25 February 2021
EMA/158534/2021
Human Medicines 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/P46/035

Note

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

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1. Introduction

On 01 December 2020, the MAH submitted a completed paediatric study for Cubicin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data were also submitted as part of the post-authorisation measure P46/035: a short Expert Overview to provide information from a recently completed (13 July 2020) Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci.

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 adult volunteers. Steady state concentrations are achieved by the third daily dose. Daptomycin is eliminated primarily by the kidney.

Cubicin was authorised via the Centralised procedure in 2006.

- Approved indication(s) and posology

Indication

Cubicin is indicated for the treatment of the following infections (see sections 4.4 and 5.1).

- 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. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- 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.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology (***of note; only the approved posology relevant for the paediatric population is shown below***):

Paediatric population (1 to 17 years of age)

The recommended dosage regimens for paediatric patients based on age and indication are shown below.

Age Group	Indication			
	cSSTI without SAB		cSSTI associated with SAB	
	Dosage Regimen	Duration of Therapy	Dosage Regimen	Duration of Therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days	7 mg/kg once every 24 hours infused over 30 minutes	(1)
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes		9 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes		12 mg/kg once every 24 hours infused over 60 minutes	
1 to < 2 years	10 mg/kg once every 24 hours infused over 60 minutes		12 mg/kg once every 24 hours infused over 60 minutes	
cSSTI = complicated skin and soft-tissue infections; SAB = *S. aureus* bacteraemia; (1) Minimum duration of Cubicin for paediatric SAB should be in accordance with the perceived risk of complications in the individual patient. The duration of Cubicin may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient. In the paediatric SAB study, the mean duration of IV Cubicin was 12 days, with a range of 1 to 44 days. The duration of therapy should be in accordance with available official recommendations.				

In paediatric patients aged 7 to 17 years, Cubicin is given by intravenous infusion over a 30-minute period (see section 6.6). In paediatric patients aged 1 to 6 years, Cubicin is given by intravenous infusion over a 60-minute period (see section 6.6).

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the paediatric study P029MK3009 (abbreviated P029) is a Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese Paediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The formulation used in study P029 was the 500 mg daptomycin lyophilized powder for reconstitution in a single-use vial and, according to the MAH, a formulation identical to that approved for use in the EU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- the paediatric study P029MK3009 (abbreviated P029): Phase II Open-Label, Single-arm Clinical Trial to Study the Safety, Efficacy and Pharmacokinetics of MK-3009 (Daptomycin) in Japanese

Pediatric Participants Aged 1 to 17 Years with Complicated Skin and Soft Tissue Infections or Bacteremia caused by Gram-positive cocci

2.3.2. Clinical study

Study P029MK3009: Phase II Open-Label, Single-arm Clinical Trial to study the safety, efficacy and pharmacokinetics of MK-3009 (daptomycin) in Japanese paediatric participants aged 1 to 17 years with complicated skin and soft tissue infections or bacteremia caused by Gram-positive cocci

Description

Methods

Objectives

The following objectives and main endpoints were evaluated in Japanese paediatric participants with cSSTI and bacteremia:

Primary Objectives	Primary Endpoints
• To assess the safety and tolerability of daptomycin.	• Adverse Events (AEs) - Participant experiencing AE - Participant discontinuing study treatment due to AEs
Secondary Objectives	**Secondary Endpoints**
• To assess the efficacy of administration of daptomycin in participants with MRSA infections.	• Clinical response at the Test of Cure (TOC) visit • Participant-level microbiological response at the TOC visit
• To evaluate steady state pharmacokinetics of daptomycin.	• Pharmacokinetic parameters such as AUC0-24 hr, Cmax, tmax, CLss, Vss, t1/2 will be evaluated if evaluable data is obtained.

Study design

P029 was an open-label, single-arm Phase II study of daptomycin (MK-3009). Japanese paediatric participants aged 1 to 17 years old with cSSTI or bacteremia caused by gram-positive cocci as an infection type were enrolled into this study. First patient, first visit was 06 December 2018, last patient, last visit was 07 April 2020. The Study completion date was 13 July 2020 and data cut-off/database lock date was 16 July 2020.

