12 October 2017
EMA/683418/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cubicin

International non-proprietary name: daptomycin

Procedure No. EMEA/H/C/000637/II/0061

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

Abbreviation	Definition
µg	Microgram
ABSSI	Acute bacterial skin and skin structure infections
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase
AST (SGOT)	Aspartate aminotransferase
AUC	mean steady state systemic exposure; Area under the curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{ss}	Area under the plasma concentration time curve at steady-state
BIP	Baseline infecting pathogen
BLQ	Below limit of quantitation
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CE	Clinically evaluable
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Total clearance, calculated as Dose/$AUC_{0-\infty}$ after an intravenous dose
CL_{cr}	Creatinine clearance rate
CL/WT	Total clearance normalized by body weight
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CrCl	Creatinine clearance
C_{trough}	Plasma concentration in sample obtained just before dosing
CoNS	Coagulase-negative Staphylococci
CPK	Creatine Phosphokinase
CRO	Contract research organization
CSR	Clinical Study Report
CV	Coefficient of variation
cSSSI	Complicated skin and skin structure infection
cSSTI	Complicated skin and soft tissue infections
DAP	Daptomycin
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Echocardiogram
eCRF	Electronic case report form

EDC	Electronic data capture
EOIV	End-of IV Therapy
EOT	End-of-Therapy
EUCAST	European Committee of antimicrobial susceptibility testing
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IWRS	Interactive Web-Based Response System
ICH	International Conference on Harmonization

IDSA	The Infectious Disease Society of America
IE	Infective endocarditis
IEAC	Independent External Adjudication Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IV LLOQ	Intravenous Lower limit of quantification
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIC	Minimum inhibitory concentration
MIC_{90}	Minimum inhibitory concentration of 90% of specific organisms
min	Minute
MITT	Modified Intent-to-Treat
mL	Milliliter
mMITT	Microbiological Modified Intent-to-Treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NOEL	No-observed-effect-levels
NCPKULN	Normalized CPK by upper limit of normal
NS	Normal saline
PD	Pharmacodynamic
PMA	Post-menstrual age
PK	Pharmacokinetic
PT	Preferred term
q12h	Every 12 hours
q24h	Every 24 hours
RIE	Right-sided infective endocarditis
RNA	Ribonucleic acid
RR	Reference range
SAB	*Staphylococcus aureus* bacteremia
SAE	Serious adverse event

SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	Standard of Care
$t_{1/2}$	Half-life
T_{max}	Time to the maximum observed plasma concentration
TEAE	Treatment-emergent Adverse Event
TOC	Test of Cure
TPN	Total parental nutrition
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
VHP	Voluntary Harmonization Procedure
V_{SS}	Volume of distribution at steady-state
V_{SS}/WT	Total volume of distribution normalized by weight $_{WT}$ Body weight
WNL	Within normal limits

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 16 December 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated accordingly.

In addition, the marketing authorisation holder (MAH) took the opportunity to bring the product information in line with the latest QRD template version 10 and to combine the SmPCs for both strengths (350 and 500 mg). The MAH also updated the RMP, from last approved version 9.1 to the current proposed version 10.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable as Cubicin is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate.

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

Not applicable

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Infections due to resistant Gram-positive bacteria are increasingly common in paediatric patients. The major target for daptomycin is *S. aureus*, an organism in which daptomycin resistance is rare. Serious infections due to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in particular are a major health problem worldwide. Few antibiotics with activity against MRSA or other serious Gram-positive bacteria are currently available, and fewer still have had their safety and efficacy carefully evaluated in paediatric patients.

Daptomycin for injection (licensed as CUBICIN [hereafter referred to as daptomycin]) is a cyclic lipopeptide antibacterial derived from the fermentation of a strain of *Streptomyces roseosporus*. The mechanism of action of daptomycin is distinct from that of any other antibacterial agent. Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential inhibits deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis, which results in bacterial cell death. Daptomycin has potent in vitro activity against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) strains.

Daptomycin is supplied in single-use vials containing 500 mg daptomycin as a sterile, lyophilized powder. In some regions of the world, single-use vials containing 350 mg daptomycin as a sterile, lyophilized powder are also available.

Cubicin was approved in the EU in January 2006, for treatment of adult with complicated skin and soft tissue infections (cSSTI). The recommended dosing was 4 mg/kg once daily. In October 2007 the indications was extended in adults to include *Staphylococcus aureus* bacteraemia (SAB), right sided infective endocarditis (RIE) due to *S. aureus* and SAB when associated with RIE or with cSSTI. The recommended daily dose for these indications is 6 mg/kg once daily. The current indication which also includes paediatric patients (1-17 years of age (yoa)) with cSSTI was approved in October 2015.

The recommended paediatric dosing (once every 24 hrs) for cSSTI are as follows: 12-17 yoa: 5 mg/kg, 7-11 yoa: 7 mg/kg, 2-6 yoa: 9 mg/kg and 1 to<2 yoa: 10 mg/kg. Duration of treatment is up to 14 days.

Clinical studies and post-marketing pharmacovigilance have demonstrated a well-characterized safety profile for daptomycin in adults. To date, the safety of daptomycin in the paediatric population appears to be comparable to that observed in adults. In clinical studies of daptomycin in both adults and paediatric patients, most adverse events (AEs) were characterized as mild or moderate in intensity and were not attributed to the study drug. Overall, the most frequently reported AEs in paediatric patients were in the following system organ classes (SOCs): gastrointestinal disorders, investigations and skin and subcutaneous tissue disorders. Elevated creatine phosphokinase (CPK) was reported as an AE more frequently in patients treated with daptomycin than in patients receiving placebo or comparator antibiotics.

Current application

The MAH has performed a number of studies to support the efficacy, safety and PK/PD in the paediatric population (please refer to table, section 2.3.1).

Studies DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-09-01, DAP-PEDS-07-03 have been assessed previously. Study DAP-PEDS-07-03 was assessed in connection with the approval of the extension to paediatric patients with cSSTI (EMEA/H/C/000637/II/0053/G).

The MAH's purpose of this Type II variation is to extend the *S. aureus* bacteraemia associated with cSSTI indication for daptomycin to include paediatric patients 1 to 17 years of age.

The proposed additional doses in the bacteraemia indication in children ages 1 to 17 years are as follows:

• Age 12 to 17 years old: 7 mg/kg once daily

• Age 7 to 11 years old: 9 mg/kg once daily

• Age 1 to 6 years old: 12 mg/kg once daily

In support of this proposal, the applicant has provided a clinical study report on **DAP-PEDBAC-11-02**.

In addition, the application also includes:

An integrated safety study data for daptomycin across the paediatric program is included in the data package. These include:

- a Phase 4 efficacy and safety study in paediatric subjects with cSSSI (Paediatric Phase 4 cSSSI study [DAP-PEDS-07-03], and
- three Phase 1 single-dose clinical studies in paediatric subjects ([DAPPEDS-05-01], [DAP-PEDS-07-02], and [DAPPEDS-09-01].

It is noted that study DAP-PEDBAC-11-02 was assessed under the Article 46. The procedure (EMA/H/C/0637/P46) has been completed. During the procedure the UK rapporteur raised two issues:

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.

The final assessment report concluded that MAH responded adequately to both issues. Thus, these issues will not be discussed further in this assessment report.

Moreover, the final assessment report of the Article 46 procedure EMA/H/C/0637/P46 concluded that "*… 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.*"

Paediatric requirements

There are no requirements applicable for this application according to the Paediatric Regulation.

In the US, the paediatric Phase 4 SAB study ([DAP-PEDBAC-11-02]) was a post-marketing FDA requirement (PMR) under PREA (PMR 804-7) to evaluate the safety and efficacy of daptomycin for the treatment of bacteraemia in paediatric subjects.

In Europe, this study is reportable according to Article 46 of the Paediatric Regulations. The DAP-PEDBAC-11-02 clinical study report (CSR) was submitted to EMA on 20-Jun-2016, consistent with the timelines required for Article 46 submissions. With the present submission, the MAH proposes to extend the *S. aureus* bacteraemia indication for daptomycin to include paediatric patients 1 to 17 years of age.

2.2. Non-clinical aspects

No new non-clinical data, except on clinical microbiology, have been submitted in this application.

Also an ecotoxicity/environmental risk assessment has been provided (original ERA submitted during the assessment).

2.2.1. Pharmacology

Clinical microbiology

The major target organism in this disease is *S. aureus*, an organism in which daptomycin resistance is rare. Daptomycin has potent *in vitro* activity against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) strains.

Development of daptomycin-resistance during therapy has been identified. The mechanisms of resistance to this agent appear to be diverse. Strains that are non-susceptible to daptomycin often exhibit accumulation of single nucleotide polymorphisms in the multipeptide resistance factor gene (mprF) and the yycFG genes in the yycFGHI operon. Both of these loci are known to be involved in key cell membrane function.

Daptomycin-resistant strains demonstrate other changes in the cell membrane physiology including resistance to cell membrane depolarization and permeabilisation, and reduced surface binding of daptomycin. Additionally, modifications of the cell wall may also contribute to daptomycin resistance, including enhanced expression of the dlt operon and progressive cell wall thickening.

Data from US and EU surveillance studies of daptomycin against Gram-positive clinical isolates are shown in the tables below. Overall, daptomycin was active against staphylococci. Only six *S. aureus* strain (0.11%) showed a reproducible daptomycin MIC value greater than 1 µg/mL. All CoNS strains were susceptible to daptomycin.

Table 1

Daptomycin MIC frequency distributions by organism group for all age groups and all infection sites combined (USA, 2012).

No. of isolates (cumulative %) inhibited at daptomycin MIC (µg/mL) of:

Organism	Total	≤0.06	0.12	0.25		1	2	4	MIC50	MIC90
S. aureus	3,747	4 (0.1)	81 (2.3)	2724 (75.0)	897 (98.9)	40 (>99.9)	1 (100.0)	--	0.25	0.5
MRSA	1,774	--	27 (1.5)	1243 (71.6)	483 (98.8)	20 (99.9)	1 (100.0)	--	0.25	0.5
MSSA	1,973	4 (0.2)	54 (2.9)	1481 (78.0)	414 (99.0)	20 (100.0)	--	--	0.25	0.5
Coagulase-negative staphylococci	287	4 (1.4)	25 (10.1)	109 (48.1)	123 (90.9)	26 (100.0)	--	--	0.5	0.5

Table 2

Daptomycin MIC frequency distributions by organism group for all age groups and all infection sites combined (USA and EU, 2014).

No. of isolates (cumulative %) inhibited at daptomycin MIC (µg/mL) of:

Organism	Total	≤0.06	0.12	0.25	0.5	1	2	4	MIC50	MIC90
Staphylococcus aureus	5,374	6 (0.1)	195 (3.7)	4186 (81.6)	955 (99.4)	26 (99.9)	5 (>99.9)	1 (100.0)	0.25	0.5
MRSA	2,065	2 (0.1)	54 (2.7)	1503 (75.5)	490 (99.2)	11 (99.8)	5 (100.0)	--	0.25	0.5
MSSA	3,309	4 (0.1)	141 (4.4)	2683 (85.5)	465 (99.5)	15 (>99.9)	0 (>99.9)	1 (100.0)	0.25	0.5
Coagulase-negative staphylococci	796	8 (1.0)	74 (10.3)	358 (55.3)	318 (95.2)	38 (100.0)	--	--	0.25	0.5

2.2.2. Ecotoxicity/environmental risk assessment

An original environmental risk assessment has been submitted during the procedure, with only Phase I testing completed.

According to the MAH, the extension of indication will not result in a substantial change in sale. However, the PEC calculation appearing in the original ERA cannot be agreed to. In case of adults, the PEC surface water is 3.6 µg/l; in case of children 0.48 µg/l. Even in case it is assumed that adults are only treated for 14 days per year, the PEC surface water is 0.08 µg/l and thus higher than the action limit of 0.01 µg/l. Therefore, a Phase II ERA is required for Cubicin.

