22 October 2015
EMA/CHMP/654096/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cubicin

International non-proprietary name: DAPTOMYCIN

Procedure No. EMEA/H/C/000637/II/0053/G

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE adverse event

ALT alanine transaminase

AST aspartate transaminase

AUC area under the plasma concentration-time curve

AUCss area under the plasma concentration-time curve at steady state

AUC0-∞ area under the plasma concentration-time curve from 0 to infinity

AUC0-t area under the plasma concentration-time curve from 0 to the last sampling time point

AUC0-tau area under the plasma concentration-time curve during one dosing interval

CE clinically evaluable

CL systemic clearance

CL/wt total clearance of drug adjusted for body weight

CLss/wt total clearance of drug at steady-state adjusted for body weight

Cmax maximum plasma concentration

CPK creatine phosphokinase

CSR clinical study report

cSSSI complicated skin and skin structure infections

cSSTI complicated skin and soft-tissue infections

DAP daptomycin

DMC data monitoring committee

ECG electrocardiogram

EU-CORE European Cubicin Outcomes Registry and Experience

FPFV first patient first visit

IE infective endocarditis

ITT intent-to-treat

LPLV last patient last visit

ME microbiologically evaluable

MedDRA Medical Dictionary for Regulatory Activities

MIC minimal inhibitory concentration

MIC50 minimal inhibitory concentration to inhibit the growth of 50% of organisms

MIC90 minimal inhibitory concentration to inhibit the growth of 90% of organisms

MITT modified intent-to-treat

MRSA methicillin-resistant Staphylococcus aureus

MSSA methicillin-susceptible Staphylococcus aureus

ND not determined

PK pharmacokinetic

RIE right-sided infective endocarditis

SAB Staphylococcus aureus bacteraemia

SAE serious adverse event

SMQ Standardized MedDRA query

SOC standard of care

SOP standard operating procedure

t1/2 half-life

TEAE treatment-emergent adverse event

TESAE treatment-emergent serious adverse event

Tmax time of maximum concentration

TOC time-of-cure

uSSSI uncomplicated skin and skin structure infections

Vss volume of distribution at steady-state

Vss/wt volume of distribution at steady-state adjusted for body weight

WT body weight (kg)

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 3 July 2015 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None

Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI) to include paediatric patients from 1 to 17 years of age for Cubicin; as a consequence, sections 4.1, 4.2, 4.4, 5.2 and 6.6 of the SmPC are proposed to be amended. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 9.0 has been submitted.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Greg Markey Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	3 July 2015
Start of procedure:	25 July 2015
CHMP Rapporteur Assessment Report	18 September 2015
PRAC Rapporteur Assessment Report	25 September 2015
PRAC members comments	30 September 2015
Updated PRAC Rapporteur Assessment Report	6 October 2015
PRAC Outcome	8 October 2015
CHMP members comments	12 October 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 October 2015
Opinion	22 October 2015

2. Scientific discussion

2.1. Introduction

Daptomycin is a cyclic lipopeptide antibacterial derived from the fermentation of a strain of Streptomyces roseosporus. It has strong potency against major Gram-positive pathogens including those resistant to other antibiotics. In the EU/EEC, Cubicin is indicated for the treatment of the following infections in adults:

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

- RIE due to Staphylococcus aureus.

- SAB when associated with RIE or with cSSTI.

As part of the clinical development programme, the MAH has performed a number of post-authorisation studies (see below table), in the paediatric population to support the safety, efficacy and dosing recommendations.

Table 1-2 Overview of pediatric studies and their status

Study number	Study title	FPFV	LPLV
[DAP-PEDS-05-01]	An Evaluation of the Pharmacokinetics of a Single Dose of Daptomycin (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	25-Aug-2005	09-Aug-2006
[DAP-PEDS-07-02]	An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin (8 and 10 mg/kg) in Pediatric Patients Aged Two to Six Years who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection	03-Jun-2008	20-Nov-2008
[DAP-PEDS-09-01]	An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin (4 and 6 mg/kg) in Pediatric Patients Aged Three Months to Twenty-Four Months Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection	13-Jan -2010	20-Mar-2012
[DAP-PEDS-07-03]	An Evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Pediatric Subjects Aged Three months to Seventeen Years With Complicated Skin and Skin Structure Infections Caused by Gram-Positive Pathogens	03-Sep-2008	07-Oct-2013
[DAP-PEDBAC-11-02]	A Comparative Evaluation of the Safety and Efficacy of Daptomycin Versus Standard of Care in Pediatric Subjects Two - Seventeen Years of Age With Bacteremia Caused by *Staphylococcus aureus*	Dec-2012	ongoing
[DAP-PEDOST-11-03]	A Multicenter, Randomized, Double-Blinded Comparative Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Daptomycin Versus Active Comparator in Pediatric Subjects With Acute Hematogenous Osteomyelitis Due to Gram-Positive Organisms	Sep-2013	ongoing

FPFV = first patient first visit, LPLV = last patient last visit

The first four studies mentioned in the above table have all been reviewed previously by the CHMP, with the conclusion that the efficacy in the paediatric population was acceptable and there were no additional safety concerns to those already known.

Based on these studies the applicant amended their basic prescribing information to extend the indication "complicated skin and soft-tissue infections" (cSSTI) to include patients from 1 to 17 years of age. The CHMP commented that a type 2 variation would be required to extend the indication by making appropriate changes to the product literature. In response, this type 2 variation application has been submitted.

As all the studies have previously been assessed, truncated summaries about the relevant paediatric studies are provided in this report.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.3.2. Pharmacokinetics/ Pharmacodynamics

The PKs 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 iv infusion for 30 or 60 minutes, the area under the plasma concentration-time curve (AUC) of daptomycin was lower in paediatric patients than in adults. The total CL/weight (wt) ranged from 10.7 to 21.5 mL/hr/kg and the volume of distribution at steady-state adjusted for body weight (Vss/wt) ranged from 106.3 to 136.3 mL/kg and both parameters increased with decrease in age. The half-life (t1/2) of daptomycin was in the range of 3.8 to 7.8 hours, which was shorter than in adults (7 to 9 hours). The exposures were similar after a single dose and repeated doses indicating that daptomycin has time invariant PKs. No significant accumulation after repeated administration was observed. Similar to adults, renal excretion was the major elimination pathway in paediatric patients. The unbound fraction was around 10% across different age groups, which was similar to the adult population. The percentage of unchanged drug excreted in urine in 24 hours was around 60% across different age groups, which was similar to the adult population.

