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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/P46/034.1

Note

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

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1. Introduction

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

The applicant has submitted a Critical Expert Overview to provide information from a recently completed phase 3 safety, efficacy and pharmacokinetic (PK) study (Study DAP-PEDOST-11-03) involving paediatric patients (aged 1 to <18 years old) with suspected or confirmed acute haematogenous osteomyelitis (AHO), sponsored by Cubist Pharmaceuticals, 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 and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated 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, as well as children between 1 and 17 years of age with *Staphylococcus aureus* bacteraemia (SAB) when associated with cSSTI. 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.

2. Scientific discussion

2.1. Clinical aspects

Study Design

Study DAP-PEDOST-11-03 [P006] was an international phase 3, multi-center, double-blinded, randomized trial comparing IV daptomycin with IV active comparator (vancomycin [or teicoplanin if vancomycin levels could not be monitored] or nafcillin [or β-lactam equivalent]) followed by optional, open label oral treatment in paediatric subjects from 12 months to <18 years of age with suspected or confirmed AHO.

The primary objective of this study was to demonstrate the non-inferiority of daptomycin compared with vancomycin (or equivalent) or nafcillin (or β-lactam equivalent) in paediatric subjects with AHO with respect to improvement in the general categories of Pain, Inflammation, and Limb Function on or before Study Day 5 in the MITT Analysis Set.

The secondary objectives of this trial, as stated in the protocol, were to evaluate the efficacy of daptomycin versus comparator with respect to the endpoints defined as follows:

• Composite Endpoint of Clinical Improvement, Body Temperature, and C-reactive Protein (defined below)

• Clinical Outcome by Subject at EOIV, EOT, and TOC in the MITT and CE Analysis Sets

• Microbiological outcome by Subject and by Baseline Infecting Pathogen at TOC in the mMITT and the ME Analysis Sets

• Sustained Clinical Improvement at EOT and TOC in the MITT Analysis Set

A subject had a favourable outcome in the composite endpoint if all 3 of the following criteria were met:

- Clinical improvement on or before Study Day 5

- Body temperature ≤38° C (100.4° F) over the preceding 24 hours

- CRP decreased from Baseline (if Baseline CRP > upper limit of normal or remained ≤ULN if ≤ULN at Baseline on or before Study Day 5

Improvement had to be met on or before Study Day 5, and the other criteria had to be met on or before the date of EOIV. The criteria that were met first and second had to be sustained until the last criterion was met.

Additional secondary objectives were to evaluate the safety and tolerability of daptomycin versus comparator and the PK of daptomycin in paediatric subjects with AHO.

Study Dates

19-Mar-2014 (first subject first visit) to 20-Dec-2016 (last subject last visit), with 125 sites eligible to enrol world-wide.

Main Inclusion/ Exclusion criteria

Key eligibility criteria required subjects to be 12 months to <18 years of age with suspected or confirmed AHO warranting hospitalization and current IV antibacterial therapy. Subjects were not to have septic arthritis only, AHO of the spine, or have received more than 24 hours of effective IV antibacterial therapy for AHO within 96 hours before randomization.

Enrolment was gated with a stepwise approach that began with enrolment of subjects aged 2 to <18 years; after review and approval by the external Data Monitoring Committee, enrolment was broadened to subjects aged 12 months to <18 years.

Subjects were randomized 1:1 to receive IV daptomycin or IV active comparator at dosages appropriate to their age cohorts, with dummy infusions as necessary to maintain the blind. The choice of active comparator was at the discretion of the investigator, based on the standard of care and epidemiology of methicillin-susceptible S aureus (MSSA) and MRSA at the site and the severity of illness of the subject at baseline.

Subjects could be switched to open-label oral therapy after the end-of-IV trial treatment (EOIV) Visit assessments had been completed and the criteria for oral switch had been met (body temperature ≤ 38 ° C [100.4° F] over the preceding 24 hours, CRP decreased by at least 30% from Baseline [if available], subject was able to tolerate oral intake, and clinical improvement had been attained).

The IV treatment in this trial was blinded to the Sponsor, investigators, study staff participating in subject care or clinical evaluations, subjects and parent(s)/legally-acceptable representative(s) until all subjects completed the trial and the database was locked. The oral therapies were open-label. Subjects participated in the trial for approximately 6 months.

Baseline assessments for trial eligibility had to occur ≤48 hours before the first dose of IV trial treatment unless otherwise specified. Every effort was to be made to get a bone aspirate for culture ± 7 days from Baseline unless the subject had radiologic confirmation of AHO or a positive blood culture.

Study population

A total of 149 subjects were randomized to the trial from 44 sites worldwide, and 146 received treatment (73 in the daptomycin arm and 73 in the active comparator arm).

Dose justification for Daptomycin

The dosing regimen of daptomycin for this study was the same as used in the cSSI and SAB studies, which was based on PK data in paediatric subjects, population PK modelling and simulation, and nonclinical effects in juvenile dogs.

