) of treatment with telavancin in the Phase 2 and Phase 3 cSSSI studies.

Table 77: Extent of Exposure to Telavancin – cSSSI Studies

Table 4-9:   Number (%) of Patients by Duration of Exposure to Telavancin - Efficacy and Safety Studies in cSSSI – Safety Population

Study Group Number (%) of Patients	Any Exposure	One Day		Number of Days Exposure 2-6 days		7-14 days		>14 days[1]	
Efficacy and Safety Studies in cSSSI - Telavancin 10 mg/kg									
Study 0017 (Post-Amendment)	426	8	(2)	45	(11)	283	(66)	90	(21)
Study 0018 (Post-Amendment)	503	6	(1)	69	(14)	404	(80)	24	(5)
Study 202b (Post-Amendment)	100	0		43	(43)	53	(53)	4	(4)
Subtotal	1029	14	(1)	157	(15)	740	(72)	118	(11)
Efficacy and Safety Studies in cSSSI - Telavancin 7.5 mg/kg									
Study 0017 (Original Protocol)	73	1	(1)	2	(3)	50	(68)	20	(27)
Study 0018 (Original Protocol)	20	3	(15)	1	(5)	14	(70)	2	(10)
Study 202b (Original Protocol)	15	0		2	(13)	13	(87)	0	
Study 202a	84	0		39	(46)	41	(49)	4	(5)
Subtotal	192	4	(2)	44	(23)	118	(61)	26	(14)
Total	1221	18	(1)	201	(16)	858	(70)	144	(12)

[1] The maximum number of days of exposure was 18.

Source: Data Set: ADAE, Program: EffSafDurationTel, Run Date: 07SEP2006

ISS, Table 4-9, pg 47.

Note: In Study 0018, 1 patient was randomized to treatment with vancomycin and was treated with telavancin instead. This patient is included in the telavancin safety population and the vancomycin AT efficacy population.

MO Comment: There were a total of 1029 patients who received telavancin in Phase 2 and Phase 3 SSSI studies at the 10 mg/kg dose. Six hundred eighty seven patients (687/740 or 92.8%) received the 7-14 day treatment specified for this NDA indication (to be marketed dose) in Phase 3 cSSSI studies. The total exposure of 740 patients to 7-14 days of treatment is close to the 750 estimate agreed to at the pre-NDA meeting for a safety database.

Table 78 below, reproduced from the ISS, shows the extent (dose/duration) of treatment with comparator in the Phase 2 and Phase 3 cSSSI studies.

Table 78: Extent of Exposure to Comparator – cSSSI Studies

Table 4-10: Number (%) of Patients by Duration of Exposure to Comparator - Efficacy and Safety Studies in cSSSI – Safety Population

Study Group Number (%) of Patients	Any Exposure	One Day		2-6 days		7-14 days		>14 days[1]	
Efficacy and Safety Studies in cSSSI - Telavancin 10 mg/kg									
Study 0017 (Post-Amendment)[2]	429	6	(1)	47	(11)	268	(62)	108	(25)
Study 0018 (Post-Amendment)[2]	509	14	(3)	58	(11)	403	(79)	34	(7)
Study 202b (Post-Amendment)[3]	95	1	(1)	48	(51)	37	(39)	9	(9)
Vancomycin	88	1	(1)	46	(52)	34	(39)	7	(8)
Antistaphylococcal penicillin	7	0		2	(29)	3	(43)	2	(29)
Subtotal	1033	21	(2)	153	(15)	708	(69)	151	(15)
Efficacy and Safety Studies in cSSSI - Telavancin 7.5 mg/kg									
Study 0017 (Original Protocol)[2]	70	0		3	(4)	38	(54)	29	(41)
Study 0018 (Original Protocol)[2]	19	0		3	(16)	15	(79)	1	(5)
Study 202b (Original Protocol)[3]	17	0		6	(35)	10	(59)	1	(6)
Study 202a[3]	83	1	(1)	35	(42)	44	(53)	3	(4)
Vancomycin	63	1	(2)	21	(33)	38	(60)	3	(5)
Antistaphylococcal penicillin	20	0		14	(70)	6	(30)	0	
Subtotal	189	1	(1)	47	(25)	107	(57)	34	(18)
Total	1222	22	(2)	200	(16)	815	(67)	185	(15)

[1] The maximum number of days of exposure was 18.

[2] Comparator = Vancomycin 1 gram IV q 12 h.

[3] Comparator = Standard Therapy (nafcillin or oxacillin 2 gm q 6 hr, or cloxacillin (in S. Africa) 0.5 -1.0 gm q 6 hr, or vancomycin 1 gram IV q 12 hr)

Source: Data Set: ADAE, Program: EffSafDurationComp, Run Date: 11SEP2006

ISS, Table 4-10, pg 48.
Note: In Study 0018, 1 patient was randomized to treatment with vancomycin and was treated with telavancin instead. This patient is included in the telavancin safety population and the vancomycin AT efficacy population.

MO Comment: There were a total of 708 patients who received comparator treatment in the telavancin Phase 2 and Phase 3 SSSI studies. Six hundred seventy one (671/740 or 94.8%) received the 7-14 day treatment specified for this NDA indication in Phase 3 cSSSI studies and serve as the comparator for determination of efficacy and safety of telavancin.

MO Comment: At the time of the NDA submission, there were 3 ongoing treatment-blinded trials. The study and number of patients enrolled in each study prior to the cutoff date of May 15, 2006 are shown in Table 79 below which is reproduced from the ISS.

Table 79:

Table 4-13: Estimated Number (%) of Patients by Duration of Exposure to Telavancin: Ongoing Studies– Safety Population (data cutoff – 21 September 2006)

Study Group	Any Exposure	One Day		Number of Days Exposure 2-6 days		7-14 days		>14 days1	
						Number (%) of Patients			
Bacteremia									
Study 203a	58	2	(3)	14	(24)	21	(36)	19	(33)
HAP									
Study 0015	213	2	(1)	55	(26)	130	(61)	26	(12)
Study 0019	144	3	(2)	29	(20)	103	(72)	9	(6)
Subtotal	357	5	(1)	84	(24)	233	(65)	35	(10)
Study 0029	1	0		0		0		1	(100)
Total	416	7	(2)	98	(24)	254	(61)	55	(13)

¹ The maximum number of days of exposure was 23.

Source: Data Set: ADAE, Program: OngoingDuration, Run Date: 01OCT2006

From ISS, Table 4-13, pg 55.

MO Comment: The number of patients shown under "any exposure" is the total number of patients enrolled in each study. With a 1:1 randomization scheme, the estimated number of patients treated with telavancin would be one-half of this number. Because the studies were blinded to treatment at the time of the NDA submission, no inferences can be made attributing a specific duration to telavancin or comparator.

7.2.2   Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1   Other studies

There were no secondary clinical data sources available to further evaluate safety.

7.2.2.2   Postmarketing experience

Telavancin is not licensed in any country and is therefore not available for commercial use.

7.2.2.3   Literature

The Applicant performed a literature search between May 31, 2006 and June 2, 2006 to identify any clinical or nonclinical studies with potential safety information pertaining to telavancin. The databases and dates covered by the search are shown in Table 80 below which is reproduced from the ISS.

Table 80: Databases Searched for Potential Safety Information for Telavancin

Database (dates of search coverage)
Medline (1958 - 5/31/2006)
Embase (1974 - 5/31/2006)
Biosis (1969 - 5/31/2006)
CAPlus (1907 - 5/31/2006)
CASReact (1840 - 5/31/2006)
Toxcenter (1907 - 5/31/2006)
Synthline (1984 - 5/31/2006)
IMS Research (5/31/2006)
IMS Patents (5/31/2006)
Prous DDR (5/31/2006)
Adis R&D Insight (5/31/2006)
USAN (06/02/2006)
USPatFull (1975 - 5/31/2006)

The Applicant states that the search identified 65 unique citations. No information not otherwise reported in this NDA submission was found by the Applicant.

7.2.3 7.2.3 Adequacy of Overall Clinical Experience

The size of the safety database for the to-be-marketed dose of 10 mg/kg was consistent with that outlined in prior agreements between the FDA and Applicant at the End-of-Phase 2 and Pre-NDA meetings.

The clinical studies were double-blind, comparator-controlled studies with a dummy placebo infusion for patients randomized to telavancin. The dummy placebo was infused at the time patients randomized to vancomycin would be getting the second of the q 12 hr infusions. These studies were of adequate design to assess safety given the current practice of medicine and nature of the infection. It would be considered unethical to perform placebo-controlled studies for this indication. Some concerns about the adequacy of blinding are raised given the nature of observable AEs for telavancin (i.e. taste disturbance and urine abnormality).

The dose and duration of treatment was likewise adequate to assess safety for the intended use and for the indication sought.

There was no information in the NDA submission regarding safety in the pediatric population. The Applicant has been granted a deferral for pediatric studies pending a decision on approvability in adults.

7.2.4 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

QTc Study
At the time that the IND was submitted, FDA requested that the Applicant conduct a "Thorough QT " study based on preliminary evidence of an effect on cardiac conduction noted in a hERG assay and canine Purkinje fiber assay. The Applicant complied with this request and designed their study based on guidelines available in 2002. The Applicant's study differed from studies currently recommended in the following characteristics:

- A 3-day infusion of IV moxifloxacin was used for the positive control compared to a single oral dose of moxifloxacin which is currently recommended.
- A single ECG was obtained at each assessment timepoint (i.e., baseline and multiple timepoints around the Day 0/D5W and D3 assigned treatment) compared to the triplicate assessments currently recommended.
- Use of the mean of baseline placebo (Day 0/D5W) infusion QTcF values instead of a baseline time matched control.

Additional ECG studies to re-evaluate QT are not recommended (necessary) at this time.

Teratogenicity
Based on findings of skeletal abnormalities in two animal species (rat and rabbit), FDA requested that the Applicant conduct teratogenicity testing in a third species. The FDA recommended a minipig study.

The analysis of the data from the minipig study analysis was confounded by the finding of a limb abnormality (polydactyly) in a control animal and additional limb abnormalities in the low and mid-dose telavancin groups, with no abnormalities noted in the high dose telavancin group. Interpretation of the findings was also made difficult by the low pregnancy rates and small number of litters available for examination. Many animals had required additional antimicrobial agents, although none had been specifically linked to limb abnormalities. There are differing scientific opinions regarding utility of this study. Refer to Section 3.2 Animal Pharmacology/Toxicology, Teratogenicity for further discussion.

At this time, no further teratogenicity testing is required.

7.2.5 7.2.5 Adequacy of Routine Clinical Testing

Central Versus Local Laboratory Issues:
- The Phase 3 cSSSI protocol for both Study 0017 and 0018 called for central laboratory assessments every 3 days (± 1 day) while on study therapy. Central laboratory results were used preferentially for study safety analyses. Local laboratory studies were to be utilized for

any acute patient management issues. If central laboratory studies were missing, local laboratory results were permitted to be included for the patient to minimize missing laboratory data. This issue had been discussed with and permitted by FDA, however it made it difficult to follow trends if there were major differences in laboratory results over a short period of time.

- Isolates of bacterial pathogens obtained in microbiological cultures at baseline or during the study were to be sent to a central laboratory for confirmation of identification and susceptibility determination. Central laboratory results were used preferentially, but the Applicant substituted local laboratory results if the central results were unavailable. The Division of Anti-Infectives and Ophthamalogy Products has previously required that all microbiological information used in analysis must be identified (or have confirmation of identification) and relevant susceptibility determination performed at the central laboratory. Therefore some patients with only local microbiological identification of pathogens were excluded from the FDA-ME population.

Follow-up of Safety Laboratory Abnormalities

- Renal AEs: The study protocol procedure for 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.

Patients with renal insufficiency diagnosed by laboratory parameters (elevated serum Cr meeting prespecified criteria) were not all followed for sufficient periods of time to determine whether there was complete resolution of the abnormality. In some cases, previously described in this review, the patients with normal baseline serum Cr were noted to be improved and while improvement was noted, their serum Cr was still elevated to a value 2X their baseline.

7.2.6   7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The CYP450 enzyme studies indicated that telavancin is not metabolized by CYP450 enzymes. It was demonstrated to be a weak inhibitor of CYP450 enzymes in human microsomes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5), however no significant (limited) interaction with midazolam (a well characterized probe substrate for CYP3A4) was noted.

Telavancin is excreted primarily unchanged in the urine. A hydroxylated metabolite with some (10% relative to telavancin) microbiological activity is also found.

See clinical pharmacology review for further discussion.

7.2.7 7.27 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant's evaluation for potential AEs was adequate in general. As noted previously in this review, it would have been helpful to have additional follow-up laboratory data on patients who developed abnormalities while on therapy. This would have been helpful particularly in those patients who were continuing to show improvement, but had not yet had resolution to baseline values. It would also have been helpful to have a more complete accounting for intercurrent events that are thought to be playing a role in the reported AE (e.g., more precise time course for evolution of major hemodynamic events or developing respiratory or cardiac events).

7.2.8 7.2.8 Assessment of Quality and Completeness of Data

Limitations in quality of CRF data:
- AEs were designated as "serious" for unknown reason (i.e. no criteria satisfying the definition of SAE could be ascertained from the CRF or accompanying narrative)
- There was insufficient information included in or attached to the CRF to ascertain the precise time from investigator detection of a change in a patient's serum Cr (increase or decrease) to telavancin dose adjustment when indicated by change in renal function.
- Inconsistency in whether central labs were available for a particular patient.
- The data definition tables for dataset variables did not always contain definitions of derived variables.

7.2.9 7.29 Additional Submissions, Including Safety Update

Deaths from the Four Month Safety Update

Bacteremia:
Eight deaths occurred in Study 203a; five patients in the telavancin-treatment group and three patients in the comparator treatment group. The AE preferred terms with death as an outcome in telavancin-treated patients were: sepsis, endocarditis bacterial, renal failure acute, dyspnea, death, renal failure chronic, pneumonia, disseminated intravascular coagulation, and empyema. None of the TEAEs with outcome of death were assessed as possibly/probably related to study medication by the investigator. The following patients, along with TEAE and treatment include:

Telavancin:
160-4011 – [sepsis, bacterial endocarditis, renal failure acute on Study Day 6, with death on Study Day 13]
272-4034 – [dyspnea on Study Day 16, death on Study Day 21]
430-5007 – [pneumonia, empyema, DIC on Study Day 4, renal failure chronic on Study Day 5, death on Study Day 7]
160-4016* [urosepsis]

441-5002* [hospital acquired pneumonia]

Comparator:

101-4009 – [neuroleptic malignant syndrome and death on Study Day 29]

148-4044 – [endocarditis on Study Day 8 and death on Study Day 33]

148-4024* - [intestinal ischemia on Study Day 8 and death on Study Day 71]

The patients with an asterisk (*) are patients who died outside of the reporting period. For a more detailed discussion, see Appendix B.

<u>HAP:</u>

The overall mortality rates from the HAP studies 0015 and 0019 continues to be 21%, with the mortality rate in Study 0019 of 24% slightly higher than that of Study 0015 (19%), but no specific events are seen more frequently in Study 0019. There have been 162 deaths (21%) in the ongoing HAP studies.

SAEs

<u>Bacteremia</u>

See Section 7.2.9 for additional updated information. There were 11 patients (11/58 or 38%) in the telavancin treatment group and 6 patients (2/29 or 21%) in the standard therapy group who had SAEs. No individual SAE occurred in more than one patient. Two patients treated with telavancin had renal SAEs (one patient with renal failure acute and one patients with renal failure chronic), while one standard therapy patient had an SAE of blood creatinine increased in the investigation category.

