CLINICAL PHARMACOLOGY REVIEW

NDA:	21- 572 (SDN#654)

Brand Name:	Cubicin®
Generic Name:	Daptomycin
Date of Original Submission:	June 30, 2016
Indication:	• Complicated skin and skin structure infections (cSSSI) in adult patients (≥18 years of age) and pediatric patients (1 to 17 years of age)
	• *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis in adult patients
Applicant:	Merck
Submission Type:	Pediatric NDA
Clinical Pharmacology Reviewer:	Sonia Pahwa, PhD
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OCP Division:	Division of Clinical Pharmacology 4 (DCP-4)

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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, (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 cSSSI caused by Gram-positive pathogens, thereby supporting the registration of daptomycin in pediatric patients for the treatment of cSSSI at the recommended, age-specific, weight-based dosing regimens summarized in Table 1(a).

Table 1(a). Recommended Daptomycin Dosage Regimens for Pediatric Patients 1 to 17 Years of Age

Age (years)	Infusion Time (hours)	Dose (mg/kg, once daily)
12-17	0.5	5
7-11	0.5	7
2-6	1	9
1-2	1	10

1.1. Recommendations

The clinical pharmacology information provided by the applicant in support of the application is acceptable. Based on the FDA analysis, the dosing regimens for the use of daptomycin in pediatric patients proposed by the applicant (Table 1(b) on page 5) are acceptable for the labeling of CUBICIN.

1.2. Phase 4 commitments

There are no Phase 4 commitments.

1.3. Summary of important clinical pharmacology and biopharmaceutics findings

Three dedicated Phase 1 studies (Study DAP-PEDS-05-01, Study DAP-PEDS-07-02, and Study DAP-PEDS-09-01) 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. Therefore, the dosing regimens evaluated in pediatric patients with cSSSI in the Phase 4 safety/efficacy study (Study DAP-PEDS-07-03) were selected based on matching projected exposures (AUC) in pediatric patients with the observed exposures in adults whereby efficacy and safety were established previously. The derived doses in pediatric patients were 5 mg/kg once daily in the adolescents (12 to 17 years of age), 7 mg/kg once daily in the older children (7 to 11 years of age), 9 mg/kg once daily in the younger children (2 to 6 years of age), and 10 mg/kg once daily in the infants (1 to less than 2 years of age), in order to provide pediatric patients with steady-state exposure (AUCss) comparable to that in the adult population receiving 4 mg/kg once-daily dosing. At the evaluated dosing regimens, the exposures in pediatric patients with cSSSI were comparable to the exposures in adult patients with cSSSI, with similar efficacy and safety profiles in pediatric and adult

patients. Therefore, the dosing regimens evaluated in the Phase 4 study are appropriate for pediatric patients (1 to 17 years of age) with cSSSI. The key pharmacokinetics of daptomycin in pediatric patients aged 1 to 17 years is summarized below:

- The pharmacokinetics of daptomycin was linear and dose-proportional over the range of doses studied (4 mg/kg to 10 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 that in adults.
- In the PK evaluation in pediatric patients (1 and 17 years, inclusive) with cSSSI total clearance normalized by body weight (CL/wt) decreased with increasing age, with mean CL/wt values were ranging from 22 mL/hr/kg for children (1-2 years of age) to 13 mL/hr/kg for adolescents (12-17 years of age) in Phase 4 study DAP-PEDS-07-03. Total volume of distribution normalized by weight (V_{SS}/wt) also decreased with increasing age, with V_{SS}/wt values ranging from 159 mL/kg in infants to 98 mL/kg in adolescents in Phase 4 study DAP-PEDS-07-03.
- It should be noted that the body weight-normalized CL in adolescent patients (i.e, 12-17 years of age) was substantially higher than that in adults 10.72 (2.23) *vs.* 8.3(1.3) mL/hr/kg) in Study DAP-PEDS-05-01, resulting in a lower AUC in adolescent patients compared with adults at the same dose (i.e., 4 mg/kg). Although the reason for the higher body weight-normalized CL in adolescent patients compared with adults was not addressed, the dose for adolescent patients for the Phase 4 safety/efficacy study (Study DAP-PEDS-07-03) was increased to 5 mg/kg based on this observation.
- Following administration of multiple doses of the recommended age-specific, weight-based doses, daptomycin exposure was similar across different age groups with mean AUC_{0-24hr} ranging from 387 to 466 μg·hr/mL and mean C_{max} ranging from 62.4 μg/ml to 81.9 μg/mL.
- In the Phase 4 study (Study DAP-PEDS-07-03), the elimination half-life of daptomycin after multiple doses in pediatric patients with cSSSI increased with increasing age, with daptomycin mean $t_{1/2}$ in pediatric patients in the range of 3.8 to 5.3 hours. Across the Phase 1 studies (DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01), the mean $t_{1/2}$ of daptomycin after a single 4-10 mg/kg dose in pediatric patients ranged from approximately 4.4 to 7.8 hours.
- Similar to adults, renal excretion was the major elimination pathway of daptomycin in pediatric patients.
- The unbound fraction (fu) and percentage excreted in urine (Fe%) for daptomycin were similar across different age groups of pediatric and adult subjects.
- Based on the population PK analysis conducted by the applicant and independently verified by the FDA clinical pharmacology team, body weight based allometric scaling including a maturation function adequately described the pharmacokinetics of daptomycin in pediatric pateints under different age groups. The pediatric PK parameters estimated using this model confirmed that the pediatric doses for the cSSSI indication are acceptable.
- Daptomycin administered at doses of 5, 7, 9, or 10 mg/kg for up to 14 days to pediatric patients aged 12 to 17 years, 7 to 11 years, 2 to 6 years, and 1 to less than 2 years, respectively, appeared to be efficacious in the treatment of cSSSI caused by Gram-positive pathogens and the safety of daptomycin at these doses was acceptable.

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2. Question based review

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Daptomycin is a cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*. It is a cyclic 13-amino acid peptide with a decanoic acid side-chain attached to the terminal L-tryptophan. The chemical formula is $C_{72}H_{101}N_{17}O_{26}$ and the molecular weight is 1620.67. The structural formula of daptomycin is provided in Figure 1 below.

Figure1. Chemical Structure of Daptomycin
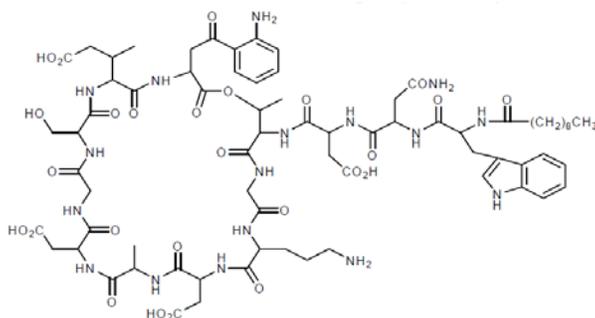
Cubicin® is 500 mg daptomycin as a sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-use vial for intravenous infusion administration.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Daptomycin is a novel cyclic lipopeptide natural product. It has a distinct mechanism of action and is rapidly bactericidal against Gram-positive bacteria with activity against growing and stationary-phase bacteria including those resistant to other antibiotics. 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. Daptomycin was originally approved for the treatment of complicated skin and skin structure infections (cSSSI) and *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis in adult patients. In this pediatric efficacy supplement, the applicant is seeking an indication for the treatment of complicated skin and skin structure infections (cSSSI) in pediatric patients (1 to 17 years of age)

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

The applicant's proposed dosage regimens of IV daptomycin is given below in Table 1(b) and are acceptable from the perspective of Clinical Pharmacology.

Table 1(b). Recommended Dosage of CUBICIN® in Pediatric Patients (1 to 17 Years of Age) with Complicated Skin and Skin Structure Infections, Based on Age

Age group	Dosage*	Duration of therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to <2 years	10 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.

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.

2.2.   *General clinical pharmacology*

2.2.1.   *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

Dose-selection for the pediatric efficacy and safety study (Study DAP-PEDS-07-03) was not based on efficacy or on efficacy-related pharmacodynamic (PD) markers, but based on the exposures achieved in the prior Phase 1 studies. The 3 pediatric Phase 1 studies (Study DAP-PEDS-05-01, Study DAP-PEDS-07-02, Study DAP-PEDS-09-01) were conducted to evaluate PK in pediatric patients in age groups 2 to 17 years, 2 to 6 years, and 3 to 24 months, respectively. The PK data was used to derive dosing regimens at which exposures in pediatric patients were projected to match those in adult subjects. Daptomycin PK has been examined in both single- and repeated-dose studies in pediatric patients in Studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and DAP-PEDS-07-03, and using a population PK model (Study CUBI-PCS-106).

The derived doses were 5 mg/kg once daily in the adolescents (ages 12 to 17 years), 7 mg/kg once daily in the older children (7 to 11 years), 9 mg/kg once daily in the younger children (2 to 6 years), and 10 mg/kg once daily in the infants (1 to less than 2 years), in order to produce steady-state exposure (AUCss) comparable to that in adult patients receiving 4 mg/kg once-daily dosing. Subsequently, Study DAP-PEDS-07-03 was conducted at the derived doses to confirm favorable safety and efficacy profile of daptomycin in patients with cSSSI. The results of Study DAP-PEDS-07-03 supported that the doses selected for this Study are safe and effective in pediatric patients 1-17 years of age with cSSSI. Summary of PK studies conducted in pediatric patients is given in Table 2.

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Table 2. Summary of Pharmacokinetic Studies in Pediatric Patients Receiving Daptomycin

Study No.	Study Objective, Population	No. of Patients	Dosage
DAP-PEDS-05-01	PK, 2 to 17 year olds	25	4 mg/kg
DAP-PEDS-07-02	PK and safety, 2 to 6 year olds	12	8, 10 mg/kg
DAP-PEDS-09-01	PK and safety, 3 to 24 month olds	24	4, 6 mg/kg
DAP-PEDS-07-03	PK, safety, and efficacy, 1 to 17 year olds	257	5, 7, 9, 10 mg/kg
CUBI-PCS-106	Population PK modeling study	101	-

PK = pharmacokinetic

Furthermore, the PK for daptomycin in pediatric patients with cSSSI at the proposed pediatric dosing regimens were comparable to those in adult with cSSSI receiving the approved 4 mg/kg dose. Based on PK data of 101 patients, a population PK model (Study CUBI-PCS-106) was also developed to describe the PK of daptomycin in pediatric patients under different age groups. The PK of daptomycin estimated using this model confirmed that the pediatric dose selected for the cSSSI indication will provide pediatric patients with the AUC_{ss} comparable to those in adult patients receiving daptomycin 4 mg/kg.

2.2.2. What are key efficacy findings for Daptomycin in pediatric patients?
The applicant performed DAP-PEDS-07-03, a multi-center, evaluator-blinded, randomized, comparative Phase 4 study, efficacy and PK of daptomycin were assessed in pediatric patients (1 to 17 years old, inclusive) with cSSSI caused by Gram-positive pathogens.

The primary objective in the study was to assess the safety of age-dependent doses of IV daptomycin administered for up to 14 days in comparison with standard of care (SOC) therapy in pediatric patients with cSSSI caused by Gram-positive pathogens. Secondary objectives included an assessment of efficacy of age-dependent doses of IV daptomycin in comparison with SOC therapy and to evaluate the population PK. The key efficacy endpoint was the applicant-defined clinical outcome, which was defined by a blinded medical director, at the test of cure (TOC) visit. The TOC visit was performed 7 to 14 days after the last dose of study medication (both IV and oral medication). The study was not powered for the primary efficacy endpoint.

This study provided clinical experience of daptomycin administration in pediatric patients at exposure levels similar to those achieved by the approved dose for adults with skin infections (i.e., 4 mg/kg). Clinical success rates at TOC for the Intent-to-Treat (ITT) population based on applicant-defined clinical outcomes were high and similar in both treatment arms (88.3% in the daptomycin arm and 86.4% in the SOC arm) as were microbiological success rates at TOC in the Modified Intent-to-Treat (MITT) population (90.5% and 88.6%, respectively). High microbiological success rates at TOC were also noted for the most common baseline infecting pathogens: MRSA (84.5% and 89.1% in the daptomycin and SOC arms, respectively), MSSA (95.3% and 91.8%, respectively), and *Streptococcus pyogenes* (100% and 70.0%, respectively).

Overall, daptomycin administered at doses of 5, 7, 9, or 10 mg/kg for up to 14 days to pediatric patients aged 12 to 17 years, 7 to 11 years, 2 to 6 years, and 1 to less than 2 years, respectively, was shown to be efficacious in the treatment of cSSSI caused by Gram-positive pathogens (Table 3). Additional details regarding efficacy of daptomycin in pediatric patients are provided in the Clinical review by the reviewing medical officer, Dr. Amol Purandare.

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Table 3. Summary of Clinical Outcome at Test-of-Cure (Population: ITT) in Pediatric Patients

Age	Success Rates	
	CUBICIN n/N (%)	Comparator* n/N (%)
All Pediatric Age Groups	227/257 (88%)	114/132 (86%)
12 to 17 years)	70/73 (96%)	34/37 (92%)
7 to 11 years	66/73 (90%)	35/38 (92%)
2 to 6 years)	67/81 (83%)	32/42 (76%)
1 to < 2 years)	24/30 (80%)	13/15 (87%)

* Comparator: IV vancomycin, clindamycin, or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin).

2.2.3.   What are the key safety findings for Daptomycin in pediatric patients?
The safety population included all 389 subjects who were randomized and received any dose of study drug, including 256 subjects who received daptomycin and 133 subjects who received SOC.

Overall 98 (38%) subjects who received daptomycin in Study DAP-PEDS-07-03 experienced at least 1 treatment-emergent adverse event (TEAE) during the study. This number compares to 48 (36%) subjects who received SOC. No safety signals were apparent from review of vital signs, neurological examinations, or physical examination findings. It was concluded that daptomycin administered at 5, 7, 9, or 10 mg/kg once daily for up to 14 days was safe and well tolerated. A detailed discussion on the safety aspects of daptomycin in pediatric patients are provided in the Clinical review by the reviewing medical officer, Dr. Amol Purandare.