The following doses were used for this study:

Cohort 1: 12 years to <18 years Daptomycin 7 mg/kg

Cohort 2: 7 years to <12 years Daptomycin 9 mg/kg

Cohort 3: 24 month to <7 years Daptomycin 12 mg/kg

Cohort 4: 12 months to <24 months Daptomycin 12 mg/kg

The subjects received the following amounts of daptomycin and comparator/s:

Table 1 Trial Treatment (Subjects with Normal Renal Function)

	Infusions (administered over 60 [± 10] minutes)			
	Infusion A[1] *0 hour*	Infusion B[1] *6 hours*[2]	Infusion C[1] *12 hours*[2]	Infusion D[1] *18 hours*[2]
Daptomycin Treatment Arm	Cohort 1: 12 years to <18 years Daptomycin 7 mg/kg Cohort 2: 7 years to <12 years Daptomycin 9 mg/kg Cohort 3: 24 month to <7 years Daptomycin 12 mg/kg Cohort 4: 12 months to <24 month Daptomycin 12 mg/kg	All Cohorts: dummy infusion	All Cohorts: dummy infusion	All Cohorts: dummy infusion
Recommended Active Comparator Treatment Arm - All Cohorts	Vancomycin[3] 10 to 15 mg/kg **OR** Nafcillin (or β-lactam equivalent) 100 to 200 mg/kg/day	Vancomycin[3] 10 to 15 mg/kg **OR** Nafcillin (or β-lactam equivalent) 100 to 200 mg/kg/day	Vancomycin[3] 10 to 15 mg/kg **OR** Nafcillin (or β-lactam equivalent) 100 to 200 mg/kg/day	Vancomycin[3] 10 to 15 mg/kg **OR** Nafcillin (or β-lactam equivalent) 100 to 200 g/kg/day
Recommended Optional Oral Switch	· PO cephalexin or equivalent (25 to 50 mg/kg/day divided q6h [maximum 4 g/day]) for subjects with proven or suspected MSSA · PO clindamycin (up to 20 to 40 mg/kg/day divided q6h or q8h) for subjects with clindamycin-susceptible MRSA (and negative D-zone test)			
	· PO linezolid (10 mg/kg/dose q8h) for subjects with proven or suspected MRSA · PO sulfamethoxazole and trimethoprim when susceptible per local practice, 6 to 12 mg/kg/day trimethoprim divided q12h · PO amoxicillin/clavulanate per local practice, preferably 45 to 90 mg/kg/day of amoxicillin divided q12h			

g=grams; h=hour; IV=intravenous; kg=kilograms; mg=milligrams; MRSA=methicillin-resistant *S aureus*; MSSA=methicillin-susceptible *S aureus*; PO=oral.

1 Infusion over 60 (± 10) minutes.

2 Timing of dose was relative to Infusion A. Infusions had to begin within ± 1 hour of the time indicated.

3 At sites where vancomycin blood levels could not be monitored, teicoplanin (10 mg/kg IV q12 hours for 3 doses, then 10 mg/kg q24 hours) was recommended as a substitute.

The analysis populations were as follows:

- The intent-to-treat (ITT) Analysis Set included all randomized subjects regardless of whether the subject received any trial treatment. Subjects were categorized based on the treatment they were randomized to, regardless of which treatment they actually received.

- The Safety Analysis Set was a subset of the ITT Analysis Set which included all randomized subjects who received any amount of IV trial treatment.
- The MITT Analysis Set included all randomized subjects who received any amount of IV trial treatment and had a confirmed diagnosis of AHO (categories I, II, and III) and excluded subjects with a confirmed culture of a gram-negative organism from any Baseline specimen.
- The mMITT Analysis Set was a subset of the MITT Analysis Set which included subjects who had at least 1 gram-positive bacterial pathogen isolated from an appropriate microbiological specimen (eg, blood, infection site) at Baseline.
- The CE Analysis Set was a subset of the MITT Analysis Set which included subjects who met all the following criteria:

• Received the drug assigned at randomization throughout the trial treatment period and did not receive any drug(s) from the other treatment arm.

• Received treatment (IV plus oral) for at least 13 days.

• Had a clinical outcome assessment of cure at the TOC Visit or was assessed a clinical failure any time up to 35 days after the last dose of IV trial treatment (if no oral switch) or oral therapy. Subjects with a clinical outcome assessment of indeterminate at the EOIV, EOT, or TOC Visits were excluded.

• Received no more than 24 hours of effective nonstudy IV antibiotics within 96 hours before dose date UNLESS

- The subject had microbiological or clinical treatment failure with nonstudy IV antibacterial therapy that was administered for at least 48 hours; failure had to be confirmed by microbiological laboratory report, documented worsening, or no improvement of clinical signs or symptoms.

- Treatment was a low-dose tetracycline derivative for acne (e.g. doxycycline 50 mg q12h)

- Prior treatment was oral antibiotics if the subject had worsening or no improvement of clinical signs and symptoms.

• If a clinical cure at TOC, did not receive more than 1 dose of effective nontribal concomitant systemic antibacterial that was potentially effective for the treatment of AHO from randomization through TOC.

• There was no unblinding that impacted the clinical outcome assessment as assessed individually by the evaluators.