2.2.3. Discussion on non-clinical aspects

In the assessment of the initial marketing authorisation application for Cubicin (submitted in 2005), it was concluded that daptomycin is not expected to pose a risk to the environment. This conclusion was solely based on a refined PECsurface water= 0.0016 µg/l and the logKow value. An application for extension of indication to include children with cSSTI was approved in 2015 (EMEA/H/C/0637/II/053/G). For that application, the 1.4 %/year increase in sale estimated by the applicant did not trigger any request for environmental data.

The justification forwarded by the applicant in both the current and the previous application for paediatric indication was based on market forecast data, and thus not in line with the guidance document on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 2). The PEC calculation appearing in the original ERA cannot be agreed to and Phase II ERA results should subsequently be submitted.

2.2.4. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation: Phase II ERA results to be submitted by end of March 2019.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- **Tabular overview of clinical studies**

Table 3: Tabular overview of all paediatric clinical studies

Trial ID	Merck Protocol Number	Trial Title	Trial Design	Dosing Regimens:	Trial Population/ Subject Exposure	FPFV; LPLV
[DAP-PEDS- 05-01] [Ref. 5.3.3.2: P028]	028	An Evaluation of the Pharmacokinetics of a Single Dose of Daptomycin (4 mg/kg) in Paediatric Patients Aged Two to Seventeen Years Who Are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection	Phase 1, multi-center, single-dose; PK	Daptomycin (MK-3009): • Single dose of 4 mg/kg given IV as a 30-minute infusion	Males/females Age: 2 to 17 years Daptomycin (MK-3009): 4 mg/kg: 25 subjects	25-Aug-2005; 09-Aug-2006
[DAP-PEDS- 07-02] [Ref: 5.3.3.2: P023]	023	An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Paediatric Subjects Aged Two to Six Years Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection	Phase 1, multi-center, single-dose; PK	Daptomycin (MK-3009): • Single dose of 8 mg/kg given IV as a 1-hour infusion • Single dose of 10 mg/kg given IV as a 1- or 2-hour infusion	Males/females Age:2 to 6 years Daptomycin (MK-3009): 8 mg/kg: 6 subjects 10 mg/kg: 6 subjects 12 subjects total	03-Jun-2008; 20-Nov-2008
[DAP-PEDS- 09-01] [Ref. 5.3.3.2: P018]	018	An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Paediatric Subjects Aged 3 Months to Twenty-four Months Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Bacterial Infection Including Peri-Operative Prophylactic Use of Antibiotics	Phase 1, multi-center, single-dose; PK	Daptomycin (MK-3009): • Single dose of 4 mg/kg given IV as a 30-minute infusion • Single dose of 6 mg/kg given IV as a 30-minute infusion	Males/females Age: 3 to 24 months Daptomycin (MK-3009): 4 mg/kg: 7 subjects 6 mg/kg: 17 subjects 24 subjects total	13-Jan-2010; 20-Mar-2012

Trial ID	Merck Protocol Number	Trial Title	Trial Design	Dosing Regimens:	Trial Population/ Subject Exposure	FPFV; LPLV
[DAP-PEDS- 07-03] [Ref. 5.3.5.1: P017]	017	An Evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Paediatric Subjects Aged One to Seventeen Years with Complicated Skin and Skin Structure Infections Caused by Gram-positive Pathogens	Phase 4, multi-center, evaluator-blind, randomized, comparative; safety, efficacy, and PK	Daptomycin (MK-3009): • 5, 7, 9, 10 mg/kg IV once daily for up to 14 days • 5 and 7 mg/kg doses given as 30-minute infusions; • 9 and 10 mg/kg dose given as 60- minute infusions Comparator: • Standard of Care deemed appropriate by the Investigator • The recommended agents were vancomycin IV, clindamycin IV, and semi synthetic penicillins (nafcillin, oxacillin, or cloxacillin) IV	Males/females Age: 1 to 17 years cSSSI caused by Gram-positive pathogens Daptomycin: 5 mg/kg: 73 subjects 7 mg/kg: 73subjects 9 mg/kg: 81 subjects 10 mg/kg: 30subjects 257 subjects total (only 256 received daptomycin)	03-Sep-2008; 11-Oct-2013
[DAP- PEDBAC-11-02] [Ref. 5.3.5.1: P005]	005	A Comparative Evaluation of the Safety and Efficacy of Daptomycin Versus Standard of Care in Paediatric Subjects One to Seventeen Years of Age With Bacteremia caused by *Staphylococcus aureus*	Phase 4, open-label (evaluator-blind), comparative, multi-center, multi-national; safety, efficacy, and PK	Daptomycin (MK-3009): • 7, 9, and 12 mg/kg IV once daily for up to 42 days • 7 and 9 mg/kg doses given as 30-minute infusions; • 12 mg/kg dose given as 1-hour infusions Comparator: • Standard of Care deemed appropriate by the Investigator • The recommended agents were vancomycin IV, clindamycin IV, semi-synthetic penicillins (penicillin [nafcillin, oxacillin, or cloxacillin] or first-generation cephalosporin) IV	Males/females Age: 1 to 17 years SAB (no subjects <2 years of age were enrolled) Daptomycin: 7 mg/kg: 14 subjects 9 mg/kg: 19 subjects 12 mg/kg: 22 subjects 55 subjects total	06-Mar-2013; 20-Jan-2016

Trial ID	Merck Protocol Number	Trial Title	Trial Design	Dosing Regimens:	Trial Population/ Subject Exposure	FPFV; LPLV
DAP-PEDOST-11-03 (Ongoing)	006	A Multicenter, Randomized, Double-Blinded Comparative Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Daptomycin Versus Active Comparator in Paediatric Subjects With Acute Hematogenous Osteomyelitis Due to Gram-Positive Organisms	Phase 4 multi-center, double-blind, randomized, multi-national; safety, efficacy, and PK	Daptomycin (MK-3009): • 7, 9, and 12 mg/kg IV once daily • 7 and 9 mg/kg doses given as 60-minute infusions; • 12 mg/kg dose given as 1-hour infusions Comparator: • Standard of Care deemed appropriate by the Investigator • The recommended agents were vancomycin IV (or equivalent) or anti-staphylococcal β-lactam (eg, nafcillin or β-lactam equivalent) IV	Not applicable (study ongoing)	Sep-2013; ongoing

cSSSI: complicated skin and skin structure infection; FPFV: first patient first visit; IV: intravenous(ly); LPLV: last patient last visit; PK: pharmacokinetic; SAB: *Staphylococcus aureus* bacteremia

2.3.2. Pharmacokinetics

The previously performed paediatric studies (three Phase 1 pharmacokinetic trials in patients with confirmed or suspected Gram-positive infections 1 to 17 years of age (DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01, and one Phase 4 safety, efficacy and PK study DAP-PEDS-07-03) have demonstrated that daptomycin exposures are generally lower in paediatric patients compared with adults at the same dose, with weight normalized clearance inversely related to age.

The two-compartment population PK model derived from existing adult and paediatric PK data has been evaluated in connection with the previously approved paediatric cSSTI indication, where daptomycin doses and dosing regimens in paediatric populations were selected by leveraging the available PK data in the adult population.

The dosing regimen used for the different age groups in study DAP-PEDBAC-11-02 [Table 2.5: 1] was derived from this same model, and was based on matching target exposure in the paediatric subjects with the adult SAB population for which efficacy and safety has been established. PK data (peak and trough) was collected during the present study to confirm exposure and PK variables.

The PK data presented in the study report for DAP- PEDBAC-11- 02 show that daptomycin exposures in paediatric SAB patients following administration of the age-specific, weight-based dosing regimens are largely contained within the range observed in adult SAB patients, including RIE patients, receiving the approved 6 mg/kg dose (Figure 2.5:1).

The key PK parameters estimated from the paediatric SAB patients are shown in **Table 4** below.

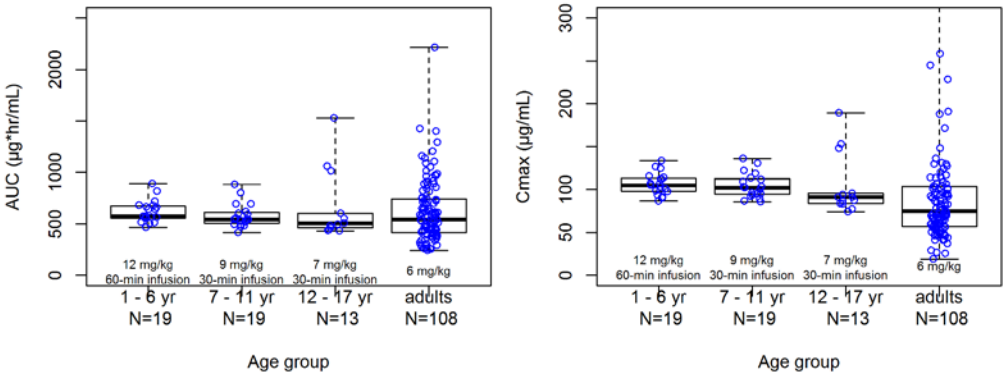
In an exposure-response analysis, no statistically significant correlation between CPK elevation and daptomycin exposure in paediatric subjects was identified within the exposures attained at the recommended age-specific, weight-based paediatric dosing regimens for cSSSI or SAB.

In conclusion, at the evaluated dosing regimens, the exposures in paediatric patients with SAB are comparable to the exposures in adult SAB/RIE patients and similar efficacy and safety profiles in paediatric and adult patients were demonstrated.

In paediatric subjects with SAB, following administration of multiple doses at the proposed age-specific, weight-based regimen in (Table 2.5: 1), model-predicted total clearance normalized by body weight (CL/WT), total volume of distribution normalized by weight (Vss/WT) and elimination half-life (t1/2) varied across different age groups as shown in Table below.

Figure 1

Figure: 2.5:1 Comparable Daptomycin exposure (AUC and C_{max}) in pedatric subjects with SAB in the paediatric phase 4 SBA study (DAP-PEDBAC-11-02), using age-specific, weight-based dose regimen, and adult subjects with SAB (study DAP-IE-01-02), using approved adult dose (6 mg/kg)



Note: For each group, box represents interquartile range; thick line within the box represents median; whiskers represent highest and lowest values; open circles represent individual values. For the C_{max} plot, 4 adult patients with C_{max} >300 µg/mL are not depicted.

Table 4

Table 2.7.2: 3 Mean (CV%) of Daptomycin Pharmacokinetics in Pediatric SAB Patients from the Phase 4 Pediatric SAB Trial DAP-PEDBAC-11-02 Estimated Using Pediatric Population Pharmacokinetics Modeling

Parameters	Mean (CV%)		
	1 to 6 years (Dose: 12 mg/kg) N=19	7 to 11 years (Dose: 9 mg/kg) N=19	12 to 17 years (Dose: 7 mg/kg) N=13
Infusion duration (hr)	0.5	0.5	1.0
C_{max} (µg/mL)	106 (12.0)	104 (13.8)	104 (34.1)
C_{min} (µg /mL)	3.46 (46.0)	4.35 (51.4)	8.00 (102.7)
AUC_{0-24} (µg*hr /mL)	620 (17.6)	579 (20.1)	656 (51.0)
CL/WT (mL/hr/kg)	19.9 (17.1)	15.9 (17.7)	12.4 (31.3)
V_{ss}/WT (mL/kg)#	137 (9.4)	126 (7.4)	115 (14.1)
Terminal elimination half-life (hr)	5.14 (11.0)	6.01 (13.7)	7.52 (30.1)

Note: Individual pharmacokinetic parameters of 5 patients without concentrations (with only BLQ or excluded unexpected low peak concentrations) were derived with the population pharmacokinetic parameters and individual covariate characteristics and included in this summary table.
CL: Systemic clearance; CV: Coefficient of variation (%);V_{ss}: Volume of distribution at steady state; WT: Body weight (kg); AUC_{0-24}: Area under the concentration-time curve at steady state; C_{max}: Maximum concentration at steady state; C_{min}: Minimum concentration at steady state
V_{ss} is estimated as the sum of central and peripheral volume of distribution

In order to produce steady-state exposure (AUCss) comparable to 6 mg/kg once-daily dosing in the adult SAB population (mean AUC 622 µg*hr/mL) the dosing shown in **Table 5** were selected for the paediatric patients with SAB.

