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 #:	57
Drug Name:	Cubicin® (Daptomycin for injection)
Indication(s):	Bacteremia
Applicant:	Cubist Pharmaceuticals, Inc.
Date(s):	Stamp Date: 03/02/2017 Filing Date: 05/15/2017 Primary Review Date: July 30, 2017 PDUFA Goal Date: September 1, 2017
Review Priority:	Priority
Biometrics Division:	DB4/OB/OTS/CDER
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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 #804-7, "Conduct a multicenter, evaluator-blinded, randomized comparator study designed to evaluate the safety, efficacy and pharmacokinetics of IV daptomycin administered for up to 14 days in the treatment of pediatric patients ages 1 to 17 years of age with *S. aureus* bacteremia versus standard of care".

This was a Phase 4 multi-national, multi-center, open-label (evaluator-blinded), randomized, comparative study. A total of 82 patients with *S. aureus* bacteremia or suspected of having *S. aureus* bacteremia were enrolled sequentially from the oldest age group (12 to 17 years) to the youngest group (1 to 6 years) and were randomized 2:1 to the daptomycin (DAP) or standard of care comparator (COM) groups. Treatment duration was 5 to 42 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 clinical response based on the blinded-evaluator's assessment at the Test of Cure visit (TOC, 7-14 days after the last dose of study medication (IV or oral).

The clinical successes (cure and improvement) at TOC for all subjects and by age group are summarized in the Microbiological Modified Intent-To-Treat population (all randomized and treated subjects with proven *S. aureus* bacteremia at baseline) as follows:

	DAP	**COM**
All	45/51 (88.2%)	17/22 (77.3%)
1 to 6 year	17/20 (85.0%)	7/8 (87.5%)
7 to 11 year	16/17 (94.1%)	7/9 (77.8%)
12 to17 year	12/14 (85.7%)	3/5 (60.0%)

The difference in clinical success proportions for all subjects overall was 11.0% with a 95% confidence interval of [-8.7%, 30.6%], which could exclude a 9% noninferiority margin. The efficacy and safety results for both groups were numerically close, overall and by age group. There were no deaths.

The primary objective of this study was safety. Efficacy was to be extrapolated from the results from adult study. Given the study design, switch to oral therapy made it more difficult to interpret (though that was also true for the adult study). We may conclude that this regimen (DAP IV administration with a possible switch to oral therapy) and COM may provide numerically similar clinical efficacy results, which provides some assurance that the DAP regimen was not much worse than COM in pediatric patients with *S. aureus* bacteremia.

In conclusion, 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.

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2. INTRODUCTION

2.1 Overview

Daptomycin for injection was approved for the treatment of complicated skin and skin structure infections (cSSSI) and *Staphylococcus aureus* (*S. aureus*) bacteremia. This submission contains a final study report for the Post-Marketing Requirement (PMR) #804-7, entitled "Conduct a multicenter, evaluator-blinded, randomized comparator study designed to evaluate the safety, efficacy and pharmacokinetics of IV daptomycin administered for up to 14 days in the treatment of pediatric patients ages 1 to 17 years with *S. aureus* bacteremia versus standard of care", 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: Study Included in Analysis

Protocol	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm (Randomized)	Study Population
DAP-PEDBAC-11-02	Phase 4	5 to 42 days	7-14 days after last dose of medication (IV or oral)	DAP: 55 COM: 27	Children aged 1 to 17 years with *S. aureus* bacteremia

DAP: Daptomycin for injection, COM: Comparator.

2.2 Data Sources

Data sources, including all material reviewed, e.g. applicant's study reports and data sets analyzed, are located at \\cdsesub1\evsprod\NDA021572\0160 (Study Report), 0161 (Data), and 0167 (Subgroup Analysis Report).

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, open-label (evaluator-blinded), randomized, comparative study conducted in North America (USA), Europe (Greece, Israel, Romania, Ukraine), Central/South America (Argentina, Brazil, Panama), and Australia/Asia (Australia, Malaysia, Thailand). The

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majority of patients were enrolled in the United States and Ukraine (36 and 25 patients, respectively). Four countries only enrolled one patient each (Australia, Greece, Malaysia, and Romania). Patients with proven or probable *S. aureus* bacteremia between the ages of 1 and 17 years were enrolled into three age groups sequentially (12 to 17, 7 to 11, and 1 to 6) and randomized in a 2:1 ratio to the daptomycin (DAP) or comparator (COM) group. Randomization was stratified by age group via a centralized computer-generated randomization schedule. Study drug started on Day 1. By Day 5 to Day 7, each subject's bacteremia was classified as complicated or uncomplicated and subjects were determined to receive 5 to 42 days of study drug depending on the source of infection, presence of endovascular infection, and metastatic foci of infection. A subject's treatment duration was left to the Investigator's discretion, although the protocol provided a range for the duration.

Age-dependent DAP doses and treatment duration are as follows:

Age group	Age	DAP Dose (mg/kg, once daily IV)	Uncomplicated bacteremia	Complicated bacteremia
1	12-17	7	5-28 days	7-42 days
2	7-11	9		7-28 days
3	1-6	12		

Source: Adapted from Table 9-3, Study Report

Recommended COM included vancomycin, semi-synthetic penicillins, first-generation cephalosporins, or clindamycin. According to the Protocol (version 1.0), clindamycin was to be used only in children whose bacteria rapidly cleared and was not related to an endovascular focus. Subjects may have switched to oral therapy following completion of IV study drug administration provided they showed clear clinical improvement and the pathogen was susceptible to an oral agent.

Study visits included end-of-IV-therapy (EOIV), end-of-therapy (IV and/or oral, EOT), test-of-cure/safety (TOC/Safety), and a last follow-up. Each subject was evaluated (by a blinded evaluator) between 7 to 14 days after their last dose of study drug (IV or oral) at the TOC/Safety Visit. The Last Follow-up Visit occurred 25 to 35 days after the last dose of study drug.

The study design is illustrated in Figure 1.

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

1. Determined the relationship of adverse events (AEs) to study drug;
2. Assessed signs and symptoms of primary site of bacteremia infection throughout the study, at the Screening/Baseline Visit, daily while on IV study medication, at the End of IV Therapy Visit, at the End of Oral Therapy Visit (for subjects who received oral study drug), and at the TOC/Safety Visit;
3. Decided on duration of treatment with IV study medication (whenever possible)
    a. Decided if IV study medication should be discontinued based on subject's clinical response;

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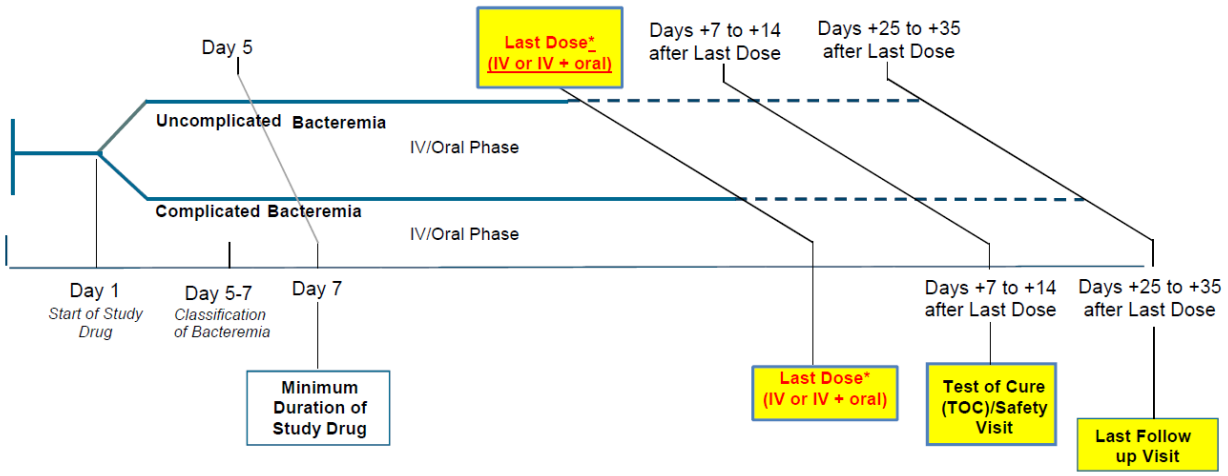
4. Decided on switch to an oral antibiotic (whenever possible);
5. Determined clinical response by comparing the subject's signs and symptoms of primary site of bacteremia infection at the End of IV Therapy (EOIV) Visit, the End of Oral Therapy (for subjects who received oral study drug), and the TOC/Safety Visits to those recorded at Study Baseline;
6. Determined microbiological response by comparing the baseline infecting pathogen (BIP) with results from cultures after initiation of study drug.