2.2.4.   What are PK characteristics for Daptomycin in pediatric patients?
The applicant conducted 3 pediatric Phase 1 studies (Study DAP-PEDS-05-01, Study DAP-PEDS-07-02, Study DAP-PEDS-09-01) to evaluate daptomycin PK in pediatric patients in age groups 2 to 17 years, 2 to 6 years, and 3 to 24 months, respectively. The PK data were used to derive dosing regimens at which exposures in pediatric patients were projected to match those in adult subjects. Daptomycin PK has been examined in both single- and repeated-dose studies in pediatric patients in Studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01, and DAP-PEDS-07-03, and using a population PK modeling study (Study CUBI-PCS-106) as listed in Table 2 above. Tables 4 to 7 summarize the PK parameters from each study and the individual study reviews are provided in appendix 4.2.

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Table 4. Summary of Pharmacokinetic Parameters for Daptomycin following the Administration of a Single 4 mg/kg (30-Minute IV infusion) Dose in Pediatric Patients between the Ages of 2 to 17 Years in Study DAP-PEDS-05-01

PK Parameter:	Group 1 Ages 12 to 17 (N=8)	Group 2 Ages 7 to 11 (N=8)	Group 3 Ages 2 to 6 (N=8)
$AUC_{0-\infty}$ ($\mu g \cdot hr/mL$)	385.09 (69.69)	279.91 (138.5)	204.33 (66.24)
C_{max} ($\mu g/mL$)	50.55 (10.56)	45.78 (10.78)	39.09 (6.26)
T_{max} (hr)[a]	0.58 (0.58, 0.77)	0.58 (0.58, 0.67)	0.58 (0.58, 0.75)
$t_{1/2}$ (hr)	7.84 (1.22)	5.29 (1.67)	5.11 (1.89)
CL/wt (mL/hr/kg)	10.72 (2.23)	16.51 (5.66)	21.54 (7.21)
CLr/wt (mL/hr/kg)	7.29 (2.03)	9.41 (2.69)	17.42 (8.05)
Fe (%)	61.78 (2.38)	59.35 (5.54)	60.44 (13.08)
% Bound	88.85 (1.01)	91.52 (4.47)	91.72 (1.80)
Vdss/wt (mL/kg)	106.31 (19.12)	110.91 (21.10)	136.25 (21.41)

a   Data presented are median (minimum, maximum)

Table 5. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of a Single 8 or 10 mg/kg Dose in Pediatric Patients Between the Ages of 2 to 6 Years

Parameter	Group 1 Ages 2-6 year 8 mg/kg n=6 Mean (SD)	Group 2 Ages 2-6 year 10 mg/kg n=6 Mean (SD)
Infusion Duration (hr)	1.0	1.0
$AUC_{0-\infty}$ ($\mu g*hr/mL$)	429.14 (113.01)	549.70 (139.35)
C_{max} ($\mu g/mL$)	68.42 (9.33)	79.18 (10.17)
T_{max} (hr)	0.86 (0.27)	1.04 (0.04)
$t_{1/2}$ (hr)	5.35 (1.41)	5.67 (0.62)
CL/wt (mL/hr/kg)	19.47 (5.01)	19.14 (4.51)
V_{ss}/wt (mL/kg)	135.67 (8.69)	144.62 (28.26)

Table 6. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of a Single 4 or 6 mg/kg Dose to Infants between the Ages of 3 to 24 Months in Study DAP-PEDS-09-01

Parameter	Age Group 1 13-24 months 6 mg/kg n=5 Mean (SD)	Age Group 2 7-12 months 4 mg/kg n=7 Mean (SD)	Age Group 3 3-6 months 4 mg/kg n=7 Mean (SD)
Infusion Duration (hr)	0.5	0.5	0.5
$AUC_{0-\infty}$ (μg*hr/mL)	281.5 (44.5)	219.3 (66.8)	215.0 (68.3)
C_{max} (μg/mL)	67.0 (14.5)	37.1 (12.6)	38.7 (5.2)
T_{max} (hr)	0.66 (0.26)	0.59 (0.20)	0.53 (0.02)
$t_{1/2}$ (hr)	4.41 (0.94)	5.45 (1.13)	5.10 (1.17)
CL/wt (mL/hr/kg)	21.76 (2.99)	19.63 (5.76)	19.72 (5.46)
V_{ss}/wt (mL/kg)	121.7 (30.7)	134.9 (28.6)	127.7 (11.7)

Table 7. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of Multiple 5 to 10 mg/kg Doses in Pediatric Patients Between the Ages of 1 to 17 Years in Study DAP-PEDS-07-03

Parameter	Age Group 1 12-17 years 5 mg/kg n=6 Mean (SD)[a]	Age Group 2 7-11 years 7 mg/kg n=2 Ind. Values[b]	Age Group 3 2-6 years 9 mg/kg n=7 Mean (SD)[a]	Age Group 4 1-<2 years 10 mg/kg n=30 Mean[c]
Infusion Duration (hr)	0.5	0.5	1.0	1.0
AUC_{0-tau} (μg*hr/mL)[#]	387 (81)	438, ND	439 (102)	466
C_{max} (μg/mL)	62.4 (10.4)	64.9, 74.4	81.9 (21.6)	79.2
T_{max} (hr)	0.9 (0.1)	0.3, 0.8	1.4 (0.4)	1.0
$t_{1/2}$ (hr)	5.3 (1.6)	4.6, ND	3.8 (0.3)	5.04
CL_{ss}/wt (mL/hr/kg)	13.3 (2.9)	16.0, ND	21.4 (5.0)	21.5
V_{ss}/wt (mL/kg)	98.1 (12.2)	104, ND	116 (19.9)	159

ND: Not determined

\# AUC_{0-tau}: Area under the plasma concentration time curve during the 24-hour dosing interval.

[a] PK parameters including AUC_{0-tau}, $t_{1/2}$, CL_{ss}, and V_{ss} could be derived for only 3 out of the 6 subjects in Age Group 1, and 4 out of the 7 subjects in Age Group 3. The mean (SD) for these PK parameters were calculated using N=3 and N=4 for Age Group 1 and Age Group 3, respectively.

[b] The numbers provided here indicate individual values (two patients provided plasma samples that were used to determine PK).

[c] Due to limited PK samples from each patient, PK parameters were computed using the mean concentration profile during a sampling interval and individual parameters were not computed, thus no variability could be calculated.

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The mean AUC_{0-24} (SD) of daptomycin at steady-state following IV administration of CUBICIN over a 30-minute period at 4 mg/kg q24h to healthy young adults is 494 (75) µg·h/mL as per package insert. Adolescents 12 to 17 years of age had mean AUC (SD) 385.09 (69.69) slightly lower than the AUC in adults at 4 mg/kg dose (Table 4).

The body weight-normalized CL in adolescent patients (i.e, 12-17 years of age) was substantially higher than that in adults 10.72 (2.23) *vs.* 8.3(1.3) mL/hr/kg), resulting in a lower AUC in adolescent patients compared with adults at the same dose (i.e., 4 mg/kg).

Daptomycin was highly bound to serum protein (~90%) and the degree of protein binding is similar across the different age groups in pediatric patients and is similar to the protein binding in healthy adult subjects, indicating no age difference in protein binding.

The body weight normalized volume of distribution (Vss/wt) ranged from 98.1 to 159 mL/kg which was similar to that in adults (Table 7).

The unbound fraction (fu) and percentage excreted in urine (Fe%) for daptomycin were similar 59-62% across different age groups of pediatric subjects. In the younger age groups, drug exposure and elimination half-life were reduced compared with adolescents while clearance normalized by body weight was increased (Table 4).

The pharmacokinetics of daptomycin was linear and dose-proportional over the range of doses studied (4 mg/kg to 10 mg/kg) in studies DAP-PEDS-05-01 and DAP-PEDS-07-02 conducted in pediatric patients between the age of 2-6 years (Table 5).

The exposure of daptomycin obtained at 4 mg/kg dose in the study DAP-PEDS-05-01 is 385 µg·h/mL, is similar to exposure obtained in the study DAP-PEDS-07-03 at 5mg/kg dose which is 387 µg·h/mL in adolescents even though dose is higher in the DAP-PEDS-07-03 study. Exact reason for less exposure obtained in study DAP-PEDS-07-03 is not clearly explained because of limited number of patients with PK data. Due to the nature of the individual plasma concentration versus time profiles, certain PK parameters (AUC_{0-tau}, $AUC_{0-\infty}$, $t_{1/2}$, CL_{SS}, and V_{SS}) could be derived for only 3 of the subjects in Age Group 1, 1 subject in Age Group 2, and 4 of the subjects in Age Group 3 (Table 7). However, when population PK model estimated mean AUCs (SD) for pediatric patients with cSSSI in Study DAP-PEDS-07-03 (Table 8) were compared to those for adult patients with cSSSI the exposure (AUCss) of daptomycin was comparable, at 4 mg/kg in adults to 5 mg/kg in adolescent. It should be noted that the population PK model estimated mean AUCss (SD) in adult cSSSI patients receiving the approved 4 mg/kg dose in Phase 3 trials DAP-SST-98-01 and DAP-SST-99-01 was 488 (214) µg·h/mL. Although, the AUCss is slightly lower in adolescent patients compared with adults, the efficacy results achieved in Study DAP-PEDS-07-03 are considered to be acceptable to support that the dose of 5 mg/kg is appropriate for adolescent patients with cSSSI (Table 3).

**Table 8. Mean (SD) Daptomycin Population Pharmacokinetic Parameters in Infected Pediatric Patients**

Age	Pharmacokinetic Parameters					
	Dose (mg/kg)	AUC_{ss} (µg•h/mL)	$t_{1/2}$ (h)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (µg/mL)
12 to 17 years (N=6)	5	434 (67.9)	7.1 (0.9)	8200 (3250)	11.8 (2.15)	76.4 (6.75)
7 to 11 years (N=2)	7	543[a]	6.8[a]	4470[a]	13.2[a]	92.4[a]
2 to 6 years (N=7)	9	452 (93.1)	4.6 (0.8)	2750 (832)	20.8 (4.29)	90.3 (14.0)
1 to <2 years (N=27)	10	462 (138)	4.8 (0.6)	1670 (446)	23.1 (5.43)	81.6 (20.7)

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; $t_{1/2}$, terminal half-life
[a]Mean is calculated from N=2

The clinical pharmacology reviewer also compared the relationships of age and body weight with body weight normalized clearance (Figures 2(a) and 2 (b)).

Figure 2(a) Scatter plots for individual clearance normalized by body weight vs. age for pediatric patients 3 months to 17 years of age in the four pediatric clinical studies (DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and DAP-PEDS-07-03; N=101) (Open Circles Represent Individual Values; Lines Represent locally weighted scatter plot smoothing (LOESS) Trend Lines) (Source: Applicant's analysis)
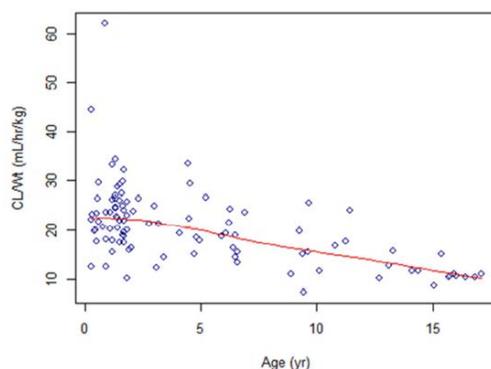
As indicated by the trend depicted in Figure 2 (a), normalization of CL by weight continued to indicate the dependency of CL on age such that utilization of a dose regimen based solely on weight alone (i.e., same mg/kg for all pediatric patients) would be unlikely to achieve similar exposures across pediatric patients.

Figure 2(b) Scatter plots for individual clearance normalized by body weight vs. body weight for pediatric patients 3 months to 17 years of age in all the four pediatric clinical studies (Source: Reviewer's analysis)
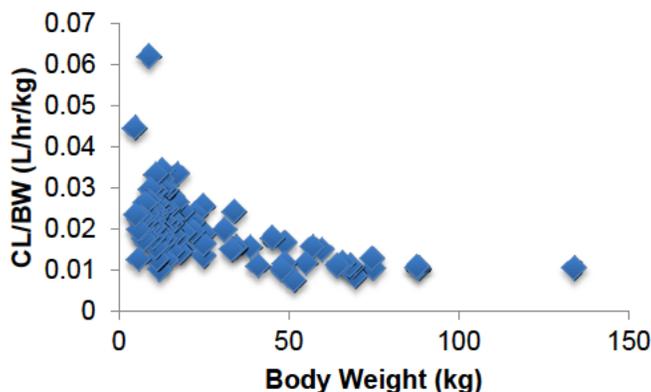
The body weight normalized clearance decreases with body weight up to 50 kg and consistent afterwards in higher body weight subjects.

2.3.   Intrinsic factors

2.3.1.   What intrinsic factors (age, gender, race, weight, height, disease) influence exposure (PK usually), and what is the impact of any differences in exposure on efficacy or safety responses?
CL increased with body weight and age, and volume of distribution increased with body weight in pediatric patients. No clinically relevant differences in the disposition of daptomycin in pediatric and adult populations, with comparable daptomycin exposures in pediatric and in adult patients with cSSSI after adjusting doses based on weight and age, supporting that the effects of all intrinsic factors observed in adults can be applied without modification for pediatric patients. Hence, the information describing effects related to intrinsic or extrinsic factors (NDA 21-572, submitted on 19-Dec-2002) reflected in the adult prescribing information are considered to be applicable to the pediatric population. The influence of other intrinsic factors on the exposure and exposure-response relationship for daptomycin was not evaluated in pediatric patients.

2.3.2.   Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.2.1. Race
No race difference was identified in pediatric patients in Study CUBI-PCS-106.

