CLINICAL REVIEW

Application Type	NDA supplement
Application Number(s)	21572
Priority or Standard	Priority
Submit Date(s)	March 1, 2017
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Division / Office	DAIP/OAP
Reviewer Name(s)	Nicholas Rister, MD
Review Completion Date	August 4, 2017
Established Name	Daptomycin
(Proposed) Trade Name	Cubicin
Therapeutic Class	Cyclic Lipopeptide
Applicant	Cubist Pharmaceuticals
Formulation(s)	Injection
Dosing Regimen	7 mg/kg (12-17 years), 9 mg/kg (7-11 years), and 12 mg/kg (1-6 years)
Indication(s)	Bacteremia caused by *Staphylococcus aureus*
Intended Population(s)	Ages 1-17 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has submitted a response to a pediatric postmarketing requirement to provide information on the use of daptomycin in pediatric patients with *Staphylococcus aureus* bacteremia (SAB). Daptomycin is currently approved in adults for treatment of SAB including those with right-sided infective endocarditis at a dose of 6 mg/kg every 24 hours. Additionally, daptomycin is currently approved in adults and pediatric patients (aged ≥1 year) with complicated skin and skin structure infections (cSSSI) at doses of 4-10 mg/kg every 24 hours based on age. The overall safety profile for daptomycin in pediatric patients with SAB was similar to the profile described in the current daptomycin product labeling for adults and pediatric patients. The point estimate for efficacy of daptomycin in treating SAB exceeded that previously reported in an adult trial which included patients with infective endocarditis. The reviewer recommends approval of daptomycin for the treatment of SAB in pediatric patients 1 year and older.

1.2 Risk Benefit Assessment

The currently available antibiotics for treatment of Gram-positive, including methicillin-resistant *Staphylococcus aureus* (MRSA), infections in the pediatric population is limited. The results of the postmarketing study DAP-PEDBAC-11-02 in pediatric patients 1 year of age and older demonstrated efficacy of IV daptomycin to current standard of care comparators for the treatment of *Staphylococcus aureus* bacteremia.

Daptomycin was dosed by weight and age to provide similar exposure as the 6 mg/kg dose in adults, with 7 mg/kg in 12-17 year olds, 9 mg/kg in 7-11 year olds, and 12 mg/kg in 1-6 year olds. This study was not powered to demonstrate efficacy, though the efficacy rate exceeded the observations in adults. The discrepancy in adult vs pediatric efficacy rates is expected due to the higher-risk condition of the adult population including advanced age, inclusion of patients with infective endocarditis, and comorbid conditions such as chronic renal disease and diabetes discussed further in the efficacy review.

The safety profile in pediatric patients is similar to what has been seen in the adult clinical trials and in postmarketing reports as well as postmarketing experience with pediatric patients with Gram-positive cSSSI. The most frequently reported adverse reactions in pediatric patients receiving daptomycin for SAB were gastrointestinal conditions such as diarrhea and vomiting. Pyrexia was also a common adverse event. No new safety signals were apparent from the review of the safety database focusing on CPK, hepatic function, and peripheral neuropathy. The pattern of skeletal muscle toxicity observed in the study was consistent with previous experiences with adults and

pediatric patients. Most CPK elevations fell between 1 and 2.5 x ULN and CPK elevations >2.5 x ULN were uncommon. There was no clinically significant new concern for drug induced liver injury (DILI) or peripheral neuropathy identified during the review.

With clinical response rates of daptomycin in pediatric SAB comparable or exceeding rates in adults, a safety profile in pediatric SAB comparable to experience with adults with SAB and patients ≥1 year of age with Gram positive cSSSI, and similarity of daptomycin to current standard of care comparators for SAB in pediatric patients, the risk-benefit assessment for use of daptomycin in pediatric patients with SAB can be considered favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommended postmarket risk management strategies other than monitoring and reporting of adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended additional postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Daptomycin is a cyclic lipopeptide class antibiotic available for intravenous use as single-use vials containing 500 mg daptomycin as a sterile, lyophilized powder.

Daptomycin is currently indicated for the treatment of adults and children at least 1 year of age with complicated skin and skin structure infections (cSSSI) caused by susceptible strains of Gram-positive organisms. Daptomycin is also indicated in adults at least 18 years of age for treatment of *Staphylococcus aureus* bacteremia and right-sided infective endocarditis.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.1 FDA-Approved Treatment for Bacteremia Caused by *Staphylococcus aureus*

Drug	Route	Pediatric Approval
Cefotaxime	Intravenous	Yes
Daptomycin	Intravenous	No
Penicillin G Potassium	Intravenous	Yes
Penicillin G Sodium	Intravenous	Yes
Vancomycin	Intravenous	Yes

Vancomycin and daptomycin are the only FDA-approved agents for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in the United States. Options for salvage therapy in vancomycin and daptomycin resistant cases, based on low-quality evidence, include linezolid, trimethoprim/sulfamethoxazole (TMP/SMX), dalbavancin, ceftaroline, quinupristin/dalfopristin, and telavancin[1].

The use of anti-staphylococcal β-lactam antibiotics whenever possible to treat methicillin-sensitive *Staphylococcus* aureus (MSSA) infections is a widely accepted standard of care. The Infectious Diseases Society of America (IDSA) guideline for infectious endocarditis in adults includes the use of oxacillin, nafcillin, and cefazolin in these circumstances[1]. While cefotaxime and penicillin G include SAB indications in their labelling when susceptibility testing supports their use, these drugs are no longer recommended due to changing resistance patterns and available alternatives with proven efficacy.

Of note, the use of clindamycin to treat *Staphylococcus aureus* endocarditis is not recommended due to a reported increased rate of relapse[1].

2.3 Availability of Proposed Active Ingredient in the United States

Daptomycin is currently available in the US marketed as a brand name Cubicin for intravenous use.

2.4 Important Safety Issues with Consideration to Related Drugs

Daptomycin is associated with a number of serious adverse reactions described in the boxed warnings and precautions section of the approved product labeling:

- Anaphylaxis/hypersensitivity
- Myopathy and rhabdomyolysis
- Eosinophilic pneumonia
- Peripheral neuropathy
- Increased International Normalized Ratio (INR)/prolonged prothrombin time

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Cubicin (daptomycin for injection) was approved for adult use in September, 2003 for the indication of cSSSI and in May, 2006 for SAB. The approval letter for the SAB indication contained a required postmarketing study commitment for a deferred study for the treatment of *S. aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates in patients 0 to 18 years of age. In response to the Sponsor's Proposed Pediatric Study Request (PPSR) from July 22, 2011 (amended February 26, 2013), to NDA 21572, the Food and Drug Administration (FDA) issued a pediatric

written request (PWR) on May 24, 2013, for pharmacokinetic studies and studies in cSSSI, SAB, and osteomyelitis. The PWR was amended on August 27, 2013, and December 19, 2014. The final study report for the pediatric *S. aureus* bacteremia indication was submitted on March 2, 2017.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and there were no meaningful concerns noted by this reviewer regarding the quality and integrity of the datasets. The datasets and the applicant's analyses were reviewed and verified. There was no evidence that the studies reviewed were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

The studies submitted were stated to be compliant with Good Clinical Practices.

3.3 Financial Disclosures

The applicant submitted financial disclosure form 3454 and debarment certification for all investigators involved in the studies conducted. The form states that the applicant had not entered into any financial arrangement with the listed clinical investigators in which compensations to the investigators could be affected by the outcome of the study. Refer to Section 9.4 Clinical Investigator Financial Disclosure Review for additional details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No additional CMC information was submitted with this application.

4.2 Clinical Microbiology

Surveillance data indicate that daptomycin continues to demonstrate *in vitro* activity against indicated pathogens. All gram positive isolates obtained in the surveillance and clinical studies were deemed susceptible to daptomycin (based on FDA breakpoints). The Phase 4 clinical microbiology data suggest that daptomycin is non-inferior to the SOC (IV vancomycin, IV clindamycin, or IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin]). Please refer to the clinical microbiology review by Avery Goodwin, PhD.

4.3 Preclinical Pharmacology/Toxicology

No additional pharmacology/toxicology information was submitted for this review.

4.4 Clinical Pharmacology

Based on the clinical pharmacology review by Sonia Pahwa, PhD, of the submitted study reports, the dosing regimens of daptomycin in pediatric patients proposed by the applicant are expected to provide the exposure comparable to that observed in adult patients receiving 6 mg/kg once daily (i.e., approved dosing regimen to treat SAB). However, the proposed dose of 12 mg/kg once daily in the age group of 1 to 6 years was evaluated only in patients ≥2 years of age for safety and efficacy of daptomycin. Because there is no clinical experience with 12 mg/kg once daily (up to 42 days) in pediatric patients aged from 1 to 2 years, the clinical pharmacology review team recommended that the use of daptomycin to treat SAB should be limited to patients ≥2 years of age.

This clinical efficacy and safety review recommends that patients aged from 1 to 2 years can be included in the proposed indication based on data from PK simulations in pediatric patients, and from safety, efficacy and PK studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections. Please refer to the full efficacy and safety analysis as well as label recommendations in Section 9.2.

4.4.1 Mechanism of Action

Daptomycin is a cyclic lipopeptide bactericidal against Gram-positive bacteria with activity against growing and stationary-phase bacteria. Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death.

4.4.2 Pharmacodynamics

Dose-selection for the treatment of pediatric bacteremia caused by *Staphylococcus aureus* (Study DAP-PEDBAC-11-02) was not based on efficacy or on efficacy-related

pharmacodynamics marker, but based on the exposures achieved in the prior Phase 1 studies.

4.4.3 Pharmacokinetics

Dosing strategy evaluated in pediatric patients in the Phase 4 bacteremia study was based on matching projected exposures (AUC) in pediatric patients with the observed exposures in adults dosed at 6 mg/kg once daily whereby efficacy and safety were established previously. In addition the three dedicated Phase 1 pediatric studies demonstrated daptomycin exposure was generally lower in pediatric patients compared with adults at the same dose. Regimen for dosing was then set as 7 mg/kg every 24 hours in 12 to 17 years of age children, 9 mg/kg every 24 hours in 7 to 11 years of aged children, and 12 mg/kg every 24 hours in 1 to 6 years of age children. The infusion rate was set to run over 30 minutes in children aged 7-17 years and over 60 minutes in children aged 1 to 6 years to avoid elevated C_{max} related to nervous system toxicity in juvenile dogs. At the evaluated dosing regimens, the exposures in pediatric patients with bacteremia are comparable to the exposures in adult patients with bacteremia, with similar efficacy and safety profiles in pediatric and adult patients.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1 briefly reviews the various studies of the pediatric development program for daptomycin. DAP-PEDBAC-11-02 is the focus of this review with reference made to additional studies when necessary. DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01, and DAP-PEDS-07-03 were reviewed previously.