- The ME Analysis Set included subjects who met the criteria for both the CE and mMITT Analysis Sets.
- The PK Analysis Set included all randomized subjects who received a known amount of daptomycin and who had at least 1 PK sample collected.

Duration of Treatment

A minimum of 4 days of IV trial treatment was recommended. Trial treatment (IV alone or IV plus optional oral treatment) was to be administered for a minimum of 14 days up to a maximum of 28 days (4 weeks) but could be extended up to 42 days at the discretion of the investigator.

Before completion of trial treatment, subjects were to demonstrate improvement in the clinical assessment of their AHO from Baseline as follows:

• Resolution or improvement of clinical symptom parameters of AHO such that no further antibacterial therapy was required

· Body temperature ≤38° C (100.4° F) over the preceding 24 hours

• No new or additional bone or joint infection (eg, abscess, spreading to other osseous or articular locations) such that no further antibacterial therapy or surgery were required

• No hematogenous metastatic infection (eg, abscess in liver, spleen, lung; other bones) or bacteremia

Results

Subject Disposition and Baseline Characteristics:

Table 2 Summary of Subject Disposition and Analysis Sets

	All Ages		
	Daptomycin (N=75)	Comparator (N=74)	Overall (N=149)
Randomized not treated[1]	2 (2.7%)	1 (1.4%)	3 (2.0%)
Randomized and treated[1]	73 (97.3%)	73 (98.6%)	146 (98.0%)
Completed IV treatment[2]	68 (93.2%)	66 (90.4%)	134 (91.8%)
Switched to oral trial treatment[2]	64 (87.7%)	63 (86.3%)	127 (87.0%)
Completed oral trial treatment[3]	61 (95.3%)	60 (95.2%)	121 (95.3%)
Completed TOC Visit[1]	69 (92.0%)	69 (93.2%)	138 (92.6%)
Completed 6-month FU Visit[1]	68 (90.7%)	70 (94.6%)	138 (92.6%)
Analysis Sets			
Safety Analysis Set	73 (97.3)	73 (98.6)	146 (98.0)
MITT Analysis Set	71 (94.7)	70 (94.6)	141 (94.6)
mMITT Analysis Set	45 (60.0)	47 (63.5)	92 (61.7)
CE Analysis Set	58 (77.3)	56 (75.7)	114 (76.5)
ME Analysis Set	37 (49.3)	36 (48.6)	73 (49.0)
Age Cohorts (Safety Analysis Sets)			
12 to <24 months	4 (5.4)	2 (2.8)	6 (4.1)
24 months to <7 years	20 (27.0)	23 (31.9)	43 (29.5)
7 to <12 years	25 (33.8)	25 (34.7)	50 (34.2)
12 to <18 years	25 (33.8)	22 (30.6)	47 (32.2)

Demographic characteristics were generally similar between the 2 treatment arms. The majority of subjects were male (62.3%) and white (82.2%), although Black/African Americans and other races were represented in both treatment arms. The mean age was 9.31 years; 34.2% of subjects were 7 to <12 years of age, and 32.2% of subjects were 12 years to <18 years of age. Demographic characteristics were also balanced across age cohorts.

Baseline disease characteristics were similar between treatment arms and across age cohorts. Most subjects (87.7%) had a diagnosis of AHO only, while 12.3% had a diagnosis of AHO plus septic arthritis. The most common AHO locations for daptomycin and comparator arm subjects were femur (36.5% and 29.2%, respectively), tibia (21.6% and 37.5%, respectively), and fibula (12.2% and 9.7%, respectively). The duration of AHO symptoms from onset to first dose of trial treatment was >4 days for 68.9% and 79.2% of daptomycin and comparator arm subjects, respectively; 83.8% and

77.8% of subjects in the daptomycin and comparator arms, respectively, had a history of prior antibiotics.

The most common imaging method for diagnosis was magnetic resonance imaging (MRI) (34 subjects (60.7%) in each treatment arm), followed by plain radiography (14 subjects [25.0%] in the daptomycin arm and 12 subjects [21.4%] in the comparator arm), and computed tomography (CT) scan (7 subjects ([12.5%] in the daptomycin arm and 8 subjects [14.3%] in the comparator arm).

More subjects in the daptomycin arm (20 subjects, 41.7%) had a positive blood culture at enrolment compared with the comparator arm (16 subjects, 34.0%). The majority of subjects overall (69 subjects, 72.6%) had an infection site specimen culture (32 subjects [66.7%] in the daptomycin arm and 37 subjects [78.7%] in the comparator arm). Overall, 13.7% of subjects (5 [10.4%] in the daptomycin arm and 8 [17.0%] in the comparator arm) had both a positive blood culture and infection site specimen culture.

Primary Efficacy Results

In the daptomycin arm, 55 subjects (77.5%) met the primary endpoint of clinical improvement on or before Study Day 5 and 16 subjects (22.5%) did not; in the comparator arm, 58 subjects (82.9%) met the primary endpoint of clinical improvement on or before Study Day 5 and 12 subjects (17.1%) did not. The observed common difference for percent of improvement between the 2 arms in clinical improvement rates was -6.1% in favour of the comparator arm (95% CI, -19.4 to 7.4). The observed lower bound of the 95% CI for the common difference was lower than -15% (the prespecified noninferiority margin); therefore, noninferiority of daptomycin to comparator was not demonstrated. Consequently, the other 2 endpoints in the gatekeeping strategy were no longer controlled for multiplicity.

