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Human Medicines Evaluation 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/P46/033

Note

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

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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 to provide information from a recently completed phase IV safety, efficacy and pharmacokinetic (PK) study (Study DAP-PEDS-11-02) involving paediatric patients (aged 1 to 17 years old) with *Staphylococcus aureus* bacteraemia (SAB) sponsored by Cubist Pharmaceuticals, LLC, a subsidiary of Merck & Co., Inc.

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:
- Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*.
- Adult patients with *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

Cubicin is indicated in children between 1 and 17 years of age with complicated skin and soft-tissue infections and the posology is based on age bands. The safety and efficacy of Cubicin in children and adolescents aged below 18 years has not been established for other indications.

1. Scientific discussion

1.1. Clinical aspects

Study Design

Study DAP-PEDS-11-02 [P005] was a Phase 4, open label (Evaluator-blinded), comparative, multi-centre, multi-national study was designed to describe the safety and efficacy of intravenous (IV) daptomycin versus standard of care (SOC) comparator in paediatric subjects aged 1 to 17 years with SAB.

The primary objective of this study was to assess the safety of IV daptomycin versus SOC comparator antibiotics (hereafter referred to as comparator) in paediatric subjects aged 1 to 17 years of age with SAB.

Key secondary objectives included comparing the efficacy of IV daptomycin versus the comparator for bacteraemia caused by *S. aureus* and determining exposure by measuring plasma levels of daptomycin at pre-dose (Ctrough) and end of infusion (Cmax) to explore exposure-response safety analyses in the target population.

The study was conducted initially in paediatric patients between the ages of > 4 and 17 years. Following review of safety data by an independent Data Monitoring Committee, the protocol was sequentially amended to allow enrolment of paediatric subjects down to 1 year of age.

Study Dates

06 March 2013 (FSFV) to 20 January 2016 (LPLV), with 65 sites eligible to enrol world-wide.

Inclusion/ Exclusion criteria

Subjects were enrolled and study medication began based on a diagnosis of proven or probable SAB. Proven infections were considered those with *S. aureus* identified from at least one blood culture bottle by conventional culture methods or by a rapid diagnostic test within 3 days prior to the first dose of study drug. Probable infections were those with a preliminary blood culture result demonstrating Gram-positive cocci in clusters upon Gram stain, suggestive of a staphylococcal infection. If the final blood culture yielded only coagulase negative Staphylococci (CoNS) after the subject was enrolled, only high risk subjects with persistent bacteraemia documented by multiple cultures taken on separate days or from separate sites yielding the same organism could continue on study therapy. Subjects at high risk included, but were not limited to, immunocompromised children, cancer patients, or those with a potential source of infection from devices or IV catheters that were not intended to be removed. In such cases the Sponsor-designated Medical Monitor was contacted to continue treatment.

Subjects were excluded if they had previous systemic antimicrobial therapy effective against *S. aureus* exceeding 72 hours in duration administered anytime during the 96 hours prior to the first dose of study drug; with the exception: Subject was eligible if culture data demonstrated in vitro resistance to prior IV antibiotic.

In this study, subjects were enrolled into three age groups and treated with daptomycin or comparator, based on a 2:1 randomization, which was stratified by age group. The study was designed to enrol ~75 paediatric subjects, including ~50 assigned to the daptomycin arm and ~25 assigned to the comparator arm. Subjects between the ages of 1 and 17 years were to be randomized and stratified by age group, to receive either daptomycin or comparator (suggested as IV vancomycin, IV clindamycin, IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin], or IV first-generation cephalosporins) in a ratio of 2:1, respectively, according to the 3 age groups. Switch to oral therapy was discouraged, but was acceptable, if allowed by study site's practice standard.

Study population

A total of 82 paediatric patients were included, 55 paediatric subjects randomized to receive daptomycin and 27 randomized to receive SOC.

Population	Total		1 to 6 year-olds		7 to 11 year-olds		12 to 17 year-olds	
Population	DAP	COM	DAP 12 mg/kg	COM	DAP 9 mg/kg	COM	DAP 7 mg/kg	COM
Randomized, n	55	27	22	11	19	9	14	7
Safety	55	26	22	10	19	9	14	7
MITT	52	24	20	9	18	9	14	6
mMITT	51	22	20	8	17	9	14	5
CE	40	12	18	6	14	3	8	3

The subjects received the following amounts of daptomycin:

Group	Ages	Daptomycin
1	12 to 17 years old	7 mg/kg once daily infused over 30 ± 3 minutes
2	7 to 11 years old	9 mg/kg once daily infused over 30 ± 3 minutes
3	1 to 6 years old	12 mg/kg once daily infused over 60 ± 6 minutes

The analysis populations were as follows:

Safety Population: The Safety population included all subjects who received any dose of IV study medication (daptomycin or comparator).

Intent-to-Treat (ITT) Population: The ITT population included all randomized subjects including those who were not exposed to any test product, and were analysed based on the treatment to which they were randomized.

Modified Intent-to-Treat (MITT) Population: The MITT population included all randomized and treated subjects with at least one dose of study drug who met the clinical criteria for the study infection at Baseline (positive blood culture for *S. aureus* or CoNS in high risk patients or probable bacteraemia [Gram-positive cocci on Gram stain at Baseline]).

Microbiological Modified Intent-to-Treat (mMITT) Population: The mMITT population included all MITT subjects who had proven *S. aureus* bacteraemia at Baseline.