Table 5.1 Overview of Studies

Study Type	Study Identifier	Study Objectives(s)	Study Design and Control	Test Product(s); Dose Administration	Number of Subjects	Patient Characteristics	Region
PK	DAP-PEDS-05-01	Evaluation of pharmacokinetics of a single dose of daptomycin in patients aged 2 to 17 years for proven or suspected Gram-positive infection	Multi-center, open label, non-comparative, single dose pharmacokinetics (Phase 1)	Daptomycin 4 mg/kg, single dose given IV over 30 min	25	Males/females aged 2 to 17 years	USA 3 sites initiated and enrolled
PK, Safety	DAP-PEDS-07-02	Evaluation of pharmacokinetics of a single dose of daptomycin in patients aged 2 to 6 years for proven or suspected Gram positive infection	Multi-center, open label, non-comparative, single dose pharmacokinetics (Phase 1)	Daptomycin 8 mg/kg, single dose given IV over 1 or 2 hr 10 mg/kg, single dose given IV over 1 or 2 hr	12	Males/females aged 2-6 years	USA 6 sites initiated, 4 sites enrolled
PK,	DAP-	Evaluation of	Multi-center,	Daptomycin	24	Males/females	USA

Safety	PEDS-09-01	pharmacokinetics and safety of a single dose of daptomycin in patients aged 3 months to 24 months concurrently receiving standard ant biotic therapy for proven or suspected bacterial infection	open label, non-comparative, single dose pharmacokinetics (Phase 1)	4 mg/kg, single dose given IV over 30 min 6 mg/kg, single dose given IV over 30 min		aged 3-24 months	8 sites initiated, 7 sites enrolled
PK, Safety, Efficacy	DAP-PEDS-07-03	Evaluation of safety, efficacy, and pharmacokinetics of daptomycin in pediatric subjects aged 1-17 years with complicated skin and skin structure infections (cSSSI) caused by gram positive pathogens	Multi-center, multi-national, evaluator blinded, randomized study of pharmacokinetics, safety, efficacy (Phase 4)	Daptomycin 5, 7, 9, or 10 mg/kg IV given q24 hr over 30-60 min Given up to 14 days	389	Males/females aged 1-17 years	USA, India 37 sites initiated, 30 sites enrolled
Safety, Efficacy	DAP-PEDBAC-11-02	A comparative evaluation of the safety and efficacy of daptomycin versus standard of care in pediatric subject 1-17 years of age with bacteremia caused by *Staphylococcus aureus*	Multi-center, multi-national, open-label with evaluator blinding, comparative, safety, efficacy (Phase 4)	Daptomycin 7, 9, and 12 mg/kg IV given q24 hr over 30-60 min Given up to 42 days or longer at investigator discretion	55	Males/females aged 1-17 years (no subjects <2 years of age were enrolled)	USA, Europe (Greece, Ukraine, Israel, Romania), South American (Argentina, Brazil, Panama), Australia, Asia (Thailand, Malaysia) 65 sites initiated, 25 enrolled patients

5.2 Review Strategy

The focus of this review's efficacy and safety evaluations was a detailed analysis of study DAP-PEDBAC-11-02, a multi-national, randomized, evaluator-blinded, comparative study in pediatric patients aged 1-17 years with *S. aureus* bacteremia. Efficacy analysis compared the study medication, daptomycin, to current standard therapies. Given the low number of pediatric patients given daptomycin in study DAP-PEDBAC-11-02, an analysis of safety includes discussion of and reference to the prior pediatric study DAP-PEDS-07-03 which evaluated the use daptomycin for the treatment of cSSSI caused by Gram-positive pathogens.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

There are a growing number of infections in the pediatric populations with resistant Gram-positive organisms. Of particular concern are methicillin-resistant *S. aureus* (MRSA) infections. There are limited therapeutic options, particularly in pediatric patients, which have been evaluated for safety and efficacy for treating MRSA and other serious Gram-positive infections including bacteremia.

6.1.1 Methods

A multi-center, multi-national, randomized, evaluator-blinded, comparative study in pediatric patients ages 1 to 17 years, with bacteremia caused by *S. aureus*, evaluating safety, efficacy, and PK of daptomycin compared to current therapies. Comparators used included vancomycin, semi-synthetic penicillins, first-generation cephalosporin (cefazolin), linezolid, and clindamycin. Study populations were assigned to treatment groups by means of computer-generated randomization stratified by disease classification (complicated or uncomplicated bacteremia) and age group, providing a 2:1 ratio of subjects in daptomycin vs comparator groups. Complicated bacteremia was defined as cases with any of the following in accordance with IDSA recommendations[1]:

- A positive culture for *S. aureus* on day 2 to 4 after first dose of study drug
- Fever lasting >72 hours after first dose of study drug
- Infective endocarditis (based on modified Duke criteria)
- Suspected metastatic disease
- Septic arthritis or osteomyelitis
- Deep tissue abscess
- Infection of prosthetic material (including intravascular catheter material not removed by day 4 of treatment)

Study investigators were not blinded to treatments; the design therefore included evaluators who did not enroll subjects, and were blinded for the entirety of the study to reduce bias and assess safety and efficacy endpoints. Patients were switched to oral therapy fitting standard of care at the discretion of investigators after completing 5 or 7 days of IV therapy for uncomplicated or complicated bacteremia, respectively.

For inclusion in the study, subjects were required to have a proven or probable diagnosis of *S. aureus* bacteremia. A proven diagnosis was defined as a patient with one or more *S. aureus* positive blood cultures by conventional culture methods or rapid testing within 3 days prior of first study drug dose. A probable diagnosis was defined as

a patient with gram positive cocci in clusters visible from blood culture. In cases where coagulase negative *Staphylococcus* grew after enrollment, only high-risk subjects with persistently positive blood cultures from multiple days remained on study drug. High-risk patients included, but were not limited to, immunocompromised patients, cancer patients, and those with potential source IV catheters or intravascular devices without removal. Patients were excluded if they had received systemic antibiotics for >72 hours in the 96 hours prior to first dose of study drug unless in vitro resistance to the agent used had been proven, had shock or hypotension unresponsive to fluids and vasopressors for >4 hours, a CPK ≥10 ULN or CPK ≥ 5 ULN with symptoms, a history of rhabdomyolysis or renal insufficiency, or had suspected *S. aureus* pneumonia, empyema, meningitis, endocarditis, or osteoarticular infections. Discontinued subjects were not replaced.

6.1.2 Demographics

Table 6.1 reviews the basic demographic and physical characteristics of the safety population for DAP-PEDBAC-11-02.

Table 6.1 Study Demographics

	All ages			1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
Parameter	**DAP (N=55)**	**COM (N=26)**	**Overall (N=81)**	**DAP 12mg/kg (N=22)**	**COM (N=10)**	**DAP 9mg/kg (N=19)**	**COM (N=9)**	**DAP 7mg/kg (N=14)**	**COM (N=7)**
Age (years)									
Mean	8.67	8.78	8.70	3.81	4.13	10.25	9.46	14.14	14.56
(SD)	(4.472)	(4.548)	(4.468)	(1.232)	(1.752)	(1.217)	(1.345)	(1.677)	(1.868)
Median	9.60	8.75	9.60	3.65	4.85	10.60	9.60	13.60	14.50
Min, Max	2.0, 16.9	2.0, 17.6	2.0, 17.6	2.0, 6.7	2.0, 6.5	8.0, 11.8	7.6, 11.4	12.2, 16.9	12.6, 17.6
Age group (years), n (%)									
1 – 6	22 (40.0)	10 (38.5)	32 (39.5)						
7 – 11	19 (34.5)	9 (34.6)	28 (34.6)						
12 – 17	14 (25.5)	7 (26.9)	21 (25.9)						
Sex, n (%)									
Male	38 (69.1)	16 (61.5)	54 (66.7)	12 (54.5)	2 (20.0)	12 (63.2)	8 (88.9)	14 (100)	6 (85.7)
Female	17 (30.9)	10 (38.5)	27 (33.3)	10 (45.5)	8 (80.0)	7 (36.8)	1 (11.1)	0	1 (14.3)
Ethnicity, n (%)									
Hispanic or Latino	16 (29.1)	7 (26.9)	23 (28.4)	4 (18.2)	2 (20.0)	9 (47.4)	3 (33.3)	3 (21.4)	2 (28.6)
Not Hispanic or Latino	39 (70.9)	19 (73.1)	58 (71.6)	18 (81.8)	8 (80.0)	10 (52.6)	6 (66.7)	11 (78.6)	5 (71.4)
Race, n (%)									
Asian	2 (3.6)	2 (7.7)	4 (4.9)	0	2 (20.0)	1 (5.3)	0	1 (7.1)	0
Black or African American	6 (10.9)	0	6 (7.4)	2 (9.1)	0	4 (21.1)	0	0	0
White	43 (78.2)	18 (69.2)	61 (75.3)	19 (86.4)	6 (60.0)	12 (63.2)	6 (66.7)	12 (85.7)	6 (85.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
American Indian or Alaska Native	0	1 (3.8)	1 (1.2)	0	0	0	1 (11.1)	0	0
Other	4 (7.3)	5 (19.2)	9 (11.1)	1 (4.5)	2 (20.0)	2 (10.5)	2 (22.2)	1 (7.1)	1 (14.3)
Height (cm)									
N	54	26	80	21	10	19	9	14	7
Mean (SD)	129.49 (30.715)	129.23 (28.415)	129.41 (29.807)	98.68 (12.184)	103.80 (19.048)	138.18 (19.058)	132.18 (13.644)	163.94 (13.895)	161.79 (15.631)
Median	128.50	126.00	127.00	99.80	109.50	133.00	129.00	163.50	164.00
Min, Max	69.5, 196.0	73.0, 176.5	69.5, 196.0	69.5, 118.0	73.0, 127.0	106.0, 170.0	111.0, 149.5	138.0, 196.0	134.0, 176.5

Weight (kg)									
N	55	26	81	22	10	19	9	14	7
Mean (SD)	32.95 (18.277)	32.81 (19.604)	32.91 (18.590)	16.19 (3.837)	16.26 (5.328)	35.88 (11.987)	30.14 (10.431)	55.34 (11.709)	59.89 (9.649)
Median	26.60	24.25	25.50	16.10	17.50	33.50	27.00	53.25	58.00
Min, Max	10.0, 83.3	9.3, 72.0	9.3, 83.3	10.0, 22.8	9.3, 23.0	20.1, 65.0	16.8, 50.0	33.0, 83.3	48.0, 72.0
Body Mass Index (kg/m^2)									
N	54	26	80	21	10	19	9	14	7
Mean (SD)	18.29 (3.658)	17.82 (4.654)	18.14 (3.985)	16.57 (3.137)	15.02 (2.695)	18.65 (4.376)	16.79 (3.173)	20.38 (1.825)	23.13 (4.291)
Median	17.36	16.64	17.29	16.27	15.68	16.99	15.51	19.80	22.53
Min, Max	11.6, 29.8	10.3, 31.6	10.3, 31.6	11.6, 24.2	10.3, 19.0	13.4, 29.8	13.6, 24.1	17.3, 23.6	18.2, 31.6
Baseline serum creatinine category									
N	55	26	81	22	10	19	9	14	7
Normal	51 (92.7%)	23 (88.5%)	74 (91.4%)	21 (95.5%)	8 (80.0%)	18 (94.7%)	9 (100.0%)	12 (85.7%)	6 (85.7%)
1-1.5 ULN	4 (7.3%)	3 (11.5%)	7 (8.6%)	1 (4.5%)	2 (20.0%)	1 (5.3%)	0	2 (14.3%)	1 (14.3%)
>1.5-3.0 ULN	0	0	0	0	0	0	0	0	0
>3 ULN	0	0	0	0	0	0	0	0	0
Baseline creatinine clearance (mL/min)									
N	54	26	80	21	10	19	9	14	7
Mean	166.170	150.269	161.003	174.471	120.620	152.574	184.778	172.171	148.257
(SD)	(77.8281)	(75.1232)	(76.8491)	(111.6404)	(76.0618)	(44.1688)	(87.3062)	(48.9748)	(37.6456)
Median	160.500	134.700	153.650	157.300	106.700	152.300	161.200	182.600	153.300
Min, Max	50.00, 497.30	52.50, 405.80	50.00, 497.30	50.00, 497.30	52.50, 318.30	64.70, 256.90	114.70, 405.80	68.50, 263.00	105.30, 200.50

Adapted from Table 11-2 from Clinical Study Report: Protocol DAP-PEDBAC-11-02
DAP = daptomycin; COM = comparator; ULN = upper limit of normal

The daptomycin and comparator groups were similar based on age, sex, race, ethnicity, height/weight, and renal function. There was adequate distribution of patients among the various age groups in pediatric patients aged 1 to 17 years. Of note, while the study was open to patients aged 1 to 2 years, no patients were enrolled in this age group. The study population was predominantly white (75.3%) and male (66.7%).