The following narratives are for patients with <u>SAEs in the Renal and Investigations SOC</u> and are based on the Applicant's narratives (Study Report and CRFs have not been submitted to FDA):

Telavancin

- 203a-160-4011 (see deaths): The patient was a 55 yo female with a history of seizure disorder, chronic hepatitis C, porphyria secondary to hepatitis C, and chronic pain syndrome, who received one dose of study medication along with linezolid and aztreonam. Following the first dose, the patient had an anxiety attack and withdrew consent and was treated with nafcillin, tobramycin, ceftriaxone, and rifampicin. An echocardiogram revealed tricuspid valve endocarditis, the patient went into renal failure, and family requested all treatment be discontinued. The investigator assessed the SAEs, including renal failure acute to be unrelated to study medication. Details are limited, but based in information thus far provided, the FDA reviewer concurs.

- 203a-430-5007 (see deaths): The patient was a 64 yo male who was treated for 5 days with study medication. The patient had a persistent SA bacteremia attributed to an infected perm-cath, along with DIC, worsening pneumonia, and empyema. The patient was switched to cloxacillin and gentamicin. After the perm-cath was removed, the patient became progressively uremic and fluid overloaded. The patient and family opted for conservative management and withholding dialysis and the patient died as a result of worsening chronic renal failure. The investigator assessed the SAEs including renal failure chronic to be unrelated to study medication. Details are limited, but based in information thus far provided, the FDA reviewer concurs.

Standard therapy

- 203a-148-4030: The patient is a 55 yo female with a history of chronic pancreatitis, chronic nausea, vomiting, and diarrhea, hypertension, and diabetes mellitus. There was no list of concomitant medications provided. The patient was treated with study medication (standard therapy comparator) for 15 days. The patient's Cr was reportedly normal through D8, but rose during the course of that day from 0.7 mg/dL to 1.3 mg/dL. The patient was hospitalized overnight for observation. The next day, the patient's creatinine was reported to be back to baseline. The investigator assessed the SAE of increased creatinine as possibly/probably related to study medication.

HAP

In the 4MSU, based on enrollment of 775 patients, there have been 246 patients (32%) with SAEs.

Table 81: Other Serious TEAEs – Ongoing Study 0015 and 0019 (figures for total SOC and preferred terms ≥1%)

	0015 N=414	0019 N=361	Total N=775
Any Serious AE	125 (30%)	121 (34%)	246 (32%)
Blood and Lymphatic System Disorders	0	6 (2%)	6 (<1%)
Cardiac Disorders	21 (5%)	15 (4%)	36 (5%)
• Cardiac arrest	7 (2%)	4 (1%)	11 (1%)
Gastrointestinal Disorders	8 (2%)	8 (2%)	16 (2%)
General Disorders and Administration Site	16 (4%)	13 (4%)	29 (4%)
Hepatobiliary Disorders	2 (<1%)	2 (<1%)	4 (<1%)
Infections and Infestations	40 (10%)	47 (13%)	87 (11%)
• Pneumonia	5 (1%)	4 (1%)	9 (1%)
• Sepsis	10 (2%)	8 (2%)	18 (2%)
• Septic shock	16 (4%)	25 (7%)	41 (5%)
Injury, Poisoning, and Procedural Complications	3 (<1)	2 (<1%)	5 (<1%)
Investigations	1 (<1%)	1 (<1%)	2 (<1%)
Metabolism and Nutrition Disorders	5 (1%)	4 (1%)	9 (1%)
Neoplasms,Benign, Malignant and Unspecified	0	2 (<1%)	2 (<1%)
Nervous System Disorders	11 (3%)	11 (3%)	22 (3%)
Renal and Urinary Disorders	21 (5%)	14 (4%)	35 (5%)
• Renal failure acute	13 (3%)	11 (3%)	24 (3%)
• Renal insufficiency	7 (2%)	1 (<1%)	8 (1%)
Respiratory, Thoracic and Mediastinal Disorders	35 (8%)	38 (11%)	73 (9%)
• Respiratory arrest	8 (1%)	0	8 (1%)
• Respiratory failure	11 (3%)	12 (3%)	23 (3%)
Skin and Subcutaneous Tissue Disorders	1 (<1%)	0	1 (<1%)
Vascular Disorders	10 (2%)	6 (2%)	16 (2%)
From 4 MSU, Table 8, pgs 29-33.			

SAEs in the Infection and Respiratory classes continue to be the most commonly observed events in the ongoing studies and are likely related to the medical condition being studied (HAP). The only preferred terms for events that have been observed in >1% (or more than 7 patients) are multi-organ failure in 25 (3%), sepsis or septic shock in 59 (7%), renal failure acute in 24 (3%), and respiratory failure in 23 (3%) patients. 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%).

In Study 0015 and 0019, there have been 36 SAEs in 31 patients (4 %) which were assessed by the investigator as possibly/probably related to study medication. These events included renal failure acute (13), renal insufficiency (6), atrial fibrillation (3), and thrombocytopenia (2). The following patients had renal SAEs assessed by the investigator as possibly probably related to study medication: [narratives reviewed, no CRFs evaluable since the study is still ongoing and treatment assignments are blinded]

- Renal failure acute: 0015-01014-4233, 0015-04008-4091, 0015-05007-4231, 0015-12016-4158, 0015-38024-4286, 0015-38102-4060, 0015-38348-4254, 0015-38350-4307, 0019-38055-6175, 0019-05000-6149, 0019-05003-6031, 0019-20014-6423
- Renal insufficiency: 0015-05002-4048, 0015-05002-4327, 0015-05002-4328, 0015-30905-4237, 0015-12006-4126, 0015-18010-4139
- Renal impairment: 0019-05000-6151
- Anuria: 0015-18010-4139

TEAEs Resulting in Discontinuation
Bacteremia
As reported in the 4MSU, four patients had TEAEs resulting in early discontinuation of study medication and occurred. Two patients had been treated with telavancin and two with standard therapy. The patients and AEs that resulted in discontinuation of medication are as follows:

- 203a-101-4005 (telavancin): Day 24 of treatment, multi-organ failure
- 203a-111-4002 (telavancin): Day 9 of treatment, fever attributed to drug
- 203a-148-4044 (vancomycin): Day 1 post 7-day course, diagnosis of infective endocarditis
- 203a-804-5016 (vancomycin): Day 12, lower extremity rash

Hospital-Acquired Pneumonia
As of the cutoff date for the 4 MSU, a total of 59/775 (8%) patients have been reported to have discontinued study medication prematurely due to an AE. Renal failure acute (9 patients, 1%) and multiorgan failure (4, 0.5%) sepsis (4, 0.5%) septic shock (5, 0.6%), QT interval prolongation (6, 0.8%), and renal insufficiency/impairment were the most frequently reported TEAEs resulting in discontinuation of study medication. Table 82 below shows the number (percent) of patients with TEAEs leading to discontinuation on study medication.

Table 82: TEAEs Resulting in Discontinuation of Study Drug (Ongoing HAP 0015 and 0019)

	0015 N=414	0019 N=381	Total N=775
Any Discontinuation AE	35 (8%)	24 (7%)	59 (8%)
Blood and Lymphatic System Disorders	3 (<1%)	0	3 (<1%)
Cardiac Disorders	4 (<1)	1 (<1)	5 (<1)
Gastrointestinal Disorders	0	2 (<1)	2 (<1)
General Disorders and Administration Site	4 (<1)	1 (<1)	5 (<1)
Hepatobiliary Disorders	1 (<1)	1 (<1)	2 (<1)
Infections and Infestations	6 (1%)	12 (3%)	18 (2%)
Investigations	8 (2%)	3 (<1%)	11 (1%)
Metabolism and Nutrition Disorders	2 (<1%)	0	2 (<1%)
Nervous System Disorders	4 (<1%)	0	4 (<1%)
Renal and Urinary Disorders	10 (2%)	3 (<1%)	13 (2%)
Respiratory, Thoracic and Mediastinal Disorders	5 (1%)	2 (<1%)	7 (<1%)
Skin and Subcutaneous Tissue Disorders	1 (<1%)	0	1 (<1%)
Vascular Disorders	1 (<1%)	1 (<1%)	2 (<1%)
Adapted From Day 120 Safety Update, Table 10, pgs 36-38.			

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Telavancin has demonstrated evidence of nephrotoxicity in clinical studies that included two independent Phase 3 studies of identical design comparing telavancin to vancomycin for treatment of cSSSI due to Gram positive organisms.

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

- There were a greater number of patients who discontinued treatment due to renal AEs in the telavancin treatment group compared to the vancomycin treatment group; 13/929 (1.4%) of telavancin-treated patients and 2/938 (0.2%) of vancomycin-treated patients discontinued treatment due to renal AEs.

- The Applicant used a variety of parameters to define nephrotoxicity. These parameters included examination of maximum change from baseline as well as the level of post-baseline change. Maximum change from baseline was 3X as likely to occur in telavancin-treated patients when looking at patients with baseline serum Cr elevations to $\geq$ 133 μmol/L (1.5 mg/dL) and either at least 44 μmol/L (0.5 mg/dL) greater than baseline or at least 50% greater than baseline. The number (percent) of telavancin-treated patients meeting these definitions were 52/929 (5.6%) and 48/929 (5.2%), respectively. The number (percent) of vancomycin-treated patients meeting these definitions were 19/939 (0.2%) and 17/939 (1.8%), respectively.

- Shift tables from the Phase 3 studies indicated that patients with a change from normal to high serum Cr at EOT were more frequent in televation-treated patients at 10%, compared to vancomycin-treated patients at $\approx$5%. These changes were noted to persist for both treatment groups through at least the TOC visit. There were more patients in the telavancin treatment

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group in Study 0017 who had high baseline values of serum Cr than in the vancomycin treatment group; one third to one half of each group had a shift to normal Cr by EOT/TOC. For Study 0018, there were a relatively equal number of patients in the telavancin and vancomycin treatment groups who had high serum Cr at baseline. More patients in the vancomycin treatment group had normal Cr at EOT/TOC ($\approx$50%) than did telavancin treatment patients ($\approx$20%).

- There were patients in the telavancin treatment groups with normal baseline serum Cr and incomplete resolution of serum Cr at TOC.
    o The two patients with reported SAEs who had incomplete resolution of elevated serum Cr had other underlying disorders; #0018-38148-2498 was a 47 yo with diabetes mellitus, peripheral vascular disease, and hypertension who was also on indomethacin and lisinopril and #0018-38260-2099 was a 50 yo female with a history of lupus who was receiving indomethacin on an as needed basis for pain.
    o One of three additional patients who discontinued telavancin therapy and had incompete resolution of elevated serum creatinine had chronic renal insufficiency (#0018-38110-2568). The other two patients did not have obvious major risk factors (i.e., diabetes or concomitant medications) for development of renal insufficiency; #0018-38304-2233 was a 51 yo male who developed nausea and vomiting on D4, elevation in serum Cr on D5 from baseline 0.8 mg/dL to 3.1 mg/dL, and improvement in Cr to 2.3 mg/dL at D12 (1 week off study medication) and #0018-38304-2233 was a 54 yo male who was receiving dyazide and clopidogrel, elevation in Cr on D4 from baseline 1.4 mg/dL to 4.5 mg/dL, with improvement to 2.3 mg/dL twenty days after discontinuing study medication.
- There were cases in both treatment groups that were confounded by comorbid conditions or concomitant medications.

Teratogenicity:
- Telavancin demonstrated multi-species teratogenicity with abnormalities noted in rats and rabbits. The effects were noted in animals treated with 1.5-2X the human equivalent dose. Limb-related defects were noted in both species. In the rat, there was one fetus in the 100 mg/kg/day group with brachymelia (associated with other abnormalities) and one fetus in the 150 mg/kg/day groups with islolated brachymelia; neither of these findings were confirmed in skeletal examination (not performed on the 150 mg/kg/day rat). The findings in one rabbit fetus treated with 75 mg/kg/day dose group included flexed front paw, brachymelia, adactyly, and gastroschisis.
- A third teratogenicity study in minipigs demonstrated limb abnormalities (including polydactyly, syndactyly, and misshapen digits), but interpretation of the study was complicated by the low number of fetuses available for examination and limb-related findings in one of the placebo-control group fetuses (placebo in other teratology studies included HP-β-CD, but was not specifically stated in this study report, instead referring to a placebo lot number).
- There has been a difference of opinion among FDA review team members on pregnancy category designation of C versus X.

Telavancin has an effect on the QT interval that appears to be less than that seen with moxifloxacin.

- The Applicant was required to perform a QT study early in development using guidance available in 2002, although requirements differ in the present regulatory environment.
- There were a higher number (percent) of patients treated with telavancin and "risk factors for torsades" (such as hypokalemia, treatment with furosemide, and/or CHF) who had prolongation of QTcF than those not having these "other risk factors" and the frequency of QTc prolongation was greater than that seen in vancomycin-treated patients with other risk factors.
- There were more patients with outlier QTcF values (i.e. QTcF > 500 msec or change in QTcF > 30 msec) in the telavancin treatment group who had study medication discontinued due to outlier values than did patients in the vancomcycin group. These outlier values, in general, were not associated with cardiac events (except for one patient with MI and a long history of coronary artery disease and another patient with cardiac failure associated with septic shock).

The most common adverse drug reaction associated with administration was taste disturbance occurring in 33% of the Phase 3 study population treated with telavancin. The other adverse reactions are nausea and vomiting; these effects did not not appear to be treatment limiting. Also noted with administration of telavancin was the finding of foamy urine.

Limitations of the data were described in Section 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Section 7.2.8 Assessment of Quality and Completeness of the Data.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Individual safety data for the Phase 3 cSSSI 10 mg/kg dose studies (Study 0017 and Study 0018) are presented alone and combined since they were of the same design and also represented the studies upon which efficacy was being determined.

Safety data from all Phase 2 and Phase 3 SSSI studies using a 7.5 mg/kg telavancin dose were combined (i.e. 202a + original protocol 202b, 0017, and 0018) and compared with the safety data from all Phase 2 and Phase 3 SSSI studies using a 10 mg/kg dose (i.e. Post Amendment 1 studies 202b, 0017 and 0018) to examine for potential dose-related effects. Although there were minor design differences between the Phase 2 and Phase 3 studies, such as allowing use of an antistaphylococcal penicillin instead of vancomycin as comparator in patients with infections caused by MSSA and minor differences in the definitions of infections which could be studied, the impact was small and the information obtained was thought to be amenable for pooling.

7.4.1.2 Combining data

The number of events occurring in a treatment group was used as numerator and the number of patients exposed to treatment indicated for the group under study was used as the denominator. For example, the number of patients treated with telavancin 7.5 mg/kg was a treatment group compared to the standard therapy comparator group from those studies. The number (percent) of events occurring in the telavancin 7.5 mg/kg treatment group were also compared to the number (percent) of events occurring in the telavancin 10 mg/kg treatment group (with consideration also given then to the difference in rate of events observed relative to comparator for each of the dose-group studies).

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

See previous sections regarding dose-related information for deaths, other SAEs, discontinuations due to AEs, common AEs, laboratory, and ECG findings. Explorations and conclusions are limited by the discrepancy in the size of the 7.5 mg/kg and 10 mg/kg telavancin dose studies, with the size of the 7.5 mg/kg study population approximately 20% that of the 10 mg/kg dose studies.