After a maximum duration of 72-hour screening period, eligible participants received a minimum of 5 days to up to a maximum of 14 days (cSSTI) or 42 days (bacteremia) of IV study therapy. While on study therapy, study visits were performed on Day 1 (initiation of IV study drug), Day 3 (on therapy visit), and at end of therapy (EOT). Following the completion of IV study therapy, all participants were evaluated for 7 days following completion of therapy (at test of cure, TOC visit). In addition, a Follow up (FU) visit was performed in all participants at 14 days after completion of IV study therapy. All participants remained in the study for a total of up to 31 days (cSSTI) or 59 days (bacteremia).

Study population /Sample size

Twenty (20) Japanese male and female participants aged 1 to 17 years old requiring intravenous antibiotic treatment for cSSTI or bacteremia known or suspected to be caused by gram-positive cocci were to be enrolled into the study. Complicated infections were defined as infections either involving deep soft tissue or requiring significant surgical intervention (e.g. cellulitis, erysipelas, infected ulcers, burns, and major abscesses), or skin and soft tissue infections accompanied by systemic signs and/or symptoms where intravenous antibiotic therapy was warranted.

Due to the difficulty of enrolling paediatric participants during the COVID-19 pandemic, the study concluded enrolment with 18 participants, as explained to the Japanese PMDA.

The patients were to demonstrate at least 3 of the following protocol-defined signs and symptoms associated with an ongoing acute infectious process: pain, tenderness to palpitation, temperature >37.0°C axillary or >37.5°C oral or >38.0°C rectal, forehead or aural, White blood count (WBC) >12,000/mm^3 or ≥10% bands, swelling and/or induration, erythema (>1cm beyond edge of wound or abscess), pus formation and CRP > Upper Limited of Normal.

If a participant met both criteria for cSSTI and bacteremia, the participant had to be allocated to the group of bacteremia.

Treatments

Daptomycin 500 mg formulated as a lyophilized powder for reconstitution was administered once daily as IV infusion. The dosing regimen for daptomycin in this study was in accordance with the previously approved dosing regiments for the respective indications, which is based on pharmacokinetic (PK) data in paediatric subjects, population PK modelling and simulation, and nonclinical effects in juvenile dogs. The dose was assigned according to weight and infection type in each age group as indicated in the following table:

Group	Age (years)	n	Infusion Duration	cSSTI
1	12 to 17	3	30 minutes	5 mg/kg q 24 hrs
2	7 to 11	5	30 minutes	7 mg/kg q 24 hrs
3	2 to 6	3	60 minutes	9 mg/kg q 24 hrs
4	1 to <2	3	60 minutes	10 mg/kg q 24 hrs

Group†	Age (years)	n	Infusion Duration	Bacteraemia
1	12 to 17	1	30 minutes	7 mg/kg q 24 hrs
2	7 to 11	1	30 minutes	9 mg/kg q 24 hrs
4	1 to <2	2	60 minutes	12 mg/kg q 24 hrs
†Participants with bacteraemia were not enrolled in Age Group 3.				

According to MAH, it has previously been established that no differences in PK, efficacy or safety occurs between Japanese and non-Japanese adults. The approved dose in non-Japanese and Japanese adults is identical.

Outcomes/endpoints

See above under "Objectives".

Statistical Methods

Safety: The APaT population was used for the analysis of safety data. It consisted of all enrolled participants who received at least one dose of study treatment. The proportions of participants were calculated for broad clinical and laboratory AE categories [e.g., any AE, a drug-related AE, a serious AE (SAE), a drug-related SAE, discontinuation of study treatment due to an AE], as well as specific AEs (system organ classes and preferred terms).

Efficacy: The primary population for efficacy analysis was the modified intent-to-treat (MITT)-MRSA population consisting of those participants with positive culture of MRSA at baseline. MRSA was the target pathogen of the Japanese adult indication. MRSA was defined with MIC test in the central laboratory (oxacillin 4 µg/mL or more).