Clinically Evaluable (CE) Population: The CE population was a subpopulation of the mMITT including subjects who met specific criteria related to the required assessments:

o Received the correct drug, as randomized

o Received appropriate duration of treatment (minimum and maximum treatment durations are outlined in the Clinical Evaluability Review Plan)

o Had the necessary clinical and microbiological efficacy evaluations performed at the TOC/Safety Visit and were not evaluated as “non-evaluable”

o Did not receive effective systemic confounding antibiotics at Baseline (>72 hours administered duration anytime during the 96 hours prior to the first dose)

o Did not receive more than one dose of effective systemic on-study antibiotics from the first dose of study drug to the TOC/Safety Visit.

Exposure Response Population: The exposure response population included any subject with at least one peak or trough sample (of daptomycin plasma concentration).

Dose justification

The dosing regimen of daptomycin for this study was based on PK data in paediatric subjects, population PK modelling and simulation, and nonclinical effects in juvenile dogs. From observations in non-clinical studies with 7-week old juvenile dogs, it was judged possible that young children may be more sensitive to the adverse effects of daptomycin than adults, especially in the developing nervous system of young children. For skeletal muscle toxicity, which is driven by AUC, the no-observed-effect-levels (NOEL) exposure for 7-week old juvenile dogs treated for 14 days was 1250 µg*h/mL. For nervous system effects, which are driven by Cmax, the NOEL in 7- week old juvenile dogs treated for 14 days was 705 µg/mL. High doses of 12 mg/kg in adults were well tolerated with a mean steady-state Cmax value of 184 µg/mL and mean AUC of 1277 µg*hr/mL (Daptomycin IB).

Daptomycin exhibits concentration-dependent bactericidal effect and AUC/MIC is the main PK/Pharmacodynamic (PD) driver of efficacy. The dose selection for this study was based on the following key points:

-The intent of dose selection was to target exposures (AUC) in paediatric patients that are comparable to the exposures seen in adults treated with 6 mg/kg for SAB. In paediatric patients, this requires a higher mg/kg dose, since clearance in paediatric patients is higher than in adults.

-Higher doses increase the potential of an elevated Cmax. This possibility was mitigated by extending the duration of the infusion from 30 to 60 minutes for paediatric patients under 7 years of age, where a higher dose (12 mg/kg) was determined necessary to achieve efficacy in this indication.

-Doses were selected to ensure AUC exposures in paediatric patients within the range of safe and efficacious exposures reported in adults treated with 6 mg/kg for bacteraemia (90% of adult subjects had AUC exposures between 270 to 1151µg*h/mL; mean 622 µg*h/mL; median 543 µg*h/mL). These exposures were well within the safety margin of the observed NOEL in the juvenile dog study.

Based on exposure matching with adults the following doses were selected for this study:

For ages 12–17 years: 7 mg/kg IV q24h

For ages 7–11 years: 9 mg/kg IV q24h

For ages 1–6 years: 12 mg/kg IV q24h

Duration of Treatment

Maximum total duration of study drug therapy was not to exceed 42 days, except in special circumstances per protocol.

Duration of therapy post randomization:

Age (years)	Uncomplicated bacteremia[a]	Complicated bacteremia[a,b]
≥ 12	Max: 28 days Min: 5 days	Max: 42 days Min: 7 days
1-11	Max: 28 days Min: 5 days	Max: 28 days[c] Min: 7 days

a Some of this therapy could have been administered at home as per local practice. Switch to oral therapy was discouraged, but was acceptable, if allowed by study site's practice standard.

b Subjects with complicated bacteremia with osteomyelitis and positive blood cultures may have received a shorter duration of IV therapy (less than 7 days) after discussion with the Sponsor designated Medical Monitor.

c Children under 12 years of age who were classified as having complicated bacteremia after IV treatment was started and who responded to treatment by Day 28 but who required additional IV treatment may have continued on IV daptomycin or SOC if benefit outweighed the potential safety risk.

Criteria for Evaluation

Evaluation of Safety:

The safety of daptomycin and SOC were evaluated by monitoring adverse events (AEs), serious adverse events (SAEs), and changes in physical and focused neurological examinations and serum chemistry (including serum CPK level), haematology, and vital signs. Safety was assessed for the entire study period from the administration of the first dose of study medication through the Last Follow-up Visit (25 to 35 days after the last dose of study drug).

Evaluation of Efficacy:

-Clinical Outcome: Clinical outcome was based on a blinded Investigator's (blinded Evaluator) assessment of clinical response at the TOC/Safety Visit. Outcomes were assessed as success (cure, improved), failure, or non-evaluable with respect to resolution or improvement of clinical signs and symptoms.

-Microbiological Response: Microbiological response was determined as microbiological success, failure, or non-evaluable, based on evaluation of Baseline infecting pathogen at the TOC/Safety Visit.

-Overall Outcome: The overall outcome was determined based on the subject's microbiological response and clinical outcome at the TOC/Safety Visit. Overall outcome was a success if both clinical and microbiological outcomes were successful.

Exposure Response Analysis:

Daptomycin exposures were determined by measuring plasma levels at pre-dose (plasma concentration in sample obtained just before dosing [Ctrough]) and end of infusion (maximum plasma concentration [Cmax]) between Days 3 and 6 of IV daptomycin treatment to explore exposure response safety analyses in all age groups. The correlation between exposure (peak and trough) and CPK levels was assessed graphically. The trough and Cmax values for all subjects with an AE in the Standard MedDRA Query (SMQ) categories of Peripheral Neuropathy and the category of Rhabdomyolysis/Myopathy were evaluated.