7.4.2.2 Explorations for time dependency for adverse findings

No formal assessment of time dependency for development of AEs was performed. In general, the time course of AE development depended on the particular AE being examined. Renal AEs and elevation of serum creatinine was often apparent at the first scheduled safety laboratory follow-up (study day 4). Gastrointestinal and some hypersensitivity reactions tended to also occur early in the time course, while other hypersensitivity reations (exanthems) occurred later in treatment.

7.4.2.3 Explorations for drug-demographic interactions

PK parameters for healthy elderly subjects were compared to the healthy young subjects participating in the renal and hepatic impairment trials. The elderly demonstrated comparable exposures to young adults based on $AUC_{0\rightarrow\infty}$ but slightly lower plasma clearance and elimination half-life. The mean creatinine clearance for for the elderly was indicative of mild renal impairment in the study population (CL_{cr} apporixmately 65 mL/kg).

Efficacy data based on age was discussed in Section 6 of the review.

The overall number (percent) of patients with at least one reported AE was lower in the population of patients > 65 (and > 75) than in younger patients. Deaths and other SAEs were reported with greater frequency in the older populations in Study 0017 and 0018 combined treated with telavancin compared to vancomycin; there were 7 deaths, 29 SAEs, and 24

discontinuations for AEs reported in patients greater than age 65 treated with telavancin (denominatior of 174) compared to 2 deaths, 16 SAEs, and 11 disconintuations in elderly patients treated with vancomycin (denominator of 179). Common TEAEs associated with telavancin such as dysgeusia, nausea, and urine abnormality were less frequent in older individuals.

PK parameters for young healthy male and female subjects were evaluated in the ECG study (104a) and in the elderly study (105a). PK parameters were similar in males and females.

Efficacy data based on gender is discussed in Section 6 of the review.

TEAEs were reported slightly more frequently in females in Studies 0017 and 0018, however deaths, SAEs, and discontinuations were balanced between genders. Nausea and vomiting were more frequent in females than males treated wuth telavancin. this difference was also noted in those treated with vancomycin but was not as great.

7.4.2.4 Explorations for drug-disease interactions

PK parameters for patients with renal impairment were discussed in the clinical pharmacology section (Section 5) of the review. Efficacy results were examined in Section 6 of the review.

The frequency of any TEAE is higher for telavancin patients relative to vancomycin patients as renal functions declines. This is also true for SAEs. Discontinuations and deaths are more evenly balanced between the two treatment arms.

Common TEAEs in patients with severe renal impairment are higher in the telavancin treatment group relative to vancomycin, particularly dysguesia and nasuesa.

The frequency of SAEs and discontinuations in diabetics treated with telavancin are 2X more frequent than in diabetic patients treated with vancomcyin; 32 SAEs and 26 discontinuations occurred in diabetic patients treated with telvancin (32/212 or 15.1% and 26/212 or 12.3%, respectively) compared to 17 SAEs and 10 discontinuations in diabetic patients treated with vancomycin (17/218 or 7.8% and 10/218 or 4.6%). The frequency is also higher in diabetic patients compared to nondiabetic patients. Patients with at least one AE were more common in both diabetic and nondiabetic patients treated with telavancin compared to diabetic and non-diabetic patients treated with vancomycin.

7.4.2.5 Explorations for drug-drug interactions

As noted previously in Sections 5 and 7.2.6, telavancin had a weak inhibitory effect on CYP450 enzymes. A subsequent Phase 1 PK study was performed in which subjects were treated with midazolam for 1 week and given a single dose of telavancin. Telavancin did not significantly alter the PK of midazolam.

Two separate Phase 1 studies were conducted to assess the potential for interaction of telavancin with aztreonam in one study and piperacillin-tazobactam in the second study. These antibiotics are being used as adjunctive Gram negative antibacterial coverage in the ongoing Phase 3 HAP studies. Aztreonam was also permitted for adjunctive Gram negative bacterial coverage in the cSSSI studies being reviewed. Subjects in the Phase 1 study received a dose of telavancin alone, a dose of aztreonam or piperacillin-tazobactam alone, and a combination of telavancin with each drug in the respective PK study in a crossover study with weekly intervals between drug doses. Telavancin did not alter the PK of aztreonam or piperacillin-tazobactam when administered in combination from when the drugs were administered alone and vice versa.

Common TEAEs such as dysgeusia, nausea, and vomiting were more common when the adjunctive Gram negative agents were administered with either telavancin or vancomycin in the Phase 3 cSSSI studies. This was also true when paracetamol, vicodin, and morphine were administered with telavancin. There was no major difference observed when either telavancin or vancomycin was administered concomitantly to patients treated with acetylsalicylic acid or furosemide. Whether or not the increase was related to a drug interaction or was representative of a sicker patient population is not clear.

7.4.3   Causality Determination

The protocol specified that the investigator was to assess the relationship of study medication to the observed AE according to the following definitions:
- 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.

The FDA guidance document regarding the adverse reactions section of labeling states that the adverse reactions section of the label is to be limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an AE and the use of the drug. The Applicant submitted the following algorithm for obtaining a list of such adverse drug reactions.
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b(4)

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b(4)

MO Comment: The FDA reviewer agrees with the Applicant's approach, although using all three criteria together would eliminate constipation, headache, and insomnia which are nonspecific and unlikely related to this class of drug.

8   ADDITIONAL CLINICAL ISSUES

8.1   Dosing Regimen and Administration

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

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

Dose adjustments were recommended for patients with renal impairment and are shown below.

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

8.2 Drug-Drug Interactions

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

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

The potential for telavancin interection with agents likely to cause torsades de pointes has been discussed in Section 7.1.7.3.3.

8.3 Special Populations

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

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

b(4)

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

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

8.4   Pediatrics

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

8.5   Advisory Committee Meeting

There was no Advisory Committee Meeting held for discussion of this NDA.

8.6   Literature Review

No additional literature review was performed.

8.7   Postmarketing Risk Management Plan

No postmarketing risk management plan was submitted for this application.

8.8   Other Relevant Materials

No other relavant materials not previously discussed were reviewed for this application.

9   OVERALL ASSESSMENT

9.1   Conclusions

EFFICACY
- In two independent, adequate and well-controlled studies which were randomized, double-blind, active comparator trials, telavancin demonstrated non-inferiority to vancomycin in treatment of adult patients with cSSSI thought to be caused by Gram positive organisms.
- Telavancin did not demonstrate superiority compared to vancomycin in Study 0017 and Study 0018 pooled analysis of All-Treated patients with MRSA as a baseline pathogen.
- The majority of patients with cSSSIs who were enrolled in these studies had either major abscesses ($\approx$44%) or deep/extensive cellulitis ($\approx$36%). Wound infections were also noted in > 10% of the study population ($\approx$14%). There was limited experience in treatment of infected ulcers or burns.

- Based on subgroup analyses of clinical response rates in the FDA-adjudicated CE population, the decrease in clinical response rates related to aging (for patients < 65 yrs and those ≥ 65 yrs) was greater for telavancin compared to vancomycin. Telavancin clinical response rates were 91% for those < 65 yrs compared to those 78% ≥ 65 yrs; vancomycin clinical response rates were 88% compared to 84% for the same age groups, respectively.
- Subgroup analysis also demonstrated a significant decrease in clinical response rates in patients treated with telavancin as baseline creatinine clearance declined compared to patients treated with vancomcyin.
- The majority of *S. aureus* isolates (both MSSA and MRSA) had MICs ≤ 0.5 µg/mL. There were no *S. aureus* isolates with MICs > 1 µg/mL. Clinical response rates for patients with *S. aureus* isolates with MICs ≤ 0.5 µg/mL were approximately 90% in both telavancin and vancomycin treatment groups. There was a slight decrease in the response rates for patients with *S. aureus* isolates (MSSA and MRSA) with MICs of 1 µg/mL in both telavancin and vancomycin treatment groups (approximately 82-83%).
- Telavancin demonstrated efficacy in a sufficient number of patients with cSSSI from whom the following microbiological isolates were identified:
  - *Staphylococcus aureus* (including methicillin-resistant isolates)
  - *Streptococcus pyogenes*
  - *Enterococcus faecalis* (vancomycin-susceptible isolates only)
  - *Streptococcus agalactiae*
  - *Streptococcus anginosus* group

SAFETY
- In two independent, adequate and well-controlled Phase 3 cSSSI studies telavancin demonstrated nephrotoxicity which appeared to be consistently greater compared to vancomycin when considered in a variety of ways:
  - Renal SAEs and discontinuations from study medication due to renal AEs were more frequent in the telavancin treatment arm than in the vancomycin treatment arm.
  - Potentially clinically significant elevations in serum creatinine occurred more frequently in the telavancin treatment groups than in vancomycin treatment groups.
  - There were five patients treated with telavancin who had relatively normal serum Cr at baseline and reported SAEs or discontinuation of medication due to renal events who had incomplete resolution of elevation in serum creatinine at the final laboratory assessment. This makes conclusions regarding reversibility of renal effects difficult.
  - Factors that may influence or exacerbate the degree of renal insufficiency, such as hydration status and time from development of increase in serum Cr to telavancin dose adjustment, have not been thoroughly examined.
- Evidence of teratogenicity was demonstrated in multiple animal species, with limb abnormalities noted in rat, rabbit, and minipig fetuses. These effects were seen at doses with exposures approximately 1-2X the human exposure at the proposed therapeutic dose. However, these effects were noted in a limited number of animals compared to the number exposed (but higher than historical rates) and findings in the minipig study were compromised by the small number of fetuses available for examination and positive findings in a control animal. It is unclear to the FDA clinical reviewer whether the limb

abnormalities are the same in all species (i.e., whether they are all skeletal and/or related to soft tissue differentiation). If approved, the FDA clinical reviewer would support Category C pregnancy labeling, but recommend not using this drug in females of childbearing potential unless the benefits of use clearly outweigh the potential risk to the fetus.

- Although a "thorough QT study" demonstrated that televancin has an effect (i.e., prolongs) the QTcF interval, the effect appears to be less than that seen with moxifloxacin based on the FDA clinical reviewer's assessment.

9.2 Recommendation on Regulatory Action

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

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

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

- o Telavancin did not demonstrate superiority relative to vancomycin in the treatment of patients who had MRSA identified from baseline microbiological cultures.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The recommendation for this NDA is not approvable.

9.3.2 Required Phase 4 Commitments

The recommendation for this NDA is not approvable.

9.3.3 Other Phase 4 Requests

The recommendation for this NDA is not approvable.

9.4 Labeling Review

The recommendation for this NDA is not approvable, therefore no line-by-line labeling review was performed.

9.5 Comments to Applicant

Comments to the Applicant will be communicated in the NDA action letter.

10 APPENDICES

10.1 Review of Individual Study Reports

The two Phase 3 studies (Study 0017 and Study 0018) used for the determination of safety and efficacy of telavancin compared to vancomycin in patients with cSSSI caused by Gram positive organisms, with emphasis on MRSA are included within Section 6 Integrated Review of Efficacy.

10.2 Line-by-Line Labeling Review

The recommendation for this NDA is not approvable, therefore no line-by-line labeling review was done.

10.3 Appendix A: DEATHS (Completed Studies)

Narratives for deaths that occurred during the Applicant defined clinical study reporting period:

Telavancin

0017-02010-0546 - ventricular arrhythmia [The patient was a 65 year-old male with a history of right-sided heart failure secondary to chronic obstructive pulmonary disease with chronic lower extremity edema, coronary artery disease, diabetes mellitus, hypercholesterolemia, and epilepsy. Concomitant medications included albuterol, tiatropium bromide, salbutamol, furosemide, isosorbide, glicazide, digoxin, phenytoin, perindopril, pravastatin, and coumadin. Baseline laboratories, including electrolytes and serum creatinine were unremarkable, but ECG revealed incomplete right bundle branch block/right ventricular conduction delay and non-specific ST/T wave abnormalities. The patient received a single dose of telavancin (10 mg/kg) for cellulitis and minor infected wounds. The Day 2 dose was missed (in error). On Day 3, more than 24 hours after the dose of study medication, the patient was found dead in bed, with a presumptive diagnosis of ventricular arrhythmia. No ECG had been done since baseline. The investigator assessed the event of "acute ventricular dysrhythmia" as being possibly related, although noted multiple confounding factors. FDA reviewer concurs.]

0017-38002-0428 renal insufficiency [The patient was a 70 year old male with a history of atrial fibrillation, unstable angina, congestive heart failure, automatic implantable cardioverter defibrillator (AICD), hypertension, diabetes, and obesity. The patient was treated with telavancin (10 mg/kg) for 6 days for cellulitis of the left calf (had been hospitalized 4 days prior for unstable angina and CHF). Concomitant medications included: furosemide, phenazopyridine, carvedilol, clopidogrel, quinapril hydrochloride, **Natrecor (IV)**, and insulin. Baseline creatinine clearance was calculated at 85 mL/min and baseline serum Cr was 1.0 mg/dL. Serum Cr on D4 was 1.9 mg/dL. Telavancin was discontinued on D6 due to renal insufficiency and on D7 serum Cr was 2.7 mg/dL. The patient's status was changed 2 days later to DNR, comfort care only and the patient died 2 days later due to renal and cardiac failure. **Natrecor (nesiritide)** was administered from 8/14 to 8/17, telavancin was administered from 8/18 to 8/23, and the patient died on ⟨ ⟩ The investigator assessed the SAE of acute renal failure as possibly/probably related to cause of death, but may also have been related to diuresis. FDA reviewer concurs and also notes administration of nesiritide which has been associated with increases in serum Cr through Day 14 post-infusion.]

b(6)

0017-04004-0677 systemic inflammatory response syndrome [The patient was a 49 year old female with a history of epilepsy, alcohol abuse, heart failure, hepatic failure, renal failure (on hemodialysis), fungal UTI, and systemic inflammatory response with onset 8 days prior to study enrollment. Concomitant medications at the time of death included: hydrocortisone, lactulose, ranitidine, cisatracurium, phenytoin, dobutamine, norepinephrine, insulin, fluconazole, and morphine. Telavancin was dosed every 48 hours due to patient's baseline (lack of) renal function (the study report narrative states that the dose should have been every 24 hours based on "creatinine clearance" at central lab). The patient received 4 days of telavancin (10 mg/kg every

48 hours) for a knee abscess. The systemic inflammatory response syndrome (SIRS) and multi-organ failure continued to progress and the patient died on Study Day 5. [The investigator assessed the SAE of SIRS as being unrelated to study medication. FDA reviewer concurs and notes the onset of SIRS preceded treatment with study medication.]

0017-27010-0474 cerebrovascular accident [The patient was a 65 year old female treated with telavancin 10 mg/kg for 15 days for multiple, infected second degree burns affecting 15% of body surface area. Her medical history was significant for stroke, hypertension, chronic heart failure, and vascular encephalopathy. Concomitant medications included enalapril, atenolol, hydrochlorothiazide, aspirin, metamizole, prednisolone, strophanthin, ranitidine, heparin, and methyluracilum. The patient's cSSSI responded well to treatment, but the patient died nine days after completing therapy due to fatal right cerebrovascular accident (CVA). The investigator assessed the event of CVA (acute right hemispheric stroke listed in CRF – left hemispheric stroke in narrative) as unrelated to study medication. FDA reviewer concurs.]

