CLINICAL PHARMACOLOGY REVIEW

NDA:	21- 572 (SDN#700)
Brand Name:	Cubicin®
Generic Name:	Daptomycin
Date of Original Submission:	March 02, 2017
Indication:	*Staphylococcus aureus* bloodstream infections (bacteremia) in pediatric patients.
Applicant:	Merck
Submission Type:	Pediatric NDA
Clinical Pharmacology Reviewer:	Sonia Pahwa, PhD
Pharmacometric Reviewer	Fang Li, PhD
Pharmacometric Team Leader:	Jeffry Florian, PhD
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1. Executive summary

Daptomycin is a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus* used in the treatment of infections caused by aerobic Gram-positive bacteria. CUBICIN® (daptomycin for injection, hereafter referred to as daptomycin) is approved for the following indications in adults: (a) complicated skin and skin structure infections (cSSSI) at the dose of 4 mg/kg once daily and (b) *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis (IE) at the dose of 6 mg/kg once daily.

The purpose of this application is to demonstrate safety and efficacy of daptomycin in pediatric patients 1 to 17 years old with *S. aureus* bacteremia (SAB), thereby supporting the registration of daptomycin in pediatric patients for the SAB at the recommended, age-specific, weight-based dosing regimens summarized in Table 1(a). However, the proposed dose of 12 mg/kg once daily in pediatric patients of 1 to <2 years age group cannot be recommended, as patients l to <2 years of age were not enrolled this study and there is no clinical experience with 12 mg/kg daptomycin in this age group (please refer to section 1.3.4 for details). Therefore, we have recommended confining the 12 mg/kg once daily dose to pediatric patients aged from 2 to 6 years (see Table 1(b)).

1.1. Recommendations

Based on the review of the submitted study reports, the dosing regimens of daptomycin in pediatric patients proposed by the Applicant (Table 1(a)) 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 has been evaluated only in patients ≥2 years of age for safety and efficacy of daptomycin (refer to section 1.3.4 for details). Because there is no clinical experience to use 12 mg/kg once daily (up to 42 days) in pediatric patients aged from 1 to 2 years, we recommend that the use of daptomycin to treat SAB should be limited in patients ≥2 years of age.

1.2. Phase 4 commitments

There are no Phase 4 commitments.

1.3. Summary of important clinical pharmacology and biopharmaceutics findings

Three Phase 1 PK studies in pediatric patients (Studies DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01) were previously conducted to characterize daptomycin pharmacokinetics in adolescents and children 1 to 17 years of age; the results of these studies informed the doses and dosing regimens for pediatric patients with cSSSI and were summarized in the previous Clinical Pharmacology review by Dr. Sonia Pahwa dated 11/15/2016 for cSSSI indication in pediatrics. These three Phase 1 PK studies demonstrated that daptomycin exposure were generally lower in pediatric patients compared with adults at the same dose, with weight-normalized clearance inversely related to age.

The same IV formulation of daptomycin as approved for adults was used in the Phase 4 study for pediatric SAB patients (Study DAP-PEDBAC-11-02) and in the three Phase 1 PK studies for pediatric cSSSI patients (i.e., Studies DAP-PEDS-05-01, DAP-PEDS-07-02 and DAP-PEDS-09-01). Based on the results of the three Phase 1 PK studies for pediatric cSSSI patients, the doses and dosing regimens evaluated in the Phase 4 study for pediatric SAB patients (Study DAP-PEDBAC-11-02) were selected to provide the exposure comparable to that observed in adult patients receiving 6 mg/kg once daily (i.e., at the approved dosing regimen to treat SAB).

The derived doses in pediatric patients were 7 mg/kg once daily in the adolescents (12 to 17 years of age), 9 mg/kg once daily in the older children (7 to 11 years of age), and 12 mg/kg once daily in the younger children (1 to 6 years of age). At the evaluated dosing regimens, the exposures in pediatric

patients with SAB were comparable to the exposure in adult SAB/RIE patients (mean AUC 622 µg·hr/mL), and efficacy was comparable with standard of care (SOC), and safety profiles in pediatric patients were acceptable.

1.3.1. What are the proposed dosage(s) and route(s) of administration?

The Applicant's proposed dosage regimens for age group 1 to 17 years of IV daptomycin is given below in Table 1(a); Because there is no clinical experience to use 12 mg/kg once daily (up to 42 days) in pediatric patients aged from 1 to <2 years, our recommended regimen is given in Table 1(b).

Table 1(a). Applicant proposed Dosage of CUBICIN® in Pediatric Patients (1 to 17 Years of Age) with *S. aureus* bacteremia, Based on Age

Age group	Dosage*	Duration of therapy[(1)]
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	
* Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established. [(1)] Minimum duration for pediatric bacteremia should be in accordance with the perceived risk of complications in the individual patient.		

Administer CUBICIN to pediatric patients intravenously in 0.9% sodium chloride, by infusion over a 30- or 60-minute period, based on age. Unlike in adults, CUBICIN should not be administered by injection over a two (2) minute period in pediatric patients.

Table 1(b). Recommended Dosage of CUBICIN® in Pediatric Patients (2 to 17 Years of Age) with *S. aureus* bacteremia, Based on Age

Age group	Dosage*	Duration of therapy[(1)]
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	12 mg/kg once every 24	

	hours infused over 60 minutes	

* Recommended dosage is for pediatric patients (2 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

(1) Minimum duration for pediatric bacteremia should be in accordance with the perceived risk of complications in the individual patient.

Administer CUBICIN to pediatric patients intravenously in 0.9% sodium chloride, by infusion over a 30- or 60-minute period, based on age. Unlike in adults, CUBICIN should not be administered by injection over a two (2) minute period in pediatric patients.

1.3.2. What are key efficacy findings for daptomycin in pediatric patients?

In Study DAP-PEDBAC-11-02, a multi-center, evaluator-blinded, randomized, comparative Phase 4 study, efficacy and PK of daptomycin were assessed in three Age Cohorts of pediatric patients with SAB [i.e., Age Cohort 1: Age 12 to 17 years old (inclusive); Cohort 2: Age 7 to 11 years old (inclusive); and Cohort 3: Age 1 to 6 years old (inclusive)]. According to the protocol of this study, the patients aged 1 to 6 years should be included in the Age Cohort 3. However, we found that all patients enrolled in the Age Cohort 3 were older than 2 years, resulting in no patient 1 to <2 years of age enrolled in the study. Thus, it should be noted that the actual age range in the Age Cohort 3 in Study DAP-PEDBAC-11-02 is from 2 years to 6 years (inclusive).

The primary objective of Study DAP-PEDBAC-11-02 was to assess the safety of IV daptomycin versus SOC in pediatric subjects with SAB. The comparison of the efficacy of IV daptomycin *versus* SOC in pediatric subjects with SAB was a secondary objective of the study. The SOC comparator agents used in Study DAP-PEDBAC-11-02 were IV vancomycin, IV clindamycin, IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin], or IV first-generation cephalosporins. The efficacy endpoint was clinical outcome based on a blinded Evaluator's assessment of clinical response at the TOC/Safety Visit in the mMITT population. Clinical outcome was determined as success (cure or improvement), failure, or non-evaluable. Another efficacy endpoint was the overall outcome based on both the subject's clinical outcome and the subject's microbiological response at the TOC/Safety Visit in the mMITT population. Microbiological response was determined as microbiological success, failure, or non-evaluable based on evaluation of baseline infecting pathogen. The overall outcome was determined as success if both clinical outcomes and microbiological outcomes were successful.

The major efficacy conclusions in pediatric subjects aged 1 to 6 years, 7 to 11 years, and 12 to 17 years receiving daptomycin at doses of 12, 9, or 7 mg/kg once daily, respectively, in the treatment of SAB were:

• Overall, the proportion of daptomycin-treated subjects with a favorable clinical response at the TOC/Safety Visit in the mMITT Population was 88.2% in the daptomycin arm and 77.3% in the comparator arm.

• Microbiological success rates at the TOC/Safety Visit for the mMITT Population were similar in the daptomycin (76.5%) and comparator (77.3%) treatment arms.

• The proportion of subjects with a favorable overall outcome at the TOC/Safety Visit in the

mMITT Population was 72.5% in the daptomycin arm and 59.1% in the comparator arm (Table 2).

Reviewer's comment: Additional details regarding efficacy of daptomycin in pediatric patients are provided in the Clinical review by the reviewing medical officer, Dr. Nicholas Rister.