Table 6.2 Subject Enrollment Region/Country for ITT Population

Region/Country	Daptomycin (n=55)	Comparator (n=27)
North America	25 (45.5%)	11 (40.7%)
United States	25 (45.5%)	11 (40.7%)
Europe	20 (36.4%)	9 (33.3%)
Greece	1 (1.8%)	0
Israel	2 (3.6%)	0
Romania	1 (1.8%)	0
Ukraine	16 (29.1%)	9 (33.3%)
Central/South America	8 (14.5%)	4 (14.8%)
Argentina	3 (5.5%)	0
Brazil	2 (3.6%)	0
Panama	3 (5.5%)	4 (14.8%)
Australia/Asia	2 (3.6%)	3 (11.1%)

Australia	0	1 (3.7%)
Malaysia	1 (1.8%)	0
Thailand	1 (1.8%)	2 (7.4%)

The largest enrolling sites were in the United States and Ukraine (43.9% and 30.5%, respectively). Of note, no patients were enrolled in India which had been a large enrollment site for the prior Study DAP-PEDS-07-03 for the indication of pediatric Gram-positive complicated skin and soft tissue infections. The distribution of patients between the daptomycin and comparator arms were generally similar in regards to country/region of enrollment.

Table 6.3 Microbiological characteristics of Safety Population at Baseline

Parameter	**Daptomycin (n=55)**	**Comparator (n=26)**
Microbiological Testing Results		
Aerobic Blood Culture Growth	55 (100.0%)	26 (100.0%)
Gram-positive stain	54 (98.2%)	26 (100.0%)
Rapid Diagnostic Test Positive	5 (9.1%)	3 (11.5%)
Baseline Infecting Pathogen		
MSSA	44 (80.0%)	19 (73.1%)
MRSA	7 (12.7%)	3 (11.5%)
CoNS	2 (3.6%)	2 (7.7%)
S. epidermidis	0	1 (3.8%)
S. saprophyticus	1 (1.8%)	0
None Established	1 (1.8%)	1 (3.8%)
Diagnostic of *S. aureus* Bacteremia		
Proven	51 (92.7%)	22 (84.6%)
Probable	3 (5.5%)	3 (11.5%)
Bacteremia Classification		
Uncomplicated	25 (45.5%)	8 (30.8%)
Complicated	27 (49.1%)	16 (61.5%)
Endocarditis	0	0
Metastatic Foci of Infection	11 (21.2%)	8 (33.3%)
Infected Prosthetic Material	2 (3.8%)	1 (4.2%)
Positive Blood Culture >4 Days	12 (23.1%)	5 (20.8%)
Fever >72 Hours	14 (26.9%)	9 (37.5%)
Not-Classified (Early Withdrawal)	3 (5.5%)	3 (12.0%)

Adapted from Table 11-4 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

As shown in Table 6.3, the majority of patients in both treatment groups had MSSA bacteremia (80.0% in daptomycin and 73.1% in comparator). All subjects had aerobic culture growth documented. Overall, the two treatment groups were similar in regards to infecting pathogen and diagnostic methodology/certainty. There were more patients in

the comparator group with complicated bacteremia (61.5% versus 49.1%). Of note, no patients had endocarditis in this study as this diagnosis was an exclusion criterion for study enrollment. Table 6.4 details the primary diagnoses made by the investigator compared by daptomycin and comparator groups. The list of diagnoses are generally those expected for patients with *S. aureus* bacteremia including device-related infections (21.2% and 16.7%), septic arthritis (7.7% and 16.7%), and osteomyelitis (19.2% and 8.4%). There were differences between the groups such as the case of osteomyelitis mentioned before, likely related to the low number of study subjects in each group (often <10).

Table 6.4 Type of Infection Diagnosed in Safety Population

Investigator's Primary Diagnosis	**Daptomycin (n=55)**	**Comparator (n=26)**
n[a]	52	24
Abscess	1 (1.9%)	0
Abscess drainage	2 (3.8%)	0
Appendiceal abscess	1 (1.9%)	0
Appendicitis	1 (1.9%)	0
Appendicitis perforated	2 (3.8%)	0
Arthritis	0	1 (4.2%)
Arthritis bacterial	4 (7.7%)	3 (12.5%)
Bacteremia	2 (3.8%)	0
Bone Abscess	1 (1.9%)	0
Cellulitis	3 (5.8%)	1 (4.2%)
Cellulitis, orbital	1 (1.9%)	0
Device-related infection	11 (21.2%)	4 (16.7%)
Induration	0	1 (4.2%)
Injury	0	1 (4.2%)
Intestinal Obstruction	1 (1.9%)	0
Joint Injury	1 (1.9%)	0
Lymph node abscess	0	1 (4.2%)
Lymphadenitis	1 (1.9%)	0
Muscle hemorrhage	1 (1.9%)	1 (4.2%)
Osteomyelitis	9 (17.3%)	1 (4.2%)
Osteomyelitis, acute	1 (1.9%)	1 (4.2%)
Pelvic hematoma	0	1 (4.2%)
Peritonitis	5 (9.6%)	2 (8.3%)
Peritonitis, bacterial	2 (3.8%)	0
Pneumonia	0	1 (4.2%)
Pyomyositis	2 (3.8%)	0
Sinusitis	1 (1.9%)	0
Staphylococcal bacteremia	0	1 (4.2%)

Unknown	10 (19.2%)	9 (37.5%)

Adapted from Table 11-4 from Clinical Study Report: Protocol DAP-PEDBAC-11-02
[a] Not all subjects had a primary diagnosis documented and several had multiple primary diagnoses. Percentages are based on the proportion of the safety population that had a primary diagnosis or diagnoses specified (including those specified by the investigator as unknown).

6.1.3 Subject Disposition

Study populations were defined by the statistical analysis plan (SAP) as follows:

- Intent-to-treat (ITT): all randomized subjects including those that were not exposed to any test product and was analyzed based on the treatment to which they were randomized.
- Modified Intent-to-Treat (MITT): all randomized and treated subjects with at least one dose of study drug who met the clinical criteria for the study infection at baseline (positive blood culture for *S. aureus* or CoNS (coagulase negative *Staph*) in high-risk patients or probable bacteremia (Gram-positive cocci on Gram stain at baseline).
- Microbiological Modified Intent-to-Treat (mMITT): all MITT subjects who had proven *S. aureus* bacteremia at baseline
- Clinically Evaluable (CE): Subpopulation of the mMITT subjects who met specific criteria related to the required assessments:
    - Received the correct drug, as randomized
    - Received appropriate duration of treatment
    - 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

Table 6.5 displays the subject disposition for study DAP-PEDBAC-11-02.

Table 6.5 Subject Disposition

Disposition	Daptomycin (N=55)	Comparator (N=27)
Randomized not treated	**0**	**1**
Completed Study	**54 (98.1%)**	**24 (92.3%)**
Did Not Complete Study	**1 (1.8%)**	**2 (7.7%)**
Subject/Guardian Decision	0	2 (7.7%)
Other	1 (1.8%)	0
Completed IV Treatment	**47 (85.5%)**	**23 (88.5%)**

Discontinued IV Treatment Prematurely	**8 (14.5%)**	**3 (11.5%)**
Adverse Event	3 (5.4%)	0
Persistent Positive Blood Cultures	2 (3.6%)	0
Subject/Guardian Decision	0	2 (7.7%)
Other	3 (5.4%)	1 (3.8%)
Converted to Oral Treatment	**32 (58.2%)**	**16 (61.5%)**
Completed Oral Treatment	**32 (58.2%)**	**14 (53.8%)**
Discontinued Oral Treatment Prematurely	**0**	**2 (7.7%)**
Adverse Event	0	2 (7.7%)

Adapted from Table 10-1 from Clinical Study Report: Protocol DAP-PEDBAC-11-02
Percentages based on number of subjects who were randomized and treated

While the ITT population was small for both treatment groups (55 for daptomycin and 27 for comparator), there was similar distribution of patients that completed the study, completed IV therapy, converted to oral therapy and completed oral therapy. Overall, the majority of patients in both groups completed the study (98.1% for daptomycin and 92.3% for comparator).

Table 6.6 Study Populations Analyzed

Population	Daptomycin, n (%)	Comparator, n (%)
ITT	55	27
Safety	55 (100.0%)	26 (96.3%)
MITT	52 (94.5%)	24 (88.9%)
mMITT	51 (92.7%)	22 (81.5%)
CE	40 (72.7%)	12 (44.4%)
Exposure Response	51 (92.7%)	0

The percentage of subjects included in the safety and MITT populations was similar in the daptomycin and comparator groups. A greater percentage of comparator subjects were excluded from the mMITT and CE populations (7.3% vs 18.5% and 27.3% vs 55.6%, respectively). Subjects were most commonly excluded from the CE population due to exclusion from the mMITT (i.e., not having confirmed *S. aureus* infection at baseline), use of effective systemic antibiotics for >72 hours within 96 hours of the first dose of study drug, or not having a TOC/Safety outcome assessment.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of study DAP-PEDBAC-11-02 was safety and is discussed further in Section 7. Efficacy was a secondary endpoint and study results are detailed below in Section 6.1.5.

6.1.5 Analysis of Secondary Endpoints(s)

Efficacy was a secondary endpoint for study DAP-PEDBAC-11-02. The presentation of efficacy is shown for three populations (MITT, mMITT, and CE) with all showing similar results in Table 6.7 . For breakdown of efficacy endpoints by age group, refer to Section 6.1.7.

Table 6.7 Clinical Outcome at TOC/Safety Visit

	mMITT		CE		MITT	
Clinical Outcome	**DAP (n=51)**	**COM (n=22)**	**DAP (n=40)**	**COM (n=12)**	**DAP (n=52)**	**COM (n=24)**
Clinical Success	45 (88.2%)	17 (77.3%)	36 (90.0%)	9 (75.0%)	46 (88.5%)	19 (79.2%)
Cure	43 (84.3%)	17 (77.3%)	35 (87.5%)	9 (75.0%)	44 (84.6%)	19 (79.2%)
Improved	2 (3.9%)	0	1 (2.5%)	0	2 (3.8%)	0
95% CI of % Success	79.4, 97.1	59.8, 94.8	80.7, 99.3	50.5, 99.5	79.8, 97.1	62.9, 95.4
Difference	11.0%		15.0%		9.3%	
95% CI of Difference	-8.7, 30.6		-11.2, 41.2		-9.1, 27.7	
Clinical Failure	6 (11.8%)	5 (22.7%)	4 (10.0%)	3 (25.0%)	6 (11.5%)	5 (20.8%)
Failure	5 (9.8%)	3 (13.6%)	4 (10.0%)	3 (25.0%)	5 (9.6%)	3 (12.5%)
Non-evaluable	1 (2.0%)	2 (9.1%)	0	0	1 (1.9%)	2 (8.3%)

Adapted from Table 11-6 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

The study was not powered to test for non-inferiority for the secondary efficacy endpoint. However, the available data demonstrate similar rates of clinical success (cure or improved) as assigned by the blinded-investigator at the TOC/safety visit. While the overall proportion of daptomycin subjects is 11.0% higher than the comparator arm, the CI for that difference overlaps zero and could be due to chance. Overall, the clinical outcomes between daptomycin and comparator are similar in all populations (MITT, mMITT, and CE).