Results

Subject Disposition and Baseline Characteristics:

A total of 82 subjects were randomized into the study. The ITT population included 55 subjects in the daptomycin treatment arm and 27 subjects in the SOC comparator treatment arm. The study was conducted in North America, Europe, Central/South America, and Australia/Asia. The majority of subjects (76.8%) were enrolled in the United States (36 subjects) and Ukraine (25 subjects). Overall, the study completion rate was high; (96.3%) subjects completed the study through the TOC/Safety Visit, which included 54 (98.2%) daptomycin-treated subjects and 24 (92.3%) SOC-treated subjects. Similarly, IV study drug completion rates were high (85.5% and 88.5% in the daptomycin and SOC treatment arms, respectively). The most common reasons for premature discontinuation of IV study drug were AEs, persistently positive blood cultures, subject/parent/legal guardian's decision, or other reasons.

In general, the Baseline demographic and disease characteristics were similar between the 2 treatment arms and consistent across age groups and analysis populations. The majority of the subjects were White (75.3%) and non-Hispanic or Latino (71.6%). The percentage of males (66.7%) was higher than females, but balanced between the 2 treatment arms. The mean age was 8.7 years (range 2.0 to 17.6 years). Mean weight, height, and body mass index (BMI) were typical of the enrolled age groups and were generally similar between the treatment arms across age groups.

Majority of subjects (77.8%) had methicillin-susceptible *S. aureus* (MSSA) as the Baseline infecting pathogen. The majority of randomized subjects (N=73) had proven *S. aureus* infection (51 on daptomycin and 22 on SOC comparator), with a similar distribution of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) in each treatment arm. MSSA infections were noted in 80.0% of the daptomycin arm and 73.1% of the SOC arm, while MSRA infections were noted in 12.7% of the daptomycin arm and 11.5% of the SOC arm. Among the subjects whose bacteraemia was classified, bacteraemia was classified as complicated in 51.9% in the daptomycin arm and 66.7% in the SOC arm.

Table 10-3 Number of Major Protocol Deviations by Category

Category of Deviation	Count of Major Deviations
Inclusion Criteria Violated	2
Other	16
Study Assessment	132
Study Medication	16
Withdrawal	1

Table 11-2 Summary of Subjects Excluded from the Analysis Populations

Population	Total		1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
	DAP	COM	DAP 12 mg/kg	COM	DAP 9 mg/kg	COM	DAP 7 mg/kg	COM
Randomized, n	55	27	22	11	19	9	14	7
Safety population, n (%)	55 (100.0)	26 (96.3)	22 (100.0)	10 (90.9)	19 (100.0)	9 (100.0)	14 (100.0)	7 (100.0)
Excluded: did not receive study medication	0	1 (3.7)	0	1 (9.1)	0	0	0	0
MITT population, n (%)	52 (94.5)	24 (88.9)	20 (90.9)	9 (81.8)	18 (94.7)	9 (100.0)	14 (100.0)	6 (85.7)
Excluded	3 (5.5)	3 (11.1)	2 (9.1)	2 (18.2)	1 (5.3)	0	0	1 (14.3)
Reason for exclusion								
Did not received study medication	0	1 (3.7)	0	1 (9.1)	0	0	0	0
Did not meet clinical criteria for infection at Baseline [a]	3 (5.5)	2 (7.4)	2 (9.1)	1 (9.1)	1 (5.3)	0	0	1 (14.3)
mMITT Population, n (%)	51 (92.7)	22 (81.5)	20 (90.9)	8 (72.7)	17 (89.5)	9 (100.0)	14 (100.0)	5 (71.4)
Excluded	4 (7.3)	5 (18.5)	2 (9.1)	3 (27.3)	2 (10.5)	0	0	2 (28.6)
Reason for exclusion								
Not in MITT	3 (5.5)	3 (11.1)	2 (9.1)	2 (18.2)	1 (5.3)	0	0	1 (14.3)
Did not have proven *S. aureus* bacteremia at Baseline	1 (1.8)	2 (7.4)	0	1 (9.1)	1 (5.3)	0	0	1 (14.3)
CE population, n (%)[b]	40 (72.7)	12 (44.4)	18 (81.8)	6 (54.5)	14 (73.7)	3 (33.3)	8 (57.1)	3 (42.9)
Excluded	15 (27.3)	15 (55.6)	4 (18.2)	5 (45.5)	5 (26.3)	6 (66.7)	6 (42.9)	4 (57.1)
Reason for exclusion								
Not in mMITT	4 (7.3)	5 (18.5)	2 (9.1)	3 (27.3)	2 (10.5)	0	0	2 (28.6)
Did not receive correct drug	0	0	0	0	0	0	0	0
Treatment duration not per Clinical Evaluability Plan [c]	1 (1.8)	3 (11.1)	0	1 (9.1)	1 (5.3)	2 (22.2)	0	0
No evaluable TOC clinical outcome assessment and/or subject level microbiological outcome [d]	3 (5.5)	4 (14.8)	2 (9.1)	1 (9.1)	0	1 (11.1)	1 (7.1)	2 (28.6)
Received prior antibiotics for >72 hours	6 (10.9)	6 (22.2)	2 (9.1)	1 (9.1)	2 (10.5)	3 (33.3)	2 (14.3)	2 (28.6)
Received >1 dose of confounding non-study antibiotics	1 (1.8)	1 (3.7)	0	0	1 (5.3)	0	0	1 (14.3)
Exposure response population, n (%)	51 (92.7)	0	19 (86.4)	0	19 (100.0)	0	13 (92.9)	0
Excluded	4 (7.3)	27 (100.0)	3 (13.6)	11 (100.0)	0	9 (100.0)	1 (7.1)	7 (100.0)
Reason for exclusion								
Did not receive Daptomycin	0	27 (100.0)	0	11 (100.0)	0	9 (100.0)	0	7 (100.0)
Did not have at least one peak or trough daptomycin plasma concentration data	4 (7.3)	0	3 (13.6)	0	0	0	1 (7.1)	0