Table 5

Table 2.5:1 Recommended Daptomycin IV Infusion Dosage Regimens for Paediatric SAB Patients (1 to 17 Years of Age)

Age (years)	Infusion Time (hours)	Dose (mg/kg, once daily)
12-17	0.5	7
7-11	0.5	9
1-6	1	12

The selected dosing regimen for the various paediatric age groups with SAB are considered justified. However, for this study with higher dosing no study subjects were below 2 y of age. Still, the dose-exposure, and thus efficacy, seems most likely appropriate even for this lower age group based on the previously available PK data. The applicant further discussed how the safety data obtained in this study and the integrated safety analysis also, is valid for this lowest age group. Together with the observations that (1) the simulated exposure distribution in paediatric SAB patients 1 to <2 years of age receiving the 60-minute 12 mg/kg daptomycin IV infusion is not higher than that in paediatric SAB patients 2 to 6 years of age receiving the same dosing regimen, and (2) the PK-CPK analysis that demonstrated no clinically meaningful increase in CPK at the exposures achieved with the proposed paediatric SAB and the approved cSSSI doses, the CPK-age analysis supports that no clinically meaningful increase in CPK for paediatric SAB patients 1 to <2 years at the 60-minute 12 mg/kg daptomycin IV infusion is expected.

Pharmacokinetics using human biomaterials

No new in vitro human biomaterial studies have been conducted in support of this paediatric application.

2.3.3. Pharmacodynamics

Mechanism of action

The mechanism of action of daptomycin is distinct from that of any other antibacterial. Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death. As such, this mechanism is not expected to be different in adult and paediatric patients.

Based on animal models of infection, the antimicrobial activity of daptomycin correlates with ratio of area under the “concentration-time curve” over “minimum inhibitory concentration” (AUC /MIC).

2.3.4. Discussion on clinical pharmacology

The selected dosing regimen for the various paediatric age groups with SAB are considered justified. However, for this study with higher dosing no study subjects were below 2 y of age. Still, the dose-exposure, and thus efficacy, seems most likely appropriate even for this lower age group based on the previously available PK data.

PK modelling data supports the 12mg/kg dose in the youngest children 1-<2 year of age, with no concerns of efficacy or safety being revealed. This dose results in slightly higher exposure of 20% compared to the 10mg/kg dose, though no CPK increases were reported.

2.3.5. Conclusions on clinical pharmacology

The selected dosing regimen for the various paediatric age groups with SAB are considered justified. The MAH further discussed how the safety data obtained in this study and the integrated safety analysis also, is valid for this lowest age group.

2.4. Clinical efficacy

2.4.1. Main study

DAP-PEDBAC-11-02: A COMPARATIVE EVALUATION OF THE SAFETY AND EFFICACY OF DAPTOMYCIN VERSUS STANDARD OF CARE IN PEDIATRIC SUBJECTS ONE TO SEVENTEEN YEARS OF AGE WITH BACTEREMIA CAUSED BY *STAPHYLOCOCCUS AUREUS*.

DAP-PEDBAC-11-02 is an open label (Evaluator-blinded), comparative, multi-centre, multi-national study designed to describe the safety and efficacy of intravenous (IV) daptomycin versus standard of care (SOC) in paediatric subjects aged 1 to 17 years with *S. aureus* bacteraemia.

Methods

Study duration: 06 March 2013 to 20 January 2016.

DAP-PEDBAC-11-02 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 (DMC), the protocol was sequentially amended to allow enrolment of paediatric subjects down to 1 year of age.

Subjects were enrolled sequentially into three age groups and treated with daptomycin or SOC, based on a 2:1 randomization. Study medication was initiated based on a diagnosis of proven or probable *S. aureus* bacteraemia.

- Proven infections: 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 first dose of study drug.
- Probable infections: those with a preliminary blood culture result demonstrating Gram-positive cocci in clusters upon Gram stain, suggestive of a staphylococcal infection.
    - Only high risk subjects with persistent bacteraemia could continue treatment if coagulase-negative Staphylococci (CoNS) were confirmed after the subject was enrolled. This was done to ensure that only subjects with true bacteraemia due to CoNS received study drug. 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.

By Days 5 to 7, each subject's bacteraemia was further classified as complicated or uncomplicated as follows:

- Uncomplicated bacteraemia: The absence of positive results for *S. aureus* in cultures obtained 2 to 4 days after the initiation of study therapy; no fever after 72 hours of initiating effective therapy; no evidence of metastatic sites of infection; no evidence of endocarditis; and no implanted devices.
- Complicated bacteraemia: Bacteraemia occurring in patients with positive blood cultures who do not meet criteria for uncomplicated bacteraemia.

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.

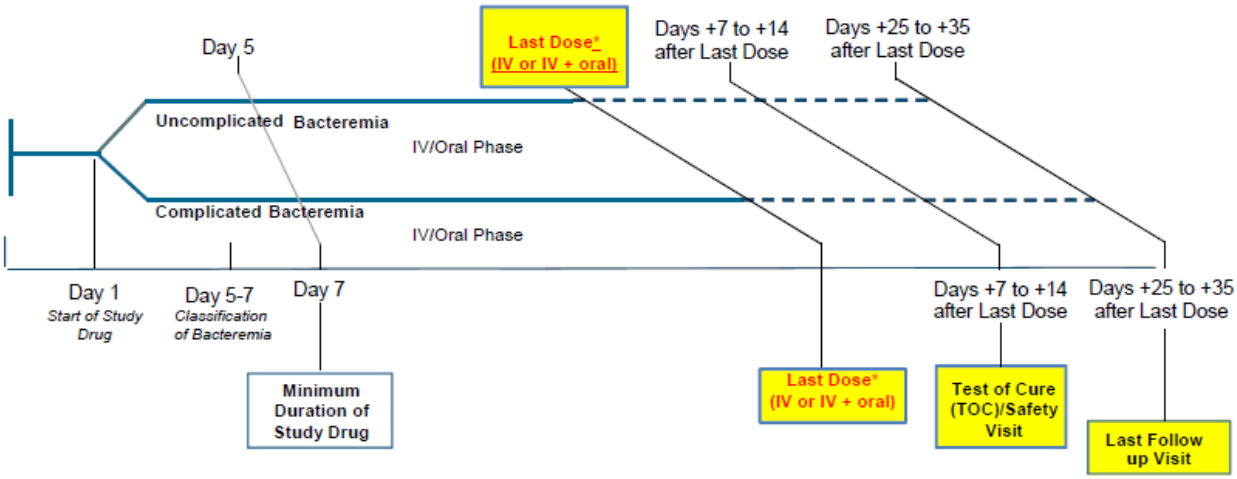
Subjects may have switched to oral therapy following completion of IV study drug administration provided they showed clear clinical improvement and the pathogen was susceptible to an oral agent.

The choice of IV comparator (if randomized to SOC arm) and oral therapy agents was left to the discretion of the Investigator based on the local SOC. Duration of study medication (either treatment arm) was guided by ranges provided in the protocol; however, the duration for a specific patient was left to the Investigator's discretion.

At randomization, all subjects were stratified by age and whether the bacteraemia was complicated or uncomplicated. By Day 5 to Day 7, each subject's bacteraemia was classified and they were randomized to receive 5 to 42 days of study drug depending on the source of infection, presence of endovascular infection, and metastatic foci of infection. Each subject was evaluated by a blinded Evaluator between 7 to 14 days after their last dose of study drug (IV or Oral) at the TOC/Safety Visit. A Last Follow-up Visit occurred 25 to 35 days after the last dose of study drug.

Safety assessments included AEs classification of bacteraemia, focused neurological examination, motor developmental skills (for subjects <7 years old), laboratory assessments, physical examination and vital signs.

Study Schematic



Study participants

Approximately 75 subjects with proven *S. aureus* bacteraemia were planned. A total of 65 study sites world-wide (Greece, Israel, Romania, Ukraine, Argentina, Brazil, Panama, Australia, Malaysia, and Thailand) received study medication, and 25 study sites actually enrolled subjects. A total of 82 paediatric patients age 1-17 year of age were included, of which 55 subjects were randomized to receive daptomycin and 27 to receive SOC.

The analysis populations were as follows:

- Safety Population: included all subjects who received any dose of IV study medication (daptomycin or comparator).
- Intent-to-Treat (ITT): 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: included all randomized and treated subjects receiving 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 Coagulase Negative Staph (CoNS) in high risk patients or probable bacteraemia [Gram-positive cocci on Gram stain at Baseline]).
- Microbiological Modified Intent-to-Treat (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:
    - Received the correct drug, as randomized
    - Received appropriate duration of treatment (minimum and maximum treatment durations)
    - 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 confounding antibiotics at Baseline (>72 hours administered duration anytime during the 96 hours prior to the first dose)
- Did not receive more than 1 dose of effective systemic non-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 1 peak or trough sample (for daptomycin plasma concentration).

Treatments

Ages 7 to 17 years:

Daptomycin was dissolved in a volume of 50 mL 0.9% sodium chloride for injection, United States Pharmacopoeia (USP) (normal saline [NS]) and administered via IV over 30 minutes (Infusion rate: 1.67 mL/min):

- For ages 12 to 17 years: 7 mg/kg IV once every 24 hours (q24h)
- For ages 7 to 11 years: 9 mg/kg IV q24h

Ages 1 to 6 years:

Daptomycin was dissolved to 12 mg/kg in a volume of 25 mL 0.9% sodium chloride for injection, USP (NS) and administered IV over 60 minutes q24h (Infusion rate: 0.42 mL/min).

Reference therapy:

The comparators for this study were SOC agents deemed appropriate by the Investigator. The recommended SOC comparator agents were intravenously administered medications as follows: vancomycin, clindamycin, semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin], or first-generation cephalosporins.

Duration of therapy post randomisation:

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

Objectives

The primary objective:

To assess the safety of IV daptomycin versus standard of care antibiotics in paediatric subjects aged 1 to 17 years of age with bacteraemia.

Secondary objective:

To compare the efficacy of IV daptomycin versus standard-of-care antibiotics in paediatric subjects aged 1 to 17 years of age with bacteraemia caused by *S. aureus*;

To determine exposure by measuring plasma levels of daptomycin at pre-dose (C_{trough}) and end of infusion (C_{max}) to explore exposure-response analyses in paediatric subjects aged 1 to 17 years of age with bacteraemia.

Outcomes / endpoints

Primary end-point analysis – Safety:

Safety was assessed by clinical review and interpretation of all safety parameters. Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA, version 17.1). The overall pattern and incidence of treatment-emergent AEs, treatment related AEs, severe AEs, serious adverse events (SAEs), and other medically important AEs including clinically significant abnormal laboratory values was used to evaluate safety.

Other safety parameters included: vital signs; echocardiogram (if performed), and clinical laboratory tests including serum CPK, results of physical examinations and focused neurological examinations, and use of concomitant medications.

Clinical laboratory values outside the normal ranges were tabulated and flagged. Descriptive statistics for the visit values and the change from Baseline values were presented by study visit, and overall based on maximum post-Baseline visit for clinical laboratory tests and vital signs. C_{max} and C_{trough} daptomycin concentrations were evaluated for correlation to any AEs in the SMQ categories of Peripheral Neuropathy and or Rhabdomyolysis/Myopathy.

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).

Secondary end-point analysis – Efficacy:

The secondary endpoint for efficacy was clinical outcome based on a blinded Investigator's (also known as blinded Evaluator's) assessment of clinical response at the Test-of-cure (TOC)/Safety Visit (primarily in the mMITT population). An assessment of cure or improved was considered clinical success (see definition below). The TOC visit was at Days +7 to + 14 after last dose.