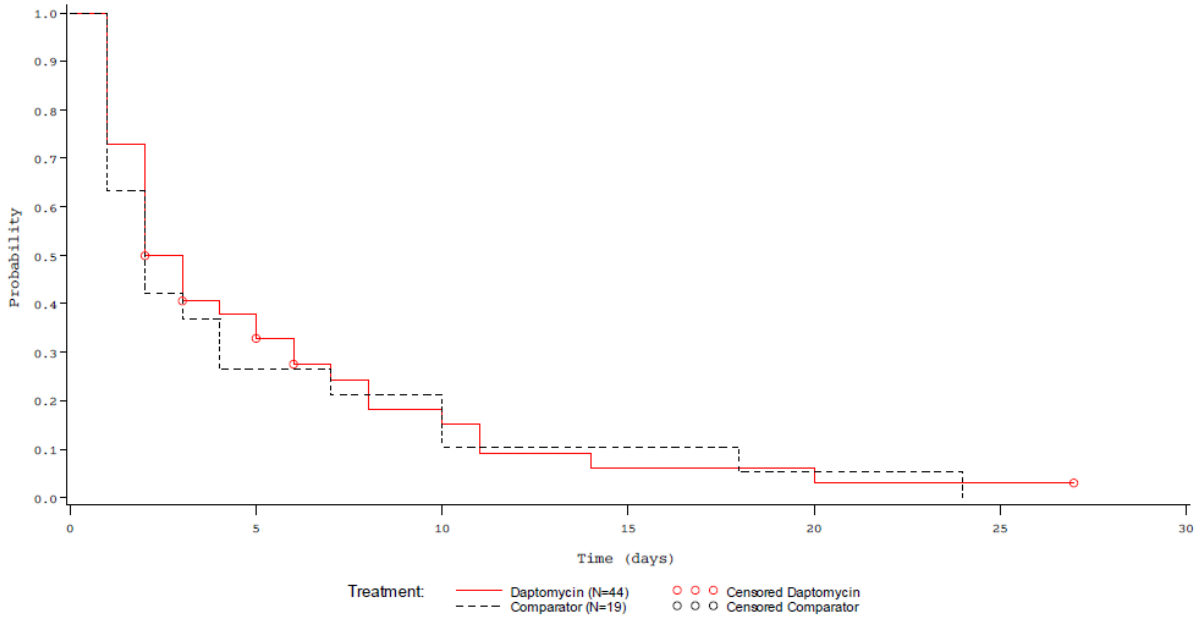
Of note, the clinical outcome efficacy of daptomycin in the treatment of adults with *S. aureus* bacteremia and right-sided endocarditis was noted to be 44.2% (53/120) and 41.7% (48/115) in the DAP and COM groups, respectively. This data was obtained the ITT population at a follow-up visit 6 weeks after the last dose of study drug. The markedly lower efficacy noted in adults is likely a reflection of many factors including the inclusion of patients with infective endocarditis. 25% of adult patients were ≥65 years of age, 36% had surgery within the past 30 days, and 24% had infective endocarditis (16% with right-sided infective endocarditis and 8% with left-sided infective endocarditis). Enrolled adult patients had risk factors not present in the pediatric studies including diabetes, moderate renal failure, and intravenous drug use. These increased risk factors are reflected in the 15% of patients receiving daptomycin who died during the study.

The differing clinical efficacy rates in adult vs. pediatric trials for SAB are felt by this reviewer to be due to the higher risk populations in the adult studies.

6.1.6 Other Endpoints

Figure 1 displays the time to clearance of bacteria as a Kaplan-Meier curve for the mMITT daptomycin arm vs comparator arm.

Figure 1 Time to Bacterial Clearance (mMITT Population)



The times to bacterial clearance for daptomycin and comparator were similar. The average time to clearance for the daptomycin arm was 2.5 days compared to 2.0 days in the comparator group. Due to the low numbers of patients in each arm (44 for daptomycin and 19 for comparator), the difference of 0.5 days is not statistically significant.

6.1.7 Subpopulations

The major stratification explored during study PED-BAC-11-02 was analysis based on age group as shown in Table 6.8. With overall low numbers of patients in the mMITT population, none of the 95% confidence intervals suggest statistically significant differences in success and failure rates based on blind-investigator assessments at the TOC/safety visits. However, the available data show success rates that are relatively similar to those reported in the general study population for daptomycin (ranging 85.0% to 94.1%). The comparator group in the 12 to 17 year old age group had a particularly low success rate at 60.0%), but with only five patients in this subgroup it is impossible to

draw any specific conclusion that cannot be explained by chance. Additional analyzed subgroups are displayed in Table 6.9.

Table 6.8 Clinical Outcome at the TOC/Safety Visit by Age Group in mMITT Population

	1 to 6 years olds		7 to 11 year olds		12 to 17 year olds	
Clinical Outcome	**DAP (n=20)**	**COM (n=8)**	**DAP (n=17)**	**COM (n=9)**	**DAP (n=14)**	**COM (n=5)**
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
95% CI of % Success	69.4, 100.0	64.6, 100.0	82.9, 100.0	50.6, 100.0	67.4, 100.0	17.1, 100.0
Difference	-2.5%		16.3%		25.7%	
95% CI of Difference	-30.3, 25.3		-13.0, 45.7		-21.0, 72.4	
Clinical Failure	3 (15.0%)	1 (12.5%)	1 (5.9%)	2 (22.2%)	2 (14.3%)	2 (40.0%)
Failure	3 (15.0%)	1(12.5%)	1 (5.9%)	1 (11.1%)	1 (7.1%)	1 (20.0%)
Non-evaluable	0	0	0	1 (11.1%)	1 (7.1%)	1 (20.0%)

Adapted from Table 11-5 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

Table 6.9 Clinical Outcome at the TOC/Safety Visit – Summary of Subgroup Analyses in mMITT Population

Subgroup **Clinical Outcome at TOC/Safety**	**Daptomycin (n=51)**	**Comparator (n=22)**
Baseline MSSA	44	19
Satisfactory Response	39 (88.6%)	15 (78.9%)
Unsatisfactory Response	5 (11.4%)	4 (21.1%)
Baseline MRSA	7	3
Satisfactory Response	6 (85.7%)	2 (66.7%)
Unsatisfactory Response	1 (14.3%)	1 (33.3%)
Complicated Bacteremia	26	14
Satisfactory Response	23 (88.5%)	10 (71.4%)
Unsatisfactory Response	3 (11.5%)	4 (28.6%)
Uncomplicated Bacteremia	24	7
Satisfactory Response	22 (91.7%)	7 (100.0)
Unsatisfactory Response	2 (8.3%)	0
Received only IV Therapy	19	7
Satisfactory Response	14 (73.7%)	5 (71.4%)
Unsatisfactory Response	5 (26.3%)	2 (28.6%)

Received IV and PO Therapy	32	15
Satisfactory Response	31 (96.9%)	12 (80.0%)
Unsatisfactory Response	1 (3.1%)	3 (20.0%)

Adapted from Table 11-9 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

The daptomycin and comparator groups were generally similar in regards to MSSA vs MRSA, uncomplicated vs complicated bacteremia, and IV vs IV+PO therapy. But, there was a trend for the comparator to be 10-15% less effective than daptomycin in multiple subgroups including MSSA bacteremia, MRSA bacteremia, complicated bacteremia, and those receiving both IV and PO therapy. Given the low population numbers (<10) in many of the comparator groups, it is impossible to say this is not due to chance. While not statistically significant, the higher success rates for IV+PO therapy versus IV only therapy (96.9% vs 73.7% in daptomycin and 80.0% vs 71.4% in comparator) is expected given the switch to oral therapy would be guided by favorable clinical responses and scenarios.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the pediatric population, with decreasing age there was higher volume of distribution and clearance of daptomycin as compared to adults. Dosing was varied by age group to produce exposures comparable to those in adults. Dosage adjustment for pediatric patients with renal impairment has not been established.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

6.2 Efficacy Summary and Conclusion

DAP-PEDBAC-11-02 was not powered to demonstrate efficacy, which was extrapolated from adult trials. Nor was it powered to demonstrate non-inferiority or equivalency to the standard of care comparator. The study indicated that pediatric patients 1 year of age and older demonstrated similar efficacy of daptomycin-treated subjects to those receiving standard of care therapy (88.2% and 77.3% in the mMITT, respectively) for the treatment of *S. aureus* bacteremia. Similar efficacy was observed across the various age groups analyzed and within subgroups including baseline *S. aureus* sensitivity (MSSA/MRSA) and uncomplicated/complicated bacteremia.

7 Review of Safety

Safety Summary

7.1 Methods

The pediatric development program for daptomycin included 5 studies: two single-dose and one repeated-dose clinical trials, as well as two safety, efficacy, and pharmacokinetic clinical trials. One of the latter is the focus of safety and efficacy data for this review (DAP-PEDBAC-11-02). The other is the focus of a previous review for the indication of pediatric complicated skin and soft tissue structures infections (DAP-PED-07-03).

The primary study was a multicenter, multinational, evaluator-blinded, comparative, pediatric study with safety of daptomycin as a primary endpoint. Pediatric patients aged 1 to 17 years with bacteremia caused by either proven or probable *S. aureus* were randomized 2:1 to daptomycin vs. a standard of care comparator and treated with age-dependent doses over a period of up to 42 days. Safety was evaluated by clinical assessment including changes in physical and neurological findings, vital signs, and lab markers including serum creatine phosphokinase (CPK) levels, in addition to tracking reports of adverse events (AEs) and serious adverse events (SAEs). Safety was assessed through the entirety of administration of study medications from the first dose through the last follow-up visit. A blinded medical monitor reviewed safety parameters to ensure any indication of an AE was documented and classified by severity and causality. A data management committee (DMC) evaluated data on patients aged 4-17 years of age at an interim assessment and recommended expansion of the study to include patients aged ≥1 years.

The safety data were collected across 25 clinical locations located in the United States, Europe, Central/South America, Australia, and Asia (see Table 6.2). Overall, the safety database included 81 treated patients who received at least one dose of study medication. Incidence of adverse events, changes in vital signs, clinical findings, and laboratory parameters were compared between the study groups.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study DAP-PEDBAC-11-02 enrolled pediatric patients 1 to 17 years of age with proven or probable *S. aureus* bacteremia. See Section 6.1.1 for definitions of bacteremia and key exclusion/inclusion criteria. Subjects were grouped by age: 1 to 6 years of age, 7 to 11 years of age, and 12 to 17 years of age. Dosing was guided through PK studies with target steady state exposure levels (AUC) in children that were comparable to the AUC in adults treated with 6 mg/kg. Using these metrics, dosing was designated as 12 mg/kg (1 to 6 year olds), 9 mg/kg (7 to 11 year olds), and 7 mg/kg (12 to 17 year olds). Patients in the 1 to 6 year old group had infusions run over extended time of 60 minutes

as compared to 30 minutes in other ages, given the potential for an elevated maximum plasma concentration (C_{max}).

7.1.2 Categorization of Adverse Events

The adverse events (AEs) and serious adverse events (SAEs) in this study were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.0. The AEs were categorized by preferred term and system organ class. Safety data in subjects were analyzed for the incidence of treatment emergent AEs (TEAEs), treatment emergent SAEs (TESAEs), relation to study drug, deaths and treatment related discontinuations of treatment or study. Table 7.1 below provides an overall view of the occurrences of AEs across study DAP-PEDS-11-02.

