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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDY

NDA/BLA #:	021572
Supplement #:	55
Drug Name:	Cubicin® (Daptomycin for injection)
Indication(s):	Complicated skin and skin structure infections (cSSSI)
Applicant:	Cubist Pharmaceuticals, Inc.
Date(s):	Stamp Date: 06/30/2016 Filing Date: 09/12/2016 PDUFA Goal Date: December 15, 2016
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Keywords: Active control, blinding, clinical study, randomization

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1. EXECUTIVE SUMMARY

This supplemental NDA contains a final study report for the Post-Marketing Requirement #2864-1 of conducting a study to assess the safety, efficacy, and PK of three age dependent doses of IV daptomycin in pediatric patients aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens.

This was a Phase 4 multi-center, evaluator-blinded, randomized, comparative study conducted in the USA and India. A total of 396 patients were enrolled sequentially from the oldest age group to the youngest group and were randomized 2:1 to the daptomycin (DAP) and standard of care (SOC) groups. Treatment duration was up to 14 days and subjects could switch to oral therapy (not containing DAP) after the completion of intravenous (IV) drug administration with a clear clinical improvement. Safety was the primary endpoint and efficacy was a secondary endpoint. The primary efficacy endpoint was sponsor-defined clinical response at the Test of Cure visit (TOC, 7-14 days after the last dose of therapy), defined by the sponsor's blinded medical monitor, based on the investigator's assessment. This study design was similar to that of the two pivotal studies used for FDA's approval.

Sponsor-defined clinical successes (cure and improvement) at TOC for all subjects and by age group are summarized in the Intent-To-Treat population as follows:

	DAP	**SOC**
All	227/257 (88.3%)	114/132 (86.4%)
Age Group 1 (12 – 17 years)	70/73 (95.9%)	34/37 (91.9%)
Age Group 2 (7 – 11 years)	66/73 (90.4%)	35/38 (92.1%)
Age Group 3 (2 – 6 years)	67/81 (82.7%)	32/42 (76.2%)
Age Group 4 (1 – < 2 years)	24/30 (80.0%)	13/15 (86.7%)

The difference in clinical success proportions in sponsor-defined clinical response for all subjects overall was 1.9% and the lower limit of 95% confidence interval for the difference was greater than -6%. The efficacy and safety results for both groups were numerically close overall and by age group. There were no deaths. However, compared with the USA, higher clinical success rates and lower adverse event rates were observed in India, although baseline infection signs and symptoms were similar between the subjects from the two countries. An explanation for these differences is requested from the applicant.

The study was designed before the FDA guidance entitled "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" was released. Understandably, there are some limitations in this study. The study was only evaluator-blinded, and it was not designed as a noninferiority study with a pre-specified noninferiority margin. The clinical response was not lesion size as the FDA guidance recommends and the evaluation time was varying and much later than the FDA guidance recommended time. In addition, about 51% of subjects in each group received antibiotics 24 hours prior to the administration of study drug, which was higher than the currently recommended level of 25% by the FDA. About 63% of subjects received antibiotics within 14 days prior to the administration of study drug. The use of antibiotics within 14 days prior to the first dose of study drug and the allowance to switch to oral therapy after IV

therapy may bias the results to noninferiority. Therefore, the study design limited the interpretation of the study results. It is difficult to fully evaluate DAP's efficacy with respect to noninferiority or to attribute the treatment effect to DAP alone. Given the design and objectives of the study, we could not conclude that DAP was non-inferior to SOC, and we can only conclude that this regimen (DAP IV administration with a possible switch to oral therapy) may provide clinical efficacy results numerically similar as SOC, which provides some assurance that the DAP regimen was not much worse than SOC in pediatric patients with cSSSI. Overall and by age group, the two treatment groups had numerically similar efficacy and safety profiles. The study met the post-marketing requirement of this NDA.

2. INTRODUCTION

2.1 Overview

Daptomycin for injection was approved with an initial indication of complicated skin and skin structure infections in 2003 based on two efficacy studies in adult subjects. This submission contains a final study report for the Post Marketing Requirement (PMR) #2864-1, entitled "Conducted a multicenter, evaluator blinded, randomized comparator study designed to assess the safety, efficacy, and PK of three age dependent doses of IV daptomycin administered for up to 14 days in pediatric patients aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens" and updated labeling within the Pediatric Use section of the Prescribing Information for this product.

There is only one efficacy study included in this submission, as shown in the following table.

Table 1: List of Study Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm (Randomized)	Study Population
DAP-PEDS-07-03	Phase 4	Up to 14 days	7-14 days after last dose of study medication	DAP: 263 SOC: 133	Children aged 1 to 17 years with cSSSI caused by Gram-positive pathogens

DAP: Daptomycin for injection, SOC: Standard of care.

There is an FDA guidance document titled "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" that was finalized in 2013, after the start of the current study. This guidance document contains FDA's current thinking regarding the conduct of trials for this indication.

2.2 Data Sources

Data sources, including all material reviewed, e.g. applicant's study report and data sets analyzed, are located at \\cdsesub1\evsprod\NDA021572\0135.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data sets were of high quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This was a Phase 4, multi-center, evaluator-blinded, randomized, comparative study conducted in the USA and India. Patients between the ages of 1 and 17 years were enrolled into four age groups following a step-wise approach (from the oldest age group to the youngest age group), and randomized by age group in a 2:1 ratio to the daptomycin (DAP) group and standard of care (SOC) group. The Indian sites only enrolled subjects between the ages of 7 and 17.

Age-dependent DAP doses are as follows:

Age group	Age	DAP Dose (mg/kg)
1	12-17	5
2	7-11	7
3	2-6	9
4	1-<2	10

The study was planned to enroll patients between 3 months and 17 years. Prior to enrolling children to age group 4, a Data Monitoring Committee (DMC) reviewed available nonclinical data and recommended the lower limit for this group be one year of age. Therefore, the youngest age in this study was one year old. Enrollment of a minimum of 50 DAP subjects per groups 1-3 and 40 DAP subjects per group 4 was planned.

SOC included vancomycin, clindamycin, or penicillinase-resistant semi-synthetic penicillins (nafcillin, oxacillin, or cloxacillin). Prior to randomization, investigators were to choose which SOC an individual would receive if randomized to SOC.

Treatment included randomized IV infusion (over 30 minutes for DAP and 60 minutes for SOC) with a possible oral switch for a total treatment period of up to 14 days. The oral switch was at the investigator's discretion following completion of IV study drug administration and provided that subjects met all criteria for switching to oral therapy including clear clinical improvement. Note that since DAP is not available as an oral therapy, subjects would be switched to an alternative oral therapy.

Comment: Since the oral therapy given to DAP subjects likely contributed to the overall efficacy, a formal assessment of non-inferiority of DAP is difficult.

Subjects were to be assessed at the following study visits: On-therapy (daily), End-of-Therapy (EOT), Test-of-cure (TOC, 7-14 days after last dose of study medication).

This study was evaluator-blinded. One physician at each site was designated the blinded evaluator. The evaluator's responsibilities are described as follows:

1. Determined the relationship of adverse events (AEs) to study drug.
2. Assessed signs and symptoms of primary site of skin infection throughout the study.

3. Decided on duration of treatment with IV study medication (whenever possible). Decided if IV study medication should have been discontinued based on subject's clinical response.
4. Decided on switch to an oral antibiotic (whenever possible).
5. Determined clinical response by comparing the subject's signs and symptoms of primary site of skin infection at the EOT and TOC Visits to those recorded at study baseline.

The main inclusion criteria were as follows.

1. Skin and skin structure infections of a complicated nature known or suspected to be caused by Gram-positive pathogen(s) that required IV antibiotic treatment. Complicated infections were defined as infections that either involved deep soft tissue or required significant surgical intervention (eg, infected ulcers, burns, and major abscesses) or infections in which the subject had a significant underlying disease state that complicated the response to treatment. For infections that did not meet this definition, but otherwise appeared appropriate for inclusion, the investigator discussed with the Medical Monitor.
2. At least three of the following clinical signs and symptoms associated with the cSSSI:
    a. Pain,
    b. Tenderness to palpitation,
    c. Temperature >37.5°C (99.5°F) oral or >38°C (100.4°F) rectal, forehead, or aural,
    d. White blood count (WBC) >12,000/mm^3 or ≥10% bands,
    e. Swelling and/or induration,
    f. Erythema (>1 cm beyond edge of wound or abscess),
    g. Pus formation.

Subjects may have received antibacterial therapy prior to enrollment into the trial; however, previous systemic antimicrobial therapy exceeding 24 hours during the 48 hours prior to the first dose of study drug was an exclusions criterion unless it was determine that subject's pathogen was not sensitive to the antibacterial therapy. All antibacterial therapy received within 14 days prior to the first dose was reported in the case report form. Additionally, subjects may have received adjunctive therapy of aztreonam and/or metronidazole for Gram-negative pathogens.

Comment: The percentages of subjects receiving antibacterials for systemic use and/or antibiotics and chemotherapy for dermatological use within 14 days prior to the first dose of study drug were 64.2% (165/257) and 61.4% (81/132) in the DAP and SOC groups, respectively. Antibacterial therapy prior to enrollment into the trial may impact the ability to fully assess the efficacy of DAP, as that therapy likely contributed to the subjects' outcomes.

Primary Endpoint

The study report states that the primary endpoint was related to safety, though no specific primary endpoint was defined. The primary objective was to assess the age-dependent doses of daptomycin IV compared to a standard of care.

Secondary Endpoints

Efficacy was a secondary endpoint. The sponsor-defined clinical outcome at TOC was the primary efficacy endpoint, which was determined by the sponsor's blinded medical monitor, based on the investigator's assessment. Additional endpoints included a blinded evaluator's assessment of clinical response at EOT and TOC and a subject-level microbiological response at TOC.

Sponsor-Defined Clinical Outcome

This outcome was based on the investigator's assessment at EOT and TOC. Subjects were deemed a failure if they met one or more of the following criteria:

- were judged a failure by the investigator at any time up to and including the TOC evaluation; or
- received potentially effective non-study antibiotics for lack of efficacy; or
- had the primary site of infection surgically removed.