Another secondary efficacy endpoint was the overall outcome based on the subject's microbiological response and clinical outcome at the TOC/Safety Visit in the mMITT population. Microbiological response was determined as microbiological success, failure, or non-evaluable based on evaluation of Baseline infecting pathogen. Clinical outcome was determined as success, failure, or non-evaluable as described

for the first secondary efficacy outcome. Overall outcome was a success if both clinical and microbiological outcomes were successful.

The subjects clinical response were assessed by the blinded Evaluator at the End of IV Therapy (EOIV) visit, the End of Oral Therapy (EOT) visit (for subjects who receive oral study drug), and the TOC/Safety Visit using the following categories:

- Cure: Resolution of clinically significant signs and symptoms associated with admission infection (i.e. return to pre-infection Baseline). No further antibiotic therapy required for the primary infection under study.
- Improvement: Partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy is required for the primary infection under study. For subjects that are switched from IV study drug to oral study drug, "Improved" at the EOIV Visit is defined as the partial resolution of clinical signs or symptoms of infection such that no further IV antibiotic therapy is required for the primary infection under study.
- Failure: Inadequate clinical response to therapy, so that additional antibiotic therapy was required for primary infection under study.
- Not evaluable: Subject was not available to be examined and assessed.

For all secondary endpoint analyses, the 95% CI was calculated for each treatment group. The difference between the treatment groups was calculated with a 95% CI around the difference between the treatment groups. The secondary endpoint was analysed by treatment arm and by treatment arm and age group.
Subgroup analysis were performed by Baseline infection pathogen subgroups (methicillin-sensitive *S. aureus* [MSSA], methicillin-resistant *S. aureus* [MRSA]), classification of bacteraemia (complicated, uncomplicated), and by subjects that received only IV therapy and subjects that received IV plus oral therapy.

Sample size

This study was not powered for safety or efficacy. Approximately 75 children with proven *S. aureus* bacteraemia cases were to be enrolled in the study. Paediatric patients were randomized 2:1 to daptomycin: SOC, respectively (with approximately 50 on daptomycin and approximately 25 on SOC planned).

The probability of observing a specific AE with a true rate of 5% among 50 subjects receiving daptomycin was at least 92%. The study was not powered to test for non-inferiority for the primary or secondary efficacy endpoints.

Randomisation

Treatment assignment was based on a centralized computer-generated randomization schedule, stratified by age group, designed to achieve a 2:1 ratio of subjects receiving daptomycin or SOC, respectively.

Blinding (masking)

Because Principal Investigators were not blinded to study treatment, a blinded Investigator (hereafter referred to as blinded Evaluator) assessed all safety and efficacy endpoints. This was done in order to minimize bias that can be associated with subjective assessments, such as those included in this study.

Prior to study start at each site, a physician was designated as the blinded Evaluator who remained blinded throughout the study period.

Blinded Evaluator's responsibilities:

1. Determined the relationship of AEs to study drug;
2. Assessed signs and symptoms of primary site of bacteraemia infection throughout the study, at the Screening/Baseline Visit, daily while on IV study medication, at the End of IV Therapy Visit, at the End of Oral Therapy Visit (for subjects who received oral study drug), and at the TOC/Safety Visit;
3. Decided on duration of treatment with IV study medication (whenever possible)
    a. Decided if IV study medication should be discontinued based on subject's clinical response;
4. Decided on switch to an oral antibiotic (whenever possible);
5. Determined clinical response by comparing the subject's signs and symptoms of primary site of bacteraemia infection at the End of IV Therapy (EOIV) Visit, the End of Oral Therapy (for subjects who received oral study drug), and the TOC/Safety Visits to those recorded at Study Baseline;
6. Determined microbiological response by comparing the Baseline infecting pathogen (BIP) with results from cultures after initiation of study drug.

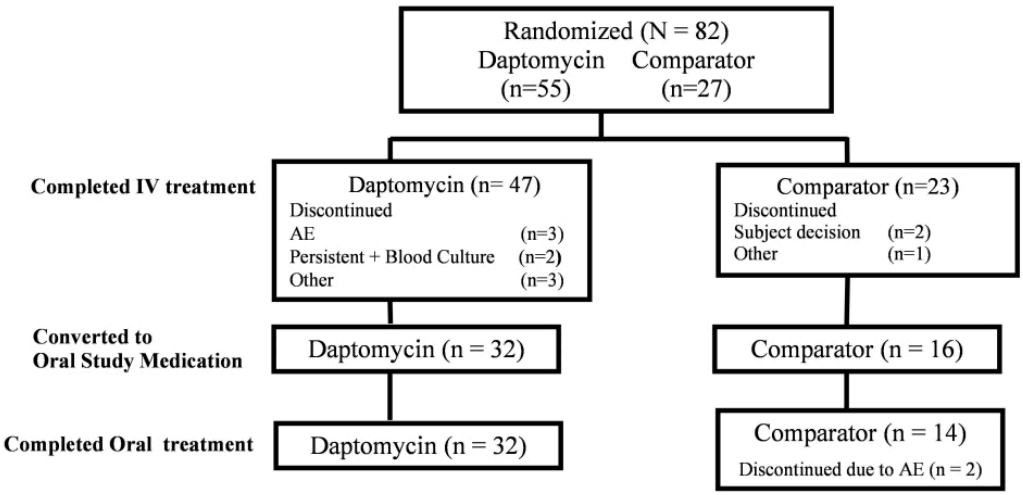
Statistical methods

Clinical data on safety were described and analysed using the Statistical Analysis System (SAS) System. Data were pooled across study centres, and presented and tabulated by treatment and age group. Descriptive statistics for continuous variables were presented by treatment group and included number of subjects (n), mean, standard deviation, median, minimum and maximum. Categorical variables were summarized by group and included the number and percentage of subjects in each category and 95% CIs were constructed around the percentage, when appropriate. A 95% CI was constructed around the difference between treatment groups in the rate of key safety and clinical outcomes. Descriptive statistics were used to guide decisions as to the clinical relevance of findings. No formal hypothesis tests were planned.

Results

Participant flow

Figure 2



AE = adverse event; Subject decision = Subject/Parent/ Legal Guardian decision; IV = intravenous

Recruitment

Conduct of the study

DAP-PEDBAC-11-02 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 (DMC), the protocol was sequentially amended to allow enrolment of paediatric subjects down to 1 year of age.

Baseline data

All subjects included in the Safety Population had Gram-positive, aerobic blood culture results at baseline. The majority of subjects was enrolled in the study based on Gram stain and conventional culture. Overall, 73 subjects had proven SAB at baseline (included in the mMITT Population), including 51/55 (92.7%) daptomycin-treated subjects and 22/26 (84.6%) comparator-treated subjects. The percentage of MSSA and MRSA infections were similar between treatment arms, with MSSA as the baseline pathogen in the majority of subjects: MSSA infections in 80.0% (44/55) of the daptomycin arm and 73.1% (19/26) of the comparator arm, MSRA infections in 12.7% (7/55) of the daptomycin arm and 11.5% (3/26) of the comparator arm.

Overall, a similar number of subjects were enrolled in each of the age groups, and, in general, the 2 treatment arms, age groups, and analysis populations were comparable. The majority of subjects were White (75.3%), the mean age was 8.7 years (range 2.0 to 17.6 years), and there was a higher distribution of male (66.7%) than female subjects in the study. Younger children and toddlers (1 to 6 years of age) comprised 39.5% of the Safety Population. Older children (7 to 11 years of age) and adolescents (12 to 17 years of age) were also well-represented in the study population overall, with 34.6% (28/81) and 25.9% (21/81) of subjects included in these age groups, respectively. No subjects 1 year of age were enrolled in this study despite enrolment being open to this age group.

Numbers analysed

Table 6

Table 2.5:4 Paediatric phase 4 Study (DA-PEDBAC-11-02): data sets analysed - Efficacy populations.

	Total 12 to 17 year olds		1 to 6 year olds				7 to 11 year-olds	
			DAP		DAP		DAP	
	DAP	COM	12 mg/kg	COM	9 mg/kg	COM	7 mg/kg	COM
Population	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized ITT	55	27	22	11	19	9	14	7
Safety	55 (100.0)	26 (96.3)	22 (100.0)	10 (90.9)	19 (100.0)	9 (100.0)	14 (100.0)	7 (100.0)
MITT	52 (94.5)	24 (88.9)	20 (90.9)	9 (81.8)	18 (94.7)	9 (100.0)	14 (100.0)	6 (85.7)
mMITT	51 (92.7)	22 (81.5)	20 (90.9)	8 (72.7)	17 (89.5)	9 (100.0)	14 (100.0)	5 (71.4)
CE	40 (72.7)	12 (44.4)	18 (81.8)	6 (54.5)	14 (73.7)	3 (33.3)	8 (57.1)	3 (42.9)
ER	51 (92.7)	0	19 (86.4)	0	19 (100)	0	13 (92.9)	0

CE: clinically evaluable; COM: standard of care comparator; DAP: daptomycin; ITT: intent-to-treat; IV: intravenous; MITT:
modified intent-to-treat; mMITT: microbiological modified intent-to-treat; ER: Exposure response population;
Percentages are based on the total number of subjects randomized (ITT) in each treatment/age group

It is noted that even if switch to oral therapy was discouraged, the majority of patients in both treatment groups converted to oral study medication.

Table 7

Disposition of Subjects (ITT Population - Paediatric Phase 4 SAB Study [DAP-PEDBAC-11-02])

	All Ages		
Disposition	Daptomycin (N=55)	Comparator (N=27)	Overall (N=82)
Number randomized	55	27	82
Randomized not treated	0	1	1
Randomized and treated	55	26	81
Completed IV treatment [a]	47 (85.5%)	23 (88.5%)	70 (86.4%)
Discontinued from IV treatment prematurely [a]	8 (14.5%)	3 (11.5%)	11 (13.6%)
Primary reason:			
Adverse Event	3 (5.5%)	0	3 (3.7%)
Microbiologic Failure	0	0	0
Persistent Positive Blood Cultures	2 (3.6%)	0	2 (2.5%)
Clinical (Symptomatic) Response Unsatisfactory	0	0	0
Major Protocol Violation	0	0	0
Investigator's Decision	0	0	0
Subject/Parent/Legal Guardian Decision	0	2 (7.7%)	2 (2.5%)
Lost to Follow-up	0	0	0
Lack of Efficacy	0	0	0
Other	3 (5.5%)	1 (3.8%)	4 (4.9%)

Converted to oral study medication [a]	32 (58.2%)	16 (61.5%)	48 (59.3%)
Completed oral study medication [b]	32 (100.0%)	14 (87.5%)	46 (95.8%)
Discontinued oral study medication prematurely [b]	0	2 (12.5%)	2 (4.2%)
Primary reason:			
Adverse Event	0	2 (12.5%)	2 (4.2%)
Microbiologic Failure	0	0	0
Persistent Positive Blood Cultures	0	0	0
Clinical (Symptomatic) Response Unsatisfactory	0	0	0
Major Protocol Violation	0	0	0
Investigator's Decision	0	0	0
Subject/Parent/Legal Guardian Decision	0	0	0
Lost to Follow-up	0	0	0
Lack of Efficacy	0	0	0
Other	0	0	0
Completed study medication (IV and/or oral) [a]	47 (85.5%)	21 (80.8%)	68 (84.0%)
Discontinued study medication (IV and/or oral) prematurely [a]	8 (14.5%)	5 (19.2%)	13 (16.0%)
Primary reason: Adverse Event	3 (5.5%)	2 (7.7%)	5 (6.2%)
Microbiologic Failure	0	0	0
Persistent Positive Blood Cultures	2 (3.6%)	0	2 (2.5%)
Clinical (Symptomatic) Response Unsatisfactory	0	0	0
Major Protocol Violation	0	0	0
Investigator's Decision	0	0	0
Subject/Parent/Legal Guardian Decision	0	2 (7.7%)	2 (2.5%)
Lost to Follow-up	0	0	0
Lack of Efficacy	0	0	0
Other	3 (5.5%)	1 (3.8%)	4 (4.9%)
Completed TOC/Safety Visit [a]	54 (98.2%)	24 (92.3%)	78 (96.3%)
Subjects discontinuing study early [a]	1 (1.8%)	2 (7.7%)	3 (3.7%)
Primary reason:			
Adverse Event	0	0	0
Microbiologic Failure	0	0	0
Persistent Positive Blood Cultures	0	0	0
Clinical (Symptomatic) Response Unsatisfactory	0	0	0
Major Protocol Violation	0	0	0
Investigator's Decision	0	0	0
Subject/Parent/Legal Guardian Decision	0	2 (7.7%)	2 (2.5%)
Lost to Follow-up	0	0	0
Lack of Efficacy	0	0	0
Other	1 (1.8%)	0	1 (1.2%)

[a] Percentages are based on number of subjects who were randomized and treated.