0017-38001-0693 pulmonary embolus, ovarian cancer [The patient was a 96 year old female treated with telavancin 10 mg/kg for 8 days for bilateral lower extremity cellulitis. The patient's medical history included left hip replacement, lumbar spine surgery, hypertension, temporal arteritis, congestive heart failure, anemia, and hypothyroidism. Baseline creatinine clearance was 24 mL/min and the patient was dosed appropriately with telavancin. Concomitant medications included isosorbide dinitrate, levothyroxine, pantoprazole, hydrochlorothiazide, and atenolol. The patient was anemic throughout her hospital stay, but was discharged to a rehab center with hemoglobin of 7.8 mg/dL. Four days after completing study medication, the patient complained of increasing fatigue, abdominal pain, shortness of breath, and flank and back pain and was readmitted to the hospital. She was found to be anemic, with hemoglobin of 7.5 g/dL and hypoxic with oxygen saturation of 75% on room air. An ultrasound of her swollen left lower extremity revealed extensive venous thrombus and lung perfusion scan was positive for pulmonary embolus (PE). CT scan of the abdomen revealed extensive ascites and MRI confirmed a pelvic mass. Paracentesis was performed to drain intra-abdominal hemorrhage. The patient died three weeks later with a diagnosis of ovarian cancer. The investigator assessed the SAE of DVT, PE, and ovarian cancer as being unrelated to study medication. FDA reviewer concurs.]

0018-01002-2474: cardiac arrest [The patient was a 75 yo female treated for 6 days with telavancin for cellulitis of the left hand resulting from a burn. The patient's past medical history included: diabetes, peripheral vascular disease, and hypertension (narrative listing, but not CRF-concomitant medicationss consistent with history). Concomitant medications included: heparin, enalapril, acetylsalicylic acid, pethidine, insulin, ibuprofen, clonazepam, morphine, furosemide, ranitidine, dipirone, dextiopopoxiphen, and metformin. The patient had received cefalothin and clindamycin prior to study entry. On D4, the patient's hemoglobin had dropped from baseline 11.3 g/dL to 8.8 g/dL, serum Cr increased from 0.8 mg/dL to 1.3 mg/dL. The patient received an overdose of morphine on D5 (no administration time in CRF) and 4 hours later the patient complained of weakness and fell. The dose of telavancin was adjusted from 10 mg/kg q 24 hr to 7.5 mg/kg q 24 hr based on declining renal function. ECG obtained after the fifth dose of telavancin showed an increase in mean QTcF from baseline of 450 msec to 479 msec. On D6 the patient was noted to have a poor response of cellulitis to treatment, although study medication was continued. The patient was found dead on D7 with no underlying cause. The

investigator assessed the event of cardiac arrest as possibly/probably related to study medication. FDA reviewer concurs.]

0018-19006-2894: cardio-respiratory arrest [The patient was an 84 yo male treated for 9 days with telavancin for cellulitis of the left foot. The patient's past medical history was significant for diabetes mellitus, rheumatoid arthritis, hypertension, PVD, and hepatic carcinoma (per follow-up death investigation). Concomitant medications included: furosemide, captopril, acetylasalicylic acid, insulin, ranitidine, paracetamol with codeine, albumin, and hydrocortisone. The patient was dosed with telavancin at 10 mg/kg q 24 hrs despite a baseline creatinine clearance < 30 mL/min, but was adjusted to 10 mg/kg q 48 on D3. Aztreonam had been added for Gram negative coverage, as was hydrocortisone on D2 following an episode of hypotension (not reported as an AE). On D7, the patient was noted to be anemic with hemoglobin of 7.1 g/dL. Baseline ECG had shown first degree AV block and on D5 showed new RBBB. Study treatment was discontinued on D9 with resolution of cellulitis. On D9, AEs of abnormal ALT and AST (local) were reported as AST 818 U/L and ALT 1186 U/L (Day 7 central ALT was 47 U/L↑, AST 48 U/L↑, bilirubin of < 3 μmol/L, and alkaline phosphatase of 270 U/L↑ - alkaline phosphatase elevated from 153 U/L on D4 – no baseline LFTs or local labs are available in CRF or dataset). On follow-up the investigator noted that the patient had cirrhosis due to hepatic carcinoma. On D10 ECG showed new atrial fibrillation and the patient died on D11, 2 days after discontinuing study treatment. The investigator assessed the event as not related to study medication of cardio-respiratory arrest as unrelated to study medication. FDA reviewer disagrees with this assessment since there is no readily apparent cause of death. The elevation of LFTs was temporally related to study medication and new onset a fib started within a day of study medication discontinuation. The elevation in LFTs was explained retrospectively.]

0018-38160-2501: myocardial infarction, acute respiratory failure [The patient was a 77 yo male who received 5 days of telavancin for left hand cellulitis. The patient's past medical history was significant for COPD, hypertension, pulmonary fibrosis, asthma, supraventricular tachycardia, CHF, angina, rheumatoid arthritis, and silicosis. Concomitant medications included: metronidazole, aztreonam, prednisone, levosalbutamol, glipizide, irbesartan, diltiazem, lorazepam, vicodin, paracetamol, potassium chloride, insulin, and furosemide. The patient's baseline serum Cr was 1.7, with creatinine clearance calculated at 30.7 mL/min and telavancin dose was appropriately adjusted to 7.5 mg/kg q 24 hr. On D3, the patient underwent excision of a hand cyst and developed a fever and elevated WBC count on post-op day 1 (D4). The patient was noted to be improving on D5, but developed acute respiratory failure, was transferred to the ICU, and was intubated. The patient was made DNR and died that night due to myocardial infarction (troponin 1 level 4.76 ng/mL). The events of acute MI and respiratory failure were assessed as unrelated to study medication. FDA reviewer disagrees. Although it is unlikely these events are related, study medication effect cannot be ruled out.]

0017-02008-0120 (Original Protocol - telavancin 7.5 mg/kg): renal insufficiency, respiratory distress, respiratory failure [The patient was an 82 yr old female with venous ulcers and cellulitis of the right leg and foot who was treated with telavancin (7.5 mg/kg, initially every 48 hrs with calculated creatinine clearance of approximately 40 mL/min – based on IBW of 57.3 kg and serum Cr 1.0 mg/dL) for nine days and aztreonam for 10 days. The patient's medical history was significant for diabetes, bilateral leg edema, recalcitrant ulceration of the right lower leg, hypercholesterolemia, gout, hypertension, fluid retention, obesity, and urinary incontinence. Concomitant medications included simvastatin, allopurinol, perindopril, metformin, glimepiride,

furosemide, potassium chloride, magnesium sulfate, omeprazole, and sodium polystyrene sulfonate. The patient's cellulitis was responding to study treatment with minimal residual cellulitis noted and serum creatinine was 0.7 mg/dL on D7. On D8, the patient experienced an episode of shortness of breath and on D10 developed oliguria, increased respiratory distress, and coffee ground hematemesis. Serum Cr was elevated at 2.1 mg/dL, arterial pO2 of 47 mm Hg, pH 7.23, and pCO2 62 mm Hg. On D11 the patient was transferred to the ICU because of severe hypotension and study medication was discontinued on that day. Respiratory fatigue progressed and the patient was intubated on D11 with serum Cr of 3.2 mg/dL. She was noted to have purulent secretions, and the patient was thought to be septic. She received treatment with vasopressors and antimicrobial agents (cipro, aztreonam and metronidazole). Mechanical ventilation was continued for 48 hrs during which the patient's renal function improved and the patient was extubated on D14, although still requiring norepinephrine to maintain blood pressure. On D16 she had an episode of atrial fibrillation and was treated with amiodarone. Her condition deteriorated and she died on D16. The investigator assessed the events as unlikely or not related to study medication, although possibly/probably related to study medication was indicated on the CRF. Confounding conditions include pre-existing renal and cardiac disease, chest infection, and tachyarrythmia. Renal failure may have been related to patient's age, underlying conditions, septic shock, and concomitant medications. FDA reviewer assesses events of renal insufficiency and respiratory failure as possibly/probably related to study medication.]

Vancomycin (all assessed by investigators as unrelated to study medication)
0017-02001-0257 pulmonary embolism [The patient was a 46 year old male treated with vancomycin for 6 days for infection at the site of a below the knee amputation (BKA) performed 12 days prior to enrollment. On D5, he was found slumped in his wheelchair and was clammy and short of breath. Medications at the time of event included heparin (SQ), digoxin, and amitriptyline. He did not respond to resuscitation and died. An autopsy revealed a large saddle embolus obstructing the pulmonary trunk. Investigator assessed the AE as not related to study medication. FDA reviewer disagrees with this assessment based on the fact that this was a blinded trial and event was temporally related to administration of study medication.]
0017-38016-0824 cardio-respiratory arrest, pulmonary embolism [The patient is a 49 year old female treated with vancomycin for 2 days for a left lower quadrant abscess. Medical history included morbid obesity, anemia, and diabetes. Concomitant medication included morphine, insulin, famotidine, heparin, promethazine, paracetamol, aztreonam, and metronidazole. On Day 2, the patient became unresponsive while getting out of bed. CPR was attempted, but was unsuccessful and the patient died. Autopsy revealed a pulmonary embolism "secondary to abdominal abscess". The investigator assessed the event as unrelated to study medication. FDA reviewer concurs given that the event occurred after only approximately 24 hours on study treatment.]
0017-38024-0695 congestive heart failure, respiratory failure [The patient was a 53 year old male treated with vancomycin for 14 days for chronic non-healing leg ulcers. Medical history included secondary polycythemia, ventricular septal defect (VSD), hypothyroidism, hypertension, CHF, pulmonary hypertension, CVA, renal failure, and seizure disorder. Baseline creatinine clearance was 32 mL/min. The patient was discharged after 11 days. The patient was readmitted to the hospital 5 days later (2 days off study medication) with shortness of breath, bilateral pleural effusion, and interstitial pulmonary edema consistent with CHF. Concomitant

medications included aztreonam, warfarin, levothyroxine, lidocaine, furosemide, silver sulfadiazine, esomeprazole, mirtazapine, acetaminophen with codeine, losartan, and atenolol. The patient died a day later from cardiac and respiratory failure. The investigator assessed the event as unrelated to study medication. FDA reviewer agrees. This patient had chronic renal insufficiency and serum Cr had decreased on study medication from baseline of 1.7 mg/dL to 1.3 mg/dL on day of hospital discharge or D11 of therapy]

0017-38271-0659 cardio-respiratory arrest, hepatic coma, respiratory failure [The patient was a 47 year old male treated with vancomycin for 6 days for right leg cellulitis. Medical history included hypertension, hepatitis C infection, and alcoholic cirrhosis with systemic complications. Study medication was discontinued on Day 6 after isolation of an aztreonam-resistant pathogen. Three days later, the patient developed respiratory distress and was started on BIPAP and subsequently mechanical ventilations. Concomitant medications included aztreonam, furosemide, vicodin, morphine, amlodipine, benazepril, lactulose, pantaprazole, spironolactone, folic acid, vitamin K, and temazepam. The patient had a cardiac arrest 1 week later. The event was assessed as unrelated by the investigator. FDA reviewer concurs]

0017-38271-1010: respiratory distress [The patient was a 90 year old male treated with 14 days of vancomycin for cellulitis. Medical history included insulin-dependent diabetes mellitus, hypertension, chronic renal failure, benign prostatic hypertrophy (BPH), hyperlipidemia, CAD, and mild Alzheimer's. Baseline creatinine clearance was 24 mL/min. The patient also required treatment during hospitalization for aspiration pneumonia, CHF, renal failure, and sepsis. The development of respiratory distress occurred after vomiting brown colored digested food. The patient required BIPAP and respiratory status improved, while renal function declined and the patient required dialysis. Concomitant medications included aspirin, aztreonam, clopidogrel, insulin, megesterol, metronidazole, morcizine, pantoprazole, simvastatin, tamulosin. The patient was to be transferred to a nursing home, but developed respiratory distress and ventricular tachycardia and died. Investigator assessed death as unrelated to study medication. FDA reviewer disagrees. Although the respiratory problems could be attributed to aspiration pneumonia, the patient's renal function declined on study medication and this could have contributed to fluid overload and pulmonary edema.]

0018-22000-2742: cardiac insufficiency, atrial fibrillation [The patient was a 55 yo male treated with vancomycin 2 days for cellulitis. The patient's past medical history was significant for dermal T-lymphoma, for which he was treated with chemotherapy approximately 6 months prior. Concomitant medications included metamizol, ketorolac, furosemide, morphine, and nutrison. The patient received ampicillin prior to study entry, but was changed to study medication when MSSA was isolated from a wound culture. On D2 of treatment, the patient was diagnosed by a cardiologist with atrial fibrillation and cardiac insufficiency and the patient was treated with metoprolol, aspirin, albumin, and furosemide and normal sinus rhythm was restored. However, on D3 of treatment anuria developed, cardiac insufficiency progressed, and the patient died. The investigator assessed the event as unrelated to study medication. FDA reviewer disagrees because the possibility that the cardiac event or anuria was related to study medication cannot be excluded.]

0018-30907-2323: septic shock, cardiogenic shock, pulmonary edema [The patient was a 66 yo female treated for 3 days with vancomycin for right arm cellulitis. The patient's past medical history was significant for hypertension, history of aortic aneurysm repair, and small bowel obstruction requiring laparotomy 3 months prior. Concomitant medications included aztreonam,

opium alkaloids, diclofenac, paracetamol, heparin, omnopon, dobutamine, and phenylephrine. The patient's pretreatment blood cultures were positive for *Staph aureus*. The patient became progressively hypoxemic and tachycardic and developed septic and cardiogenic shock. The patient died on D3. The investigator assessed the events as unrelated to study medication. FDA reviewer concurs.]

0018-38260-2555: cardiac arrest, renal failure chronic, ascites [The patient was a 53 yo male treated with a single dose of vancomycin and died before the next scheduled dose (based on renal function, the vancomycin level should have been adequate for a week). The patient's past medical history was significant for cirrhosis with ascites, CHF, atrial fibrillation, gout, hypertension, and ESRD requiring hemodialysis. Concomitant medications included digoxin, carvedilol, clonidine, pantoprazole, epogen, cyproheptadine, promethazine, paracetamol, temazepam, metoprolol, allopurinol, and morphine. The patient underwent incision and drainage of an abscess on D2 and was discharged from the hospital on D3. The patient was readmitted on D6 with worsening of ESRD and ascites, however the patient's serum creatinine was unchanged. On D8, the patient underwent removal of a peritoneal subclavian shunt and went to the ICU. He was started on an anti-arrhythmic and dialyzed. The patient died prior to his scheduled second dose of vancomycin. The investigator assessed the events as unrelated to study medication and SAE is listed as not related in the ISS AE dataset. However, the narrative in the clinical study report indicates that the event was considered to be possibly/probably related to study medication. FDA reviewer has concerns with adequacy of blinding in this case given the anticipated infrequent dosing of study medication and CRF indicating that study medication doses were "missed" on Days 2-9. A data clarification form attached to the CRF states that treatment assignment was not unblinded.]

202b-00903-9037 (Phase 2): multiorgan failure [The patient was a 41 yo female with a left foot wound infection treated with standard therapy (chosen as vancomycin). On admission to the hospital, the patient was noted to have elevated LFTs (total bilirubun 78 μmol/L, alkaline phosphatase 344 U/L, AST 109 U/L, and GGT 396 U/L) and anemia (hemoglobin 7.4 g/dL) and admitted to chronic alcohol use. Concomitant medications included paracetamol and ibuprofen. The patient was subsequently found to be septicemic and study treatment was augmented with aztreonam and metronidazole. Study drug was discontinued on D6 at which time the patient's LFTs were (bilirubun 152 μmol/L, alkaline phosphatase 285 U/L, ALT 169 U/L, AST 94 U/L) and serum creatinine was 200 μmol/L. The patient developed respiratory distress 5 days later and died. The investigator assessed the AE of multiorgan failure as unrelated to study medication. FDA reviewer concurs.]