Table 7.1 Overview of TEAEs

	Total		1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
Category (Subject with ≥1)	**DAP n=55**	**COM n=26**	**DAP 12mg/kg n=22**	**COM n=10**	**DAP 9mg/kg n=19**	**COM n=9**	**DAP 7mg/kg n=14**	**COM n=7**
TEAE	36 (65.6%)	20 (76.9%)	15 (68.2%)	6 (60.0%)	12 (63.2%)	9 (100.0%)	9 (64.3%)	5 (71.4%)
Severe TEAE	5 (9.1%)	4 (15.4%)	2 (9.1%)	0	1 (5.3%)	3 (33.3%)	3 (21.4%)	2 (28.6%)
TEAE leading to discontinuation of study drug	3 (5.5%)	2 (7.7%)	1 (4.5%)	1 (10.0%)	1 (5.3%)	1 (11.1%)	1 (7.1%)	0
TEAE leading to discontinuation of study	0	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0	0

Adapted from Table 12-3 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

Any new adverse events which occurred after study drug was initiated were listed as treatment emergent, so there are no non-treatment emergent adverse events for the study. Any causality discussed in this review is based on this clinical reviewer's analysis of data provided in the supplement application.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from a single large multi-dose safety trial in pediatric patients with *S. aureus*, protocol DAP-PEDBAC-11-02, were analyzed for safety. Reference and comparison is made to another large multi-dose safety trial in pediatrics patients with cSSSI treated with daptomycin vs. comparator, protocol DAP-PEDS-07-03, which included a larger number of pediatric subjects.

7.2 Adequacy of Safety Assessments

Overall safety assessments performed in Study DAP-PEDBAC-11-02 are adequate given the safety profile of daptomycin. The study was divided into two arms: daptomycin and a standard of care comparator. Dosing was based on age and weight, guided by the pharmacokinetic parameters determined from prior single dose data as well as extrapolation from adult data. Patients were evaluated for entry into the study, within 72 hours prior to dosing. Adverse events were reported throughout the treatment phase, including on-therapy evaluations, end of IV therapy (EOIV) and/or end of oral therapy (EOOT) occurring within 2 days of last dose of study drug of that formulation, test of cure (TOC) visits 7-14 days after last dose of study drug, and last follow-up visits 25-35 days after last dose of study drug. Adverse events were categorized by organ system or investigation, and labeled as treatment emergent, serious, or those resulted in premature termination per investigator's assessment. Laboratory safety monitoring included routine hematology, chemistry, and urinalysis.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per study protocol, patients were randomized (2:1) to either daptomycin or comparator for a planned duration of 5 to 42 days dependent on the type of underlying infection; however patients were continued longer than 42 days at the blinded investigator's discretion. Patients were switched to oral medication at the investigator's discretion; with a single dose of study medication being the minimum criteria for study inclusion. Table 7.2 below summarizes the length of treatment for IV/PO therapies in both study arms and Table 7.3 below analyses the same data by age group.

Table 7.2 Summary of Treatment Exposure

	Daptomycin	**Comparator**
Duration of IV treatment (days) Mean Median Range	n=55 12.2 11.0 1, 44	n=26 12.3 11.5 2, 31
Duration of PO treatment (days) Mean Median Range	n=32 22.7 15.0 5, 125	n=16 17.7 16.0 6, 33
Duration of IV+PO treatment (days) Mean Median Range	n=55 25.3 20.0 1, 141	n=26 22.6 18.0 2, 58

Received study drug for <3 days	3 (5.5%)	2 (7.7%)
Received study drug for 3-7 days	6 (10.9%)	1 (3.8%)
Received study drug for >7-14 days	6 (10.9%)	6 (23.1%)
Received study drug for >14-21 days	15 (27.3%)	7 (26.9%)
Received study drug for >21-28 days	11 (20.0%)	2 (7.7%)
Received study drug for >28-35 days	2 (3.6%)	1 (3.8%)
Received study drug for >35-42 days	4 (7.3%)	5 (19.2%)
Received study drug for >42 days	8 (14.5%)	2 (7.7%)

Adapted from Table 12-1 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

Overall, the duration of daptomycin and comparator treatments were similar in regards to IV (12.2 days vs. 12.3 days) and IV+PO (25.3 days vs. 22.6 days). There was a slight trend for the daptomycin arm to have longer PO treatment durations (22.7 days vs. 17.7 days). Additionally, there were several patients in the daptomycin arm with prolonged treatment courses of up to 141 days relative to the longest course of comparator drug being 58 days. This does lead to a slight skewing of the daptomycin arm to longer durations especially in the oral treatment duration with a range of up to 125 days relative to 33 days in the comparator. 9 of the 10 patients with treatment durations >42 days were diagnosed with osteomyelitis which was a more common cause of complicated bacteremia in the daptomycin group. In particular, one patient (Subject 102-3029) was treated for 141 days as prophylaxis to prevent the recurrence of osteomyelitis. The majority of patients in both groups received 8-35 days of study medication (58.2% for daptomycin and 57.7% for comparator).

Table 7.3 Summary of Treatment Exposure by Age Group

	1 to 6 years old		**7 to 11 years old**		**12 to 17 years old**	
Treatment Durations (days)	**DAP 12 mg/kg**	**COM**	**DAP 9 mg/kg**	**COM**	**DAP 7 mg/kg**	**COM**
Duration of IV treatment	n=22	n=10	n=19	n=9	n=14	n=7
Mean	13.1	11.7	10.8	14.1	12.7	10.9
Median	10.5	11.0	10.0	15.0	12.0	11.0
Range	1, 44	5, 31	5, 26	2, 31	2, 27	2, 21
Duration of PO treatment	n=11	n=8	n=11	n=5	n=10	n=3
Mean	23.8	13.5	23.0	25.4	21.1	16.0
Median	15.0	11.0	21.0	28.0	12.0	17.0
Range	8, 125	6, 27	7, 56	15, 33	5, 55	10, 21
Duration of PO+IV treatment	n=22	n=10	n=19	n=9	n=14	n=7
Mean	24.8	21.7	24.2	27.8	27.8	17.3
Median	17.5	18.0	18.0	21.0	22.0	12.0
Range	1, 141	7, 42	5, 66	2, 58	2, 82	2, 41

Adapted from Table 12-2 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

Some variation between treatment arms in duration of IV and/or PO treatment duration by age group exists but the small sample sizes limits drawing conclusions. Of note, the

patients diagnosed with osteomyelitis and treated with >42 days of study medication (8 in the daptomycin group and 1 in the comparator group) skew towards longer treatment duration and higher total exposure in the daptomycin groups.

The most commonly administered IV therapy in the comparator treatment arm was vancomycin. The distribution of subjects receiving comparator drugs was as follows: vancomycin (n=15, 57.7%), cefazolin (n=6, 23.1%), oxacillin (n=4, 15.4%), flucloxacillin (n=1, 3.8%), and linezolid (n=1, 3.8%). One subject took two different comparator drugs when he received 5 days of IV vancomycin before being switched to IV linezolid. Vancomycin was the most commonly administered comparator in the 1 to 6 year old group (n=7, 70%) and 12 to 17 year old group (n=5, 71.4%). Cefazolin was the most commonly administered comparator in the 7 to 11 year old group (n=5, 55.6%).

The most commonly administered oral study drugs in the daptomycin treatment group were amoxicillin/clavulanate (n=10, 18.2%) and cephalexin (n=10, 18.2%). The most commonly administered oral study drugs in the comparator treatment group were similar including amoxicillin/clavulanate (n=7, 26.9%) and cephalexin (n=6, 23.1%).

7.2.2 Explorations for Dose Response

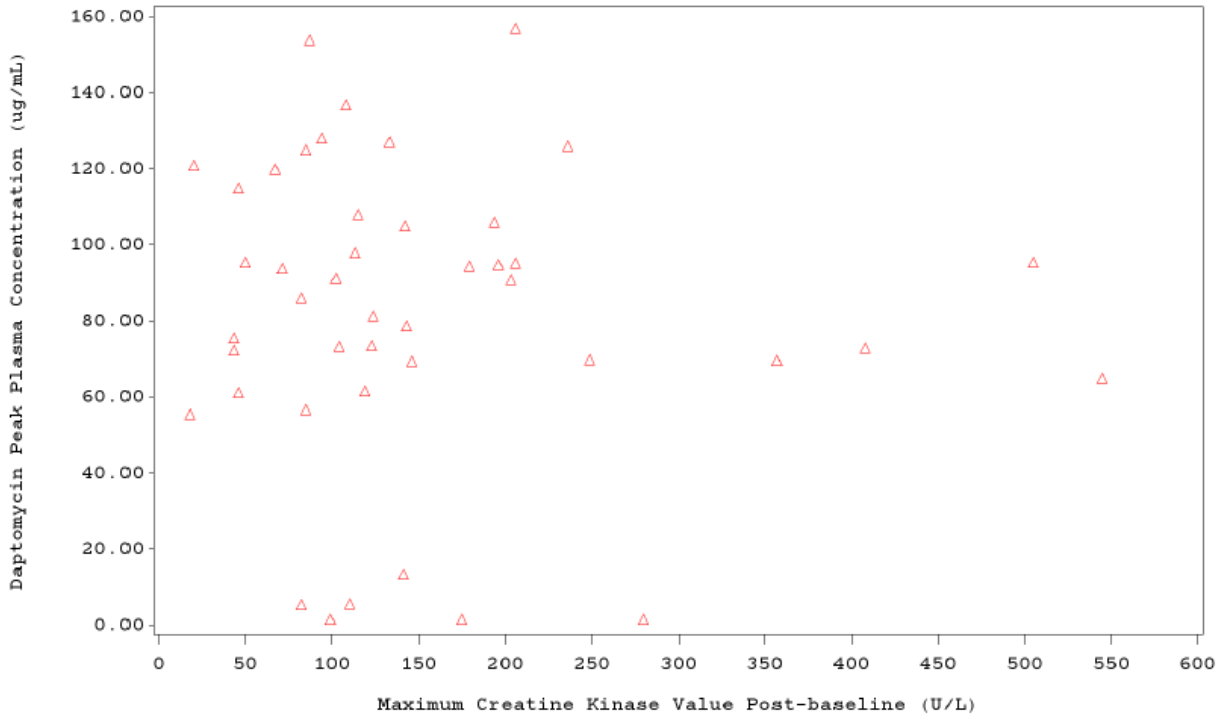
During the IV phase of the study, 20 patients had trough daptomycin levels obtained and 41 patients had peak daptomycin levels obtained. Table 7.4 summarizes the PK data for IV daptomycin.

Table 7.4 PK Parameters for Daptomycin Treated Subjects by Age Group

Parameter	Overall n=51	1-6 years old 12 mg/kg n=19	7-11 years old 9 mg/kg n=19	12-17 years old 7 mg/kg n=13
Infusion Duration		60 minutes	30 minutes	30 minutes
Trough (C_{trough} µg/mL)	n=20	n=3	n=10	n=7
Mean	9.05	4.72	6.39	14.69
Median	5.49	4.32	5.63	4.93
Range	3.3, 54.7	3.3, 6.5	3.9, 14.5	3.5, 54.7
Peak (C_{max}, µg/mL)	n=41	n=15	n=18	n=8
Mean	88.43	96.69	87.66	74.7
Median	91.20	95.40	83.75	73.05
Range	5.3, 157.0	13.4, 154.0	5.3, 157.0	5.6, 128.0

A daptomycin exposure safety analysis was conducted comparing daptomycin peak plasma concentrations versus maximum CPK during IV therapy and during the entire study. These analyses (see Figure 2) did not identify a trend of CPK increase with peak daptomycin values.