Table 2. Summary of Overall Outcome at TOC (mMITT Population - Pediatric Phase 4 SAB Study [DAP-PEDBAC-11-02])

	Total		1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
Overall Therapeutic Response	**DAP (N=51) n (%)**	**COM (N=22) n (%)**	**DAP (N=20) n (%)**	**COM (N=8) n (%)**	**DAP (N=17) n (%)**	**COM (N=9) n (%)**	**DAP (N=14) n (%)**	**COM (N=5) n (%)**
Number of Subjects with Responses	51	22	20	8	17	9	14	5
Overall success	37 (72.5)	13 (59.1)	16 (80.0)	6 (75.0)	14 (82.4)	4 (44.4)	7 (50.0)	3 (60.0)
% Difference in Success Rate [a] (95% CI of difference) [b]	13.5 (-10.5, 37.4)		5.0 (-29.8, 39.8)		37.9 (0.7, 75.1)		-10.0 (-60.3, 40.3)	
Overall failure or non-evaluable	14 (27.5)	9 (40.9)	4 (20.0)	2 (25.0)	3 (17.6)	5 (55.6)	7 (50.0)	2 (40.0)
Overall failure	9 (17.6)	5 (22.7)	4 (20.0)	2 (25.0)	1 (5.9)	2 (22.2)	4 (28.6)	1 (20.0)
Non-evaluable	5 (9.8)	4 (18.2)	0	0	2 (11.8)	3 (33.3)	3 (21.4)	1 (20.0)

CI: confidence interval; COM: standard of care comparator; DAP: daptomycin; mMITT: microbiological modified intent-to-treat; TOC: test of cure

a. Difference is calculated as Daptomycin – Comparator in the corresponding age groups

b. 95% CI of the difference in percent of subjects with a success response between the two treatment arms (DAP – COM) was constructed based on the Wilson score method

1.3.3. What are the key safety findings for daptomycin in pediatric patients?

The primary objective of the pediatric Phase 4 SAB study (Study DAP-PEDBAC-11-02) was to assess the safety of IV daptomycin versus comparator in pediatric subjects with SAB. The safety of daptomycin and comparator were evaluated by monitoring adverse events, serious adverse events (SAEs), and changes in physical and focused neurological examinations and serum chemistry (including serum Creatine Phosphokinase (CPK) level), hematology, and vital signs. Eighty-one of the 82 subjects (98.8%) received study drugs; 55 daptomycin-treated subjects and 26 comparator-treated subjects. Daptomycin was generally well tolerated when administered to pediatric subjects with SAB at doses of 7 to 12 mg/kg once daily. A detailed discussion on the safety aspects of daptomycin in pediatric patients in different age cohorts are provided in the Clinical review by the reviewing medical officer Dr. Nicholas Rister. It should be also noted that all patients enrolled in Study DAP-PEDBAC-11-02 were ≥ 2 years of age and, accordingly, there is no data/information to evaluate whether the dosing regimen used for Age Cohort of 1 to 6 years (i.e., 12 mg/kg once daily up to 42 days) is safe or not in pediatric patients aged 1 to 2 years.

1.3.4. What are PK characteristics for daptomycin in pediatric patients?

Pharmacokinetics of daptomycin in pediatric SAB patients were assessed using sparse pharmacokinetic samples collected in the Phase 4 safety and efficacy studies in pediatric SAB patients (Study DAP-PEDBAC-11-02), and a previously developed pediatric population pharmacokinetic model (Study CUBI-PCS-106, described in a previous Clinical Pharmacology review by Dr. Sonia Pahwa dated 11/15/2016 for cSSSI indication), and using a updated population PK model (Study MERC-PCS-121; see Appendix 3.2 for Pharmacometrics review).

Based on the results of the above-mentioned three Phase 1 PK studies submitted for cSSSI indication and Study DAP-PEDBAC-11-02, the following conclusions were made about PK characteristics of daptomycin in pediatric patients:

- The pharmacokinetic properties of daptomycin were linear and dose-proportional over the range of doses studied (4 mg/kg to 12 mg/kg).

- After a single dose of 4 mg/kg intravenous infusion for 30 minutes, the AUC of daptomycin was generally lower in pediatric patients than in adults.
- Renal excretion was the major elimination pathway of daptomycin in pediatric patients.
- The unbound fraction and percentage excreted in urine for daptomycin were similar across different age groups of pediatric patients.
- Model-predicted total clearance normalized by body weight (CL/WT), total volume of distribution normalized by weight (Vss/WT) and elimination half-life ($t_{1/2}$) varied across different age groups. The CL/WT and Vss/WT decreased with increasing age in pediatric patients with SAB (Table 3).
- Mean CL/WT values ranged from 20 mL/hr/kg (2 to 6 years of age) to 12 mL/hr/kg (12-17 years of age) in pediatric patients with SAB.
- Mean Vss/WT values ranged from 137 mL/kg (2 to 6 years of age) to 115 mL/kg (12 to 17 years of age) in pediatric patients with SAB.
- The mean $t_{1/2}$ increased with increasing age, ranging from 5.1 (2 to 6 years of age) to 7.5 hours (12 to 17 years of age) in pediatric patients with SAB, consistent with that observed in the Phase 1 pharmacokinetic studies in pediatric patients.
- Daptomycin exposure was similar across different age groups with mean AUC ranging from 579 to 656 μg·hr/mL, and mean C_{max} ranging from 104 to 106 μg/mL. The comparable exposure in pediatric SAB patients to that in adults, together with the similar safety and efficacy profiles between pediatric and adult patients as well as between daptomycin *versus* SOC in pediatric patients with SAB, supports that dosing regimens evaluated in Study DAP-PEDBAC-11-02 are appropriate for pediatric patients with SAB.

Table 3. Mean (SD) of Daptomycin Pharmacokinetics in Pediatric SAB Patients from the Phase 4 Pediatric SAB Study DAP-PEDBAC-11-02 Estimated Using Pediatric Population Pharmacokinetics Modeling

Age	Pharmacokinetic Parameters						
	Dose (mg/kg)	**Infusion Duration (min)**	**AUC_{ss} (mcg•h/mL)**	**$t_{1/2}$ (h)**	**V_{ss} (mL)**	**CL_T (mL/h/kg)**	**$C_{max,ss}$ (mcg/mL)**
12 to 17 years (N=13)	7	30	656 (334)	7.5 (2.3)	6420 (1980)	12.4 (3.9)	104 (35.5)
7 to 11 years (N=19)	9	30	579 (116)	6.0 (0.8)	4510 (1470)	15.9 (2.8)	104 (14.5)
2 to 6 years (N=19)	12	60	620 (109)	5.1 (0.6)	2200 (570)	19.9 (3.4)	106 (12.8)

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalized to body weight; V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life

Reviewer's comment:

- *Exposures in pediatric patients aged from 2 to 17 years with SAB at the proposed age-specific, weight-based dosing regimens are largely contained within those observed in adult patients with SAB/RIE receiving the approved 6 mg/kg dose regimens. There are no clinically relevant differences and there is similarity in disease progression between adult and pediatric populations. Therefore, the derived dosage regimen in Table 3 based on matching adult*

exposure is appropriate in terms of effectiveness for the treatment of pediatric patients with SAB.