2.3.2.2. Renal impairment
No additional study was not conducted in pediatric patients with renal impairment.

2.3.2.3. Hepatic impairment
No additional study was conducted in pediatric patients with hepatic impairment.

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2.4. Extrinsic factors

2.4.1. What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
See previous response for 2.3.1

2.5. Analytical section

The clinical pediatric bioanalytical method was developed using the original human plasma method (LC 309) for daptomycin. The sample volume was decreased from 300 μL to 50 μL to account for a smaller sample collected in pediatric patients. The change in assay sample volume was qualified in an analytical run that included a precision and accuracy assessment at four quality control (QC) levels as well as a specificity experiment using six different lots of human plasma with sodium heparin (LC 309.7). The development and validation of the bioanalytical methods as well as the analyses of daptomycin in clinical samples reported in this submission were performed by the following laboratories:

Laboratory	Laboratory Method	Matrix	Study Supported	Analyte	Laboratory Address
PPD	LC 309.7	Plasma	DAP-PEDS-05-01 DAP-PEDS-07-02 DAP-PEDS-07-03 DAP-PEDS-09-01	Daptomycin	(b) (4)
PPD	LC 309.1	Urine	DAP-PEDS-05-01	Daptomycin	

Daptomycin and its internal standard, ethyl 4-hydroxybenzoate, were isolated from plasma using protein precipitation extraction with methanol followed by high performance liquid chromatography separation with ultraviolet absorbance detection.

2.5.1. What bioanalytical methods are used to assess concentrations? Briefly describe the methods and summarize the assay performance.
Plasma Analysis:
Concentrations of daptomycin in human plasma and urine were determined using high performance liquid chromatography with ultraviolet detection (HPLC-UV) methods that were validated in accordance with current regulatory guidances FDA Guidance for Industry: Bioanalytical Method Validation (2001). Quantitation of Daptomycin in Human Plasma via HPLC with Ultraviolet Absorbance Detection was conducted according to (b) (4) SOPs. A wavelength of 214 nm was used to detect daptomycin and the internal standard at a retention time of 15.0 minutes and 7.0 minutes respectively. The linearity of this procedure was evaluated by analyzing nine calibration standards in duplicate over the nominal concentration range of 3.00 to 500 μg/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. Linearity was indicated by a correlation coefficient of 0.9992-0.9995 from standard curves. Limit of quantitation was 3.00 μg/mL.

Human plasma samples, containing sodium heparin, from six individuals were extracted and analyzed for daptomycin and its internal standard during validation. There were no significant

chromatographic peaks detected at the mass transitions and expected retention times of the analytes or their internal standards which would interfere with quantitation.

Precision and accuracy were evaluated by analyzing quality control pools prepared at 2.5 times the lower limit of quantitation, the approximate midpoint of the calibration range, and approximately 80% of the upper limit of quantitation. Intra assay precision ranged from 1.27% to 12.3% (± ___ %), and accuracy was between 0.68% and 6.1% (± (b)(4) %) of nominal QC concentrations.

Inter-assay accuracy range from 99.72-109.72 (100 ± (b)(4) %) % and precision range from 92.37-98.13(100 ± (b)(4) %) % for QC concentrations, which is within acceptance criteria.

Urine Analysis:
For daptomycin analysis in human urine, linearity of procedure was evaluated by analysis of nine calibration standards over the range of 3.00 to 500 µg/mL using a linear weighted (1/concentration squared) least squares regression algorithm to plot the peak height ratio of daptomycin to internal standard versus concentration. Linearity was indicated by an average correlation coefficient of 0.9994 from three standard curves. Analysis was by high performance liquid chromatography with ultraviolet absorbance detection. The method was validated with a minimum quantifiable level of 3.00 µg/mL. The mean recovery was 91.8% for QC1 with a coefficient of variation of 3.19% and the mean recovery for QC3 was 91.5% with a coefficient of variation of 6.80%. Absolute recovery of the internal standard for the QC pools was determined in a similar manner. The recovery of the internal standard was 100% with a coefficient of variation of 0.300% for QC1 and 101% with a coefficient of variation of 1.29% for QC3. Intra-assay precision and accuracy were evaluated for each quality control pool by multiple analyses of the pool on one assay day. The limit of quantitation pool had an inter-assay precision of 99.218-97.4% and accuracy of 99.251 -105.34%.

Stability:
The stability of daptomycin in plasma and urine was assessed under various conditions. Daptomycin was shown to be stable in plasma at 4°C, in extracted samples at 4°C, following long-term storage at -20°C, and following three freeze-thaw cycles. Daptomycin was shown to be stable in urine at room temperature, in urine at 4°C, in extracted samples at 4°C, and following three freeze-thaw cycles.

2.5.2.   What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
See section 2.5.1.

3.   Detailed labeling recommendations

Please see appendix 4.1 for the package insert.

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4. Appendices

    4.1.   Proposed package insert

    4.2.   Clinical pharmacology individual study review

    4.3.   Population PK Modeling of Daptomycin

Appendix 4.1

Proposed package insert (Clean version as of November 15, 2016)

31 PAGES WITHHELD IN FULL AS DRAFT LABELING - b(4)

Appendix 4.2

INDIVIDUAL STUDY REVIEWS

Study # DAP-PEDS-05-01
TITLE OF STUDY: An Evaluation of the Pharmacokinetics of a Single Dose of Daptomycin (DAP) (4 mg/kg) in Pediatric Patients Aged Two to Seventeen Years Who Are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-Positive Infection

STUDY OBJECTIVES:
- The primary objective of this study was to evaluate the single-dose pharmacokinetics (PK) of intravenous (i.v.) daptomycin in pediatric patients, divided into 3 age groups (2-6 years, 7-11 years and 12-17 years), with proven or suspected Gram-positive infection who were receiving standard antibiotic therapy.
- The secondary objective was to describe the tolerability of a single dose of i.v. daptomycin in this group of patients.

METHODOLOGY:
This was a Phase 1, multicenter, single dose, open-label, non-comparative study designed to assess the PK and safety of daptomycin in up to 30 pediatric patients between the ages of 2 and 17 years, inclusive, who were receiving treatment for suspected or diagnosed Gram-positive infection. Patients were to be sequentially enrolled into 3 groups based on age: Group 1, 12 to 17 year olds; Group 2, 7 to 11 year olds; and Group 3, 2 to 6 year olds. Eligible patients were to receive a single dose of 4 mg/kg (30 minute i.v. infusion) daptomycin on Day 1 in addition to antibiotics administered as standard of care for their Gram-positive infections. PK plasma, serum and urine samples were to be obtained at selected time points during the study. Pharmacokinetic analyses were conducted on data from 24 patients who received the full 4 mg/kg dose. Plasma samples for determination of daptomycin plasma PK were to be obtained: pre-dose and at 5, 10, 15, and 30 minutes and 1, 2, 4, 6, 10 and 24 hours after the end of infusion. Urine was to be collected from predose, 0-6, 6-12, and 12-24 hours from the start of study drug administration on any patient who was toilet trained.

Bioanalytical Method Description:
Plasma:
The bioanalyses of daptomycin in plasma and urine samples were conducted a ___(b) (4)___ . Quantitation of Daptomycin in Human Plasma via HPLC with Ultraviolet Absorbance Detection was conducted according to (b) (4) , SOPs under the assigned project code "NKG4."

The method is applicable to the quantitation of daptomycin within a nominal range of 3.00 to 500 µg/mL and requires a 300-µL aliquot of human plasma containing sodium heparin. Samples are kept frozen at -20 °C or colder prior to analysis. A 300-µL sample aliquot is fortified with 700 µL of ethylparaben internal standard working solution. All tubes are then vortexed and centrifuged. The extract is transferred to glass inserts in autosampler vials and injected and analyzed via HPLC with ultraviolet detection. The linearity of this procedure was evaluated by analyzing nine calibration standards in duplicate over the nominal concentration range of 3.00 to 500 µg/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. Linearity was indicated by a correlation coefficient of 0.9992 from standard curve. The inter-assay precision in plasma was 92.37-96.34% (100 ± __ %) and the accuracy ranged was within 103-109.72 % ___(b) (4)___ %).

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Analyte Name:	daptomycin
Matrix and Species:	human plasma
Matrix Additive:	sodium heparin
Proposed Sample Volume*:	50.0 µL
Calibration Range:	3.00 to 500 ng/mL
Sample Storage Temperature:	-20 °C or colder
Special Handling:	none

* If necessary, the assay sample volume may be adjusted with (b) (4) management approval. Such a change will not be considered a deviation from the plan and will not require a plan amendment.

Quality control pools are prepared on ice in human plasma, containing sodium heparin, at nominal daptomycin concentrations of 7.50, 75.0, and 400 µg/mL. After thorough mixing each quality control pool is frozen in daily portions and stored in polypropylene tubes at -20 °C or colder.

Urine:
For daptomycin analysis in human urine, linearity of procedure was evaluated by analysis of nine calibration standards over the range of 3.00 to 500 µg/mL using a linear weighted (1/concentration squared) least squares regression algorithm to plot the peak height ratio of daptomycin to internal standard versus concentration. Linearity was indicated by an average correlation coefficient of 0.9994 from three standard curves. Analysis was by high performance liquid chromatography with ultraviolet absorbance detection. The method was validated with a minimum quantifiable level of 3.00 µg/mL. The mean recovery was 91.8% for QC1 with a coefficient of variation of 3.19% and the mean recovery for QC3 was 91.5% with a coefficient of variation of 6.80%. Absolute recovery of the internal standard for the QC pools was determined in a similar manner. The recovery of the internal standard was 100% with a coefficient of variation of 0.300% for QC1 and 101% with a coefficient of variation of 1.29% for QC3. Intra-assay precision and accuracy were evaluated for each quality control pool by multiple analyses of the pool on one assay day. The limit of quantitation pool had an inter-assay precision of 99.218-97.4% and accuracy of 99.251 -105.34%.

Stability:
The stability of daptomycin in plasma and urine was assessed under various conditions. Daptomycin was shown to be stable in plasma at 4°C, in extracted samples at 4°C, following long-term storage at -20°C, and following three freeze-thaw cycles. Daptomycin was shown to be stable in urine at room temperature, in urine at 4°C, in extracted samples at 4°C, and following three freeze-thaw cycles.

Figure 1. Mean Daptomycin Plasma Concentrations (µg/mL) Over Time by Age Group (Linear Plot) (PK Population)
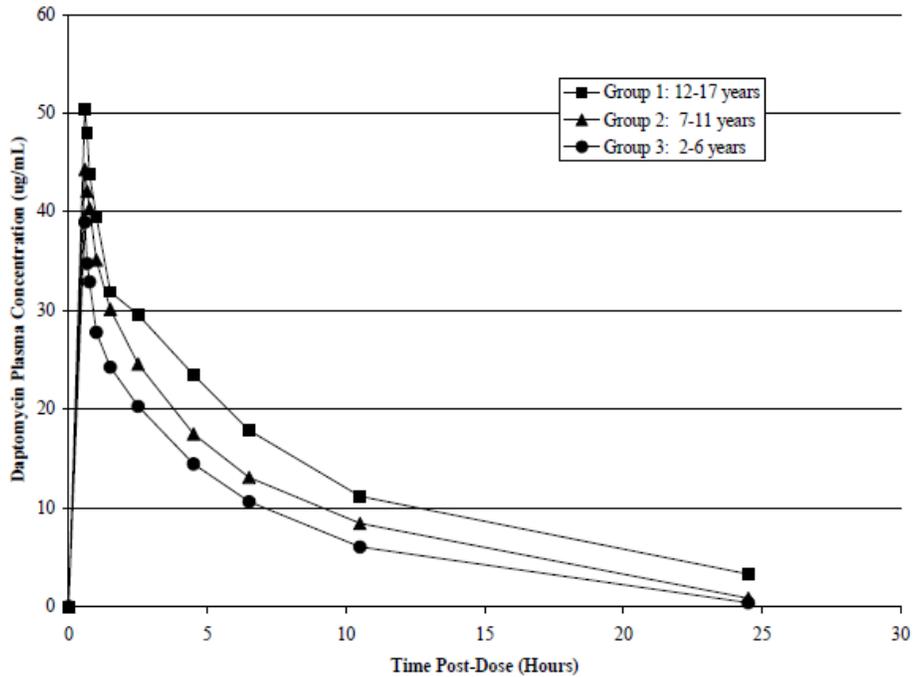
SUMMARY OF PHARMACOKINETICS:

An overview of the daptomycin plasma pharmacokinetic parameters for the 3 age groups is provided in the Table 1 below. Mean daptomycin concentrations over time were lower in the younger age groups compared with the oldest age group (Figure1). This led to peak (C_{max}) and total (AUC) exposures that were lower in Groups 2 and 3 compared to Group 1. C_{max} in each of the age groups occurred at the end of the infusion (median T_{max} of 0.58 hours). Both total clearance and renal clearance of drug adjusted for weight (CL/wt and CLr/wt, respectively) were lower in Group 1 compared with Groups 2 and 3 and mean half-life was longer in Group 1 relative to the younger patient groups. Following i.v. infusion, ~60% of the administered daptomycin dose was excreted as unchanged drug within 24 hours. The percent of daptomycin excreted in the urine (59-62%) was similar across the age groups. Furthermore, the proportion of metabolized drug (sum of metabolites M-1, M-2, M-3 and M-4) excreted in the urine was similar across the 3 age groups (5.4%, 5.0% and 7.2% for Groups 1, 2 and 3, respectively). Daptomycin was highly bound to serum protein (~90%) and the level of serum protein binding was similar across age groups. The mean values of body weight adjusted steady-state volume of distribution (Vdss/wt) were <140 mL/kg. Vdss/wt was higher in the youngest age group compared with the older age groups.