Subjects were considered "Non-evaluable" (also referred to as "Unable to evaluate") if they were judged to be "Cure" or "Improved" by the investigator at the EOT evaluation but are missing or non-evaluable at the TOC evaluation.

Subjects who, following blinded review of the data, were not judged by the sponsor to be a failure or non-evaluable were considered to be a success.

Blinded Evaluator's Clinical Assessments

Post-therapy clinical response was determined by comparing the subject's signs and symptoms at the EOT and TOC visits to those recorded at baseline as follows:

- **Cure**: Resolution of clinically significant signs and symptoms associated with the skin infection present at study baseline.
- **Improved**: Partial resolution of clinical signs and symptoms of the skin infection.
- **Failure**: Inadequate clinical response to therapy. NOTE: if it was determined that the primary site of infection required additional antibiotic treatment, the Assessment of Clinical Response had to be a "failure."
- **Unable to Evaluate**: Unable to determine response because subject was lost to follow-up.

For the outcomes of discontinued subjects, an "Improved" status was assigned if treatment was more than 3 days and the subject's infection was clearly resolving. Subjects who discontinued study therapy within 3 days were considered as "unable to evaluate" unless otherwise deemed a clinical failure.

At EOT and TOC, "Cure" and "Improved" were considered satisfactory (success) clinical responses. Any subjects who still required further antibiotic therapy at TOC was considered a "Failure".

Subject-level microbiological response

Each subject's skin infection due to one or more Gram-positive pathogens was assigned a microbiological response.

- **Microbiologic Success:** All baseline infecting pathogens were eradicated or presumed eradicated and no superinfecting pathogen(s) (Gram-positive) were isolated post therapy.

- **Microbiologic Failure:** Presence of a persisting pathogen or a superinfecting pathogen (Gram-positive) post therapy (EOT through TOC).

- **Microbiologic Non-evaluable:** All baseline infecting pathogens had a pathogen-level microbiological response of non-evaluable.

Baseline infecting pathogen was Gram-positive organism(s) isolated from the primary infection site and considered a cSSSI pathogen by the medical monitor.

3.2.2 Statistical Methodologies

Analysis Populations

***Efficacy populations*:** Efficacy was analyzed by the randomized treatment group (overall and by age group) in four efficacy populations:

- Intent-to-Treat (ITT) – all randomized subjects who received any dose of the study drug.
- Modified Intent-to-Treat (MITT) – subjects in the ITT population who have a Gram-positive pathogen cultured at baseline.
- Clinically Evaluable (CE) – subpopulation of the ITT subjects who meet the following criteria:
    - Met the clinical criteria for the study infection (confirmed cSSSI);
    - Received the correct study drug, as randomized, at the correct dose;
    - Received ≥3 days of study medication (IV and oral combined) or < 3 days of study medication and evaluated as "failure";
    - Had the necessary clinical evaluations performed at TOC and were not evaluated as "Unable to Evaluate";
    - Did not receive potentially non-study antibiotics; and
    - Did not have a curative surgical procedure to remove the primary site of infection.
- Microbiologically Evaluable (ME) – CE subjects who had a Gram-positive pathogen culture at baseline.

In the protocol, no analysis population was specified as the population for the primary efficacy analysis. Efficacy was analyzed in these four populations.

Comment: The CE and ME populations excluded subjects based on post-baseline information that might be affected by study treatment. Therefore, this review focuses on the ITT and MITT populations.

Comment: Since the study was not fully blinded and decision to take randomized study medication could be related to which therapy a subject was assigned, we do not believe that the

ITT population should exclude subjects not receiving study medication. We conducted a sensitivity analysis to assess the impact of this exclusion.

Safety Population: The safety population included all subjects who received any dose of study medication and for whom at least 1 post-dose safety evaluation had been completed. Subjects were analyzed according to actual treatment received and age group.

Analysis Methods for Efficacy Primary Endpoint and Secondary Endpoints

Differences in clinical success rates and microbiological eradication rates between the DAP and SOC treatment groups within age groups and for the total were presented in the study report. A normal approximation 95% confidence interval (CI) (for age groups 1, 2, 3, and total) and an exact 95% CI (for age group 4) were constructed around the differences between the treatment groups (DAP minus SOC). Exact 95% CIs may have been provided for certain subgroup analyses, regardless of age group. The study was not powered for the test of non-inferiority for the primary or the secondary endpoints.

Comment: The FDA guidance on Acute Bacterial Skin and Skin Structure Infections makes recommendations regarding the amount of prior antibacterial therapy and discusses the timing of the primary efficacy endpoint. The guidance states that prior antibacterial therapy should be limited because it could affect the outcome of the subject and possibly obscure potential treatment differences between test drug and control. The guidance recommends that prior antibacterial therapy be limited to 25% of subjects receiving a single dose of prior therapy in the 24 hours prior to enrollment. As stated above, over 60% of subjects received some prior antibacterial therapy.

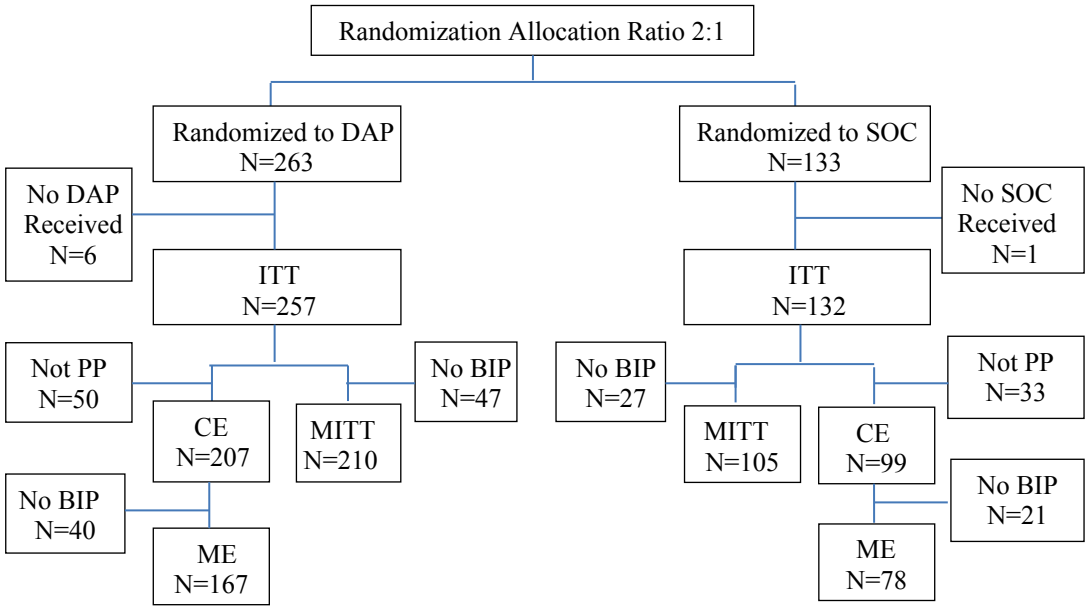
The guidance recommends that the primary efficacy endpoint be assessed early at 48 to 72 hours after start of treatment and should be based on lesion size. The reason for this is that the treatment effect is greater at this point making non-inferiority assessments more informative. The current study did not measure lesion size.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition and Demographic Characteristics

The first subject was enrolled on 9/3/2008, and the last subject was enrolled on 9/11/2013. The following figure shows the flow chart of this study. The following table shows a summary of analysis populations. A total of 396 subjects were randomized to the two groups (263 on DAP, and 133 on SOC). Among those randomized, 6 subjects and 1 subject in the DAP and SOC group, respectively, did not receive study drug. One subject in Age Group 1 was randomized to the DAP group but treated with SOC and included in the DAP group per the ITT principle for efficacy. There were 257 and 132 subjects included in the ITT population in the DAP and SOC groups, respectively.

Figure 1. Patient Disposition for Efficacy Analyses



Source: Figure 11-1
BIP: Baseline Infecting Pathogen. CE: Clinically Evaluable Population. ME: Microbiologically Evaluable

Table 2. Summary of Analysis Populations

Population	DAP	SOC
Randomized, n	263	133
Safety Population as dosed	256	133
ITT Population	257	132
MITT Population, n (%)	210 (81.7)	105 (79.5)
CE Population, n (%)	207 (80.5)	99 (75.0)
ME Population, n (%)	167 (80.7)	78 (78.8)

Table 3. Number of Subjects by Country and Age Group (ITT Population)

Age group	DAP N=257	SOC N=132
Age Group 1 (12 – 17 years)	73	37
USA	32 (43.8)	16 (43.2)
India	41 (56.2)	21 (56.8)
Age Group 2 (7 – 11 years)	73	38
USA	49 (67.1)	25 (65.8)
India	24 (32.9)	13 (34.2)
Age Group 3 (2 – 6 years)	81	42
USA	81 (100%)	42 (100%)
India	-	-
Age Group 4 (1 to less than 2 years)	30	15
USA	30 (100%)	15 (100%)
India	-	-

There were 23 sites in the USA and 7 sites in India.

As designed this study enrolled subjects into four age groups with planned sample sizes of a minimum of 50 subjects in age groups 1 – 3 and 40 subjects in age group 4. Sites in India only enrolled subjects into age groups 1 and 2. Table 3 contains information on enrollment by age and country.

The following table shows a summary of demographics, baseline characteristics, and baseline pathogens for all subjects in the ITT population. The two groups were well balanced, except for race. There were a higher proportion of Black or African American and a lower proportion of White in the DAP group. This information by age group is included in the appendix. No concerning imbalances were seen between the treatment groups by these baseline characteristics.