[b] Percentages are based on number of subjects who converted to oral treatment.

Note: ITT = intent-to-treat; percentages are based on the total number of subjects randomized and treated in each treatment group unless otherwise specified.

Table 8

Table 2.7.3-pedbac: 5: Summary of Primary Diagnosis and Disease History (Safety Population - Paediatric Phase 4 SAB Study [DAP- PEDBAC-11-02])

	Total			1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
Investigator's Primary Diagnosis	DAP (N=55) n (%)	COM (N=26) n (%)	Overall (N=81) n (%)	DAP 12 mg/kg (N=22) n (%)	COM (N=10) n (%)	DAP 9 mg/kg (N=19) n (%)	COM (N=9) n (%)	DAP 7 mg/kg (N=14) n (%)	COM (N=7) n (%)
Microbiological Testing Results									
Aerobic Blood culture growth [a]	55 (100.0)	26 (100.0)	81 (100.0)	22 (100.0)	10 (100.0)	19 (100.0)	9 (100.0)	14 (100.0)	7 (100.0)
Gram-positive statin	54 (98.2)	2 (100.0)	80 (98.8)	21 (95.5)	10 (100.0)	19 (100.0)	9 (100.0)	14 (100.0)	7 (100.0)
Rapid Diagnostic test positive	5 (9.1)	3 (11.5)	8 (9.9)	2 (9.1)	0	3 (15.8)	2 (22.2)	0	1 (14.3)
Microbiological enrollment method [b]									
Blood culture only	2 (3.6)	0	2 (2.5)	1 (4.5)	0	1 (5.3)	0	0	0
Gram stain only	0	0	0	0	0	0	0	0	0
Rapid Diagnostic Test only	0	0	0	0	0	0	0	0	0
Blood culture and Gram stain	46 (83.6)	23 (88.5)	69 (85.2)	19 (86.4)	10 (100.0)	13 (68.4)	7 (77.8)	14 (100.0)	6 (85.7)
Blood culture and Rapid Diagnostic Test	0	0	0	0	0	0	0	0	0
Gram stain and Rapid Diagnostic Test	0	0	0	0	0	0	0	0	0
Blood culture and Gram stain and Rapid Diagnostic Test	6 (10.9)	3 (11.5)	9 (11.1)	2 (9.1)	0	4 (21.1)	2 (22.2)	0	1 (14.3)
Not marked	1 (1.8)	0	1 (1.2)	0	0	1 (5.3)	0	0	0

Table 2.7.3-pedbac: 5 (cont.): Summary of Primary Diagnosis and Disease History (Safety Population - Paediatric Phase 4 SAB Study [DAP- PEDBAC-11-02])

Investigator's Primary Diagnosis	Total			1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
	DAP (N=55) n (%)	COM (N=26) n (%)	Overall (N=81) n (%)	DAP 12 mg/kg (N=22) n (%)	COM (N=10) n (%)	DAP 9 mg/kg (N=19) n (%)	COM (N=9) n (%)	DAP 7 mg/kg (N=14) n (%)	COM (N=7) n (%)
Gram Positive Baseline Infecting Pathogen [c]									
MSSA	44 (80.0)	19 (73.1)	63 (77.8)	17 (77.3)	7 (70.0)	14 (73.7)	8 (88.9)	13 (92.9)	4 (57.1)
MRSA	7 (12.7)	3 (11.5)	10 (12.3)	3 (13.6)	1 (10.0)	3 (15.8)	1 (11.1)	1 (7.1)	1 (14.3)
CoNS	2 (3.6)	2 (7.7)	4 (4.9)	2 (9.1)	1 (10.0)	0	0	0	1 (14.3)
S. epidermidis (MRSE)	0	1 (3.8)	1 (1.2)	0	0	0	0	0	1 (14.3)
S. saprophyticus	1 (1.8)	0	1 (1.2)	0	0	1 (5.3)	0	0	0
No BIP established	1 (1.8)	1 (3.8)	2 (2.5)	0	1 (10.0%)	1 (5.3)	0	0	0
Diagnosis of *Staphylococcus aureus* bacteremia, n	54	25	79	22	9	18	9	14	7
Proven	51 (94.4)	22 (88.0)	73 (92.4)	20 (90.9)	8 (88.9)	17 (94.4)	9 (100.0)	14 (100.0)	5 (71.4)
Probable	3 (5.6)	3 (12.0)	6 (7.6)	2 (9.1)	1 (11.1)	1 (5.6)	0	0	2 (28.6)
Bacteremia classification									
Subjects with no classification, withdrew prior to assessment (Days 5-7) [d]	3 (5.5)	2 (7.7)	5 (6.2)	2 (9.1)	0	0	1 (11.1)	1 (7.1)	1 (14.3)
Uncomplicated[d]	25 (45.5)	8 (30.8)	33 (43.4)	10 (45.5)	3 (30.0)	11 (57.9)	3 (33.3)	4 (28.6)	2 (28.6)
Complicated[d]	27 (49.1)	16 (61.5)	43 (53.1)	10 (45.5)	7 (70.0)	8 (42.1)	5 (55.6)	9 (64.3)	4 (57.1)
Endocarditis [e, f]	0	0	0	0	0	0	0	0	0
Metastatic Foci of Infection [f]	11 (21.2)	8 (33.3)	19 (25.0)	2 (10.0)	3 (30.0)	5 (26.3)	3 (37.5)	4 (30.8)	2 (33.3)
Infection of Prosthetic Material [f]	2 (3.8)	1 (4.2)	3 (3.9)	2 (10.0)	1 (10.0)	0	0	0	0
Positive Blood Culture >4 days [f]	12 (23.1)	5 (20.8)	17 (22.4)	7 (35.0)	3 (30.0)	1 (5.3)	1 (12.5)	4 (30.8)	1 (16.7)
Fever after 72 hours [f]	14 (26.9)	9 (37.5)	23 (30.3)	5 (25.0)	5 (50.0)	4 (21.1)	3 (37.5)	5 (38.5)	1 (16.7)

Despite that conversion to oral treatment was discouraged a large proportion of the study subjects converted to oral study medication. All subjects included in the Safety Population had Gram-positive, aerobic blood culture results at baseline. The majority of subjects were enrolled in the study based on Gram stain and conventional culture. Overall, 73 subjects had proven SAB at baseline (included in the mMITT Population), including 51/55 (92.7%) daptomycin-treated subjects and 22/26 (84.6%) comparator-treated subjects. The percentage of MSSA and MRSA infections were similar between treatment arms, with MSSA as the baseline pathogen in the majority of subjects: MSSA infections in 80.0% (44/55) of the daptomycin arm and 73.1% (19/26) of the comparator arm, MSRA infections in 12.7% (7/55) of the daptomycin arm and 11.5% (3/26) of the comparator arm. The percentage of patients with complicated and uncomplicated bacteraemia was nearly similar in the daptomycin group (45.5% vs. 49.1%) while in the comparator group nearly twice as many patients had complicated bacteraemia (61.5% vs. 30.8% with uncomplicated). However, the number of patients in the comparator group is overall limited.

Outcomes and estimation

In study DAP-PEDBAC-11-02 most subjects in both treatment groups received ≤3 weeks of IV therapy. The mean duration of IV treatment was similar in the 2 treatment groups (12.2 days in daptomycin- and 12.3 days in comparator-treated subjects). The mean duration of oral treatment was 22.7 days in daptomycin- and 17.7 days in comparator-treated subjects.

The summary of results for the mMITT population by treatment arm and age group is shown in table 2.5:5 below. 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 comparator arm. Clinical success rates at the TOC/Safety Visit were also generally similar across age groups for the 2 treatment arms.

In mMITT, CE, and MITT populations, the clinical success rates were generally comparable between the daptomycin- and comparator-treated arms.

Table 9

Table 2.5: 5

Pediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): 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-Years of Age		7- to 11-Years of Age		12- to 17-Years of Age	
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	-

CI: confidence interval; DAP: daptomycin; COM: standard of care comparator; mMITT: microbiological modified intent-to-treat; TOC: test-of-cure

[a] 95% CI of the percent of subjects with satisfactory response was constructed with the Wilson score method

[b] Difference was calculated as Daptomycin – Comparator

[c] 95% CI of the difference in percent of subjects with a satisfactory response between the two treatment arms (Daptomycin – Comparator), constructed based on the Wilson score method

Table 10

Table 11-7 Summary of Clinical Outcome at End of Treatment (EOIV and EOT) Visit by Treatment Group and by Age Group (mMITT Population)

	Total		1 to 6 year olds		7 to 11 year olds		12 to 17 year olds	
	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 (%)
Clinical Outcome at EOIV								
Number of Subjects with Responses	51	22	20	8	17	9	14	5
Clinical Success (Satisfactory Response)	48 (94.1)	19 (86.4)	19 (95.0)	8 (100.0)	16 (94.1)	7 (77.8)	13 (92.9)	4 (80.0)
Cure	14 (27.5)	4 (18.2)	7 (35.0)	1 (12.5)	5 (29.4)	2 (22.2)	2 (14.3)	1 (20.0)
Improved	34 (66.7)	15 (68.2)	12 (60.0)	7 (87.5)	11 (64.7)	5 (55.6)	11 (78.6)	3 (60.0)
95% CI for percent of Satisfactory Response[a]	87.7, 100.0	72.0, 100.0	85.4, 100.0	100.0, 100.0	82.9, 100.0	50.6, 100.0	79.4, 100.0	44.9, 100.0
Difference[b]	7.8%	-	-5.0%	-	16.3%	-	12.9%	-
95% CI of Difference[c]	-8.0, 23.5	-	-14.6, 4.6	-	-13.0, 45.7	-	-24.7, 50.4	-
Clinical Failure (Unsatisfactory Response)	3 (5.9)	3 (13.6)	1 (5.0)	0	1 (5.9)	2 (22.2)	1 (7.1)	1 (20.0)
Failure	2 (3.9)	0	1 (5.0)	0	1 (5.9)	0	0	0
Non-evaluable	1 (2.0)	3 (13.6)	0	0	0	2 (22.2)	1 (7.1)	1 (20.0)
Clinical Outcome at EOT								
Number of Subjects with Responses[d]	48	22	19	8	16	9	13	5
Clinical Success (Satisfactory Response)	44 (91.7)	17 (77.3)	18 (94.7)	7 (87.5)	15 (93.8)	6 (66.7)	11 (84.6)	4 (80.0)
Cure	42 (87.5)	15 (68.2)	17 (89.5)	7 (87.5)	15 (93.8)	5 (55.6)	10 (76.9)	3 (60.0)
Improved	2 (4.2)	2 (9.1)	1 (5.3)	0	0	1 (11.1)	1 (7.7)	1 (20.0)
95% CI for percent of Satisfactory Response[a]	83.8, 99.5	59.8, 94.8	84.7, 100.0	64.6, 100.0	81.9, 100.0	35.9, 97.5	65.0, 100.0	44.9, 100.0
Difference[b]	14.4%	-	7.2%	-	27.1%	-	4.6%	-
95% CI of Difference[c]	-4.8, 33.6	-	-17.8, 32.3	-	-5.9, 60.1	-	-35.6, 44.8	-
Clinical Failure (Unsatisfactory Response)	4 (8.3)	5 (22.7)	1 (5.3)	1 (12.5)	1 (6.3)	3 (33.3)	2 (15.4)	1 (20.0)
Failure	2 (4.2)	2 (9.1)	1 (5.3)	1 (12.5)	1 (6.3)	1 (11.1)	0	0
Non-evaluable	2 (4.2)	3 (13.6)	0	0	0	2 (22.2)	2 (15.4)	1 (20.0)

CI: confidence interval; DAP: daptomycin; COM: standard of care comparator; EOIV: end of IV therapy; EOT: end of treatment; Mmitt: microbiological modified intent-to-treat

a. 95% CI of the percent of subjects with satisfactory response was constructed with the Wilson score method

b. Difference was calculated as Daptomycin – Comparator

c. 95% CI of the difference in percent of subjects with a satisfactory response between the two treatment arms (Daptomycin – Comparator), constructed based on the Wilson score method

d. Note: Three subjects *[confidential information deleted]* completed oral therapy without a clinical assessment.