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Table 1. Summary of Pharmacokinetic Parameters for Daptomycin following the Administration of a Single 4 mg/kg (30-Minute IV infusion) Dose in Pediatric Patients between the Ages of 2 to 17 Years in Study DAP-PEDS-05-01

PK Parameter:	Group 1 Ages 12 to 17 (N=8)	Group 2 Ages 7 to 11 (N=8)	Group 3 Ages 2 to 6 (N=8)
$AUC_{0-\infty}$ ($\mu g \cdot hr/mL$)	385.09 (69.69)	279.91 (138.5)	204.33 (66.24)
C_{max} ($\mu g/mL$)	50.55 (10.56)	45.78 (10.78)	39.09 (6.26)
T_{max} (hr)[a]	0.58 (0.58, 0.77)	0.58 (0.58, 0.67)	0.58 (0.58, 0.75)
$t_{1/2}$ (hr)	7.84 (1.22)	5.29 (1.67)	5.11 (1.89)
CL/wt (mL/hr/kg)	10.72 (2.23)	16.51 (5.66)	21.54 (7.21)
CLr/wt (mL/hr/kg)	7.29 (2.03)	9.41 (2.69)	17.42 (8.05)
Fe (%)	61.78 (2.38)	59.35 (5.54)	60.44 (13.08)
% Bound	88.85 (1.01)	91.52 (4.47)	91.72 (1.80)
Vdss/wt (mL/kg)	106.31 (19.12)	110.91 (21.10)	136.25 (21.41)

a   Data presented are median (minimum, maximum)

Additional individual regression analyses were performed to determine the association of each of 5 predictor variables (age, weight, BMI, BSA and CL_{cr}) with each of 6 PK parameters (AUC, C_{max}, CL, $t_{1/2}$, Vdss and CLr). Associations of CL and Vdss were observed with age, weight and BSA. AUC had an association with weight and BMI. In addition C_{max} had an association with BMI.

APPLICANT'S CONCLUSIONS:
A single dose of daptomycin was safe and well tolerated in pediatric patients. In general, the PK profile in adolescents 12 to 17 years old was similar to that of healthy adults. However, in the younger age groups, exposure (C_{max} and AUC) and elimination half-life ($t_{1/2}$) were reduced compared with adolescents while weight adjusted clearance was increased. Taken together, these results suggest that further study is warranted to determine whether dose modification may be necessary in pediatric patients.

Reviewer's Comments:
As per Dr. Bonapace's review of NDA-21572, at the dose of 4 mg/kg multiple dose PK study, mean AUC_{0-24} (%CV) in healthy adults was 354 (18%) and 494 (15%) $\mu g \cdot hr/mL$ on Day 1 and day 7, respectively. In adult patients, mean AUC (SD) was 417(155) $\mu g \cdot h/mL$ at the dose of 4 mg/kg.

In this study, mean $AUC_{0-\infty}$ (SD) in adolescents patients from 12-17 yrs was 385(69.69) $\mu g \cdot hr/ml$. Therefore, daptomycin exposure (i.e., AUC) in adolescent patients was less than that in healthy adults. Based on the label of CUBICIN ®, dose in adults for cSSSI is 4 mg/kg to be administered intravenously once every 24 hours for 7 to 14 days. Some drugs can be eliminated at differing rates depending on differences in age. Both total clearance and renal clearance of daptomycin adjusted for weight (CL/wt and CLr/wt, respectively) were inversely related to age. Total CL in healthy adults was 8.3(1.3) ml/hr/kg and the CL in adolescents was 10.72 (2.23) ml/hr/kg. Considering higher CL in adolescents as compared to adults the applicant proposed using a higher dose (5 mg/kg) in adolescent patients in Phase 4 study.

Study # DAP-PEDS-07-02
TITLE OF STUDY:
An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged Two to Six Years Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection

STUDY RATIONALE:
One single-dose PK study was conducted with daptomycin in children age 2-17 years (Study DAP-PEDS-05-01). Plasma concentrations of daptomycin at 4 mg/kg in children less than 7 years were substantially lower than in adults or older children. Therefore it was necessary to further investigate the pharmacokinetics of daptomycin in children aged 2 to 6 years. This study, DAP-PEDS-07-02, was conducted to further investigate the pharmacokinetics in children ages 2-6 years, inclusive. Simulations have shown that following administration of doses of 8-10 mg/kg in children ages 2 to 6 years, the expected C_{max} (75–93 µg/mL) and AUC (392–490 µg·h/mL) would be within reasonable safety margins and are likely to be efficacious.

PHASE OF DEVELOPMENT: Phase 1

STUDY OBJECTIVES:
The primary objective of this study was to evaluate single-dose pharmacokinetic (PK) data on intravenous (i.v.) daptomycin administered at 8 mg/kg as a 1 hour infusion or 10 mg/kg as either a 1 or 2 hour infusion in pediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infection who were receiving standard antibiotic therapy.

The secondary objective was to assess the safety of an 8 or 10 mg/kg single dose of i.v. daptomycin administration as either a 1 or 2 hour infusion in pediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infections who were receiving standard antibiotic therapy.
No control group was required as the primary objective of this study was the assessment of PK.

METHODOLOGY:
This was a Phase 1, multicenter, single-dose, open-label study designed to assess the PK and safety of daptomycin in 12 to 24 pediatric subjects between the ages of 2 and 6 years, inclusive, who were receiving treatment for suspected or diagnosed Gram-positive infection. Subjects were to be enrolled into 2 consecutive groups. Group 1 was to include 6 to 12 subjects dosed at 8 mg/kg as a 1-hour infusion. Group 2 was to include 6 to 12 subjects dosed at 10 mg/kg as either a 1-or 2-hour infusion; the duration of the infusion was dependent on the PK profile observed following the 8 mg/kg dose.

Bioanalytical Assay Methodology:
The bioanalyses of daptomycin in plasma samples were conducted at ⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛. The linearity of this procedure was evaluated by analyzing nine calibration standards in duplicate over the nominal concentration range of 3.00 to 500 µg/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. Linearity was indicated by a correlation coefficient of 0.9995 from six standard curves. Limit of quantitation was 3.00 µg/mL. The mean recovery was 92.4% for QC1 with a coefficient of variation of 1.66% and the mean recovery for QC3 was 95% with a coefficient of variation of 1.53%. Absolute recovery of the internal standard for the QC pools was determined in a similar manner. The recovery of the internal standard was 103% with a coefficient of variation of 0.48% for QC1 and 103% with a coefficient of variation of 0.82% for QC3. Inter-assay precision was 95.15-98.13 % and accuracy was 99.902-102.60 %, which is satisfactory.

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PHARMACOKINETICS:

The plasma sampling times were based on the known PK profile of daptomycin in adults and the results of the previous PK study in the pediatric population, DAP-PEDS-05-01. The PK population was to include all subjects who received the full dose of daptomycin 8 or 10 mg/kg. Plasma samples for determination of daptomycin plasma PK were to be obtained at: 0 minutes (prior to infusion), 30 minutes (during infusion), 60 minutes (within 2 minutes following the end of 1 hour infusion or during the 2 hour infusion), 120 minutes (within 2 minutes following the end of the 2 hour infusion), and 4, 7, 12, and 24 hours relative to the start of the infusion.

Figure 2a. Median (Range) Plasma Concentration-Time Profile of Daptomycin Following the Administration of a Single 8 mg/kg Dose
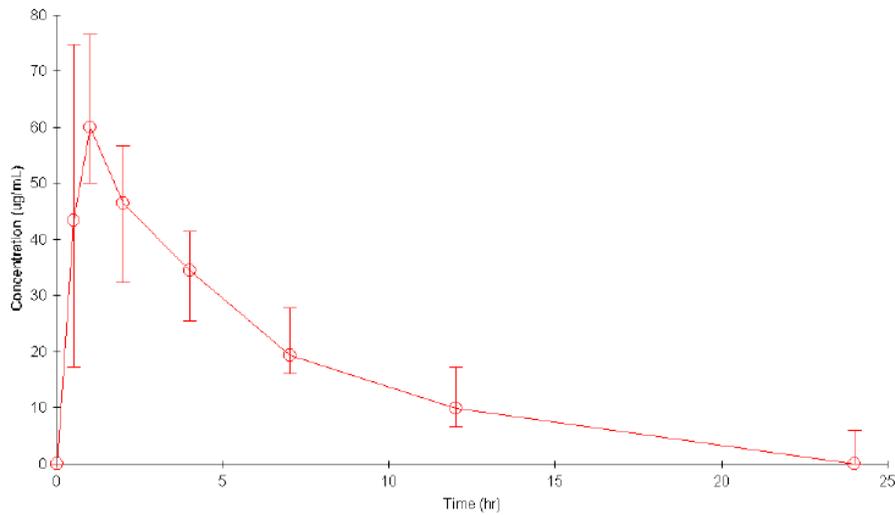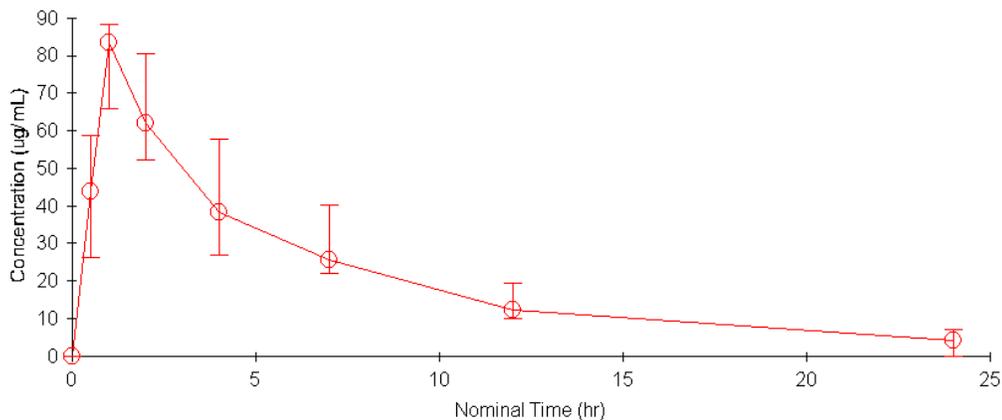

Figure 2b. Median (Range) Plasma Concentration-Time Profile of Daptomycin Following the Administration of a Single 10 mg/kg Dose

SUMMARY OF PHARMACOKINETICS:

The concentrations of daptomycin increased following the start of the infusion to reach an average C_{max} of 68.42 µg/mL following the 8 mg/kg dose and 79.18 µg/mL following the 10 mg/kg dose (Figures

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2a and 2b). The median T_{max} occurred at about 1 hour, the end of the infusion at both doses. Average $t_{1/2}$ of daptomycin remained unchanged between the two doses administered: 5.4 and 5.7 hours for the 8 and 10 mg/kg doses, respectively (Table 2).

Similarly, the CL/wt and Vss/wt of daptomycin did not appear to be significantly different between the two doses, indicating linear PK of daptomycin at the doses and age-group studied. C_{max} and area under the plasma concentration time curve (AUC) increased about 16% and 28% with the 25% increase in dose from 8 to 10 mg/kg as shown in Table 2.

Table 2. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of a Single 8 or 10 mg/kg Dose in Pediatric Patients Between the Ages of 2 to 6 Years in study DAP-PEDS-07-02

Parameter	Group 1 Ages 2-6 year 8 mg/kg n=6 Mean (SD)	Group 2 Ages 2-6 year 10 mg/kg n=6 Mean (SD)
Infusion Duration (hr)	1.0	1.0
$AUC_{0-\infty}$ (µg*hr/mL)	429.14 (113.01)	549.70 (139.35)
C_{max} (µg/mL)	68.42 (9.33)	79.18 (10.17)
T_{max} (hr)	0.86 (0.27)	1.04 (0.04)
$t_{1/2}$ (hr)	5.35 (1.41)	5.67 (0.62)
CL/wt (mL/hr/kg)	19.47 (5.01)	19.14 (4.51)
V_{ss}/wt (mL/kg)	135.67 (8.69)	144.62 (28.26)

APPLICANT'S CONCLUSIONS:
In addition, the C_{max} and AUC values were generally predictable across doses among 2 to 6 year olds based on data from Study DAP-PEDS-05-01 and this study, indicating linear PK. The total exposure (AUC) seen in adults at the 4.0 mg/kg dose was approximately 495 µg·hr/mL at steady-state. The mean exposure seen in the present study were approximately 429 and 550 mg·hr/mL, respectively, at the 8 and 10 mg/kg doses. This suggests that a dose of 9 mg/kg in children in the age-group of 2-6 years may produce exposure equivalent to that seen in adults at the 4 mg/kg dose.
Single doses of 8 and 10 mg/kg were safe and well tolerated in children aged 2-6 years. The pharmacokinetics of daptomycin appears to be linear and predictable in the dose range studied.

Reviewer's comments:
- *Previous information indicates that daptomycin exhibits concentration-dependent killing and, based on animal models, AUC/MIC is the principal PK/PD index to determine bacteria killing effect. To ensure efficacy, the doses in children were identified to provide children with the AUC compared to that in infected adult and non-infected subjects receiving the approved dose for treatment of cSSSI (i.e., 4mg/kg).*
- *Daptomycin doses of 8 and 10 mg/kg were selected based on simulations to investigate the PK of daptomycin in children aged 2-6 years prior to expanded use in pediatric populations. This approach of dose selection is acceptable from clinical pharmacology perspective. Selected doses have achieved desired exposure for efficacy in pediatric patients.*

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Study# DAP-PEDS-09-01

TITLE OF STUDY:
An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged 3 Months to Twenty-four Months Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Bacterial Infection including Peri-Operative Prophylactic Use of Antibiotics

PHASE OF DEVELOPMENT: Phase 1

PRIMARY OBJECTIVE:
To evaluate single dose pharmacokinetic (PK) data of intravenous (i.v.) daptomycin administered at 4 mg/kg or 6 mg/kg as a 30 minute infusion in pediatric subjects aged 3 months to 24 months, inclusive, with proven or suspected bacterial infection who were receiving standard antibiotic therapy, including subjects who were receiving prophylactic antibiotics perioperatively.