Figure 1. Study Schematic



Source: Figure 9-1, Study Report.

In addition to the blinded evaluator at each site, the Sponsor medical, safety, and microbiology teams also remained blinded through the study.

One of the inclusion criteria was proven or probable *S. aureus* bacteremia, defined as:

> Proven infections were considered those with *S. aureus* identified from at least one blood culture bottle by conventional culture methods or by a rapid diagnostic test within 3 days prior to first dose of study drug.
>
> Probable infections were those with a preliminary blood culture result demonstrating Gram-positive cocci in clusters upon Gram stain, suggestive of a staphylococcal infection. If the final blood culture yielded CoNS (coagulase-negative staphylococci) after the patient was enrolled, only high-risk patients with persistent bacteremia, documented by multiple cultures taken on separate days or from different sites yielding the same organism, continued on study therapy. Patients at high risk included, but were not limited to, immunocompromised children, cancer patients, or those with a potential source of infection from devices or IV catheters that were not intended to be removed.

The exclusions criteria included, but were not limited to:

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1. Previous systemic antimicrobial therapy effective against *S. aureus* exceeding 72 hours duration administered anytime during the 96 hours prior to the first dose of study drug; Exception: A subject was eligible if culture data demonstrated in vitro resistance to prior IV antibiotic;

2. Anticipated to require non-study systemic antibiotics that might have been potentially effective against *S. aureus*; Had received an investigational drug or participated in any experimental procedure within 30 days of randomization (investigational use of approved products was permitted with the approval of the Sponsor-designated Medical Monitor);

Primary Endpoint
The primary endpoint was related to safety. The primary objective was to assess the age-dependent doses of daptomycin IV compared to a standard of care.

Secondary Endpoints
Clinical response determined by the blinded evaluator was the efficacy endpoint at the TOC/Safety visit. The results at the EOIV and the end of oral therapy visits were also available in the Study Report. A subject-level microbiological response at TOC and pathogen-level response at TOC were included. Overall clinical outcome, based on the subject's clinical and microbiological responses, was also reported.

Blinded evaluator's clinical assessments

- **Cure**: Resolution of clinically significant signs and symptoms associated with admission infection (i.e., return to pre-infection Baseline). No further antibiotic therapy was required for the primary infection under study.
- **Improved**: Partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy was required for the primary infection under study. For subjects that were switched from IV study drug to oral study drug, "Improved" at the EOIV Visit was defined as the partial resolution of clinical signs or symptoms of infection such that no further IV antibiotic therapy was required for the primary infection under study.
- **Failure**: Inadequate clinical response to therapy, so that additional antibiotic therapy required for primary infection under study.
- **Unable to Evaluate**: Subject was not available to be examined and assessed.

For subjects who discontinued study medication (IV and oral combined, if switched to oral) after either 5 days of therapy (uncomplicated bacteremia) or 7 days of therapy (complicated bacteremia), for reasons other than lack of clinical improvement in signs and symptoms, an evaluation of "improved" indicated that the subject's infectious process was clearly resolving and that, if the subject had continued for the duration of the study, there was every expectation that a successful outcome would have been achieved without further antibiotics.

Comment: There was only one subject who discontinued IV therapy with improvement status. The subject was in the DAP group and had complicated bacteremia and discontinued IV therapy on Day 7 due to the reason that "the subject was removed from the study because he was to be discharged and there was no research home health set up"[sic]. The subject had both post-IV

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visit and TOC visit at Day 21 (with an improvement in clinical response but missing subject-level microbiological outcome) and a follow-up visit at Day 42.

Subjects who discontinued study drug therapy before 3 days were classified “unable to evaluate” unless otherwise deemed a clinical failure. Clinical failures were carried through as failures for purposes of evaluation at subsequent visits.

"Cure" and "improved" were considered satisfactory clinical responses (clinical success).

Pathogen-level microbiological response

This response at the TOC/Safety Visit includes the following categories:

- **Presumed Eradicated:** The BIP was absent in only the last blood culture taken.
- **Documented Eradicated:** The BIP was absent in the last two blood cultures taken on separate days.
- **Presumed Persisted:** The BIP was isolated from the last blood culture taken during therapy (IV or oral [for subjects who receive oral study drug]).
- **Documented Persisted:** The BIP was isolated from the last blood culture taken during therapy (IV or oral [for subjects who receive oral study drug]) and a blood culture taken any time between the EOIV (if no oral study drug therapy) or end of oral therapy visit (if oral study drug therapy administered) and the TOC/Safety Visit.
- **Non-evaluable:** No blood cultures taken during therapy (IV or oral [for subjects who receive oral study drug]) post baseline.

Subject-level microbiological response

- **Microbiologic Success:** A subject for whom all BIPs were eradicated (presumed or documented) within 7 days from the start of study drug for uncomplicated bacteremia with no source of infection present, or within 10 days for complicated bacteremia or when the source of infection has not been removed.

- **Microbiologic Failure:** A subject for whom any BIP persisted (presumed or documented) more than 7 days for uncomplicated bacteremia, after the start of study drug to which the pathogen is sensitive and when no ongoing source of infection is present, or after 10 days for complicated bacteremia or when the source of infection has not been removed;
  OR
  Presence of a superinfecting Gram-positive pathogen(s) in blood cultures at any time after initiating study drug.

- **Non-evaluable:** A subject with a pathogen-level microbiological response of non-evaluable for any BIP;
  OR

A subject who did not have positive cultures at baseline (those were enrolled due to diagnoses of probable *S. aureus* bacteremia or a negative blood culture prior to the first dose).

3.2.2 Statistical Methodologies

Analysis Populations

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

- Intent-to-Treat (ITT) Population: All randomized subjects regardless of doses of the study drug received.
- Modified Intent-to-Treat (MITT) Population: All randomized and treated subjects with at least one dose who met the clinical criteria for the study infection at Baseline (positive blood culture for *S. aureus* or CoNS in high-risk patients or probable bacteremia [Gram-positive cocci on Gram stain at Baseline]).
- Microbiological Modified Intent-to-Treat (mMITT) Population: All MITT subjects who had proven *S. aureus* bacteremia at Baseline.
- Clinically Evaluable (CE): Subpopulation of the mITT subjects who meet the following criteria:
    - Received the correct drug, as randomized;
    - Received appropriate duration of treatment (minimum and maximum treatment durations are outlined in the Clinical Evaluability Review Plan);
    - Had the necessary clinical and microbiological efficacy evaluations performed at the TOC/Safety Visit and were not evaluated as "non-evaluable";
    - Did not receive effective systemic on-study antibiotics at Baseline (>72 hours administered duration anytime during the 96 hours prior to the first dose);
    - Did not receive more than one dose of effective systemic on-study antibiotics from the first dose of study drug to the TOC/Safety Visit.

Comment: Although ITT population was defined, efficacy analysis was not conducted in this population by the sponsor. The CE population excluded subjects based on post-baseline information that might be affected by study treatment. Therefore, this review focuses on Sponsor's results in the MITT and mMITT populations. The reviewer will present one efficacy analysis in the ITT population.

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 MITT population should exclude subjects not receiving study medication. Note only one subject in the COM group did not receive treatment. Therefore, the effect of this exclusion on the overall efficacy assessment was minimal.

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Safety population: The safety population included all subjects who received any dose of IV study medication. Subjects were analyzed according to actual treatment received (overall by treatment group and by age group with treatment groups).