Narratives for deaths that occurred outside the Applicant designated reporting period for clinical studies:
Telavancin:
- 0017-18015-0802 (10 mg/kg): The patient was a 77 yo female with a history of COPD, CHF, hypertension, and diabetes mellitus, who developed renal insufficiency on D4 of study medication (serum Cr went from baseline 1.1 to 2.2 mg/dL) and study medication was discontinued. The patient developed respiratory distress on D5 and required mechanical ventilation for dyspnea and respiratory failure. She was unable to be weaned from the ventilator and developed ventilator-associated pneumonia (approximately D10-11). Although renal function was noted to have improved (D15 serum Cr 1.2 mg/dL), the

patient's respiratory status did not and the patient died 27 days after discontinuing study medication. The cause of death was respiratory failure and the investigator assessed the death as unrelated to study medication. FDA reviewer concurs, although renal insufficiency may have contributed to the initial respiratory distress.

- 0017-38271-0517 (10 mg/kg): The patient was a 54 yo female with multiple comorbidities including cirrhosis, CHF, and pre-existing ESRD (on hemodialysis) who had inappropriate dose adjustment of telavancin (study narrative and edited CRF 6 months after study indicate q 48 hr dosing / ISS narrative q 24 hr dose) based on renal function (received telavancin q 24 hrs instead of q 48 hrs). The patient developed respiratory distress and hypotension on D8 of study medication, required non-study antibiotics, and was discontinued from study medication. The patient had a follow-up (TOC) assessment 8 days after discontinuation. Despite mechanical ventilation, the patient developed ARDS and multi-system organ failure and died 12 days after study therapy was discontinued 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): The patient was a 65 yo male with a history of diabetes, hypertension, congestive heart failure, and chronic renal failure (baseline serum Cr 2.1 mg/dL) who developed worsening renal insufficiency with serum Cr 6.2 mg/dL on Day 5. Study medication was discontinued due to acute renal failure and hyperkalemia. The follow-up visit (TOC) was completed on Day 12 and serum Cr had decreased to 2.9 mg/dL. On the same day, the patient had a brainstem infarction with concomitant dyspnea, hypoxia, pulmonary edema, and decreased consciousness and died the following day. The cause of death was brainstem infarction unrelated to study medication. FDA reviewer concurs.

- 0018-38160-2007 (original protocol, 7.5 mg/kg): The patient was a 53 yo male with pre-existing alcohol-induced liver disease, cirrhosis, chronic pancreatitis, and ascites who was treated for cellulitis for 10 days. On D3, serum Cr was noted to have increased from baseline 0.7 mg/dL to 2.6 mg/dL (renal insufficiency); spironolactone was administered for presumed acute tubular necrosis (ATN) secondary to cellulitis-induced sepsis syndrome until D4. The patient also received furosemide. The patient's serum Cr reached a maximum of 3.4 mg/dL on D7 and had decreased to 2.6 mg/dL at the time of study medication discontinuation on D10 with resolution of infection. The patient was discharged on D15 with resolution of ATN, although serum Cr remained elevated at 1.9 mg/dL. The patient died 85 days after last dose of telavancin due to liver failure from continued alcohol abuse. The cause of death was liver failure and was unrelated to study medication. FDA reviewer concurs, although last measured serum Cr of 1.9 mg/dL was not suggestive of resolution of renal insufficiency in this patient who had a baseline Cr of 0.7 mg/dL.

- 0018-38160-3068 (10 mg/kg): The patient is a 95 yo male with a history of profound congestive heart failure and chronic renal insufficiency (baseline serum Cr 4.1 mg/dL) who received an inappropriate dose of telavancin (q 24 hr instead of q 48 hr). The patient was also undergoing aggressive diuresis during the study. The patient's renal function was noted to begin deteriorating on Day 4 (Cr 5.5 mg/dL) and continued to deteriorate after study medication was discontinued on Day 7 (cellulitis was resolved at F/U D15 with Cr 10.3 mg/dL). Three days after the study period, the patient refused dialysis and subsequently

died. The cause of death was acute renal failure. The investigator assessed this event as possibly/probably relating to study medication, although noting comorbidities. FDA reviewer agrees and although outside the reporting period (i.e. after TOC assessment) it would be reasonable to include with study deaths due to the progressive rise in Cr through and after the study.

Vancomycin:

- 0017-38111-0646 (vancomycin): The patient was a 54 yo female who had study medication discontinued at D3 due to QTc prolongation >500 msec (local read not confirmed centrally, central lab readings all <500 msec). The patient had a TOC visit at D10 and was noted to have mild hypotension, dyspnea, and pulmonary congestion and was subsequently diagnosed with hospital-acquired pneumonia. She died from pneumonia-related complications 20 days following TOC. The cause of death was respiratory failure and was unrelated to study medication. FDA reviewer concurs.

- 0017-38271-0856 (vancomycin): The patient was a 46 yo female treated with vancomycin for 14 days for cellulitis. She was considered cured on D22. The patient died approximately one month later from unknown causes while on vacation. The cause of death was "unknown" and believed to be unrelated to study medication. FDA reviewer concurs.

10.4 Appendix B: Deaths (Ongoing Studies)

Studies were treatment-blinded at the time of NDA submission

Summaries of Deaths in Study 203a (Staph aureus bacertemia)
Study Treatment Assignments included in 4MSU
(*deaths occurring after the reporting period)
Telavancin:

- 160-4011 – [sepsis, bacterial endocarditis, renal failure acute on Study Day 6, with death on Study Day 13] The patient was a 55 yo female with a history of seizure disorder, chronic hepatitis C, porphyria secondary to hepatitis C, and chronic pain syndrome, who received one dose of study medication along with linezolid and aztreonam. Following the first dose, the patient had an anxiety attack and withdrew consent and was discontinued from study medication. She was treated with nafcillin, tobramycin, ceftriaxone, and rifampicin. An echocardiogram revealed tricuspid valve endocarditis, the patient went into renal failure, and family requested all treatment be discontinued. The investigator assessed the events as unrelated to study medication.

- 272-4034 – [dyspnea on Study Day 16, death on Study Day 21] The patient was an 85 yo male who was treated with study medication for 15 days. The patient had a history of lymphoma, chronic renal failure, prostate carcinoma, thyroid disease, radiation proctitis, peripheral vascular disease, paroxysmal atrial fibrillation, and Parkinson's disease. The patient had been hospitalized 6 weeks prior for rectal bleeding. After completing a course of therapy with study medication, the patient complained of shortness of breath with oxygen saturation of 75% on room air. CXR showed small bilateral pleural effusions and VQ scan was negative for pulmonary embolism. The patient died 6 days after study medication was discontinued due to hypoxia. The investigator assessed the event as unrelated to study medication.

- 430-5007 – [pneumonia, empyema, DIC on Study Day 4, renal failure chronic, death on Study Day 7] The patient was a 64 yo male who was treated for 5 days with study medication. The patient had a persistent SA bacteremia attributed to an infected perm-cath, along with DIC, worsening pneumonia, and empyema. The patient was switched to cloxacillin and gentamicin. After the perm-cath was removed, the patient became progressively uremic and fluid overloaded. The patient and family opted for conservative management and withholding dialysis and the patient died as a result of worsening chronic renal failure. The investigator assessed the events as unrelated to study medication.

- 160-4016* [urosepsis] The patient was an 88 yo male with past medical history significant for cancer of the penis, renal insufficiency, hypertension, prostatitis, polymyalgia rheumatica, and anemia who received 19 days of study medication therapy (inadvertently exteneded 4 days). The patient was off study medication for approximately 4 weeks and was admitted to the hospital for urosepsis. The patient's family withdrew consent for life saving care and the patient died. The event was assessed as unrelated by the investigator.

- <u>441-5002*</u> [hospital acquired pneumonia] The patient was a 77 yo male with a history of hemorrhagic stroke and left hemiparesis. The patient was admitted to the hospital with fever and started on study therapy. A subsequent echocardiogram showed endocarditis and the patient was withdrawn from the study. The patient remained stable for approximately 3 weeks and then developed a fever along with CXR findings of right lower lobe pneumonia. Aztreonam was started (in addition to cloxacillin and gentamicin) and the patient died from HAP 4 days later. The investigator assessed the study medication as unrelated to study medication.

Comparator:

- <u>101-4009</u> – [neuroleptic malignant syndrome and death on Study Day 29] The patient was a 59 yo male with a history of neuroleptic malignant syndrome and schizoaffective disorder. The patient was treated for 14 days with study medication. One day after starting study medication the patient was noted to have elevated LFTs and 13 days into therapy was noted to have increased eosinophils and hematuria. The patient died 15 days after study therapy was discontinued due to neuroleptic malignant syndrome. The neuroleptic malignant syndrome was unrelated to study medication as assessed by investigator.

- <u>148-4044</u> – [endocarditis on Study Day 8 and death on Study Day 33] The patient was a 64 yo male with a history of peripheral vascular disease with femoral/popliteal bypass surgery, multiple orthopedic surgeries, rheumatoid arthritis, chronic steroid use, hypertension, TIAs, CABG, diabetes mellitus, etc. A transthoracic echocardiogram on D2 showed aortic valve sclerosis with moderate calcification and a normal mitral valve with mitral annular calcification. A transesophageal echocardiogram on D6 showed endocarditis involving the aortic valve and Eustachian valve (embryologic remnant of the valve of the inferior vena cava). Study medication was discontinued and the next day the patient developed respiratory distress. Repeat transesophageal echocardiogram (TEE) 10 days later showed a bicuspid aortic valve with moderate regurgitation and mobile density consistent with vegetation, moderate mitral regurgitation, and severe tricuspid valve regurgitation. The patient had progressive respiratory and renal deterioration and was found unresponsive 25 days after study medication was discontinued. The investigator assessed the event as unrelated to study medication.

- <u>148-4024*</u> - [intestinal ischemia on Study Day 8 and death on Study Day 71] The patient was a 75 yo male with a history of CAD, chronic renal insufficiency, peripheral vascular disease, ischemic cardiomyopathy, femoral popliteal bypass, diabetes, pacemeaker, etc. Approximately 1 month after study medication the patient was hospitalized with fever and urosepsis and pacemaker lead infection and intraabdominal ischemia. He underwent AICD system placement. The patient subsequently was found to have a MSSA infection, became lethargic, and was transferred to the ICU. His condition deteriorated and he died due to ongoing intestinal ischemia. The intestinal ischemia was not related to study medication as assessed by investigator.

Summaries of Renal SOC AEs Resulting in Death (Ongoing Studies 0015 and 0019 HAP)

- <u>0015-38049-4143</u>: [sepsis, acute renal failure] oliguria prior to hospital admission (baseline Cr 1.2 mg/dL), recurrent HAP, serum Cr 1.0 mg/dL after 5 days of treatment, acute sepsis syndrome 10 days post-admission with possible sources urinary tract, lung, or abdomen,

consult for dialysis (diagnosis of ATN), received 17 days of study medication, Cr 1.8 mg/dL one day after study med discontinued, do not resuscitate (DNR) including no dialysis (comorbid med conditions: diabetes, cardiac disease, respiratory disease)

- 0015-38049-4187: [acute renal failure] admitted with septic shock and bilateral pneumonia, oliguria and renal insufficiency 24-48 hour post-admission (baseline serum Cr 1.1 mg/dL, D2 1.8 mg/dL, and D3 2.2 mg/dL), nephrology consult confirmed progressive, oliguric acute renal failure (ARF) multifactorial (sepsis, ischemia, recent contrast, hypertension), patient treated with Xigris and died hospital D5

- 0019-05003-6084: [multiorgan failure – recovered with sequelae, septic shock, acute renal failure] S/P TURP with 2 month hospitalization, colectomy for lower gastrointestinal (GI) bleed (prior to study), worsening respiratory status on D4 of study medication with aspiration pneumonia, hypotension, fever, and leukocytosis (septic), atrial fibrillation, multi-organ failure (MOF), study med discontinued on D6 due to diagnosis of "enterococcal pneumonia", MOF resolved the next day (?), but ARF was diagnosed, required dialysis, family refused further treatment

- 0019-38069-6174: [acute renal failure, hepatic failure] comorbidities including cirrhosis due to alcohol use, 6 days prior to treatment (one dose) had a perforated sigmoid colon from colonoscopy, where a mass was noted in the hepatic flexure of the colon and required surgery, post-colonoscopy serum was Cr 0.9 mg/dL, but continued to increase post-operatively (2.8 mg/dL with further increases to 4.7 mg/dL), diagnosed with ARF by consultant (diagnosis ATN from sepsis, prior aminoglycoside, hypotension), Cr maximum 5.2 mg/dL, with decrease to 3.5 mg/dL approx 5 days after study med, peritonitis did not respond to treatment and the patient developed multi-organ failure and died

- 0015-38049-4192: [oliguria, septic shock] comorbidities include history of cervical cancer and radiation-induced cystitis, single kidney (s/p right nephrectomy), recurrent DVT, morbid obesity, received 7 days of treatment for suspected sepsis without clear source (but had respiratory difficulties), developed labile blood pressure and oliguria, patient evaluated for dialysis, but patient made DNR. No serum Cr reported in narrative.