There was no apparent difference in PKs across different cSSSI-type (major abscess, complicated cellulitis, or others) patients or paediatric patients with suspected or diagnosed Gram-positive infection. There was no ethnicity difference on PKs observed in paediatric patients either. Studies in adult populations have demonstrated that because daptomycin is eliminated primarily by the kidney, an adjustment of Cubicin dosage interval (once every 48 hours) is recommended for patients with creatinine clearance < 30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis [Cubicin Package Insert]. These studies have not been repeated in children. Population PK analysis indicated that in addition to body weight, systemic clearance (CL), and volume distribution of daptomycin was associated with maturation function in pediatric patients. After iv infusion of 5 mg/kg (12 to 17 years), 7 mg/kg (7 to 11 years) for 30 min, and 9 mg/kg (2 to 6 years), and 10 mg/kg (1 to < 2 years) for 60 min, the mean AUC0-tau were 387, 438, 439, and 466 µg×hr/mL, respectively. Daptomycin exposure that was predicted and observed in children across the age groups was similar to that seen in adults based on these dose recommendations and within the range of the targeted area under the plasma concentration-time curve at steady state (AUCss) (347 to 641 µg×hr/mL) for the treatment of cSSSI.

2.3.3. PK/PD modelling

The population PK modeling and simulation report CUBI-PCS-106 ([Pharsight Consulting Services Report CUBI-PCS-106]) was submitted to EMA in March 2015 and assessed along with study DAP-PEDS-07-03.

The modelling report concurred 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. The optimal doses for attaining the targeted AUCss (347 to 641 µg x hr/mL) for the treatment of cSSSI were 5 mg/kg, 7 mg/kg infused for 30 min, and 9 mg/kg and 10 mg/kg infused for 60 minutes for age groups of 12 to 17, 7 to 11, 2 to 6, and 1 to < 2 years old, respectively.

2.3.4. Discussion on clinical pharmacology

While the exposure of daptomycin in adolescents 12 to 17 years of age are similar to those

seen in adults, it appears that younger patients (< 18 years old) clear the drug faster, therefore requiring a higher dose to achieve the target exposure levels (347 to 641 µg x hr/mL) that are both efficacious and safe to treat the infection as confirmed by the clinical outcomes from both the adult and paediatric patients with cSSSI.

Results from Study DAP-PEDS-07-03 indicate that compared with adults, children show progressively higher (weight-adjusted) daptomycin clearance and higher volume of distribution with decreasing age. Hence, higher doses will be required in children and will vary by age groups in order to produce exposures equivalent to that seen for efficacy in adults.

A PK modelling and simulation analysis CUBI-PCS-106 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.

2.3.5. Conclusions on clinical pharmacology

Higher doses will be required in children and will vary by age groups in order to produce exposures equivalent to that seen for efficacy in adults.

2.4. Clinical efficacy

2.4.1. Main studies (including dose-response studies)

***DAP-PEDS-05-01:* An Evaluation of the Pharmacokinetics of a Single Dose of Daptomycin (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**

This Phase 1, multicentre, single dose, open-label, non-comparative study was designed to assess the PK of daptomycin in paediatric patients between the ages of 2 and 17, inclusive. Patients with suspected or diagnosed Gram-positive infection were enrolled sequentially into 3 groups so that PK data were available for each age group as follows:

Age Group 1: 12 to 17 years old, inclusive;

Age Group 2: 7 to 11 years old, inclusive;

Age Group 3: 2 to 6 years old, inclusive.

The sequential enrolment of subjects into Groups 1, 2, and 3 occurred only after review of pertinent tolerability information, including AEs, serious adverse events (SAEs), and relevant laboratory parameters. The protocol originally required that 2 or more 2-year olds and 2 or more 3-year olds be enrolled; however, this stipulation was dropped as an appropriate number of 2- and 4-year olds had been enrolled in the study.

The primary objective of this study was to evaluate the single-dose PKs of intravenous (iv) daptomycin in paediatric patients in 3 age groups (2 to 6 years, 7 to 11 years, and 12 to 17 years), with proven or suspected Gram-positive infection, and who were receiving standard antibiotic therapy. The secondary objective was to describe the tolerability of a single dose of *iv* daptomycin in this group of patients.

An overview of daptomycin plasma PK parameters is provided below:

Table 3-5 DAP-PEDS-05-01: Summary of pharmacokinetics for daptomycin in patients between the ages of 2 to 17 years

Parameter	Age group 1 12 to 17 yr 4 mg/kg N = 8	Age group 2 7 to 11 yr 4 mg/kg N = 8	Age group 3 2 to 6 yr 4 mg/kg N = 8
	Mean (SD)	Mean (SD)	Mean (SD)
Infusion duration (hr)	0.5	0.5	0.5
$AUC_{0-\infty}$ (µg x hr/mL)	385 (69.7)	280 (139)	204 (66.2)
C_{max} (µg/mL)	50.6 (10.6)	45. 8 (10.8)	39.1 (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)	10.7 (2.23)	16.5 (5.66)	21.5 (7.21)
V_{ss}/wt (mL/kg)	106.3 (19.1)	110.9 (21.1)	136.3 (21.4)

Peak (Cmax) and total (AUC) exposures were lower in Age Groups 2 and 3 (7 to 11 and 2 to 6 years, respectively) compared to Age Group 1 (12 to 17 years old). Total clearance of drug adjusted for body weight (CL/wt) was lower in Age Group 1 compared with Age Groups 2 and 3, and elimination t1/2 was longer in Age Group 1 relative to the younger patient groups.