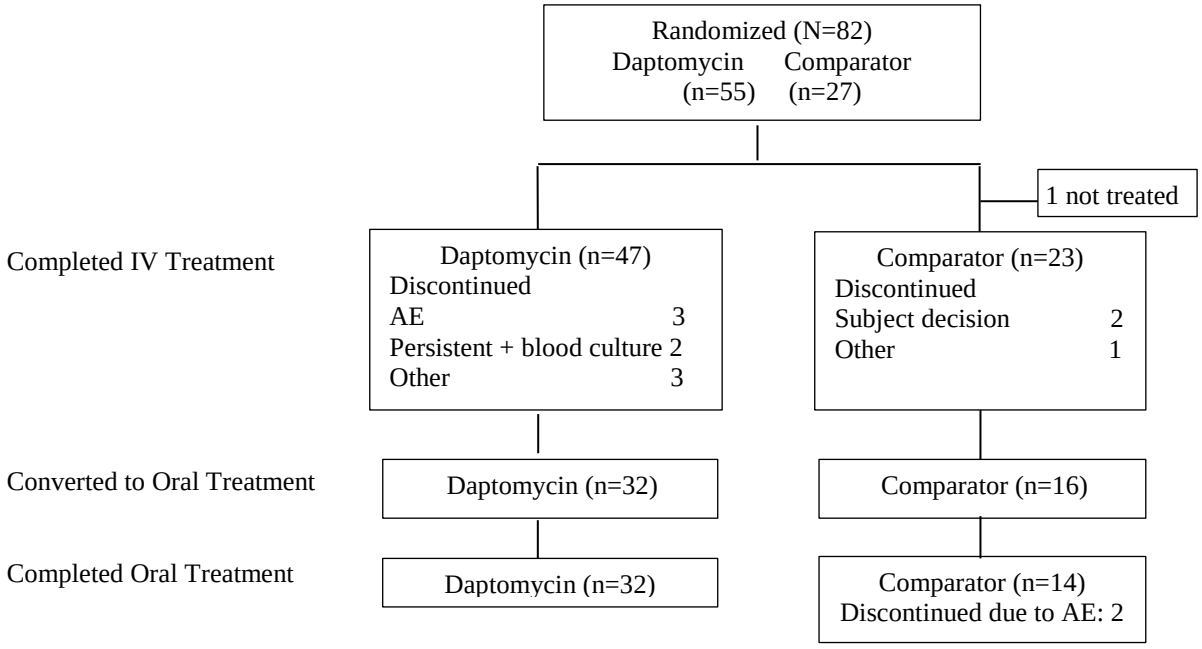
Analysis Methods for Efficacy Primary Endpoint and Secondary Endpoints

Differences in clinical success rates and microbiological eradication rates between the DAP and COM treatment groups by age group and for the total and 95% CIs for the differences were presented in the study report. These 95% CIs for the difference in success proportions were constructed based on the Wilson score method, which was based on standard errors for proportions evaluated at the null hypothesis, rather than at the maximum likelihood estimates (Agresti and Caffo, 2000). This is not a common method used to compare two proportions and like most parametric procedures, it likely has poor coverage when sample proportions are close to 0 or 1. Therefore, the reviewer reported exact 95% CIs based on inverting two one-sided tests when any cell size was less than 5 for comparison with the Wilson score method.

The study was not powered for the assessment of safety or efficacy. The selection of the sample size was based on the fact that the probability of observing a specific AE with a true rate of 5% among 50 subjects receiving DAP was at least 92%.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Figure 2. Patient Disposition



Source: Figure 10-1, Study Report.

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The first subject was enrolled on 3/6/2013, and the last subject was enrolled on 10/3/2015. Figure 2 shows the flow chart of this study and Table 2 shows a summary of the analysis populations. A total of 82 subjects were randomized to the two groups (55 on DAP, and 27 on COM). Among those randomized, one subject in the COM group did not receive study drug. All randomized patients were included in the ITT population. A total of 6 subjects were excluded from the MITT population for not receiving study therapy (1 on COM) or not meeting clinical criteria for infection at baseline (3 on DAP and 2 on COM). Therefore, 52 and 24 subjects were included in the MITT population. Three additional subjects were excluded from the mMITT population for not having proven *S. aureus* bacteremia at baseline.

Table 2. Summary of Analysis Populations

Population	**DAP**	**COM**
Randomized, n	55	27
Safety Population as dosed (randomized and treated)	55 (100)	26 (96.3)
Completed TOC/Safety Visit	54 (98.2)	24 (88.9)
ITT Population	55 (100)	27 (100)
MITT Population, n(%)	52 (94.6)	24 (88.9)
Reason for exclusion		
Not receiving study medication	0	1 (3.7)
Not meeting clinical criteria for infection at baseline	3 (5.5)	2 (7.4)
mMITT Population, n(%)	51 (92.7)	22 (81.5)
Reason for further exclusion from MITT		
Not having proven *S. aureus* bacteremia at baseline	1 (1.8)	2 (7.4)
CE Population, n(%)	40 (72.7)	12 (44.4)
Reason for exclusion		
Not in mITT	4 (7.3)	5 (18.5)
Treatment duration not per clinical evaluability plan	1 (1.8)	3 (11.1)
No evaluable TOC clinical outcome assessment and/or subject-level microbiological outcome	3 (5.5)	4 (14.8)
Received prior antibiotics for >72 hours	6 (10.9)	6 (22.2)
Received >1 dose of confounding non-study antibiotics	1 (1.8)	1 (3.7)
Completed study medication (IV or IV + oral if switched)	47 (85.5)	21 (77.7)

Source: Tables 10-1, 10-2, and 11-2, Study Report.

The following two tables show a summary of demographics, baseline characteristics, and baseline pathogens for all subjects in the Safety Population. The two groups were well balanced, except for race. Given the small sample size and the number of race categories, it was expected that some imbalances could occur. A summary of these variables by age group is available in the Appendix.

As mentioned previous, bacteremia was classified at Day 5-7. This was after the randomization and receiving the first 5 days of treatment and could confound the study. It is important to consider that these subjects with no classification, or withdrew prior to assessment were well balanced between the two groups. The DAP group had a higher proportion of uncomplicated bacteremia. However, it was difficult to attribute this imbalance to treatment because initial classification of bacteremia at baseline was not available.

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Table 3. Demographics and Baseline Characteristics for All Subjects (Safety Population)

	DAP N=55	COM N=26
Age (years)		
Mean (SD)	8.7 (4.5)	8.8 (4.5)
Median	9.6	8.8
Range	2.0, 16.9	2.0, 17.6
Sex, n (%)		
Male	38 (69.1)	16 (61.5)
Female	17 (30.9)	10 (38.5)
Race, n (%)		
American Indian or Alaska Native	0	1 (3.8)
Asian	2 (3.6)	2 (7.7)
Black or African American	6 (10.9)	0
Other	4 (7.3)	5 (19.2)
White	43 (78.2)	18 (69.2)
Height (cm)		
Mean (SD)	129.5 (30.7)	129.2 (28.4)
Median	128.5	126.0
Range	69.5, 196.0	73.0, 176.5
Weight (kg)		
Mean (SD)	33.0 (18.3)	32.8 (19.6)
Median	26.6	24.3
Range	10.0, 83.3	9.3, 72.0
Body Mass Index (kg/m^2)		
N	54	26
Mean (SD)	18.3 (3.7)	17.8 (4.7)
Median	17.4	16.6
Range	11.6, 29.8	10.3, 31.6
Baseline serum creatinine category		
Normal	51 (92.7)	23 (88.5)
1-1.5 upper limit of normal	4 (7.3)	3 (11.5)
Baseline creatinine clearance (mL/min)		
Mean (SD)	166.2 (77.8)	150.3 (75.1)
Median	160.5	134.7
Range	50.0, 497.3	52.5, 405.8
Country		
Argentina	3	0
Australia	0	1
Brazil	2	0
Greece	1	0
Israel	2	0
Malaysia	1	0
Panama	3	4
Romania	1	0
Thailand	1	2
Ukraine	16	9
United States	25	10

Source: Adapted from Tables 11-3 and 11-4, Study Report.

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Table 4. Baseline Pathogens and Classification of Bacteremia at Day 5-7 for All Subjects (Safety Population)

Baseline infection pathogen n (%)		
Coagulase negative *staphylococcus*	2 (3.6)	2 (7.7)
Staphylococcus Aureus (MRSA)	7 (12.7)	3 (11.5)
Staphylococcus Aureus (MSSA)	44 (80.0)	19 (73.1)
Staphylococcus epidermidis (MRSE)	0	1 (3.9)
Staphylococcus saprophyticus	1 (1.8)	0
No BIP established	1 (1.8)	1 (3.9)
Diagnosis of *S. aureus* bacteremia, n	54	25
Proven	51 (94.6)	22 (88.0)
Probable	3 (5.6)	3 (12.0)
Bacteremia classification		
Subjects with no classification, withdrew prior to assessment (Days 5-7)	3 (5.5)	2 (7.7)
Complicated	27 (49.1)	16 (61.5)
Uncomplicated	25 (45.4)	8 (30.8)
Metastatic foci of infection	11 (21.2)	8 (33.3)
Infection of prosthetic material	2 (3.8)	1 (4.2)
Positive blood culture > 4 days	12 (23.1)	5 (20.8)
Fever after 72 hours	14 (26.9)	9 (37.5)

Source: Adapted from Tables 11-3 and 11-4, Study Report.