- 0015-38148-4218: [renal insufficiency] admitted from nursing home with confusion and respiratory distress, was intubated, treated with antibiotics including levofloxacin, ceftriaxone, and vancomycin for 5 days, then study treatment, baseline serum Cr 1.2 mg/dL and on D3 2.0 mg/dL, then started on vancomycin, investigator attributed renal insufficiency to dehydration, the patient died 4 days later

- 0019-18004-6107: [SAEs: renal insufficiency, neurological symptom, meningitis, septic shock, bradycardia, hypotension] baseline serum Cr 1.4 mg/dL on Day 3 Cr 2.5 mg/dL, diagnosed with renal insufficiency, neurological deterioration (brain edema by CT, "meningitis" suspected following craniotomy) and leukocytosis noted, study medication was discontinued due to diagnosis of meningitis, the patient subsequently developed septic shock with hypotension and bradycardia and died

- 0019-18005-6035: [anuria, septic shock, sepsis] patient admitted for pacemaker for complete AV block, unclear whether D4 fever occurred after pacemaker placement, the patient was started on study medication and imipenem on D9 when fever continued despite piperacillin/tazobactam and sputum grew MRSA, subsequent culture grew *Acinetobacter*,

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fever continued and patient was started on colistin and ampicillin/sulbactam, the patient continued to deteriorate with oliguria and Gram negative sepsis and died on hospital D17

10.5 APPENDIX C

RENAL SAEs

Telavancin (7.5 mg/kg dose)
- 0017-02008-0120 (see deaths): 82 yo female with a history of diabetes, hypertension, obesity, fluid retention, and bilateral leg edema and baseline calculated creatinine clearance of 40 mL/min and serum Cr of 89 μmol/L (1.0 mg/dL). The patient's concomitant medications included metformin, glimepiride, furosemide, perindopril, and simvastatin. The telavancin dose was adjusted for renal function and the patient initially received 7.5 mg/kg q 48 hr (800 q 48 hr). On D4, serum Cr was 74 μmol/L (0.8 mg/dL) and on D7, 65 μmol/L (0.7 mg/dL). On D7, the dose of telavancin was decreased to 600 mg and dose frequency increased to q 24 hr (600 mg q 24 hr). On D8 the patient was noted to have an episode of shortness of breath and per medication log, began to receive IV furosemide. Respiratory distress was attributed to pulmonary edema (communication from investigator, appended to the CRF who notes the presence of pulmonary edema which was not noted in CRF as AE). On D10, the patient began developing respiratory distress, along with oliguria, and had an episode of coffee ground emesis. Serum Cr on D10 was 183 μmol/L (2.1 mg/dL). The patient was intubated on D11 and had a serum Cr of 282 μmol/L (3.2 mg/dL). The patient had purulent secretions, was thought to be septic, and was started on additional antibiotics and dopamine. The narrative in the ISS notes that the patient's renal function improved and the patient was extubated 2 days later (D14), although the patient was still requiring norepinephrine to maintain blood pressure. On D16, the patient developed atrial fibrillation and was given amiodarone, but expired later that day. **The investigator assessed the SAEs of respiratory distress, respiratory failure, and renal insufficiency as possibly/probably related to study medication** and sepsis and pulmonary edema as unrelated. The investigator did note that the renal failure may have been related to age, underlying comorbidities, concomitant medications, and septic shock. **FDA agrees with investigator assessment.** It is difficult given **comorbidities and concomitant medications** to determine the primary cause of the patient's respiratory problems, but relationship to study medication cannot be ruled out.
- 0018-38160-2007 (see also deaths): 51 yo male with pre-existing alcohol-induced liver disease, cirrhosis, chronic pancreatitis, and ascites who was treated for cellulitis for 10 days. On D3, serum Cr was noted to have increased from baseline 0.7 mg/dL to 2.6 mg/dL; spironolactone was administered for presumed acute tubular necrosis (ATN) secondary to cellulitis-induced sepsis syndrome until D4. The patient's serum Cr reached a maximum of 3.4 mg/dL on D7 and had decreased to 2.6 mg/dL at the time of study medication discontinuation on D10 with resolution of infection. The patient was noted to have watery diarrhea and on D14 *C. difficile* was isolated from the stool. The patient was discharged on

D15 with **resolution of ATN, although serum Cr remained elevated** at 1.9 mg/dL. The patient died 85 days after last dose of telavancin due to liver failure from continued alcohol abuse. The cause of death was liver failure and was assessed as unrelated to study medication by the investigator. **The investigator reported the TEAE of renal tubular necrosis as being secondary to a cellulitis-induced sepsis syndrome and unrelated to study medication. The FDA reviewer does not agree with the investigator assessment** and believes there is insufficient evidence provided to exclude study medication as being possibly/probably related renal tubular necrosis (and secondarily to elevated serum Cr).

- 202b-00101-7008 (no baseline general medicine history in CRF): 76 yo female with a history of diabetes and hypertension and baseline serum Cr of 0.9 mg/dL who was treated with telavancin for 10 days for a postoperative abscess at the left second toe and metatarsal amputation. The patient's concomitant medications included ibuprofen, keratolac, and benazepril. On D7, serum Cr had increased to 3.1 mg/dL and D10 to 3.4 mg/dL (local laboratory) and study medication was discontinued. A nephrology consult was obtained and concluded that the likely etiologies of acute renal insufficiency could be prerenal azotemia, medication [study drug, benazepril, or nonsteroidal anti-inflammatory drug (NSAID)], renal artery stenosis, or interstitial nephritis. A renal ultrasound was reportedly normal. Three days after discontinuing study medication the serum Cr was 2.0 mg/dL and 10 days after was 1.2 mg/dL and renal insufficiency was considered to be resolved. **The investigator (and reportedly nephrology consultant) assessed SAE of acute renal insufficiency, prerenal azotemia, elevated BUN, and elevated Cr to be possibly/probably related to study medication** and to have resolved off study medication. The **FDA reviewer agrees with assessment of SAE** as possibly related to study medication, although other medications certainly may have contributed (NSAID or angiotesin-converting enzyme inhibitor). Given that the baseline Cr was 0.6 mg/dL and last measured Cr was 1.2 mg/dL, the FDA reviewer does not believe elevation in Cr was resolved.

Telavancin (10 mg/kg dose)

- 0017-38117-0240: 51 yo female with a history of morbid obesity, diabetes, pulmonary hypertension, renal disease, discoid lupus erythematosis, and rheumatoid arthritis who was treated for 6 days with telavancin. Concomitant medications included insulin, prednisone, lisinopril, erythropoietin, glyceryl trinitrate, and glipizide. The patient's baseline serum creatinine was 88 μmol/L (1.0 mg/dL). The patient inadvertently received approximately double the recommended dose of telavancin (2000 mg q 24 hrs instead of 1110 mg q 24 hrs). On D3, serum Cr was 71 μmol/L (0.8 mg/dL). On D4 the patient had a CT scan with IV contrast and on D7 was noted to have serum Cr of 2.8 mg/dL, increasing to 3.1 mg/dL on D7. The event was noted as resolved 2 days after discontinuing therapy and D16 (10 days after discontinuing telavancin) was back to baseline at 1.1 mg/dL. The **investigator assessed the SAE of acute renal failure as unrelated to study medication** and with **resolution off therapy. The FDA does not agree with assessment and although the renal failure may have been associated with IV contrast, the possible relationship of study medication can not be ruled out.** The renal failure as assessed by serum Cr did resolve.

- 0017-38271-0953: The patient was a 93 yo male with a history of CHF, aortic stenosis, atrial fibrillation, mild renal insufficiency, BPH, and DVT who was treated with telavancin adjusted to baseline calculated creatinine clearance of 30 mL/min and serum Cr of 1.4 mg/dL for 9 days. The patient's concomitant medications included warfarin, lovastatin, atenolol,

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lisinopril, metolazone, and finasteride. The serum Cr increased to 1.6 mg/dL on D3, 2.0mg/dL on D6, and 2.3 mg/dL on D9 at which time the patient had study medication discontinued. He also received a blood transfusion for decreased hemoglobin of 8.2 mg/dL and IV fluids, with improvement noted in serum Cr. On D17 (8 days after discontinuing study medication), serum Cr had decreased to 1.8 mg/dL and renal impairment was said to have resolved. The investigator assessed the SAE of worsening renal function/ renal impairment that prolonged hospitalization as unrelated to study medication. The FDA reviewer agrees that comorbidities may have contributed to worsening renal function, however study medication may have been possibly related. Although serum Cr had improved, the patient was still not back to baseline at last measurement (although given baseline insufficiency, difficult to tell if there was residual impairment from the study period).

- 0017-38002-0428: The patient is a 70 yo male with a history of atrial fibrillation, left atrial clot, CHF, unstable angina, with defibrillator placement in 2005, hypertension, diabetes, and extrapulmonary tuberculosis who was treated with telavancin for 6 days. Concomitant medications included furosemide, nitrofurantoin, clopidogrel, insulin, warfarin, quinapril, simvastatin, and carvediolol. He had been hospitalized for unstable angina and CHF and developed cellulitis which was initially treated with piperacillin./tazobactam and ampicillin. His baseline Cr was 1.0 mg/dL, increased to 1.9 mg/dL on D4 (telavancin dose was not adjusted), and on D7 was noted to have Cr of 2.7 mg/dL, at which time study medication was discontinued due to renal insufficiency. Due to his underlying condition, the patient was DNR and died 2 days later. The **investigator assessed the SAE of renal insufficiency as possibly/probably related to study medication** although noting **concomitant medications** may have played a role. The **FDA reviewer agrees** with this assessment. The patient **died without resolution** of renal insufficiency.

- 0017-18001-0721: The patient is a 46 yo male with a history of chronic renal insufficiency, diabetes with retinopathy and nephropathy, hypertension, ischemic heart disease, and morbid obesity who was treated with telavancin adjusted for renal function (q2-3 days) for 9 days for cellulitis of the leg. Three days prior to initiating telavancin, the patient's creatinine had increased from 3.8 to 5.5 mg/dL (484 µmol/L) and continued to rise throughout treatment. On D3, serum Cr was 735 µmol/L (8.3 mg/dL) and hemodialysis was initiated on D4, although Cr continued to rise. The cellulitis resolved with treatment and at EOT serum Cr was 954 µmol/L (10.8 mg/dL). By the TOC visit, with continuing dialysis, serum Cr had decreased to 648 µmol/L (7.3 mg/dL). The **investigator assessed the development of renal impairment as possibly/probably related** to study medication. **The FDA reviewer agrees, although this patient had considerable documented decline in renal function prior to initiating study medication.** The patient required **hemodialysis.** [creatinine rise prior to study not documented in the CRF / is contained in study narrative]

- 0018-060030-2353: The patient is an 84 yo female with diabetes, chronic renal failure, rheumatoid arthritis, and sigmoidectomy with colostomy, who was treated with telavancin for 6 days for cellulitis of the right leg. Concomitant medications included glibenclamide, atenolol, levothyroxine, prednisone, ramipril, insulin, chronic trimethoprim-sulfamethoxizole, and hydrochlorathiazide. Baseline serum Cr was 1.7 mg/dL and the patient was dosed q 48 hr. On D4 the patient's systolic blood pressure fell below 100 mmHg. On D5 serum Cr was noted to be 2.9 mg/dL, with D6 Cr 3.0 mg/dL. Study

medication, ramipril, and hydrochlorathiazide were discontinued and on D8, serum Cr had decreased to 1.9 mg/dL and the patient was noted to be hypotensive and with drop in hemoglobin to 7.1 mg/dL. The patient was given a blood transfusion and treated with norepinephrine and furosemide for ARF. By day 13, ARF had resolved with serum Cr of 1.2 mg/dL. **The investigator initially assessed the event of ARF to be possibly/probably related, however changed this to unrelated to study medication.** Hypotension and ACE inhibitor were thought to be primary causes, along with other nephrotoxic medications (trimethoprim-sulfa and hydrochlorathiazide). The **FDA reviewer agrees with the initial assessment that the event may have been possibly related to study medication, although clearly there were confounding factors (hypotension and concomitant medications).** The patient's creatinine **improved** with discontinuation of multiple medications and was actually better than baseline.

- 0018-06003-2721: The patient is a 56 yo female with diabetes, COPD, morbid obesity, venous insufficiency with chronic edema and stasis dermatitis who was treated for left leg cellulitis with 14 days of telavancin. Concomitant medications included furosemide, glyburide, metformin, naproxen, and warfarin. The patient was treated with clindamycin and ciprofloxacin for 8 days and then changed to telavancin and aztreonam. Baseline serum Cr was 0.9 mg/dL. While hospitalized the patient had gastroscopy, colonoscopy, and barium enema. The patient was discharged on D11 with serum Cr 0.8 mg/dL. Serum Cr 1 day prior to completing a course of therapy was 1.2 mg/dL. She completed 14 days of treatment and on that day the home health nurse noted the patient to be confused and not eating well. The patient was readmitted to the hospital the following day for severe hypoglycemia, dehydration, diarrhea (8-10 stools per day), and electrolyte disorders. The patient's creatinine was 1.7 mg/dL and the patient was diagnosed with acute renal failure. The patient was treated with IV fluids with resolution of hypoglycemia and confusion and started on oral metronidazole. The renal failure resolved on D19 and the patient was discharged from the hospital on D22 with serum Cr of 0.7 mg/dL. The **investigator** assessed the episode of **acute renal failure and hypoglycemia as possibly/probably related to study medication.** The **FDA reviewer agrees with the assessment, although it is likely that diarrhea could have precipitated the dehydration and electrolyte balance and sever dehydration could easily have explained the creatinine increase and electrolyte disturbances.** The renal failure **resolved.**

- 018-38160-3068: (see deaths): The patient is a 95 yo male with a history of profound congestive heart failure and <u>chronic renal insufficiency</u> (baseline serum Cr 4.1 mg/dL) who received an <u>inappropriate dose</u> of telavancin (q 24 hr instead of q 48 hr). The patient was also undergoing aggressive <u>diuresis</u> during the study. The patient's renal function was noted to begin deteriorating on Day 4 (Cr 5.5 mg/dL) and continued to deteriorate after study medication was discontinued on Day 7 (cellulitis was resolved at F/U D15 with Cr 10.3 mg/dL). Three days after the study period, the patient refused dialysis and subsequently died. The **cause of death was acute renal failure which the investigator assessed as possibly/probably related study medication, but may have been due to excessive diuresis and renal hypoperfusion,** although the event occurred outside of the reporting period (i.e. the patient had a TOC visit). **FDA: Concur, although the patient died outside of the official reporting period, acute (on chronic) renal failure was listed by the investigator as the cause of death.**

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- 0018-38148-2498: The patient is a 47 yo female with a history of diabetes mellitus, hypertension, peripheral vascular disease with left BKA who was treated with telavancin for 3 days for a leg abscess. Concomitant medications included insulin, indomethacin, rosiglitazone, topiramate, quetiapine, and lisinopril. Baseline serum Cr was 0.7 mg/dL (local lab) and on D3 was 2.7 mg/dL (central lab). Telavancin, along with indomethacin and lisinopril were discontinued. The patient was noted to be anemic and was transfused with packed RBC. The following day, she was noted to be hypoxic and developed respiratory failure and was intubated on D4 for 5 days. By D10, the patient's Cr had decreased to 1.5 mg/dL and the event was considered to be resolved (although Cr was still 2X normal). The narrative states that 5 days later the Cr had decreased further to 1.2 mg/dL, but this lab result is not included with the case report form. The investigator assessed the event of **elevated blood creatinine and urea** to be **possibly/probably** related to study medication, although the patient had **multiple comorbidities and concomitant medications which confounded** assessment as well. **Reportedly, renal function returned to baseline. The FDA reviewer concurs.**

- 0018-38260-2099: The patient is a 50 yo female with a history of lupus, seizure disorder, hypothyroidism, bilateral lower extremity edema, and chronic abscesses who received 5 days of telavancin for a left foot abscess. Concomitant medications included hydroxychloroquine, tegaserod, topiramate, hydrochlorathiazide, lamotrigine, carisoprodol, and naproxen for pain as needed. Baseline serum Cr was 0.9 mg/dL, D3 serum Cr had increased to 2.2 mg/dL, and by D6 was 4.6 mg/dL. On D8, the patient was admitted to the hospital with a diagnosis of renal failure (primary diagnosis: interstitial nephritis) and serum Cr of 6.0 mg/dL. Telavancin was discontinued and the patient received hydration. By D13, serum Cr had decreased to 2.8 mg/dL and D15 2.0 mg/dL. The investigator assessed the **SAE of renal insufficiency to be possibly/probably related to study medication**, with **resolution of renal failure and improving serum BUN and Cr**. The **FDA reviewer agrees with this assessment**, although the patient's comorbid diagnosis of lupus may have played a role.

- 0018-38148-2359: The patient is a 57 yo female with a history of diabetes mellitus, hypertension, morbid obesity, hypercapneic respiratory failure, obstructive sleep apnea, and bilateral knee replacement who received 4 days of telavancin for left leg cellulitis. Concomitant medications included furosemide, gabapentin, and naproxen. The patient had received prior treatment with levofloxacin and linezolid and at the time of change to telavancin, was noted to have septic shock. Baseline serum Cr was 0.9 mg/dL and by D5 had increased to 2.1 mg/dL. Telavanicn, naproxen, and furosemide were discontinued. Eighteen days after change in medications, serum creatinine had decreased to 1.0 mg/dL. The investigator assessed the **SAE of elevated Cr as possibly/probably related to study medication**, although the patient did have comorbidities and was reportedly in septic shock at enrollment. **The FDA reviewer agrees with assessment** of possible relationship to study medication, as well as confounding from **comorbidities and possibly naproxen (NSAID)** and with assessment of **resolution**.

