Primary Efficacy Outcome

The Clinical Success rates for the pooled MITT population from Studies 9801 and 9901 were 75.8% in the daptomycin group and 76.2% in the comparator group (95% CI: -5.7, 5.0) (see Table 40). The results indicate that daptomycin at 4 mg/kg q24h for 7 to 14 days is clinically and statistically non-inferior to the comparator agents for the treatment of cSSSI.

Table 40: Primary efficacy endpoint: Sponsor-Defined Clinical Outcome, Primary Comparative cSSSI Studies (MITT population)

| | Pooled cSSSI 9801 + 9901 | | | | |
| | Daptomycin (N=422) | | Comparator[a] (N=467) | | |
Clinical Response	n	%	n	%	95% CI[b]
Clinical Success	320	(75.8%)	356	(76.2%)	(-5.7, 5.0)
Cure	173	(41.0%)	195	(41.8%)	
Clinical Improvement	147	(34.8%)	161	(34.5%)	
Clinical Failure	102	(24.2%)	111	(23.8%)	
Clinical Failure	64	(15.2%)	66	(14.1%)	
Nonevaluable	38	(9.0%)	45	(9.6%)	

a. Vancomycin 1 g q12h or semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) 4 to 14 grams daily in equal divided doses.
b. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the confidence interval is calculated stratifying on protocol.

Clinical Success Rates by Pathogen

Clinical Success rates by pathogen for the ME population (Table 41) were similar to those of the MITT population (Table 42) when these rates for daptomycin were assessed against all comparators. Tables showing data for clinical success rates for both populations comparing daptomycin to either semi-synthetic penicillins or vancomycin are not shown here but can be found in Microbiology Section 8.6.10 as tables 8-16, 8-17, 10-59, and 10-60.

Table 41: Sponsor Defined Clinical Success Rates by Pathogen (ME population: Daptomycin arm versus Comparator arm) for comparative cSSSI studies at test-of-cure[a]

Pathogen[b]	Daptomycin		Comparator[c]		95% CI[d]
Staphylococcus aureus (all)	222/265	(83.8%)	240/285	(84.2%)	(-5.8, 6.7)
Staphylococcus aureus (MSSA)[d]	176/208	(84.6%)	185/216	(85.6%)	(-5.9, 7.9)
Staphylococcus aureus (MRSA)[d]	21/30	(70.0%)	27/39	(69.2%)	(-23.1, 21.6)
Streptococcus pyogenes	80/87	(92.0%)	82/94	(87.2%)	(-13.7, 4.3)
Streptococcus agalactiae	24/28	(85.7%)	22/31	(71.0%)	(-35.7, 6.2)
Streptococcus dysgalactiae equisimilis	9/10	(90.0%)	9/11	(81.8%)	(-38.2, 21.8)
Viridans Streptococci Group	15/22	(68.2%)	27/32	(84.4%)	(-7.5, 39.8)
Enterococcus faecalis (all)	27/39	(69.2%)	41/54	(75.9%)	(-12.1, 25.5)
Enterococcus faecalis (VSE)[d]	25/36	(69.4%)	39/52	(75.0%)	(-13.9, 25.0)

a. Based on the Sponsor-Defined Clinical Outcome.
b. Only pathogens for which an indication is being sought are shown.
c. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin).
d. Susceptibility determinations were made only for Central Lab isolates.
e. Seven subjects in the pooled ME population were initially treated with semi-synthetic penicillins and had MRSA

isolated as a baseline pathogen. Six of these subjects were then switched to vancomycin: five of these were clinical successes. The remaining subject was continued on semi-synthetic penicillin and was a clinical success.