- *According to the protocol of the study DAP-PEDBAC-11-02, the patients aged 1 to 6 years should be included in the Age Cohort 3. However, the Reviewer noticed that despite of this age range being included in the study inclusion criteria, all of the patients in the study were ≥2 years of age. The Reviewer stratified the age cohort to sub-groups of 2-<3 years of age and ≥3-6 years of age and assessed exposure in the two subgroups. Based on the Reviewer's analysis, the mean (SD) AUCss in patients with age range of 2-<3 years was 555.9 (65.2) µg·hr/mL (n=6) as compared to mean (SD) AUCss of 649.7(113.9) µg·hr/mL in age range of ≥3-6 years (n=13), indicating that exposure in pediatric patients aged from 1 to 2 years receiving the same dose may potentially be lower than in pediatric patients aged from 2 to 6 years. In addition, PK data to support the dosing regimens for pediatric patients with cSSSI demonstrated that the daptomycin clearance in infants (1 to <2 years of age) were higher than in young children (2-6 years of age) (refer to Table 13 in CUBICIN label). Thus, our Pharmacometrics review team simulated the exposure in pediatric patients aged 1-2 years receiving different dosing regimens. Simulation results are summarized in Table 4.*

Table 4. Simulated Daptomycin Exposure in Children 1 to 2 Years after Dosage Regimen of 12 mg/kg and 13 mg/kg once daily

Age Group **Dose (mg/kg)**	**1 to 1.5 years** **12 mg/kg**	**1 to 1.5 Years** **13 mg/kg**	**1.5 to 2 Years** **12 mg/kg**	**1.5 to 2 Years** **13 mg/kg**	**Adults (Median)** **6 mg/kg**
AUCss (µg·h/mL) Median (P25-P75)	534 (429-681)	578 (465-739)	553 (436-694)	599 (472-751)	543.8
AUCss (µg·h/mL) Geo Mean	537	582	547.9	593.6	

Based on the results of the above simulation, a dose of 13 mg/kg once daily in children between 1 to 2 years of age will provide comparable exposure to that in adults. In addition, as observed previously in pediatric patients with cSSSI, a higher dose (10 mg/kg) of daptomycin has been approved in 1 to <2 years age group than that in 2-6 years age group (9 mg/kg). Accordingly, a higher dose of 13 mg/kg in age group 1-2 years may be more appropriate to provide desired exposure and efficacy as compared to that of 12 mg/kg dose for pediatric patients with SAB. However, as mentioned above, there is no data/information to support the safety of the dosing regimen (i.e., either 12 mg/kg or 13 mg/kg once daily up to 42 days) in pediatric patients aged 1 to 2 years.

1.4. Intrinsic factors and Extrinsic factors

No additional study was conducted in pediatric patients with renal and hepatic impairment.
The influence of intrinsic or extrinsic factors on the exposure of daptomycin was not evaluated in pediatric patients.

1.5. Analytical section

Please refer to Appendix 3.1.

2. Detailed labeling recommendations

The label will be filed in DARRTS separately after agreement with the applicant.

3. Appendices

3.1 Clinical pharmacology individual study review

3.2 Pharmacometric review

Appendix

3.1. Individual study reviews

Study # DAP-PEDBAC-11-02
TITLE OF STUDY: 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*.

STUDY OBJECTIVES: The primary objective of this study was to assess the safety of intravenous daptomycin versus standard of care antibiotics in pediatric subjects aged 1-17 years of age with bacteremia.
Secondary objectives:

- To compare the efficacy of IV daptomycin versus standard of care antibiotics in pediatric subjects aged 1 to 17 years of age with bacteremia caused by *S. aureus*.
- To determine exposure by measuring plasma levels of daptomycin at pre-dose (C_{trough}) and end of infusion (C_{max}) to explore exposure-response analyses in pediatric subjects aged 1 to 17 years of age with bacteremia.

METHODOLOGY:
This Phase 4, open label (Evaluator-blinded), comparative, multi-center, multi-national study was designed to describe the safety and efficacy of intravenous (IV) daptomycin versus standard of care (SOC) in pediatric subjects aged 1 to 17 years with *S. aureus* bacteremia. Subjects were enrolled and study medication began based on a diagnosis of proven or probable *S. aureus* bacteremia.

Subjects were enrolled into three age groups and treated with daptomycin or SOC comparator, based on a 2:1 randomization, which was stratified by age group. A total of 82 pediatric subjects between the ages of 1 and 17 years were randomized and stratified by age group, to receive either daptomycin or SOC comparator (suggested as IV vancomycin, IV clindamycin, IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin], or IV first-generation cephalosporins) in a ratio of 2:1, respectively, according to the following 3 age groups:
• Age Group 1: Age 12 to 17 years old (inclusive) treated with daptomycin dosed at 7 mg/kg once daily or SOC;
• Age Group 2: Age 7 to 11 years old (inclusive) treated with daptomycin dosed at 9 mg/kg once daily or SOC;
• Age Group 3: Age 1 to 6 years old (inclusive) treated with daptomycin dosed at 12 mg/kg once daily or SOC;
In the ITT Population, 55 pediatric subjects were randomized to receive daptomycin and 27 were randomized to receive SOC.

Reviewer's Comments: The Reviewer noticed that despite this age range being included in the study inclusion criteria, all the patients in the study were ≥2 years of age.

Bioanalytical Method Description:
Plasma:
The clinical pediatric bioanalytical method was developed using the original human plasma method (LC 309) for daptomycin. The bioanalyses of daptomycin in plasma samples were conducted at PPD

2244 Dabney Road, Richmond, VA 23230. Quantitation of Daptomycin in Human Plasma via HPLC with Ultraviolet Absorbance Detection" was conducted as per method description given below.

Method Description	PPD Method LC 309.7 V 1.00
Analyte	Daptomycin
Method Validation Report	PPD Validation Report, Project KLP, Quantitation of Daptomycin in Human Plasma via HPLC with Ultraviolet Detection
Reference Standards	Daptomycin, 670103A Ethyl 4-Hydroxybenzoate, 04816TA
Matrix	Human Plasma
Anticoagulant	Sodium Heparin
Method of Detection	HPLC with Ultraviolet
Sample Aliquot Volume	50 µL
Calibration Range	3.00 to 500 µg/mL
Quality Control (QC) Concentrations	3.00, 7.50, 75.0, and 400 µg/mL
Highest Dilution QC Concentration	N/A
Regression, Weighting	Linear, $1/conc.^2$
Demonstrated Storage Stability	637 days at -20 °C
Maximum Sample Storage Duration From Collection to Analysis	601 days at -20 °C (within Stability Limits)

The lower limit of quantification (LLOQ) for daptomycin is 3.00 µg/mL. The assay is applicable to the quantitation of daptomycin within a calibration range of 3.00 to 500 µg/mL.
Linearity was indicated by a correlation coefficient of ≥0.990 from the standard curve. Accuracy for low, medium, and high QCs was within 85.0 – 115.0%. The difference between the lowest and highest means recovery values was ≤ 20.0% which met the acceptance criteria. Precision (% CV) for the LLOQ QC was ≤ 20.0%. Precision (% CV) for low, medium, and high QCs was ≤ 15.0%. Storage and freeze-thaw stability was demonstrated by daptomycin samples.

Reviewer Comment: In general, the bioanalytical assay validation and QC performance for daptomycin were acceptable.

SUMMARY OF PHARMACOKINETICS:

The peak (C_{max}) and trough (C_{trough}) plasma concentrations of daptomycin were determined in each daptomycin-treated subject on Day 3, Day 4, Day 5, and Day 6. The pharmacokinetics of pediatric SAB patients in DAP-PEDBAC-11-02 are summarized in Table 1; Refer to the Appendix 3.2 for Population PK (MERC-PCS-121) details.

- The median C_{max} and C_{trough} values observed with the age-specific, weight-based doses ranged from 73 to 95 µg/mL and 4.3 to 5.6 µg/mL in pediatric SAB patients, respectively.

- The median C_{trough} appears to be comparable across the different age groups with age specific, weight-based dosing regimens, and that the median C_{max} appears to be higher for the youngest age group (2 to 6 years of age) compared to older patients ranging from 7 to17 years of age.
- Model-predicted total clearance normalized by body weight (CL/WT), total volume of distribution normalized by weight (Vss/WT) and elimination half-life ($t_{1/2}$) varied across different age groups. The CL/WT and Vss/WT decreased with increasing age.
- Mean CL/WT values ranged from 20 mL/hr/kg (2 to 6 years of age) to 12 mL/hr/kg (12 to 17 years of age) in pediatric SAB patients.
- Mean Vss/WT values ranged from 137 mL/kg (2 to 6 years of age) to 115 mL/kg (12 to 17 years of age) in pediatric SAB patients.
- The elimination half-life increased with increasing age with mean $t_{1/2}$ ranging from 5.1 hours (2 to 6 years of age) to 7.5 hours (12 to 17 years of age), consistent with that observed in the Phase 1 pharmacokinetic trials in pediatric patients.
- Daptomycin exposure was similar across different age groups with mean steady-state AUC_{0-24} ranging from 579 to 656 μg·hr/mL, and mean steady-state C_{max} ranging from 104 μg/mL to 106 μg/mL.

