21 May 2015
EMA/460377/2015
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cubicin

DAPTOMYCIN

Procedure No. EMEA/H/C/000637/P46/007.5

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

The applicant has submitted a Critical Expert Overview is to provide information from a Phase 4 safety, efficacy and pharmacokinetic (PK) study [Study DAP-PEDS-07-03] involving paediatric patients with complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens.

Study DAP-PEDS-07-03, an evaluator-blinded, randomized, comparative study, was conducted in the US and in India. Originally, the study was designed to include paediatric patients aged 7 to 17 years. However, the protocol was amended multiple times and, subsequently, paediatric patients aged 1 to 17 years were enrolled into the study. A total of 389 children received either daptomycin or standard of care (SOC) in a ratio of 2:1, respectively, with 256 children receiving daptomycin.

Study DAP-PEDS-07-03 is also part of a Post Authorisation Commitment (FUM 007.5-P46) where European Medicines Agency (EMA) requested the MAH to discuss differences in the PKs in adult patients with and without infection by providing simulations for paediatric patients with infection accounting for the observed differences in infected and non-infected adults when submitting a final report for Study DAP-PEDS-07-03.

About the product

Daptomycin is a cyclic lipopeptide natural product that is active against Gram positive bacteria only. The mechanism of action involves binding to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose by 30-minute intravenous infusion for up to 14 days in healthy volunteers. Steady state concentrations are achieved by the third daily dose. Daptomycin is eliminated primarily by the kidney.

Cubicin was first authorised via the centralised route in 2006.

Approved indication(s) and posology

Indication

Cubicin is indicated for the treatment of the following infections in adults:

- Complicated skin and soft-tissue infections (cSSTI).

- Right-sided infective endocarditis (RIE) due to Staphylococcus aureus.

- Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI.

Posology

Adults

- cSSTI without concurrent *Staphylococcus aureus* bacteraemia: Cubicin 4 mg/kg is administered once every 24 hours for 7-14 days or until the infection is resolved

- cSSTI with concurrent *Staphylococcus aureus* bacteraemia: Cubicin 6 mg/kg is administered once every 24 hours. The duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.

- Known or suspected right-sided infective endocarditis due to *Staphylococcus aureus*: Cubicin 6 mg/kg is administered once every 24 hours. The duration of therapy should be in accordance with available official recommendations. .

In patients with renal impairment, dose adjustment is needed.

Paediatric population

The safety and efficacy of Cubicin in children and adolescents aged below 18 years has not been established. Currently available data are described in section 5.2 of the SPC but no recommendation on posology are made.

2. Scientific discussion

2.1. Information on the development program

In 2007, the clinical study report (CSR) for DAP-PEDS-05-01 was submitted. This Phase 1 single dose, open-label, non-comparative study was designed to assess PKs and safety of daptomycin (4 mg/kg) in up to 30 paediatric patients aged 2 to 17 years with proven or suspected Gram-positive infection. Subsequently section 5.2 of the SmPC was updated. The MAH committed to inform the CHMP on further plans to identify a dose regimen for children aged 2 to 12 years.

In 2009, Novartis submitted Study DAP-PEDS-07-02, a single-dose PK study of daptomycin (8 mg/kg or 10 mg/kg) in 12 paediatric patients aged 2 to 6 years with proven or suspected Gram-positive infection. As an outcome of this submission, the CHMP requested Novartis to update section 5.2 of the European (EU) SmPC to include data from Study DAP-PEDS-07-02 and considered the FUM partially fulfilled. Novartis was therefore requested to assess the potential difference in PKs in paediatric patients accounting for the observed differences in infected and noninfected adults by providing simulations for paediatric patients with infection and to address the observation that differences in PKs were largest for the youngest age group (< 6 years) in Study DAP-PEDS-05-01 when submitting a final report for Study DAP-PEDS-07-03.

In 2012, Novartis provided the CHMP with the study report for DAP-PEDS-09-01, an evaluation of the PK profile and safety of a single dose of daptomycin (4 mg/kg and 6 mg/kg) in 24 paediatric subjects aged 3 months to 24 months with proven or suspected Gram-positive infection. As an outcome of this submission, the CHMP considered that FUM007 was partially fulfilled and commented that the results from Study DAP-PEDS-07-03 are still awaited. At that time, no update of the SmPC was considered necessary.