Table 42: Clinical Success Rates by Pathogen, Primary Comparative cSSSI Studies: Pooled Analysis (MITT population)

Pathogen[b]	Daptomycin		Comparator[c]		95% CI[d]
	n/N	(%)	n/N	(%)	
Staphylococcus aureus (all)	223/299	(74.6%)	241/320	(75.3%)	(-6.2, 7.7)
Staphylococcus aureus (MSSA)[e]	177/227	(78.0%)	185/237	(78.1%)	(-7.6, 7.8)
Staphylococcus aureus (MRSA)[e]	21/39	(53.8%)	27/46	(58.7%)	(-16.7, 26.4)
Streptococcus pyogenes	81/92	(88.0%)	82/103	(79.6%)	(-18.9, 2.0)
Streptococcus agalactiae	24/30	(80.0%)	23/39	(59.0%)	(-42.5, 0.5)
Streptococcus dysgalactiae equisimilis	9/13	(69.2%)	9/12	(75.0%)	(-30.0, 41.6)
Viridans Streptococci Group	15/23	(65.2%)	27/32	(84.4%)	(-4.5, 42.8)
Enterococcus faecalis (all)	27/45	(60.0%)	42/61	(68.9%)	(-10.0, 27.7)
Enterococcus faecalis (VSE)[e]	25/41	(61.0%)	40/56	(71.4%)	(-9.0, 29.9)

    a.   Based on the Sponsor-Defined Clinical Outcome.
    b.   Only pathogens for which an indication is being sought are shown.
    c.   Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
    d.   95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal
approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
    e.   Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory

Reviewer's comments: In both populations, the clinical success rates for daptomycin and comparators were very similar for *Staphylococcus aureus* including MSSA and MSRA. Daptomycin was less effective ($\geq$5% lower clinical success rate) than semi-synthetic penicillins against MRSA.

Overall, clinical success rates of daptomycin for the treatment of *Streptococcus pyogenes, Streptococcus agalactiae* and *Streptococcus dysgalactiae equisimilis* were rather superior ($\geq$5% higher clinical success rate) to comparators. However, clinical success rates of daptomycin for the treatment of viridans streptococci were lower overall to comparators. Daptomycin seemed more successful against viridans streptococci than semi-synthetic penicillins.

Overall, clinical success rates of daptomycin for the treatment of *Enterococcus faeçalis,* including VSE, were lower than comparators. This was due to the observation that clinical success rates of daptomycin were superior to vancomycin but inferior to that for semi-synthetic penicillins.

Pathogen Eradication Rates

Pathogen eradication rates by pathogen and treatment group for the pooled ME population is shown in Table 43 and for the MITT population in Table 44. Pathogen eradication rates were comparable for the two populations. Additional data for pathogen eradication rates for both populations comparing daptomycin to either semi-synthetic penicillins or vancomycin are not shown here but can be found in Microbiology Section 8.6.1 as Tables 8-19, 8-20, 10-62, and 10-63.

Table 43: Eradication Rates By Pathogen and Treatment Group For The Primary Comparative cSSSI Studies: Pooled Analysis (ME population)

Pathogen[a]	Daptomycin		Comparators[b]		95% CI[c]
	nN	(%)	nN	(%)	
Staphylococcus aureus (all)	186/265	(70.2%)	211/285	(74.0%)	(-3.8,11.5)
Staphylococcus aureus (MSSA)[d]	148/208	(71.2%)	161/216	(74.5%)	(-5.3,12.0)
Staphylococcus aureus (MRSA)[d]	15/30	(50.0%)	23/39	(59.0%)	(-15.1,33.1)
Streptococcus pyogenes	77/87	(88.5%)	74/94	(78.7%)	(-20.6,1.1)
Streptococcus agalactiae	22/28	(78.6%)	19/31	(61.3%)	(-40.7,6.1)
Streptococcus dysgalactiae equisimilis	9/10	(90.0%)	9/11	(81.8%)	(-38.2,21.8)
Viridans Streptococci Group	17/25	(68.0%)	28/38	(73.7%)	(-17.8,29.2)
Enterococcus faecalis (all)	25/39	(64.1%)	35/54	(64.8%)	(-19.4,20.8)
Enterococcus faecalis (VSE)[d]	23/36	(63.9%)	33/52	(63.5%)	(-21.3,20.4)

a. Only pathogens for which an indication is being sought are shown.
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
c. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
d. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.