Summary of Safety:

Eighty-one of the 82 subjects (98.8%) in the ITT population received study drug. Hence, the Safety population includes 81 subjects; 55 daptomycin-treated subjects and 26 SOC-treated subjects. Daptomycin administered at doses of 7 to 12 mg/kg once daily for up to 6 weeks to paediatric subjects aged 2 to 17 years, respectively, with *S. aureus* bacteraemia was generally safe and well tolerated.

The overall incidence of TEAEs was 65.5% and 76.9% subjects in the daptomycin and SOC (comparator) arms, respectively. Treatment-related TEAEs were noted in 14.5% and 15.4% subjects in the daptomycin and SOC arms, respectively. The safety profile was comparable across age groups and similar to the SOC.

The type, incidence, and severity of TEAEs reported for daptomycin were comparable to SOC. Most TEAEs were reported as mild or moderate in severity and were typical for this subject population.

The most common AEs in the daptomycin treatment arm were diarrhoea (6 subjects, 10.9%), vomiting (6 subjects, 10.9%), and pyrexia (5 subjects, 9.1%). The most common AEs reported in the SOC arm

were diarrhoea (5 subjects, 19.2%), followed by osteomyelitis (4 subjects, 15.4%), pyrexia (3 subjects, 11.5%), and arthritis bacterial (3 subjects, 11.5%).

It is stated that these AEs are expected events when antibiotic treatments are administered to paediatric subjects with *S. aureus* bacteraemia. There were no reported cases of drug hypersensitivity, eosinophilic pneumonia, or bone marrow toxicity among the adverse reactions reported in the daptomycin group.

Overall, the incidence of SAEs was balanced between the 2 treatment arms (23.6% for daptomycin-treated subjects and 26.9% for SOC-treated subjects), and there were no drug-related SAEs or deaths.

The rates of TEAEs leading to treatment discontinuation were uncommon, and rates were similar between the 2 treatment arms. Three (5.5%) daptomycin-treated subjects and 2 (7.7%) SOC-treated subjects discontinued study drug due to a TEAE.

Review of the SMQ of Peripheral Neuropathy and Rhabdomyolysis/Myopathy with a broad or narrow relationship showed there were 6 subjects overall who experienced TEAEs that fell into this category, including 5 subjects (9.1%) in the daptomycin treatment arm and 1 subject (3.8%) in the SOC treatment arm; no events were considered SAEs and only one event (blood CPK increased) which led to study drug discontinuation. The most commonly reported SMQ term was blood CPK increased reported in 4 (7.3%) of daptomycin-treated subjects. One TEAE was identified by SMQ for peripheral neuropathy (muscle weakness). The observed events were consistent with the prior treatment experience in adult patients with bacteraemia and do not indicate a difference in frequency, severity, or outcomes of skeletal muscle adverse reactions in paediatric patients.

No new safety signals were apparent from the review of clinical laboratory results.

The pattern of skeletal muscle toxicity observed in this study was consistent with previous experience in adults. Most post Baseline elevations of blood CPK fell between 1 and 2.5 × ULN (13 [24.1%] of subjects in the daptomycin group and 5 [19.2%] of SOC group). Sustained CPK elevations were reported in 14.5% of the subjects receiving daptomycin versus 11.5% receiving SOC. Blood CPK increased was reported by the investigators as a TEAE in 4 (7.3%) and 0 subjects in the daptomycin and SOC groups, respectively. CPK elevations >2.5 times the ULN were uncommon in both treatment groups (2 on daptomycin and 0 on SOC). One patient discontinued daptomycin therapy due to blood CPK increased.

No safety signals were apparent from review of vital signs, neurological examinations, or physical examination findings.

Summary of Efficacy Results

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

Overall, the proportion of daptomycin-treated subjects with a favourable clinical response at the TOC/Safety Visit in the mMITT population was 88.2% in the daptomycin arm and 77.3% in the SOC arm. Similar efficacy was observed at the TOC/Safety Visit in daptomycin-treated subjects irrespective of methicillin susceptibility in the mMITT population (88.6% versus 85.7% for MSSA versus MRSA, respectively). Among the 40 subjects with complicated bacteraemia in the mMITT population, the clinical success rate was generally similar in the 2 treatment arms at the TOC/Safety Visit. At the TOC/Safety visit, 88.5% of subjects with complicated bacteraemia in the daptomycin group had a favourable clinical response.

No significant difference was found in the time to clearance of the *S. aureus* bacteraemia between daptomycin and SOC-treated subjects in the mMITT population. Median times to clearance were 2.5 and 2.0 days in the daptomycin and SOC arms, respectively.

Microbiological success rates at the TOC/Safety Visit for the mMITT population were similar in the daptomycin (76.5%) and SOC (77.3%) treatment arms. The proportion of subjects with a favourable overall outcome at the TOC/Safety Visit in the mMITT population was 72.5% in the daptomycin arm and 59.1% in the SOC arm.