Consistent with high protein binding in serum, the mean values of volume of distribution at steady-state adjusted for body weight (Vss/wt) were < 140 mL/kg. Vss/wt was higher in the youngest age group compared with the older age groups.

In general, the PK profile of daptomycin in adolescents 12 to 17 years of age determined in this study was similar to that of healthy adults. However, in the younger age groups, drug exposure and elimination t1/2 were reduced compared with adolescents while body weight adjusted clearance was increased, which warranted further investigations. The PK results from [Study DAP-PEDS-05-01] and linear PKs of daptomycin suggest that AUC and Cmax from 8 to 10 mg/kg in children ages 2 to 6 years may produce exposure equivalent to that seen in adults at 4 mg/kg dose.

Consequently, Study DAP-PEDS-07-02 was performed using the 8 and 10 mg/kg doses.

***DAP-PEDS-07-02*: 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**

This Phase 1, multicentre, single dose, open-label, non-comparative study was designed to assess the PK and safety of daptomycin in paediatric subjects between the ages of 2 and 6 years, inclusive. Subjects with suspected or diagnosed Gram-positive infection were enrolled in 2 groups as follows:

Group 1: 8 mg/kg as a 1-hour infusion;

Group 2: 10 mg/kg as either a 1-hour or 2-hour infusion

The sequential enrolment of subjects into Groups 1 and 2 occurred only after review of safety and PK data from the previous group. 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 paediatric population, DAP-PEDS-05-01. No control group was required as the primary objective of this study was the assessment of PK.

An overview of daptomycin plasma PK parameters is provided below:

Table 3-7 DAP-PEDS-07-02: Summary of pharmacokinetics for daptomycin in patients between the ages of 2 to 6 years

Parameter	Group 1 2 to 6 yr 8 mg/kg N = 6	Group 2 2 to 6 yr 10 mg/kg N = 6
	Mean (SD)	Mean (SD)
Infusion duration (hr)	1.0	1.0
$AUC_{0-\infty}$ (µg x hr/mL)	429.1 (113)	549.7 (139)
C_{max} (µg/mL)	68.4 (9.33)	79.2 (10.2)
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)	19.5 (5.01)	19.1 (4.51)
V_{ss}/wt (mL/kg)	135.7 (8.69)	144.6 (28.3)

The concentrations of daptomycin increased rapidly following the start of the infusion to reach an average maximum concentration of 68.4 µg/mL following the 8 mg/kg dose and 79.2 µg/mL following the 10 mg/kg dose. The median time of maximum concentration (Tmax) occurred at about 1 hour, the end of the infusion at both doses. The elimination t1/2 of daptomycin remained unchanged between the 2 doses administered and was 5.4 and 5.7 hours, respectively, for the 8 and 10 mg/kg doses. Similarly, the CL of daptomycin did not appear to be significantly different between the 2 doses. The Cmax and AUC values were generally predictable across doses among 2 to 6 years old based on data from Study DAP-PEDS-05-01 and this study, indicating linear PKs. Overall, PK parameters were comparable with those obtained among 2 to 6 years old receiving a 4 mg/kg dose in Study DAP-PEDS-05-01.

Drug exposure (AUC) seen in adults at the 4 mg/kg dose was 494 µg x hr/mL at steady-state. Drug exposure seen in the present study was 429 and 550 µg x hr/mL, respectively, at the 8 and 10 mg/kg doses. This suggests that a dose of 9 mg/kg in 2 to 6 year old children may produce exposure equivalent to that seen in adults at 4 mg/kg dose.

Due to larger PK differences seen in children aged 2 to 6 years, further investigation of the PKs of daptomycin in younger children (3 to 24 months old) was considered necessary prior to expanded use in this paediatric population. Consequently, Study DAP-PEDS-09-01 was conducted.

***DAP-PEDS-09-01*: 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**

This study was multicentre, single dose, open-label, non-comparative, and designed to assess the PK and safety of daptomycin in paediatric subjects between the ages of 3 months to 24-months, inclusive. Subjects with suspected or diagnosed bacterial infection, including those receiving prophylactic antibiotics peri-operatively, were included in this study in 3 age groups:

- Age Group 1: 13 to 24 months, inclusive, dosed at 6 mg/kg as a 0.5-hour infusion;
- Age Group 2: 7 to 12 months, inclusive, dosed at 4 mg/kg as a 0.5-hour infusion;
- Age Group 3: 3 to 6 months, inclusive, dosed at 4 mg/kg as a 0.5-hour infusion.

Plasma PK sampling (0.5 mL/sample) for each age group occurred at 5 time points: end of infusion, 1 hour, 2 hours, 6 hours, and 12 hours after the start of infusion.

The primary objective of this study was to evaluate single dose PK data of iv daptomycin administered at 4 mg/kg or 6 mg/kg as a 0.5-hour infusion in paediatric subjects aged 3 to 24 months, inclusive, with

proven or suspected bacterial infection who were receiving standard antibiotic therapy, including subjects receiving prophylactic antibiotics peri-operatively. The secondary objective of this study was to describe the safety of a single dose of iv daptomycin in this subject population.

An overview of daptomycin plasma PK parameters is provided below:

Table 3-9 DAP-PEDS-09-01: Summary of pharmacokinetics for daptomycin in patients between the ages of 3 to 24 months

Parameter	Age group 1 13 to 24 months 6 mg/kg N = 5	Age group 2 7 to 12 months 4 mg/kg N = 7	Age group 3 3 to 6 months 4 mg/kg N = 7
	Mean (SD)	Mean (SD)	Mean (SD)
Infusion duration (hr)	0.5	0.5	0.5
$AUC_{0-\infty}$ (µg x hr/mL)	282 (44.5)	219 (66.8)	215 (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)	0.60 (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)	21.8 (2.99)	19.6 (5.76)	19.7 (5.46)
V_{ss}/wt (mL/kg)	122 (30.7)	135 (28.6)	128 (11.7)

Following the administration of daptomycin at 6 mg/kg to infants in Age Group 1 (13 to 24 months of age), the mean area under the concentration time curve from 0 to infinity (AUC0-∞) was 282 µg x hr/mL, which was markedly lower than a corresponding dose in adults. Mean CL of daptomycin was high at 21.8 mL/hr/kg which was approximately twice that of adults with normal renal function. Compared with adults, the mean volume of distribution at steady-state (Vss) was increased while mean t1/2 was reduced.