Table 4 Clinical Improvement by Study Day 5 (MITT Analysis Set)

	All Ages	
	Daptomycin (N=71)	Comparator (N=70)
Number of subjects evaluable	71	70
Number (%) of subjects who:		
Met improvement criteria for primary endpoint[1]	55 (77.5)	58 (82.9)
Did not meet improvement criteria	16 (22.5)	12 (17.1)
95% CI for % of improvement[2]	(67.7, 87.2)	(74.0, 91.7)
Difference for % of improvement (daptomycin – comparator)	-5.4	
P-value from Wald method [3]	0.421	
Common difference for % of improvement (daptomycin – comparator)[4]	-6.1	
95% CI of common difference[3,4]	(-19.4, 7.4)	

The proportion of subjects in each age cohort with clinical improvement by Study Day 5 was generally similar in both treatment arms, with the exception of the 12 to <18 year age cohort in which a lower proportion of subjects in the daptomycin group met improvement criteria for the primary endpoint (18 of 24 subjects; 75% [95% CI, 57.7%- 92.3%]) versus comparator group (21 of 23 subjects; 91.3% [95% CI, 79.8%-100%]). In subjects who met improvement criteria on or before Study Day 5, the median time to clinical improvement was longer for the daptomycin arm (63.7 hours) compared with the comparator arm (45.3 hours).

Secondary Efficacy Results

Composite Endpoint

The CHEOPS scale was used for pain assessment in subjects <4 years old, and the FPS-R was used for assessing pain in subjects ≥4 years to <18 years of age.

In the MITT Analysis Set, the percentage of subjects with a favourable outcome was similar between the daptomycin arm (71.0%) and comparator arm (76.5%). However, the rate was higher in the daptomycin arm compared to the comparator arm for the proportion of subjects whose time from onset of AHO symptoms to first dose of study drug was ≤4 days (31.1% in the daptomycin arm and 20.8% in the comparator arm).

Slightly higher proportions of subjects within each of the 3 age cohorts older than 24 months of age in the comparator arm met the composite endpoint of clinical improvement compared to the corresponding age cohorts in the daptomycin arm; the small number of subjects in the 12 to <24 month age cohort in both treatment groups was noted.

Table 5 Composite Endpoint of Clinical Improvement, Body Temperature, and C-reactive Protein (MITT Analysis Set)

	All ages	
	Daptomycin (N=71)	Comparator (N=70)
Number of subjects evaluable	69	68
Number (%) of subjects with:		
Favorable outcome[1]	49 (71.0)	52 (76.5)
Unfavorable outcome	20 (29.0)	16 (23.5)
95% CI for % of subjects with favorable outcome[2]	(60.3, 81.7)	(66.4, 86.6)
Difference for % of favorable (daptomycin – comparator)	-5.5	
P-value from Wald method	0.467	
Common difference for % of favorable (daptomycin-comparator)[3]	-7.1	
95% CI of common difference[3]	(-21.6, 7.9)	

A higher proportion of subjects in the comparator arm achieved a favourable clinical outcome (clinical cure or clinical recovery) at the EOIV, EOT, and TOC Visits (MITT Analysis Set) compared with the daptomycin arm, although a similar proportion of subjects in the daptomycin and comparator arms experienced clinical cure at EOIV (26.8% versus 23.2% in the daptomycin and comparator arms, respectively). The differences were not statistically significant. The majority of subjects (85.9% and 91.3% in the daptomycin and comparator arms, respectively) had a favourable clinical outcome at the EOIV Visit.

At the TOC Visit, 58 subjects (81.7%) in the daptomycin arm and 61 subjects (87.1%) in the comparator arm had a favourable clinical outcome. More subjects in the daptomycin arm than in the comparator arm had an outcome assessment of indeterminate at EOIV (3 subjects [4.2%] versus 0 subjects, respectively), at EOT (4 subjects [5.6%] versus 1 [1.4%] subjects, respectively) and at TOC (5 subjects [7.0%] versus 3 subjects [4.3%], respectively). The differences in the unfavourable outcome between the 2 treatment groups appeared to be due to the higher number of indeterminate outcomes in the daptomycin arm.