Table 1. Mean (SD) of Daptomycin Pharmacokinetics in Pediatric SAB Patients from the Phase 4 Pediatric SAB Trial DAP-PEDBAC-11-02 Estimated Using Pediatric Population Pharmacokinetics Modeling

Age	Pharmacokinetic Parameters						
	Dose (mg/kg)	**Infusion Duration (min)**	**AUC_{ss} (mcg•h/mL)**	**$t_{1/2}$ (h)**	**V_{ss} (mL)**	**CL_T (mL/h/kg)**	**$C_{max,ss}$ (mcg/mL)**
12 to 17 years (N=13)	7	30	656 (334)	7.5 (2.3)	6420 (1980)	12.4 (3.9)	104 (35.5)
7 to 11 years (N=19)	9	30	579 (116)	6.0 (0.8)	4510 (1470)	15.9 (2.8)	104 (14.5)
2 to 6 years (N=19)	12	60	620 (109)	5.1 (0.6)	2200 (570)	19.9 (3.4)	106 (12.8)

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalized to body weight; V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life

Note: Individual pharmacokinetic parameters of 5 patients without concentrations (with only BLQ or excluded unexpected low peak concentrations) were derived with the population pharmacokinetic parameters and individual covariate characteristics and included in this summary table.

Summary of Efficacy Results

The efficacy results in pediatric subjects aged 1 to 6 years, 7 to 11 years, and 12 to 17 years receiving daptomycin at doses of 12, 9, and 7 mg/kg once daily, respectively, in the treatment of *S. aureus* bacteremia are as follows:

- Overall, the proportion of daptomycin-treated subjects with a favorable clinical response at the TOC/Safety Visit in the mMITT population was 88.2% in the daptomycin arm and 77.3% in the SOC arm.
- Microbiological success rates at the TOC/Safety Visit for the mMITT population were similar in the daptomycin (76.5%) and SOC (77.3%) treatment arms.
- The overall outcome was determined based on the subject's microbiological response and clinical

outcome at the TOC/Safety Visit. The overall outcome was a success if both clinical and microbiological outcomes were successful. The proportion of subjects with a higher overall outcome at the TOC/Safety Visit in the mMITT population was 72.5% in the daptomycin arm and 59.1% in the SOC arm.

Summary of Safety:
Eighty-one of the 82 subjects (98.8%) in the ITT population received study drug. Hence, the Safety population includes 81 subjects; 55 daptomycin-treated subjects and 26 SOC-treated subjects. Daptomycin administered at doses of 7 to 12 mg/kg once daily to pediatric subjects aged 1 to 17 years, with *S. aureus* bacteremia was generally safe and well tolerated.

- Overall, the incidence rates of TEAEs, drug-related TEAE, TEAEs leading to discontinuation of study drug, and SAEs reported for daptomycin were comparable to those reported for SOC.
- There were no reported cases of drug hypersensitivity, eosinophilic pneumonia, or bone marrow toxicity in the daptomycin group. The observed events identified by Standardized MedDRA Queries (SMQs) for Peripheral Neuropathy or skeletal toxicity (Rhabdomyolysis/Myopathy) do not indicate a difference in frequency, severity, or outcomes of skeletal muscle adverse reactions in pediatric patients with bacteremia compared to adult patients. No new safety concerns were identified relative to data obtained from adult clinical trials.

APPLICANT'S CONCLUSIONS:
Daptomycin was effective in the treatment of *S. aureus* bacteremia.

- Daptomycin administered intravenously at doses of 7, 9, or 12 mg/kg for up to approximately 6 weeks to pediatric subjects aged 12 to 17 years, 7 to 11 years, and 1 to 6 years respectively, was shown to be safe and well tolerated in pediatric subjects with *S. aureus* bacteremia.
- Daptomycin was as effective as the SOC in the treatment of *S. aureus* bacteremia.

Reviewer's Comments:

- *To ensure efficacy, the doses in children 2-17 years were derived to provide children with the projected AUC of daptomycin compared to that in adult SAB patients receiving the approved dose for treatment of SAB (i.e., 6 mg/kg once daily dosing), which is acceptable approach from clinical pharmacology perspective.*

- *Because there is no clinical experience to use 12 mg/kg once daily (up to 42 days) in pediatric patients aged from 1 to 2 years, we recommend that the use of daptomycin to treat SAB should be limited in patients ≥2 years of age. Please see Table 1(b) in the QBR for the recommended dose regimen.*

3.2. Pharmacometric review

PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

The pharmacometric review focused on exploring the PK of daptomycin in children and exposure-response relationship between daptomycin exposure and creatine phosphokinase (CPK). Key conclusions are: i) the steady-state AUC in children 1 to 17 years of age is comparable to that in adults with bacteremia following IV treatment of 6 mg/kg; and ii) there was no clear exposure-response relationship for CPK in pediatric patients at the doses evaluated in this study.

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the exposure (e.g., AUC_{ss}, C_{max}, and C_{min}) of daptomycin support the proposed once-daily dosing regimen for the treatment of *Staphylococcus aureus* Bacteremia (SAB) in children 1 to 17 years old?

Yes. Pediatric patients age 1 to 17 years old using the proposed dosage regimen achieved comparable steady-state AUC to that observed in adults administered 6 mg/kg with the same indication. The C_{max} in pediatric patients was a little higher than in adults and the C_{min} was a little lower; however, these differences were not considered clinically significant.

PK samples were collected from pediatric patients in a Phase 4 study (DAP-PEDBAC-11-02). The study evaluated safety, efficacy, and pharmacokinetics of daptomycin in pediatric patients 1 to 17 years of age with bacteremia caused by *S. aureus.* In this study, patients received once daily (q.d) daptomycin (7 mg/kg, 9 mg/kg, or 12 mg/kg) or standard of care for 5 to 42 days depending on age and bacteremia infection status. Two PK samples (a trough and a peak) per patient were collected on Days 3, 4 or 5. Overall, 101 samples were collected from 51 patients. Individual PK parameters were derived based on a population PK analysis. Model based PK parameters of daptomycin in pediatric patients are summarized in Table 1 and Figure 1.

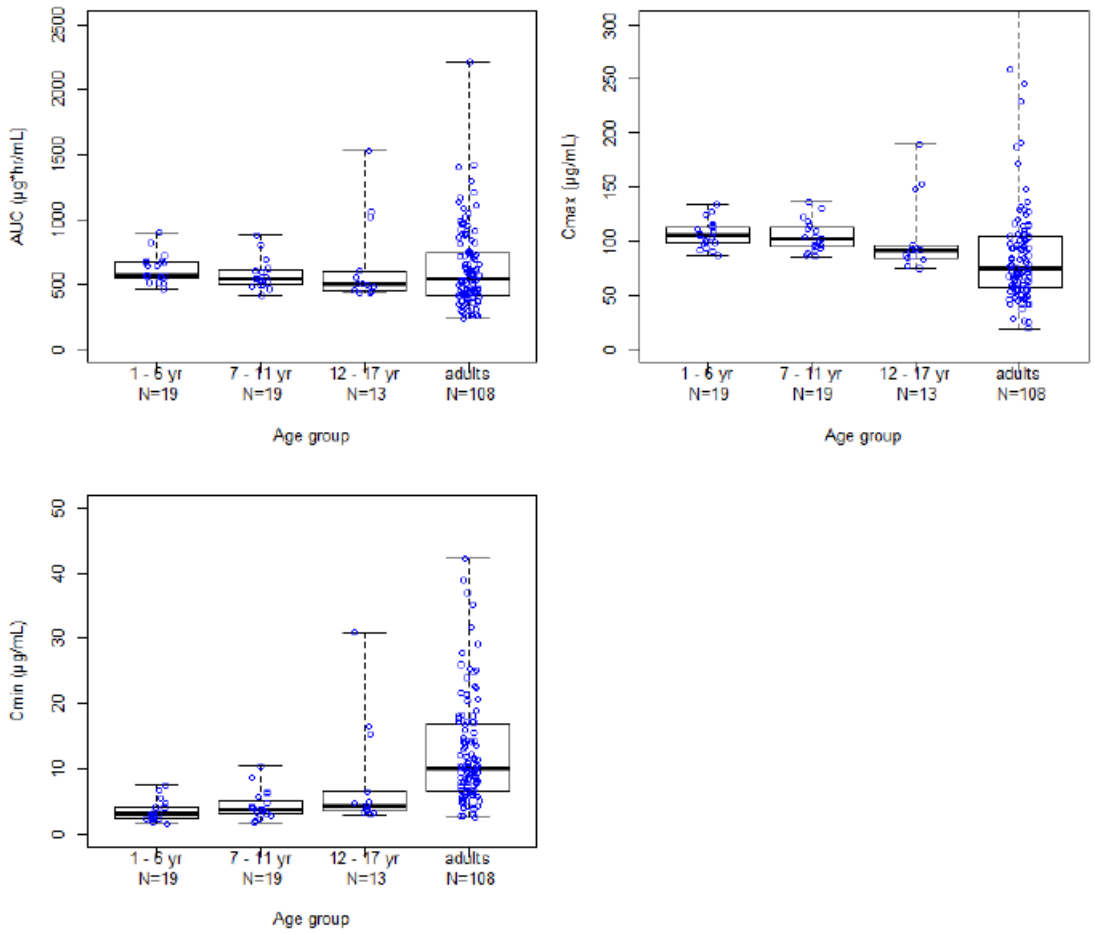
As shown in Table 1 and Figure 1, the C_{max} in pediatric patients for the once-daily regimen was higher than in adults, while C_{min} was a little lower than in adults. AUC_{ss} in pediatric patients and adults was comparable. Given the similarity in AUC_{ss} between pediatrics and adults as well as the comparable clinical success rate for daptomycin versus the standard of care comparator, the proposed dosing regimen is considered to be acceptable in terms of effectiveness to treat SAB in pediatric patients. The slight difference in C_{max} and C_{min} between adults and children was not considered to be clinically significant, as no evidence of lower clinical success rate or increased incidence of adverse events was observed.