PK parameters following a 4 mg/kg dose infused to infants were similar in Age Group 2 and Age Group 3 (7 to 12 months and 3 to 6 months of age, respectively). Compared with adults and older children, the patients in this study ages 3 to 24 months had more rapid daptomycin clearance and shorter half-lives resulting in lower drug exposures (AUC), confirming that dosage adjustment is needed to ensure adequate exposure and satisfactory efficacy in infants.

***DAP-PEDS-07-03:* An evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Paediatric subjects aged one to seventeen years with Complicated Skin and Skin Structure Infections caused by Gram-positive Pathogens**

Methods

Multicentre, evaluator-blinded, randomized, comparative Phase 4 study. Safety, efficacy, and PKs of daptomycin were assessed in paediatric patients (1 to 17 years old, inclusive) with cSSSI caused by Gram-positive pathogens.

Treatments

Patients were enrolled in a stepwise approach into well-defined age groups and given age-dependent doses as follows, over a period of up to 14 days:

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.

The comparator agent for this study was the SOC deemed appropriate by the Investigator. The recommended SOC agents were iv vancomycin, iv clindamycin, and iv semi-synthetic penicillins (nafcillin, oxacillin, or cloxacillin). Patients were randomized 2:1 to daptomycin vs. comparator SOC.

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 paediatric 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.

The key efficacy endpoint was the sponsor-defined clinical outcome at time-of-cure (TOC), which was defined by a blinded medical director. The study was not powered for efficacy.

Outcomes/endpoints

Post-therapy ***clinical response*** was determined by comparing the subject's signs and symptoms at the EOT and TOC Visits to those recorded at Study Baseline as follows:

> **Cure:** Resolution of clinically significant signs and symptoms associated with the skin infection present at Study Baseline.
>
> **Improved:** Partial resolution of clinical signs and symptoms of the skin infection.
>
> **Failure:** Inadequate clinical response to therapy. NOTE: if it was determined that the primary site of infection required additional antibiotic treatment, the Assessment of Clinical Response had to be a "Failure."
>
> **Unable to Evaluate:** Unable to determine response because subject was lost to follow up

Microbiological Response at Test of Cure

It was acknowledged that DAP did not exert any significant activity against Gram-negative bacteria. Thus, any outcomes for Gram-negative bacteria were attributable to the concomitant use of aztreonam and/or metronidazole and not to study drug. Only Gram-positive bacteria should have been evaluated for Microbiological Response.

Pathogen-level microbiological response:
Utilizing data provided in the CRF, the sponsor assigned each Gram-positive pathogen isolated at Study Baseline to one of the microbiologic response categories, based on the TOC culture results, according to the following criteria:

Persisted: Presence of the Baseline Infecting Pathogen in any Primary site of infection or blood culture obtained Post-Therapy (EOT through TOC).

Presumed Persisted: Presumed presence of the Baseline Infecting Pathogen(s) when no post-therapy cultures were taken and the Investigator did not indicate that there was Nothing to Culture.

Eradicated: Absence of the Baseline Infecting Pathogen(s) in any Primary site of infection or blood culture obtained (eg, No Growth Result) in a Post-Therapy Culture (EOT through TOC) as demonstrated by an organism classification of Not Classified.

Presumed Eradicated: Presumed absence of the Baseline Infecting Pathogen(s) when no post therapy culture was taken and the Investigator indicated that there was Nothing to Culture.

Non-evaluable: These subjects were missing the TOC evaluation.

Not applicable: Organism classification is non-study Baseline infecting pathogen

Subject-level microbiological response:
Each subject's skin infection due to one or more Gram-positive pathogens was assigned a microbiological response. The post-therapy microbiological response for infection was based on these criteria:

Microbiologic Success: All Baseline Infecting pathogens were Eradicated or Presumed Eradicated and no Superinfecting pathogen(s) (Gram-positive) were isolated post therapy.

Microbiologic Failure: Presence of a Persisting Pathogen or a Superinfecting pathogen (Gram-positive) post therapy (EOT through TOC).

Microbiologic Non-evaluable: All Baseline Infecting Pathogens had a Pathogen-level Microbiological Response of Non-Evaluable.

For each Gram-positive pathogen and each infection, "eradicated" or "presumed eradicated" was considered as a satisfactory microbiologic response. "Persisted," "presumed persisted," or a positive culture for a Superinfecting Pathogen (Gram-positive) at EOT through TOC was considered as an unsatisfactory microbiologic response.

Randomisation

Multicentre, evaluator-blinded, randomized, comparative study. Treatment assignment was based on a centralized computer-generated randomization schedule, stratified by age group, designed to achieve a 2:1 ratio of subjects receiving DAP or comparator, respectively. Prior to randomization, the Investigator had to choose which comparator agent the subject would receive if randomized to SOC.

Blinding (masking)

This was an evaluator-blinded study. A site blinding plan was developed at each site detailing exactly how the blind was maintained throughout the study.

Statistical methods

Efficacy populations: Efficacy was analyzed by the randomized treatment group (Daptomycin or SOC) by age group in four efficacy populations

Intent-to-Treat (ITT) – all randomized subjects who received any dose of the study drug;

Modified Intent-to-Treat (MITT) – subjects in the ITT population who have a Grampositive pathogen cultured at Baseline;

Clinically Evaluable (CE) – subpopulation of the ITT subjects who meet the following:

Met the clinical criteria for the study infection (confirmed cSSSI);

- Received the correct study drug, as randomized, at the correct dose;
- Received ≥3 days of study medication (IV and oral combined) or < 3 days of study medication and evaluated as "failure";
- Had the necessary clinical evaluations performed at TOC and were not evaluated as "Unable to Evaluate";
- Did not receive potentially non-study antibiotics; and
- Did not have a curative surgical procedure to remove the primary site of infection.