In 2013, the CHMP agreed to reclassify the post-authorisation commitments into appropriate legal framework (Art. 46 of the Regulation No 1901/2006) and further extended the due date for submitting the study report for Study DAP-PEDS-07-03. In December 2013, Novartis informed the CHMP about the status of paediatric trials and, particularly, about an enrollment-hold for Study DAP-PEDS-07-03 for the youngest age cohort (3 months to < 1 year). In August 2014, Novartis informed the CHMP that Cubist reached an agreement with the US Food and Drug Administration (FDA) to exclude patients < 1

year from the study based on findings from a neonatal dog toxicity study. The formal waiver from the FDA was received on 11-Feb-2015.

With this submission, Novartis provides the CHMP with the CSR for Study DAP-PEDS-07-03, as well as the population PK modeling and simulation report CUBI-PCS-106 (Pharsight Consulting Services Report CUBI-PCS-106) which confirmed that the dose regimens used in Study DAP-PEDS-07-03 were appropriate, supported by the observed exposure values, simulated target attainment and the observed high success rates.

Rapporteur's comments:

The MAH recently submitted the toxicity study in dogs and based on the conclusions, the exclusion of subjects under 1 years of age is acceptable.

2.2. Clinical aspects

a. Clinical Study

Study DAP-PEDS-07-03 is a multi-center, evaluator-blinded, randomized, comparative Phase 4 study, to assess safety, efficacy, and PKs of daptomycin in paediatric patients (1 to 17 year olds, inclusive) with cSSSI caused by Gram-positive pathogens. IRB/ Ethics approval was obtained.

Because higher clearance of daptomycin was observed in previous single-dose paediatric PK studies (DAP-PEDS-05-01, DAP-PEDS-07-02 and DAP-PEDS-09-01), age-adjusted daptomycin doses were given once daily up to 14 days in order to achieve exposures equivalent to those documented in successful adult cSSSI studies.

Children were enrolled in a stepwise approach into well-defined age groups and given age-dependent doses as follows:

- Age Group 1: 12 to 17 years treated with daptomycin dosed at 5 mg/kg or SOC;
- Age Group 2: 7 to 11 years treated with daptomycin dosed at 7 mg/kg or SOC;
- Age Group 3: 2 to 6 years treated with daptomycin dosed at 9 mg/kg or SOC;
- Age Group 4: 1 to < 2 years treated with daptomycin dosed at 10 mg/kg or SOC.

In children 1 to 6 years old, because of the potential for an elevated maximum plasma concentration (Cmax), the duration of the infusion was extended from 30 to 60 minutes.

Samples for population PK analysis (goal of at least 12 subjects in age groups 1, 2 and 3 and in group 4, sparse PK sampling was done for all subjects assigned to DAP who consented to participate in the study.) were collected at the following time points (relative to end-of-infusion [EOI]):

- Age Group 1 (12–17 years old): Day 3: Pre-dose (T0), 0.25 hr (15 min), 1 hr, 4 hr, and 12 hr;
- Age Group 2 (7–11 years old): Day 3: Pre-dose (T0), 0.25 hr (15 min), 1 hr, 6 hr, and 10 hr;
- Age Group 3 (2–6 years old): Day 1, 2, or 3: Pre-dose (T0), 0.25 hr (15 min), 1 hr, 6, and 8 hr
- Age Group 4 (1–<2 years old): Day 1, 2, or 3: 0 hr (EOI), 1, 2, 4, and 6 hr

Appropriate inclusion/exclusion criteria were applied.

Study Objectives

The primary objective of this study was to assess the safety of age-dependent doses of intravenous (IV) DAP administered for up to 14 days in comparison with standard of care (SOC) therapy in pediatric subjects aged 1 to 17 years with 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 in pediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.
- To evaluate the population PK of age-dependent doses of IV DAP administered for up to 14 days in pediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.

Study population

A total of 396 children were randomized and stratified by age group, to receive either daptomycin or SOC in a ratio of 2:1, respectively, with 256 children receiving daptomycin.