The comparator group received IV cefazolin, flucloxacillin, linezolid, oxacillin, or vancomycin. As discussed above, investigators were allowed to switch subjects to oral therapy. Exposure to study medication is summarized in the following table. Subjects received IV therapy with a comparable duration. About 60% of patents switched to an oral therapy, with similar antibiotics received across the two arms. Patients in the DAP group received a longer duration of oral therapy (mean: 22.7 days versus 17.7 days). Patients received total treatment (IV and oral) on average for 25.3 and 22.6 days for the two groups, respectively. One subject with uncomplicated bacteremia infected with MSSA in the DAP group was treated with IV for 16 days and oral therapy for 125 days with an improvement outcome, which was an outlier. Nevertheless, the evaluation time at the EOIV or TOC visits was comparable between the two groups.

Table 5. Exposure to IV and Oral Study Medication and Timing of TOC Visit (ITT Population)

	DAP N=55 n (%)	**COM N=26 n (%)**
IV Study Drug Administration		
Mean (SD)	12.2 (7.9)	12.3 (7.3)
Median	11.0	11.5
Range	1.0, 44.0	2.0, 31.0
Oral Switch		
Converted to Oral Study Drug	32 (58.2)	16 (61.5)
Not Converted to Oral Study Drug	23 (41.8)	10 (38.5)
Oral Drug Administration		
Mean (SD)	22.7 (23.1)	17.7 (9.0)
Median	15.0	16.0
Range	5.0, 125.0	6.0, 33.0

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	DAP N=55 n (%)	COM N=26 n (%)
Oral Therapy Medication Episodes*	36	20
Amoxicillin/Clavulanate	10 (27.8)	7 (35.0)
Cephalexin	11 (30.6)	9 (45.0)
Cefuroxime	2 (5.6)	0
Clindamycin	7 (19.4)	1 (5.0)
Dicloxacillin	2 (5.6)	3 (15.0)
Other	4 (11.1)	0
Total Study Drug Administration (IV and Oral)		
Mean (SD)	25.3 (23.0)	22.6 (14.9)
Median	20.0	18.0
Range	1.0, 141.0	2.0, 58.0
End of IV Therapy Visit Time (Days)*		
N	54	25
Mean (SD)	13.0 (8.0)	12.4 (7.4)
Median	12	12
Range	3-44	2-31
TOC/Safety Visit Time (Days)*		
N	54	24
Mean (SD)	35.5 (20.6)	32.8 (15.8)
Median	29	28
Range	12-112	8-66

Source: Adapted from Table 14.1.5.1a. *From the reviewer's analysis.

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Efficacy Analysis

We summarized the clinical outcome based on blinded evaluator's assessment, subject-level and pathogen-level microbiological responses, and overall response in this section.

Clinical Outcome at TOC Visit

The clinical outcome based on blinded evaluator's assessment at the TOC visit in the mMITT population is summarized in the following table (Table 6). The clinical success (cure or improvement) proportions were 88.2% versus 77.3% in the DAP and COM groups, respectively, with a difference of 11.0% (95% CI: [-8.7%, 30.6%]). The difference was mainly due to the higher proportion of the non-evaluable subjects in the COM group. The lower bound of the 95% CI indicated that the efficacy results could have met a 9% noninferiority margin. However, the treatment effect could result from both IV and oral therapy. Table 7 contains the results by age group. Due to the small sample sizes, it was expected that there would be considerable variability in the observed success proportions by age group. Nevertheless, except for the youngest age group, DAP achieved a numerically higher success proportion.

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Table 6. Clinical Outcome at TOC in the mMITT Population

Clinical Outcome	**DAP N=51**	**COM N=22**
Clinical Success	45 (88.2)	17 (77.3)
Cure	*43 (84.3)*	*17 (77.3)*
Improved	*2 (3.9)*	*0*
Clinical Failure	6 (11.8)	5 (22.7)
Failure	*5 (9.8)*	*3 (13.6)*
Unable to Evaluate	*1 (2.0)*	*2 (9.1)*
Difference in Success proportions [95% CI]	11.0% [-8.7%, 30.6%]	

Source: Table 11-5, Study Report.

Table 7. Clinical Outcome at TOC by Age Group in the mMITT Population

Clinical Outcome	**1 to 6 year olds**		**7 to 11 year olds**		**12 to 17 year olds**	
	DAP N=20 n (%)	**COM N=8 n (%)**	**DAP N=17 n (%)**	**COM N=9 n (%)**	**DAP N=14 n (%)**	**COM N=5 n (%)**
Clinical Success	17 (85.0)	7 (87.5)	16 (94.1)	7 (77.8)	12 (85.7)	3 (60.0)
Cure	*16 (80.0)*	*7 (87.5)*	*16 (94.1)*	*7 (77.8)*	*11 (78.6)*	*3 (60.0)*
Improved	*1 (5.0)*	*0*	*0*	*0*	*1 (7.1)*	*0*
Clinical Failure	3 (15.0)	1 (12.5)	1 (5.9)	2 (22.2)	2 (14.2)	2 (40.0)
Failure	*3 (15.0)*	*1 (12.5)*	*1 (5.9)*	*1 (11.1)*	*1 (7.1)*	*1 (20.0)*
Unable to Evaluate	*0*	*0*	0	*1 (11.1)*	*1 (7.1)*	*1 (20.0)*
Difference in Success proportions [95% CI] [Exact 95% CI] [1]	-2.5% [-30.3%, 25.3%] [-29.9%, 37.8%][1]		16.3% [-13.0%, 45.7%] [-14.3%, 52.5%][1]		25.7% [-21.0%, 72.4%] [-17.9%, 71.6%][1]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Table 11-5, Study Report.

The clinical success proportions were 88.5% and 79.2% in the DAP and COM groups in the MITT population and 90.0% and 75.0% in the CE population, respectively, as the following table shows. There were no differences in clinical success proportions between the two treatment groups.

Table 8. Clinical Outcome at TOC in the MITT and CE Populations

	MITT		**CE**	
Clinical Outcome	**DAP N=52 n (%)**	**COM N=24 n (%)**	**DAP N=40 n (%)**	**COM N=12 n (%)**
Clinical Success	46 (88.5)	19 (79.2)	36 (90.0)	9 (75.0)
Cure	*44 (84.6)*	*19 (79.2)*	*35 (87.5)*	*9 (75.0)*
Improved	*2 (3.8)*	*0*	*1 (2.5)*	*0*
Clinical Failure	6 (11.5)	5 (20.8)	4 (10.0)	3 (25.0)
Failure	*5 (9.6)*	*3 (12.5)*	*4 (10.0)*	*3 (25.0)*
Unable to Evaluate	*1 (1.9)*	*2 (8.3)*	*0*	*0*
Difference in Success Proportions [95% CI] [Exact 95% CI] [1]	9.3% [-9.1%, 27.7%]		15.0% [-11.2%, 41.2%] [-7.7%, 46.9%][1]	

[1]Exact 95% CI was calculated by the reviewer.
Source: Table 11-6, Study Report.