Table 11

Table 14.1.5.1a

Summary of Duration of Treatment (Safety Population)

	All Ages		
	Daptomycin (N=55)	Comparator (N=26)	Overall (N=81)
Duration of treatment with IV study drug			
n	55	26	81
Mean	12.2	12.3	12.3
(SD)	(7.94)	(7.30)	(7.69)
Median	11.0	11.5	11.0

Min, Max	1, 44	2, 31	1, 44
<3 days	3 (5.5%)	2 (7.7%)	5 (6.2%)
3-7 days	18 (32.7%)	5 (19.2%)	23 (28.4%)
>1-2 weeks	16 (29.1%)	11 (42.3%)	27 (33.3%)
>2-3 weeks	12 (21.8%)	6 (23.1%)	18 (22.2%)
>3-4 weeks	4 (7.3%)	0	4 (4.9%)
>4-5 weeks	1 (1.8%)	2 (7.7%)	3 (3.7%)
>5-6 weeks	0	0	0
>6 weeks	1 (1.8%)	0	1 (1.2%)
Duration of oral treatment (days) [2]			
n	32	16	48
Mean	22.7	17.7	21.0
(SD)	(23.08)	(9.03)	(19.57)
Median	15.0	16.0	15.0
Min, Max	5, 125	6, 33	5, 125

Ancillary analyses

Clinical outcome was also evaluated by *S. aureus* organism at baseline (MSSA versus MRSA), type of bacteraemia (complicated versus uncomplicated), and study therapy route (IV only versus IV plus oral). Overall, response rates were generally similar between the 2 treatment arms across these subgroups. Clinical outcome results by these subgroups are presented in **Table 12.**

Table 12

Paediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): Summary of Subgroup Analyses of Clinical Outcome at the Test-of-Cure/Safety Visits by Treatment Group (mMITT Population)

Clinical Outcome	DAP (N=51) n (%)	COM (N=22) n (%)
Baseline MSSA Subgroup	44	19
Satisfactory Response at TOC	39 (88.6)	15 (78.9)
Unsatisfactory Response at TOC	5 (11.4)	4 (21.1)
Baseline MRSA Subgroup	7	3
Satisfactory Response at TOC	6 (85.7)	2 (66.7)
Unsatisfactory Response at TOC	1 (14.3)	1 (33.3)
Complicated Bacteremia	26	14
Satisfactory Response at TOC	23 (88.5)	10 (71.4)
Unsatisfactory Response at TOC	3 (11.5)	4 (28.6)
Uncomplicated Bacteremia	24	7
Satisfactory Response at TOC	22 (91.7)	7 (100.0)
Unsatisfactory Response at TOC	2 (8.3)	0
Received Only IV Therapy	19	7
Satisfactory Response at TOC	14 (73.7)	5 (71.4)
Unsatisfactory Response at TOC	5 (26.3)	2 (28.6)
Received IV Plus Oral Therapy	32	15
Satisfactory Response at TOC	31 (96.9)	12 (80.0)
Unsatisfactory Response at TOC	1 (3.1)	3 (20.0)

CI: confidence interval; COM: standard of care comparator; DAP: daptomycin; EOT: End of treatment; ITT: intent-to-treat; MRSA: methicillin resistant *Staphylococcus aureus*; MSSA: methicillin susceptible *Staphylococcus aureus*; TOC: test-of- cure

Among the 63 subjects in the mMITT Population who were infected with MSSA at baseline, the rate of clinical success was generally similar in the daptomycin-treated subjects at the TOC/Safety Visit (88.6% for daptomycin versus 78.9% for comparator). 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 (88.5% for daptomycin versus 71.4% for comparator). As expected, subjects who received both IV and oral study therapy fared better than those receiving IV study therapy only, as subjects were predominantly switched to oral therapy after clinical improvement with IV study therapy had already been documented.

Microbiological success rates at the TOC/Safety Visit for the mMITT Population were similar in the daptomycin (76.5%) and comparator (77.3%) treatment arms (data not shown). The analyses of the CE and MITT Populations gave similar results to those shown for the mMITT Population. Subjects in the youngest (1- to 6-year old) age group had similar microbiological response in the 2 treatment groups (90.0% [18/20] daptomycin-treated subjects versus 87.5% [7/8] comparator-treated subjects). In the middle (7 to 11 years of age) age group, daptomycin treated subjects had a higher rate of microbiological success (82.4% [14/17]) than comparator-treated subjects (55.6% [5/9]). In contrast, among the oldest age group (12 to 17 years of age) subjects, higher microbiological responses were seen in the comparator group (100% [5/5]) versus the daptomycin group (50.0% [7/14]). However, the results by age group should be interpreted with caution due to small sample sizes.

Time to clearance was assessed using Kaplan-Meier methods. The median times to clearance were 2.5 and 2.0 days in the daptomycin and comparator groups, respectively. For those subjects with infections caused by MSSA (38 subjects in the daptomycin arm and 16 subjects in the comparator arm), the median times to clearance were 3.0 and 2.5 days, respectively. For subjects with infections caused by MRSA (6 in daptomycin group and 3 in comparator group), the median times to clearance were 2.0 and 1.0 days, respectively (subjects who achieved clearance prior to Day 1 were not included in the time to clearance analysis). No significant difference between the treatment groups for time to clearance was observed in the mMITT Population, either overall or for the subset of subjects with MSSA infection or MRSA infection. When the same analysis was done by age group, no significant differences were observed between treatment arms.

Results for a favourable overall outcome, defined as both a favourable clinical and microbial outcome are summarised in **Table 13**

Table 13

Paediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): Summary of Overall Outcome at the Test-of-Cure/Safety Visit by Treatment Group, Overall and by Age Group (mMITT Population)

Overall Therapeutic Response	Total		1 to 6 Years of Age		7 to 11 Years of Age		12 to 17 Years of Age	
	DAP (N=51) n (%)	COM (N=22)	DAP (N=20)	COM (N=8)	DAP (N=17)	COM (N=9)	DAP (N=14)	COM (N=5)
Number of Subjects With Responses	51	22	20	8	17	9	14	5
Overall Success	37 (72.5)	13 (59.1)	16 (80.0)	6 (75.0)	14 (82.4)	4 (44.4)	7 (50.0)	3 (60.0)
% Difference in Success Rate [a] (95% CI of Difference) [b]	13.5 (-10.5, 37.4)		5.0 (-29.8, 39.8)		37.9 (0.7, 75.1)		-10.0 (-60.3, 40.3)	
Overall Failure or Non-evaluable	14 (27.5)	9 (40.9)	4 (20.0)	2 (25.0)	3 (17.6)	5 (55.6)	7 (50.0)	2 (40.0)
Overall Failure	9 (17.6)	5 (22.7)	4 (20.0)	2 (25.0)	1 (5.9)	2 (22.2)	4 (28.6)	1 (20.0)
Non-evaluable	5 (9.8)	4 (18.2)	0	0	2 (11.8)	3 (33.3)	3 (21.4)	1 (20.0)

CI: confidence interval; COM: standard of care comparator; DAP: daptomycin; mMITT: microbiological modified intent-to- treat; TOC: test of cure

[a.] Difference is calculated as Daptomycin – Comparator in the corresponding age groups.

b. 95% CI of the difference in percent of subjects with a success response between the two treatment arms (DAP – COM) was constructed based on the Wilson score method.

Clinical outcome and microbiological outcome by type of primary infection:

The clinical outcome (clinical success vs. clinical non-success [failure or non-evaluable]) and microbiological outcome (microbiological success vs. microbiological non-success [failure or non-evaluable]) by category of primary infection are shown in Table 14 and Table 15, respectively.

For each of the 5 categories of primary infection, the proportion of subjects with a favourable clinical outcome (i.e., clinical success) was similar between the two treatment groups (**Table 14**). Moreover, for each of the 5 categories of primary infection, the proportion of subjects with a favourable microbiological outcome (i.e., microbiological success) was similar between the two treatment groups (**Table 15**). Lastly, in each treatment group, the proportion of subjects with favourable “clinical and microbiological outcome” were similar across the infection categories. These results are presented and interpreted with

the understanding that such results are in the context of small numbers of subjects in the infection categories.

Similar clinical outcome results were observed at the end of IV therapy time-point. Microbiological outcomes were not measured at the end of IV therapy in the study.

Table 14

Summary of Investigator's Assessment of Clinical Outcomes at TOC - by Type of Infection (mMITT population)

	Daptomycin (N=51)	Comparator (N=22)	Total (N=73)
Subjects with bacteremia classification assessment [1]	50	21	71
Subjects with type of infection '**device-related infection**'	10	3	13
Clinical Success	7 (70.0%)	3 (100.0%)	10 (76.9%)
Clinical non-success (failure and non-evaluable)	3 (30.0%)	0	3 (23.1%)
Subjects with type of infection '**osteomyelitis**' [2]	10	2	12
Clinical Success	10 (100.0%)	2 (100.0%)	12 (100.0%)
Clinical non-success (failure and non-evaluable)	0	0	0
Subjects with type of infection **related to cSSTI** [3]	5	3	8
Clinical Success	5 (100.0%)	1 (33.3%)	6 (75.0%)
Clinical non-success (failure and non-evaluable)	0	2 (66.7%)	2 (25.0%)
Subjects with type of infection '**unknown**'	10	8	18
Clinical Success	10 (100.0%)	7 (87.5%)	17 (94.4%)
Clinical non-success (failure and non-evaluable)	0	1 (12.5%)	1 (5.6%)
Subjects with any **other type of infection**	16	7	23
Clinical Success	14 (87.5%)	6 (85.7%)	20 (87.0%)
Clinical non-success (failure and non-evaluable)	2 (12.5%)	1 (14.3%)	3 (13.0%)

TOC: test-of-cure; mMITT: microbiological modified intent-to-treat; cSSTI: complicated skin and soft-tissue infection.
Note: Percentages are based on the number of with the specific type of infection in the corresponding treatment arm. Clinical Success includes both cure and improvement; Clinical non-success includes both failure and non-evaluable. [1] Two subjects, (one from Daptomycin and one from Comparator arm) were not assigned a bacteremia classification since they withdrew from study drug prior to the Day 5-7 assessments where these classifications were determined. [2] Type of infection 'osteomyelitis' includes 'osteomyelitis' and 'osteomyelitis acute'. [3] Includes cases that can be classified as cSSTI based on the Preferred Term diagnosis and available Med History as in Listing 16.2.4.7 in the CSR.