Table 1: Median (Range) Exposure (AUCss, C_{max} and C_{min}) and Efficacy of Daptomycin in Children 1 to 17 Years Old

	N	AUCss (µg*h/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	Clinical Success Daptomycin vs.COM**
1-6 years (12 mg/kg)	19	572.2 (466.8, 894.9)	105.4 (86.8,133.5)	3.0 (1.4,7.3)	85.0% vs. 87.5%
7-11 years (9 mg/kg)	19	542.8 (417.7,883.0)	102.0 (85.9, 135.9)	3.7 (1.8,10.4)	94.1% vs. 77.8%
12-17 years (7 mg/kg)	13	507.3 (434.4, 1526.0)	91.0 (74.2,189.2)	4.3 (2.8, 30.9)	85.7% vs. 60.0%
Adults*	108	543.8 (240.4, 2214.4)	74.8 (19.0, 1882.2)	10.0 (2.5, 42.5)	

*Adult data was from a Phase 3 study DAP-IE-01-02 in adults with bacteremia due to *S. aureus* or right-sided infective endocarditis (RIE)
**COM: Standard care comparator

Figure 1: Daptomycin Steady-State Exposure Comparison for SAB Pediatric Patients (1 to 17 years) and Adults with SAB or RIE; Dosage Regimens: 7 mg/kg for 12 to 17 years of Age, 9 mg/kg for 7 to 11 Years of Age, 12 mg/kg for 1 to 6 Years of Age, and 6 mg/kg for Adults.



Source: Figure 1 on page 12 of Modeling & Simulation Report

Of note, the reviewer team observed that the age range of children in study DAP-PEDBAC-11-02 was from 2.0 to 16.9 years old; therefore, the PK data for children less than two years old are not available. To understand the PK in in children 1 to 2 years administered 12 mg/kg, exposures were simulated using the Applicant's population PK model and demographic information obtained from the CDC growth charts.

Table 2: Simulated Daptomycin Exposure in Children 1 to 17 Years old after Proposed Dosage Regimen

	1 to 1.5 Years 12 mg/kg	**1.5 to 2 years 12 mg/kg**	**2 to 6 Years 12 mg/kg**	**7 to 11 Years 9 mg/kg**	**12 to 17 Years 7 mg/kg**	**Adults 6 mg/kg**
AUC_{ss}(h.µg/mL) Median (P25-P75)	529 (423-653)	543 (433-661)	591 (473-737)	551 (442-672)	524 (419-652)	543.8 (418-743)
AUC_{ss}(h.µg/mL) Geo Mean	527.1	538.1	590.9	549.0	526.6	566.7
C_{max} (µg/mL) Median (P25-P75) Geo Mean	94.0 (80-110) 93.2	96.8 (83-113) 96.4	121.8 (104-147) 122.2	107.4 (91-127) 107.5	94.4 (80-112) 94.4	74.8 (57-104) 82.9
C_{min} (µg/mL) Median (P25-P75) GeoMean	2.5 (1.3-4.4) 2.3	2.6 (1.3-4.3) 2.3	2.9 (1.5-4.9) 2.6	3.6 (2.0-5.5) 3.3	4.6 (2.7-7.1) 4.3	10.0 (6.5-16.9) 10.3

*Adult data was from a Phase 3 study DAP-IE-01-02 in adults with bacteremia due to *S. aureus* or right-sided infective endocarditis (RIE)

As shown in Table 2, the estimated exposures in children age 2 to 17 years old using CDC growth chart and the proposed dosing regimen were consistent with those estimated by the Applicant using subjects from study DAP-PEDBAC-11-02 (Table 1). Children between 1.5 to 2 years old are predicted to have the same AUC_{ss} relative to adults. Children 1 to 1.5 years of age are predicted to have 3% lower AUC_{ss} relative to adults. Children 2 to 6 years, 7 to 11 years, and 12 to 17 years have 8% higher, 1% higher, and 4% lower of AUC_{ss} relative to adults, respectively. Similar to children from 2 to 17 years old, children between 1 to 2 years old have higher C_{max} and lower C_{min} compared to adults. The exposures in children 1 to 2 years old administered 12 mg/kg would be ~20% higher than the exposures in children 1 to 2 years old administered 10 mg/kg.

In summary, the exposure of daptomycin in children between 1 to 2 years old with *S. aureus* bacteremia is estimated to be slightly lower than that in children 2 to 6 years old if administered 12 mg/kg and is 20% higher than the exposure in children 1 to 2 years old administered 10 mg/kg from the previous study. It would require a slightly higher dose (13 mg/kg) to have comparable exposure in children 2 to 6 years old (Section 3).

1.1.2 Do the Applicant's efficacy results support the proposed once-daily dosing of daptomycin in children for *Staphylococcus aureus* Bacteremia?

Yes, the once-daily pediatric dosing of daptomycin was similarly effective relative to the standard of care comparator in the treatment of children with *Staphylococcus aureus* bacteremia. Overall, the proportion of daptomycin-treated subjects with a clinical success (satisfactory response) at the TOC/Safety Visit was 88.2%, which was 11.0% higher than the proportion of comparator-treated subjects with a satisfactory response (77.3%). The clinical success rate in different age groups was similar, all showing numerically higher response rates than that in the standard of care group.

Exposure-response analyses for efficacy were not conducted for this submission as the exposure of daptomycin in the pediatric age groups were similar and are already on flat portion of the exposure-response curve.

1.1.3 Do the Applicant's safety results support the proposed once-daily dosing of daptomycin in children?

Yes, the Applicant's analysis from the DAP-PEDBAC-11-02 showed a similar safety profile based on severe adverse event (SAE) rates in patients who received daptomycin treatment versus comparator treatment. A total of 24 SAEs were reported for 20 subjects (16 events for 13-daptomycin-treated subjects [23.6%] and 8 events for 7 comparator-treated [26.9%] subjects). No SAEs were classified by the investigator as being related to study drug or as having resulted in study discontinuation or death. The proportions of subjects who discontinued study drug due to treatment emergent adverse events (TEAE) was similar between daptomycin group and comparator group. Three (5.5%) daptomycin-treated subjects and 2 (7.7%) comparator-treated subjects discontinued study drug due to a TEAE. Independent analysis for exposure-relationship for CPK was conducted by the reviewer which did not reveal any significant relationship between daptomycin exposure in children and change in CPK.

Given the discussion in 1.1.1, it is expected that exposures in children 1 to 2 years of age administered 12 mg/kg would be similar to that of other age groups in this study. Also, exposures in this age group would be ~20% higher than exposures in children 1 to 2 years of age administered 10 mg/kg in the previous study. If the exposure-response relationship for safety is the same between infants (1 to 2 years of age) and children (older than 2 years), which the current analysis could not identify any differences between, the 12 mg/kg dose in children 1 to 2 years is not expected to have different safety profile than that in other pediatrics from the current study nor would it be different than that from pediatrics 1 to 17 years of age from the previous study.