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Clinical Outcome at EOIV and EOT Visits

The following table summarizes the clinical outcome at the EOIV and EOT visits in the MITT and mMITT populations. In the DAP group, the success proportions were numerically higher than in the COM group, although there were no statistically significant differences detected, both at the EOIV and EOT Visits. The results at EOIV captured only the effect of DAP versus COM before switching to oral therapy. The numerically higher success proportions in the DAP group reflected a potential treatment effect. In addition, at the EOIV visit, the cure proportions were lower than the improvement proportions, while at the EOT visit, the cure proportions increased and were higher than the improvement proportions, indicating the improvement of clinical outcome, on average, as treatment progressed

Table 9. Clinical Outcome at EOIV and EOT Visits in the MITT and mMITT Populations

	MITT		**mMITT**	
	DAP N=52 n (%)	**COM N=24 n (%)**	**DAP N=51 n (%)**	**COM N=22 n (%)**
EOIV				
Clinical Success	49 (94.2)	21 (87.5)	48 (94.1)	19 (86.4)
Cure	*15 (28.8)*	*6 (25.0)*	*14 (27.5)*	*4 (18.2)*
Improved	*34 (65.4)*	*15 (62.5)*	*34 (66.7)*	*15 (68.2)*
Clinical Failure	3 (5.7)	3 (12.5)	3 (5.9)	3 (13.6)
Failure	2 (3.8)	0	*2 (3.9)*	*0*
Unable to Evaluate	1 (1.9)	3 (12.5)	*1 (2.0)*	*3 (13.6)*
Difference in success proportions [95% CI] [Exact 95% CI] [1]	6.7% [-7.9%, 21.4%] [-6.9%, 27.0%][1]		3.3% [-13.7%, 20.4%] [-6.6%, 29.2%][1]	
EOT				
N[§]	49	24	48	22
Clinical Success	45 (91.8)	19 (79.2)	44 (91.7)	17 (77.3)
Cure	*43 (87.8)*	*17 (70.8)*	*42 (87.5)*	*15 (68.2)*
Improved	*2 (4.1)*	*2 (8.3)*	*2 (4.2)*	*2 (9.1)*
Clinical Failure	4 (8.2)	5 (20.8)	4 (8.3)	5 (22.7)
Failure	*2 (4.1)*	*2 (8.3)*	*2 (4.2)*	*2 (9.1)*
Unable to Evaluate	*2 (4.1)*	*3 (12.5)*	*2 (4.2)*	*3 (13.6)*
Difference in success proportions [95% CI] [Exact 95% CI] [1]	12.7% [-5.3%, 30.6%] [-4.2%, 34.3%][1]		14.4% [-4.8%, 33.6%] [-3.3%, 37.8%][1]	

[§]Three subjects in the DAP group had no outcome evaluation at the EOT visit. They were excluded from the Sponsor's analysis but should have been considered as "unable to evaluate".

[1]Exact 95% CIs were calculated by the reviewer.

Source: Modified from Table 11-8, Study Report and based on submitted data sets.

The blinded evaluator's assessment of clinical outcome by age group at the EOIV and EOT visits in the mMITT population is listed in Table 10. At the EOIV visit, the success proportions did not show a clear pattern; at the EOT visit, the success proportions were numerically higher in the DAP group than in the COM group.

Reference ID: 4134362

Table 10. Clinical Outcome at EOIV and EOT by Age Group (mMITT Population)

	1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
	DAP N=20 n (%)	**COM N=8 n (%)**	**DAP N=17 n (%)**	**COM N=9 n (%)**	**DAP N=14 n (%)**	**COM N=5 n (%)**
EOIV						
N	20	8	17	9	14	5
Clinical Success	19 (95.0)	8 (100.0)	16 (94.1)	7 (77.8)	13 (92.9)	4 (80.0)
Cure	*7 (35.0)*	*1 (12.5)*	*5 (29.4)*	*2 (22.2)*	*2 (14.3)*	*1 (20.0)*
Improved	*12 (60.0)*	*7 (87.5)*	*11 (64.7)*	*5 (55.6)*	*11 (78.6)*	*3 (60.0)*
Clinical Failure	1 (5.0)	0	1 (5.9)	2 (22.2)	1 (7.1)	1 (20.0)
Failure	*1 (5.0)*	*0*	*1 (5.9)*	*0*	*0*	*0*
Unable to Evaluate	*0*	*0*	*0*	*2 (22.2)*	*1 (7.1)*	*1 (20.0)*
Difference in Success proportions [95% CI] [Exact 95% CI] [1]	-5.0% [-14.6%, 4.6%] [-26.1%, 31.2%][1]		16.3% [-13.0%, 45.7%] [-14.3%, 52.5%][1]		12.9% [-24.7%, 50.4%] [-22.0%, 62.2%][1]	
EOT						
N	19	8	16	9	13	5
Clinical Success	18 (94.7)	7 (87.5)	15 (93.8)	6 (66.7)	11 (84.6)	4 (80.0)
Cure	*17 (89.5)*	*7 (87.5)*	*15 (93.8)*	*5 (55.6)*	*10 (76.9)*	*3 (60.0)*
Improved	*1 (5.3)*	*0*	*0*	*1 (11.1)*	*1 (7.7)*	*1 (20.0)*
Clinical Failure	1 (5.3)	1 (12.5)	1 (6.3)	3 (33.3)	2 (15.4)	1 (20.0)
Failure	*1 (5.3)*	*1 (12.5)*	*1 (6.3)*	*1 (11.1)*	*0*	*0*
Unable to Evaluate	*0*	*0*	*0*	*2 (22.2)*	*2 (15.4)*	*1 (20.0)*
Difference in Success proportions [95% CI] [Exact 95% CI] [1]	7.2% [-17.8%, 32.3%] [-18.0%, 45.6%][1]		27.1% [-5.9%, 60.1%] [-6.2%, 63.4%][1]		4.6% [-35.6%, 44.8%] [-33.2%, 55.0%][1]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Study Report, Table 11-7.

Subject Level Microbiological Outcome at TOC/Safety Visit

Subject-level microbiologic outcome 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 11. Subject-Level Microbiologic Response at TOC by Age Group (mMITT Population)

	1 to 6 year olds		7 to 11 year olds		12 to 17 year olds		Total	
	DAP N=20 n (%)	**COM N=8 n (%)**	**DAP N=17 n (%)**	**COM N=9 n (%)**	**DAP N=14 n (%)**	**COM N=5 n (%)**	**DAP N=51 n (%)**	**COM N=22 n (%)**
Success	18 (90.0)	7 (87.5)	14 (82.4)	5 (55.6)	7 (50)	5 (100.0)	39 (76.5)	17 (77.3)
Failure	2 (10.0)	1 (12.5)	1 (11.1)	1 (11.1)	3 (21.4)	0	6 (11.8)	2 (9.1)
Non-Evaluable	0	0	2 (11.8)	3 (33.3)	4 (28.6)	0	6 (11.8)	3 (13.6)
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	2.5% [-23.9%, 28.9%] [-23.2%, 41.0%][1]		26.8% [-10.4%, 64.0%] [-10.8%, 63.3%][1]		-50.0% [-76.2%, -23.8%] [-77.1%, 5.4%][1]		-0.8% [-21.8%, 20.2%]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Table 11-10, Study Report.

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Table 12. Pathogen-Level Microbiological Outcome at TOC by *S. Aureus* (mMITT Population)

	1 to 6 year olds		7 to 11 year olds		12 to 17 year olds		Total	
Microbiologic Outcome	DAP N=20 n (%)	COM N=8 n (%)	DAP N=17 n (%)	COM N=9 n (%)	DAP N=14 n (%)	COM N=5 n (%)	DAP N=51 n (%)	COM N=22 n (%)
All Staphylococcus aureus								
Success	19 (95.0)	8 (100.0)	16 (94.1)	9 (100.0)	14 (100.0)	5 (100.0)	49 (96.1)	22 (100.0)
Documented eradicated	19 (95.0)	8 (100.0)	16 (94.1)	9 (100.0)	13 (92.9)	5 (100.0)	48 (94.1)	22 (100.0)
Presumed eradicated	*0*	*0*		*0*	*1 (7.1)*	*0*	*1 (2.0)*	*0*
Failure	1 (5.0)	0	1 (5.9)	0	0	0	2 (3.9)	0
Documented persisted	*1 (5.0)*	*0*	*1 (5.9)*	*0*	*0*	*0*	*2 (3.9)*	*0*
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	-5.0% [-14.6%, 4.6%] [-26.1%, 31.2%][1]		-5.9% [-17.1%, 5.3%] [-29.4%, 27.9%][1]		Not estimable		-3.9% [-9.2%, 1.4%] [-13.8%, 12.7%][1]	
Methicillin-sensitive Staphylococcus aureus (MSSA)								
N at baseline	17	7	14	8	13	4	44	19
Success	16 (94.1)	7 (100.0)	14 (100.0)	8 (100.0)	13 (100.0)	4 (100.0)	43 (97.7)	19 (100.0)
Documented eradicated	*16 (94.1)*	*7 (100.0)*	*14 (100.0)*	*8 (100.0)*	*13 (100.0)*	*4 (100.0)*	*42 (95.5*	*19 (100.0)*
Presumed eradicated	0	0	0	0	0	0	1 (2.3)	0
Failure	1 (5.9)	0	0	0	0	0	1 (2.3)	0
Documented persisted	*1 (5.9)*	*0*	*0*	*0*	*0*	*0*	*1 (2.3)*	*0*
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	-5.9% [-17.1%, 5.3%] [-29.6%, 35.3%][1]		Not estimable		Not estimable		-2.3% [-6.7%, 2.1%] [-12.5%, 16.2%][1]	
Methicillin-resistant Staphylococcus aureus (MRSA)								
N at baseline	3	1	3	1	1	1	7	3
Success	3 (100.0)	1 (100.0)	2 (66.7)	1 (100.0)	1 (100.0)	1 (100.0)	6 (85.7)	3 (100.0)
Documented eradicated	*3 (100.0)*	*1 (100.0)*	*2 (66.7)*	*1 (100.0)*	*1 (100.0)*	*1 (100.0)*	*6 (85.7)*	*3 (100.0)*
Presumed eradicated	0	0	0	0	0	0	0	0
Failure	0	0	1 (33.3)	0	0	0	1 (14.3)	0
Documented persisted	*0*	*0*	*1 (33.3)*	*0*	*0*	*0*	*1 (14.3)*	*0*
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	Not estimable		-33.3% [-86.7%, 20.0%] [-90.6%, 81.1%][1]		Not estimable		-14.3% [-40.2%, 11.6%] [-58.9%, 54.1%][1]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Table 11-11, Study Report.