Table 11-5 Summary of Clinical Outcome at the Test of Cure/Safety Visit by Treatment Group, Overall and by Age Group (mMITT Population)

	Total		1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
Clinical Outcome	DAP (N=51) n (%)	COM (N=22) n (%)	DAP (N=20) n (%)	COM (N=8) n (%)	DAP (N=17) n (%)	COM (N=9) n (%)	DAP (N=14) n (%)	COM (N=5) n (%)
Outcome at TOC								
Number of Subjects with Responses	51	22	20	8	17	9	14	5
Clinical Success (Satisfactory Response)	45 (88.2)	17 (77.3)	17 (85.0)	7 (87.5)	16 (94.1)	7 (77.8)	12 (85.7)	3 (60.0)
Cure	43 (84.3)	17 (77.3)	16 (80.0)	7 (87.5)	16 (94.1)	7 (77.8)	11 (78.6)	3 (60.0)
Improved	2 (3.9)	0	1 (5.0)	0	0	0	1 (7.1)	0
Clinical Failure (Unsatisfactory Response)	6 (11.8)	5 (22.7)	3 (15.0)	1 (12.5)	1 (5.9)	2 (22.2)	2 (14.3)	2 (40.0)
Failure	5 (9.8)	3 (13.6)	3 (15.0)	1 (12.5)	1 (5.9)	1 (11.1)	1 (7.1)	1 (20.0)
Non-evaluable	1 (2.0)	2 (9.1)	0	0	0	1 (11.1)	1 (7.1)	1 (20.0)
95% CI for percent of Satisfactory Response[a]	79.4, 97.1	59.8, 94.8	69.4, 100.0	64.6, 100.0	82.9, 100.0	50.6, 100.0	67.4, 100.0	17.1, 100.0
Difference [b]	11.0%	-	-2.5%	-	16.3%	-	25.7%	-
95% CI of Difference [c]	-8.7, 30.6	-	-30.3, 25.3	-	-13.0, 45.7	-	-21.0, 72.4	-

Summary of Pharmacokinetics:

The median Cmax and Ctrough values observed with the age-specific, weight-based doses ranged from 73 to 95 ug/mL and 4.3 to 5.6 ug/mL, respectively. The median peak concentrations were 95.40 µg/mL for the 1 to 6 year olds who received 12 mg/kg of daptomycin, 83.75 µg/mL for the 7 to 11 year olds who received 9 mg/kg of daptomycin, and 73.05 µg/mL for the 12 to 17 year olds who received 7 mg/kg of daptomycin. The median trough concentrations were 4.32 µg/mL for the 1 to 6 year olds who received 12 mg/kg of daptomycin, 5.63 µg/mL for the 7 to 11 year olds who received 9 mg/kg of daptomycin, and 4.93 µg/mL for the 12 to 17 year olds who received 7 mg/kg of daptomycin. The median Ctrough appears to be comparable across the different age groups with age-specific, weight-based dosing regimens, and the median Cmax appears to be higher for the youngest age group (1 to 6 years of age) compared to older patients ranging from 7 to17 years of age.

Results suggest that there was no apparent correlation between peak daptomycin concentrations and CPK elevations or SMQ adverse events in the categories of Peripheral Neuropathy or Rhabdomyolysis/Myopathy.

Conclusions

The applicant concludes that Daptomycin was effective in the treatment of *S. aureus* bacteraemia.

Rapporteurs comments:

No new adverse events of concern were identified and the safety data from the paediatric patients in this study were consistent with the known safety profile of daptomycin. The efficacy data showed daptomycin to achieve outcomes similar to other SOC treatments while PK data were as expected.

1.1.1. Discussion on clinical aspects

The applicant has submitted a clinical overview and the complete CSR for this paediatric study.

There were no new or unexpected safety findings from the 82 paediatric patients enrolled in study, although the incidence of short bowel syndrome was higher in the daptomycin vs control group. There were a large number of SAEs in both groups, reflecting the serious condition of these patients.

The number of patients in each age band were generally quite small, and considering the high number of major protocol violations, it is not clear how robust the results are.

While the doses selected for each age band based on PK considerations appear appropriate, it is noted that the doses are different from those recommended for paediatric patients with CSSTIs. This will have to be justified and taken in to account when extending the paediatric indications, to prevent confusion and under exposure.

On the basis of the results of this paediatric study, there is currently no change in the benefit-risk profile of Cubicin for the existing indications. The clinical safety and efficacy findings remain consistent with the information in the Company Core Data Sheet and prescribing information for Cubicin. Therefore, no SmPC changes are needed based on the results of this study at present.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

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

The following concerns need to be addressed.

3. List of Questions

1. The incidence of short bowel syndrome was higher in the daptomycin vs control group. Please provide details and provide further comment.

2. There were a high number of major protocol violations. Please comment on whether these had any impact on the safety/ efficacy conclusions.

4. Assessment of Responses

QUESTION 1: The incidence of short bowel syndrome was higher in the daptomycin vs control group. Please provide details and provide further comment.

COMPANY RESPONSE 1:

Demographics

In the DAP-PEDBAC-11-02 trial, the proportion of subjects (n=81 overall) in the Safety population with a prior medical history of short bowel syndrome was greater in the daptomycin group (14.5%; [8/55]) than in the comparator group (3.8% [1/26]). The majority (7 of 9) of the subjects with a history of short bowel syndrome was reported in the younger children (1 to 6 years of age); the remaining 2 cases were reported in subjects in older children (7 to 11 years).