Microbiologically Evaluable (ME) – CE subjects who had a Gram-positive pathogen cultured at Baseline.

Results

Participant flow

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)

Conduct of the study

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.

Baseline data

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

Outcomes and estimation

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% in the 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)

Overall therapeutic response, which combined both sponsor-defined clinical outcome and the microbiological response, was evaluated in the ME population. Overall therapeutic response was similar in the daptomycin and SOC treatment arms with success rates of 97% and 99%, respectively (-1.7% difference). Success rates between daptomycin and SOC-treated patients were generally similar across age groups.

<u>EU-CORE:</u> European CUBICIN Outcomes Registry and Experience for the Treatment of Serious Gram positive Infections

EU-CORE was a multicentre, retrospective, non-interventional registry designed to collect outcome data on patients who had received at least 1 dose of daptomycin for the treatment of a serious Gram-positive bacterial infection.

No dose selection was applicable due to retrospective and non-interventional data collection. The main objective of this study was to characterize the actual use of daptomycin in a large number of patients in a non-controlled, real-world setting. Data were collected retrospectively from patient files at investigators' centres.

This registry study included 6075 patients in 18 countries at 314 sites. Of the 6075 patients, a total of 81 paediatric patients were treated with daptomycin. Forty-nine (60.5%) paediatric patients completed daptomycin therapy, 27 (33.3%) switched to another antibiotic, and 4 (4.9%) discontinued daptomycin therapy due to AEs. The majority of the paediatric patients were male (65.4%) and Caucasian (92.5%). Median age was 13 years (0 to < 1 years, 2 (2.5%) patients; 1 to < 2 years, 3 (3.7%) patients; 2 to < 7 years, 10 (12.3%) patients; 7 to < 12 years, 20 (24.7%) patients; and 12 to < 18 years, 46 (56.8%) patients. Median body weight was 46.5 kg.

The most common primary infection among the paediatric patients was bacteraemia, which was reported in 16 patients (19.8%), followed by cSSSI (15 patients, 18.5%), osteomyelitis non-prosthetic and prosthetic device-related (11 patients, 13.6%), IE (10 patients, 12.3%) and foreign body/prosthetic infection (10 patients, 12.3%). The overall clinical success rate in paediatric patients was 100% for bacteraemia, IE, osteomyelitis non-prosthetic and prosthetic device-related, and uncomplicated skin and skin structure infection (uSSSI); and 73.3% for cSSSI. Clinical success rates among the paediatric patients were high for both first-line and second-line treatment (93.3% and 92.0%, respectively). Clinical outcome by indication and dosing group for paediatric patients was difficult to interpret due to small numbers.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy *[and safety]* for trial DAP-PEDS-07-03

Title: An evaluation of the safety, efficacy and pharmacokinetics of daptomycin in paediatric subjects aged one to seventeen years with complicated skin and skin structure infections caused by gram-positive pathogens.	
Study identifier	DAP-PEDS-07-03

Design	This was a multi-centre, evaluator-blinded, randomised, comparative study originally designed to assess the safety, efficacy, and PK of DAP in paediatric 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 as outlined below, over a period of up to 14 days. Enrolment into each age group followed a step-wise approach. Subjects were first enrolled into Age Groups 1 and 2 (7 years of age and older), followed by subjects 1-6 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 enrolment into younger age groups. Prior to opening enrolment to include children 3 months to <1 year of age a Data Monitoring Committee (DMC) reviewed newly available nonclinical data and recommended that due to the benefit/risk ratio, the lower limit of enrolment for this study be 1 year of age. The DMC's recommendation to stop the trial prior to enrolment of the youngest age group was submitted to and agreed upon with the US Food and Drug Administration (FDA). No subjects were enrolled in Age Group 5 (3 months - < 1 year). A total of 396 children were randomised and stratified by age group, to receive either daptomycin (DAP) or standard of care (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 improvement and the pathogen was susceptible to an oral agent. The choice of oral therapy was left to the discretion of the Investigator. A sufficient number of subjects were randomized to ensure that a minimum of 50 subjects each in Age Groups 1, 2, and 3 and 30 subjects in Age Group 4 received DAP. In Age Groups 1, 2, and 3, PK sampling was done only for subjects assigned to DAP who volunteered at the time of Informed Consent, with a goal of at least 12 subjects in each age group (Age Groups 1, 2 and 3). This sample size per age group, in addition to previously obtained data in paediatric subjects, should have been adequate for population PK analysis. Subjects who volunteered for PK sampling had a 0.5 mL blood sample collected for PK analysis 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 hr, and 8 hr. If enrolment in Age Group 3 was completed without collection of adequate PK data, the cohort remained open for subjects consenting to PK sampling only. In Age Group 4, sparse PK sampling was done for all subjects assigned to DAP who consented to participate in the study. Subjects randomized to DAP had a 0.5 mL blood sample collected for PK analysis at 2 of 5 time points relative to the end of the infusion • Age Group 4 (1–<2 years old): Day 1, 2, or 3: 0 hr (EOI), 1, 2, 4, and 6 hr relative to end of infusion. Time points were randomly assigned for each subject. A randomization schema ensured an equal distribution of blood samples at each of the 5 time points. A population PK approach was used for Group 4. The windows for the sample time points were as follows: EOI (<10 minutes), 1 hour (+15 minutes), 2 hours (+15 minutes), 4 hours (+20 minutes), and 6 hours (+30 minutes).