Table 12 shows a summary of pathogen-level microbiological outcome at the TOC visit by *S. aureus* in the mMITT population The overall success proportions in patients with *S. aureus* and

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MSSA were close between the two treatment groups. Note the sample sizes were too small to reliably estimate the proportions in subjects with MRSA or within each age group.

Overall Outcome at TOC/Safety Visit

A favorable overall outcome included both a favorable clinical outcome (clinical success, as assessed by the blinded evaluator) and a favorable microbiological outcome. The results in the mMITT population are shown in the following table. The overall success proportion in the DAP group for all subjects was numerically higher than that in the COM group. In each age group, the results varied mainly due to the small sample sizes.

Table 13. Overall Outcome at TOC Visit (mMITT Population)

	1 to 6 year olds		**7 to 11 year olds**		**12 to 17 year olds**		**Total**	
Microbiologic Outcome	**DAP N=20 n (%)**	**COM N=8 n (%)**	**DAP N=17 n (%)**	**COM N=9 n (%)**	**DAP N=14 n (%)**	**COM N=5 n (%)**	**DAP N=51 n (%)**	**COM N=22 n (%)**
Success	16 (80.0)	6 (75.0)	14 (82.4)	4 (44.4)	7 (50.0)	3 (60.0)	37 (72.5)	13 (59.1)
Failure or non-evaluable	4 (20.0)	2 (25.0)	3 (17.6)	5 (55.6)	7 (50.0)	2 (40.0)	14 (27.5)	9 (40.9)
Failure	*4 (20.0)*	*2 (25.0)*	*1 (5.9)*	*2 (22.2)*	*4 (28.6)*	*1 (20.0)*	*9 (17.6)*	*5 (22.7)*
Non-evaluable	*0*	*0*	*2 (11.8)*	*3 (33.3)*	*3 (21.4)*	*1 (20.0)*	*5 (9.8)*	*4 (18.2)*
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	5.0% [-29.8%, 39.8%] [-27.2%, 45.6%][1]		37.9% [0.7%, 75.1%] [-2.7%, 71.5%][1]		-10.0% [-60.3%, 40.3%] [-55.9%, 42.8%][1]		-13.5% [-10.5%, 37.4%]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Table 11-12, Study Report.

Sponsor's Main Efficacy Conclusions

The sponsor concluded that the favorable clinical success in the mMITT population was higher at the TOC/safety visit in the DAP group than in the COM group (88.2% versus 77.3%). The microbiological outcome success proportions were comparable at the TOC/safety visit in both treatment groups (DAP: 76.5%; COM: 77.3%) in the mMITT population. The favorable overall outcome success proportions were 72.5% in the DAP group and 59.1% in the COM group in the mMITT population.

3.2.4.2 Reviewer's Analysis Results

The reviewer conducted an analysis for the ITT population. A total of 6 subjects were excluded from the MITT population and 4 of them completed the TOC visit evaluation. The subject in the COM group not receive treatment was not evaluated at the TOC visit. This subject was included in our ITT analysis as a treatment failure. One subject in the DAP group did not complete the TOC visit and had a "not evaluable" status at the TOC visit (Table 14).

Table 15 shows the results of our ITT analysis. These results were consistent with the mITT results reported above.

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Table 14. Information for subjects in the ITT population but excluded from the MITT population

Planned Treatment	Actual Treatment	Bacteremia at Baseline	TOC Completion	Clinical Response at TOC
COM	Not Treated	Not done		
COM	COM	Not done	Y	Not evaluable
COM	COM	Complicated	Y	Failure
DAP	DAP	Not done	N	Not evaluable
DAP	DAP	Complicated	Y	Cure
DAP	DAP	Not done	Y	Not evaluable

Table 15. Clinical Outcome at TOC in the ITT Population

Clinical Outcome	DAP N=55	COM N=27
Clinical Success	47 (85.5)	19 (70.4)
Cure	*45 (81.8)*	*19 (70.4)*
Improved	*2 (3.6)*	*0*
Clinical Failure	8 (14.5)	8 (29.6)
Failure	*5 (9.1)*	*5 (18.5)*
Unable to Evaluate	*3 (5.5)*	*3 (11.1)*
Difference in Success proportions [95% CI]	15.1% [-8.3%, 36.6%]	

The reviewer can replicate the main results included in this review with slight differences noted. There were no additional analysis results from the reviewer, except for efficacy by country in the following Section 4.1.3.

Overall, the treatment effect of IV and possible oral therapy could have met a 9% noninferiority margin at the EOIV, EOT, and TOC visits.

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 (TEAEs) are listed in the following tables. Table 16 reports the results for all patients and by age group. Overall, similar proportions of subjects with adverse events were seen between the two treatment groups. Given the small numbers of subjects by age group, it is difficult to make any conclusions regarding the comparability of the treatment groups within an age group.

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Table 16. Treatment-Emergent Adverse Events (Safety Population)

	1 to 6 year olds		7 to 11 year olds		12 to 17 year olds		Total	
TEAE	DAP N=22 n (%)	COM N=10 n (%)	DAP N=19 n (%)	COM N=9 n (%)	DAP N=14 n (%)	COM N=7 n (%)	DAP N=55 n (%)	COM (N=26) n (%)
At least one TEAE	15 (68.2)	6 (60.0)	12 (63.2)	9 (100.0)	9 (64.3)	7 (71.4)	36 (65.5)	20 (76.9)
At least one severe TEAE	2 (9.1)	0	1 (5.3)	3 (33.3)	2 (14.3)	1 (14.3)	5 (9.1)	4 (15.4)
At least one serious TEAE	6 (27.3)	2 (20.0)	4 (21.1)	3 (33.3)	3 (21.4)	2 (28.6)	13 (23.6)	7 (26.9)
TEAE leading to discontinuation of study drug	0	1 (10.0)	1 (5.3)	1 (11.1)	1 (7.1)	0	3 (5.5)	2 (7.7)
TEAE leading to discontinuation of study	0	0	0	0	0	0	0	0

Treatment-emergent AEs (TEAEs) that occurred on or after the first dose of study drug through the last study evaluation.
Source: Table 12-3, Study Report.

Since DAP is an IV only drug, the following table provides a summary of AE during the IV therapy and oral medication phases (Safety Population). In the IV treatment phase, 52.7% and 69.2% of patients had at least one TEAE in the DAP and COM groups, respectively; in the oral medication treatment phase, the proportions were 9.4% and 37.5%. No concerning differences were observed.

Table 17. Treatment-Emergent Adverse Events by Treatment Phase (Safety Population)

	DAP N=55 n (%)	COM (N=26) n (%)
IV Treatment Phase		
At least one TEAE	29 (52.7)	18 (69.2)
At least one serious TEAE	5 (9.1)	3 (11.5)
TEAE leading to discontinuation of study drug	2	0
Oral Medication Treatment Phase		
N	32	16
At least one TEAE	3 (9.4)	6 (37.5)
At least one serious TEAE	0 (9.1)	3 (18.8)
TEAE leading to discontinuation of study drug	0	2

Source: Table 12-5, Study Report

3.3.2 Frequent Adverse Events by Preferred Term

Treatment-emergent adverse events by preferred term reported in ≥5% of subjects in either treatment group (safety population) are presented in the following table. There were no noticeable differences between the two groups. Analyses by age group were limited by the small sample sizes; however, no overly concerning results were seen (analyses not shown).