Table 15

Summary of Subject-Level Microbiological Outcomes at TOC - by Type of Infection (mMITT population)

	Daptomycin (N=51)	Comparator (N=22)	Total (N=73)
Subjects with bacteremia classification assessment [1]	50	21	71
Subjects with type of infection '**device-related infection**'	10	3	13
Microbiological Success	9 (90.0%)	3 (100.0%)	12 (92.3%)
Microbiological non-success (failure and non-evaluable)	1 (10.0%)	0	1 (7.7%)
Subjects with type of infection '**osteomyelitis**' [2]	10	2	12
Microbiological Success	7 (70.0%)	1 (50.0%)	8 (66.7%)
Microbiological non-success (failure and non-evaluable)	3 (30.0%)	1 (50.0%)	4 (33.3%)
Subjects with type of infection **related to cSSTI** [3]	5	3	8
Microbiological Success	4 (80.0%)	3 (100.0%)	7 (87.5%)
Microbiological non-success (failure and non-evaluable)	1 (20.0%)	0	1 (12.5%)
Subjects with type of **infection 'unknown'**	10	8	18
Microbiological Success	8 (80.0%)	8 (100.0%)	16 (88.9%)
Microbiological non-success (failure and non-evaluable)	2 (20.0%)	0	2 (11.1%)
Subjects with any **other type of infection**	16	7	23
Microbiological Success	12 (75.0%)	3 (42.9%)	15 (65.2%)
Microbiological non-success (failure and non-evaluable)	4 (25.0%)	4 (57.1%)	8 (34.8%)

TOC: test-of-cure; mMITT: microbiological modified intent-to-treat; cSSTI: complicated skin and soft-tissue infection.
Note: Percentages are based on the number of with the specific type of infection in the corresponding treatment arm. Microbiological non-success includes both failure and non-evaluable.
[1] Two subjects, (one from Daptomycin and one from Comparator arm) were not assigned a bacteremia classification since they withdrew from study drug prior to the Day 5-7 assessments where these classifications were determined. [2] Type of infection 'osteomyelitis' includes 'osteomyelitis' and 'osteomyelitis acute'. [3] Includes cases that can be classified as cSSTI based on the Preferred Term diagnosis and available Med History as in Listing 16.2.4.7 in the CSR.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study DAP-PEDBAC-11-02 is an open label (Evaluator-blinded), comparative, multi-centre, multi-national study designed to describe the safety and efficacy of intravenous (IV) daptomycin versus standard of care (SOC) in paediatric subjects aged 1 to 17 years with *S. aureus* bacteraemia (SAB). All enrolled patients had either proven or probable SAB.

The primary end-point for study DAP-PEDBAC-11-02 was safety. For efficacy there were two secondary end-points for efficacy. One was the clinical outcome ("cure" or "improved") based on the blinded Evaluator's assessment at the TOC/Safety Visit (primarily in the mMITT population). The second secondary efficacy endpoint was the overall outcome based on the subject's microbiological response and clinical outcome at the TOC/Safety Visit in the mMITT population.

Efficacy data and additional analyses

The baseline data show that the patient population of the daptomycin and comparator groups were comparable. The distribution of study participants in the age cohorts were relatively similar with a slightly higher proportion in the lower age group (total number for both study groups): 39.5% in the 1-6 y of age group, 34.6% in the 7-11 y of age group and 25.9% in the 12-17 y of age group.

The MAH distributed test medicine to 65 sites around the world, but only 25 sites provided data. There is not information on the number of subjects screened for enrolment.

The enrolled population is heterogeneous with regard to primary infection, and only a limited number of enrolled patients seem to belong to the cSSTI category.

In the mMITT population at TOC clinical success were obtained in 45 (88.2%) in the daptomycin group and 17 (77.3%) in the comparator group. The majority were defined as "cured" in both treatment groups. The data on at end of IV treatment (EOIV), 48 (91. 4%) patients in the daptomycin group were categorised as clinical success, defined as "cure" or "improved". Of these 14 (27.4%) were cured. In the comparator group 19 (95%) patients obtained clinical success of which only four (18.2%) patients defined as cured. The efficacy at TOC/safety visit in the mMITT population is based on variable duration of daptomycin treatment, as well as, different subsequent oral treatments. In addition, the comparator is very heterogeneous, consisting of various antibiotics. Hence, the results are difficult to interpret.

Of the 55 patients randomised and treated, 47 (85.5%) and 23 (88.5%) completed the IV/oral treatment in the daptomycin and comparator arm, respectively. The switch to oral treatment was discouraged in the protocol. Despite this, 32 patients (58.2%) in the daptomycin arm and 16 patients (61.5%) in the comparator arm converted to oral treatment. All of the 32 in the daptomycin arm converting to oral treatment completed the oral study medication, whereas two of the 16 in the comparator arm discontinued the oral treatment medication due to adverse events. It is acknowledged that a switch to oral therapy was only acceptable if clinical improvement to IV treatment had already been documented. Still it is a prerequisite that the outcome at end of i.v. treatment can be assessed by objective endpoints and that the EOIV outcome is convincing. An early switch to oral therapy can always be questioned since it may be difficult to attribute efficacy to the i.v. drug therapy before switching to oral therapy.

In the daptomycin group, the proportion of subjects with microbiological success following treatment with ≤14 days of IV antibiotics was slightly higher than that for subjects treated with >14 days of IV antibiotics (79.4% vs. 70.6%, respectively). A similar trend based on the duration of IV antibiotics was observed in

the comparator group (≤14 days of IV antibiotics: 78.6%; >14 days of IV antibiotics: 75.0%). Across treatment groups, the proportion of subjects with microbiological success was similar regardless of the duration of IV antibiotics (≤14 days or >14 days).

The mean treatment duration for the daptomycin and comparator group (safety population) was 12.3 and 12.2 days, respectively. It is noted that the treatment duration range was 1-44 days and the majority of patients (approx. 85%) have been treated with daptomycin for less than 3 weeks. Also, it is noted that the current duration of treatment of cSSTI in the paediatric patients is 14 days. The MAH was therefore asked to justify the proposed duration of treatment of up to 42 days as proposed in the SmPC in for the paediatric patients with SAB associated with cSSTI. In its response, the MAH asserted that some clinical guidelines recommend treatment for SAB for up to 42 days, usually 4-6 weeks. As exposure up to 6 weeks has not been studied, this is still considered a limitation. Hence, in line with the recommendation for adults with SAB the posology section was revised, emphasizing that the duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.

Additional expert consultation

Not applicable

Conclusions on the clinical efficacy

The efficacy (and safety) data with daptomycin did not reveal a difference between those treated for < than or > than 14 days

In addition, the MAH presented the outcome (i.e. clinical success and microbiologic success) at end of IV treatment (EOIV) and at TOC by primary infection site *and* by treatment duration. The analysis is restricted by the small number of patients, particularly for different subsets. This is further complicated by the heterogeneity in the terms used for diagnosis. Based on the available data though, the clinical and microbiologic outcome at EOIV and at TOC (mMITT population) by type of primary infection and by duration of daptomycin treatment appears to be similar.

No exposure up to 42 days has not been studied and CHMP recommends to align the duration of treatment for SAB with cSSTI in paediatric population with the duration stated in the Product Information for the corresponding indication in adults.

2.5. Clinical safety

Introduction

Safety profile of daptomycin in the currently approved indication:

The clinical study reports (CSRs) were submitted to European Medicines Agency (EMA) in the context of FUM 007 (Study DAPPEDS-05-01 – January 2007; Study DAP-PEDS-07-02 – July2009; Study DAP-PEDS-09-01 – September2012 and Study DAP-PEDS-07-03 - March2015).

Most adverse events (AEs) in the above mentioned studies were characterized as mild or moderate in intensity and were not attributed to daptomycin by either the sponsor or investigator. Overall, the most frequently reported AEs were in the following system organ classes (SOCs): gastrointestinal disorders,

investigations and skin and subcutaneous tissue disorders. Elevated creatine phosphokinase (CPK) was reported as an AE more frequently in patients treated with daptomycin than in patients receiving placebo or comparator antibiotics.

Cumulatively, for both adults and paediatric populations, the three most frequently reported serious adverse events (SAEs) in clinical trials were from the following the SOCs: infections and infestations, followed by cardiac disorders, and respiratory, thoracic and mediastinal disorders.

Serious and non-serious adverse events from post-marketing sources were most frequently reported from the following SOCs: investigations, general disorders and administration site conditions, and infections and infestations.

Study DAP-PEDBAC-11-02

Patient exposure

Eighty-one of the 82 subjects (98.8%) received study drug. Therefore, the Safety Population included 81 subjects, including 55 daptomycin-treated subjects and 26 comparator-treated subjects. Daptomycin was generally well tolerated when administered to paediatric subjects (1 to 17 years of age) with SAB at doses of 7 to 12 mg/kg once daily for up to 6 weeks.

Adverse events

The overall incidence of TEAEs was 65.5% and 76.9% subjects in the daptomycin and comparator arm respectively. Treatment related TEAEs were noted in 14.5% and 15.4% of subjects in the daptomycin and comparator arm, respectively. The safety profile was comparable across age groups and similar to the comparator. The type, incidence, and severity of TEAEs reported for daptomycin and comparator were comparable.

In the study overall, reported TEAEs were mostly mild (20 subjects, 24.7%) or moderate (27 subjects, 33.3%) in intensity. Five (9.1%) daptomycin-treated subjects and 4 (15.4%) comparator-treated subjects reported events, which were considered severe in intensity.

Treatment-related TEAEs were reported in similar proportions of subjects in the treatment groups (8 [14.5%] daptomycin-treated and 4 [15.4%] comparator-treated subjects) (see table 2.5:10). Three (5.5%) daptomycin-treated and 2 (7.7%) comparator-treated subjects discontinued study drug due to a TEAE.

Table 16. Paediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): Overview of Treatment-Emergent Adverse Events (Safety Population)

TEAE Category	Daptomycin (N=55) n (%)	Comparator (N=26) n (%)
Subjects experiencing at least one:		
TEAE	36 (65.5%)	20 (76.9%)
Severe TEAE	5 (9.1%)	4 (15.4%)
Serious TEAE	13 (23.6%)	7 (26.9%)
Treatment-related TEAE	8 (14.5%)	4 (15.4%)
Severe treatment-related TEAE	0	0
Serious treatment-related TEAE	0	0
TEAE leading to discontinuation of study drug	3 (5.5%)	2 (7.7%)

TEAE leading to discontinuation of study	0	0
Treatment-related TEAE leading to discontinuation of study drug	1 (1.8%)	0
Treatment-related TEAE leading to discontinuation of study	0	0
Serious TEAE leading to discontinuation of study drug	2 (3.6%)	2 (7.7%)
Serious TEAE leading to discontinuation of study	0	0
Serious treatment-related TEAE leading to discontinuation of study drug	0	0
TEAE leading to death	0	0
Treatment-related TEAE leading to death	0	0

AE: adverse event; TEAE: treatment-emergent adverse event

Most TEAEs were not considered to be related to study drug by the blinded Evaluator for either treatment group (**Table 16**). In general, the proportion of subjects with one or more treatment-related TEAE was similar in the two treatment groups with 8 (14.5%) subjects in the daptomycin group and 4 (15.4%) subjects in the comparator group experienced TEAEs considered related to the study drug by the blinded Evaluator.

The most common AEs in the daptomycin treatment arm were diarrhoea (6 subjects, 19.9%), vomiting (6 subjects, 10,9%) and pyrexia (5 subjects, 9.1%) (**Table 17**).

The most common AEs reported in the comparator 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%).

Table 17: Paediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): Overall Summary of Treatment- Emergent Adverse Events Reported in ≥5% of Subjects by Preferred Term (Safety Population)

System Organ Class Preferred Term	Daptomycin (N=55)	Comparator (N=26)
Subjects with at least one TEAE [a]	36 (65.5)	20 (76.9)
Diarrhoea	6 (10.9)	5 (19.2)
Pyrexia	5 (9.1)	3 (11.5)
Vomiting	6 (10.9)	2 (7.7)
Osteomyelitis	1 (1.8)	4 (15.4)
Blood creatine phosphokinase increased	4 (7.3)	0
Arthritis bacterial	0	3 (11.5)
Bacteraemia	3 (5.5)	0
Cellulitis	1 (1.8)	2 (7.7)
Drug hypersensitivity	0	2 (7.7)
Erythema	0	2 (7.7)

AE: adverse event; COM: standard-of-care comparator; DAP: daptomycin; TEAE: treatment-emergent adverse event

a. Treatment-emergent AEs were AEs occurring with an onset date on or after the first administration of study drug (including Day 1) through the last study evaluation.