	Duration of main phase:	Up to 14 days
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Comparative	
Treatments groups	Age Group 1: age 12–17 years old (inclusive)	DAP dosed at 5 mg/kg or SOC up to 14 days Randomized: 75(DAP) 38 (SOC)
	Age Group 2: age 7–11 years old (inclusive)	DAP dosed at 7 mg/kg or SOC up to 14 days Randomized: 75(DAP) 38 (SOC)
	Age Group 3: age 2–6 years old (inclusive)	DAP dosed at 9 mg/kg or SOC up to 14 days Randomized: 83 (DAP) 42(SOC)
	Age Group 4: age 1–<2 years old	DAP dosed at 10 mg/kg or SOC up to 14 days Randomized: 30 (DAP) 15 (SOC)
Endpoints and definitions	Primary Objective	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 paediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.
	Secondary Objective	To assess the **efficacy** of age-dependent doses of IV DAP administration for up to 14 days in comparison with SOC therapy in paediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.
	Secondary Objective	To evaluate the **population PK** of age-dependent doses of IV DAP administered for up to 14 days in paediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.
Database lock:	17Jan2014	

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	- **Efficacy populations:** Efficacy was analyzed by the randomized treatment group (DAP or SOC) by age group in four efficacy populations - I**ntent-to-Treat (ITT)** – all randomized subjects who received any dose of the study drug; - **Modified Intent-to-Treat (MITT)** – subjects in the ITT population who have a Gram positive pathogen cultured at Baseline; - **Clinically Evaluable (CE)** – subpopulation of the ITT subjects who meet the following criteria: • Met the clinical criteria for the study infection (confirmed cSSSI); • Received the correct study drug, as randomized, at the correct dose; • Received ≥3 days of study medication (IV and oral combined) or < 3 days of study medication and evaluated as "failure"; • Had the necessary clinical evaluations performed at TOC and were not evaluated as "Unable to Evaluate"; • Did not receive potentially non-study antibiotics; and • Did not have a curative surgical procedure to remove the primary site of infection. - **Microbiologically Evaluable (ME)** – CE subjects who had a Gram- positive pathogen cultured at Baseline. - **Safety Population:** The Safety population included all subjects who received any dose of study medication and for whom at least 1 post-dose safety evaluation had been completed. Subjects were analyzed according to actual treatment received and age group. - **Pharmacokinetic Population:** The PK population included subjects who had at least one PK sample drawn. Subjects who volunteered for PK sampling had a 0.5 mL blood sample collected for PK analysis (see details under *design*, on time points of sample collection)

Descriptive statistics and estimate variability	Treatment group	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
	Randomized	113	113	125	45
	IIT population*	110	111	123	45
	Dap-treated	*73*	*73*	*81*	*30*
	SOC-treated	*37*	*38*	*42*	*15*
	PK population	6	2	7	30
	3. Source: [Study DAP-PEDS-07-03-Table 11-1] * Intent-to-treat population includes those patients who received at least one dose of study medication.				

Effect estimate per comparison	Primary endpoint (Safety)	**System organ class**	**DAP (N=256)**	**SOC (N=133)**
		Preferred term	**n (%)**	**n (%)**
		Patients with at least one drug related TEAE	***98 (38.3)***	***48 (36.1)***
		Gastrointestinal disorders	30 (11.7)	14 (10.5)
		Skin and subcutaneous tissue disorders	23 (9.0)	12 (9.0)
		Infections and Infestations	14 (5.5)	15 (11.3)
		General disorders and administration site conditions	20 (7.8)	8 (6.0)
		Investigations	19 (7.4)	11 (8.3)
		Respiratory thoracic and mediastinal disorders	12 (4.7)	5 (3.8)
		Nervous system disorders	9 (3.5)	4 (3.0)
		Injury, poisoning and procedural complications	8 (3.1)	3 (2.3)
		Metabolism and nutrition disorders	4 (1.6)	3 (2.3)
		Musculoskeletal and connective tissue disorders	6 (2.3)	1 (0.8)
		Reproductive system and breast disorders	3 (1.2)	0
Notes	Source: [Study DAP-PEDS-07-03-Table 12-3]			

	Secondary Endpoint (Efficacy): Summary of blinded evaluator's assessment of clinical response at test-of-cure		**Patients**		**Clinical success**		
			DAP	**SOC**	**DAP**	**SOC**	**% Diff. in success rate (95% CI)**
		Intent-to-Treat	257	132	91%	87%	4.0 (-2.7,10.7)
		Modified Intent-to-Treat	210	105	91%	87%	4.2 (-3.3,11.8)
		Clinically Evaluable	207	99	100%	100%	-0.5 (-1.4,0.5)
		Microbiologically Evaluable	167	78	99%	100%	-0.6 (-1.8,0.6)
Notes	Source: [Study DAP-PEDS-07-03-Table 11-6] and [Study DAP-PEDS-07-03-Table 11-7]						

Pharmacokinetics	Secondary endpoint:	Parameter	Age group 1	Age group 2	Age group 3	Age group 4
			12 to 17 yr	7 to 11 yr	2 to 6 yr	1 to <2 yr

	Summary of pharmacokinetics for daptomycin in patients between the ages of 1 to 17 years		5 mg/kg	7 mg/kg	9 mg/kg	10 mg/kg
			N=6	N=2	N=7	N=30
			Mean (SD)	Ind. Values[a]	Mean (SD)	Mean[b]
		Infusion duration (hr)	0.5	0.5	1.0	1.0
		AUC_{0-tau} (µg x hr/mL)	387 (81)	438, ND	439 (102)	466
		AUC_{0-t} (µg x hr/mL)	318 (62.2)	314, 347	318 (68.6)	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
Notes:	4. Source: Source: [Study DAP-PEDS-07-03-Table 11-14] 5. ND: Not determined 6. [a.] The numbers provided here indicate individual values (two patients provided plasma samples that were used to determine PK). **7.** [b.] Due to limited PK samples, PK parameters were computed using the mean concentration-time profile during a sampling interval.					

7.1.1. Discussion on clinical efficacy

The MAH has submitted a phase 4 clinical study in paediatric patients to determine the appropriate doses of daptomycin in different age groups. 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 < 2 years, respectively, was effective in the treatment of cSSTI caused by Gram-positive pathogens:

- Clinical success rates for daptomycin (88.3%) and SOC (86.4%) were comparable.