Table 4. Summary of Demographics, Baseline Characteristics, and Baseline Pathogens for All Subjects (ITT population)

	DAP N=257	**SOC N=132**
Age (yrs)		
Mean (SD)	8.2 (5.16)	8.1 (5.10)
Median	7.6	7.65
Range	1.1-17.9	1.1-17.7
Sex n (%)		
Male	131 (51.0)	70 (53.0)
Female	126 (49.0)	62 (47.0)
Race n (%)		
Asian	83 (32.3)	42 (31.8)
Black or African American	65 (25.3)	25 (18.9)
White	104 (40.5)	61 (46.2)
Native Hawaiian or Other Pacific Islander	0	2 (1.5)
Other	5 (1.9)	2 (1.5)
Height (in percentile)		
N	254	131
Mean (SD)	45.93 (36.52)	42.89 (34.86)
Median	45.5	40.3
Range	0.01, 99.99	0.01, 99.99
Weight (in percentile)		
Mean (SD)	48.12 (35.98)	46.91 (35.67)
Median	51.7	50
Range	0.01, 99.90	0.01, 99.90
Body Mass Index		
N	254	131
Mean (SD)	18.11 (4.94)	18.28 (4.82)
Median	17	16.9

	DAP N=257	SOC N=132
Range	8.7, 53.3	10.3, 36.3
Pathogens		
Any Gram Negative Pathogen	10 (3.9)	3 (2.3)
Gram Positive Baseline Infecting Pathogen[a] (MITT)	210 (81.7)	105 (79.5)
MRSA	94 (36.6)	44 (33.3)
MSSA	78 (30.4)	41 (31.1)
S. pyogenes	19 (7.4)	7 (5.3)
Other[b]	19 (7.4)	13 (9.8)
Investigator's Primary Diagnosis: Type of cSSSI		
Major Abscess	136 (52.9)	72 (54.5)
Wound Infection	21 (8.2)	9 (6.8)
Complicated Cellulitis	95 (37.0)	49 (37.1)
Diabetic Ulcer Infection	0	0
Infected Ulcer Other than Diabetic	3 (1.2)	0
Other	2 (0.8)	2 (1.5)
Prior Antibiotic Therapy		
Use of antibiotics within 14 Days prior to the first Dose of Study Drug	165 (64.2)	81 (61.4)
Use of antibiotics within 1 Day prior to the first Dose of Study Drug	132 (51.4)	67 (50.8)

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; cSSSI: complicated skin and skin structure infections

[a] Subjects counted in one row. Subjects counted for specific pathogens had only that pathogen isolated.

[b]Other contains subjects with multiple pathogens or the following *Bacillus cereus and Micrococcus luteus, Enterococcus facecalis (VSE), Peptostreptococcus app.,Staphylococcus hominis, Staphylococcus lugdunensis, Staphylococcus constellatus*, etc.

Source: adapted from Table 11-2

As discussed above, investigators were allowed to switch subjects to non-study oral therapy. Exposure to study medication is summarized in the following table. Subjects received IV therapy for an average of 3.6 to 4.1 days (median 3 days) with a range of 1 to 14 days. Subjects received total treatment (IV and oral) on average for 11.9-12.6 days (median 12) with a range of 1 to 35 days. A higher proportion of subjects in the DAP arm received IV study medication for <3 days. However, the total study drug administration days were comparable between both treatment groups.

Comment: Note that the sponsor reports the efficacy analysis stratified by duration of IV therapy. We do not agree with this analysis as this duration of therapy grouping is a post-treatment variable defining subgroups of subjects that could be related to the effect of the randomized treatment. For this reason, this review does not report this analysis.

Comment: The study did not define a fixed evaluation time from randomization, but instead assessed subjects based on an amount of time from the end of treatment which could vary from subject to subject and could depend on their outcome. The planned total treatment duration was

3 to 14 days. The planned TOC visit was 7-14 days after the last dose of therapy. This means that the TOC assessment could occur anytime between Day 10 to Day 28. The problem or limitation with the non-fixed evaluation time used in the study is that subjects' evaluation time could vary between the treatment groups. If a drug was less effective, the treatment duration might be longer and the visits might occur later, such that the treatment groups would not be comparable. For this reason, we looked at the timing of these visits.

Table 5. Exposure to IV and Oral Study Medication (ITT Population)

	DAP N=257 n (%)	SOC N=132 n (%)
IV Study Drug Administration		
Number of IV Dosing Days		
Mean (SD)	3.6 (2.36)	4.1 (2.49)
Median	3.0	3.0
Range	1-10	1-14
Received IV study medication for < 3 days	121 (47.8)	46 (34.9)
Received IV study medication for 3-7 days	118 (45.9)	72 (54.6)
Received IV study medication for > 7 days	18 (7.0)	14 (10.6)
Oral Switch		
Converted to Oral Study Drug	245 (95.3)	124 (93.9)
Not Converted to Oral Study Drug	12 (4.7)	8 (6.1)
Total Study Drug Administration (IV and Oral)		
Number of Total Dosing Days		
N	251	129
Mean (SD)	12.0 (4.03)	12.5 (5.31)
Median	12.0	12.0
Range	1-31	1-35
Unknown	6 (2.3)	3 (2.3)
Received study medication for < 3 days	11 (4.3)	6 (4.6)
Received study medication for 3-7 days	12 (4.7)	7 (5.3)
Received study medication for > 7 days	228 (88.7)	118 (87.9)

Source: Adapted from Table 12-1

Table 6 contains a summary of the day of the TOC visit for DAP and SOC subjects. One subject in the DAP arm had missing value in evaluation time and missing outcome. The means of evaluation time were 21.5 and 22.3 days, with a range from 1 or 2 to 39 days in the DAP and SOC groups, respectively. Based on the study design, it is not possible to conduct an analysis of clinical outcomes at a fixed time-point after the start of treatment. Fortunately, the evaluation times had a similar distribution between the two treatment groups.

Table 6. Study Day of Evaluation at TOC for All Available Subjects

	DAP N=256	SOC N=131
N	251	126
Mean (SD)	21.5 (5.32)	22.3 (5.37)
Median	21	21
Range	1, 39	2, 39

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Efficacy Analysis

We summarized the sponsor-defined clinical outcomes (primary efficacy endpoints) and blinded evaluator's assessment of clinical response, and microbiological response in this section.

Sponsor-defined Clinical Outcome at TOC

The sponsor-defined outcome in the ITT population is summarized in the following table. The percentages of clinical success (cure or improvement) were similar (88.3% versus 86.4%), with a difference of 2.0% (95% CI: [-5.1%, 9.1%]), calculated by the sponsor.

Table **8** contains the results by age group.

Table 7. Summary of Sponsor-Defined Clinical Outcome at TOC (ITT Population)

Clinical Outcome	**DAP N=257**	**SOC N=132**
Clinical Success (Cure or Improvement)	227 (88.3)	114 (86.4)
Cure	*220 (85.6)*	*113 (85.6)*
Improvement	*7 (2.7)*	*1 (0.8)*
Clinical Failure	3 (1.2)	1 (0.8)
Unable to Evaluate	27 (10.5)	17 (12.9)
Difference in Success Rates (95% CI)	2.0 (-5.1, 9.1)	

Source: Table 11-4. The method of normal approximation of binomial distribution was used for confidence interval by the sponsor.

Difference in success rates [95% CI] from Mantel-Haenszel method stratified by age group was -0.02% [-7.28%, 7.25%], calculated by the reviewer.

Table 8. Summary of Sponsor-Defined Clinical Outcome at TOC by Age Group (ITT Population)

Clinical Outcome	**Age Group 1 (12 – 17 years)**		**Age Group 2 (7 – 11 years)**		**Age Group 3 (2 – 6 years)**		**Age Group 4 (1 - < 2 years)**	
	DAP N=73 n (%)	**SOC N=37 n (%)**	**DAP N=73 n (%)**	**SOC N=38 n (%)**	**DAP N=81 n (%)**	**SOC N=42 n (%)**	**DAP N=30 n(%)**	**DAP N=15 n(%)**
Clinical Success	70 (95.9)	34(91.9)	66 (90.4)	35 (92.1)	67 (82.7)	32 (76.2)	24 (80.0)	13 (86.7)
Cure	*67 (91.8)*	*34(91.9)*	*64 (87.7)*	*35 (92.1)*	*65 (80.3)*	*32 (76.2)*	*24 (80.0)*	*12 (80.0)*
Improvement	*3 (4.1)*	*0*	*2 (2.7)*	*0*	*2 (2.5)*	*0*	*0*	*1 (6.7)*
Clinical Failure	0	1 (2.7)	2 (2.7)	0	1 (1.2)	0	0	0
Unable to Evaluate	3 (4.1)	2 (5.4)	5 (6.9)	3 (7.9)	13 (16.1)	10 (23.8)	6 (20.0)	2 (13.3)
Difference in Success Rates (95% CI)	4.0 (-6.0, 14.0) (-5.6, 17.9)*		-1.7 (-12.6, 9.2) (-12.6, 12.1)*		6.6 (-8.7, 21.9) (-8.2, 23.5)*		-6.7 (-38.0, 25.5)	

The method of normal approximation of binomial distribution was used for CI by the sponsor for the first three age groups and an exact 95% CI was constructed for age group 4. *Exact 95% CI calculated by the reviewer.

Source: Table 11-4.

The clinical success proportions in the MITT, CE, and ME populations were similar with no statistically significant differences, as the following table shows.

Table 9. Summary of Sponsor-Defined Clinical Outcome at TOC in the MITT, CE, and ME populations

	MITT		CE		ME	
Clinical Outcome	**DAP N=210 n (%)**	**SOC N=105 n (%)**	**DAP N=207 n (%)**	**SOC N=99 n (%)**	**DAP N=167 n (%)**	**SOC N=78 n (%)**
Clinical Success (Cure or Improvement)	186 (88.6)	92 (87.6)	204 (98.6)	99 (100.0)	164 (98.2)	78 (100.0)
Clinical Failure	2 (1.0)	1 (1.0)	2 (1.0)	0	2 (1.2)	0
Unable to Evaluate	22 (10.5)	12 (11.4)	1 (0.5)	0	1 (0.6)	0
Difference in Success Rates (95% CI)	0.9 (-6.7, 8.5)		-1.5 (-3.2, 0.2)		-1.8 (-3.8, 0.2)	

Source: Table 11-5

Comment: As can be seen in the table, the CE and ME analysis populations contain subjects with an outcome of unable to evaluate. It appears that the definition of the CE and the ME populations used the investigator's assessment rather than the sponsor's assessment to determine exclusions based on having an outcome of "unable to evaluate."