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Table 18. Treatment-Emergent Adverse Events by Preferred Term Reported in ≥5% Subjects in Either Treatment Group (Safety Population)

Preferred Term	DAP N=55 n (%)	COM N=26 n (%)
Subjects with at least one TEAE	36 (65.5)	20 (76.9)
Diarrhea	6 (10.9)	5 (19.2)
Pyrexia	5 (9.1)	3 (11.5)
Vomiting	6 (10.9)	2 (7.7)
Osteomyelitis	1 (1.8)	4 (15.4)
Blood creatine phosphokinase increased	4 (7.3)	0
Arthritis bacterial	0	3 (11.5)
Bacteremia	3 (5.5)	0
Cellulitis	1 (1.8)	2 (7.7)
Drug hypersensitivity	0	2 (7.7)
Erythema	0	2 (7.7)

Treatment-emergent AEs (TEAEs) that occurred on or after the first dose of study drug through the last study evaluation.
Subjects experiencing more than one TEAE with the same PT are counted only once.
Source: Table 12-4.

3.3.3 Death and Severe Adverse Events

No deaths occurred in this study. Treatment-emergent severe adverse events (TESAEs) are summarized in the following table. The proportion of subjects with at least one TESAE was 9.1% and 15.4% in the two groups, respectively. Two subjects in the COM group developed osteomyelitis. All other TESAEs occurred in at most one subject in each group.

Table 19. Treatment-Emergent Serious Adverse Events by Preferred Term (Safety Population)

System Organ Class Preferred Term	DAP N=55 n (%)	COM N=26 n (%)
Subjects with at least one severe TEAE	5 (9.1)	4 (15.4)
Immune system disorders		
Intestine transplant rejection	0	1 (3.8)
Infections and infestations		
Bacteremia	1 (1.8)	0
Osteomyelitis	0	2 (7.7)
Pneumonia	1 (1.8)	
Staphylococcal bacteremia	1 (1.8)	0
Metabolism and nutrition disorders		
Malnutrition	1 (1.8)	0
Musculoskeletal and connective tissue disorders		
Synovitis	1 (1.8)	0
Respiratory, thoracic and mediastinal disorders		
Pulmonary oedema	0	1 (3.8)

Treatment-emergent AEs (TEAEs) that occurred on or after the first dose of study drug through the last study evaluation.
Subjects experiencing more than one AE with the same System Organ Class and Preferred Term are counted only once at the corresponding System Organ Class or PT level with the highest severity.
Source: Table 12-7, Study Report.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Country

Efficacy analyses by age group are reported in Section 3 of this review. The following sections reported results by gender, race, and country.

4.1.1 Efficacy by Gender and by Age and Gender

Clinical outcome at TOC by gender and by age and gender in the mMITT population is listed in the following table. Due to the small sample sizes, for the overall results and these subgroup analyses, it is difficult to make any conclusions.

Table 20. Clinical Outcome at TOC by Gender (mMITT Population)

	Male		**Female**	
All	**DAP N=35 n (%)**	**COM N=13 n (%)**	**DAP N=16 n (%)**	**COM N=9 n (%)**
Clinical Success	30 (85.7)	8 (61.5)	15 (93.8)	9 (100.0)
Clinical Failure	5 (14.3)	5 (38.5)	1 (6.2)	0
Difference in Success Proportions [95% CI] [Exact 95% CI][1]	24.2% [-4.7%, 53.1%] [-4.0%, 54.1%][1]		-6.3% [-18.1%, 5.6%] [-31.3%, 27.0%][1]	
1 to 6 year olds	**N=11**	**N=1**	**N=9**	**N=7**
Clinical Success	8 (72.7)	0	9 (100)	7 (100.0)
Clinical Failure	3 (27.3)	1 (100)	0	0
7 to 11 year olds	**N=10**	**N=8**	**N=7**	**N=1**
Clinical Success	10 (100.0)	6 (75.0)	6 (85.7)	1 (100.0)
Clinical Failure	0	2 (25.0)	1 (14.3)	0
12 to 17 year olds	**N=14**	**N=4**	**N=0**	**N=1**
Clinical Success	12 (85.7)	2 (50.0)	0	1 (100.0)
Clinical Failure	2 (14.3)	2 (50.0)	0	0

[1]Exact 95% CIs were calculated by the reviewer. Analysis by age and gender was conducted by the reviewer.
Source: Table 14.2.1.2.1, Subgroup Analysis Report.

4.1.2 Efficacy by Race

Clinical outcome at TOC/Safety visit by race in the mMITT population is listed Table 21. Because of the small sample sizes, it is difficult to make conclusions for any race except for White, where the two treatment groups had similar success proportions.

4.1.3 Efficacy by Country

Clinical outcome at TOC/Safety visit by country in the mMITT population is listed in the following table. In the US, the success proportion in the DAP group was numerically higher than that in the COM group. In Ukraine, the success proportion was 100% for both groups. In Ukraine, MSSA was the only BIP for all subjects in the mMITT population. All other main baseline characteristics in Ukraine were similar to other countries. All subjects only having MSSA at baseline might explain the high success rate in Ukraine. In other countries, the

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proportion in the DAP group was higher but the sample sizes in these countries were too small to make a reliable comparison.

Table 21. Summary of Clinical Outcome at TOC by Race (mMITT Population)

	Asian		Black/African American		White		Other	
	DAP N=2 n (%)	COM N=1 n (%)	DAP N=5 n (%)	COM N=0 n (%)	DAP N=41 n (%)	COM N=15 n (%)	DAP N=3 n (%)	COM N=6 n (%)
Clinical Success	1 (50.0)	1 (100.0)	5 (100.0)	0	36 (87.8)	13 (86.7)	3 (100.0)	3 (50.0)
Clinical Failure	1 (50.0)	0	0	0	5 (12.2)	2 (13.3)	0	3 (50.0)
Difference in Success Proportions [95% CI] [Exact 95% CI] [1]	-50% [-100.0%, 19.3%] [-98.7%, 77.0%][1]		Not estimable		1.1% [-18.8%, 21.0%] [-17.3%, 28.5%][1]		50% [10.0%, 90.0%] [-28.3%, 90.2%][1]	

[1]Exact 95% CIs were calculated by the reviewer.
Source: Table 14.2.1.2.2, Subgroup Analysis Report.

Table 22. Summary of Clinical Outcome at TOC by Country (mMITT Population)

	USA		Ukraine		Other	
	DAP N=24 n (%)	COM N=8 n (%)	DAP N=16 n (%)	COM N=8 n (%)	DAP N=11 n (%)	DAP N=6 n (%)
Clinical Success	20 (83.3)	6 (75.0)	16 (100.0)	8 (100.0)	9 (81.8)	3 (50.0)
Clinical Failure	4 (16.7)	2 (25.0)	0	0	2 (18.2)	3 (50.0)
Difference in Success Proportions [Exact 95% CI]	8.3% [-21.4%, 49.0%]		Not estimable		31.8% [-17.3%, 74.0%]	

Source: Calculated by the reviewer.

4.2 Other Special/Subgroup Populations

Table 23. Summary of Clinical Success at TOC by Baseline Characteristic (mMITT Population)

Baseline characteristic	DAP (N=51)	COM (N=22)
MSSA	39/44 (88.6%)	15/19 (78.9%)
MRSA	6/7 (85.7%)	2/3 (66.7%)
Bacteremia classification		
Complicated	23/26 (88.5%)	10/14 (71.4%)
Uncomplicated	22/24 (91.7%)	7/7 (100.0%)
Classification not done	0/1	0/1
Received only IV therapy	14/19 (73.7%)	5/7 (71.4%)
Received IV plus oral therapy	31/32 (96.9%)	12/15 (80.0%)

Source: Adapted from Table 11-9, Study Report.