Table 2-2 DAP-PEDS-07-03: Patient numbers

	Age group 1 12 to 17 yr 5 mg/kg	Age group 2 7 to 11 yr 7 mg/kg	Age group 3 2 to 6 yr 9 mg/kg	Age group 4 1 to < 2 yr 10 mg/kg	Overall
Randomized	113	113	125	45	**396**
ITT population*	110	111	123	45	**389**
of which DAP-treated	*73*	*73*	*81*	*30*	*256*
of which SOC-treated	*37*	*38*	*42*	*15*	*133*
PK population	6	2	7	30	**45**

Table 10-3: Overall Summary of Subject Disposition – Study Completion (ITT Population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
Disposition	DAP 5 mg/kg (N=73) n (%)	SOC (N=37) n (%)	DAP 7 mg/kg (N=73) n (%)	SOC (N=38) n (%)	DAP 9 mg/kg (N=81) n (%)	SOC (N=42) n (%)	DAP 10 mg/kg (N=30) n (%)	SOC (N=15) n (%)	DAP (N=257) n (%)	SOC (N=132) n (%)
Completed study[a]	73 (100)	32 (86.5)	69 (94.5)	35 (92.1)	69 (85.2)	34 (81.0)	25 (83.3)	13 (86.7)	236 (91.8)	114 (86.4)
Discontinued study	0	5 (13.5)	4 (5.5)	3 (7.9)	12 (14.8)	8 (19.0)	5 (16.7)	2 (13.3)	21 (8.2)	18 (13.6)
Primary reason for early study discontinuation										
Adverse event	0	0	0	0	1 (1.2)	1 (2.4)	0	0	1 (0.4)	1 (0.8)
Microbiological failure	0	1 (2.7)	0	0	0	1 (2.4)	0	0	0	2 (1.5)
Investigator's decision	0	2 (5.4)	0	1 (2.6)	0	0	0	0	0	3 (2.3)
Subject's decision	0	1 (2.7)	0	1 (2.6)	0	0	0	0	0	2 (1.5)
Lost to follow-up	0	0	3 (4.1)	1 (2.6)	10 (12.3)	6 (14.3)	4 (13.3)	2 (13.3)	17 (6.6)	9 (6.8)
Other	0	1 (2.7)	1 (1.4)	0	1 (1.2)	0	1 (3.3)	0	3 (1.2)	1 (0.8)

Baseline / Demographic characteristics

Baseline and demographic characteristics between the two groups were similar, including age, sex and types of infection.

Treatment received

Most subjects in both treatment groups received ≤ 7 days of IV therapy and most switched to oral therapy. A higher proportion of DAP-treated subjects received IV study drug for less than 3 days (47%) compared to SOC-treated subjects (35%). Standard of care IV medication was primarily clindamycin (50%) and vancomycin (42%); the most common oral anti-infective administered after IV therapy was clindamycin which was administered to 39% and 35% of subjects who converted to oral therapy in the DAP and SOC groups, respectively.

Efficacy data

Clinical success rates at TOC for the ITT population based on Sponsor-defined clinical outcomes were high and similar in both treatment arms (88.3% in the DAP arm and 86.4% inthe SOC arm) as were microbiological success rates at TOC in the MITT population (90.5% and 88.6%, respectively). Although clinical success rates based on the sponsor-defined clinical outcomes at TOC in the ITT population were similar for subjects in the DAP and SOC arms, subjects in the DAP arm were converted from IV therapy to oral therapy earlier than those subjects in the SOC arm. High microbiological success rates at TOC were also noted for the most common Baseline infecting pathogens: MRSA (84.5% and 89.1% in the DAP and SOC arms, respectively), MSSA (95.3% and 91.8%, respectively), and S. pyogenes (100% and 70.0%, respectively).

Overall, similar results were obtained in the two groups:

Table 11-4: Summary of Sponsor-Defined Clinical Outcome at TOC (ITT Population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
Clinical Outcome	DAP 5 mg/kg (N=73) n (%)	SOC (N=37) n (%)	DAP 7 mg/kg (N=73) n (%)	SOC (N=38) n (%)	DAP 9 mg/kg (N=81) n (%)	SOC (N=42) n (%)	DAP 10 mg/kg (N=30) n (%)	SOC (N=15) n (%)	DAP (N=257) n (%)	SOC (N=132) n (%)
Subjects in Analysis	73	37	73	38	81	42	30	15	257	132
Clinical Success	70 (95.9)	34 (91.9)	66 (90.4)	35 (92.1)	67 (82.7)	32 (76.2)	24 (80.0)	13 (86.7)	227 (88.3)	114 (86.4)
Clinical Failure	0	1 (2.7)	2 (2.7)	0	1 (1.2)	0	0	0	3 (1.2)	1 (0.8)
Unable to Evaluate	3 (4.1)	2 (5.4)	5 (6.9)	3 (7.9)	13 (16.1)	10 (23.8)	6 (20.0)	2 (13.3)	27 (10.5)	17 (12.9)
% Diff in Success Rate (95% CI)[a]	4.0 (-6.0,14.0)		-1.7 (-12.6,9.2)		6.6 (-8.7,21.9)		-6.7 (-38.0,25.5)		2.0 (-5.1,9.1)	