Blinded Evaluator's Assessment of Clinical Response at EOT and TOC

The following table summarizes the blinded evaluator's assessment of clinical response at EOT in the ITT population. Clinical success percentages were 92.6% and 90% in the DAP and SOC groups, respectively.

Table 10. Summary of Blinded Evaluator's Assessment of Clinical Response at EOT (ITT population)

	DAP N=257 n (%)	**SOC N=132 n (%)**
Clinical Success	237 (92.6)	117 (90.0)
Cure	215 (84.0)	107 (82.3)
Improvement	22 (8.6)	10 (7.7)
Clinical Failure	3 (1.2)	2 (1.5)
Unable to Evaluate	17 (6.6)	13 (8.5)

The blinded evaluator's assessment of clinical response at TOC in the ITT population is listed in Table 11 in total and by age group. The clinical success percentages in the two treatment groups were similar (91% vs 87%). The difference in clinical success proportions was not statistically significant. A higher failure rate in the SOC group was mainly due to a higher percentage of non-evaluable outcomes. Within each age group, the clinical success proportions were comparable between the DAP and SOC groups. It is noticed that the success proportions in Age Groups 3 and 4 were relatively low (ranging from 78.1% to 86.7%) compared to the older age groups.

Table 11. Summary of Blinded Evaluator's Assessment of Clinical Response at TOC (ITT population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
Clinical Outcome	**DAP N=73 n (%)**	**SOC N=37 n (%)**	**DAP N=73 n (%)**	**SOC N=38 n (%)**	**DAP N=81 n (%)**	**SOC N=42 n (%)**	**DAP N=30 n (%)**	**SOC N=15 n (%)**	**DAP N=257 n (%)**	**SOC N=132 n (%)**
N	73	37	73	38	80*	41*	30	15	256*	131*
Clinical Success	71 (97.3)	34 (91.9)	68 (93.2)	35 (92.1)	69 (86.3)	32 (78.1)	25 (83.3)	13 (86.7)	233 (91.0)	114 (87.0)
Cure	*69 (94.5)*	*34 (91.9)*	*66 (90.4)*	*35 (92.1)*	*67 (83.8)*	*31 (75.6)*	*25 (83.3)*	*13 (86.7)*	*227 (88.7)*	*113 (86.3)*
Improved	*2 (2.7)*	*0*	*2 (2.7)*	*0*	*2 (2.5)*	*1 (2.4)*	*0*	*0*	*6 (2.3)*	*1 (0.8)*
Clinical Failure	0	1 (2.7)	1 (1.4)	0	0	0	0	0	1 (0.4)	1 (0.8)
Unable to Evaluate	2 (2.7)	2 (5.4)	4 (5.5)	3 (7.9)	11 (13.8)	9 (22.0)	5 (16.7)	2 (13.3)	22 (8.6)	16 (12.2)
Difference in Success Rates (95% CI)	5.4 (-4.2, 14.9)		1.0 (-9.3, 11.4)		8.2 (-6.6, 23.0)		-3.3 (-34.9, 28.7)		4.0 (-2.7, 10.7)	

Source: Table 11-6.

*One subject in each group (#3013 and #3027) had a missing response at TOC. The reason that they were not considered as "unable to evaluate" by the sponsor was not clear.

The blinded evaluator's assessment results of clinical response at TOC in the MITT, CE, and ME populations are listed in Table 12. The clinical success proportions in each analysis population were comparable between the two treatment groups. The clinical success proportions were higher in the CE and ME populations than in the MITT population because unable-to-evaluate subjects were excluded from the analyses.

Table 12. Summary of Blinded Evaluator's Assessment of Clinical Response at TOC (MITT, CE, and ME populations)

	MITT		CE		ME	
Clinical Outcome	**DAP N=210 n (%)**	**SOC N=105 n (%)**	**DAP N=207 n (%)**	**SOC N=99 n (%)**	**DAP N=167 n (%)**	SOC **N=78 n (%)**
N in analysis	**209**	**105**	**207**	**99**	**167**	**78**
Clinical Success	190 (90.9)	91 (86.7)	206 (99.5)	99 (100.0)	166 (99.4)	78 (100.0)
Cure	*186 (89.0)*	*91 (86.7)*	*202 (97.6)*	*99 (100.0)*	*163 (97.6)*	*0*
Improvement	*4 (1.9)*	*0*	*4 (1.9)*	*0*	*3 (1.8)*	*0*
Clinical Failure	1 (0.5)	1 (1.0)	1 (0.5)	0	1 (0.6)	0
Unable to evaluable	18 (8.6)	13 (12.4)	0	0	0	0
Difference in Success Proportions (95% CI)	4.2 (-3.3, 11.8)		-0.5 (-1.4, 0.5)		-0.6 (-1.8, 0.6)	

Source: Table 11-7

Microbiologic Response at TOC

Subject-level microbiologic response is summarized in the following table. The success proportions were similar and there was no statistically significant difference in success proportions between the two treatment groups.

Table 13. Summary of Subject-Level Microbiologic Response at TOC (MITT population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
Microbiologic Outcome	DAP N=66	SOC N=31	DAP N=58	SOC N=31	DAP N=59	SOC N=32	DAP N=27	SOC N=11	DAP N=210	SOC N=105
Microbiologic Success	66 (100)	30 (96.8)	54 (93.1)	29 (93.6)	50 (84.8)	24 (75.0)	20 (74.1)	10 (90.9)	190 (90.5)	93 (88.6)
Microbiologic Failure	0	0	1 (1.7)	0	0	0	1 (3.7)	0	2 (1.0)	0
Microbiologic Non-Evaluable	0	1 (3.2)	3 (5.2)	2 (6.5)	9 (15.3)	8 (25.0)	6 (22.2)	1 (9.1)	18 (8.6)	12 (11.4)
Difference in Success Proportions (95% CI)	3.3 (-3.0, 9.6)		-0.4 (-11.3, 10.5)		9.7 (-7.9, 27.3)		-16.8 (-49.3, 18.6)		1.9 (-5.4, 9.2)	

Source: Table 11-8

The following table shows a summary of pathogen-level microbiological outcome at TOC by selected baseline pathogens in the MITT population by the sponsor. The success proportions in patients with MRSA or MSSA were close between the two treatment groups. In patients infected with *S. pyogenes*, DAP had a significantly higher cure rate compared with SOC. This significance should be viewed with caution given the lack of type I error control.

Table 14. Summary of Pathogen-Level Microbiological Outcome at TOC by Selected Baseline Pathogens (MITT Population)

	***Staphylococcus aureus* (MRSA)**		***Staphylococcus aureus* (MSSA)**		***Streptococcus pyogenes***	
	DAP n (%)	SOC n (%)	DAP n (%)	SOC n (%)	DAP n (%)	SOC n (%)
N in the Analysis	97	46	85	49	24	10
Microbiological Success	82 (84.5)	41 (89.1)	81 (95.3)	45 (91.8)	24 (100.0)	7 (70.0)
Microbiologic Failure	0	0	1 (1.18)	0	0	0
Microbiologic Non-Evaluable	15 (15.46)	5 (10.87)	3 (3.53)	4 (8.16)	0	3 (30.00)
Difference in Success Proportions (95% CI)	-4.6 (-16.1, 6.9)		3.4 (-5.5, 12.3)		30.0 (1.6, 58.4)	

In this table the sample sizes are larger than those in the baseline characteristics table because this table includes subjects with two or more types of pathogens (such as MRSA and other pathogen).
Note: Based on the data set provided, the DAP success and failures in the MSSA group were 80 and 2, respectively, leading to a difference (exact 95% confidence interval) in success proportions of 2.3% [-7.0%, 13.9%].
Source: Table 11-9.

Sponsor's Main Efficacy Conclusions

The sponsor concluded that the clinical success rates of the sponsor-defined outcome and blinded evaluator-defined outcome were high at TOC in both treatment groups and the results were consistent in different analysis populations. The success rates of microbiological outcome were also high at TOC in both treatment groups for commonly isolated pathogens at the primary infection sites.

3.2.4.2 Reviewer's Analysis Results

The reviewer assessed the sponsor's analysis methods used for the primary and secondary efficacy endpoints and has replicated or almost replicated the efficacy results included in this review.

As discussed in the previous sections, there were two endpoints that measured clinical response based on either the investigator's or blinded evaluator's assessments. The agreement between the two assessments was more than 96.4%. There were more disagreements with the DAP subjects than the SOC subjects, but most of the changes based on the sponsor-defined analysis downgraded subjects considered cures based on the blinded evaluator's assessment. These discrepancies were minimal and would not affect the overall conclusions of the study.

As discussed above, subjects who did not take any dose of study drug were excluded from the ITT population. Since this was an open-label study (only evaluator blinded), the exclusion of subjects based on taking assigned study drug may introduce bias into the study results. Therefore, the reviewer conducted the following sensitivity analyses by assigning these subjects as failures. As noted in Figure 1, there were 6 DAP subjects and 1 SOC subject who did not receive randomized treatment. There was no baseline infecting pathogen for these subjects and the reason for discontinuation of study was "subject's decision" or "other". These subjects stayed in the study for 1-2 days after signing the informed consent form. Including these excluded subjects, the clinical success rates were 86.3% (227/263) and 85.7% (114/133), with a difference of 0.6% (95% CI [-7.2%, 8.4%], using a normal approximation method).