SECONDARY OBJECTIVES:
To assess the safety of a single dose of i.v. daptomycin administration as a 30 minute infusion in pediatric subjects aged 3 months to 24 months, inclusive, with proven or suspected bacterial infection who were receiving standard antibiotic therapy, including subjects who were receiving prophylactic antibiotics perioperatively.

METHODOLOGY:
This was a multicenter, single dose, open-label, non-comparative study designed to assess the PK and safety of daptomycin in pediatric subjects between the ages of 3 months to 24 months, inclusive. Subjects who had suspected or diagnosed bacterial infection, including subjects that were receiving prophylactic antibiotics perioperatively were included in this study in three age groups:
Group 1: Ages 13 months to 24 months inclusive. Seven subjects dosed at 6 mg/kg as a 30 minute infusion;
Group 2: Ages 7 months to 12 months inclusive: Eight subjects dosed at 4 mg/kg as a 30 minute infusion;
Group 3: Ages 3 months to 6 months inclusive: Nine subjects dosed at 4 mg/kg as a 30 minute infusion.

Bioanalytical Assay Methodology:
The bioanalyses of daptomycin in plasma and urine samples were conducted at ⟨(b) (4)⟩
. Internal standard was ethyl 4-hydroxybenzoate. The linearity of this procedure was evaluated by analyzing nine calibration standards in duplicate over the nominal concentration range of 3.00 to 500 µg/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. Linearity was indicated by a correlation coefficient of 0.9994 from standard curves. Limit of quantitation was 3.00 µg/mL. Inter-assay precision was 95.41 - 97.24 % and accuracy was 99.877 - 103.37% for the QC range.

SELECTION OF DOSES IN THE STUDY:
The median AUC values in the DAP-PEDS-07-02 study at 8 mg/kg and 10 mg/kg in children ages 2 to 6 years old were 396 and 506 µg·hr/mL, respectively. Median C_{max} values were about 72 and 83 µg/mL, respectively. In order to produce exposure (mean AUC of 494 µg·hr/mL) comparable to 4 mg/kg dosing in the adult population for treatment of cSSSI, it is estimated that the appropriate dose in 2 to 6 year old children is 9 mg/kg. However, the starting dose for this study was 6 mg/kg since there is little or no experience with daptomycin in children less than 2 years of age. For children less than 13 months of age, the dose was lowered to 4 mg/kg as this ensured that measurable concentrations were obtained at sufficient time points without unacceptably high plasma concentrations.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Male or female subjects between the ages of 3 months and 24 months, inclusive, with suspected or diagnosed bacterial infection for which the subject was receiving standard antibiotic therapy, including prophylactic use of antibiotics peri-operatively. Subjects were required to be clinically stable with no evidence of hemodynamic instability in the 24-hour window prior to the first dose and were to have no history or evidence of renal or hepatic compromise, with calculated creatinine clearance (CLcr) rate ≥ 80 mL/min/1.73m^2 as determined by the Schwartz equation at Baseline, CPK levels less than $2 \times$ upper limit of normal (ULN) at Baseline, and presence of 2 patent i.v. lines when possible.

PHARMACOKINETICS:
The PK population included subjects in the three age groups who received a single daptomycin infusion and who had adequate blood samples collected. Plasma samples for determination of daptomycin PK were to be obtained immediately prior to infusion (0 minutes), at the end of the infusion, 1, 2, 6, and 12 hours after the start of the infusion.

Figure 3a. Mean (SD) Plasma Concentration-Time Profile of Daptomycin Following the Administration of a Single 6 mg/kg Dose to Infants in Age Group 1 (13-24 Months of Age)
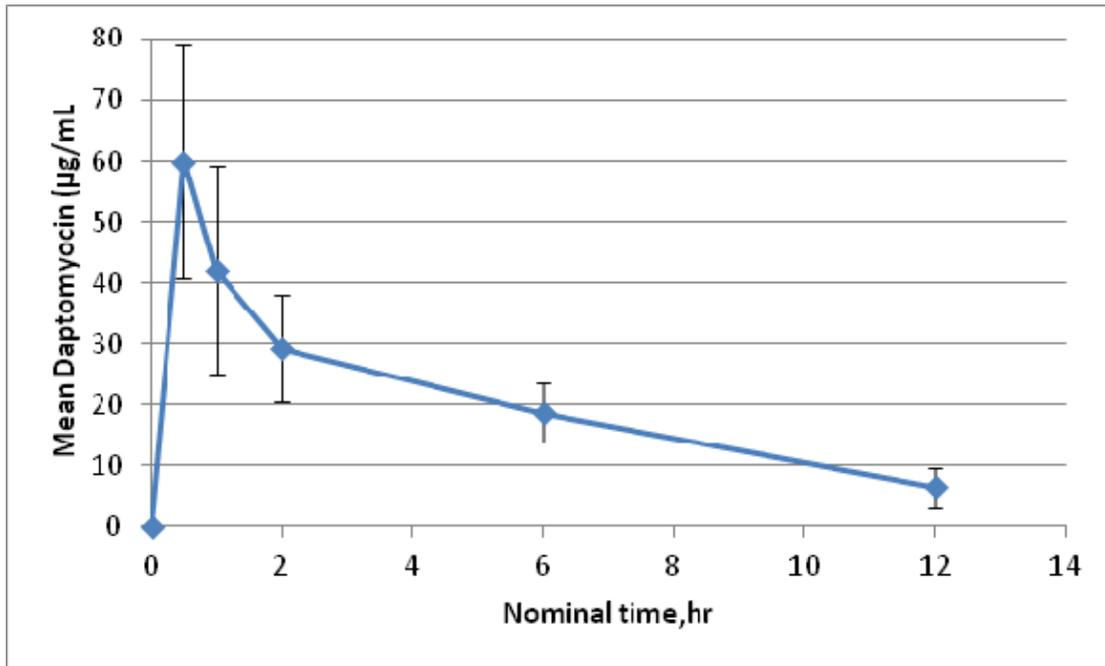
Figure 3b. Mean (SD) Plasma Concentration-Time Profile of Daptomycin Following the Administration of a Single 4 mg/kg Dose to Infants in Age Group 2 (7-12 Months of Age)
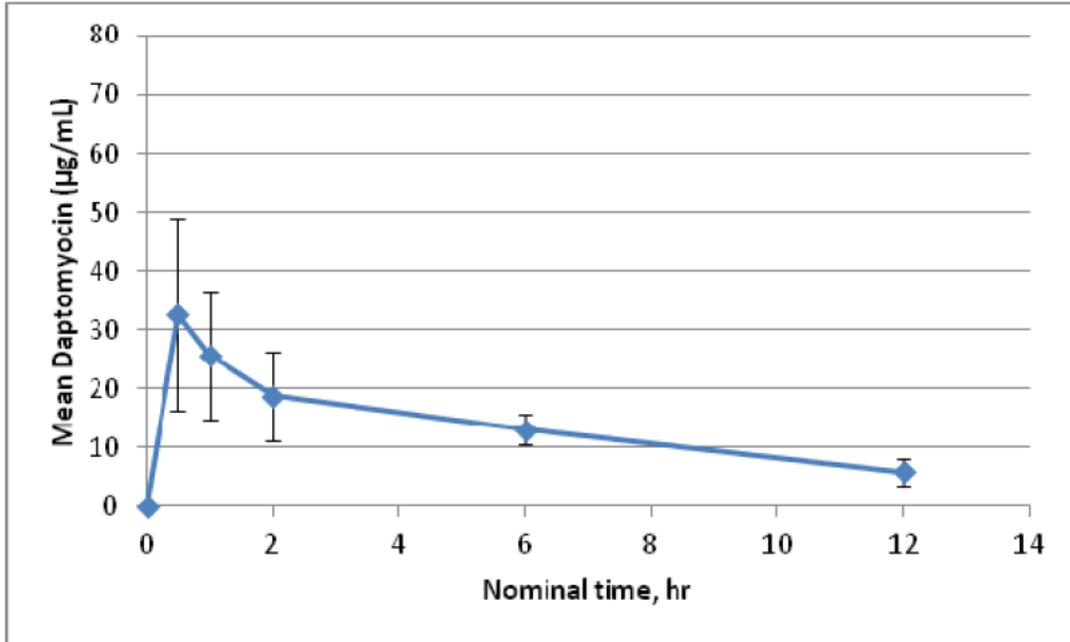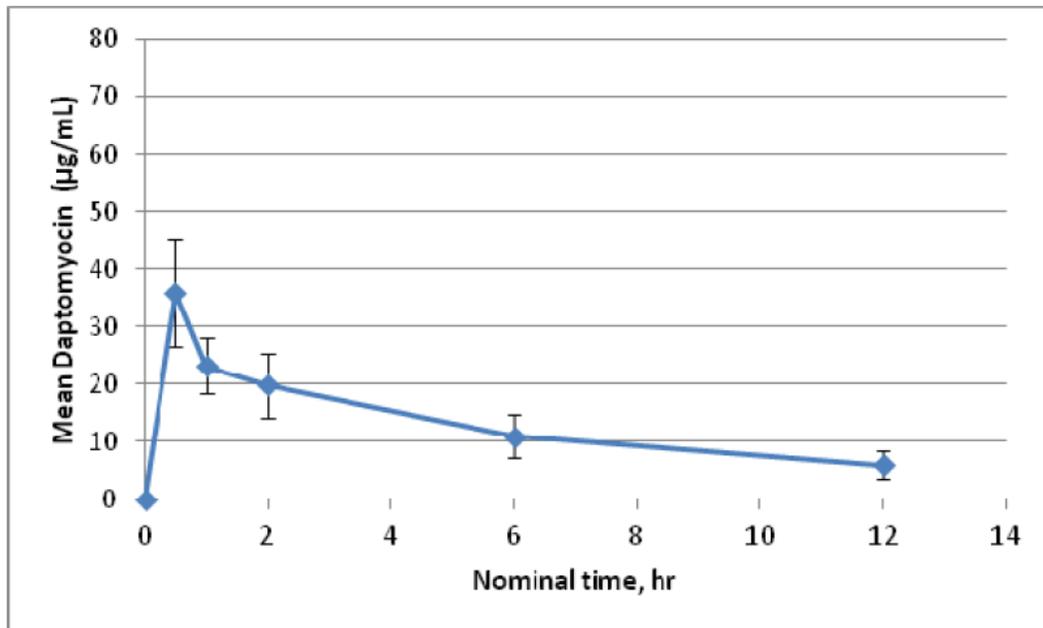

Figure 3c. Mean (SD) Plasma Concentration-Time Profile of Daptomycin Following the Administration of a Single 4 mg/kg Dose to Infants in Age Group 3 (3-6 Months of Age)

SUMMARY OF PHARMACOKINETICS:

Following the administration of daptomycin at 6 mg/kg to infants in Age Group 1 (13-24 months of age), the mean observed C_{max} was 67.0 µg/mL at a median of 0.55 hour from the start of the 0.5 hour infusion as shown in Figures 3a, 3b and 3c. The mean $AUC_{0-\infty}$ was 281.5 µg·hr/mL, which was markedly lower than a corresponding dose in adults. Mean CL of daptomycin was high at 21.76 mL/hr/kg which was approximately twice that of adults with normal renal function. Compared with adults, the mean Vss was increased (121.7 mL/kg) while mean $t_{1/2}$ was reduced (4.41 hr).

The PK of daptomycin was similar in infants in Age Group 2 and Age Group 3 (7-12 months of age and 3-6 months of age, respectively) after a single 4 mg/kg dose infused over 0.5 hr. Mean C_{max} was 37.1 and 38.7 µg/mL, respectively, and T_{max} occurred shortly after the end of the infusion (median T_{max} of 0.53 hours in both Age Group 2 and Age Group 3). The mean $AUC_{0-\infty}$ (219.3 and 215.0 µg·hr/mL, respectively), were also similar in the 2 age groups and were considerably lower than that in adults at the same dose (Table 3).

Compared with adults and older children, the subjects in this study ages 3 to 24 months had more rapid daptomycin CL and shorter half-lives resulting in lower drug exposures (area under the curve; AUC). Thus, dosage adjustment will be needed to insure adequate exposure and satisfactory efficacy.

Table 3. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of a Single 4 or 6 mg/kg Dose to Infants between the Ages of 3 to 24 Months in Study DAP-PEDS-09-01

| Parameter	Age Group 1 13-24 months 6 mg/kg n=5 Mean (SD)	Age Group 2 7-12 months 4 mg/kg n=7 Mean (SD)	Age Group 3 3-6 months 4 mg/kg n=7 Mean (SD)
Infusion Duration (hr)	0.5	0.5	0.5
$AUC_{0-\infty}$ (µg*hr/mL)	281.5 (44.5)	219.3 (66.8)	215.0 (68.3)
C_{max} (µg/mL)	67.0 (14.5)	37.1 (12.6)	38.7 (5.2)
T_{max} (hr)	0.66 (0.26)	0.59 (0.20)	0.53 (0.02)
$t_{1/2}$ (hr)	4.41 (0.94)	5.45 (1.13)	5.10 (1.17)
CL/wt (mL/hr/kg)	21.76 (2.99)	19.63 (5.76)	19.72 (5.46)
V_{ss}/wt (mL/kg)	121.7 (30.7)	134.9 (28.6)	127.7 (11.7)

APPLICANT'S CONCLUSIONS:

Daptomycin administered as a single i.v. dose of 4 or 6 mg/kg was safe and well-tolerated in infants aged 3 to 12 months of age and in infants 13 to 24 months of age, respectively. Compared with adults and older children, the subjects in this study, ages 3 to 24 months, had more rapid daptomycin CL and shorter half-lives, resulting in lower drug exposures (AUC). Thus, dosage adjustments will be needed to insure adequate exposure and satisfactory efficacy in infants.