At the TOC (and EOT) visit, the investigator determined the participant's clinical response based on consideration of the participant's signs and symptoms compared with those present at baseline.

At the TOC (and EOT) visit, the participant's microbiological response was derived from the pathogen-level microbiological response for all of the participant's baseline infecting pathogens and from the presence or absence of a superinfecting pathogen or new infecting pathogen (gram-positive cocci).

The proportions of participants achieving clinical success and microbiological success, respectively, were calculated by visit, along with corresponding 95% confidence intervals by the method of Clopper and Pearson.

Clinical pharmacology: The population for PK analysis included all enrolled participants who received at least 3 consecutive IV infusions of daptomycin, had at least one PK sample following treatment administration on the PK sampling day and did not have any important protocol violations affecting the PK profile.

After initiation of IV treatment, PK sampling was scheduled for day 3: pre-dose, after 15 minutes, 1 hr, 4 hrs and 12 hrs after the end of infusion for all subjects. No clinical PD measurements were collected. The pharmacokinetic parameters (C_{max} (µg/mL), T_{max} (hr), C_{12hr} (µg/mL), $AUC_{0\text{-}24hr}$ (µg*hr/mL), $t_{1/2}$ (hr), CL_{ss} (mL/hr), $CL_{ss/wt}$ (mL/hr/kg), V_{ss} (mL), and $V_{ss/wt}$ (mL/kg)) were calculated using non-compartmental PK analysis.

Results

Recruitment/ Number analysed

A total of 18 participants (14 with cSSTI and 4 with bacteremia) were enrolled across 12 study sites in Japan. No participants were enrolled in violation of the entry criteria. All participants received at least 1 dose of daptomycin and completed the study. One participant with bacteremia (1 to <2 years old) discontinued study medication on Day 5 due to lack of efficacy. This patient also suffered from acute myeloid leukaemia and received concomitant systemic antibacterials which were prohibited by the protocol (such as e.g., vancomycin and meropenem). *Streptococcus oralis* was detected from the blood culture, and on Day 15 (TOC), the clinical response was "Failure", and the microbiological response was "Eradication". No superinfection or new infection was reported in this subject.

Of note, 2 participants in the bacteremia cohort had protocol deviations for prohibited medication (vancomycin, meropenem and sulfamethoxazole trimethoprim). However, the investigators and the sponsor still agreed to allow the use of these treatments. No participant's data were excluded from analyses due to an important protocol deviation.

Baseline data

The majority of participants (cSSTI: 9/14, 64.3%, bacteremia: 3/4, 75.0%) were male. The median age was 7 years and 6 years in the cSSTI and bacteremia groups, respectively. In participants with cSSTI, 3 participants were included in each of the age groups 1-<2 years, 2-6 years and 12-17 years, while 5 participants were included in the age group 7-11 year. In participants with bacteremia, 2 participants were included in the age group 1-<2 years and 1 participant in each of the age groups 7-11 year and 12-17 years (no participant was between 2-6 years). The age range was 1-13 years for cSSTI and 1-15 years for bacteremia, thus no participant was above 15 years. Please also see table above under "Treatments".

The most frequently occurring diagnosis in participants with cSSTI was cellulitis and infected skin ulcer (4/14, 28.6% each). The other diagnoses were abscess (2/14, 14.3%), skin infection (2/14, 14.3%), wound infection (1/14, 7.1%) and burn infection (1/14, 7.1%). Most participants (cSSTI: 13/14, 92.9%, bacteremia: 4/4, 100%) had gram-positive monomicrobial infection.

The most common baseline pathogens were MRSA (6/14 in the cSSTI group, 42.9%) and MSSA (4/14 in the cSSTI-group, 28.6%). For other pathogens there were only one baseline pathogen identified per patient. In the bacteremia group there was no more than one baseline pathogen identified per patient.

Extent of exposure: In the APaT population, all participants received daptomycin for the protocol-specified range of 5 through 14 days (cSSTI) or 5 through 21 days (bacteremia). Mean exposure time for the cSSTI-group was 6.9 days (SD 2.6) and median 6.0 days (range 5-14 days). In the bacteraemia-group, the mean exposure time was 14.3 days (SD 6.7) and median 15.5 days (range of 5-21 days).