- 0018-38322-2757: The patient is a 66 yo female with a history of hypertension, psoriasis, bilateral lower extremity edema, sleep apnea, and impaired glucose tolerance, who was treated with telavancin for a deep and extensive cellulitis of the left lower extremity. Concomitant medication included atenolol with chlorthalidone and rosuvastatin. Baseline serum Cr was 0.6 mg/dL and on D5 the patient complained of nausea and vomiting and had a

serum Cr of 3.7 mg/dL. The patient was advised to discontinue study medication on D6, but continued to self-administer the drug for two additional doses. The patient was hospitalized for acute renal failure on D7 at which time the serum Cr was 2.6 mg/dl. The patient's renal failure was considered to have resolved 6 days after study medication discontinuation. At the TOC visit (D16 – 9 days after medication discontinuation), serum Cr was back to 0.9 mg/dL. The investigator assessed the SAE **of acute renal failure as possibly/probably related** to study medication and **event resolved**. The **FDA reviewer agrees** with this assessment.

- 202b-00910-9058: The patient is a 28 yo male who was treated with telavancin for 4 days for a gluteal abscess. Prior to treatment, the patient had been recently started on diclofenac and ibuprofen (ISS says 3 weeks / study narrative says same duration). The patient's baseline serum Cr was 1.0 mg/dL and noted to have increased to 1.8 mg/dL by D2. The serum creatinine continued to rise and by D4 was 3.5 mg/dL. Physical exam was normal and study medication was discontinued and the patient was not oliguric. At follow-up 10 days later, serum Cr had decreased to 1.6 mg/dL and approximately 2 weeks after that at 1.1 mg/dL. The investigator assessed the **SAE of acute renal failure as possibly/probably related to study medication**, although **NSAIDs** may have played a role. **The FDA reviewer agrees** with this assessment and confounding by concomitant NSAID and agrees that event has **resolved**.

Vancomycin

- 0017-38005-0180: The patient is a 77 yo female with a history of diabetes mellitus, peripheral vascular disease, hypertension, and peripheral neuropathy who was treated for 3 days with vancomycin for an infected foot wound. Concomitant medications included aztreonam, metronidazole, heparin, clotrimazole, methyldopa, lisinopril, glibenclamide, pravastatin, verapamil, and insulin. Prior to entering the study, the patient had been treated with levofloxacin. She also had an angiogram and percutaneous angioplasty to restore optimal circulation and received a dose of vancomycin. At study entry, the patient's Cr was 1.4 mg/dL. On D5, the patient underwent a planned amputation of the right great toe. On D6, serum Cr was increased to 3.4 mg/dL and the patient also complained of nasusea and diarrhea. Ten days after discontinuation of study medication the episode was considered to be resolved and the serum Cr was 1.0 mg/dL. The investigator assessed the **SAE of increased Cr to be possibly/probably related to study medication** and event **resolved**. The FDA reviewer **agrees** with this assessment, although **comorbidities and concomitant medications confound attribution**.

- 0017-38024-0697: The patient is a 62 yo male with a history of hypertension who was admitted to the hospital with a gunshot wound to the pelvis which resulted in exploratory laparotomy, end-sigmoid colostomy, and partial urethral disruption. Concomitant medications included aztreonam, metoprolol, esomeprazole, ibuprofen, and heparin. The patient was treated with vancomycin for 5 days for a post-op wound infection. Baseline serum Cr was 0.7 mg/dL and on D5 was 2.1 mg/dL (local), at which time study medication was discontinued and the patient was treated with nafcillin followed by oxacillin. On D7, serum Cr was further increased to 3.0 mg/dL (central). Three weeks later, the patient's creatinine had normalized to 1.0 mg/dL. The investigator assessed the **SAE of increased creatinine** as possibly related to study medication and **resolved**. The **FDA reviewer agrees** with assessment, although use of ibuprofen and recent pelvic gunshot wound and resultant surgery certainly may have **confounded** this assessment.

- 0018-38260-2555 (see deaths): The patient was a 53 yo male treated with a single dose of vancomycin (based on renal function levels should have been adequate for a week). The patient's past medical history was significant for cirrhosis with ascites, CHF, atrial fibrillation, gout, hypertension, and ESRD requiring hemodialysis. Concomitant medications included digoxin, carvedilol, clonidine, pantoprazole, epogen, cyproheptadine, promethazine, paracetamol, temazepam, metoprolol, allopurinol, and morphine. The patient underwent incision and drainage of abscess on D2 and was discharged from the hospital on D3. The patient was readmitted on D6 with worsening of ESRD and ascites, however, the patient's serum creatinine was unchanged. On D8, the patient underwent removal of a peritoneal subclavian shunt and went to the ICU. He was started on an anti-arrhythmic and dialyzed. The patient **died** prior to his scheduled second dose of vancomycin. The investigator assessed the **SAEs of cardiac arrest, renal failure chronic, and ascites as unrelated** to study medication. The FDA reviewer has concerns with adequacy of blinding given the anticipation of infrequent, weekly doses of study medication expected for this patient.

- 202b-00903-9037 (see deaths): The patient was a 41 yo female with a left foot wound infection treated with standard therapy (chosen as vancomycin). On admission to the hospital, the patient was noted to have elevated LFTs (bilirubun 78 µmol/L, alkaline phosphatase 344 U/L, AST 109 U/L, and GGT 396 U/L) and anemia (hemoglobin 7.4 g/dL) and admitted to chronic alcohol use. The patient was subsequently found to be septicemic and study treatment was augmented with aztreonam and metronidazole. Study drug was discontinued on Day 6 at which time the patient's LFTs were (bilirubun 152 µmol/L, alkaline phosphatase 285 U/L, ALT 169 U/L, AST 94 U/L) and serum creatinine of 200 µmol/L (2.3 mg/dL). The patient developed respiratory distress 5 days later and died. The investigator assessed the SAEs of multiorgan failure, sepsis, hepatic failure, **renal failure acute,** and respiratory failure as **unrelated** to study medication. The FDA reviewer agrees with this assessment.

CARDIAC SAEs

SAEs resulting in death (telavancin)
0017-02010-0546: (included with death narratives in Appendix A) - ventricular arrhythmia [The patient was a 65 year-old male with a history of right-sided heart failure secondary to chronic obstructive pulmonary disease with chronic lower extremity edema, coronary artery disease, diabetes mellitus, hypercholesterolemia, and epilepsy. Concomitant medications included albuterol, tiatropium bromide, salbutamol, furosemide, isosorbide, glicazide, digoxin, phenytoin, perindopril, pravastatin, and coumadin. Baseline laboratories, including electrolytes and serum creatinine were unremarkable, but ECG revealed incomplete right bundle branch block/right ventricular conduction delay and non-specific ST/T wave abnormalities. The patient received a single dose of telavancin (10 mg/kg) for cellulitis and minor infected wounds. The Day 2 dose was missed (in error). On Day 3, more than 24 hours after the dose of study medication, the patient was found dead in bed, with a presumptive diagnosis of ventricular arrhythmia. No ECG had been done since baseline. The investigator assessed the event of "acute ventricular dysrhythmia" could not rule out study medication as being possibly related, although noted multiple confounding factors. FDA reviewer concurs.]

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0018-01002-2474: (included with death narratives in Appendix AA) cardiac arrest [The patient was a 75 yo female treated for 6 days with telavancin for cellulitis of the left hand resulting from a burn. The patient's past medical history included: diabetes, peripheral vascular disease, and hypertension (narrative listing, but not CRF- concomitant medications consistent with history). Concomitant medications included: heparin, enalapril, acetylsalicylic acid, pethidine, insulin, ibuprofen, clonazepam, morphine, furosemide, ranitidine, dipirone, dextiopopoxiphen, and metformin. The patient had received cefalothin and clindamycin prior to study entry. On D4, the patient's hemoglobin had dropped from baseline 11.3 g/dL to 8.8 g/dL, serum Cr increased from 0.8 mg/dL to 1.3 mg/dL. The patient received an overdose of morphine on D5 (no administration time in CRF) and 4 hours later the patient complained of weakness and fell. The dose of telavancin was adjusted from 10 mg/kg q 24 hr to 7.5 mg/kg q 24 hr based on declining renal function. ECG obtained after the fifth dose of telavancin showed an increase in mean QTcF from baseline of 450 msec to 479 msec. On D6 the patient was noted to have a poor response of cellulitis to treatment, although study medication was continued. The patient was found dead on D7 with no underlying cause. The investigator assessed the event of cardiac arrest as possibly/probably related to study medication. FDA reviewer concurs.]

0018-19006-2894: (included with death narratives in Appendix A) cardio-respiratory arrest [The patient was an 84 yo male treated for 9 days with telavancin for cellulitis of the left foot. The patient's past medical history was significant for diabetes mellitus, rheumatoid arthritis, hypertension, PVD, and hepatic carcinoma (per follow-up death investigation). Concomitant medications included: furosemide, captopril, acetylasalicylic acid, insulin, ranitidine, paracetamol with codeine, albumin, and hydrocortisone. The patient was dosed with telavancin at 10 mg/kg q 24 hrs despite a baseline creatinine clearance < 30 mL/min, but was adjusted to 10 mg/kg q 48 on D3. Aztreonam had been added for Gram negative coverage, as was hydrocortisone on D2 following an episode of hypotension (not reported as an AE). On D7, the patient was noted to be anemic with hemoglobin of 7.1 g/dL. Baseline ECG had shown first degree AV block and on D5 showed new RBBB. Study treatment was discontinued on D9 with resolution of cellulitis. On D9, AEs of abnormal ALT and AST (local) were reported as AST 818 U/L and ALT 1186 U/L (Day 7 central ALT was 47 U/L↑, AST 48 U/L↑, bilirubin of < 3 μmol/L, and alkaline phosphatase of 270 U/L↑ - alkaline phosphatase elevated from 153 U/L on D4 – no baseline LFTs or local labs are available in CRF or dataset). On follow-up the investigator noted that the patient had cirrhosis due to hepatic carcinoma. On D10 ECG showed new atrial fibrillation and the patient died on D11, 2 days after discontinuing study treatment. The investigator assessed the event of cardio-respiratory arrest as unrelated to study medication. FDA reviewer disagrees with this assessment since there is no readily apparent cause of death. The elevation of LFTs was temporally related to study medication and new onset a fib started within a day of study medication discontinuation. The elevation in LFTs was explained retrospectively.]

0018-38160-2501: (included with death narratives in Appendix A) myocardial infarction, acute respiratory failure [The patient was a 77 yo male who received 5 days of telavancin for left hand cellulitis. The patient's past medical history was significant for COPD, hypertension, pulmonary fibrosis, asthma, supraventricular tachycardia, CHF, angina, rheumatoid arthritis, and silicosis. Concomitant medications included: metronidazole, aztreonam, prednisone, levosalbutamol, glipizide, irbesartan, diltiazem, lorazepam, vicodin, paracetamol, potassium chloride, insulin, and furosemide. The patient's baseline serum Cr was 1.7, with creatinine clearance calculated at

30.7 mL/min and telavancin dose was appropriately adjusted to 7.5 mg/kg q 24 hr. On D3, the patient underwent excision of a hand cyst and developed a fever and elevated WBC count on post-op day 1 (D4). The patient was noted to be improving on D5, but developed acute respiratory failure, was transferred to the ICU, and was intubated. The patient was made DNR and died that night due to myocardial infarction (troponin 1 level 4.76 ng/mL, normal < 0.4). The events of acute MI and respiratory failure were assessed as unrelated to study medication. FDA reviewer disagrees. Although it is unlikely these events are related, study medication effect cannot be ruled out.]

SAEs (not causing death) that were possibly/probably related to telavancin

0017-38101-0436: bradycardia [The patient was a 30 yo male with a history of heroin use, on methadone and hydromorphone. Baseline ECG sinus bradycardia with HR 49-50 BPM and the patient was placed on telemetry floor. On D3, the patient was noted to be lethargic with HR 45 BPM but without chest pain, dizziness or shortness of breath. His blood pressure was 112/65 and O2 sat on room air was 96%. On D7 the patient was transferred to a regular floor, was no longer lethargic, and the event was considered to be completely resolved. The investigator assessed "worsening bradycardia" as possibly related to study medication, although I am not sure this constituted an event of concern]

0017-38111-0380: myocardial infarction [The patient was a 78 yo male with a history of MI and CABG, bilateral carotid endarterectomies, atrial fibrillation, hypertension, pacemaker, peripheral vascular disease, COPD, and myelodysplastic syndrome. Concomitant medications included isosorbide mononitrate, digoxin, amiodarone, Vicodin, erythropoietin, heparin, and hydrocortisone. Telavancin was initiated at a skilled nursing facility ("dosed appropriately"). Baseline ECG showed QTcF of 360 msec (single value) and increased to 443 msec on D4 (increase of 83 msec). On D10 of medication, the patient became diaphoretic with decreased O2 sat, new LBBB, and elevated CPK with MB fraction consistent with MI. A cardiac catheterization was performed and the event was considered to be resolved on the same day. The patient recovered with sequelae that included delirium, renal insufficiency, and CHF. The investigator assessed the event of MI as possibly related to study drug, although the patient continued on study medication. FDA reviewer agrees that the event was temporally related, although with previous arrhythmias and coronary artery disease it is hard to know what caused increased QTcF or event]

SAEs that were not related to study medication (telavancin)

0017-18004-0768: myocardial ischemia [The patient was a 79 yo female with a history of diabetes, atrial fibrillation, CVA, hypertension, and right hemiplegia. Concomitant medications included dextropropoxyphene, metamizole, ipratropium bromide, Solvex (?), salbutamol, furosemide, paracetamol, clopidogrel, spironolactone, enalopril, warfarin, and troxerutin. On D3 of study treatment, the patient had pulmonary congestion, myocardial ischemia, and elevated INR noted (although a chromogenic factor X assay was not done) and the patient was discontinued from therapy. Myocardial ischemia and pulmonary congestion were ongoing and the patient was treated for a Gram negative bacterial infection from needle aspirate. The investigator assessed the pulmonary congestion and myocardial ischemia as unrelated to study medication. FDA reviewer tends to concur, confounded]

0017-38101-0059: atrial fibrillation [The patient is a 36 yo male with a history of polysubstance abuse, schizophrenia, and reported "arrhthymia" prior to intiating therapy. Concomitant medications include risperdone, bupropion, lorazepam, and benzotropine mesylate. On D3 the

patient's ECG was read as "ectopic supraventricular rhythm", the patient was asymptomatic but was sent to telemetry for observation. No specific medications were administered and on D4, the patient was transferred back to a regular floor and continued study medication. The investigator assessed study medication as unrelated. FDA reviewer tends to concur, unlikely related]

0017-38101-0069: congestive cardiac failure [The patient is a 77 yo male with a history of coronary artery disease, CABG, CHF, intermittent atrial fibrillation, hypertension, diabetes, peripheral vascular disease, and BPH. The patient's baseline serum Cr was 2.2 mg/dL. Concomitant medications included furosemide, insulin, glimepride, methylprednisolone, paroxetine, clopidogrel, levothyroxine, and isosorbide mononitrate. On D15, study medication was discontinued due to reaching maximum allowable therapy and the patient left AMA on D16. The patient was readmitted on D17 with increased shortness of breath and leg swelling, not associated with elevation in serum Cr. The patient was treated for an exacerbation of CHF and also had a PICC line infection and hypoglycemia. The investigator assessed SAE of congestive cardiac failure as not related to study medication. FDA reviewer tends to concur]

0017-18001-0722: myocardial infarction [The patient is a 67 yo female with a history of MI, CABG, tricuspid and mitral insufficiency, endarterectomy, diabetes, peripheral vascular disease, hypertension, and anemia. The patient had been admitted to the hospital complaining of nausea, weakness, and dizziness attributed to CHF exacerbation, along with cellulitis. Concomitant medications included warfarin, heparin, spironolactone, oxazepam, enalopril, atenolol, candesartan, brotizolam, insulin, and furosemide. The patient complained of nausea on D2 of study medication and was treated with metoclopramide. The patient was discontinued from study medication on D3 and changed to piperacillin/tazobactam. The patient's ECG from Day 3 was read as acute septal MI (confirmed by central ECG lab) and the patient was diagnosed with MI with elevated troponin on D4 (one day after study medication was discontinued). The investigator assessed MI as not related to study medication. FDA reviewer disagrees that relationship to study medication can be excluded.]