Table 6 Clinical Outcome by Subject at the EOIV, EOT, and TOC Visits (MITT Analysis Set)

	All Ages	
	Daptomycin (N=71)	Comparator (N=70)
EOIV		
Number of Subjects Evaluable[1]	71	69
Number (%) of subjects with:		
Favorable outcome	61 (85.9)	63 (91.3)
Clinical recovery	42 (59.2)	47 (68.1)
Clinical cure	19 (26.8)	16 (23.2)
Unfavorable outcome	10 (14.1)	6 (8.7)
Clinical failure	7 (9.9)	6 (8.7)
Indeterminate	3 (4.2)	0
95% CI for % of favorable[2]	(77.8, 94.0)	(84.7, 98.0)
Difference for % of favorable (daptomycin – comparator)	-5.4	
P-value from Wald method	0.313	
Common difference for % of favorable (daptomycin-comparator)[3]	-6.2	
95% CI of common difference[3]	(-17.5, 5.0)	
EOT		
Number of Subjects Evaluable	71	69
Number (%) of subjects with:		
Favorable outcome (cure)	59 (83.1)	62 (89.9)
Clinical cure	59 (83.1)	62 (89.9)
Unfavorable outcome	12 (16.9)	7 (10.1)
Clinical failure	8 (11.3)	6 (8.7)
Indeterminate	4 (5.6)	1 (1.4)
95% CI for % of favorable[2]	(74.4, 91.8)	(82.7, 97.0)
Difference for % of favorable (daptomycin – comparator)	-6.8	
P-value from Wald method	0.239	
Common difference for % of favorable (daptomycin-comparator)[3]	-7.9	
95% CI of common difference[3]	(-19.8, 4.0)	
TOC		
Number of Subjects Evaluable	71	70
Number (%) of subjects with:		
Favorable outcome (cure)	58 (81.7)	61 (87.1)
Clinical cure	58 (81.7)	61 (87.1)
Unfavorable outcome	13 (18.3)	9 (12.9)
Clinical Failure	8 (11.3)	6 (8.6)
Indeterminate	5 (7.0)	3 (4.3)
95% CI for % of favorable[2]	(72.7, 90.7)	(79.3, 95.0)
Difference for % of favorable (daptomycin – comparator)	-5.5	
P-value from Wald method	0.370	
Common difference for % of favorable (daptomycin-comparator)[3]	-6.7	
95% CI of common difference[3]	(-19.1, 5.8)	

Similar results were observed in the CE Analysis Set.

Overall, the majority of subjects in the daptomycin arm (89.1%) and comparator arm (94.7%) sustained the Study Day 5 clinical improvement and had a favourable clinical outcome at the EOT Visit. Similarly, at the TOC Visit, 48 of 55 subjects assessed in the daptomycin arm had a favourable outcome

Efficacy Conclusions

The primary objective of this trial was to demonstrate the noninferiority of daptomycin compared with vancomycin (or equivalent) or nafcillin (or β-lactam equivalent) in paediatric subjects with AHO. The observed common difference for percent improvement in clinical improvement rates between the 2

arms was -6.1% in favour of the comparator arm with a 95% CI of (-19.4, 7.4). The observed lower bound of the 95% CI for the common difference was lower than -15% (the prespecified noninferiority margin); therefore, noninferiority of daptomycin to comparator was not demonstrated and the primary objective was not met. Prespecified secondary efficacy outcomes also favoured the comparator arm, although differences were not statistically significant.

The difference between treatment groups was driven by the lower proportion of subjects in the daptomycin arm achieving clinical improvement on or before Study Day 5 in the oldest cohort (age 12 to <17 years) and in the subgroup of subjects in who received the first dose of trial treatment more than 4 days after onset of AHO symptoms. Additionally, the time of assessment for the primary endpoint (Day 5) may have been too early for an optimal assessment for this type of infection, which generally requires prolonged antibiotic therapy.

In general, favourable efficacy outcomes were achieved in the majority of patients in both treatment groups.

Safety Results

Exposure to Treatment

Mean treatment duration (days) was similar across treatment arms for the IV treatment phase, the oral treatment phase, and overall duration (IV + oral). The duration of IV, oral, and IV + oral treatment was generally similar for both treatment arms in each age cohort.

Table 9 Summary of Duration of Treatment (Safety Analysis Set)

	All Ages		
	Daptomycin (N=74)	Comparator (N=72)	Overall (N=146)
Duration of IV trial treatment (days)			
N	74	72	146
Mean (SD)	11.4 (9.61)	10.6 (5.99)	11.0 (8.01)
Median (range)	8.0 (1-42)	8.5 (2-27)	8.0 (1-42)
1-7 days	30 (40.5)	28 (38.9)	58 (39.7)
>1-2 weeks	28 (37.8)	27 (37.5)	55 (37.7)
>2-3 weeks	7 (9.5)	12 (16.7)	19 (13.0)
>3-4 weeks	3 (4.1)	5 (6.9)	8 (5.5)
>4-5 weeks	2 (2.7)	0	2 (1.4)
>5-6 weeks	4 (5.4)	0	4 (2.7)
Duration of oral trial treatment (days)			
N	65	62	127
Mean (SD)	21.0 (10.72)	22.3 (19.81)	21.7 (15.77)
Median (range)	22.0 (4-42)	21.0 (4-151)	22.0 (4-151)
1-7 days	6 (8.1%)	11 (15.3%)	17 (11.6%)
>1-2 weeks	16 (21.6%)	11 (15.3%)	27 (18.5%)
>2-3 weeks	8 (10.8%)	10 (13.9%)	18 (12.3%)
>3-4 weeks	8 (24.3%)	14 (19.4%)	32 (21.9%)
>4-5 weeks	10 (13.5%)	6 (8.3%)	16 (11.0%)
>5-6 weeks	7 (9.5%)	9 (12.5%)	16 (11.0%)
>6 weeks	0	1 (1.4%)	1 (0.7%)
Duration of IV + oral trial treatment (days)			
N	74	72	146
Mean (SD)	29.1 (13.69)	29.1 (19.30)	29.1 (16.64)
Median (range)	28.5 (1-61)	28.0 (2-157)	28.0 (1-157)
1-7 days	5 (6.8)	3 (4.2)	8 (5.5)
>1-2 weeks	7 (9.5)	7 (9.7)	14 (9.6)
>2-3 weeks	10 (13.5)	17 (23.6)	27 (18.5)
>3-4 weeks	15 (20.3)	12 (16.7)	27 (18.5)
>4-5 weeks	12 (16.2)	11 (15.3)	23 (15.8)
>5-6 weeks	15 (20.3)	14 (19.4)	29 (19.9)
>6 weeks	10 (13.5)	8 (11.1)	18 (12.3)