Efficacy results

In this study, efficacy outcomes were evaluated as secondary and exploratory endpoints (the latter not shown).

A key secondary efficacy endpoint was the clinical response at TOC in participants with MRSA infections. The MITT-MRSA population included a total of 8 participants (7 with cSSTI and 1 with bacteremia). In this population, 6 of 7 (85.7%) participants with cSSTI and the sole participant with bacteraemia achieved favourable clinical response at TOC, see table below. For 5/7 in the cSSTI group and 1/1 in the bacteremia group, the clinical response was "cure". In the cSSTI group, there was also one "Improvement" and one "Failure".

Proportion of participants with clinical success by visit (MITT-MRSA population)

	cSSTI			Bacteremia		
Visit	n/m	(%)	95% CI[†]	n/m	(%)	95% CI[†]
EOT	7/7	(100.0)	(59.0, 100.0)	1/1	(100.0)	(2.5, 100.0)
TOC	6/7	(85.7)	(42.1, 99.6)	1/1	(100.0)	(2.5, 100.0)

[†] Based on Clopper-Pearson method.
n = number of subjects with clinical success.
m = number of subjects in population

Source: [Ref. 5.3.5.2: P029MK3009: Table 11-1]

Another key secondary efficacy endpoint was the per-participant microbiological response at TOC in participants with MRSA infections. In the MITT-MRSA population, 5 of 7 (71.4%) participants with cSSTI and the sole participant with bacteraemia achieved favourable microbiological response at TOC, see table below.

Proportion of participants with Microbiological Success by Visit (MITT-MRSA population)

	cSSTI			Bacteremia		
Visit	n/m	(%)	95% CI†	n/m	(%)	95% CI†
EOT	5/7	(71.4)	(29.0, 96.3)	1/1	(100.0)	(2.5, 100.0)
TOC	5/7	(71.4)	(29.0, 96.3)	1/1	(100.0)	(2.5, 100.0)

†Based on Clopper-Pearson method.
n = number of subjects with microbiological success.
m = number of subjects in population

Source: [Ref. 5.3.5.2: P029MK3009: Table 11-2]

When including presumed eradication in addition to confirmed eradication to define favourable microbiological response, 6 of 7 (85.7%) participants with cSSTI achieved favourable microbiological response at TOC in the MITT-MRSA population.

Safety results

In the APaT population (N= 18 paediatric patients), AEs are reported in 55.6% (10/18) of all participants; 42.9% (6/14) of participants with cSSTI and 100% (4/4) of participants with bacteremia experienced at least 1 AE. All AEs were mild except moderate rash which occurred in 1 participant with cSSTI. 2 participants (11.1%) had drug-related AEs.

The most frequently reported AEs (reported in two or more participants) were pyrexia and rash (n=2 each). Two participants each experienced one drug-related AE. Platelet count increased occurred in one participant (bacteremia, 1–< 2 years) on Day 5 and resolved (duration: 1 week). Infusion site swelling occurred in one participant (cSSTI, 12–17 years) on Day 5 and resolved (duration: 3 hours). Both AEs were mild, and no action was taken in regard to study medication administration.

There were no SAEs, deaths and discontinuations of study medication due to an AE reported.

In this study, Events of clinical interest was defined for hepatic transaminase. In this study, hepatic transaminase ECI was defined as AST or ALT ≥3 X ULN and total bilirubin ≥2 X ULN and alkaline phosphatase <2 X ULN. One participant with bacteremia, (7–11 years) met the criterion of aminotransferase (ALT or AST) elevation. This participant had high aminotransferase values at screening period (e.g. ALT ≥10 x ULN and AST 5 to 10 x ULN) and Day 7 (e.g. ALT ≥10 x ULN) and the values decreased during treatment period [e.g. ALT (Day 12) and AST (Day 7) < 3 x ULN]. No AEs related to liver dysfunction were reported in this participant.