Subjects could switch to oral therapy if there was a clear clinical improvement, and the pathogen was susceptible to an oral agent. In the Case Report Form, there was a variable which collected the investigator's assessment of this clear clinical improvement. Based on this variable, the proportions of subjects for whom the investigator's assessment was clear clinical improvement were similar (95.3% (244/256) and 94.0% (125/133)). However, it was not apparent how this variable really measured the clinical response because no definition for "clear clinical improvement" was specified.

3.3 Evaluation of Safety

Using the submitted data sets, the reviewer can duplicate the following safety results from the applicant. The safety analysis method is acceptable. For a full assessment of safety, please see the medical officer's review.

3.3.1 Summary of Adverse Events

The numbers of subjects with any treatment-emergent AEs are listed in the following tables. Table 15 reports the results across all age groups and by age groups. Similar results were seen across the two arms. Given the small numbers by age group, it is difficult to make any conclusions regarding the comparability of the treatment arms.

Table 15. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

All Subjects

Exposure Parameter	DAP N=256 n (%)	SOC (N=133) n (%)
At least one TEAE	98 (38.3)	48 (36.1)
At least one TESAE	6 (2.3)	3 (2.3)
TEAE by severity		
Mild	71 (27.7)	30 (22.6)
Moderate	21 (8.2)	15 (11.3)
Severe	6 (2.3)	3 (2.3)

By Age Group

	Age Group 1		Age Group 2		Age Group 3		Age Group 4	
Exposure Parameter	DAP N=72 n (%)	SOC N=38 n (%)	DAP N=73 n (%)	SOC N=38 n (%)	DAP N=81 n (%)	SOC N=42 n (%)	DAP N=30 n (%)	SOC N=15 n (%)
At least one TEAE	26 (36.1)	14 (36.8)	17 (23.3)	7 (18.4)	41 (50.6)	16 (38.1)	14(46.7)	11(73.3)
At least one TESAE	3 (4.2)	1 (2.6)	1 (1.4)	1 (2.6)	2 (2.5)	1 (2.4)	0	0
TEAE by severity								
Mild	16 (22.2)	7 (18.4)	13 (17.8)	5 (13.2)	35 (43.2)	9 (21.4)	7 (23.3)	11(73.3)
Moderate	8 (11.1)	5 (13.2)	2 (2.7)	2 (5.3)	5 (6.2)	7 (16.7)	6 (20.0)	2 (13.3)
Severe	2 (2.8)	2 (5.3)	2 (2.7)	0 (0.0)	1 (1.2)	0 (0.0)	1 (3.3)	1 (6.7)

Treatment-emergent AEs (TEAEs) that occurred from the time of first dose of study drug through the last study evaluation or pre-existing AEs that were aggravated in severity or frequency during the dosing period.
TESAE: Treatment-emergent serious adverse event
Subjects were only counted once for the AE with the highest relationship to study drug.
Subjects were only counted once for the AE with the highest severity.
Source: Table 12-2 and Table 14.3.1.1

Since DAP is an IV only drug, the following table provides a summary of AE during IV therapy (Safety Population). No concerning differences were seen.

Table 16. Summary of AE during IV Therapy (Safety Population)

Exposure Parameter	DAP N=256 n (%)	SOC N=133 n (%)
At least one TEAE	37 (14.5)	21 (15.8)
At least one TESAE	0	2 (1.5)
TEAE by severity		
Mild	29 (11.3)	11 (8.3)
Moderate	8 (3.1)	8 (6.0)
Severe	0	2 (1.5)

3.3.2 Frequent Adverse Events by Body System or Organ Class

Treatment-emergent adverse events by system organ class and preferred term reported in 2 or more subjects in either treatment group (safety population) are presented in the following table. There were no noticeable differences between the two group, except for infections and

infestations, where DAP had a lower proportion. Analyses by age group were limited by the small sample sizes; however, no overly concerning results were seen (analyses not shown).

Table 17. Overall Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported in 2 or more Subjects in Either Treatment Group (Safety Population)

System Organ Class Preferred Term	DAP N=256 n (%)	SOC N=133 n (%)
Subjects with at least one TEAE	98 (38.3)	48 (36.1)
Gastrointestinal disorders	30 (11.7)	14 (10.5)
Diarrhea	18 (7.0)	7 (5.3)
Vomiting	7 (2.7)	1 (0.8)
Abdominal pain	5 (2.0)	0
Nausea	3 (1.2)	1 (0.8)
Abdominal pain upper	2 (0.8)	0
Cheilitis	0	2 (1.5)
Lip swelling	0	2 (1.5)
Skin and subcutaneous tissue disorders	23 (9.0)	12 (9.0)
Pruritus	8 (3.1)	2 (1.5)
Dermatitis diaper	2 (0.8)	3 (2.3)
Erythema	2 (0.8)	3 (2.3)
Rash	1 (0.4)	4 (3.0)
Rash papular	3 (1.2)	1 (0.8)
Blister	2 (0.8)	0
Urticaria	0	2 (1.5)
Infections and infestations	14 (5.5)	15 (11.3)
Cellulitis	4 (1.6)	0
Upper respiratory tract infection	0	3 (2.3)
General disorders and administration site conditions	20 (7.8)	8 (6.0)
Pyrexia	10 (3.9)	4 (3.0)
Infusion site pain	3 (1.2)	2 (1.5)
Infusion site extravasation	1 (0.4)	2 (1.5)
Chest pain	2 (0.8)	0
Investigations	19 (7.4)	11 (8.3)
Blood creatine phosphokinase increased	14 (5.5)	7 (5.3)
Blood phosphorus increased	2 (0.8)	1 (0.8)
Aspartate aminotransferase increased	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders	12 (4.7)	5 (3.8)
Rhinorrhoea	4 (1.6)	1 (0.8)
Nervous system disorders	9 (3.5)	4 (3.0)
Headache	7 (2.7)	3 (2.3)
Dizziness	2 (0.8)	0
Injury, poisoning and procedural complications	8 (3.1)	3 (2.3)
Arthropod bite	3 (1.2)	0
Excoriation	3 (1.2)	0
Mouth injury	1 (0.4)	2 (1.5)
Metabolism and nutrition disorders	4 (1.6)	3 (2.3)
Hyperphosphataemia	3 (1.2)	0
Musculoskeletal and connective tissue disorders	6 (2.3)	1 (0.8)
Arthralgia	2 (0.8)	0
Myalgia	2 (0.8)	0
Reproductive system and breast disorders	3 (1.2)	0
Genital lesion	2 (0.8)	0

Treatment-emergent AEs (TEAEs) that occurred from the time of first dose of study drug through the last study evaluation or pre-existing AEs that were aggravated in severity or frequency during the dosing period.
Source: Table 12-3

The following table shows a summary of severe treatment-emergent adverse events in the safety population. Only 2.3% of subjects in each group had at least one severe treatment-emergent adverse event. Analyses by age groups were limited by the small sample sizes; however, no overly concerning results were seen (analyses not shown).

Table 18. Overall Summary of Severe Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term	DAP N=256 n (%)	SOC N=133 n (%)
Subjects with at least one severe TEAE	6 (2.3)	3 (2.3)
Gastrointestinal disorders	1 (0.4)	0
Abdominal pain	1 (0.4)	0
General disorders and administration site conditions	1 (0.4)	1 (0.8)
Pyrexia	1 (0.4)	1 (0.8)
Infections and infestations	1 (0.4)	1 (0.8)
Abscess	1 (0.4)	0
Toxic shock syndrome	0	1 (0.8)
Investigations	1 (0.4)	1 (0.8)
Blood creatine phosphokinase increased	1 (0.4)	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Myopathy	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0
Status asthmaticus	1 (0.4)	0
Skin and subcutaneous tissue disorders	0	1 (0.8)
Dermatitis diaper	0	1 (0.8)

Only the most severe event was included when an event occurred more than once for a subject.
Treatment-Emergent Adverse Events that occurred from the time of first dose of study drug through the last study evaluation or pre-existing AEs that were aggravated in severity or frequency during the dosing period.
Source: Table 12-4

Based on the known safety profile of DAP in adults, the Standardized MedDRA Query (SMQ) of rhabdomyolysis and myopathy with both a broad or narrow relationship was examined by the sponsor and reported in the following table. The two treatment groups had a numerically similar proportion of subjects with at least one of these TEAEs. Of note, all 3 subjects with musculoskeletal and connective tissue disorders were in the DAP group and occurred in Age Group 1 (12 - 17 years old).

3.3.3 Death and Serious Adverse Events

No deaths occurred in this study. Treatment-emergent serious adverse events (TESAEs) are summarized in the following table. The proportion of subjects with at least one TESAE was 2.3% in each group. There were at most two subjects in each preferred term. Analyses by age groups were limited by the small sample sizes; however, no overly concerning results were seen (analyses not shown).
Section 4 contains additional safety analyses by race and region. For the conclusions of safety assessment, please see the medical officer's review.

Table 19. Summary of Standardized MedDRA Query Terms Rhabdomyolysis/Myopathy with a Broad or Narrow Relationship by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	DAP N=256 n (%)	SOC N=133 n (%)
Subjects with at least one Rhabdomyolysis/Myopathy TEAE	15 (5.9)	8 (6.0)
Investigations	14 (5.5)	7 (5.3)
Blood creatine phosphokinase increased	14 (5.5)	7 (5.3)
Metabolism and nutrition disorders	0	1 (0.8)
Hypocalcaemia	0	1 (0.8)
Musculoskeletal and connective tissue disorders	3 (1.2)	0
Myalgia	2 (0.8)	0
Myopathy	1 (0.4)	0

TEAE: Treatment-emergent adverse event
Source: Table 12-6 and 14.3.1.11

Table 20. Treatment-Emergent Serious Adverse Events, by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	DAP N=256 n (%)	SOC N=133 n (%)
Subjects with at least one serious adverse event	6 (2.3)	3 (2.3)
General disorders and administration site	3 (1.2)	0
Pyrexia	2 (0.8)	0
Chest pain	1 (0.4)	0
Infections and infestations	2 (0.8)	3 (2.3)
Abscess	1 (0.4)	0
Bacteremia	0	1 (0.8)
Osteomyelitis	0	1 (0.8)
Subcutaneous abscess	1 (0.4)	0
Toxic shock syndrome	0	1 (0.8)
Investigations	1 (0.4)	0
Blood creatine phosphokinase increased	1 (0.4)	0
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Myopathy	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0
Status asthmaticus	1 (0.4)	0
Surgical and medical procedures	1 (0.4)	0
Wound drainage	1 (0.4)	0

Source: Table 12-7

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Efficacy analyses by age group are reported in Section 3 of this review and in the following sections by gender and region.