2 RESULTS OF SPONSOR'S ANALYSIS

The Applicant submitted a population PK modeling and simulation report entitled *Bayesian Analysis of Daptomycin in Pediatric Patients from One to Seventeen Years of Age with Bacteremia Caused by Staphylococcus aureus*. The study used a previously developed population PK model of daptomycin to derive the *posteriori* Bayes parameters and estimate the daptomycin exposure levels (AUCss, C_{min} and C_{max}) at steady state for

Study DAP-PEDBAC-11-02 patients. The exposure in children was compared with that in adults to confirm the dosing regimens for children.

2.1 Population PK of Daptomycin and Exposure in Pediatric Patients from 1 to 17 Years Old

Objectives: 1) The objective of this analysis was to use an existing population PK model of daptomycin, which includes a maturation function for renal function, to derive the posteriori Bayes parameters and estimate the daptomycin exposure levels at steady state (AUC_{ss}, maximum concentration [C_{max}] at the end of IV infusion, minimum concentration [C_{min}] at 24 hr after infusion) for Study DAP-PEDBAC-11-02 patients.

Data: In Study DAP-PEDBAC-11-02, pediatric patients were enrolled into three age groups (12 to 17 years, 7 to 11 years and 1 to 6 years of age) and treated with daptomycin (IV q.d) or standard of care, based on a 2:1 randomization stratified by age group. Two PK samples (a trough and a peak) per patient were collected on Days 3, 4 or 5 following IV administration of daptomycin at 7 to 12 mg/kg for 5 to 28 days (uncomplicated bacteremia irrespective of age) or 7 to 28 days (1-11 year-old with complicated bacteremia) or 7 to 42 days (12-17 year-old with complicated bacteremia). Continuous and categorical demographic characteristics of pediatric patients are summarized in Table 3 and Table 4.

Table 3: Population Baseline Characteristics-Continuous Data

Covariates	Mean (CV%) Median [Minimum-Maximum]			
	1 - 6 years N=19	7 - 11 years N=19	12 - 17 years N=13	Total N=51
Age (years)	3.87 (32.3) 3.70 [2.00-6.70]	10.3 (11.9) 10.6 [8.00-11.8]	14.0 (12.0) 13.5 [12.2-16.9]	8.84 (49.2) 9.80 [2.00-16.9]
Weight (kg)	16.1 (25.6) 14.5 [10.0-22.8]	35.9 (33.4) 33.5 [20.1-65.0]	55.4 (22.0) 52.5 [33.0-83.3]	33.5 (54.7) 27.7 [10.0-83.3]
Height (cm)	99.5 (12.6) 101 [69.5-118]	138 (13.8) 133 [106-170]	164 (8.8) 162 [138-196]	130 (23.1) 130 [69.5-196]

Note: All values were measured at baseline (completed within 2 weeks prior to dosing or 48 h prior to dosing).
CV: Coefficient of variation; N: Number of patients
Source data: Study dataset from Phoenix excl tad.csv

Source: Table 8-1 on page 13 of applicant's Population PK Modeling and Simulation report

Table 4: Population Baseline Characteristics-Categorical Data

Covariates	Category	N (%)			
		1 - 6 years N=19	7 - 11 years N=19	12 - 17 years N=13	Total N=51
Sex	Female	8 (42.1%)	7 (36.8%)	0	15 (29.4%)
	Male	11 (57.9%)	12 (63.2%)	13 (100%)	36 (70.6%)
Race	Black	1 (5.26%)	4 (21.1%)	0	5 (9.80%)
	Caucasian	17 (89.5%)	12 (63.2%)	12 (92.3%)	41 (80.4%)
	Other	1 (5.26%)	3 (15.8%)	1 (7.69%)	5 (9.80%)

N: Number of subjects

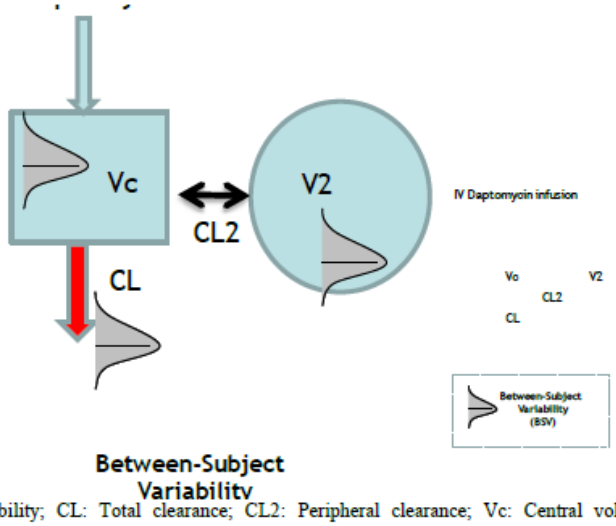
Source: Table 8-2 on page 13 of applicant's Population PK Modeling and Simulation report

Methods:

Software: Phoenix™ Nonlinear Mixed Effects (NLME) v1.3 was used to compute *Posterior Bayes* PK parameters (mean of the posterior distribution) based on the final parameter estimates from the previously developed final population PK model using first order conditional estimation-extended least squares (FOCE ELS).

Population PK Model : The previously developed population PK model was a two-compartment model with body weight-based allometric scaling and a renal maturation function which described daptomycin PK in the pediatric population 3 months to 17 years of age with cSSSI caused by Gram-positive pathogens or with suspected/diagnosed Gram-positive infection. The schematic representation of the model is shown in Figure 2. The final population PK parameters are summarized in Table 5.

Figure 2: Schematic Representation of Two-Compartment PK Model of Daptomycin



BSV: Between subject variability; CL: Total clearance; CL2: Peripheral clearance; Vc: Central volume of distribution; V2: Peripheral volume of distribution.

Table 5: Final Population PK Parameters of Daptomycin in Pediatric Population

PK Parameters	Final Model
Vc (L)	$16.7 \times (WT/70) \times (PMA^{-0.299}/(PMA^{-0.299}+30^{-0.299}))$
V2 (L)	$3.53 \times (WT/70)$
CL (L/h)	$0.829 \times (WT/70)^{0.635}$
CLnr (L/h)	0.4 x CL
CLr (L/h)	$0.6 \times CL \times (PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$
CL2 (L/h)	$2.36 \times (WT/70)^{0.75}$
BSV Vc (%)	33.0
BSV CL (%)	28.3
BSV V2 (%)	0 Fixed
BSV CL2 (%)	0 Fixed
Error Proportional (%)	15.3
Error Additive (µg/mL)	0.025

Note: Fractions of CLr and CLnr were fixed at 0.6 and 0.4 of total systemic clearance, respectively.
BSV: Between-subject variability; CL: Total systemic clearance; CL2: Peripheral clearance; CLnr: Non-renal clearance; CLr: Renal clearance; PMA: Post-menstrual age (week); Vc: Central volume of distribution; V2: Peripheral volume of distribution; WT: Body weight (kg).

Posteriori Bayes Estimation of PK Parameters

Bayesian analysis was performed based on the final pediatric population PK model as describe above. All PK parameters except residual error were fixed to the final model output values shown in Table 5, and the model was fitted to the individual daptomycin concentration data in order to derive the posteriori Bayes parameters of patients enrolled in Study DAP-PEDBAC-11-02. Bayesian PK Parameters of daptomycin for each age group are summarized in Table 6.