Safety

No subject in the Safety population experienced a TEAE of short bowel syndrome during the trial. Of the 9 subjects in the Safety population with a prior medical history of short bowel syndrome, 8 (88.9%) subjects reported at least 1 Treatment-Emergent Adverse Event (TEAE) and 5 (55.6%) subjects experienced at least 1 serious AE (SAE). None of the TEAEs or SAEs experienced by these 9 subjects led to discontinuation of study medication and none were considered related to study medication (by the investigator). The incidence of TEAEs (88.9%) and SAEs (55.6%) in these 9 subjects was higher than those in the overall Safety population (TEAEs: 69.1%; SAEs: 24.7%); this observation should be taken in context of the limited number (n=9) of subjects with short bowel syndrome and the potential contribution of the underlying short bowel syndrome to the overall AE profile of such subjects.

Of the 5 subjects with a prior history of short bowel syndrome that experienced 1 or more SAEs, 2 subjects experienced SAEs that were deemed unrelated to study treatment but related to the existing condition of short bowel syndrome (Gram-negative bacteraemia in one subject and broken central line in another subject who required chronic central line for total parenteral nutrition (TPN) therapy). Such complications of short bowel syndrome are not unexpected given the altered gastrointestinal structure and function as well as the clinical requirement for long-term central line access and TPN administration.

Efficacy

In general, subjects with short bowel syndrome are at increased risk for compromised absorption of oral drug formulations. However, in this trial, all subjects with a reported medical history of short bowel syndrome were treated with only intravenous (IV) study medication throughout the duration of

the trial (Table 1). Therefore, it is unlikely that the numerical imbalance in the proportion of short bowel syndrome reported in the daptomycin versus comparator arm had any clinically relevant impact on the efficacy evaluation of the study medication across treatment groups. The proportion of subjects in the daptomycin group with a history of short bowel syndrome who achieved clinical cure at the Test of Cure (TOC) visit (75%; 6 out of 8 subjects) was similar to that of the overall trial population (88% for the microbiological modified intent-to-treat (mMITT) population). The one comparator-treated subject with short bowel syndrome also achieved clinical cure.

Table 1. Duration of Therapy, Diagnosis and Clinical Outcomes in Subjects with Reported Medical History of Short Bowel Syndrome

Duration of IV Therapy (days)	**Duration of Oral Therapy (days)**	**Complicated/ Uncomplicated Bacteraemia**	**Clinical Outcome**
Daptomycin-Treated			
16	0	uncomplicated	Failure
22*	0	uncomplicated	Cure
15	0	uncomplicated	Cure
17	0	uncomplicated	Cure
16	0	uncomplicated	Failure
15	0	uncomplicated	Cure
16	0	uncomplicated	Cure
20	0	complicated	Cure
Comparator-Treated			
15	0	uncomplicated	Cure

*Subject received 8 days of IV daptomycin, was discharged and given 15 days of IV cefazolin (only available in IV formulation) 350mg every 8 hours for a total of 22 days of IV therapy. In Listing 16.2.5.4 and Listing 16.2.5.5, the subject is noted as receiving oral therapy; however, the investigator noted the cefazolin as an 'oral switch' as the subject was being removed from study medication to be sent home but was unable to be treated with oral therapy due to short bowel disease.

Conclusions

There is no evidence to suggest that the numerical imbalance in the proportion of subjects reporting a Medical History of short bowel syndrome in the daptomycin group as compared to the comparator group impacted the overall safety or efficacy conclusions of the DAP-PEDBAC-11-02 trial. Moreover, short bowel syndrome was not reported as a TEAE during the trial.

Rapporteur's comments: The short bowel condition was pre-existing in all subjects and was not a TEAE. The safety and efficacy results in these subjects were similar to the rest.

Response is accepted. Point resolved.

QUESTION 2: There were a high number of major protocol violations. Please comment on whether these had any impact on the safety/ efficacy conclusions.

COMPANY RESPONSE 2:

A review of the major protocol deviations (MPDs) reported during the conduct of the DAP-PEDBAC-11-02 trial did not reveal any impact of MPDs on the overall safety or efficacy conclusions.

Overview of Major Protocol Deviations Reported in the DAP-PEDBAC-11-02 Trial Using the criteria in the Protocol Deviation Review Process (a Cubist Legacy process which was predefined and finalized before database lock and before deviations were categorized as major or minor), each protocol deviation in the DAP-PEDBAC-11-02 trial was assessed as major (i.e., fulfilled at least 1 MPD criterion) or minor; a subject may have had more than one MPD reported during the trial. Protocol deviations were predefined and reported by sites as outlined by the Cubist Legacy processes (Protocol Deviation Entry Guidance and Protocol Deviation Reporting Guidelines). The Protocol Deviation Review Process was primarily for Sponsor's oversight and review of protocol deviations.

Among the 81 subjects who were randomized and received study therapy in this study (i.e., 55 daptomycin-treated and 26 comparator-treated subjects included in the Safety population), a total of 169 MPDs were reported in 55 subjects. This includes 108 MPDs among 38 daptomycin-treated subjects and 61 MPDs among 17 comparator-treated subjects. The total number of MPDs includes two MPDs of Visit Window category that occurred in two subjects in the comparator group and were inadvertently not included in Table 10-3 in the CSR due to an editing issue; the two MPDs are documented in the formal Listing 16.2.2.3) . The 169 MPDs were further categorized as follows:

-Study Assessment (n=132), which included protocol-specified evaluations either not conducted or conducted with errors and included assessments of chemistry and/or haematology laboratory parameters, neurological exam, motor skills questionnaire, vital signs, physical exam, and/or microbiologic susceptibility. Based on the Protocol Deviation Review Process, any missing protocol-specified assessments, including those for a single laboratory test on a single trial visit, were categorized as a MPD.