0017-38271-0402: angina pectoris [The patient is a 26 F with a history of hypertension, obesity, GERD, nicotine addiction, and spider bites. Concomitant medications include macrogol and pantoprazole. The patient had chest pain on D5 treated with metoprolol, morphine, aspirin, and nitro paste. Troponin was negative, ECG showed normal sinus rhthym, and chest CT scan was negative for PE. The patient was transferred to telemetry for observation and the event resolved by D8. The patient continued on study medication for total of 11 days. The investigator assessed the event as not related to study medication, unknown, not clear it was cardiac, study med may have exacerbated GERD. FDA reviewer believes that event was possibly/probably related to study drug, but may not have been cardiac in origin given the history of GERD]

0018-06005-2728: myocardial infarction [The patient is a 63 yo male with a history of MI, CABG, hypertension, diabetes with retinopathy, BPH, gastritis, TIAs, peripheral vascular disease, and diverticulosis. Concomitant medications included aspirin, spironolactone, pravastatin, telmisartan, amiodopine, furosemide, insulin, metformin, and bisoprolol. On D2 of study treatment, the patient was admitted to the hospital with a non-Q wave MI and study medication was continued for a total of 7 days. The investigator assessed the event as unrelated to study medication. FDA reviewer disagrees and believes that study medication relationship should not be excluded as a possible contributor to event.]

202b-00111-7055: atrial fibrillation [The patient was an 82 yo male with a history of coronary artery disease, CHF, atrial fibrillation, diabetes mellitus, and peripheral vascular disease.

Concomitant medications included furosemide, aspirin, insulin, terazosin, nortriptyline, clopidogrel, carbamazepime, and quinine. The patient was reported to have worsening of atrial fibrillation on Day 5 of study medication but continued on study medication for a total of 10 days treatment. The investigator assessed the event as not related to study medication. FDA reviewer tends to concur.]

<u>SAEs resulting in death (vancomycin)</u>
0018-22000-2742: (included with death narratives in Appendix A) cardiac failure, atrial fibrillation [The patient was a 55 yo male treated with vancomycin 2 days for cellulitis. The patient's past medical history was significant for dermal T-lymphoma, for which he was treated with chemotherapy approximately 6 months prior. Concomitant medications included metamizol, ketorolac, furosemide, morphine, and nutrison. The patient received ampicillin prior to study entry, but was changed to study medication when MSSA was isolated from a wound culture. On D2 of treatment, the patient was diagnosed by a cardiologist with atrial fibrillation and cardiac insufficiency and the patient was treated with metoprolol, aspirin, albumin, and furosemide and normal sinus rhythm was restored. However, on D3 of treatment anuria developed, cardiac insufficiency progressed, and the patient died. The investigator assessed the event as unrelated to study medication. FDA reviewer disagrees because the possibility that the cardiac event or anuria was related to study medication cannot be excluded.]
0017-38024-0695: (included with death narratives in Appendix A) cardiac failure congestive, respiratory failure [The patient was a 53 year old male treated with vancomycin for 14 days for chronic non-healing leg ulcers. Medical history included secondary polycythemia, VSD, hypothyroidism, hypertension, CHF, pulmonary hypertension, CVA, renal failure, and seizure disorder. Baseline creatinine clearance was 32 mL/min. The patient was discharged after 11 days. The patient was readmitted to the hospital 5 days later (2 days off study medication) with shortness of breath, bilateral pleural effusion, and interstitial pulmonary edema consistent with CHF. Concomitant medications included aztreonam, warfarin, levothyroxine, lidocaine, furosemide, silver sulfadiazine, esomeprazole, mirtazapine, acetaminophen with codeine, losartan, and atenolol. The patient died a day later from cardiac and respiratory failure. The investigator assessed event as unrelated to study medication. FDA reviewer agrees. This patient had chronic renal insufficiency and serum Cr had decreased on study medication from baseline of 1.7 mg/dL to 1.3 mg/dL on day of hospital discharge or D11 of therapy]
0018-30907-2323: (included with death narratives in Appendix A) septic shock, cardiogenic shock, pulmonary edema [The patient was a 66 yo female treated for 3 days with vancomycin for right arm cellulitis. The patient's past medical history was significant for hypertension, history of aortic aneurysm repair, and small bowel obstruction requiring laparotomy 3 months prior. Concomitant medications included aztreonam, opium alkaloids, diclofenac, paracetamol, heparin, omnopon, dobutamine, and phenylephrine. The patient's pretreatment blood cultures were positive for *Staph aureus*. The patient became progressively hypoxemic and tachycardic and developed septic and cardiogenic shock. The patient died on D3. The investigator assessed the events as unrelated to study medication. FDA reviewer concurs.]
0018-38260-2555: (included with death narratives in Appendix AA) cardiac arrest, renal failure chronic, ascites [The patient was a 53 yo male treated with a single dose of vancomycin and died before the next scheduled dose (based on renal function, the vancomycin level should have been adequate for a week). The patient's past medical history was significant for cirrhosis with

ascites, CHF, atrial fibrillation, gout, hypertension, and ESRD requiring hemodialysis. Concomitant medications included digoxin, carvedilol, clonidine, pantoprazole, epogen, cyproheptadine, promethazine, paracetamol, temazepam, metoprolol, allopurinol, and morphine. The patient underwent incision and drainage of an abscess on D2 and was discharged from the hospital on D3. The patient was readmitted on D6 with worsening of ESRD and ascites, however the patient's serum creatinine was unchanged. On D8, the patient underwent removal of a peritoneal subclavian shunt and went to the ICU. He was started on an anti-arrhythmic and dialyzed. The patient died prior to his scheduled second dose of vancomycin. The investigator assessed the events as unrelated to study medication and SAE is listed as not related in the ISS AE dataset. However, the narrative in the clinical study report indicates that the event was considered to be possibly/probably related to study medication. FDA reviewer believes event is unlikely related to study medication, although concerned with adequacy of blinding in this case given the anticipated infrequent dosing of study medication and CRF indicating that study medication doses were "missed" on Days 2-9. A data clarification form attached to the CRF states that treatment assignment was not unblinded.]

0017-38271-0659: (included with death narratives in Appendix A) bradycardia, cardio-pulmonary arrest, hepatic coma, respiratory failure [The patient was a 47 year old male treated with vancomycin for 6 days for right leg cellulitis. Medical history included hypertension, hepatitis C infection, and alcoholic cirrhosis with systemic complications. Concomitant medications included aztreonam, furosemide, vicodin, morphine, amlodipine, benazepril, lactulose, pantaprazole, spironolactone, folic acid, vitamin K, and temazepam. Study medication was discontinued on Day 6 after isolation of an aztreonam-resistant pathogen. Three days after study medication was discontinued the patient had an episode of desaturation, required BIPAP and norepinephrine, phenylephrine, midodrine, and albumin for hypotension, and atropine and epinephrine for **bradycardia**. The patient required mechanical ventilation for respiratory failure, had hepatic coma, and then fatal cardio-respiratory arrest. Three days later, the patient developed respiratory distress and was started on BIPAP and subsequently mechanical ventilation. The events of bradycardia and cardio-respiratory arrest were assessed as unrelated by the investigator. FDA reviewer concurs.]

0017-38016-0824: (included with death narratives in Appendix A) cardio-respiratory arrest (not classified in ISS AE database as a "serious adverse event"), pulmonary embolism [The patient is a 49 year old female treated with vancomycin for 2 days for a left lower quadrant abscess. Medical history included morbid obesity, anemia, and diabetes. Concomitant medication included morphine, insulin, famotidine, heparin, promethazine, paracetamol, aztreonam, and metronidazole. On Day 2, the patient became unresponsive while getting out of bed. CPR was attempted, but was unsuccessful and the patient died. Autopsy revealed a pulmonary embolism "secondary to abdominal abscess". The investigator assessed the event as unrelated to study medication. FDA reviewer concurs given that the event occurred after only approximately 24 hours on study treatment.]

<u>SAEs (not causing death) that were possibly/probably related to vancomycin</u>
0017-38101-0247: atrial fibrillation [The patient was a 66 yo male with a history of diabetes, hypertension, BPH, and alcohol abuse. Concomitant medications included losartan, rosuvastatin, tamsulosin, insulin, metformin, and aspirin. On D2, the patient underwent surgical excision of an infected sebacious cyst on the back and perioperatively was given propofol, midazolam,

fentanyl, and bupivicain. On D3, ECG monitoring showed new onset atrial fibrillation, no chest pain, and stable vital signs. The patient had spontaneous return to NSR in 30 minutes and was ultimately treated with digoxin and potassium and transferred to telemetry. Further episodes of atrial fibrillation occurred on D4 and lovenox and warfarin were added. The investigator assessed the event as possibly/probably related to study medication. The FDA reviewer concurs, the event temporally coincides with study medication, although confounded.]

0017-38271-0434: atrial fibrillation [The patient was a 53 yo female with a history of rheumatic fever, mitral valve prolapse, asthma, and fibromyalgia. Concomitant medications included colchicine, Vicodin, hydromorphone, conjugated estrogens, gabapentin, lamotrigine, ibuprofen, olopatadine, pantoprazole, propanalol, seretide, mometasone, paroxetine, heparin, and lorazepam. Baseline ECG showed evidence of an old anterior infarct. On D4 the ECG was unchanged except for low voltage noted in the chest leads and QT/QTc interval was shorter. On D7 the patient developed shortness of breath with CXR evidence of mild CHF, and an echocardiogram showed mild to moderate mitral regurgitation. The patient was treated with methylprednisolone, furosemide, salbutamol, and ipratropium. On D10 the patient had increased anxiety and heart palpitations and ECG showed atrial fibrillation with rapid ventricular response and the patient was transferred to a telemetry bed. The patient was treated with diltiazem, amiodarone, and aspirin. The event resolved and the patient was discharged 3 days later. The investigator assessed the event as possibly/probably related to study medication. FDA reviewer concurs.]

Discontinuations in patients with cardiac SAEs treated with vancomycin

0017-38101-0873: bradycardia [The patient was a 47 yo male with a history of IV drug abuse, bradycardia, and hyperglycemia. Concomitant medications included Vicodin, glibenclamide, insulin, methadone, nicotine patch, and morphine. On admission the patient was noted to be hypoxic due to a subglottic mass. The patient's pre-existing bradycardia became symptomatic with heart rate in the 30's and a temporary transvenous pacemaker was placed. The patient had surgery to remove the mass and received propofol, fentanyl, midazolam, methocarbamol, neostigmine, and lidocaine. One week later the patient underwent placement of a permanent pacemaker. The investigator assessed the event of bradyacrdia as unrelated to study medication. The FDA reviewer concurs, bradycardia preceded study medication.]

0017-09002-0765: cardiac failure [The patient was a 69 yo female with a history of diabetes, gangrene of the 5th toe, hypertension, femoro-popliteal bypass, chronic bronchitis, and hyperlipidemia. Concomitant medications include insulin, amiodipine, atorvastatin, losartan, and furosemide. On D3 the patient developed life-threatening pneumonia, bronchitis, and cardiac decompensation at which time study medication was discontinued. The patient was also noted to have bronchospasm and cyanosis. The investigator assessed the event as unrelated to study medication. The FDA reviewer disagrees since the decompensation is temporally related to administration of study medication and although comorbidities exist, it is not clear what led to the events.]

0018-33002-2605: acute myocardial infarction [The patient is an 80 yo female with a history of coronary artery disease and diabetes. Concomitant medications included isosorbide dinitrate, propranolol, repaglinide, Moduretic, insulin, diphenhydramine, furosemide, dopamine, dalteparin, aspirin, hydrocortisone, and propofol. On D3 the patient developed dyspnea and hypotension and was started on dopamine. ECG showed evidence of an MI, the patient

developed respiratory failure requiring intubation and vancomycin was discontinued. Approximately 2 weeks later the patient was extubated and discharged 3 days after that. The investigator assessed the MI as unrelated to study medication. The FDA reviewer disagrees since the decompensation is temporally related to administration of study medication and although comorbidities exist, it is not clear what led to the events.]

0018-38025-2330: myocardial infarction [The patient was a 67 yo male with a history of MI, hypertension, diabetes mellitus, peripheral neuropathy, HIV infection, common bile duct stricture with stent, hepatitis C, anemia, and candidiasis. Concomitant medications included doxepin, aspirin, metoprolol, isosorbide dinitrate, lopinavir/ritonavir, tenofivir, Trizivir, sertraline, omeprazole, atovaquone, heparin, enalapril, morphine, oxycodone, and insulin. The patient was found to have MRSA bacteremia (1/2 baseline cultures were positive) and baseline serum Cr was 1.2 mg/dL. The patient developed hypotension on D2. The patient's serum Cr had increased to 3.5 mg/dL on D3 which prompted discontinuation of the study medication. Serum Cr decreased to 2.7 mg/dL nine days later. On D9 (7 days after study med d/c) the patient developed severe chest pain and required treatment for hypertensive crisis and pulmonary edema. He was treated with nifedipine, glyceryl trinitrate, acetylcysteine, eptifibatide, furosemide, labetolol, and ipratropium. The patient had an MI along with *Klebsiella pneumoniae* septicemia diagnosed. The investigator assessed the cardiac SAE of MI as unrelated to study medication, although increased serum Cr was assessed as possibly/probably related. The FDA reviewer concurs.]

0017-38111-0098: cyanosis (versus televancin 7.5 mg/kg dose) [The patient was an 86 yo male with a history of atrial fibrillation, CHF, cor pulmonale, hyperlipidemia, chronic renal insufficiency, obstructive sleep apnea, BPH, hematuria, and prior PE. Concomitant medications included metoprolol, lisinopril, warfarin, digoxin, celecoxib, spironolactone, oxymetolazone, furosemide, tamsulosin, and enoxaparin. On D10 the patient developed cough, fever, and malaise, and was readmitted to the hospital for pneumonia. Chest X-ray showed a right upper lobe infiltrate, sputum culture grew *Pseudomonas* and aztreonam was added. The patient was discharged on D16 (study med discontinued on D15 with resolution of cSSSI), developed cyanosis and hypotension and was readmitted with PE. The investigator assessed the event of cyanosis as unrelated to study medication. FDA reviewer disagrees and although other factors are likely, treatment with study medication is temporally related to event.]

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/s/

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10/18/2007 10:29:08 PM
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