The results indicate that following a single 4 or 6 mg/kg dose, daptomycin clearance and elimination half-life in patients 3 to 24 months old were similar to those in patients 2 to 6 years old who received a single dose of 4, 8, or 10 mg/kg in Study DAP-PEDS-05-01 and Study DAP-PEDS-07-02. Compared to the clearance and elimination half-life values in adolescents (12-17 years) receiving 4 mg/kg daptomycin in

the previous study (CL/wt=10.7 mL/hr/kg, $t_{1/2}$= 7.8 hr in Study DAP-PEDS-05-01), daptomycin clearance (20-22 mL/hr/kg) is higher and $t_{1/2}$ (4-5 hr) is shorter in patients 3-24 months old.

Figure 4. Scatter plots for individual clearance normalized by body weight vs. age for pediatric patients 3 months to 17 years of age in the four pediatric clinical studies (DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and DAP-PEDS-07-03; N=101) (Open Circles Represent Individual Values; Lines Represent LOESS Trend Lines (Source: Study report by applicant)
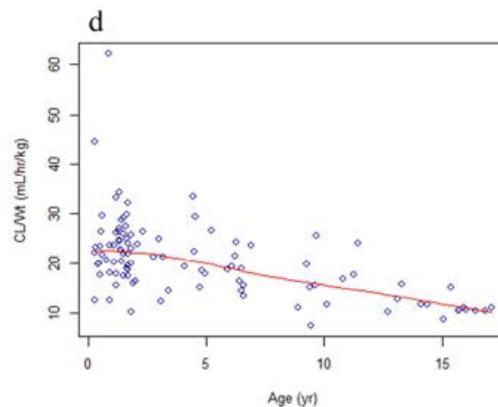
Reviewer's comment:
- *The applicant's assessment of the study results and their conclusions are acceptable from the perspective of Clinical Pharmacology.*
- *Clearance normalized by body weight in 3-12 months old pediatric patients was almost double of that in adults and adolescent patients (Figure 4).*

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Study# DAP-PEDS-07-03

TITLE OF STUDY:
An Evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Pediatric Subjects Aged One to Seventeen Years with Complicated Skin and Skin Structure Infections Caused by Gram-Positive Pathogens

PHASE OF DEVELOPMENT: Phase 4

SELECTION OF DOSES IN THE STUDY:
The intention was to target an AUC in children that was comparable to the AUC in adults treated with 4 mg/kg. This study provides clinical experience of DAP administration in children and infants at exposure levels similar to those achieved by the approved dose for adults with skin infections. In order to produce steady-state exposure (AUC) comparable to 4 mg/kg dosing in the adult population, it was estimated from PK modeling that the appropriate doses are 5 mg/kg in the 12 to 17 year olds, 7 mg/kg in the 7 to 11 year olds, 9 mg/kg in the 2 to 6 year olds, and 10 mg/kg in the 1 to less than 2 year olds. In children 1 to 6 years old, because of the potential for an elevated maximum plasma concentration (C_{max}), the duration of the infusion was extended from 30 to 60 minutes.

OBJECTIVES:
The primary objective of this study was to assess the safety of age-dependent doses of intravenous (IV) daptomycin (DAP) administered for up to 14 days in comparison with standard of care (SOC) therapy in pediatric subjects aged 3 months to 17 years with complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens.

The secondary objectives of this study were to assess the efficacy of age-dependent doses of IV DAP administration for up to 14 days in comparison with SOC therapy and to evaluate the population pharmacokinetics (PK) of age-dependent doses of IV DAP administered for up to 14 days in pediatric subjects aged 3 months to 17 years with cSSSI caused by Gram-positive pathogens.

METHODOLOGY:
This was a multicenter, evaluator blinded, randomized, comparative study originally designed to assess the safety, efficacy, and PK of DAP in pediatric subjects between the ages of 3 months to 17 years, inclusive, with cSSSI caused by Gram-positive pathogens. Subjects were enrolled into well-defined age groups and given age-dependent doses over a period of up to 14 days. Enrollment into each age group followed a step-wise approach. Subjects 7 years of age and older were enrolled first (Age Groups 1 and 2), followed by subjects 1 to 6 years of age (Age Groups 3 and 4). Safety and clinical data collected in children 7 years of age and older supported the extension of enrollment into younger age groups. Prior to opening enrollment to include children 3 months of age and older, a Data Monitoring Committee (DMC) reviewed new nonclinical data and recommended that due to the new benefit/risk ratio, the lower limit of enrollment for this study be 1 year of age. The recommendation to stop the study at this time was submitted to and agreed upon with the Food and Drug Administration. Therefore, no subjects were enrolled in this study less than 1 year of age. Daptomycin dosage regimens and pharmacokinetic sampling scheme for this study are presented in Table 4.

A total of 396 children were randomized and stratified by age group, to receive either DAP or SOC (suggested as IV vancomycin, IV clindamycin, or IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin]) in a ratio of 2:1, respectively, with 263 children receiving DAP. Subjects may have switched to oral therapy following completion of IV study drug administration provided they showed clear clinical

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improvement and the pathogen was susceptible to an oral agent. The choice of oral therapy was left to the discretion of the Investigator. Children were enrolled in this study in four age groups:

- Age Group 1: age 12–17 years old (inclusive) treated with DAP dosed at 5 mg/kg or SOC;
- Age Group 2: age 7–11 years old (inclusive) treated with DAP dosed at 7 mg/kg or SOC;
- Age Group 3: age 2–6 years old (inclusive) treated with DAP dosed at 9 mg/kg or SOC;
- Age Group 4: age 1–<2 years old treated with DAP dosed at 10 mg/kg or SOC.

A sufficient number of subjects were randomized to ensure that a minimum of 50 subjects in Age Groups 1, 2, and 3 and 30 subjects in Age Group 4 received DAP.

Bioanalytical Assay Methodology:
The bioanalyses of daptomycin in plasma and urine samples were conducted at   (b) (4)
                    . Plasma samples from this study were analyzed using a validated high performance liquid chromatography (HPLC) method using ultraviolet (UV) detection. The lower limit of quantitation (LLOQ) was 3 µg/mL and the upper limit of quantitation was 100 µg/mL. The assay was linear between 3 µg/mL and 100 µg/mL. The precision of the assay was 95.33% to 97.98% and the accuracy was 99.72% to 102.73%, respectively.

DRUG DOSE, DRUG CONCENTRATION, AND RELATIONSHIP TO RESPONSE:
A total of 6 subjects in Age Group 1 (12-17 year old), 2 subjects in Age Group 2 (7-11 year old), 7 subjects in Age Group 3 (2-6 year old), and 30 subjects in Age Group 4 (1–< 2 years old) provided at least one PK plasma sample and were therefore included in the PK population. Due to the nature of the individual plasma concentration versus time profiles, certain PK parameters (AUC_{0-tau}, $AUC_{0-\infty}$, $t_{1/2}$, CL_{SS}, and V_{SS}) could be derived for only 3 of the subjects in Age Group 1, 1 subject in Age Group 2, and 4 of the subjects in Age Group 3. Other PK parameters such as C_{max} and T_{max} were taken from the observed data and are reported.

Plasma concentrations increased during the course of the infusion reaching a maximum concentration at the end of the infusion. However, since a plasma sample was not taken at the end of infusion in every subject in all dosing groups, the C_{max} should be considered an approximation. The mean C_{max} ranged between 62.4 µg/mL in Age Group 1 to 81.9 µg/mL in Age Group 3. The terminal $t_{1/2}$ ranged from 3.8 to 5.3 hours across the different age groups while the mean steady-state clearance ranged from 13.3 to 21.4 mL/hr/kg.

SUMMARY OF PHARMACOKINETICS:
A total of 15 subjects across Age Groups 1-3 and 30 subjects in Age Group 4 contributed at least one PK sample and were included in the PK Population. The PK parameters for DAP computed from the limited data available indicate that consistent with previous observations, the clearance of DAP decreases with an increase in age. Although statistical comparisons were not possible due to the small sample size, the elimination $t_{1/2}$ in younger subjects appeared to be shorter than that in older subjects, confirming observations from previous studies. Plasma concentration versus time profiles for daptomycin in subjects in groups 1, 2, and 3 is presented in Figure 5. Plasma concentration versus time profiles for daptomycin in subjects in group 4 are shown in Figure 6. The PK parameters of DAP in children 12-17 years of age appear to be similar to those seen in adult subjects as shown in Table 5. Mean C_{max} ranged from 62.4 to 81.9 µg/mL across the age groups. The $t_{1/2}$ ranged from 3.8 to 5.3 hours across the different age groups while the mean steady-state clearance ranged from 13.3 to 21.5 mL/hr/kg.

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Table 4. Daptomycin Dosage Regimens and Pharmacokinetic Sampling Scheme for Pediatric Patients 1 to 17 Years of Age with Complicated Skin and Skin Structure Infections in Study DAP-PEDS-07-03

Age Group	Age (years)	Number of Patients with PK Samples	Dose (mg/kg)	Infusion (hours)	PK Sampling (PK time points are relative to EOI)
1	12-17	6	5	0.5	Day 3 at Pre-dose, 0.25 , 1, 4 and 12 hr
2	7-11	2	7	0.5	Day 3 at Pre-dose, 0.25, 1, 6 and 10 hr
3	2-6	7	9	1	Day 1, 2, or 3 at Pre-dose, 0.25, 1, 6 and 8 hr
4	1-<2	30	10	1	Sparse PK sampling (2 of 5 time points) on Day 1, 2, or 3 at 0 hr (EOI), 1, 2, 4 and 6 hr

Figure 5. Mean Plasma Concentration versus Time Profiles for Daptomycin in Subjects in Groups 1, 2, and 3
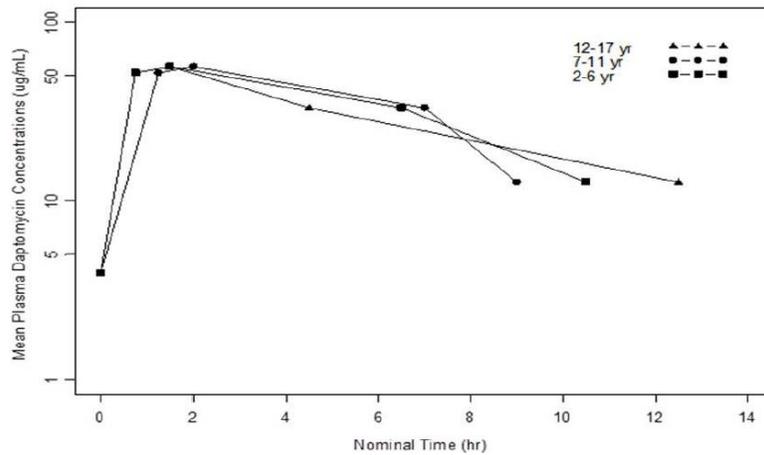

Figure 6. Mean Plasma Concentration versus Time Profiles for Daptomycin in Subjects in Group 4
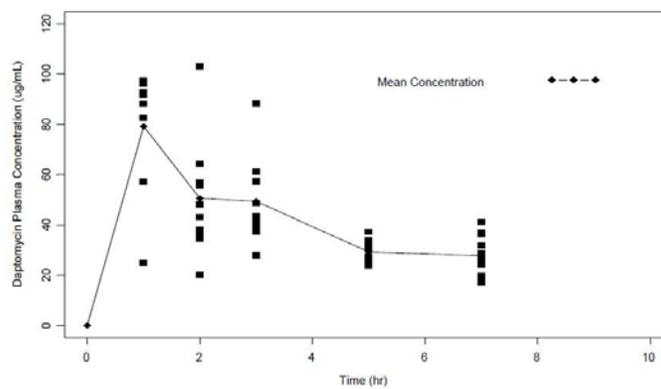

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Table 5. Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of Multiple 5 to 10 mg/kg Doses in Pediatric Patients Between the Ages of 1 to 17 Years in Study DAP-PEDS-07-03

Parameter	Age Group 1 12-17 years 5 mg/kg n=6 Mean (SD)[a]	Age Group 2 7-11 years 7 mg/kg n=2 Ind. Values[b]	Age Group 3 2-6 years 9 mg/kg n=7 Mean (SD)[a]	Age Group 4 1-<2 years 10 mg/kg n=30 Mean[c]
Infusion Duration (hr)	0.5	0.5	1.0	1.0
AUC_{0-tau} (μg*hr/mL)[#]	387 (81)	438, ND	439 (102)	466
C_{max} (μg/mL)	62.4 (10.4)	64.9, 74.4	81.9 (21.6)	79.2
T_{max} (hr)	0.9 (0.1)	0.3, 0.8	1.4 (0.4)	1.0
$t_{1/2}$ (hr)	5.3 (1.6)	4.6, ND	3.8 (0.3)	5.04
CL_{ss}/wt (mL/hr/kg)	13.3 (2.9)	16.0, ND	21.4 (5.0)	21.5
V_{ss}/wt (mL/kg)	98.1 (12.2)	104, ND	116 (19.9)	159

ND: Not determined

\# AUC_{0-tau}: Area under the plasma concentration time curve during the 24-hour dosing interval.

[a] PK parameters including AUC_{0-tau}, $t_{1/2}$, CL_{ss}, and V_{ss} could be derived for only 3 out of the 6 subjects in Age Group 1, and 4 out of the 7 subjects in Age Group 3. The mean (SD) for these PK parameters were calculated using N=3 and N=4 for Age Group 1 and Age Group 3, respectively.

[b] The numbers provided here indicate individual values (two patients provided plasma samples that were used to determine PK).

[c] Due to limited PK samples from each patient, PK parameters were computed using the mean concentration profile during a sampling interval and individual parameters were not computed, thus no variability could be calculated.

EFFICACY ANALYSES:

For all efficacy outcome variables, difference in success rate and a normal approximation 95% CI (for Age Groups 1, 2, 3 and total) or an exact 95% CI (for Age Group 4) around the difference between SOC and Daptomycin (Daptomycin minus SOC) were presented for each age group.

Overall, daptomycin response rates were comparable with response rates observed with SOC with clinical success noted in 88.3% and 86.4% of patients who received daptomycin and SOC, respectively.