- Study Medication (n=16), which involved treatment duration (e.g., extending beyond the protocol defined duration) or compliance (e.g., oral medication not taken as prescribed).

- Inclusion Criteria Violated (n=2), which involved Inclusion Criterion #7 (full disease criteria were not met).

- Visit Window (n=2), which involved collection of samples outside the pre-specified visit window.

- Withdrawal (n=1), for which one subject in the comparator group was not properly withdrawn from the trial after not meeting Inclusion Criterion #7.

- Other (n=16), which included issues involving delays in SAE reporting, consent, or unblinding of the blinded Evaluator.

Following the categorization of each MPD into one of the above categories, there were no further sub-categorizations of MPDs performed on a programmatic basis. For example, the MPDs categorized as Study Assessments were not sub-categorized in a systematic manner with respect to the type and timing of the affected protocol-specified assessments. Of the 55 subjects in the Safety Population that had one or more MPDs, 48 were included in the Microbiologic Modified Intent-to-Treat (mMITT) population, and 31 in the Clinically Evaluable (CE) population. The distribution of subjects with one or more MPDs by treatment group in the Safety population and the categories of MPD are shown in Table 2.

Table 2. Summary of Subjects (Safety Population) with Major Protocol Deviations

	Daptomycin N=108	Comparator N=61	Total N=169
Number of subjects with Major Protocol Deviations			
Safety Population	38	17	55
Categories of Major Protocol Deviations in the Safety Population			
Inclusion Criterion Violated	1	1	2
Other	8	8	16
Study Assessment	88	44	132
Study Medication	11	5	16
Visit Window	0	2	2
Withdrawal	0	1	1

MPDs and Safety Assessments in the Trial

In the DAP-PEDBAC-11-02 trial, all subjects that received any amount of study medication were included in the Safety Population and the corresponding safety data were used for safety analysis, regardless of whether MPDs were reported for such subjects. Of the 81 subjects in the Safety Population, 55 (67.9%) subjects reported at least one MPD (Table 2). A total of 38 (69.0%) out of the 55 daptomycin-treated subjects and 17 (65.4%) of the 26 comparator-treated subjects experienced

one or more MPDs. The most commonly reported category of MPDs (132 out of 169 events; 78.1%) was Study Assessments and was reported in 47 out of 81 (58.0%) subjects in the Safety Population (daptomycin group: 34 out of 55 (61.8%) subjects; comparator group: 13 out of 26 (50.0%) subjects).

Overall, the daptomycin- and comparator-treated groups had similar distribution of MPDs by category and proportion of subjects with one or more MPDs (by all categories and Study Assessment category). These data are in accord with the safety conclusions of the trial (CSR Section 12.6), in which the safety profile of the daptomycin group was similar to that of the comparator group. Given the type of observations and the distribution of these observations across the 2 treatment groups, the MPDs reported in this trial were unlikely to impact the overall safety conclusion of the trial or the overall safety outcomes in an individual subject.

MPD and Efficacy Assessments in the Trial

Efficacy populations

In the DAP-PEDBAC-11-02 trial, the efficacy populations were programmatically defined as follows:

Modified Intent-to-Treat (MITT) Population: The MITT population was composed of all randomized and treated subjects with at least one dose who met the clinical criteria for the study infection at Baseline (positive blood culture for *S. aureus* or CoNS (coagulase-negative Staphylococci) in high-risk patients or probable bacteraemia [Gram-positive cocci on Gram stain at Baseline]).

Microbiological Modified Intent-to-Treat (mMITT) Population: The mMITT population consisted of all MITT subjects who had proven *S. aureus* bacteraemia at Baseline.

Clinically Evaluable (CE) Population: Subpopulation of the mMITT subjects who met specific criteria related to the required assessments: Received the correct drug, as randomized; Received appropriate duration of treatment (minimum and maximum treatment durations are outlined in the Clinical Evaluability Review Plan); Had the necessary clinical and microbiological efficacy evaluations performed at the TOC/Safety Visit and were not evaluated as “non-evaluable”; Did not receive effective systemic on-study antibiotics at Baseline (>72 hours administered duration anytime during the 96 hours prior to the first dose); Did not receive more than one dose of effective systemic non-study antibiotics from the first dose of study drug to the TOC/Safety Visit.

As described above, the sequentially selective assignment of subjects from the MITT to mMITT and CE populations was based on progressively more rigorous set of factors that would potentially affect efficacy (e.g., mMITT population = MITT subjects with proven *S. aureus* bacteraemia at Baseline) and not based on safety assessments. The efficacy of study medications was primarily assessed in the mMITT population. Efficacy was also assessed in the CE population, which was limited to subjects that

were compliant with pre-specified protocol requirements with the potential to impact the efficacy outcome. Clinical success rates in the CE population (daptomycin: 90.0%; comparator: 75.0%) were comparable or higher than those for the mMITT population (daptomycin: 88.2%; comparator: 77.3%) at the Test of Cure (TOC)/safety visit.

Of the 55 subjects with MPDs, 48 were included in the mMITT population and 31 were included in the CE population. Additional details are provided below.