Chemistry Findings That Met Predetermined Criteria for Change: Regarding creatine phosphokinase (CPK), the abovementioned patient also had increased CPK values of 1,026 IU/L (>2.5 to 5 x ULN) on Day 1 (screening period) and 1,265 IU/L on Day 3 (treatment period), however, no AEs associated with musculoskeletal disorders or abnormal investigations reported. Note that this participant had complicated concomitant diseases which included B-cell lymphoma, bone marrow failure and tumor lysis syndrome. The MAH states that no clinically meaningful change of CPK over study days was observed in any infection types and age categories except the one participant described above.

The relationship between CPK elevations and daptomycin exposures (AUC0-24hr, Cmax and C12hr) in Japanese paediatric participants was evaluated. The MAH claims that the analysis showed no apparent relationship between CPK elevations and daptomycin exposure in Japanese paediatric participants. See the Pharmacology heading/section for details.

Otherwise, regarding laboratory values over time, the MAH states that there were no clinically meaningful changes from baseline in chemistry and hematology laboratory values. The assessments

and observations were comparable across age categories and infection types. No clinically meaningful findings were reported from assessments of vital signs, physical and neurological examinations, or motor development skills.

In addition to this study, the MAH states there have been no new safety concerns identified from review of the post-marketing experience in paediatric patients; and the safety profile in paediatric patients appears similar to the safety profile in adults.

In conclusion, there were 2 drug-related AEs in 2 participants reported (platelet count increased and infusion site swelling), and CPK elevation was observed in one participant (1,265 U/I, 2.5 to 5x upper limit of normal range), but IV administration of daptomycin was apparently well tolerated in general with no SAEs, deaths, ECIs or AE leading to study medication discontinuation. Based on the results of the present study, there do not appear to be any new safety concerns in the paediatric population. However, having in mind there is a very limited number of included patients – only 18 of which only 4 participants with bacteremia - in this study, the results should be interpreted with caution.

Clinical Pharmacology

cSSTI population

In the cSSTI population (N=14), all participants provided 5 PK plasma samples each. The mean $AUC_{0\text{-}24hr}$ and C_{max} observed with the age-specific, weight-based doses ranged from 316 to 574 µg*hr/ml and 49.1 to 91.7 µg/ml, respectively. See table below for presentation by age group.

A target exposure window for treatment of cSSTI in the paediatric population have previously been described (347-641 µg*h/mL). This have been derived from the exposure levels observed in healthy volunteers administered the same daily dose as the one approved in the treatment of complicated skin and skin structure infections (cSSSI) in adult patients (4 mg/kg).

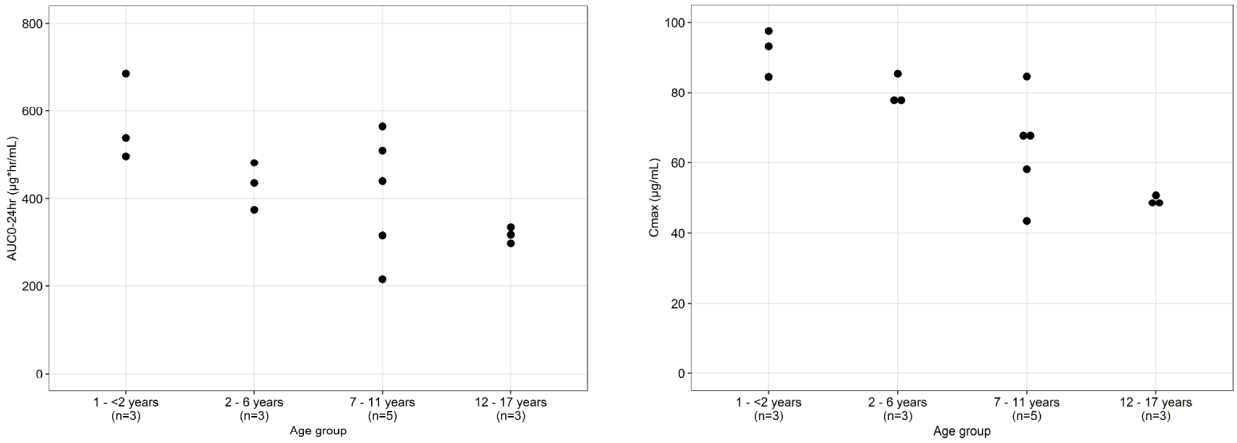
Summary of Pharmacokinetic Parameters for Daptomycin Following the Administration of Multiple 5 to 10 mg/kg Doses in Japanese Paediatric Participants with cSSTI Between the Ages of 1 to 17 Years in P029