Table 44: Eradication Rates By Pathogen and Treatment Group for the Primary Comparative cSSSI Studies: Pooled Analysis (MITT population)

Pathogen[a]	Daptomycin		Comparator[b]		95% CI[c]
	n/N	(%)	n/N	(%)	
Staphylococcus aureus (all)	186/299	(62.2%)	211/320	(65.9%)	(-4.0,11.4)
Staphylococcus aureus (MSSA)[d]	148/227	(65.2%)	161/237	(67.9%)	(-6.0,11.5)
Staphylococcus aureus (MRSA)[d]	15/39	(38.5%)	23/46	(50.0%)	(-9.9,33.0)
Streptococcus pyogenes	77/92	(83.7%)	74/103	(71.8%)	(-23.6,-0.1)
Streptococcus agalactiae	22/30	(73.3%)	19/39	(48.7%)	(-47.4,-1.9)
Streptococcus dysgalactiae equisimilis	9/13	(69.2%)	9/12	(75.0%)	(-30.0,41.6)
Viridans Streptococci Group	17/26	(65.4%)	28/38	(73.7%)	(-15.2,31.8)
Enterococcus faecalis (all)	25/45	(55.6%)	35/61	(57.4%)	(-17.7,21.3)
Enterococcus faecalis (VSE)[d]	23/41	(56.1%)	33/56	(58.9%)	(-17.5,23.2)

a. Only pathogens for which an indication is being sought are shown.
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
c. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
d. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.

Reviewer's comments: In the ME population, the pathogen eradication rates for daptomycin and comparator were similar for *Staphylococcus aureus* however, daptomycin was less effective (9% lower pathogen eradication rate) comparator against MRSA. In the MITT population, the pathogen eradication rate among MRSA was significantly lower (11.5%) for daptomycin versus comparator.

Overall, pathogen eradication rates of daptomycin for the treatment of *Streptococcus pyogenes* and *Streptococcus agalactiae* were significantly superior to comparators. Daptomycin had higher eradication rates in both the ME and MITT populations (9.8% and 11.9% higher, respectively) against *Streptococcus pyogenes*.

Again, daptomycin had higher eradication rates in both the ME and MITT populations (17.3% and 24.6% higher, respectively) against *Streptococcus agalactiae*. However, pathogen eradication rates of daptomycin for the treatment of viridans streptococci and *Streptococcus dysgalactiae equisimilis* were lower overall to comparators. Eradication rates in both the ME and MITT populations were lower for daptomycin versus comparators (5.7% and 8.3% lower, respectively) against viridans streptococci. However, against *Streptococcus dysgalactiae equisimilis,* the eradication rate in the ME population was 8.2% <u>higher</u> against comparator while the eradication rate in the MITT population was 5.8% <u>lower</u> for daptomycin versus comparators. The disagreement in eradication rates between the two populations is odd but may be partially explained by particularly low numbers of isolates.

Overall, pathogen eradication rates of daptomycin for the treatment of *Enterococcus faecalis*, including VSE, were similar to comparators. This was due to the observation that pathogen eradication rates of daptomycin were somewhat superior to vancomycin but somewhat inferior to that of semi-synthetic penicillins.

Clinical success rates and pathogen eradication rates of daptomycin versus comparators for the various pathogens paralleled one another with two exceptions. First, pathogen eradication rates for daptomycin versus comparators was somewhat lower for MRSA than clinical success rates. Thus it seems, daptomycin may have a similar clinical success rate for the treatment of MRSA as compared to comparators but the drug will not be as effective in eradicating the pathogen as the comparator drugs. The second exception is that daptomycin has a comparable rate of eradicating *E. faecalis* as do the comparator drugs despite the fact that the comparator drugs seem to be more successful clinically.