Table 11-5: Summary of Sponsor-defined Clinical Outcome at TOC for the MITT, CE and ME Populations

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

The above results were supported by the blinded evaluator's assessment:

Table 11-6: Summary of Blinded Evaluator's Assessment of Clinical Response at TOC (ITT Population)

	Age Group 1		Age Group 2		Age Group 3		Age Group 4		All Subjects	
Clinical Outcome	DAP 5 mg/kg (N=73) n (%)	SOC (N=37) n (%)	DAP 7 mg/kg (N=73) n (%)	SOC (N=38) n (%)	DAP 9 mg/kg (N=81) n (%)	SOC (N=42) n (%)	DAP 10 mg/kg (N=30) n (%)	SOC (N=15) n (%)	DAP (N=257) n (%)	SOC (N=132) n (%)
Outcome at TOC	73	37	73	38	80	41	30	15	256	131
Clinical Success	71 (97.3)	34 (91.9)	68 (93.2)	35 (92.1)	69 (86.3)	32 (78.1)	25 (83.3)	13 (86.7)	233 (91.0)	114 (87.0)
Cure	69 (94.5)	34 (91.9)	66 (90.4)	35 (92.1)	67 (83.8)	31 (75.6)	25 (83.3)	13 (86.7)	227 (88.7)	113 (86.3)
Improved	2 (2.7)	0	2 (2.7)	0	2 (2.5)	1 (2.4)	0	0	6 (2.3)	1 (0.8)
Clinical Failure	2 (2.7)	3 (8.1)	5 (6.9)	3 (7.9)	11 (13.8)	9 (22.0)	5 (16.7)	2 (13.3)	23 (9.0)	17 (13.0)
Failure	0	1 (2.7)	1 (1.4)	0	0	0	0	0	1 (0.4)	1 (0.8)
Unable to Evaluate	2 (2.7)	2 (5.4)	4 (5.5)	3 (7.9)	11 (13.8)	9 (22.0)	5 (16.7)	2 (13.3)	22 (8.6)	16 (12.2)
% Diff in Success Rate[a] (95% CI)	5.4 (-4.2,14.9)		1.0 (-9.3,11.4)		8.2 (-6.6,23.0)		-3.3 (-34.9,28.7)		4.0 (-2.7,10.7)	

Table 11-7: Summary of Blinded Evaluator's Assessment of Clinical Response at TOC for the MITT, CE and ME Populations Across Combined Age Groups

	MITT		CE		ME	
Clinical Outcome	DAP (N=210) n (%)	SOC (N=105) n (%)	DAP (N=207) n (%)	SOC (N=99) n (%)	DAP (N=167) n (%)	SOC (N=78) n (%)
Subjects in Analysis	209	105	207	99	167	78
Clinical Success	190 (90.9)	91 (86.7)	206 (99.5)	99 (100.0)	166 (99.4)	78 (100.0)
Clinical Failure	19 (9.1)	14 (13.3)	1 (0.5)	0	1 (0.6)	0
Percent Difference in Success Rate (95% CI)[a]	4.2 (-3.3,11.8)		-0.5 (-1.4,0.5)		-0.6 (-1.8,0.6)	

Microbiological results

Overall, 206 (98.1%) of daptomycin-treated and 105 (100%) of subjects who received SOC in the Modified-Intent-to-Treat (MITT) population had MRSA, MSSA, or Streptococcus pyogenes. Results were similar except for S.pyogenes, where DAP showed better outcomes.