Figure 2 Peak Serum Daptomycin Concentrations vs. Maximum Post-Baseline CPK Values



Of the ten subjects who experienced sustained CPK elevations and/or reported AEs in the peripheral neuropathy or rhabdomyolysis/myopathy SMQ categories (refer to Section 7.3.5), two had daptomycin peak concentrations higher than their age group median by 10.6 and 22.6 µg/mL. The subject with a median value 22.6 µg/mL higher than their age group had an elevated CPK treatment emergent adverse event related to a hip arthrotomy unlikely to be related to study drug (see Section 7.3.5). There was no observed trend for peak or trough CPK values to be correlated with SMQ AEs.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing while on study treatment included evaluation of the parameters potentially affected by daptomycin, such as: complete blood count, comprehensive metabolic panel including liver function tests, creatine phosphokinase, and urinalysis.

7.2.5 Metabolic, Clearance, and Interaction Workup

PK modeling was performed to guide dosing in the pediatric population, to provide similar exposure as 6 mg/kg in adults. Modeling data from adult exposure indicated targets of 632 µg*h/mL for AUC_{0-24} and 93.9 µg/mL for C_{max}. The C_{max} for all groups was similar to adult values with a mean of 96.69 µg/mL in ages 1 to 6 years, 87.66 µg/mL in ages 7 to 11 years, and 74.7 µg/mL in ages 12 to 17 years. Refer to Table 7.4 for additional PK parameter data by age group.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during the study or its follow-up period.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were defined in the protocol as those resulting in death, were life-threatening, required hospitalization or prolonged current hospitalization, resulted in persistent/significant disability, congenital anomaly, or were deemed medically important by the investigator. As noted, all adverse events listed in the study were labeled as treatment emergent. Table 7.5 lists the SAEs encountered during the study in the daptomycin and comparator groups.

Table 7.5 Serious Adverse Events

Body System or Organ Class Term Dictionary Derived Term	**Daptomycin n=55**	**Comparator n=26**
Subjects with ≥1 TESAE	13 (23.6%)	7 (26.9%)
Cardiac disorders	0	1 (3.8%)
Cardiac failure congestive	0	1 (3.8%)
General disorders and administration site condition	1 (1.8%)	0
Device breakage	1 (1.8%)	0
Immune system disorders	0	1 (3.8%)
Intestine transplant rejection	0	1 (3.8%)
Infections and Infestations	7 (12.7%)	3 (11.5%)
Arthritis bacterial	0	2 (7.7%)
Bacteremia	3 (5.5%)	0
Bone abscess	1 (1.8%)	0

Muscle abscess	1 (1.8%)	0
Osteomyelitis	1 (1.8%)	1 (3.8%)
Pneumonia	1 (1.8%)	0
Staphylococcal bacteremia	1 (1.8%)	0
Investigations	1 (1.8%)	0
Hepatic enzyme increased	1 (1.8%)	0
Metabolism and nutrition disorders	1 (1.8%)	0
Malnutrition	1 (1.8%)	0
Musculoskeletal and connective tissue disorders	2 (3.6%)	0
Bone fistula	1 (1.8%)	0
Synovitis	1 (1.8%)	0
Respiratory, thoracic and mediastinal disorders	2 (3.6%)	2 (7.7%)
Pneumonia aspiration	0	1 (3.8%)
Pneumothorax	1 (1.8%)	0
Pulmonary edema	0	1 (3.8%)
Respiratory failure	1 (1.8%)	0
Vascular disorders	1 (1.8%)	0
Venous thrombosis limb	1 (1.8%)	0

Adapted from Table 12-8 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

There were similar rates of TESAEs in the daptomycin and comparator arms, 23.6% and 26.9%, respectively. On review of case narratives, there are no SAEs felt by this reviewer to be likely related to use of daptomycin. While one patient had elevations in hepatic enzymes, which is a known adverse reaction to daptomycin, this patient had known liver disease and elevations in hepatic enzymes prior to administration of daptomycin. The TESAE rates are higher than those previously reported in another pediatric daptomycin study (DAP-PEDS-07-03) for Gram-positive complicated skin and skin structure infections which described rates of 2.3% for daptomycin and 2.3% for comparator. The difference in rates described may be partially related to the shorter duration of study drug administration (14 days in DAP-PEDS-07-03), prolonged follow-up period in DAP-PEDBAC-11-02 (up to 35 days after last dose of study medication, and the greater severity of illness in patients with SAB. Additionally, DAP-PEDBAC-11-02 and DAP-PEDS-07-03 enrolled patients at different study sites, which may account for some variability because of AE reporting practices. Of note, a large proportion of TESAEs were reported in the post-treatment follow-up phase with 10 subjects (12.8%). The events do not appear to be correlated with daptomycin dose although interpretation is limited given small sample sizes: 6 subjects in the 1 to 6 year old age group (27.3%), 3 subjects including 2 subjects with two TESAEs in the 7 to 11 year old age group (15.8%), and 4 subjects including 1 subject with two TESAEs in the 12 to 17 year old age group (28.6%).

7.3.3 Dropouts and/or Discontinuations

Eighty-two patients were randomized for study treatment in the ITT population (55 in the daptomycin arm and 27 in the comparator arm). One patient discontinued the study prior to receiving a dose of study medication in the comparator arm and is not considered in the safety population. Eleven of 81 subjects (13.6%) discontinued IV study drug therapy prematurely. Of these 11 subjects, 8 were part of the daptomycin arm and 3 were part of comparator treatment. Two of 48 subjects (4.2%) who converted to oral therapy discontinued oral study drug prematurely and were both in the comparator arm. Table 7.6 compares the study discontinuations between the daptomycin and comparator groups.

Table 7.6 Study Drug Discontinuations

Primary reason for study drug discontinuation in the safety population	**Daptomycin**	**Comparator**
IV Study Treatment	n=55	n=26
Adverse Event	3 (5.5%)	0
Microbiological failure	2 (3.6%)	0
Subject decision	0	2 (7.7%)
Other	3 (5.5%)	1 (3.8%)
Oral Study Treatment	n=32	n=16
Adverse Event	0	2 (12.5%)

There were more adverse events resulting in study drug discontinuation during the IV treatment phase on the daptomycin arm (5.5%) as compared to the comparator arm (0%). The opposite is true for the oral phase during which IV daptomycin and comparator were switched to an alternate oral regimen to complete therapy (0% and 12.5%, respectively).

Three subjects stopped IV daptomycin due to adverse events:

- Subject 106-3022, a 2-year-old patient, experienced an AE of elevated blood CPK described further in Section 7.3.5. The elevation was mild but did lead to discontinuation of IV daptomycin and subsequently resolved without withdrawal from the study.
- Subject 118-3022, a 9-year-old patient, experienced an SAE of bone fistula of the right tibia during IV treatment. The blind-investigator considered the event unrelated to the study drug but resolved after patient was switched to IV linezolid and oral TMP/SMX along with osteotomy and curettage of the area.
- Subject 241-1004, a 15-year-old patient, experienced an SAE of hospital acquired pneumonia considered unrelated to study drug by the blinded investigator which resolved after switch to IV piperacillin-tazobactam and IV cloxacillin.

Two subjects stopped oral comparator due to adverse events:

- Subject 016-3016, a 4-year-old patient, experienced an SAE of worsening bacterial arthritis considered unrelated to study drug by the blinded investigator and resolved after switch to IV cefazolin and arthrocentesis of the right ankle joint.
- Subject 118-2011, a 9-year-old patient, experienced an SAE of worsening osteomyelitis considered unrelated to study drug by the blinded investigator and resolved after switch to oxacillin, levofloxacin, and trimethoprim/sulfamethoxazole along with curettage of the right iliac bone.

Two patients on the daptomycin arm were discontinued from the IV study drug early due to microbiological failures. The listed cause in both cases was persistently positive blood cultures. One of these was a patient in the 1 to 6 year old age group who had a central IV catheter in placed throughout therapy with IV daptomycin and bacteremia was only noted to resolve once the catheter was removed several weeks into therapy.

Three patients in the daptomycin group discontinued study medication for reasons categorized as other. One patient had a suspected skin contaminant with coagulase negative *Staphylococci* (CoNS), one patient had a non-relevant bacteremia (non-*Staphylococcal*), and one patient did not have proper set-up of research home healthcare.

No subjects dropped out of the study due to adverse events.

7.3.4 Significant Adverse Events

Significant adverse events coinciding with IV drug treatment were described in Section 7.3.2 and Section 7.3.3 as SAEs or causes for discontinuation.

7.3.5 Submission Specific Primary Safety Concerns

Safety data from adults indicated skeletal muscle a target of daptomycin toxicity. Preclinical trials in neonatal dogs showed evidence of peripheral neuropathy that has not been seen in adult and pediatric human trials to date. The SMQs of Peripheral Neuropathy and Rhabdomyolysis/Myopathy with both a broad or narrow relationship were examined including CPK elevations reported as AEs under the Rhabdomyolysis/Myopathy SMQ.

A single subject in the comparator group had a qualifying AE of myositis with all other SMQ qualifying AEs belonging to the daptomycin treatment group.

There was 1 subject in the daptomycin group with muscle weakness which was identified by both the Peripheral Neuropathy and Rhabdomyolysis/Myopathy SMQs:

- Subject 014-3013, a 2-year-old patient, experienced muscle weakness on day 31 of IV daptomycin treatment. Study drug was not discontinued and patient completed IV therapy on day 44 without any additional evidence of AEs or required interventions. CPK remained in the normal range throughout the study.

There were 4 subjects identified by the Rhabdomyolysis/Myopathy SMQ with elevated CPK during the study which all occurred in the daptomycin group:

- Subject 106-3022, a 2-year-old patient, experienced an AE of elevated blood CPK (545 U/L, normal range 39-308 U/L) on day 3 of IV daptomycin therapy. While the elevation was mild, given the known association of daptomycin and myopathy described in adults, the patient discontinued IV therapy prematurely. The day after discontinuation, the CPK value had dropped to 19 U/L and remained normalized along with all CPK isoenzymes (BB, MM, MB) through checks on day 8.
- Subject 013-2019, an 11-year-old patient, experienced an AE of elevated blood CPK (222 U/L, normal range 38-324 U/L) on day 8 of IV daptomycin which is a normal value but elevated from patient's baseline. Study drug was not discontinued and a recheck of the CPK value at EOIV visit on day 15 showed a slightly elevated value of 357 U/L. This patient also experienced an AE of renal failure on day 11 of IV daptomycin which appeared mild and resolved with adequate hydration. The reported CPK values are far below the expected values to associate the renal failure with severe myopathy such as rhabdomyolysis.
- Subject 241-1004 had an ankle arthrotomy 2 days prior to the blood CPK increase to 1740 U/L. AE likely not study drug related with subsequent resolution at follow-up.
- Subject 102-1006 had a hip arthrotomy due to pyomyositis 2 days prior to the blood CP increase to 505 U/L. AE likely not study drug related with subsequent resolution at follow-up.

There was an increased incidence of adverse events related to myopathy in the daptomycin group compared to the comparator group (9.1% vs. 3.8%) especially in regards to CPK elevations (7.3% vs. 0%). A prior safety study of daptomycin in the pediatric population for the indication of complicated skin and skin structure infections with similar design and dosing (DAP-PEDS-07-03, refer to Table 5.1) showed 5.5% of the daptomycin safety population developed elevated CPK with a larger overall safety population size of 256. These values suggest the already known increased rates of myopathy in adults treated with IV myopathy apply to pediatric patients. Of note, the prior study (DAP-PEDS-07-03) did not find evidence for a trend for rates of myopathy related to age and there are not enough new data to adjust this assessment. None of the patients in the study developed a severe myopathy or overt rhabdomyolysis.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Nearly ¾ of patients, 56/81 (69.1%), in the clinical study experienced at least one adverse event. The percentage of patients who experienced an AE was similar between the two randomized groups, with 36/55 (65.5%) patients in the daptomycin group and 20/26 (76.9%) patients in the comparator group. A summary of all reported TEAEs is provided in Table 7.7.