Overall, compared to subjects infected with a single pathogen, subjects infected with two pathogens had lower success rates (see Table 45); the clinical success rates for those subjects were similar for daptomycin (70.1%) and comparator (67.5%). The most prevalent combination of dual infecting pathogens was *S. pyogenes* and *S. aureus*, which was found in 48 subjects in each treatment group in the pooled MITT population (see Table 10-64 of the Microbiology Section). Among these subjects, the clinical success rates were higher in the daptomycin group than in comparator (81.3% vs. 68.8%, respectively); the individual pathogen eradication rates against *S. aureus* were 66.7% and 54.2%, respectively, and against *S. pyogenes,* 77.1% and 62.5%.

Table 45: Clinical Success Rates by Number of Infecting Gram-Positive Pathogens at Baseline, Primary Comparative cSSSI Studies: Pooled analysis. (MITT population)

Number of Infecting Gram-Positive Pathogens at Baseline	Daptomycin		Comparator	
	n/N	(%)	n/N	(%)
One Pathogen	250/322	(77.6)	269/342	(78.7)
Two Pathogens	68/97	(70.1)	79/117	(67.5)
Three Pathogens	2/3	(66.7)	8/8	(100.0)
All MITT Subjects	320/422	(75.8)	356/467	(76.2)

a. Using Sponsor-Defined Clinical Outcome
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.

The overall *in vitro* daptomycin susceptibility of all pathogens from the MITT populations of trials DAP-SST-9801 and DAP-SST-9901 is shown in Table 46. Overall, the two trials yielded MIC_{50} and MIC_{90} values that were within one doubling dilution. The maximum MIC values in DAP-SST-9901 for *E. faecalis* (MIC = 8 µg/ml), and *S. aureus* MRSA (MIC = 2 µg/ml) were more than one doubling dilution higher than the corresponding combined MIC_{90} values of 2 and 0.5 µg/ml, respectively.

Table 46: *In vitro* susceptibility to daptomycin of Infecting Pathogens at Baseline, Primary Comparative cSSSI Studies[a] (MITT population)

Pathogen[b]	N	Daptomycin Susceptibility (µg/mL)			
		Minimum	Maximum	MIC_{50}	MIC_{90}
Enterococcus faecalis (VSE)					
DAP-SST-9801	54			1	2
DAP-SST-9901	43			2	2
Combined	97			1	2
Staphylococcus aureus (MRSA)					
DAP-SST-9801	69			0.25	0.5
DAP-SST-9901	16			0.5	1
Combined	85			0.25	0.5
Staphylococcus aureus (MSSA)					
DAP-SST-9801	200			0.25	0.5
DAP-SST-9901	264			0.25	0.25
Combined	464			0.25	0.5
Staphylococcus aureus (total)					
DAP-SST-9801	269			0.25	0.5
DAP-SST-9901	280			0.25	0.25
Combined	549			0.25	0.5
Streptococcus agalactiae					
DAP-SST-9801	37			0.25	0.25
DAP-SST-9901	27			0.25	0.25
Combined	64			0.25	0.25
Streptococcus dysgalactiae equisimilis					
DAP-SST-9801	13			=0.03	0.06
DAP-SST-9901	10			0.06	0.06
Combined	23			0.06	0.06
Streptococcus pyogenes					
DAP-SST-9801	61			=0.03	0.06
DAP-SST-9901	114			=0.03	0.06
Combined	175			=0.03	0.06
Viridans Streptococci Group[c]					
DAP-SST-9801	29			0.5	0.5
DAP-SST-9901	28			0.5	1
Combined	57			0.5	1

a. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.
b. Only pathogens for which an indication is being sought are shown; all geographic regions combined.
c. Three isolates were not tested by the Central Lab for susceptibility to daptomycin and are not included in this analysis.

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