Adverse Events

Table 11 Adverse Events Overview by Age Cohort and Treatment Arm (Safety Analysis Set)

	12 to <18 Years		7 to <12 Years		24 Months to <7 Years		12 to < 24 Months	
	Daptomycin (n=25)	Comparator (n=22)	Daptomycin (n=25)	Comparator (n=25)	Daptomycin (n=20)	Comparator (n=23)	Daptomycin (n=4)	Comparator (n=2)
Subjects with at least 1 TEAE	14 (56.0%)	13 (59.1%)	8 (32.0%)	17 (68.0%)	10 (50.0%)	14 (60.9%)	2 (50.0)	1 (50.0)
Subjects with at least 1 severe TEAE	1 (4.0%)	0	0	0	1 (5.0%)	1 (4.3%)	0	0
Subjects with at least 1 serious TEAE	3 (12.0%)	0	0	0	2 (10.0%)	4 (17.4%)	0	0
Subjects with at least 1 treatment-related TEAE	1 (4.0%)	5 (22.7%)	0	5 (20.0)	3 (15.0%)	3 (13.0%)	1 (25.0)	0
Subjects with at least 1 treatment-related serious TEAE	0	0	0	0	0	3 (13.0%)	0	0
Subjects with a TEAE leading to discontinuation of trial treatment	0	2 (9.1%)	0	2 (8.0)	1 (5.0%)	3 (13.0%)	0	0
Subjects with a treatment-related TEAE leading to discontinuation of trial treatment	0	2 (9.1%)	0	1 (4.0)	0	3 (13.0%)	0	0
Subjects with a serious TEAE leading to discontinuation of trial treatment	0	0	0	0	1 (5.0)	3 (13.0)	0	0
Subjects with a serious treatment-related TEAE leading to discontinuation of trial treatment	0	0	0	0	0	3 (13.0%)	0	0

Table 12 Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

	All Ages		
	Daptomycin (N=74)	Comparator (N=72)	Overall (N=146)
Subjects with at least 1 serious TEAE	5 (6.8)	4 (5.6)	9 (6.2)
General Disorders and Administration Site Conditions	0	1 (1.4%)	1 (0.7)
Pyrexia	0	1 (1.4%)	1 (0.7)
Infections and Infestations	1 (1.4%)	2 (2.8)	3 (2.1)
Device related infection	0	1 (1.4%)	1 (0.7)
Osteomyelitis	1 (1.4%)	0	1 (0.7)
Sepsis	1 (1.4%)	0	1 (0.7)
Viral infection	0	1 (1.4%)	1 (0.7)
Injury, Poisoning and Procedural Complications	1 (1.4%)	1 (1.4%)	2 (1.4%)
Femur fracture	1 (1.4%)	0	1 (0.7)
Joint injury	0	1 (1.4%)	1 (0.7)
Musculoskeletal and Connective tissue Disorders	3 (4.1)	0	3 (2.1)
Myalgia	1 (1.4%)	0	1 (0.7)
Pain in extremity	1 (1.4%)	0	1 (0.7)
Pathological fracture	1 (1.4%)	0	1 (0.7)
Skin and Subcutaneous Tissue Disorders	0	2 (2.8)	2 (1.4)
Drug reaction with eosinophilia and systemic symptoms	0	1 (1.4%)	1 (0.7)
Red man syndrome	0	1 (1.4%)	1 (0.7)

The proportion of subjects with TEAEs was higher in the comparator arm compared to the daptomycin arm. During the trial, 34 (45.9%) and 45 (62.5%) subjects in the daptomycin and comparator arms, respectively, experienced at least 1 TEAE. Five (6.8%) and 13 (18.1%) subjects in the daptomycin and comparator arms, respectively, had at least 1 treatment-related TEAE. Severe TEAEs were observed in 2 (2.7%) and 1 (1.4%) subjects in the daptomycin and comparator arms, respectively.