Table 11-9: Summary of Pathogen-Level Microbiological Outcome at TOC by Selected Baseline Pathogens (MITT Population)

	Staphylococcus aureus (MRSA)		*Staphylococcus aureus* (MSSA)		*Streptococcus pyogenes*	
Microbiological Outcome	DAP (N=210) n (%)	SOC (N=105) n (%)	DAP (N=210) n (%)	SOC (N=105) n (%)	DAP (N=210) n (%)	SOC (N=105) n (%)
Subjects in the Analysis	97	46	85	49	24	10
Microbiological Success	82 (84.5)	41 (89.1)	81 (95.3)	45 (91.8)	24 (100.0)	7 (70.0)
Percent Difference in Success Rate (95% CI)[a]	-4.6 (-16.1,6.9)		3.4 (-5.5,12.3)		30.0 (1.6,58.4)	
Microbiologic Failure	0	0	1 (1.18)	0	0	0
Microbiologic Non-Evaluable	15 (15.46)	5 (10.87)	3 (3.53)	4 (8.16)	0	3 (30.00)

PK results

An objective of this study was to evaluate the PK of DAP following the administration of single or multiple doses of DAP in subjects between the ages of 1-17 years. Since the dose and duration of infusion varied significantly in subjects of different age-groups, the effect of age on the Cmax was difficult to evaluate. In addition, not all subjects provided a plasma sample immediately at the end of infusion.

Based on the limited data available, the Cmax values were in the range seen previously in subjects dosed with 8 or 10 mg/kg dose. The mean apparent terminal t1/2 ranged between 3.8 and 5.3 hours in this study which is consistent with that seen previously. The corresponding clearance in subjects in the lower age group was also higher, which is consistent with previous observations. While the PK parameters of DAP in the older subjects (Age Group 1; 12-17 years) are similar to those seen in adults, these results show that the younger subjects appear to clear the drug faster, therefore requiring a higher dose to achieve plasma concentrations similar to older subjects and adults. However robust interpretation is difficult due to the small sample size.

Table 11-14: Summary of Pharmacokinetic Parameters (Mean and SD) for Daptomycin in Subjects Between the Ages of 1 to 17 Years

Parameter	Age Group 1 (12-17 Years) N=6	Age Group 2 (7-11 Years)[a] N=2	Age Group 3 (2-6 Years) N=7	Age Group 4 (1-<2 Years)[b] N=30
Dose (mg/kg)	5.0	7.0	9.0	10.0
Infusion Duration (hr)	0.5	0.5	1.0	1.0
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
AUC_{0-tau} (µg*hr/mL)	387 (81)	438, ND	439 (102)	466
AUC_{0-t} (µg*hr/mL)	318 (62.2)	314, 347	318 (68.6)	466
CL_{ss} (mL/kg/hr)	13.3 (2.9)	16.0, ND	21.4 (5.0)	21.5
V_{ss} (mL/kg)	98.1 (12.2)	104, ND	116 (19.9)	159

Safety data

Safety assessments consisted of all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and regular assessments of physical condition, vital signs, weight, and laboratory parameters. Safety analysis included all patients given at least 1 dose of the study drug.

The majority of reported AEs were mild to moderate in severity. Events deemed related to study drug were reported in 35 (14%) DAP-treated subjects and 22 (17%) SOC-treated subjects. Serious adverse events were reported in 6 (2%) DAP-treated subjects and 3 (2%) SOC-treated subjects. Overall, 3% and 5% of subjects in the DAP and SOC treatment arms discontinued treatment due to TEAEs. All TEAEs resulting in discontinuation were mild or moderate in severity.

Gastrointestinal disorders (12% of DAP-treated subjects and 11% of SOC-treated subjects), most frequently diarrhea (7% and 5%, respectively) and investigations (7% of DAP-treated subjects and 8% of SOC-treated subjects), most frequently increased blood creatine phosphokinase (6% and 5%, respectively), were the most common types of AEs, by system organ class, reported during the study with no notable differences across age groups.

Based on the known safety profile of DAP in adults, the use of SMQ of rhabdomyolysis and myopathy was examined as a surrogate of muscle toxicity. Such events were reported with similar incidence in DAP-treated and SOC-treated subjects (6% in each arm). Further, the incidence of clinically significant post-Baseline elevations in CPK (>500 U/L and 3 × Baseline level) was similar in the 2 treatment arms (2% in each).

No safety signals were apparent from the safety examination.

b. POPPK Study

Additionally, a study (CUBI-PCS-106) entitled “Population PK Modeling and Simulations to Support Optimal Dosing of Daptomycin in Pediatric Patients” was carried out. Population PK analysis was performed using nonlinear mixed effect models (NLME) and Monte-Carlo simulations. Results from four paediatric studies were utilised (DAP-PEDS-05-01, DAP-PEDS-09-01, DAP-PEDS-07-02 and DAP-PEDS-07-03) to update the previously constructed PK model (2-compartment full PK model) that included allometric scaling and maturation functions on apparent clearance and volume of distribution of daptomycin. The effects of continuous (weight, age, creatinine clearance (CRCL)) and categorical (age group, cSSSI, infection type, race) covariates on inter-individual variability in the PK parameters were evaluated.