Table 7.7 Summary of TEAEs

System Organ Class Preferred Term	Daptomycin n=55	Comparator n=26
Subjects with ≥1 TEAE	36 (65.5%)	20 (76.9%)
Blood and lymphatic system disorders	3 (5.5%)	3 (11.5%)
Abdominal lymphadenopathy	0	1 (3.8%)
Anemia	1 (1.8%)	1 (3.8%)
Lymphadenopathy	0	1 (3.8%)
Neutropenia	1 (1.8%)	0
Thrombocytopenia	1 (1.8%)	0
Thrombocytosis	1 (1.8%)	1 (3.8%)
Cardiac disorders	1 (1.8%)	2 (7.7%)
Cardiac failure congestive	0	1 (3.8%)
Ventricular extrasystoles	1 (1.8%)	1 (3.8%)
Eye disorders	0	1 (3.8%)
Vision blurred	0	1 (3.8%)
Gastrointestinal disorders	10 (18.2%)	7 (26.9%)
Abdominal distension	1 (1.8%)	0
Abdominal pain	1 (1.8%)	1 (3.8%)
Constipation	1 (1.8%)	0
Diarrhea	6 (10.9%)	5 (19.2%)
Nausea	1 (1.8%)	1 (3.8%)
Vomiting	6 (10.9%)	2 (7.7%)
General disorders and administration site conditions	7 (12.7%)	4 (15.4%)
Catheter site discharge	1 (1.8%)	0
Catheter site edema	1 (1.8%)	0
Catheter site pain	1 (1.8%)	0
Device breakage	1 (1.8%)	1 (3.8%)
Infusion site pain	1 (1.8%)	0
Pyrexia	5 (9.1%)	3 (11.5%)
Immune system disorders	0	3 (11.5%)
Drug hypersensitivity	0	2 (7.7%)
Intestine transplant rejection	0	1 (3.8%)

Infections and infestations	11 (20.0%)	11 (42.3%)
Abdominal abscess	0	1 (3.8%)
Abscess	1 (1.8%)	0
Arthritis bacterial	0	3 (11.5%)
Bacteremia	3 (5.5%)	0
Bone abscess	1 (1.8%)	0
Candida infection	1 (1.8%)	0
Cellulitis	1 (1.8%)	0
Clostridium difficile colitis	1 (1.8%)	0
Ear infection	1 (1.8%)	0
Epstein-Barr viremia	1 (1.8%)	0
Infected skin ulcer	0	1 (3.8%)
Lung abscess	0	1 (3.8%)
Muscle abscess	1 (1.8%)	0
Nasopharyngitis	0	1 (3.8%)
Osteomyelitis	1 (1.8%)	4 (15.4%)
Osteomyelitis acute	0	1 (3.8%)
Pneumonia	1 (1.8%)	1 (3.8%)
Postoperative wound infection	0	1 (3.8%)
Rash pustular	0	1 (3.8%)
Rhinovirus infection	1 (1.8%)	1 (3.8%)
Staphylococcal bacteremia	1 (1.8%)	0
Systemic candida	0	1 (3.8%)
Varicella	1 (1.8%)	0
Viral infection	0	1 (3.8%)
Injury, poisoning and procedural complications	6 (10.9%)	2 (7.7%)
Anemia postoperative	1 (1.8%)	0
Arthropod bite	1 (1.8%)	0
Contusion	1 (1.8%)	0
Excoriation	0	1 (3.8%)
Laceration	1 (1.8%)	0
Wound	0	1 (3.8%)
Wound dehiscence	1 (1.8%)	0
Wound secretion	1 (1.8%)	0
Investigations	9 (16.4%)	3 (11.5%)
Alanine aminotransferase increased	0	1 (3.8%)
Blood creatine phosphokinase increased	4 (7.3%)	0
Blood potassium decreased	1 (1.8%)	0
Blood sodium decreased	1 (1.8%)	0
Body temperature increased	0	1 (3.8%)
Hepatic enzyme increased	2 (3.6%)	0
Roseolovirus test positive	1 (1.8%)	0
Transaminases increased	1 (1.8%)	1 (3.8%)
Metabolism and nutrition disorders	3 (5.5%)	2 (7.7%)
Fluid overload	1 (1.8%)	1 (3.8%)
Hypernatremia	0	1 (3.8%)
Hyperphosphatemia	1 (1.8%)	1 (3.8%)
Hypophosphatemia	1 (1.8%)	0
Malnutrition	1 (1.8%)	0

Musculoskeletal and connective tissue disorders	6 (10.9%)	4 (15.4%)
Arthralgia	0	1 (3.8%)
Bone fistula	1 (1.8%)	0
Hemarthrosis	0	1 (3.8%)
Joint range of motion decreased	1 (1.8%)	0
Muscle spasms	1 (1.8%)	0
Muscular weakness	1 (1.8%)	0
Myositis	0	1 (3.8%)
Neck pain	1 (1.8%)	0
Pain in extremity	1 (1.8%)	1 (3.8%)
Synovitis	1 (1.8%)	0
Nervous system disorders	0	2 (7.7%)
Headache	0	1 (3.8%)
Lethargy	0	1 (3.8%)
Psychiatric disorders	1 (1.8%)	0
Abnormal behavior	1 (1.8%)	0
Renal and urinary disorders	3 (5.5%)	1 (3.8%)
Dysuria	1 (1.8%)	0
Pollakiuria	1 (1.8%)	0
Pyuria	1 (1.8%)	0
Renal failure acute	1 (1.8%)	0
Renal necrosis	0	1 (3.8%)
Reproductive system and breast disorders	0	1 (3.8%)
Epididymal cyst	0	1 (3.8%)
Respiratory, thoracic and mediastinal disorders	6 (10.9%)	5 (19.2%)
Atelectasis	0	1 (3.8%)
Cough	2 (3.6%)	1 (3.8%)
Hypoxia	0	1 (3.8%)
Pharyngeal ulceration	1 (1.8%)	0
Pneumonia aspiration	0	1 (3.8%)
Pneumothorax	1 (1.8%)	0
Pulmonary mass	1 (1.8%)	1 (3.8%)
Pulmonary edema	0	1 (3.8%)
Respiratory failure	1 (1.8%)	0
Rhinorrhea	1 (1.8%)	0
Wheezing	1 (1.8%)	0
Skin and subcutaneous tissue disorders	4 (7.3%)	4 (15.4%)
Acne	1 (1.8%)	0
Decubitus ulcer	1 (1.8%)	1 (3.8%)
Dermatitis contact	1 (1.8%)	0
Erythema	0	2 (7.7%)
Pruritus	0	1 (3.8%)
Rash	1 (1.8%)	0
Rash erythematous	0	1 (3.8%)
Rash macular	0	1 (3.8%)
Rash maculo-papular	0	1 (3.8%)
Skin exfoliation	0	1 (3.8%)

Vascular disorders	2 (3.6%)	2 (7.7%)
Hypotension	0	1 (3.8%)
Phlebitis	1 (1.8%)	0
Thrombophlebitis	0	1 (3.8%)
Venous thrombosis limb	1 (1.8%)	0

Adapted from DAP-PEDBAC-11-02 Protocol Table 14.3.1.2.1a

There was a diverse range of adverse events reported for both daptomycin and comparator groups during the study. The majority of these events occurred only in individual patients at rates of <5% given the small safety population of 81 subjects. In the daptomycin group, the most common adverse events in descending order include: diarrhea (10.9%), vomiting (10.9%), pyrexia (9.1%), blood creatine phosphokinase increase (7.3%), and bacteremia (5.5%). In the comparator group, the most common adverse events in descending order include: diarrhea (19.2%), osteomyelitis (15.4%), pyrexia (11.5%), arthritis bacterial (11.5%), vomiting (7.7%), drug hypersensitivity (7.7%), and erythema (7.7%). Several of the most common adverse events overall (diarrhea, vomiting, pyrexia) are similar between the two groups and are expected given the clinical scenario of bacteremia and antibiotic treatment. Other common adverse events, including osteomyelitis and bacterial arthritis, were more common in the comparator group but not unexpected given the clinical scenario and it remains difficult to establish significance given low patient numbers.

Of study specific investigations established from adult trials (discussed further in Section 7.3.5), increased blood creatine phosphokinase was noted in 7.3% of daptomycin treated patients. None of these elevations in CPK were severe but one patient discontinued IV daptomycin to complete the study due this concern.

7.4.2 Laboratory Findings

Various laboratory measures were tracked during the study as discussed previously. Table 7.8 displays mean values at baseline and at various key visits.

Table 7.8 Mean Values of Chemistry Parameters over Time

Chemistry Parameter, Mean (SD)	n	DAP (n=55)	n	COM (n=26)
Albumin (g/L)				
Baseline	53	32.7 (7.06)	26	31.7 (7.66)
EOIV Therapy	51	36.8 (6.16)	21	36.0 (4.22)
Maximum Value Post-Baseline	54	39.6 (6.26)	26	37.3 (6.97)
Alkaline Phosphatase (U/L)				
Baseline	53	166.8 (80.62)	26	194.2 (80.81)
EOIV Therapy	50	190.6 (104.08)	20	179.7 (75.09)
Maximum Value Post-Baseline	54	214.4 (102.48)	26	236.2 (109.92)
Alanine Aminotransferase (U/L)				

Baseline	53	49.9 (96.90)	26	38.0 (39.56)
EOIV Therapy	51	37.8 (42.73)	21	39.0 (48.00)
Maximum Value Post-Baseline	54	53.5 (70.52)	26	46.7 (42.37)
Aspartate Aminotransferase (U/L)				
Baseline	53	51.1 (68.28)	26	43.7 (52.12)
EOIV Therapy	51	37.5 (31.20)	21	39.5 (40.27)
Maximum Value Post-Baseline	54	48.1 (33.16)	26	45.3 (34.46)
Bilirubin (µmol/L)				
Baseline	53	9.31 (7.794)	26	13.04 (14.094)
EOIV Therapy	49	8.22 (4.382)	21	9.99 (7.912)
Maximum Value Post-Baseline	54	11.46 (6.455)	26	13.15 (8.817)
BUN (mmol/L)				
Baseline	55	4.03 (2.017)	26	3.37 (1.275)
EOIV Therapy	51	4.41 (2.122)	22	3.81 (1.440)
Maximum Value Post-Baseline	54	5.29 (2.041)	26	4.73 (1.357)
Creatinine (µmol/L)				
Baseline	55	46.99 (21.203)	26	50.81 (20.993)
EOIV Therapy	51	46.07 (18.277)	22	52.95 (16.850)
Maximum Value Post-Baseline	54	54.18 (21.511)	26	58.49 (21.785)
Protein (g/L)				
Baseline	52	61.9 (8.35)	26	61.3 (8.76)
EOIV Therapy	51	69.0 (8.98)	21	68.0 (7.68)
Maximum Value Post-Baseline	54	72.4 (7.75)	26	69.6 (9.36)

Adapted from DAP-PEDBAC-11-02 Protocol Table 14.3.3.1.1a

Overall, chemistry values over time were similar between the daptomycin and comparator groups. The increases over time in albumin and protein are expected for patients recovering from bacteremia. On average, transaminases improved over time in daptomycin treated patients. Additional analysis of liver chemistries is discussed below (see Table 7.9). There were no significant changes in renal chemistries.