Reviewer's comments:

Although the applicant has concluded that the PK parameters of daptomycin in children 12-17 years of age appear to be similar to those seen in adult subjects, AUC in adolescents is approximately 10 to 20% less than that in adults. The exposure obtained in Study # 05-01 and in Study # 07-03 in adolescents appears similar even though dose was increased from 4 mg/kg to 5mg/kg. After increasing the dose there was no change in the exposure in Study #07-03, the clear rationale for selecting 5 mg/kg dose in adolescents instead of 4mg/kg was not provided by the applicant. Up on our information request, applicant has provided comparison of PK parameters estimated from Population PK Model from adults and pediatric patients and demonstrated the comparable AUCss, which shows that 5 mg/kg dose in adolescents instead of 4mg/kg is acceptable. Additionally, the efficacy, tolerability was achieved at 5 mg/kg dose with large number of patients. Considering the supportive efficacy and safety data in Study #07-03 and the limited number (n=3) of patients with PK data, 5mg/kg dose appears to be justifiable.

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COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Dose Proportionality

As shown in, daptomycin exposure in pediatric patients receiving a single IV infusion dose increases in a manner consistent with dose proportionality within the evaluated dose range (4 mg/kg to 10 mg/kg). Furthermore daptomycin $t_{1/2}$, total clearance (CL/wt), and distribution volume (Vss/wt) are dose independent. These results indicate that daptomycin has linear pharmacokinetics in pediatric patients similar to adults.

Reviewer's comment:

CL/wt for 4, 8, 10 mg/kg dose in the age group of 2-6 years was 21.5, 19.5, 19.1 mL/hr/kg, respectively, suggesting the dose proportionality at the evaluated dose range.

Pharmacokinetics after Repeated Administration

The dose-normalized exposures are similar after a single dose ($AUC_{0-\infty}$) and after multiple doses (AUC_{0-24hr}) except the age group of 12-17 years, indicating that daptomycin has time-independent pharmacokinetics (Table 6). No significant accumulation after repeated administration is expected based on the short $t_{1/2}$ (around 4 to 7 hours) and the once daily (q24hr) dosing.

Table 6. Comparison of Dose-Normalized Daptomycin Pharmacokinetic Parameter Values after a Single Dose and Multiple Doses in Pediatric Patients Ages 1 to 17 Years

Age group	Single dose Dose normalized $AUC_{0-\infty}$ (µg*hr/mL)/(mg/kg)			Multiple doses Dose normalized AUC_{0-tau} (µg*hr/mL)/(mg/kg)
	DAP-PEDS-05-01	DAP-PEDS-07-02	DAP-PEDS-09-01	DAP-PEDS-07-03
12-17 years	96.3	-	-	77.4
7-11 years	70.0	-	-	62.6
2-6 years	51.1	53.6 to 55.0	-	48.8
13-24 months	-	-	46.9	46.6

Distribution and Protein Binding

Daptomycin is highly bound; the degree of protein binding is similar across the different age groups in pediatric patients and is similar to the protein binding in healthy adult subjects, indicating no age difference in protein binding (Table 7). The body weight normalized volume of distribution (V_{SS}/wt) ranged from 98.1 to 159 mL/kg which was similar to that in adults.

Table 7. Percentage of Protein-bound Daptomycin in Adult and Pediatric Patients

	Adult[a]	Ages 12 to 17[b] n=7	Ages 7 to 11[b] n=6	Ages 2 to 6[b] n=7
	Mean	Mean (SD)	Mean (SD)	Mean (SD)
Percentage of bound (%)	90 to 93	88.85 (1.01)	91.52 (4.47)	91.72 (1.80)

Renal Excretion:
Percentage of renal excretion is similar across the age groups and it is generally similar to the renal excretion in healthy adult subjects (Table 8).

Table 8. Daptomycin Percentage of Renal Excretion in Adult and Pediatric Patients

Parameter	Adult[a] n=5	Ages 12 to 17[b] n=7	Ages 7 to 11[b] n=7	Ages 2 to 6[b] n=3
	Mean	Mean (SD)	Mean (SD)	Mean (SD)
Fe (%)	78[c]	61.78 (2.4)[d]	59.35 (5.5)[d]	60.44 (13.1)[d]

Source: a: USPI; b: Study DAP-PEDS-05-01; c: radiolabeled drug, d: unchanged drug in cold batch.

Appendix 4.3

POPULATION PK MODEL OF DAPTOMYCIN

The population PK model of daptomycin in pediatric patients was developed by the applicant and the objective was to optimize clinical dose in pediatric patients with cSSSI. The development and validation of the proposed population PK model are summarized below and were found acceptable from the perspective of Clinical Pharmacology.

A pediatric population pharmacokinetic model (Study CUBI-PCS-106) was developed based on all available data from Studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and Study DAP-PEDS-07-03 (Table1). The pediatric patient population included subjects with various degrees of infection from cSSSI to relatively mild local infection that would not meet criteria for cSSSI.

The objectives of developing a population pharmacokinetic model were to:

- describe the pharmacokinetics of daptomycin in pediatric population.
- identify sources of inter-individual variability in the pharmacokinetics of daptomycin.
- explore potential differences in the pharmacokinetics of pediatric patients by cSSSI types and other infections.
- confirm the exposure in pediatric patients with cSSSI achieved with the dosing regimens used in the clinical study (Study DAP-PEDS-07-03) to be comparable with the exposure achieved in adult patients with cSSSI receiving the approved 4 mg/kg dose.

Population pharmacokinetic analysis for daptomycin was performed using a nonlinear, mixed effect, 2-compartment PK model that included allometric scaling and maturation functions on central clearance and volume of distribution. The kidney maturation was expressed as a function of post-menstrual age (PMA) in a sigmoidal model and was included in the renal excretion portion of the central clearance and central volume of distribution. The effects of continuous covariates (weight, age, creatinine clearance [CRCL]) and categorical covariates (age group, cSSSI, infection type, race and sex) on inter-individual variability in the pharmacokinetic parameters were evaluated.

A summary of the numbers of subjects across age groups and studies is provided in Table 1:

Table 1. Number of Pediatric Pharmacokinetic Patients in the Studies Included in the Population Pharmacokinetic Model Development

	DAP-PEDS-05-01 N=24	DAP-PEDS-07-02 N=12	DAP-PEDS-09-01 N=23	DAP-PEDS-07-03 N=42	Total N=101
1 to <2 years	0	0	23	27[a]	50 (49.5%)*
2 to 6 years	8	12	0	7	27 (26.7%)
7 to 11 years	8	0	0	2	10 (9.90%)
12 to 17 years	8	0	0	6	14 (13.9%)

* Within the ~50% of patients that are <2 years old, majority are >1 year old. There are only 17 patients who are < 1 year which accounts for 16.8% of the total dataset.

[a] In Age Group 1 (1 to <2 years old), 30 subjects provided at least one plasma PK sample; three subjects had no reportable daptomycin concentrations.

METHODOLOGY

Software
Population PK analysis was performed using nonlinear mixed effect models (NLME) in Phoenix™ NLME v1.2 with the first order conditional estimation – extended least squares (FOCE-ELS). FOCE involves only a single optimization of a top-level approximate marginal log likelihood function.

Dataset preparation, exploration and visualization of the data were performed using R 2.15.2 and Phoenix™ NLME v1.2.

Population PK Modeling: PK Model Update
The full PK model was updated using combined plasma concentration-time data collected from pediatric patients enrolled in four clinical studies (DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and DAP-PEDS-07-03).

Since daptomycin is mainly eliminated by kidneys, non-renal (CLnr) and renal (CLr) clearances of daptomycin were included in the above model with an effect of maturation on CLr based on the glomerular maturation function. Fixed asymptotic fraction (0.60) of CLr reflected total urinary excretion fraction of daptomycin observed in pediatric patients from 2 to 17 years of age. The equation for total systemic clearance (CL) in previous model is presented below.

$$CL_j = 0.871 \times \left(\frac{WT_j}{70}\right)^{0.75} \times \left(0.40 + 0.60 \times \frac{PMA_j^{3.4}}{47^{3.4} + PMA_j^{3.4}}\right)$$

The maturation function in the previous model integrated on Vc is presented below:

$$V_j = Vc \times \left[\frac{PMA_j^{-0.247}}{PMA_j^{-0.247} + 30^{-0.247}}\right] \times \left(\frac{WT_j}{70}\right)^1$$

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CL_j and V_j, are the clearance and volume of distribution of daptomycin, respectively, for subject j of any given post-menstrual age (PMA_j), and body weight (WT_j) values. *Hill* coefficient (herein referred to as gamma) of maturation function included in Vc was estimated to be equal to -0.247. A race effect was also included in the clearance. Note that the gamma and maturation half-time included in CL were fixed at 3.4 and 47 weeks, respectively.

Post-menstrual age in weeks (PMA) used in previous model was derived as:

$$PMA = Age_{year} \times 52 \text{ weeks/year} + 40 \text{ weeks of pregnancy}$$

Where Age_{year} is the actual age in years.

The model consists of the following:

- Description of the relationships between plasma concentration and time

- A variance component characterizing between-subject variability in model parameters

  Model had the form:

$$C_{p_{ij}} = C\left(D_i, t_j, \theta_i\right) + \varepsilon_{ij}$$

$$\theta_i = \left(\theta_{i1}, ..., \theta_{im}\right)$$

where C_{pij} is plasma concentration at j^{th} collection time t_j for subject i, D_i represents dosing history for subject i, θ_i is the vector of m PK parameters for subject i, and ε_{ij} is random residual error associated with j^{th} concentration for subject i. Between-subject variability (BSV) in parameters may be modeled in a number of ways. For example, the following may have been used if a log-normal distribution was used to model BSV:

$$\theta_{in} = \theta_{TVn} \exp(\eta_{in})$$

$$(\eta_1, ..., \eta_m) \approx MVN(0, \Omega)$$

where $\theta_{TV\eta}$ is the population typical value for the nth PK parameter, e.g. clearance, and η_{in} is the random between-subject effect on the nth parameter for subject i. Each individual random effect ($\eta_1, ... \eta_m$) is normally distributed with mean 0 and estimated variance ω_n^2. The overall random effects were expressed with a multivariate normal distribution MVN(0, Ω), centering at 0, with a covariance matrix of Ω. Residual variability was described by a statistical model with an additive and a proportional component, as described below:

$$y_{ij} = \hat{y}_{ij} \cdot \left(1 + \varepsilon_{1ij}\right) + \varepsilon_{2ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted concentration, respectively, for the ith individual, and ε_{1ij} and ε_{2ij} are respectively the proportional and additive random residual effect. Each ε is normally distributed with mean 0 and variance σ^2.

Model validation/qualification of population PK models for daptomycin was based on the following diagnostic plots:

- Observed data versus population predicted data (DV vs. PRED) and individual predicted data (DV vs. IPRED) with a line of unity and a trend line,

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- Observed Data versus Time after the last dose (DV vs time and DV vs TAD) with LOESS lines of DV and PRED,

- Conditional weighted residuals versus predicted data (CWRES vs. PRED) with zero line and a LOESS line,

- Conditional weighted residuals versus time after the 1st dose and last dose (CWRES vs. time and CWRES vs TAD) with zero line and a trend line.

- Quantiles-quantiles plot of CWRES (QQ plot).

Outlier data (i.e., concentration values associated to absolute CWRES greater than 4) were reviewed for daptomycin.

Population PK Modeling: Covariates Analysis

The relationships between covariates and PK parameters of daptomycin derived with the population PK model were explored graphically to obtain preliminary information of covariates likely to affect the PK of daptomycin and to guide the selection of an appropriate covariate model (e.g. power or linear model). For continuous variables, the covariate-PK relationship was assessed using locally weighted scatter plot smoothing (LOESS), Pearson coefficients of correlation, and the corresponding p-value for each relationship. Only covariates with important trend were included in the full models.

Potential covariates included:

- Post-natal age in years (AGE)

- Post-menstrual age in weeks (PMA)

  (PMA=Age$_{year}$×52 weeks/year + 40 weeks of pregnancy)

- Body weight at baseline in kg (WT)

- Glomerular filtration rate according to Schwartz in mL/min/1.73 m^2 (GFRsw)

  calculated as:

  $$GFRsw_{Age\ (1w-1y)} = 0.45 \times Height_{cm} / SCr_{mg/dL}$$

  $$GFRsw_{Age\ (1-12y)} = 0.55 \times Height_{cm} / SCr_{mg/dL}$$

  $$GFRsw_{Male\ Age\ (13-18y)} = 0.70 \times Height_{cm} / SCr_{mg/dL}$$

  $$GFRsw_{Female\ Age(13-18y)} = 0.55 \times Height_{cm} / SCr_{mg/dL}$$

  Where SCr mg/dL is the serum creatinine expressed in mg/dL

- Creatinine clearance according to Cockcroft and Gault (CRCLcg)

- Sex (male = 1, female = 0)

- Race (1= Caucasian, 2= Black, and 3= Others)

- Infection (0= other infections in other 3 studies; 1= cSSSI as defined in DAPPEDS-07-03)

- Infection type (other, major abscess, complicated cellulitis, as defined in DAP-PEDS-07-03)

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Goodness-of-Fit Assessment and Model Performance

Model validation/quantification was performed according to FDA and EMA Guidance for Industry. The performance of the full population PK model was evaluated with several methods including diagnostic plots and shrinkage of population PK parameters as described above.

Prediction-corrected visual predictive check (VPC) was also performed on the final population PK model to allow visual comparison between distributions of simulated daptomycin concentrations derived with the final models and those derived from the original dataset. In prediction-corrected VPC, both the observations and the model predictions were corrected with population prediction in each bin of the independent variable (e.g., time after last dose). Based on the estimates of the final model, daptomycin concentration-time profile were simulated using 1000 replicates. Within each bin, nonparametric 95% confidence intervals (CI) of the 2.5^{th}, 50th and 97.5^{th} percentiles of predicted-corrected concentrations were computed and compared to the 2.5^{th}, 50th and 97.5^{th} percentiles of observed-corrected concentrations. These percentiles were plotted versus time after IV dosing of daptomycin to visually assess concordance between the model-based simulated data and the observed data.