Table 6: Posteriori Bayesian PK Parameters of Daptomycin in Pediatric Patients

Parameters	Mean (CV%) Median [Minimum-Maximum]		
	1 - 6 years (Dose: 12 mg/kg) N=19	7 - 11 years (Dose: 9 mg/kg) N=19	12 - 17 years (Dose: 7 mg/kg) N=13
CL(L/h)	0.316 (25.9) 0.335 [0.203-0.462]	0.553 (27.0) 0.511 [0.387-0.845]	0.685 (41.0) 0.723 [0.292-1.32]
Vss (L)#	2.20 (25.9) 2.13 [1.32-3.16]	4.51 (32.5) 4.18 [2.77-8.20]	6.42 (30.8) 6.43 [3.88-11.5]
CL/WT (L/h/kg)	0.0199 (17.1) 0.0203 [0.0133-0.0257]	0.0159 (17.7) 0.0166 [0.0102-0.0216	0.0124 (31.3) 0.0138 [0.00458-0.0161]
Vss/WT (L/kg)#	0.137 (9.4) 0.136 [0.115-0.164]	0.126 (7.4) 0.126 [0.110-0.141]	0.115 (14.1) 0.118 [0.0849-0.138]
Terminal elimination half-life (h)	5.14 (11.0) 5.05 [4.45-6.46]	6.01 (13.7) 5.86 [4.74-7.91]	7.52 (30.1) 6.59 [5.63-13.5]

Note: Individual PK parameters of the 5 patients without concentrations were derived with the population PK parameters and individual covariate characteristics and included in this summary table.
CL: Systemic clearance; Vc: Central volume of distribution; CV: Coefficient of variation (%); V2: Peripheral volume of distribution; Vss: Volume of distribution at steady state; WT: Body weight (kg)
Vss=Vc + V2

Source: Table 8-1 on page 13 of applicant's Population PK Modeling and Simulation report

Estimation of Daptomycin Exposure in Pediatric Patients

Individual steady state concentration-time profiles of daptomycin were simulated on Day 6 with 6–minute intervals between time points based on posteriori Bayes PK parameters and actual dosing regimens each patient received in Study DAP-PEDBAC-11-02. For patients receiving less than 6 days of daptomycin treatment, rich profiles were simulated on the last treatment day. The following PK parameters were derived for daptomycin from these individual profiles: AUC_{ss}, C_{max} (i.e., concentration at 60 min for 1-6 years old and at 30 min for 7-17 years old), C_{min}, terminal elimination half-life (t1/2). AUC_{ss} parameters were calculated using the linear trapezoidal method and t1/2 was derived using posteriori Bayes parameters (i.e., CL, CL2, Vc and V2) based on the following equation:

t1/2=ln(2)/β,
with β = (1/2)×(k12+k21+k−((k12+k21+k)2-(4×k21×k))1/2) and k=CL/Vc, k12=CL2/Vc, k21=CL2/V2

Descriptive statistics of PK parameters and posteriori Bayes values were summarized for all patients and stratified by age groups (i.e., 1–6 years, 7–11 years and 12–17 years) (Table 7). The goodness-of-fit between observed and predicted individual concentrations is presented in Figure 3.

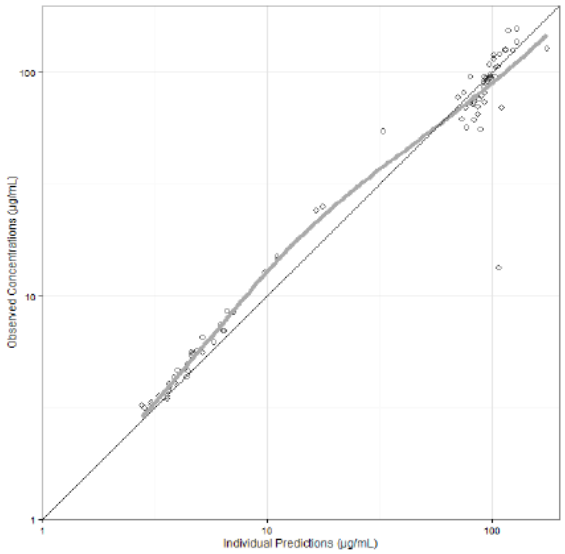
Table 7: Predicted Steady State Exposure of Daptomycin in Pediatric Patients

Parameters	Mean (CV%) Median [Minimum-Maximum]		
	1 - 6 years (Dose: 12 mg/kg) N=19	7 - 11 years (Dose: 9 mg/kg) N=19	12 - 17 years (Dose: 7 mg/kg) N=13
C_{max} (µg/mL)	106 (12.0) 105 [86.8-134]	104 (13.8) 102 [85.9-136]	104 (34.1) 91.0 [74.2-189]
C_{min} (µg /mL)	3.46 (46.0) 3.02 [1.45-7.34]	4.35 (51.4) 3.66 [1.79-10.4]	8.00 (102.7) 4.32 [2.82-30.9]
AUCss (h×µg /mL)	620 (17.6) 572 [467-895]	579 (20.1) 543 [418-883]	656 (51.0) 507 [434-1526]

Note: Individual PK parameters of the 5 patients without concentrations were derived with the population PK parameters and individual covariate characteristics
AUCss: Area under the concentration-time curve at steady state; C_{max}: Maximum concentration at steady state; C_{min}: Minimum concentration at steady state; CV: Coefficient of variation (%)

Source: Table 8-5 on page 18 of Applicant's population PK Modeling and Simulation Report

Figure 3: **Goodness-of-Fit Plot of Bayesian Estimation Model**



Solid grey line represent locally weighted scatterplot smoothing, black lines represent the line of unity.
Source data: Residuals_exc.csv; Source code: GOF.R

Source: Figure 8.2 on page 16 of Applicant's population PK Modeling and Simulation Report

Reviewer's Comments: The goodness-of-fit plot shows the Bayesian estimation model can predict the observed pediatric concentration of daptomycin well. The PK parameter estimates appear reasonable. Therefore, the Applicant's population PK analyses are acceptable. Independent analysis by the FDA reviewer was conducted for daptomycin PK parameters by age group and exposure-response for CPK in children.

3 REVIEWER'S ANALYSIS

3.1 Introduction

The Division of Pharmacometrics has reviewed the modeling and simulation analyses provided in this submission. The review team identified that while the indication in this submission was for treatment of pediatric patients 1 to 17 years old with *S. aureus* bacteremia, subjects enrolled in study DAP-PEDBAC-11-02 ranged from 2 to 16 years old. There was no subject between 1 to 2 years age included in the pediatric study. As a result, PK and safety of daptomycin in children of 1 to 2 years old at 12 mg/kg is not available from this study.

3.2 Objectives

Independent analyses were conducted by FDA pharmacometric reviewers to: 1) explore the relationship between age and daptomycin PK parameters; 2) to simulate exposures in pediatrics 1 to 2 years of age and compare them to exposures in other pediatrics from DAP-PEDBAC-11-02; and 3) to use available exposure data to conduct an exposure-response analysis for CPK.

3.3 Methods

3.3.1 Data Sets

The datasets used by the reviewer were from the modeling and simulation analysis. Datasets used and their sources are summarized in Table.

Table 8: Analysis Data Sets

Study Number	Name	Link to EDR
Daptomycin exposure data	Posthoc.xpt	~\0160\m5\datasets\04hxdz\analysis\legacy\datasets

3.3.2 Software

SAS for windows 9.3 was used for all graphing and statistical analyses. R 3.0.2 was used for simulation of exposures in children between 1 to 2 years of age.

3.4 Results

3.4.1 PK and Exposure by Age Group

Daptomycin exposures by age group for the proposed dosing regimen of 12 mg/kg, 9 mg/kg, and 7 mg/kg in pediatric patients from 1 to 6 years, 7 to 11 years, and 12 to 17 years, respectively, are summarized in Table 9. This summary uses the post-hoc estimates from the Applicant's population PK model and is similar to the results summarized by the Applicant in the submission.

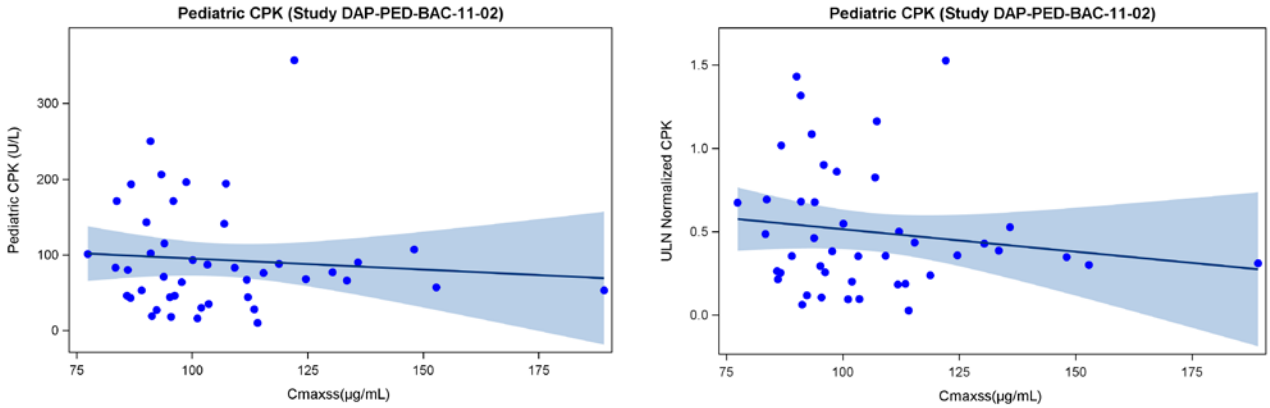
Table 9: Mean (SD) of Daptomycin Pharmacokinetics in Bacteremia Pediatric Patients