Parameter	Age Group 1 12 to 17 years 5 mg/kg n=3 Mean (SD)	Age Group 2 7 to 11 years 7 mg/kg n=5 Mean (SD)	Age Group 3 2 to 6 years 9 mg/kg n=3 Mean (SD)	Age Group 4 1 to <2 years 10 mg/kg n=3 Mean (SD)
Infusion Duration (min)	30	30	60	60
AUC0-24hr (µg*hr/mL)	316 (18.2)	409 (143)	431 (53.6)	574 (99.1)
Cmax (µg/mL)	49.3 (1.33)	64.4 (15.1)	80.3 (4.48)	91.7 (6.66)
Tmax (hr)	0.750 (0.00)	0.863 (0.0939)	1.21 (0.0788)	1.34 (0.0193)
t1/2 (hr)	5.71 (0.942)	5.07 (1.09)	3.87 (0.514)	4.94 (0.460)
CLss/wt (mL/hr/kg)	15.8 (0.917)	19.4 (8.27)	21.1 (2.69)	17.8 (2.86)
Vss (mL)	6410 (1090)	3930 (2030)	1750 (486)	1150 (299)

Source: Adapted from [Ref. 5.3.5.2: P029MK3009: Table 14.2-38, 14.2-39, 14.2-40, 14.2-41]

The MAH has presented graphically the distribution of individual $AUC_{0\text{-}24hr}$ and C_{max} for daptomycin in cSSTI patients by age group (figure below). The comparison of the different age groups indicates that

in Japanese cSSTI paediatric patients, the $AUC_{0\text{-}24hr}$ and C_{max} tend to increase slightly with younger age.



The Distribution of Individual $AUC_{0\text{-}24hr}$ and C_{max} for Daptomycin at Steady State of a Repeated Intravenous Administration of Daptomycin 5, 7, 9 or 10 mg/kg q24 hrs infused over 30 or 60 minutes in Japanese Paediatric Participants with cSSTI Aged 1 to 17 Years, with Stratification by Age Group. Source: Clinical study report Figure 11-2.

Bacteremia population

In the bacteremia population (N=4), three participants provided 5 PK samples, while one provided two PK samples. The Rapporteur could not find any explanation in the study report for the patient only providing two PK samples. Due to the limited number of patients included in the bacteremia population, individual values are presented, see table below.

The dosing regimen for treatment of bacteremia in paediatric patients has previously been selected to ensure AUC exposures within the range of safe and efficacious exposures reported in adults treated with 6 mg/kg for bacteremia (270-1151 µg*h/mL).

Individual Pharmacokinetic Parameters for Daptomycin Following the Administration of Multiple 7 to 12 mg/kg Doses in Japanese Paediatric Participants with Bacteraemia Between the Ages of 1 to 17 Years in P029

Parameter	Age Group 1 12 to 17 years 7 mg/kg n=1 Ind. Values[a]	Age Group 2 7 to 11 years 9 mg/kg n=1 Ind. Values[a]	Age Group 4 1 to <2 years 12 mg/kg n=2 Ind. Values[a,b]
Infusion Duration (min)	30	30	60
AUC0-24hr (µg*hr/mL)	422	599	502, ND
Cmax (µg/mL)	94.0	73.1	97.7, 110
Tmax (hr)	0.733	0.800	1.20, 1.33
t1/2 (hr)	3.98	5.85	4.46, ND
CLss/wt (mL/hr/kg)	16.6	15.0	23.9, ND
Vss (mL)	5110	4010	1920, ND