4.1.1 Efficacy by Gender and by Age and Gender

Sponsor-defined outcome at TOC by gender and by age and gender in the ITT population is listed in the following table. For the overall results, no noticeable differences were seen in rates of clinical success between treatments within gender. Due to the small sample sizes within age groups, it is difficult to make any conclusions; however, the most notable differences were seen in Age Group 3 and 4 in female subjects.

Table 21. Sponsor-Defined Clinical Outcome at TOC by Gender (ITT Population)

	Male		**Female**	
All	**DAP N=131 n (%)**	**SOC N=70 n (%)**	**DAP N=126 n (%)**	**SOC N=62 n (%)**
Clinical Success	120 (91.6)	61 (87.1)	107 (84.9)	53 (85.5)
Clinical Failure	1 (0.8)	1 (1.4)	3 (1.6)	0
Unable to Evaluate	10 (7.6)	8 (11.4)	17 (13.5)	9 (14.5)
Diff in Success Proportions (95% CI)	4.5 (-4.7, 13.6)		-0.6 (-11.3, 10.2)	
Age Group 1	**N=44**	**N=22**	**N=29**	**N=15**
Clinical Success	43 (97.7)	20 (90.9)	27 (93.1)	14 (93.3)
Clinical Failure	0	1 (4.5)	0	0
Unable to Evaluate	1 (2.3)	1 (4.5)	2 (6.9)	1 (6.7)
Age Group 2	**N=45**	**N=23**	**N=28**	**N=15**
Clinical Success	42 (93.3)	21 (91.3)	24 (85.7)	14 (93.3)
Clinical Failure	1 (2.2)	0	1 (3.6)	0
Unable to Evaluate	2 (4.4)	2 (8.7)	3 (10.7)	1 (6.7)
Age Group 3	**N=33**	**N=22**	**N=48**	**N=20**
Clinical Success	27 (81.8)	19 (86.4)	40 (83.3)	13 (65.0)
Clinical Failure	0	0	1 (2.1)	0
Unable to Evaluate	6 (18.2)	3 (13.6)	7 (14.6)	7 (35.0)
Age Group 4	**N=9**	**N=3**	**N=21**	**N=12**
Clinical Success	8 (88.9)	1 (33.3)	16 (76.2)	12 (100)
Clinical Failure	0	0	0	0
Unable to Evaluate	1 (11.1)	2 (66.7)	5 (23.8)	0

4.1.2 Efficacy and Safety by Race

Sponsor-defined outcome at TOC by race in the ITT population is listed in the following table. Asians in the DAP group had a 100% clinical success rate, which was unexpectedly high. For the overall results in other race groups, no noticeable differences were seen in rates of clinical success between treatments within race.

Table 22. Summary of Sponsor-Defined Clinical Outcome at TOC by Race (ITT Population)

	Asian		Black/African American		White		Other	
	DAP N=83 n (%)	**SOC N=42 n (%)**	**DAP N=65 n (%)**	**SOC N=25 n (%)**	**DAP N=104 n (%)**	**SOC N=61 n (%)**	**DAP N=5) n (%)**	**SOC N=4 n (%)**
Clinical Success	83 (100)	40 (95.2)	48 (73.8)	18 (72.0)	93 (89.4)	52 (85.2)	3 (60.0)	4(100)
Clinical Failure	0	0	1 (1.5)	0	1 (1.0)	1 (1.6)	1 (20.0)	0
Unable to Evaluate	0	2 (4.8)	16 (24.6)	7 (28.0)	10 (9.6)	8 (13.1)	1 (20.0)	0
Diff in Success Proportions (95% CI)	4.8 (-1.7, 11.2)		1.8 (-18.7, 22.4)		4.2 (-6.5, 14.9)		-40.0 (-85.5, 26.2)	

Given the high clinical response rates in Asians, the reviewer explored safety by race as well. The following table shows a summary of subjects with at least one treatment-emergent adverse event by age group and race. It is obvious that Asian subjects had very low percentages compared with other racial groups. Note that since 122 out of 125 Asian subjects and none of the subjects in other racial groups were from India, these differences will be seen in India versus USA as well, as shown in the following section.

Table 23. Summary of Subjects with at least One Treatment-Emergent Adverse Event (Safety Population)

	Asian		Black/African American		White		Other	
	DAP (N=83) n (%)	SOC (N=42) n (%)	DAP (N=64) n (%)	SOC (N=26) n (%)	DAP (N=104) n (%)	SOC (N=61) n (%)	DAP (N=5) n (%)	SOC (N=4) n (%)
TEAE	1 (1.2)	1 (2.4)	25 (39.1)	13 (50)	69 (66.3)	32 (52.5)	3 (60)	2 (50)

4.1.3 Efficacy and Safety by Geographic Region

Sponsor-defined outcome at TOC by geographic region in the ITT population is listed in the following table. As stated earlier, this study was conducted in the USA and India with India only enrolling subjects in Age Groups 1 and 2. The clinical success rates were unexpectedly high in India. The low success rates in the USA were mainly due to "unable to evaluate". Twenty-four out of 41 unable-to-evaluate subjects (58.5%) in the USA were lost to follow-up.

Table 24. Sponsor-Defined Clinical Outcome at TOC by Geographic Region (ITT Population)

	India		USA	
	DAP N=81 n (%)	**SOC N=41 n (%)**	**DAP N=176 n (%)**	**SOC N=91 n (%)**
Clinical Success	81 (100)	39 (95.1)	146 (83.0)	75 (82.4)
Clinical Failure	0	0	3 (1.7)	1 (1.1)
Unable to Evaluate	0	2 (4.9)	27 (15.3)	15 (15.6)
Diff in Success Proportions (95% CI)	4.9 (0.1, 17.1)		0.1 (-9.6, 10.7)	
Age Group 1	**N=32**	**N=16**	**N=41**	**N=21**
Clinical Success	32 (100)	15 (93.8)	38 (92.7)	19 (90.5)
Clinical Failure	0	0	0	1 (4.8)
Unable to Evaluate	0	1 (6.3)	3 (7.3)	1 (4.8)

	India		USA	
	DAP N=81 n (%)	**SOC N=41 n (%)**	**DAP N=176 n (%)**	**SOC N=91 n (%)**
Age Group 2	**N=49**	**N=25**	**N=24**	**N=13**
Clinical Success	49 (100)	24 (96.0)	17 (70.8)	11 (84.6)
Clinical Failure	0	1 (4.0)	2 (8.3)	0
Unable to Evaluate	0	0	5 (20.8)	2 (15.4)
Age Group 3			**N=81**	**N=42**
Clinical Success			67 (82.7)	32 (76.2)
Clinical Failure			1 (1.2)	0
Unable to Evaluate			13 (16.0)	10 (23.8)
Age Group 4			**N=30**	**N=15**
Clinical Success			24 (80%)	13 (86.7)
Clinical Failure			0	0
Unable to Evaluate			6 (20%)	2 (13.3)

Sites in India only enrolled subjects into Age Groups 1 and 2.

Given the high clinical success rates in India, the reviewer explored safety by region as well. The following table shows a summary of subjects with at least one treatment-emergent adverse event by age group and country. It is obvious that subjects in India had lower AE percentages than in USA for the same age group, especially in the DAP group. Baseline symptoms and signs were compared between the two countries (analyses not shown here) and no reasons for these differences were found.

Table 25. Summary of Subjects with at least One Treatment-Emergent Adverse Event (Safety Population)

	India		USA	
	DAP	**SOC**	**DAP**	**SOC**
Age Group 1	6.3% (2/32)	12.5% (2/16)	60.0% (24/40)	54.5% (12/22)
Age Group 2	6.1% (3/49)	8.0% (2/25)	58.3% (14/24)	38.5% (5/13)
Age Group 3	-	-	50.6% (41/81)	38.1% (16/42)
Age Group 4	-	-	46.7% (14/30)	73.3% (11/15)
All	6.2% (5/81)	9.8% (4/41)	53.1% (93/175)	47.8% (44/92)

We further explored the efficacy and safety in India by study site. The following table shows a summary of sponsor-defined successes and subjects with at least one treatment-emergent adverse event by study site in India. The vast majority of subjects in India were enrolled in only two sites, Sites 200 and 203. These two sites had very high efficacy and very low rates of AEs.

Table 26. Summary of Sponsor-Defined Clinical Success (ITT Population) and Subjects with at least One Treatment-Emergent Adverse Event (Safety Population by India Study Site

	Efficacy n/N(%)		Safety n/N (%)	
Site	**DAP**	**SOC**	**DAP**	**SOC**
200	48/48 (100)	26/26 (100)	4/48 (8.3)	0/26 (0)
201	2/2 (100)	0/1	0/2	1/1 (100)
202	2/2 (100)	5/6 (83.3)	1/2 (50)	3/6 (50)
203	25/25 (100)	8/8 (100)	0/25	0/8
204	2/2 (100)	-	0/2	-
205	1/1 (100)	-	0/1	-
207	1/1 (100)	-	0/1	-

4.2 Other Special/Subgroup Populations

Sponsor-Defined Clinical Response at TOC by SOC

As planned, the standard of care used in the control arm was either clindamycin, vancomycin or a penicillinase-resistant semi-synthetic penicillin (nafcillin, oxacillin, or cloxacillin) with the majority of subjects in the control arm receiving either clindamycin or vancomycin. The design of the study required that the investigator choose which SOC would be received prior to randomization. The following table contains the sponsor-defined clinical response by SOC using the SOC chosen prior to randomization. Note that 82% of SOC subjects in the Indian sites used vancomycin. The clinical success proportions in the DAP and SOC group were comparable across the SOC chosen. Note among subjects with pre-selected vancomycin, the success proportions were higher than those with clindamycin or other antibiotics.