An analysis of potential drug induced liver injury (DILI) was performed for the safety population. This potential risk was presented in the most recent Periodic Safety Update Report where post-marketing data regarding this risk was presented. Table 7.9 summarizes new data from Study DAP-PEDBAC-11-02.

Table 7.9 Summary of Laboratory Values for Drug-Induced Liver Injury Criteria

Criterion (anytime during treatment)	Daptomycin (n=55)	Comparator (n=26)
AST or ALT >3x ULN	4 (7.3%)	1 (3.8%)
1-6 years old	1	0
7-11 years old	2	1
12-17 years old	1	0
AST or ALT >5x ULN	2 (3.6%)	0
1-6 years old	1	0
7-11 years old	0	0
12-17 years old	1	0
AST or ALT >10x ULN	1 (1.8%)	0

1-6 years old	0	0
7-11 years old	0	0
12-17 years old	1	0
Total Bilirubin >1.5x ULN	1 (1.8%)	1 (3.8%)
1-6 years old	1	0
7-11 years old	0	1
12-17 years old	0	0
Total Bilirubin >2x ULN	0	0
AST or ALT >3x ULN and Total Bilirubin >2x ULN	0	0
AST or ALT >3x ULN and Total Bilirubin >2x ULN and ALP ≤2x ULN	0	0

Adapted from Table 12-13 from Clinical Study Report: Protocol DAP-PEDBAC-11-02

The new presented data do not demonstrate any clinically significant new concerns for DILI. Three patients treated with daptomycin had elevations in transaminases documented as TEAEs, but all had significant elevations at baseline:

- Subject 005-2016 had an elevated ALT of 200 U/L (RR 3-35 U/L) at baseline of unknown etiology. An ALT of 211 U/L and AST of 286 U/L (RR 3-46 U/L) were flagged as >5x UNL on Day 1 of IV therapy. The patient was discontinued from study drug on Day 2 due to withdrawal of parental consent but had improved enzyme levels prior to stopping medication which continued to decline.
- Subject 005-3017 had an elevated ALT of 270 U/L and AST of 181 U/L at baseline. These remained consistently elevated throughout the study at similar levels apparently unrelated to study drug. The subject had an ongoing history of hepatomegaly, short bowel syndrome, and cholestasis due to total parenteral nutrition.
- Subject 005-1008 had an elevated ALT of 689 U/L and AST of 490 U/L at baseline. Baseline values were also the peak values for the patient but elevated AST/ALT lead to reporting of TEAE on Day 3 of IV therapy. Values improved throughout therapy and were near normal by Post-IV therapy visit. While the etiology of the patient's increased transaminases remained unknown, they had been previously documented in the subject's medical history.

Myopathy and associated elevations in CPK values is a known adverse event in adults and children treated with daptomycin. Four patients in the daptomycin treated group had adverse events reported for elevations in CPK values as detailed in Section 7.3.5. A comparison of CPK shifts from baseline is provided below in Table 7.10.

Table 7.10 CPK Shift from Baseline

	Baseline Value (n=55, Daptomycin Safety Population)					
Worst Post-Baseline Value	**≤ULN**	**>ULN to 2.5x ULN**	**>2.5x ULN to 5x ULN**	**>5x ULN to 10x ULN**	**>10x ULN**	**Total**
≤ULN	37 (68.5%)	2 (3.7%)	0	0	0	39 (72.2%)

>ULN to 2.5x ULN	9 (16.7%)	3 (5.6%)	1 (1.9%)	0	0	13 (24.1%)
>2.5x ULN to 5x ULN	1 (1.9%)	0	0	0	0	1 (1.9%)
>5x ULN to 10x ULN	1 (1.9%)	0	0	0	0	1 (1.9%)
>10x ULN	0	0	0	0	0	0
Total	48 (88.9%)	5 (9.3%)	1 (1.9%)	0	0	54
	Baseline Value (n=26, Comparator Safety Population)					
≤ULN	18 (69.2%)	3 (11.5%)	0	0	0	21 (80.8%)
>ULN to 2.5x ULN	2 (7.7%)	3 (11.5%)	0	0	0	5 (19.2%)
>2.5x ULN to 5x ULN	0	0	0	0	0	0
>5x ULN to 10x ULN	0	0	0	0	0	0
>10x ULN	0	0	0	0	0	0
Total	20 (76.9%)	6 (23.1%)	0	0	0	26

Adapted from Study DAP-PEDBAC-11-02 Table 14.3.3.5.1a

Both daptomycin and comparator treated subjects showed elevations in CPK values from baseline. 27.9% of daptomycin treated subjects had peak CPK values >ULN compared to 19.2% of comparator treated subjects (not including baseline values). Of note, 11.2% of daptomycin subjects had baseline CPK values >ULN compared to 23.1% of comparator subjects. While none of these elevations are considered severe adverse events, there was a clear trend of daptomycin patients to have elevated CPK values consistent with muscle toxicity described in prior adult and pediatric studies including DAP-PED-07-03.

One patient discontinued daptomycin due to elevations in CPK values as discussed in Section 7.3.3.

Two patients who had initial CPK values below ULN at baseline went on to develop peak CPK elevations of >2.5x ULN while on IV therapy with daptomycin. Both patients developed their CPK elevations two days after having arthrotomy procedures (one on an ankle and another on a hip) with subsequent improvement. Given the relationship of the CPK elevations to these procedures and subsequent improvement, a significant contribution from daptomycin toxicity is unlikely.

7.4.3 Vital Signs

Table 7.11 reviews differences in several analyzed vital signs from baseline to EOIV and TOC visits for daptomycin and comparator.

Table 7.11 Changes in Vital Signs from Baseline to EOIV and TOC visits

	Daptomycin		Comparator	
Parameter	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Systolic Blood Pressure (mmHg)				
Baseline Value	55	107.5 (14.64)	25	105.4 (9.95)
Difference at EOIV Visit	51	-0.7 (14.42)	23	0.9 (7.56)
Difference at TOC Visit	52	0.5 (13.33)	24	0.5 (7.78)

Diastolic Blood Pressure (mmHg)				
Baseline Value	55	63.3 (9.67)	25	63.0 (8.09)
Difference at EOIV Visit	51	-0.3 (13.26)	23	0.2 (7.39)
Difference at TOC Visit	52	1.8 (12.04)	23	-0.9 (8.11)
Heart Rate (beats/minute)				
Baseline Value	55	105.8 (20.92)	26	101.2 (20.68)
Difference at EOIV Visit	51	-10.6 (19.65)	25	-7.0 (19.35)
Difference at TOC Visit	52	-15.0 (16.37)	24	-9.9 (16.42)
Temperature (°C)				
Baseline Value	55	37.63 (0.950)	26	37.88 (1.178)
Difference at EOIV Visit	51	-0.78 (1.122)	24	-0.94 (1.239)
Difference at TOC Visit	51	-1.03 (1.016)	24	-1.23 (1.112)

Adapted from Study DAP-PEDBAC-11-02 Table 14.3.4.1a

Vital signs analyzed throughout the study were generally similar. While not statistically significant due given small sample sizes, there was a trend for decreasing heart rate and temperature consistent with a resolving bacterial infection. As noted previously in Section 7.4.1, pyrexia was one of the most common adverse events reported for both daptomycin and comparator.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

Not applicable.

7.5.1 Dose Dependency for Adverse Events

Refer to Section 7.2.2 for a daptomycin exposure safety analysis comparing daptomycin peak plasma concentrations with maximum CPK during IV therapy and during the entire study.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were assessed.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were assessed.

7.5.5 Drug-Drug Interactions

No dug-drug interactions were assessed.

7.6 Additional Safety Evaluations

Not applicable.

7.7 Additional Submissions / Safety Issues

Not applicable.

7.8 Safety Summary

Overall, daptomycin doses at 7, 9, or 12 mg/kg for ages 12-17, 7-11, and 1-6 years respectively for up to 42 days has a similar safety profile in the pediatric population as in adults. In comparing overall clinical trial safety between daptomycin and standard of care comparators, the incidence of adverse events was similar. Study design and safety findings are similar to data in adult trials. There were no deaths reported in this SAB trial. In adult clinical trials deaths which occurred, primarily were due to adverse events secondary to infection or infestations.

The majority of AEs were ranked as either mild or moderate with no indication of persistence. There was similar proportion of study patients reporting at least one AE between the daptomycin group (65.5%) and comparator (76.9%). The most common adverse events noted to occur in the daptomycin arm were gastrointestinal conditions such as diarrhea and vomiting. Pyrexia was also a common adverse event. The severe TEAEs occurred less commonly in the daptomycin group (9.1%) relative to comparator (15.4%). There were 20 subjects with serious adverse events: 13 subjects were in the group treated with daptomycin and 7 subjects in the group treated with comparator. An increase of blood CPK in 2 patients in the daptomycin arm were considered possibly related to study daptomycin. No other serious adverse events indicated causality to study drug. The safety profile was comparable across age groups.

In the clinical trial of the 81 subjects, 11 prematurely discontinued IV study treatment. Of those who discontinued, 8 subjects (14.5%) were treated with daptomycin and 2 (7.7%)

with a comparator. Three patients discontinued IV study drug due to adverse events (all in the daptomycin arm) with only 1 felt to be possibly related to study drug (elevated CPK value). Microbiologic failure leading to discontinuation occurred in 2 patients treated with daptomycin (3.6%) and no patients in the comparator group. No patients in the daptomycin arm discontinued from the study after switching for IV therapy.

No new safety signals were apparent from the review of the safety database focusing on CPK, hepatic function, and peripheral neuropathy. The pattern of skeletal muscle toxicity observed in the study was consistent with previous experiences with adults and pediatric patients. Most CPK elevations fell between 1 and 2.5 x ULN (13 [24.1%) of daptomycin subjects and 5 [19.2%] of comparator subjects). CPK elevations >2.5 x ULN were uncommon (2 daptomycin treated subjects and 0 comparator treated subjects). There was no clinically significant new concern for DILI or peripheral neuropathy identified during this review.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

1. Liu, C., Bayer, A., Cosgrove, S. E., Daum, R. S., Fridkin, S. K., Gorwitz, R. J., . . . Chambers, H. F. (2011). Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. *Clinical Infectious Diseases,* 1-38. doi:10.1093/cid/ciq146

9.2 Labeling Recommendations

Recommended changes were generally related to formatting and presentation of data. The SAB indication is extended to pediatric patients 1 to 17 years of age, and Sections 2 (Dosage and Administration), 6.1 (Clinical Trials Experience), 8.4 (Pediatric Use), 14 (Clinical Studies), and 12.3 (Pharmacokinetics) were updated to include information from the pediatric SAB study.

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure Review

Application Number: 21572

Submission Date(s): March 1, 2017

Applicant: Cubist Pharmaceuticals

Product: Cubicin (Daptomycin for injection)

Reviewer: Nicholas Rister, MD

Date of Review: August 4, 2017

Covered Clinical Study (Name and/or Number): DAP-PEDBAC-11-02 A Comparative Evaluation of the Safety and Efficacy of Daptomycin Versus Standard of Care in Pediatric Subjects One to Seventeen Years of Age With Bacteremia Caused by *Staphylococcus aureus*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 144		

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There were no interests/arrangements between the sponsor and its investigators that were likely to affect the study outcome. A single site investigator did receive a research grant and a description of the steps taken to minimize potential bias was not provided; however, this site enrolled three patients total and is unlikely to significantly alter the analysis. None of the clinical investigators on the study were sponsor employees.

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/s/

NICHOLAS S RISTER
08/24/2017

THOMAS D SMITH
08/25/2017