Posteriori Bayes Parameters Estimation

The individual post-hoc PK parameters (i.e., total systemic clearance (CL), central volume of distribution (Vc), peripheral clearance (CL2), peripheral volume of distribution (V2)) derived from the final model were used to obtain area under the plasma concentration-time curve within a dose interval at steady state (AUCss) and maximum concentration (Cmax). PK simulations were performed to generate steady state (Day 14) end of infusion concentration (Cmax) for each individual subject included in the post-hoc analysis with same amount of doses the individual subject received in clinical studies administrated in q24 hr for 14 days. The AUCss was calculated as Dose/CL. The individual total volume of distribution (Vss) was calculated as the sum of Vc and V2 and distribution and elimination half-life ($t_{1/2\alpha}$ and $t_{1/2\beta}$) were computed using the individual PK parameters (CL, Vc, CL2, V2).

Individual and descriptive statistics of post-hoc estimates derived with the final population PK model were summarized by age groups (i.e., < 2 years old, 2 – 6 years old, 7 – 11 years old and 12 – 17 years old).

Previous PK Model

Based on PK data of daptomycin and the maturation of renal function in pediatric patients, previous PK model was constructed based on a 2-compartment model with an allometric function on clearance, peripheral clearance, and central and peripheral volumes of distribution. The maturation function with PMA was included as covariate on Vc in the previous model for explaining the variability observed between Vc and height, age and serum creatinine.

Base PK Model

The previous PK model for daptomycin was used as a starting point. The model was first updated using PK dataset with additional data from Study DAP-PEDS-07-03.

The first step of base model update was to evaluate various OMEGA structures. The relevant model was selected based on statistical significance criteria at a p-value of 0.05.

Individual observed and population predicted concentrations of daptomycin of the updated model were tightly grouped along the identity curve. CWRES were generally distributed around 0 suggesting no bias in the predictions of high and low concentrations of daptomycin.

The first step of base model update was to evaluate various OMEGA structures. Overall, the models with block OMEGA of CL and Vc showed important decrease in MOF when compared to diagonal

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OMEGA. One model with a block OMEGA between CL and Vc, no BSV V2 and without race effect on CL showed the most significant decrease in MOF (ΔMOF= -25.4, p<0.05).

Covariate Analysis
Statistically significant trends were observed between random effect of CL, age and WT. No significant trends between Vc and continuous covariates were observed. Small trends between individual random effects of CL and race (higher for Blacks and others) and between the individual random effects of CL and Vc and the 12-17 years age group were observed (lower for this age group). The estimated allometric scaling exponent, 0.635, was still close to the typically fixed value of 0.75 and more importantly, the quality of fit was similar and the parameter estimates were all equally reliable while the model became more stable and simpler. This simpler model with the unfixed allometric scaling exponent on CL was selected as final PK model for daptomycin in pediatric patients with cSSSI.

RESULTS:
Final Model: Model Diagnostic – Goodness-of-Fit Plots
The performance of the final population PK model of daptomycin was evaluated with several methods including diagnostic plots, shrinkage of population PK parameters and model validation based on corrected-prediction VPC. The comparison of observed vs. population predicted daptomycin concentrations derived with the final model are presented in Figure 1.

Figure 1. Goodness-of-Fit – Full PK Model of Daptomycin
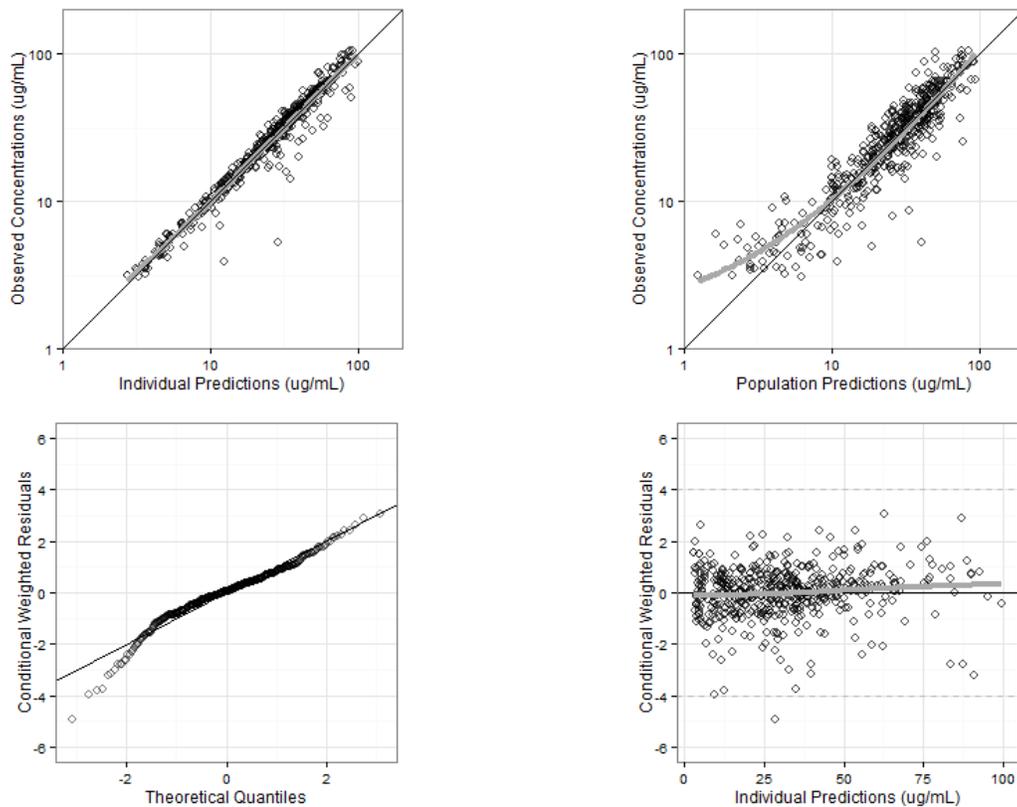
DV: Observed concentration (µg/mL); IDENT: Identity line; LOESS: Locally weighted scatter smoothing; PRED: Population predicted concentrations (µg/mL). Solid grey line represent locally weighted scatterplot smoothing and black lines represent the identity and zero lines
Source data: Residuals_ModelB1.csv; Source code: CUBI-PCS-106 GOF.R

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The final population pharmacokinetic parameters of daptomycin are summarized in Table 2:

Table 2. Final Population PK Parameters of Daptomycin

| PK parameters	Final model
Number of patients	101
Number of observations	514
Covariance step	Achieved
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)	$0.4 \times CL$
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 V2 (%)	0 Fixed
BSV CL (%)	28.3
BSV CL2 (%)	0 Fixed
Error Prop (%)	15.3
Error Additive (µg/mL)	0.025

BSV: Between patient variability; CL: 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).

Note: the fractions of CLr and CLnr were fixed at 0.6 and 0.4 of systemic clearance, respectively.

Shrinkage: BSV Vc= 11.0%; BSV CL= 7.0%. Correlation between BSV Vc and BSV CL: 0.725.

The results indicated that the body weight based allometric scaling including the maturation function adequately described daptomycin pharmacokinetics in pediatric patients 1 to 17 years of age. The differences in pharmacokinetics with age observed in Studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and Study DAP-PEDS-07-03 were accounted for in the population PK model using body weight adjustment and a maturation function of age, as shown in the prediction-corrected visual predictive check (VPC) using the final population PK model (Figure 2). Predicted clearance and volume of distribution were consistent with the observed data in all four studies. There was no significant difference in pharmacokinetics within the same age group across studies; different cSSSI types (major abscess, complicated cellulitis, or others as defined in Study DAP-PEDS-07-03), or between cSSSI and other infections (with suspected or diagnosed Gram-positive infection) represented by Studies DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01. There were no additional covariates identified to be significant.

Figure 2. Prediction-corrected Visual Predictive Check Demonstrated that the Final Population Pharmacokinetic Model Adequately Described the Pharmacokinetics of Daptomycin in Pediatric Patients
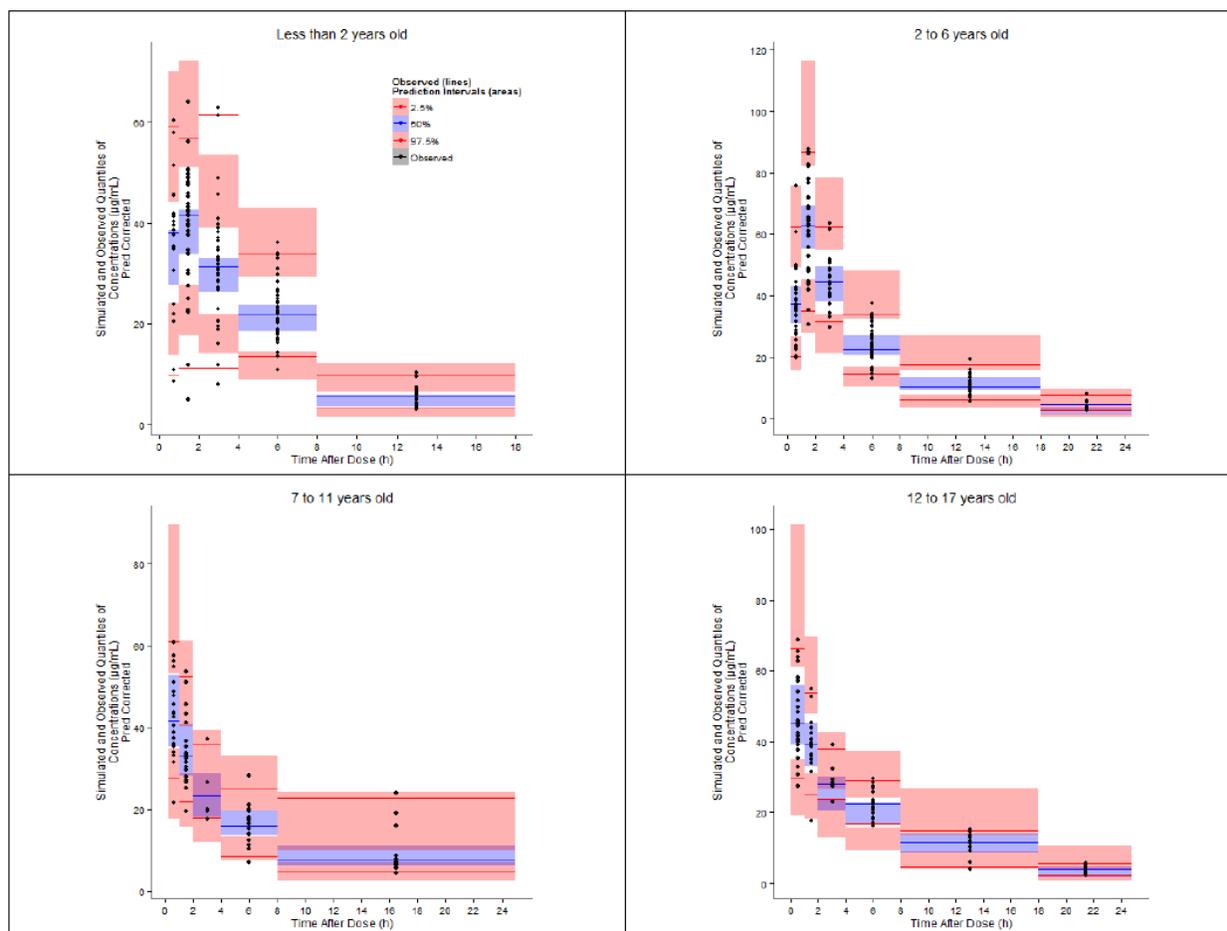
PRED: Population predicted concentrations
Note: The time-points of observed concentrations are presented in the middle of each bin.
Source data: predout.csv; Source code: CUBI-PCS-106 VPC_update.R

Overall, these results suggested a good performance of the final population PK model was able to generate robust individual post-hoc parameters of daptomycin, such as CL and Vc values (Table 3), to derive AUCss. The AUCss values ranged from 65.2 to 980 μg·h/mL, with the age-grouped geometric means ranged from 289 to 389 μg·h/mL. The median AUCss values were 342 μg·h/mL, 382 μg·h/mL, 253 μg·h/mL and 382 μg·h/mL in <2 years old, 2-6 years old, 7-11 years old and 12-17 years old age groups, respectively.

Table 3. Daptomycin Posthoc Clearance and Volume of Distribution (Normalized by weight) by Age Group Using the Final Population PK Model

PK Parameters	Mean (CV%)			
	1-<2 years old	2-6 years old	7-11 years old	12-17 years old
	N= 50	N=27	N= 10	N= 14
CL/wt (mL/h/kg)	23.8 (34.3)	20.5 (25.1)	16.4 (34.7)	11.4 (16.8)
Vss/wt (mL/kg)	156 (35.0)	135 (14.8)	126 (16.1)	113 (10.5)

CL: Systemic clearance; V_{ss}: Volume of distribution under steady state; WT: Body weight (kg)

CONCLUSION

The following conclusions were reached from this analysis:

- The body weight based allometric scaling including the maturation function can well describe the daptomycin PK in plasma in pediatric patients.
- No significant difference was observed in PK within the same age group across studies, different cSSSI types (DAP-PEDS-07-03), or between cSSSI and other infections represented by the other 3 studies.
- The dose regimens used in Study DAP-PEDS-07-03 were appropriate, supported by the observed exposure values and post-hoc estimation results.

Reviewer's Comment:

The population PK model for daptomycin in pediatric patients was developed by the applicant and was used to estimate pediatric daptomycin exposure at steady state in order to investigate whether proposed dose regimen is appropriate. From the perspective of Clinical Pharmacology, the development and validation of the proposed population PK model are acceptable and the model is considered adequate for estimation of exposure of daptomycin with the proposed dosing regimen in pediatric patients.

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/s/

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