Model evaluation was based on standard model diagnostics and goodness-of-fit criteria (e.g. log-likelihood difference) and by looking at pertinent graphical representations of goodness-of-fit (e.g. fitted and observed concentrations versus time, weighted residuals vs. time). This approach allowed a robust evaluation of the population PK parameters of daptomycin.

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,
- 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).

A total of 101 paediatric subjects with at least one measurable concentration of daptomycin were included in the population PK analysis. Mean age, weight and BMI values in the overall population were 4.93 years old, 23.8 kg and 18.0 kg/m2, respectively. Mean serum creatinine levels were lower in the younger paediatric subjects in Study DAP-PEDS-09-01 with a mean value of 0.262 mg/dL, as compared to 0.588 mg/dL in Study DAP-PEDS-05-01.

Table 2-10 CUBI-PCS-106: Subject numbers

	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
< 2 yrs	0	0	23	27	50 (49.5%)*
2 to 6 yrs	8	12	0	7	27 (26.7%)
7 to 11 yrs	8	0	0	2	10 (9.90%)
12 to 17 yrs	8	0	0	6	14 (13.9%)

Population PK parameters of daptomycin derived with the final model:

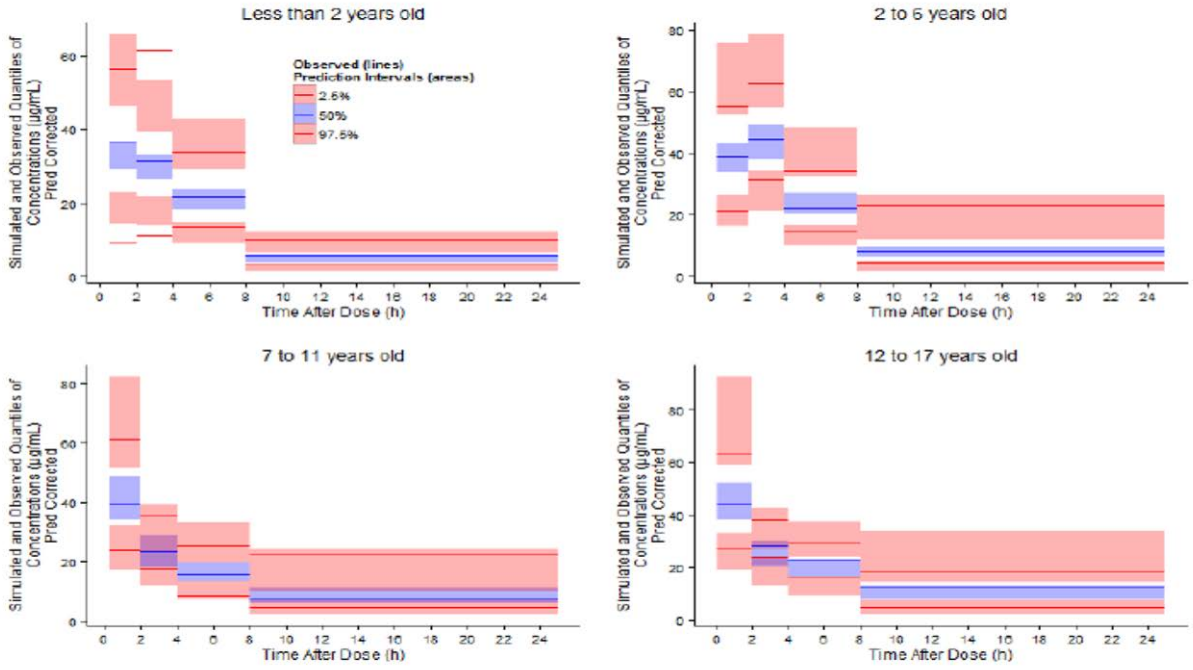
Table 8.4 Final Population PK Parameters of Daptomycin

PK Parameters	Final Model (Updated Data)
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 x CL
CLr (L/h)	$0.6 \times CL \times (PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$
CL2 (L/h)	$2.36 \times (WT/70)^{0.75}$
BSV Vc (%)	33.0
BSV V2 (%)	0 Fixed
BSV CL (%)	28.3
BSV CL2 (%)	0 Fixed
Error Prop (%)	15.3
Error Additive (µg/mL)	0.025