The sponsor conducted subgroup analyses of clinical outcome (success) response at the TOC/Safety Visit in the mMITT population (Table 23). As noted before, in the DAP group, the proportion of subjects with complicated bacteremia was lower. However, the clinical success proportion among subjects with complicated bacteremia was numerically higher in the DAP group than in the COM group. Therefore, the lower proportion of subjects with complicated bacteremia in the DAP group should not be a concern in the assessment of efficacy of the two

treatment groups. In subjects infected with MSSA, MRSA, or with/without switching to an oral therapy, the success proportions were numerically higher in the DAP group than in the COM group. The subgroup analysis for subjects with/without switching to an oral therapy was not proper because switching to oral therapy was based on post-randomization/post-IV-treatment events, which could be affected by treatment assignment.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The objectives of this study were to assess the safety and efficacy of daptomycin for injection compared with standard of care in pediatric patients with bacteremia. 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. The average duration of IV treatment was about 12 days in the two groups and similar proportions of subjects switched to an oral therapy. The clinical success proportions in the DAP group was numerically higher than in the COM group at the EOIV and EOT visits in the three analysis populations. There was no indication of reduced safety or efficacy of daptomycin compared to control at the point of oral switch.

This study was not designed to assess superiority or non-inferiority with any pre-specified non-inferiority margin.

5.2 Collective Evidence

Daptomycin for injection was approved for the treatment of *S. aureus* bacteremia in adults. One randomized, multicenter, open-label, investigator-blinded non-inferiority efficacy study was conducted to compare the efficacy of DAP with conventional IV therapy in the treatment of *S. aureus* bacteremia in adults, including those with known or suspected endocarditis caused by MSSA and MRSA. The minimum length of treatment ranged from 10 to 42 days. In the modified intent-to-treat (MITT) population, 44.2% (53/120) and 41.7% (48/115) in the DAP and COM groups achieved a successful outcome at the TOC/Safety Visit (6 weeks after the last treatment dose), with a difference in success proportion of 2.4% [95% CI: -10.2%, 15.1%], meeting the 20% noninferiority margin. The noticed difference was the exclusion of patients with endocarditis in the pediatric study. The primary clinical endpoint was defined similarly (cure+improvement as success), except for the timing (42 days after the last dose of treatment in the adult study versus 7-14 days in the pediatric study). It is noticed that the success proportions in adult bacteremia study were much lower than those in this pediatric bacteremia study. In adults, 75% of the ITT population had systemic inflammatory response syndrome at baseline.

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We communicated with the medical reviewer about the difference in success proportions between the adult and pediatric studies. The reasons for the difference remain unknown.

According to the FDA's letter to the Sponsor dated 8/1/2016, efficacy for the cSSSI and *S. aureus* bacteremia indications in children can be extrapolated from the adult studies because of the sufficiently similar course of the diseases and the effects of therapy.

Based on the review of this sNDA, DAP and COM had similar efficacy results and safety profiles. The study was not designed to test non-inferiority of the efficacy of DAP to COM; however, for the blinded-evaluator assessed clinical success the 95% confidence intervals for the difference in success proportions (DAP - COM) could have ruled out a difference of -9%. The sample sizes in the various age groups were too small to make any strong conclusions; however, only the DAP subjects in the youngest age group performed numerically slightly worse than the COM subjects.

Due to the limitations in study design (switching to oral therapy), it is very difficult to attribute the treatment effect at the TOC Visit to DAP alone. At the EOIV Visit, DAP showed a numerically better efficacy profile than COM; however, most clinical successes were due to improvement, not cure; therefore, the EOIV Visit may be too early to determine efficacy, although it was an appropriate time to compare the efficacy of DAP alone with COM. From this study, 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 COM.

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 bacteremia in pediatric population were supported by the submitted data because of the numerically similar efficacy and safety results between the DAP and COM groups. This study met the previously mentioned post-marketing requirement for this NDA.

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. In general, the subjects in the two groups were comparable with respect to these baseline variables. However, due to the small sample sizes in each group, it is difficult to make reliable conclusions.

Table 24. Demographics, Baseline Characteristics, and Baseline Pathogens for All Subjects (ITT population)

	1 to 6 year olds		7 to 11 year olds		12 to 17 year olds		Total	
	DAP 12 mg/kg N=22 n (%)	COM N=10 n (%)	DAP 9 mg/kg N=19 n (%)	COM N=9 n (%)	DAP 7 mg/kg N=14 n (%)	COM N=7 n (%)	DAP N=55 n (%)	COM N=26 n (%)
Age (years)								
Mean (SD)	3.8 (1.2)	4.1 (1.8)	10.3 (1.2)	9.5 (1.3)	14.1 (1.7)	14.6 (1.9)	8.7 (4.5)	8.8 (4.5)
Median	3.7	4.9	10.6	9.6	13.6	14.5	9.6	8.8
Min, Max	2.0, 6.7	2.0, 6.5	8.0, 11.8	7.6, 11.4	12.2, 16.9	12.6, 17.6	2.0, 16.9	2.0, 17.6
Sex, n (%)								
Male	12 (54.5)	2 (20.0)	12 (63.2)	8 (88.9)	14 (100.0)	6 (85.7)	38 (69.1)	16 (61.5)
Female	10 (45.5)	8 (80.0)	7 (36.8)	1 (11.1)	0	1 (14.3)	17 (30.9)	10 (38.5)
Race, n (%)								
American Indian or Alaska Native	0	0	0	1 (11.1)	0	0	0	1 (3.8)
Asian	0	2 (20.0)	1 (5.3)	0	1 (7.1)	0	2 (3.6)	2 (7.7)
Black or African American	2 (9.1)	0	4 (21.1)	0	0	0	6 (10.9)	0
Other	1 (4.5)	2 (20.0)	2 (10.5)	2 (22.2)	1 (7.1)	1 (14.3)	4 (7.3)	5 (19.2)
White	19 (86.4)	6 (60.0)	12 (63.2)	6 (66.7)	12 (85.7)	6 (85.7)	43 (78.2)	18 (69.2)
Height (cm)								
N	21	10	19	9	14	7	54	26
Mean (SD)	98.7 (12.2)	103.8 (19.0)	138.2 (19.1)	132.2 (13.6)	163.9 (13.9)	161.8 (15.6)	129.5 (30.7)	129.2 (28.4)
Median	99.8	109.5	133.0	129.0	163.5	164.0	128.5	126.0
Min, Max	69.5, 118.0	73.0, 127.0	106.0, 170.0	111.0, 149.5	138.0, 196.0	134.0, 176.5	69.5, 196.0	73.0, 176.5
Weight (kg)								
N	22	10	19	9	14	7	55	26

Mean (SD)	16.2 (3.8)	16.3 (5.3)	35.9 (12.0)	30.1 (10.4)	55.3 (11.7)	59.9 (9.5)	33.0 (18.3)	32.8 (19.6)
Median	16.1	17.5	33.5	27.0	53.3	58.0	26.6	24.3
Min, Max	10.0, 22.8	9.3, 23.0	20.1, 65.0	16.8, 50.0	33.0, 83.3	48.0, 72.0	10.0, 83.3	9.3, 72.0
BMI (kg/m^2)								
N	21	10	19	9	14	7	54	26
Mean (SD)	16.6 (3.1)	15.0 (2.7)	18.7 (4.4)	16.8 (3.2)	20.4 (1.8)	23.1 (4.3)	18.3 (3.7)	17.8 (4.7)
Median	16.3	15.7	17.0	15.5	19.8	22.5	17.4	16.6
Range	11.6, 24.2	10.3, 19.0	13.4, 29.8	13.6, 24.1	17.3, 23.6	18.2, 31.6	11.6, 29.8	10.3, 31.6
Baseline infection pathogen, n(%)								
Coagulase negative staphylococcus	2 (9.1)	1 (10.0)	0	0	0	1 (14.3)	2 (3.6)	2 (7.7)
Staphylococcus Aureus (MRSA)	3 (13.6)	1 (10.0)	3 (15.8)	1 (11.1)	1 (7.1)	1 (14.3)	7 (12.7)	3 (11.5)
Staphylococcus Aureus (MSSA)	17 (77.3)	7 (70.0)	14 (73.7)	8 (88.9)	13 (92.9)	4 (57.1)	44 (80.0)	19 (73.1)
Staphylococcus Epidermidis (MRSE)	0	0	0	0	0	1 (14.3)	0	1 (3.9)
Staphylococcus Saprophyticus	0	0	1 (5.3)	0	0	0	1 (1.8)	0
No BIP established	0	1 (10.0)	1 (5.3)	0	0	0	1 (1.8)	1 (3.9)

Reference

Alan Agresti and Brian Caffo (2000). Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures. The American Statistician, 54 (4), 280-288.
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/s/

XIANBIN LI
08/03/2017

KAREN M HIGGINS
08/03/2017
I concur.