ND: Not determined

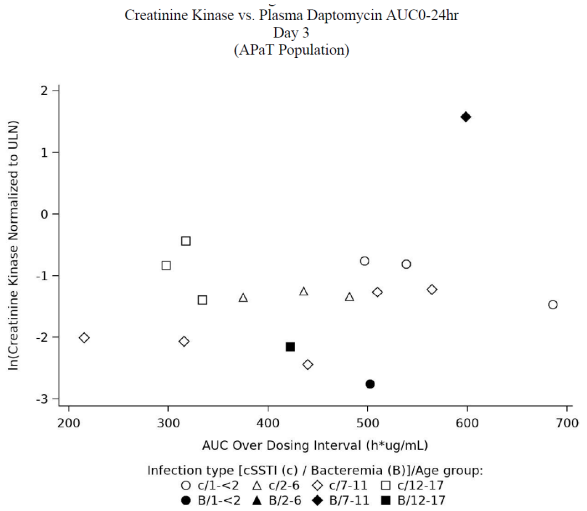
[a] The numbers provided here indicate individual values.

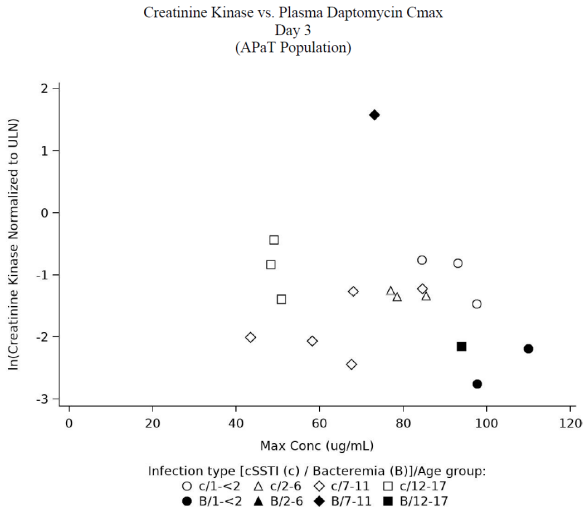
[b] For the two participants in Age Group 4, Cmax and Tmax were determined for both, while AUC, half-life, Vss, and CLss/wt were determined for only one.

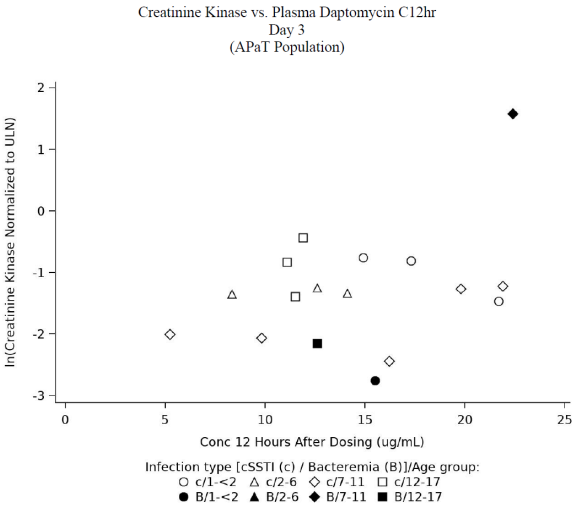
Source: Adapted from [Ref. 5.3.5.2: P029MK3009: Table 14.2-42]

Exposure-safety relationships

One safety concern with daptomycin is elevation of CPK, hence the relationship between CPK elevations and daptomycin exposures ($AUC_{0\text{-}24hr}$, C_{max} and C_{12hr}) was evaluated graphically. The MAH states that no apparent relationship was shown between CPK elevations and daptomycin exposure in Japanese paediatric patients (see figure below). The MAH concludes that the potential increase in CPK is not expected to be clinically relevant.







Relationship between Creatinine Phosphokinase (CPK) elevations and daptomycin $AUC_{0\text{-}24hr}$, C_{max} and C_{12hr} in Japanese paediatric patients at day 3. Source: Clinical study report Figure 12-1, 12-2 and 12-3.