Table 27. Summary of Sponsor-Defined Clinical Response at TOC by SOC (ITT Population)

Selected SOC Prior to Randomization		DAP N=257 n (%)	SOC N=132 n (%)
Clindamycin	Clinical Success	103 (82.4)	54 (83.1)
	Clinical Failure	2 (1.6)	0
	Unable to Evaluate	20 (16.0)	11 (16.9)
	Subtotal	125 (65.8)	65 (34.2)
Vancomycin	Clinical Success	110 (93.2)	49 (92.5)
	Clinical Failure	1 (0.8)	1 (1.9)
	Unable to Evaluate	7 (5.9)	3 (5.7)
	Subtotal	118 (69.0)	53 (31.0)
Other	Clinical Success	14 (100.0)	11 (78.6)
	Clinical Failure	0	0
	Unable to Evaluate	0	3 (21.4)
	Subtotal	14 (50.0)	14 (50.0)

One of the exclusion criteria was to exclude subjects with previous systemic antimicrobial therapy exceeding 24 hours during the 48 hours prior to the first dose of study drug. But a subject was eligible if on previous antibiotics without any clinical improvement and/or a wound culture was not sensitive to prior therapy. The study collected information on use of any antibiotics from 14 days to the first dose of study drug. The following table shows a summary of sponsor-defined clinical response at TOC by use of antibiotics (systemic use or dermatological use) within 14 days prior to the first dose of study drug. No reduction in efficacy was seen with DAP compared to SOC in the subgroup of subjects who did not receive prior antibiotics. It appears that among prior users of antibiotics the clinical success rates were slightly lower for both arms. This is not surprising since certain patient's factors and disease conditions may have affected whether or not a subject received antibiotics prior to the first dose of study drug.

Table 28. Summary of Sponsor-Defined Clinical Response at TOC by Use of Antibiotics within 14 Days prior to Randomization (ITT Population)

Use of Antibiotics within 14 Days prior to the first Dose of Study Drug		DAP N=257 n (%)	SOC N=132 n (%)
Yes	Clinical Success	137 (83.0)	68 (83.9)
	Clinical Failure	3 (1.8)	1 (1.2)
	Unable to Evaluate	25 (15.2)	12 (14.8)
No	Clinical Success	90 (97.8)	46 (90.2)
	Clinical Failure	0	0
	Unable to Evaluate	2 (2.2)	5 (9.8)

The following table shows a summary of sponsor-defined clinical response at TOC by use of antibiotics (systemic use or dermatological use) within one day prior to the first dose of study drug. It appears that the clinical success rates across all groups were close. In neither of these analyses do the results appear concerning in the subgroup of subjects who did not receive prior therapy, the group that may have had a greater ability to detect differences between treatments.

Table 29. Summary of Sponsor-Defined Clinical Response at TOC by Use of Antibiotics within 1 day prior to Randomization (ITT Population)

Use of Antibiotics within 1 Day prior to the first Dose of Study Drug		DAP N=257 n (%)	SOC N=132 n (%)
Yes	Clinical Success	115 (87.1)	58 (86.6)
	Clinical Failure	1 (0.8)	1 (1.5)
	Unable to Evaluate	16 (12.1)	8 (11.9)
No	Clinical Success	112 (89.6)	56 (86.2)
	Clinical Failure	2 (1.6)	0
	Unable to Evaluate	11 (8.8)	9 (13.8)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

As discussed previously, some issues of this study were varying evaluation time at TOC, the use of antibacterial therapy prior to the first dose of study drug, switch to oral therapy during the treatment period, and difference in efficacy and safety profiles in the two countries.

The objectives of this study were to assess the safety and efficacy of daptomycin for injection compared to standard of care in pediatric patients with complicated skin and skin structure infection. There were some elements of the design that made certain comparative assessments of the safety and efficacy difficult.

The greatest concern was the fact that subjects were allowed to switch to an oral therapy early in their treatment. The primary efficacy endpoint was measured 7 – 14 days after the last day of the IV and oral therapy, well after a patient could have switched to oral therapy. In order to try to

address this, the review evaluated the timing of the switch to oral therapy, adverse events while on IV treatment, and efficacy at the point of the switch to oral therapy. A higher proportion of subjects in the DAP group received IV study drug <3 days than in the SOC group (46.9% versus 35.3%). It is impossible to know if this is due to the open label nature of the study and potential concerns of the investigator on keeping subjects on the test product, or if this points to an earlier improvement in subjects. The measurement of efficacy at the point of oral switch was limited; however, there was no indication of reduced safety or efficacy of daptomycin compared to control at the point of oral switch.

Another concern was the ability of the study to have detected a difference in efficacy if one were to have existed, i.e., assay sensitivity. As discussed, this study was designed and started prior to the release of the FDA's Acute Bacterial Skin and Skin Structure Infections Guidance dated 10/15/13. In the guidance, it states that the primary efficacy endpoint is lesion response (as percent reduction in lesion size ≥20% compared to baseline) at 48-72 hours because the best treatment effect from historical data shows this early time point. The efficacy of this study was evaluated 7-14 days after the last dose of the IV and oral therapy, which may have missed the best window to evaluate efficacy. As this study was not designed to assess this endpoint at this time point, we were not able to conduct this analysis.

The guidance also points out the problem in detecting a difference in efficacy if subjects have received prior antibacterial therapy. The guidance recommends that no more than 25% of subjects receive a single dose of antibacterial therapy 24 hours prior to the administration of randomized treatment. In this study, about 51% of subjects received antibiotics 24 hours prior to the first dose of study drug. It is much higher than the recommended percentage. Prior use of antibiotics was one of the concerns because it may potentially bias the results towards noninferiority of the treated arm to the SOC. However, results in those subjects not receiving prior antibacterial therapy appear similar across arms.

The objective of the study was to assess the efficacy and safety in pediatric populations with the assessment of safety being the primary objective. This study was not designed to assess non-inferiority with any pre-specified non-inferiority margin.

One concern arose during the review of the results of the study. The efficacy and safety results from the sites in India appear different than the results from the sites in the United States. The sponsor-defined clinical success rate was 100% for DAP and the rates of treatment-emergent adverse events were much lower in the Indian sites (7.4%) compared to the US sites (52%). This could potentially point to less stringent clinical trial procedures being in place in India. An information request was made to the sponsor to help explain these differences.

5.2 Collective Evidence

In 2003, daptomycin for injection was approved for CSSSI in adults. Two randomized, investigator-blinded efficacy studies were conducted. In these two pivotal studies, DAP (4 mg/kg QD) was compared with vancomycin with a noninferiority margin of 10%. Patients could switch to oral therapy after a minimum of 4 days of IV treatment if clinical improvement was demonstrated. The treatment duration was 7 to 14 days. TOC was 7-20 days post treatment. The

efficacy endpoint was clinical outcome (success including cure and clinical improvement, failure, and non-evaluable). The two trials were similar in study design but conducted in different locations (primarily in the USA and South Africa versus at non-US sites only) and differed in patient characteristics (including history of diabetes and peripheral vascular disease). In the first study, the clinical success rates in the ITT population were 62.5% (165/263) and 60.9% (162/266) in the DAP and comparator groups. In the second study, the clinical success rates in the ITT population were 80.4% (217/270) and 80.5% (235/292) in the DAP and comparator groups. This pediatric study under review was also similar to the two pivotal studies in study design (allowance of switching to oral therapy, duration of treatment, and timing of evaluation).

Based on the review of this sNDA, DAP and SOC had similar efficacy results and safety profiles. The study was not designed to test non-inferiority of the efficacy of DAP to SOC; however, for the primary efficacy endpoint of sponsor-defined clinical success the 95% confidence intervals for the difference in success proportions (DAP - SOC) could have ruled out a difference of -6%, although it is likely that the design of the study may have biased the results towards noninferiority. The sample sizes in the various age groups were too small to make any strong conclusions; however, the DAP subjects in the youngest age group, notably with the smallest sample size, performed the worst relative to control.

Due to the limitations in study design, it is difficult to fully evaluate DAP's efficacy with respect to noninferiority. It is very difficult to attribute the treatment effect to DAP alone. We can only conclude that this regimen (DAP IV administration with a possible switch to oral therapy) may provide clinical efficacy results numerically similar to SOC.