- Consistent results were noted in all analysis populations, including MITT, CE, and ME, indicating the robustness of the results in the primary analysis population.

- Based on excellent clinical and microbiological success rates, the overall therapeutic success rate also was high and similar in the DAP (97.0%) and SOC (98.7%) treatment arms.

Regarding the retrospective, non-interventional registry (EUCORE), inferential analyses were not conducted and no formal statistical methodology other than simple descriptive statistics was used. All analyses are considered to be exploratory. The overall clinical success rate in pediatric patients was 100% for bacteremia, IE, osteomyelitis non-prosthetic and prosthetic device-related, and uSSSI, and 73.3% for cSSTI. Clinical success rates were high for both the first-line and second-line treatment (93.3% and 92.0%, respectively). Clinical outcome by indication and dosing group for paediatric patients was difficult to interpret due to small numbers.

7.1.2. Conclusions on the clinical efficacy

A well-characterized, efficacious, dosing regimen for paediatric patients with cSSTIs has been established.

7.2. Clinical safety

Introduction

The safety profile of daptomycin in the currently approved indications (in adults) is summarised hereafter:

In clinical studies, 2,011 subjects received Cubicin. Within these trials, 1,221 subjects received a daily dose of 4 mg/kg, of whom 1,108 were patients and 113 were healthy volunteers; 460 subjects received a daily dose of 6 mg/kg, of whom 304 were patients and 156 were healthy volunteers. Adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported at similar frequencies for Cubicin and comparator regimens.

The most frequently reported adverse reactions (frequency common (≥ 1/100 to < 1/10)) are: Fungal infections, urinary tract infection, candida infection, anaemia, anxiety, insomnia, dizziness, headache, hypertension, hypotension, gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension, liver function tests abnormal (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP)), rash, pruritus, limb pain, serum creatine phosphokinase (CPK) increased, infusion site reactions, pyrexia, asthenia.

Less frequently reported, but more serious, adverse reactions include hypersensitivity reactions, eosinophilic pneumonia, drug rash with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

Safety in paediatric populations

DAP-PEDS-05-01:

Daptomycin administered as a single *i.v.* dose of 4 mg/kg was safe and well-tolerated in children aged 2 to 17 years. No serious adverse events were reported and none of the patients discontinued the study due to adverse events. There was no clinically meaningful difference in the adverse event reporting rates or profile of adverse events across the different age groups. A total of 6 (24%) of the 25 patients reported at least one adverse event, including 2 patients in each age group. All reported events were mild in severity; no events of moderate or severe intensity were reported. The most commonly reported types of events were gastrointestinal in nature and included diarrhea in 2 (8%) of the 25 patients and nausea, upper abdominal pain and tongue disorder in one (4%) patient each. Other events reported in one (4%) patient each were infusion site reaction, injection site reaction and headache. Only one event, infusion site reaction (infiltration of the i.v. catheter) was assessed as drug-related by the Investigators.

There was no difference in the incidence of adverse events between age groups with 2 subjects in each group experiencing adverse events. The incidence of gastrointestinal events was also similar with one patient each reporting events in Groups 1 and 2 and 2 patients reporting events in Group 3. No other event was seen to be more common in any age group. No safety issues were noted from review of clinical laboratory tests, vital signs or ECG evaluations. None of the patients had a clinically significant elevation in CPK and no adverse events related to the musculoskeletal or peripheral nervous systems were reported.

DAP-PEDS-07-02:

Daptomycin administered as a single *i.v.* dose of 8 or 10 mg/kg was safe and well-tolerated in paediatric subjects aged 2 to 6 years. One SAE of moderate groin abscess was reported by 1 subject in Group 2 who was receiving treated with standard antibiotic therapy for cellulitis of the groin. This event was assessed as unrelated to study treatment. Overall, a total of 6 (50%) of the 12 subjects experienced at least one AE during the study, including 2 subjects in Group 1 and 4 subjects in Group 2. Most reported events were mild in severity. The most commonly reported event was tonsillar hypertrophy in 2 subjects. All

other events were reported in 1 subject each. The adverse events noted were, for the most part, typical of a young patient population being treated for infection.

There were no treatment-emergent clinically relevant changes observed in clinical laboratory, vital signs, or ECG findings.

DAP-PEDS-09-01:

The most frequently reported TEAEs were increased blood CPK (3 subjects, 13%) and constipation, teething, and pyrexia (2 subjects each, 8%). All other TEAEs were reported in 1 subject each overall. One (4%) subject experienced a TEAE, pyrexia that was assessed as both severe and serious due to hospitalization. Three (13%) of the 24 subjects experienced 5 TEAEs that were assessed as possibly related to study drug and included increased blood CPK, increased ALT, increased AST in 1 subject, increased blood CPK in 1 subject, and rash in 1 subject; all 3 subjects were in Age Group 2. No subjects discontinued from study medication due to a TEAE.

DAP-PEDS-07-03:

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 (refer also to Table 1: summary for trial DAP-PEDS-07-03).

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.

EU-CORE:

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.

Six (7.4%) out of 81 paediatric patients reported adverse events (rash (2), tachycardia (1), anaphylactic reaction (1), hypersensitivity (1), increased blood creatine phosphokinase (1), osteosarcoma (1), acute renal failure (1), dyspnoea (1), and pulmonary haemorrhage (1). Four patients had an increase in CPK levels but none of these patients reported myopathy related AEs. Three patients had SAEs that led to permanent discontinuation of study drug (anaphylactic reaction, pulmonary haemorrhage and death, acute renal failure). One patient died but the death was considered not related to daptomycin.

7.2.1. Discussion on clinical safety

Most AEs in all of the above mentioned studies were characterized as mild or moderate in intensity and were not attributed to daptomycin by either the sponsor or investigator. Overall, the most frequently reported AEs were in the following system organ classes: gastrointestinal disorders, investigations and skin and subcutaneous tissue disorders. Elevated CPK was reported as an AE more frequently in patients treated with daptomycin than in patients receiving placebo or comparator antibiotics.