As mentioned in the section above, *Safety Results*, one patient with bacteremia had elevated CPK-values, 1,026 IU/L (>2.5 to 5 x ULN) on Day 1 (screening period) and 1,265 IU/L on Day 3 (treatment period). The AUC in this patient (599 µg*hr/mL on Day 3) was generally comparable to those from other participants with bacteremia, and according to the MAH, it should be noted that this patient also had concomitant diseases including B-cell lymphoma, bone marrow failure and tumour lysis syndrome.

2.3.3. Discussion on clinical aspects

In the EU, Cubicin is already approved for paediatric patients (1 to 17 years of age) with complicated skin and soft-tissue infections (cSSTI; in 2015, EMEA/H/C/0637/II/053/G) and for bacteraemia associated with cSSTI (in 2017, EMEA/H/C/0637/II/061).

The MAH has now submitted a paediatric study performed in Japanese children in accordance with Article 46 of Regulation (EC) No1901/2006.

The doses selected in the study were identical to the paediatric doses for Cubicin as already approved in the EU. Of note, 2 of 4 participants in the bacteraemia cohort had protocol deviations for prohibited medication, making it difficult to conclude on the efficacy of daptomycin in these patients. However, considering the very low total number of bacteremic patients, no firm overall conclusions can in any case be drawn. Besides, efficacy was not the primary objective in this study.

The primary objective of this study was to evaluate the safety and tolerability of daptomycin in paediatric Japanese patients. No SAEs, deaths, ECIs or AE leading to study drug discontinuation were reported, and no new safety signals were identified in this study, recognizing the limited number of patients included which precludes detecting possible uncommon and rare events.

Evaluation of steady state pharmacokinetics of daptomycin was a secondary objective of this study. Exposure in paediatric Japanese patients tend to increase slightly with younger age. The Rapporteur has not identified similar trends of age-dependent daptomycin exposure in previous paediatric studies but as the MAH points out, the PK data in the current study are limited and trends should be interpreted with caution. The exposure of daptomycin across the age range studied are still within the previously determined target exposure windows and comparable with $AUC_{0\text{-}24hr}$ and C_{max} determined in previous studies in the paediatric population. Additionally, $t_{1/2}$ and $CL_{ss/Wt}$ of daptomycin observed in this study is consistent with previous observations in the paediatric population. According to the 2009

Guideline on Summary of Product Characteristics (SmPC), pharmacokinetic characteristics in special populations should be described in section 5.2 of the SmPC. Since there seems to be no apparent difference in exposure between the currently studied Japanese paediatric population and previously studied Caucasian subjects, the findings are considered to be clinically relevant and should be included in the Cubicin SmPC (see section 3. for proposed wording).

Based on the limited number of subjects included, there seems to be no apparent correlation between CPK elevations and investigated PK measures (AUC_{0-24hr}, C_{12}, and C_{max}), which is in line with previous findings (C_{12} and C_{max}).

The results based on the limited number of 18 paediatric Japanese patients from study P029MK3009 appear to be consistent for efficacy and safety with those from patients obtained in previous clinical trials with Cubicin.

On the basis of this study, there is no change in the benefit-risk profile of Cubicin for the existing indications. However, an amendment in section 5.2 of the SmPC is proposed, to include relevant information to the clinicians that the PK are similar across the races studied, in order to generate increased confidence in the extrapolation of the current dosing regimen established in one population to other populations. According to the SmPC guideline section 5.2. c), characteristics in specific groups of patients should be described.

3. Overall conclusion and recommendation

Although limited, the data provided in this submission are not considered to raise any safety or efficacy concerns for daptomycin in the paediatric population. Hence, the benefit/risk balance remains unchanged and positive in the approved indications at present.

Based on these results the MAH proposed no amendments to the basic prescribing information or in the RMP. This is not completely endorsed and an amendment in section 5.2 of the SmPC is recommended, with the wording provided below.

☒ Fulfilled:

In view of the new data regarding pharmacokinetics in the Japanese population, the SmPC (section 5.2.) should be updated to include the following recommended wording:

Race

No dosage adjustment is necessary in Japanese subjects. After administration of the recommended dose in 18 Japanese paediatric subjects (1-15 years), exposure was similar across the age range as previously observed in Caucasian paediatric subjects.

The MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.