MPDs in the mMITT population

Of the 73 subjects in the mMITT Population, 48 (65.8%) subjects reported at least one MPD (Table 3).

Table 3. Summary of Subjects (mMITT Population) with Major Protocol Deviations

	Daptomycin N=97	Comparator N=51	Total N=148
Number of subjects with Major Protocol Deviations			
mMITT Population	34	14	48
Categories of Major Protocol Deviations in the mMITT Population			
Other	6	8	14
Study Assessment	80	37	117
Study Medication	11	4	15
Visit Window	0	2	2

The overall distribution of MPDs by categories was similar between the two treatment groups. A total of 34 (66.7%) out of the 51 daptomycin-treated subjects and 14 (63.6%) of the 22 comparator-treated subjects experienced one or more MPDs. The most commonly reported category of MPDs (117 out of 148 events; 79.1%) was Study Assessments and was reported in 41 out of 73 (56.2%) subjects in the mMITT Population (daptomycin group: 31 out of 51 (60.8%) subjects; comparator group: 10 out of 22 (45.6%) subjects). These observations suggest that the MPDs noted among subjects in the two treatment groups of the mMITT population are similar with respect to the distribution of MPD categories and the proportion of subjects with one or more MPDs (overall and by Study Assessment category). Given that the primary efficacy results that demonstrate slightly higher cure rates at TOC visits for the daptomycin group as compared to the comparator group in the mMITT population, it is unlikely that the MPDs had any clinically relevant effect on the efficacy assessments in this subpopulation.

To further examine the potential effect of MPDs on the efficacy assessments for the mMITT population, a post-hoc analysis on the clinical success rates for the 48 mMITT subjects with MPDs relative to those

for the 25 mMITT subjects without MPDs by treatment group was performed. In the daptomycin group, the clinical success rates were 82.4% (28/34) and 100.0% (17/17) for subjects with MPDs and without MPDs, respectively. In the comparator group, the clinical success rates were 78.6% (11/14) and 75.0% (6/8) for subjects with MPDs and without MPDs, respectively.

For each of the two treatment groups in the mMITT population, there was no appreciable difference between the clinical success rates of the subgroups with and without MPDs. Moreover, the clinical success rates of MPD-based subgroups were similar to the overall efficacy rate of the corresponding treatment group. These results demonstrate that MPDs did not affect the efficacy results in the mMITT population.

MPDs in the CE population

To further assess the potential effects of MPDs on efficacy results of the trial, a similar analysis was performed for the CE population, the most selective efficacy population that was programmatically defined (Table 4). Of the 52 subjects in the CE Population, 31 (59.6%) subjects reported at least one MPD (Table 4).

Table 4. Summary of Subjects (CE Population) with Major Protocol Deviations

	Daptomycin N=73	Comparator N=12	Total N=85
Number of subjects with Major Protocol Deviations			
CE Population	27	4	31
Categories of Major Protocol Deviations in the CE Population			
Other	5	4	9
Study Assessment	59	7	66
Study Medication	9	1	10
Visit Window	0	0	0
Withdrawal	0	0	0

The proportion of subjects with at least one MPD across the two treatment groups was numerically higher in the daptomycin group (27 out of 40; 67.5%) than the comparator group (4 out of 12; 33.3%). The most commonly reported category of MPDs (66 out of 85 events; 77.6%) was Study Assessments and was reported in 26 out of 52 (50.0%) subjects in the CE Population (daptomycin group: 24 out of 40 (60.0%) subjects; comparator group: 2 out of 12 (16.7%) subjects). Within the CE population, the proportion of subjects in the daptomycin group with one or more MPDs (all categories and Study Assessments category) was higher than in the comparator group.

The numerical imbalance of MPDs across treatment groups in the CE population should be taken in the context of: (1) the rigorous definition of MPDs, i.e., any missing protocol-specified assessments, including those for a single laboratory test on a single trial visit, were categorized as a MPD; (2) the programmatic definition of the CE population as a subset of the mMITT population that was limited to subjects that were compliant with pre-specified protocol requirements with the potential to impact the efficacy outcome; and (3) the efficacy assessment of the CE population, which was comparable to that of the mMITT population (which had a more balanced distribution of MPDs across treatment groups than the CE population). Taken together, these observations suggest that the potential effect of Study Assessment MPDs on the efficacy assessments of the CE population was unlikely to be substantial.

To further examine the potential effect of MPDs on efficacy assessments for the CE population, a post-hoc analysis on the clinical success rates for the 31 CE subjects with MPDs relative to those for the 21 CE subjects without MPDs by treatment group was performed. In the daptomycin group, the clinical success rates were 85.2% (23/27) and 100.0% (13/13) for subjects with MPDs and without MPDs, respectively. In the comparator group, the clinical success rates were 75.0% (3/4) and 75.0% (6/8) for subjects with MPDs and without MPDs, respectively.

For each of the two treatment groups in the CE population, there was no appreciable difference between the clinical success rates of the subgroups with and without MPDs. Furthermore, the clinical success rates of MPD-based subgroups were similar to the overall efficacy rate of the corresponding treatment group. As was the case in the mMITT population, these results demonstrate that MPDs did not affect the efficacy results in the CE population.

Rapporteur's comments: The applicant has reviewed the causes of the major protocol deviations on the safety and efficacy of daptomycin and it is concluded that there was no evidence of MPDs impacting safety and efficacy results in the study subjects.

Response is accepted. Point resolved.

5. Rapporteur's updated overall conclusion and recommendation

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