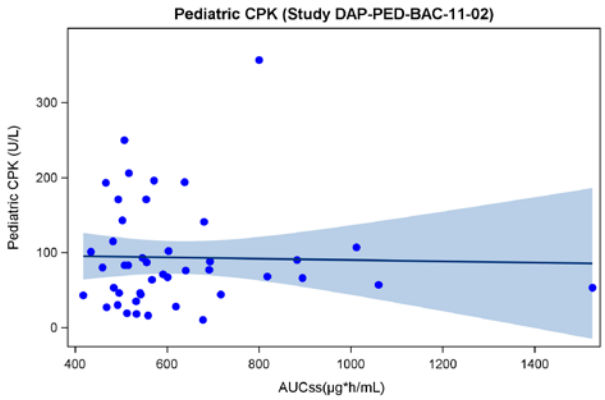
Age	Pharmacokinetic Parameters							
	Dose	Infusion Duration (min)	AUC_{ss} (µg•h/mL)	$t_{1/2}$ (h)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (µ/mL)	$C_{min,ss}$ (µ/mL)
12 to 17 years (N=13)	7 mg/kg	30	656 (334)	7.5 (2.3)	6422.3 (1979.8)	12.4 (3.9)	104.1 (35.5)	8.0(8.2)
7 to 11 years (N=19)	9 mg/kg	30	579 (116)	6.0 (0.8)	4510.2 (1465.5)	15.9 (2.8)	104.5 (14.5)	4.3(2.2)
1 to 6 years (N=19)	12 mg/kg	60	620 (109)	5.1 (0.6)	2198.3 (570.4)	19.9 (3.4)	106.3 (12.8)	3.5(1.6)

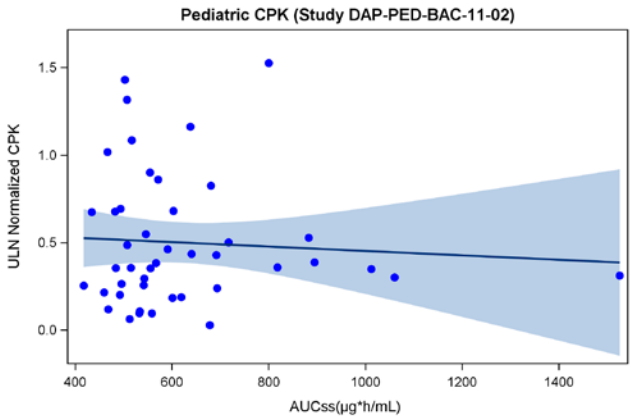
3.4.2 Exposure-response Relationship for CPK

The relationships between CPK and daptomycin AUC_{ss} or $C_{max,ss}$ were explored by the Applicant and no significantly relationship was revealed in children. However, a significant relationship between daptomycin exposure and change in CPK in adults was identified by Applicant. Independent analysis of the exposure-response relationship for CPK in children was conducted by the reviewer using data from study PEDBAC-11-02. Linear regression analysis was applied to see the overall trend of change between CPK and daptomycin AUC_{ss} or $C_{max,ss}$. The results are described in Figure 4. Similar to results submitted by the Applicant, there was no clear relationship between CPK values or ULN normalized CPK and daptomycin AUC_{ss} or $C_{max,ss}$. Higher daptomycin exposure was not associated with greater change in CPK in children with *S. aureus* bacteremia.

Figure 4: Relationship between Daptomycin Exposure and CPK Change.







3.4.3 Estimation of Daptomycin Exposure in Children between 1 to 2 Years Old

As mentioned earlier, the study DAP-PEDBAC-11-02 did not enroll children between 1 to 2 years old. As such, PK and safety of daptomycin in children less than 2 years old at 12 mg/gk is not available. To address this issue, the pharmacometrics reviewer conducted independent analysis that estimated the daptomycin exposure in this population of interest.

The overall objective was to estimate the steady-state exposure (AUC_{ss}, C_{max}, and C_{min}) of daptomycin in children group of between 1 to 1.5 years old, 1.5 to 2 years old, 2 to 6 years old, 7 to 11 years old, and 12 to 18 years old. PK parameters from the Applicant's population PK model described in Section 2 were used to simulate daptomycin exposure based on body weights and ages obtained from the CDC growth chart. The software R 3.0.2 was used for the simulation. A total of 1000 subjects were simulated in each age group and exposures were calculated using analytical equations for a two-compartment model with repeated infusions.

Daptomycin exposure in children administered the proposed regimen for bacteremia is summarized and compared with that in adults (Table 2).

Using the same approach, another simulation was conducted to evaluate daptomycin exposure in children between 1 to 2 years old after a dose of 10 mg/kg, 12 mg/kg, 13 mg/kg, respectively. The purpose of the simulation was to find the dosage regimen that would achieve similar exposure as in children 2 to 6 years old. The results of the simulation are shown in Table 10. As indicated, the 13 mg/kg dose in children 1 to 1.5 years old and 1.5 to 2 years old group would have 2% lower and 1% higher AUC_{ss} in age 2 to 6 years group administering 12 mg/kg, respectively. The dose would also achieve 6% and 10% higher AUC_{ss} relative to adults administering 6 mg/kg, respectively. In contract, the 10 mg/kg dose in children 1 to 1.5, and 1.5 to 2 years of age would have 75% and 90%, respectively, of AUC_{ss} in children aging 2-6 years administered 12 mg/kg. The 10 mg/kg dose would also achieve 82% and 85% of AUC_{ss} relative to adults administering 6 mg/kg, respectively. Additionally, the simulated 10 mg/kg exposure was consistent with those observed in children 1 to less than 2 years old with cSSSI.

Table 10: Simulated Daptomycin Exposure in Children < 2 Years after Dosage Regimen of 10 mg/kg, 12 mg/kg, and 13 mg/kg, Respectively

	1 to 1.5 Years 10 mg/kg	1 to 1.5 Years 12 mg/kg	1 to 1.5 Years 13 mg/kg	1.5 to 2 Years 10 mg/kg	1.5 to 2 Years 12 mg/kg	1.5 to 2 Years 13 mg/kg	Adults* 6 mg/kg
AUCss (h.µg/mL) Median (P25-P75)	445 (358-568)	534 (429-681)	578 (465-739)	461 (363-578)	553 (436-694)	599 (472-751)	543.8 (418-743)
AUCss (h.µg/mL) Geo Mean	448	537	582	456	547.9	593.6	566.7
Cmax (µg/mL) Median (P25-P75) Geo Mean	80.3 (67-94) 78.7	96.4 (81-112) 94.5	104.5 (88-122) 99.9	82.3 (69-96) 81.4	98.7 (83-116) 97.7	107.0 (90-125) 105.8	74.8 (57-104) 82.9
Cmin (µg/mL) Median (P25-P75) GeoMean	2.1 (1.2-3.8) 2.0	2.6 (1.4-4.5) 2.4	2.8 (1.5-4.9) 2.6	2.1 (1.2-3.9) 2.0	2.6 (1.4-4.6) 2.4	2.8 (1.5-5.0) 2.6	10.0 (6.5-16.9) 10.3

*Adult data was from a Phase 3 study DAP-IE-01-02 in adults with bacteremia due to *S. aureus* or right-sided infective endocarditis (RIE)

In summary, the exposure of daptomycin in children between 1 to 2 years of age with *S. aureus* bacteremia is estimated to be slightly lower than that in children 2 to 6 years of age. A dose of 13 mg/kg in this group of children will have comparable exposure in children 2 to 6 years old and would be similar to the dosing strategy used for the cSSSI indication. A dose of 12 mg/kg or 13 mg/kg in children 1 to 2 years of age would result in exposures that are 20% and 30% higher than exposures in children 1 to 2 years of age administered 10 mg/kg (i.e., dosing regimen administered to this age group in the cSSSI indication). If the exposure-response relationship for safety is the same between infants (1 to 2 years of age) and children (older than 2 years), the 12 mg/kg dose in children 1 to 2 years is not expected to have different safety profile than children 2 to 6 years old. Likewise, the 20% higher exposures from the cSSSI study are not expected to result in an increase in serious safety events based on the available data.

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