BSV: Between-subject variability; CL: Total systemic clearance; CL2: Peripheral clearance; CLnr: Non-renal clearance; CLr: Renal clearance; PMA: Post-menstrual age (week); Vc: Central volume of distribution; V2: Peripheral volume of distribution; WT: Body weight (kg). Note: the fractions of CLr and CLnr were fixed at 0.6 and 0.4 of total systemic clearance, respectively.
Shrinkage: BSV Vc= 11.0%; BSV CL= 7.0%. Correlation between BSV Vc and BSV CL: 0.725
Source data: Theta_ModelB1.csv and Omega_ModelB1.csv

The model was validated (Corrected-Prediction VPC):

Figure 8.5-2 Corrected-Prediction Visual Predictive Check – Final PK Model



PRED: Population predicted concentrations

The results indicated that the body weight based allometric scaling including the maturation function can well describe daptomycin PKs in paediatric patients under different age groups. Age based PK difference observed in studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01 and DAP-PEDS-07-03 can be well explained in the model using body weight adjustment and maturation function of age. Predicted clearance and volume of distribution were consistent with the observed data in 4 studies. There was no significant difference in PKs within the same age group across studies, different cSSSI types (Study DAP-PEDS-07-03), or between cSSSI and other infections represented by other 3 studies. There were no additional covariates identified to be significant.

The simulated daptomycin concentrations at various time points post infusion were co-plotted with the observed data. The median lines of observed daptomycin concentrations were generally within the 95% prediction interval of the predicted median over 24 hr after infusion of daptomycin across all age groups suggesting that the final model has a reasonably good predictive performance of a clinical trial conducted in paediatric patients from age 1 to 17 years old.

Simulation results

Using the final population PK model, area under the plasma concentration-time curve at steady state (AUCss) derived for subjects in Study DAP-PEDS-07-03 was simulated. The simulated individual AUCss values were ranged from 291 to 980 µg x hr/mL, with the age-grouped medians from 429 to 543 µg x hr/mL and the age-grouped means ranged from 434 to 543 µg x hr/mL, respectively, which was generally consistent with the observed data. Overall, there were > 84.6% of the individual AUCss values that fell into the target window (347 to 641 µg x hr/mL) that was confirmed efficacious in adult patients.

The simulations furthermore suggested that a loading dose would help to rapidly achieve the target attainment on Day 1. However, the clinical data without a loading dose demonstrated a clinical success rate of >97% in pediatric patients with cSSSI. In addition, a loading dose increases the probability of achieving exposure above the NOAEL in neonates/infants, and thus potentially increases the risk of these patients. Thus, a loading dose is not considered to be appropriate nor necessary in pediatric patients with cSSSI based on the totality of the preclinical and clinical data.

Therefore the applicant concluded that the dose regimens used in Study DAP-PEDS-07-03 (5 mg/kg, 7 mg/kg infused for 30 min and 9 mg/kg and 10 mg/kg infused for 60 min for age groups of 12 to 17, 7 to 11, 2 to 6 and 1 to < 2 years old, respectively) were appropriate, supported by the observed exposure values, simulated target attainment and the observed high clinical success rates.

2.2.1. Discussion on clinical aspects

The applicant has submitted a phase 4 clinical study in paediatric patients to determine the appropriate doses of daptomycin in different age groups. The safety and efficacy results from this study, along with results from previous study show that the doses used were appropriate for the age bands, with no new safety issues arising. The proposed doses are further supported by POPPK analysis.

Both safety and efficacy results are consistent with those from adult patients obtained in this and previous clinical trials and with data from the literature.

On the basis of the paediatric results of study DAP-PEDS-07-03, there is no change in the benefit-risk profile of Cubicin for the existing indications. The clinical safety and efficacy findings have led the MAH to propose changes to the Basic Prescribing information.

Appendix 1 to
DAP-PEDS-07-03--Cri

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The benefit/risk balance remains positive in the approved indications at present.

The data provided in this submission demonstrate the safety and efficacy of daptomycin in the paediatric population. Appropriate doses for the various age bands are also acceptable.

The PAM is considered to have been fulfilled.

Changes to the SPC in line with amendments to the Basic Prescribing Information will be acceptable. This will also result in changes to the PIL. Therefore it is considered that a type 2 variation is submitted to implement these changes, which will necessitate further assessment of the proposed wordings, primarily for the PIL.