Five (6.8%) and 4 (5.6%) subjects in the daptomycin and comparator arms, respectively, had at least 1 serious TEAE. No subjects in the daptomycin arm had at least 1 treatment-related serious TEAE compared with 3 subjects (4.2%) in the comparator arm. Treatment-emergent AEs leading to discontinuation of trial treatment were reported in 1 (1.4%) and 7 (9.7%) subjects in the daptomycin and comparator arms, respectively. Serious TEAEs led to discontinuation of trial treatment in 1 subject (1.4%) in the daptomycin arm and 3 subjects (4.2%) in the comparator arm. Serious treatment-related TEAEs leading to discontinuation of the trial were reported in the comparator arm only.

No deaths occurred in either treatment arm during the trial. Treatment-emergent SAEs were uncommon in this trial, occurring in 5 subjects (6.8%) in the daptomycin arm and 4 subjects (5.6%) in the comparator arm.

There were no treatment-related SAEs in the daptomycin arm; 3 of the 4 SAEs in the comparator arm (pyrexia, drug reaction with eosinophilia and system symptoms, and red man syndrome) were considered treatment-related.

Eight subjects discontinued trial treatment, 1 subject in the daptomycin arm and 7 subjects in the comparator arm. The TEAE leading to trial treatment discontinuation in the daptomycin arm was an SAE of pathological fracture at Study Day 32. In the comparator arm, 3 TEAEs leading to

discontinuation of trial treatment were reported in the 24 month to <7 year age cohort, 2 in the 7 to <12 year age cohort, and 2 in the 12 to <18 year age cohort.

Elevations of CPK/ liver enzymes were infrequent in both the daptomycin and comparator arms. Other lab values, vital signs and physical findings were generally fine.

Safety Conclusions

Daptomycin was generally well tolerated in the treatment of AHO due to gram-positive organisms, and no new safety concerns were identified in this trial. Treatment-emergent AEs related to daptomycin were consistent with the reported safety profile from adult clinical trials.

Summary of Pharmacokinetics

Of 129 samples from daptomycin subjects that were analyzed, plasma daptomycin levels in 121 samples were above the lower limit of quantification. Detectable plasma concentrations of daptomycin were summarized by timepoint of collection and age cohort. Taking variability into consideration, plasma daptomycin concentrations were generally as predicted from prior trials and were similar across age groups.

Conclusions

The applicant concludes that the overall benefit-risk balance of daptomycin in the target paediatric population is favourable. Although the primary endpoint for this trial in paediatric subjects with AHO was not met, the majority of the patients (77.5%) in the daptomycin arm achieved clinical improvement on or before Study Day 5. The proportion of subjects reporting any TEAE and TEAEs leading to treatment discontinuation was higher in the comparator arm than in the daptomycin arm.

CHMP comments on efficacy and safety:

The efficacy data failed to show that daptomycin was non-inferior to other standard treatments for the treatment of AHO. The primary endpoint was not met, and neither were the secondary endpoints met. However over 75% patients showed improvement with daptomycin. The PK data were as expected. 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.

2.1.1. Discussion on clinical aspects

The applicant has submitted a clinical overview and the complete phase 3 safety, efficacy and pharmacokinetic (PK) study (Study DAP-PEDOST-11-03) involving paediatric patients (aged 1 to <18 years old) with suspected or confirmed acute haematogenous osteomyelitis (AHO).
There were no new or unexpected safety findings from the 146 paediatric patients enrolled in this study. There were no deaths and CPK elevations were uncommon.
The number of patients in each age band was generally quite small. While the doses selected for each age band based on PK considerations appear appropriate, it is not clear whether the recommended duration of initial iv treatment of 4 days was adequate or whether a slightly longer duration before oral switch would have been more optimal. Similarly, the primary effect to be observed at day 5 may have

been too early. Various studies reported in the literature as well as clinical guidelines differ in the recommended duration of treatment, which varies from 3 days to up to 4-6 weeks.
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.

3. CHMP 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.

4. List of Questions

1. Please clarify the choice of the duration of intial iv treament and the total treatment time.
2. Please clarify the choice of day 5 for the primary effects.
3. The difference between treatment groups was driven by the lower proportion of subjects in the daptomycin arm achieving clinical improvement on or before Study Day 5 in the oldest cohort (age 12 to <17 years). Please clarify whether this could be due to the dose being too less for this age group, or any other alternative explanation.
4. The differences in the unfavourable outcome between the 2 treatment groups appeared to be due to the higher number of indeterminate outcomes in the daptomycin arm. Please clarify the reasons for this.

5. ASSESSMENT OF RESPONSES

QUESTION 1: Please clarify the choice of the duration of initial iv treatment and the total treatment time.

COMPANY RESPONSE 1:

The choice of treatment duration was determined after a thorough literature search and discussion with scientific leaders. Guidelines and literature regarding standard therapy for acute hematogenous osteomyelitis (AHO) in children suggest that the duration of therapy should be individualized and typically ranges from a 4 to 6 week course. However, there were no prospective, randomized, controlled clinical trials published at the time the study was designed to inform the best agent, route, or duration of antibiotic therapy for these infections. Previous study by Peltola, et al. suggested the possibility of reducing the duration of IV therapy to a few days and then continuing the therapy orally for patients with methicillin-sensitive Staphylococcus aureus (MSSA) AHO. However, in AHO cases of methicillin-resistant Staphylococcus aureus (MRSA) and Panton-Valentine Leukocidin (PVL) S. aureus, 4 to 6 weeks total duration of treatment are recommended. For this protocol, the minimum of 4 days' duration of IV treatment was selected by the Applicant to ensure sufficient exposure to assess safety and harmonize treatment across global sites.