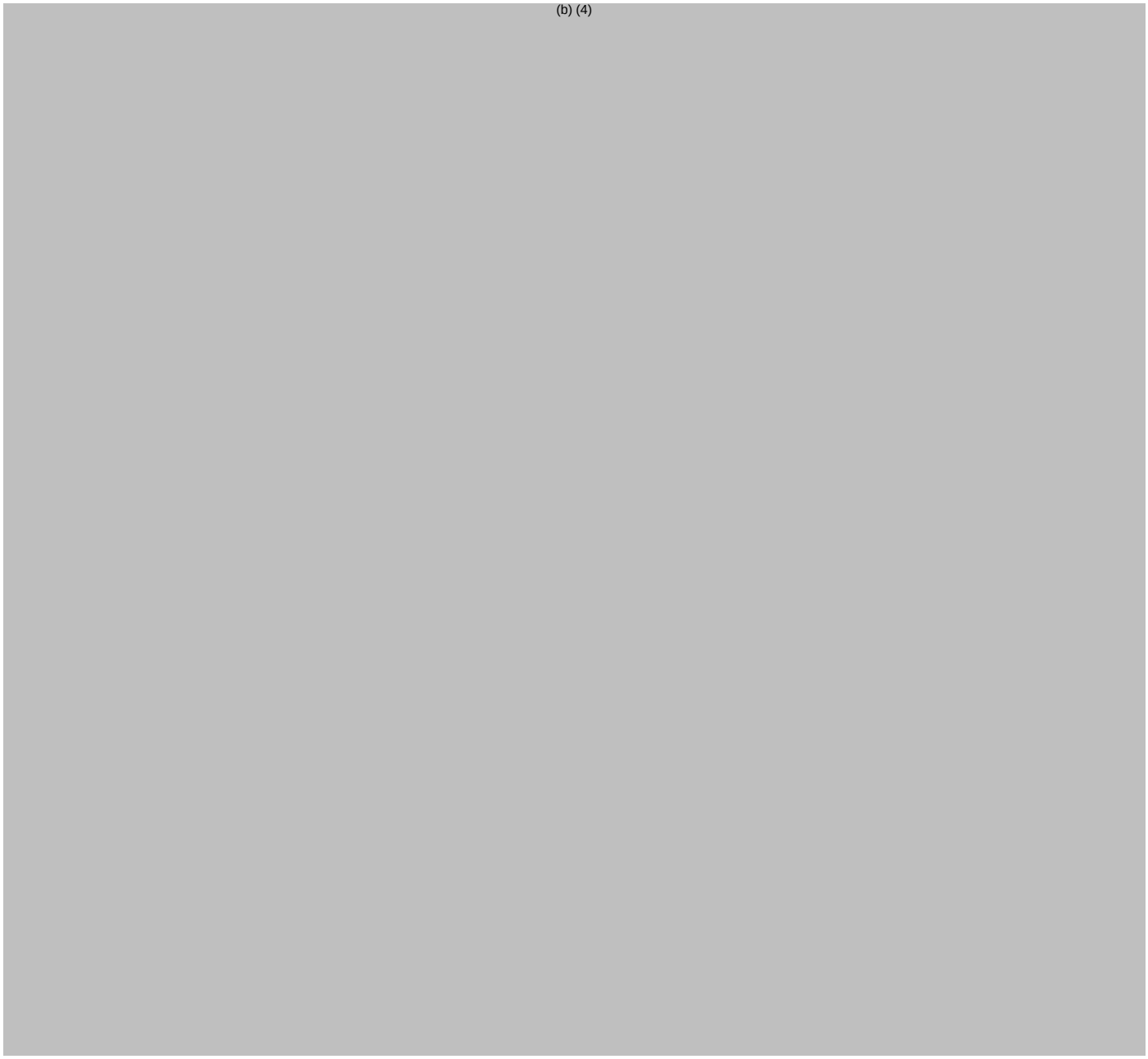
5.3 Conclusions and Recommendations

Based on the statistical review of this sNDA, it is concluded that the efficacy and safety of IV DAP with a possible switch to oral therapy in the treatment of cSSSI in pediatric population were supported by the submitted data because of the numerically similar efficacy and safety results between the DAP and SOC group. This study met the previously mentioned post-marketing requirement for this NDA. However, it was difficult to claim non-inferiority based on the data submitted.

5.4 Labeling Recommendations

The following is the section of the labeling that contains the results of the pediatric CSSSI study with our proposed edits (section 14.1).

(b) (4)


(b) (4)

6. APPENDIX

The following table shows a summary of demographic, baseline characteristics, and baseline pathogens by age group for all subjects in the ITT population.

Table 30. Summary of Demographics, Baseline Characteristics, and Baseline Pathogens for All Subjects (ITT population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
	DAP 5 mg/kg N=73 n (%)	SOC N=37 n (%)	DAP 7 mg/kg N=73 n (%)	SOC N=38 n (%)	DAP 9 mg/kg N=81 n (%)	SOC N=42 n (%)	DAP 10 mg/kg N=30 n (%)	SOC N=15 n (%)	DAP N=257	SOC N=132
Age (yrs)										
N	73	37	73	38	81	42	30	15	257	132
Mean (SD)	15.02 (1.58)	14.84 (1.74)	9.05(1.44)	8.98(1.31)	3.92(1.56)	3.86(1.56)	1.46(0.23)	1.43(0.30)	8.2 (5.16)	8.1 (5.10)
Median	15.2	14.8	9.2	9	3.3	3.45	1.45	1.3	7.6	7.65
Range	12.1,17.9	12.1,17.7	7.1,11.8	7.1,11.8	2.1,6.9	2.0,7.0	1.1,1.9	1.1,1.9	1.1,17.9	1.1,17.7
Sex n (%)										
Male	44 (60.3)	22 (59.5)	45 (61.6)	23 (60.5)	33 (40.7)	22 (52.4)	9 (30.0)	3 (20.0)	131 (51.0)	70 (53.0)
Female	29 (39.7)	15 (40.5)	28 (38.4)	15 (39.5)	48 (59.3)	20 (47.6)	21 (70.0)	12 (80.0)	126 (49.0)	62 (47.0)
Race n (%)										
Asian	33 (45.2)	16 (43.2)	49 (67.1)	25 (65.8)	1 (1.2)	0	0	1 (6.7)	83 (32.3)	42 (31.8)
Black or African American	12 (16.4)	6 (16.2)	8 (11.0)	5 (13.2)	33 (40.7)	10 (23.8)	12 (40.0)	4 (26.7)	65 (25.3)	25 (18.9)
White	28 (38.4)	14 (37.8)	15 (20.5)	7 (18.4)	43 (53.1)	31 (73.8)	18 (60.0)	9 (60.0)	104 (40.5)	61 (46.2)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (2.6)	0	1 (2.4)	0	0	0	2 (1.5)
Other	0	1 (2.7)	1 (1.4)	0	4 (4.9)	0	0	1 (6.7)	5 (1.9)	2 (1.5)
Height (in										

percentile)										
N	71	37	73	37	80	42	30	15	254	131
Mean (SD)	33.35 (31.69)	39.71 (35.9)	30.24 (33.89)	28.94 (35.74)	64.045 (32.62)	52.31 (29.52)	65.56 (33.92)	58.75 (32.58)	45.93 (36.52)	42.89 (34.86)
Median	23.8	38.2	16.3	8.6	77.6	51.05	81.4	68.1	45.5	40.3
Weight (in percentile)										
N	73	37	73	38	81	42	30	15	257	132
Mean (SD)	45.19 (35.20)	49.15 (38.96)	31.47 (37.95)	27.86 (33.47)	64.89 (29.95)	59.47 (30.50)	50.46 (28.11)	54.42 (28.05)	48.12 (35.98)	46.91 (35.67)
Median	47.5	48.9	9.7	11.6	67.3	56.45	52.3	62.2	51.7	50
BMI										
N	71	37	73	37	80	42	30	15	254	131
Mean (SD)	21.7 (6.03)	22.29 (5.58)	16.65 (4.93)	16.01 (4.20)	16.85 (2.60)	17.03 (2.75)	16.49 (1.64)	17.5 (2.57)	18.11 (4.94)	18.28 (4.82)
Median	20.5	21.5	15.3	15	16.5	16.6	16.5	16.9	17	16.9
Range	13.3, 53.3	13.7,36.3	8.7,30.0	10.3,28.4	12.5,29.7	13.0,27.5	13.8,20.8	14.2,24.5	8.7, 53.3	10.3, 36.3
Pathogen										
Any Gram Negative Pathogen	5 (6.8)	3 (8.1)	4 (5.5)	0	1 (1.2)	0	0	0	10 (3.9)	3 (2.3)
Gram Positive Baseline Infecting Pathogen[a] (MITT)	66 (90.4)	31 (83.8)	58 (79.5)	31 (81.6)	59 (72.8)	32 (76.2)	27 (90.0)	11 (73.3)	210 (81.7)	105 (79.5)
MRSA	22 (30.1)	10 (27.0)	13 (17.8)	6 (15.8)	41 (50.6)	20 (47.6)	18 (60.0)	8 (53.3)	94 (36.6)	44 (33.3)
MSSA	34 (46.6)	16 (43.2)	28 (38.4)	16 (42.1)	8 (9.9)	8 (19.0)	8 (26.7)	1 (6.7)	78 (30.4)	41 (31.1)
S. pyogenes	4 (5.5)	1 (2.7)	13 (17.8)	5 (13.2)	2 (2.5)	1 (2.4)	0	0	19 (7.4)	7 (5.3)
Other[b]	6 (8.2)	6 (16.2)	4 (5.5)	4 (10.5)	8 (9.9)	3 (7.1)	1 (3.3)	2 (13.3)	38 (14.8)	20 (15.2)
Investigator's Primary Diagnosis: Type of cSSSI										

Major Abscess	32 (43.8)	25 (67.6)	44 (60.3)	20 (52.6)	42 (51.9)	18 (42.9)	18 (60.0)	9 (60.0)	136 (52.9)	72 (54.5)
Wound Infection	10 (13.7)	5 (13.5)	8 (11.0)	3 (7.9)	3 (3.7)	1 (2.4)	0	0	21 (8.2)	9 (6.8)
Complicated Cellulitis	28 (38.4)	7 (18.9)	19 (26.0)	14 (36.8)	36 (44.4)	22 (52.4)	12 (40.0)	6 (40.0)	95 (37.0)	49 (37.1)
Diabetic Ulcer Infection	0	0	0	0	0	0	0	0	0	0
Infected Ulcer Other than Diabetic	2 (2.7)	0	1 (1.4)	0	0	0	0	0	3 (1.2)	0
Other	1 (1.4)	0	1 (1.4)	1 (2.6)	0	1 (2.4)	0	0	2 (0.8)	2 (1.5)

BMI: body mass index; DAP: daptomycin; ITT: intent-to-treat; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; SD: standard deviation; SOC: standard of care; cSSI: complicated skin and skin structure infections

[a]Subjects counted in one row. Subjects counted for specific pathogens had only that pathogen isolated.

[b]Other contains subjects with multiple pathogens or the following *Bacillus cereus and Micrococcus luteus, Enterococcus facecalis (VSE), Peptostreptococcus app.,Staphylococcus hominis, Staphylococcus lugdunensis, Staphylococcus constellatus*, etc.

Source: Table 11-2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIANBIN LI
11/19/2016

KAREN M HIGGINS
11/21/2016
I concur.