7.2.2. Conclusions on clinical safety

No new adverse events of concern were identified and the safety data from obtained in paediatric patients were consistent with the known safety profile of daptomycin.

7.2.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

7.3. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 9.1 with the following content:

Safety concerns

Important identified risks	Severe skeletal muscle toxicity Reduced susceptibility to daptomycin in *S. aureus* Peripheral neuropathy Severe hypersensitivity reactions (including pulmonary eosinophilia) Eosinophilic pneumonia
Important potential risks	Bone marrow toxicity Severe hepatotoxicity Dysregulation of *in vivo* coagulation
Missing information	Patients with underlying renal impairment Patients with hepatic impairment Pregnant or lactating women

Pharmacovigilance plan

There are no additional pharmacovigilance activities for Cubicin.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Severe skeletal muscle toxicity	Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Relevant preferred terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	Daptomycin dosage card physicians
Reduced susceptibility to daptomycin in S. aureus	Section 4.4 Special warnings and precautions for use Section 5.1 PD properties: "Mechanisms of resistance.	Package leaflet for laboratories
Peripheral neuropathy	Sections 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects of the SmPC.	None planned
Severe hypersensitivity reactions (including pulmonary eosinophilia)	Sections 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects.	None planned
Eosinophilic pneumonia	Section 4.8 Undesirable effects: SOC Respiratory system disorders: Eosinophilic pneumonia Section 4.4 Special warnings and precautions for use	None planned
Important potential risks		
Bone marrow toxicity	Routine pharmacovigilance activities including close monitoring in the PSUR.	None planned
Severe hepatotoxicity	Routine pharmacovigilance activities including close monitoring in the PSUR.	None planned
Dysregulation of in vivo coagulation	Routine pharmacovigilance activities including close monitoring in the PSUR.	Daptomycin dosage card
Missing information		
Patients with underlying renal impairment	Section 4.2: Posology and method of administration Section 4.4 Special warnings and precautions for use. Section 5.2 Pharmacokinetic properties	None planned
Patients with hepatic impairment	Section 4.2: Posology and method of administration Section 5.2 Pharmacokinetic properties	None planned
Pregnant or lactating women	Section 4.6 Pregnancy, fertility and lactation	None planned

7.4. Update of the Product information

During the procedure it was requested by CHMP that the proposed text for section 5.2, related to efficacy and safety, be placed into SmPC section 5.1 instead and the number of patients included per age group specified. Pertinent pharmacokinetic data should be added to SmPC section 5.2.

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Detailed changes are highlighted in Annex 1.

7.4.1. User consultation

Not applicable.

8. Benefit-Risk Balance

Benefits

Beneficial effects

Daptomycin has been used widely in adult patients with a favorable benefit-risk profile as well as a well-known efficacy and safety profile. Daptomycin has now been studied in the paediatric population, and a well characterized dosing regimen for treating children with cSSTIs has been established providing clinicians an alternative to other available treatments in an easily administered (once daily) iv infusion. Daptomycin has also been shown to have activity against MRSA, an emerging major health problem worldwide. Because few antibiotics to treat MRSA have been evaluated in children, a need exists for alternative treatment options with demonstrated and well characterized safety and efficacy in the paediatric population.

Uncertainty in the knowledge about the beneficial effects

Daptomycin has been used in the paediatric population off-label till now. With this variation Daptomycin has been shown to be safe and effective in children for the treatment of cSSTIs. However other indications approved for adults (RIE and SAB) have still not got sufficient data in the paediatric population.

Risks

Unfavourable effects

Risks that are known to occur in adult patients could also occur in paediatric patients; however, they may occur with different frequency or severity. In studies conducted to date, daptomycin has been shown to be safe at the doses being proposed for treatment of cSSTI. In the studies used to support this submission, limited data are available from long-term exposure. Many patients had only a single iv dose or a short treatment duration ($\leqslant$ 7 days) such as in Study DAP-PEDS-07-03 for which the median duration of treatment was 3 days for both DAP-treated subjects and SOC-treated subjects. The PopPK study confirmed that target daptomycin levels were achieved in the target population; however, this will need to be confirmed by additional clinical observations in other types of paediatric infections.

Uncertainty in the knowledge about the unfavourable effects

No unexpected adverse effects were observed in the clinical studies in the paediatric population. However further information will only be obtained when an increased number of subjects receive daptomycin in normal clinical practice.

Benefit-Risk Balance

Discussion on the Benefit-Risk Balance

A well-characterized, efficacious, dosing regimen for paediatric patients with cSSTIs has been established. In studies conducted to date, daptomycin has been shown to be safe at the doses being proposed for treatment of cSSTI. The overall benefit-risk balance of daptomycin in the target paediatric population is deemed as favourable.

9. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None

Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.2 and 6.6 of the Cubicin SmPC are amended. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 9.1 has been agreed.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

10. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.2 and 6.6 of the Cubicin SmPC are amended. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 9.1 has been agreed.

Summary

As part of the clinical development programme, the Market Authorisation holder (MAH) has performed a number of post-authorisation studies in the paediatric population to support the safety, efficacy and dosing recommendations. Results from single dose, pharmacokinetic/safety studies paediatric subgroups, together with results obtained in DAP-PEDS-07-03 (a phase IV, multicentre, randomised, investigator blinded trial in 389 paediatric patients; age range: 1 to 17 years old), established that higher doses are required in children (varying according to age groups), in order to produce exposures equivalent to that seen for efficacy in adults. These trials led to the selection of a well-characterised, efficacious, dosing regimen for paediatric patients with cSSTIs. Moreover, from these studies, as well as from data obtained in 81 paediatric patients included in a retrospective registry (with daptomycin for the treatment of a

serious Gram-positive bacterial infection), no new adverse events of concern were identified and the safety data from these paediatric patients were consistent with the known safety profile of daptomycin.

The overall benefit-risk balance of daptomycin for the treatment of cSSTI in the paediatric population (1-17 years of age) is favourable.

For more information please refer to the scientific discussion Cubicin H-C-637-II-53-G.