CHMP comment

There are various guidelines which recommend a longer duration of treatment with antibiotics for AHO. One prospective randomized study demonstrated that a shorter duration of therapy with high doses of antibiotics can be used successfully. Based on this, the dosing regimen was selected, however no conclusion can be made on whether this was the optimal approach.

Response accepted. *Point resolved*.

QUESTION 2:

Please clarify the choice of day 5 for the primary effects.

COMPANY RESPONSE 2:

The Primary assessment of clinical improvement on or before day 5 was selected for assessment of clinical improvement at interim stages prior to resolution as well as clinical progress while on intravenous (IV) therapy and to test for superiority of daptomycin with respect to comparator in time to improvement in the general categories of pain, inflammation, and limb function.

CHMP comment

Again there are no definitive guidelines/ studies to determine the optimal approach. Therefore no firm conclusion can be made.

Response accepted. *Point resolved*.

QUESTION 3:

The difference between treatment groups was driven by the lower proportion of subjects in the daptomycin arm achieving clinical improvement on or before Study Day 5 in the oldest cohort (age 12 to <17 years). Please clarify whether this could be due to the dose being too less for this age group, or any other alternative explanation.

COMPANY RESPONSE 3:

The Applicant's position is that the difference between treatment groups in subjects achieving clinical improvement on or before day 5 in the oldest cohort is not due to the exposure/dose in this age group. The Applicant has no alternative explanation regarding this observation. Sparse plasma PK samples were collected in the study to assess daptomycin plasma concentrations in pediatric AHO patients. As summarized in Table 11-11 and discussed in Section 11.1.3 of the clinical study report, daptomycin plasma concentrations were generally as predicted from previous trials and were similar across age cohorts when variability was taken in to consideration. The daptomycin pharmacokinetic/pharmacodynamics (PK/PD) parameter that has been correlated with efficacy is the ratio of area under the concentration-time curve and minimal inhibitory concentration (AUC/MIC) based on mouse thigh infection model (Louie et al, 2011), and the AUC/MIC ratio has been used in probability of target attainment analyses to support product registration for other indications. While the sparse plasma concentrations from the current study could not be used to directly derive individual AUC values and were not used to generate individual AUC estimates based on the established pediatric population PK model, the age-specific, weight-based dosing regimens used in this study were also used in the pediatric Staphylococcus aureus bacteremia study DAP-PEDBAC-11-02 (P005), which demonstrated comparable efficacy of daptomycin vs. comparator across age groups in the study population. The distributions of individual AUC estimates based on population PK modelling in DAP-PEDBAC-11-02 were comparable across age groups and were similar to estimates in adults receiving the 6 mg/kg dose. As PK is not expected to be impacted by the different types of infection, the observation does not support a lower exposure in the cohort of 12 to 17 years of age compared to other age groups in the current study, and suggests that the dose for the oldest cohort cannot be used to explain the apparent difference in achieving clinical improvement on or before Study Day 5 across age groups. It should be noted that discontinuation from study medication was not the major factor for not achieving clinical improvement on or before Day 5. In addition, five of the six subjects in the daptomycin arm that did not show improvement on or before Day 5, had a clinical outcome of cure at End of Therapy (EOT) and Test of Cure (TOC) visits.

CHMP comment

There appears to be no specific reason for this observation.

Response accepted. *Point resolved*.

QUESTION 4:

The differences in the unfavourable outcome between the 2 treatment groups appeared to be due to the higher number of indeterminate outcomes in the daptomycin arm. Please clarify the reasons for this.

COMPANY RESPONSE 4:
The investigator-assessed clinical outcome of indeterminate at the End of Intravenous Study Drug (EOIV), End of Therapy (EOT), and Test of Cure (TOC) visits were based on the definitions as specified in the protocol. In the DEP-PEDOST-11-03 study, a higher proportion of subjects in the daptomycin arm had an outcome assessment of indeterminate at EOIV (3 subjects versus 0 subject in the daptomycin and comparator arms, respectively), at EOT (4 subjects versus 1 subject in the daptomycin and comparator arms, respectively), and at TOC (5 subjects versus 3 subjects in the daptomycin and comparator arms, respectively). The main reasons for assessing the outcome as indeterminate for the subjects was failure to switch to oral therapy at designated time and patient/carer unavailable for the scheduled visit.

CHMP comment

The investigator-assessed clinical outcome of indeterminate was based on protocol-specified definitions. The assessments appear to be reasonable across the two groups.

Response accepted. *Point resolved*.

6. CHMP updated overall conclusion and recommendation

Overall conclusion

The benefit/risk balance remains positive in the approved indications at present. No further regulatory action is considered necessary at this time.