The most commonly reported treatment-related TEAEs in the daptomycin treatment arm were diarrhea and blood CPK increased (2 subjects each, 3.6%). These events are known adverse drug reactions reported in the label for daptomycin. For the comparator group, diarrhea was the only TEAE considered related to study drug that was reported in more than 1 subject (2 subjects, 7.7%).

Table 18

CSR Table 12-6: Summary of TEAEs by Relationship to Study Drug and Preferred Term (Safety Population - Paediatric Phase 4 SAB Study [DAP- PEDBAC-11-02])

System Organ Class Preferred Term	DAP (N=55) n (%)	COM (N=26) n (%)
Subjects with at least one drug-related TEAE	8 (14.5%)	4 (15.4%)
Gastrointestinal disorders	2 (3.6%)	2 (7.7%)
Diarrhoea	2 (3.6%)	2 (7.7%)
Infections and infestations	1 (1.8%)	0
Candida infection	1 (1.8%)	0
Investigations	4 (7.3%)	0
Blood creatine phosphokinase increased	2 (3.6%)	0
Hepatic enzyme increased	1 (1.8%)	0
Transaminases increased	1 (1.8%)	0
Metabolism and nutrition disorders	0	1 (3.8%)
Hypernatraemia	0	1 (3.8%)
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	
Cough	1 (1.8%)	
Skin and subcutaneous tissue disorders	0	1 (3.8%)
Rash macular	0	1 (3.8%)
Rash maculopapular	0	1 (3.8%)
Vascular disorders	0	1 (3.8%)
Thrombophlebitis	0	1 (3.8%)

AE: adverse event; COM: standard of care comparator; DAP: daptomycin; TEAE: treatment-emergent adverse event

Overall, the majority of TEAEs were mild or moderate in severity. Nine subjects had TEAEs that were considered to be severe (11.1%), including 5 (9.1%) daptomycin-treated subjects and 4 (15.4%) comparator-treated subjects (Table 2.5: 10). Eight of these 9 subjects had severe events also reported as SAEs. None of the severe events were considered to be treatment-related, and 2 of these events (pneumonia and osteomyelitis) led to study drug discontinuation.

Serious adverse event/deaths/other significant events

The incidence of SAEs was similar in the 2 treatment groups, and there were no drug-related SAEs or deaths. A total of 20 subjects, including 13 subjects who received daptomycin (23.6%) and 7 subjects who received comparator (26.9%), experienced at least 1 SAE **(Table 19)**.

Table 19. Paediatric Phase 4 SAB Study (DAP-PEDBAC-11-02): Summary of Treatment-Emergent Serious Adverse Events (Safety Population)

Event	All Ages		
	Daptomycin (N=55)	Comparator (N=26)	Overall (N=81)

Subjects with at least one serious TEAE	13 (23.6%)	7 (26.9%)	20 (24.7%)
Cardiac disorders	0	1 (3.8%)	1 (1.2%)
Cardiac failure congestive	0	1 (3.8%)	1 (1.2%)
General disorders and administration site conditions	1 (1.8%)	0	1 (1.2%)
Device breakage	1 (1.8%)	0	1 (1.2%)
Immune system disorders	0	1 (3.8%)	1 (1.2%)
Intestine transplant rejection	0	1 (3.8%)	1 (1.2%)
Infections and Infestations	7 (12.7%)	3 (11.5%)	10 (12.3%)
Arthritis bacterial	0	2 (7.7%)	2 (2.5%)
Bacteraemia	3 (5.5%)	0	3 (3.7%)
Bone abscess	1 (1.8%)	0	1 (1.2%)
Muscle abscess	1 (1.8%)	0	1 (1.2%)
Osteomyelitis	1 (1.8%)	1 (3.8%)	2 (2.5%)
Pneumonia	1 (1.8%)	0	1 (1.2%)
Staphylococcal bacteraemia	1 (1.8%)	0	1 (1.2%)
Investigations	1 (1.8%)	0	1 (1.2%)
Hepatic enzyme increased	1 (1.8%)	0	1 (1.2%)
Metabolism and nutrition disorders	1 (1.8%)	0	1 (1.2%)
Malnutrition	1 (1.8%)	0	1 (1.2%)
Musculoskeletal and connective tissue disorders	2 (3.6%)	0	2 (2.5%)
Bone fistula	1 (1.8%)	0	1 (1.2%)
Synovitis	1 (1.8%)	0	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	2 (3.6%)	2 (7.7%)	4 (4.9%)
Pneumonia aspiration	0	1 (3.8%)	1 (1.2%)
Pneumothorax	1 (1.8%)	0	1 (1.2%)
Pulmonary oedema	0	1 (3.8%)	1 (1.2%)
Respiratory failure	1 (1.8%)	0	1 (1.2%)
Vascular disorders	1 (1.8%)	0	1 (1.2%)
Venous thrombosis limb	1 (1.8%)	0	1 (1.2%)

TEAE: treatment-emergent adverse event

Notes: Adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Treatment-emergent adverse events (TEAEs) are AEs occurring with an onset date on or after the first administration of study drug (including Day 1) through the last study evaluation. Subjects experiencing more than one AE with the same system organ class and preferred term are counted only once at the corresponding system organ class or preferred term level.

SAEs belonging to the infections and Infestations system organ class was the most commonly reported. Overall, 12 SAEs which occurred in 10 subjects belonged to the infections and Infestations SOC. Eight SAEs that were infections occurred in 7 daptomycin-treated subjects (12.7%), and 4 SAEs that were infections occurred in 3 comparator-treated subjects (11.5%). Events in this system organ class included bacteraemia (4 subjects, with 1 reported as Staphylococcal bacteraemia) in the daptomycin arm and bacterial arthritis (2 subjects) in the comparator arm. Two subjects in each arm discontinued due to a TEAE that was also a SAE, as follows.

The MAH justified the proposed treatment duration also in light of safety in the youngest age group 1-6 year of age for which the highest dosing is proposed, based on PK modelling.

Thus, the safety data obtained from this study and the integrated safety analysis can be considered valid for this lower age group.

Integrated safety Evaluation across two paediatric studies (DAP-PEDBAC-11-02 and DAP-PEDS-07-03):

The safety population included 311 daptomycin and 159 comparator-treated paediatric subjects. The overall incidence of TEAEs was 43.1% in daptomycin-treated and 42.8% in comparator-treated subjects. Treatment-related TEAEs were noted in 13.8% of daptomycin- and 16.4% of comparator-treated subjects. The safety profile for daptomycin was comparable in the various age groups and was similar to the comparator. The type, incidence, and severity of TEAEs reported for daptomycin were comparable to those reported for comparator.

Table 20. Adverse Events Overview (Safety Population - Paediatric cSSSI Study [DAP-PEDS-07-03] and Paediatric SAB Study [DAP-PEDBAC-11-02])

	Daptomycin All Ages (N = 311) n (%)	Comparator All Ages (N = 159) n (%)
Subjects with at least one TEAE	134 (43.1%)	68 (42.8%)
Subjects with at least one severe TEAE	11 (3.5%)	7 (4.4%)
Subjects with at least one serious TEAE	19 (6.1%)	10 (6.3%)
Subjects with at least one treatment-related TEAE	43 (13.8%)	26 (16.4%)
Subjects with at least one severe treatment-related TEAE	1 (0.3%)	1 (0.6%)
Subjects with at least one serious treatment-related TEAE	1 (0.3%)	0 (0.0%)
Subjects with TEAE leading to discontinuation of study drug	10 (3.2%)	9 (5.7%)
Subjects with TEAE leading to discontinuation of study	1 (0.3%)	1 (0.6%)
Subjects with treatment-related TEAE leading to discontinuation of study drug	5 (1.6%)	5 (3.1%)
Subjects with treatment-related TEAE leading to discontinuation of study	1 (0.3%)	1 (0.6%)
Subjects with serious TEAE leading to discontinuation of study drug	4 (1.3%)	3 (1.9%)
Subjects with serious TEAE leading to discontinuation of study	0 (0.0%)	0 (0.0%)
Subjects with serious treatment-related TEAE leading to discontinuation of study	0 (0.0%)	0 (0.0%)
Subjects with TEAE leading to death	0 (0.0%)	0 (0.0%)
Subjects with treatment-related TEAE leading to death	0 (0.0%)	0 (0.0%)

TEAE: treatment emergent adverse event; cSSSI: complicated skin and skin-structure infections; SAB: *staphylococcus aureus* bacteremia;
Note: TEAEs are adverse events occurring with an onset date on or after the first administration of study drug (including Day 1) through the last study evaluation.
Source-Clinical data from studies: DAP-PEDS-07-03 and DAP-PEDBAC-11-02.

Treatment-emergent adverse events that were considered by the investigator to be related to study drug were reported in similar proportions of subjects in the treatment arms, including 43 (13.8%) daptomycin-treated subjects and 26 (16.4%) comparator-treated subjects (Table 2.5:13). Ten (3.2%) daptomycin-treated subjects and 9 (5.7%) comparator-treated subjects discontinued study drug due to a TEAE (Table 2.5: 13).

The incidence of SAEs was similar in the two treatment arms (6.1% in daptomycin-treated subjects and 6.3% in comparator-treated subjects) (Table 2.5: 13). Altogether, there was 1 study drug-related SAE and there were no deaths.

In the combined Safety Populations of the two Phase 4 paediatric (SAB and cSSSI) studies, the 3 most common adverse events (preferred terms) in daptomycin-treated subjects were diarrhoea (24 subjects, 7.7%), blood CPK increased (18 subjects, 5.8%), and pyrexia (14 subjects, 4.5%). The incidences reported for these adverse events were similar in the comparator arm, as follows: diarrhoea (12 subjects,

7.5%), blood CPK increased (7 subjects, 4.4%), and pyrexia (7 subjects, 4.4%). In general, these adverse events were expected events when antibiotic treatments are administered to paediatric subjects with cSSSI or SAB.

Integrated safety Evaluation

Integrated safety Evaluation across two paediatric studies (DAP-PEDBAC-11-02 and DAP-PEDS-07-03, DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01):

The combined Safety Populations in these studies included 372 daptomycin-treated subjects.

Overall, 42.2% of daptomycin-treated subjects reported a TEAE. Treatment-related TEAEs were reported for 13.2% of subjects and 3.0% (11/372) subjects discontinued study drug due to a TEAE. Overall, 5.6% (21/372) of subjects experienced a SAE, 1 (0.3%) subject experienced a drug-related SAE, and there were no deaths. The safety profile was generally comparable across age groups.

The most common AEs among daptomycin-treated paediatric subjects in the 5 completed studies were: diarrhea (27 subjects, 7.3%), blood CPK increased (21 subjects, 5.6%), and pyrexia (17 subjects, 4.6%). There were no reports of drug hypersensitivity, eosinophilic pneumonia, dysregulation of in vivo coagulation, serious hepatotoxicity, or bone marrow toxicity among the adverse events reported.

2.5.1. Discussion on clinical safety

Integrated data from all the paediatric studies are reassuring and raise no new safety issues for daptomycin. The most commonly reported treatment-related TEAEs in the daptomycin treatment arm were diarrhea and blood CPK increased, which are well known adverse drug reactions already reported in the label for daptomycin.

However, safety data from patients <2 year of age were lacking. This was flagged as a concern as the proposed dose for the SAB indication is higher compared to the paediatric cSSTI indication. The MAH discussed the appropriateness of the proposed lower age cut-off of one year. The obtained PK data demonstrate that daptomycin exposure and safety data (based on CPK data) in patients 2 to 17 years of age is similar to the exposure seen in adults receiving the 6 mg/kg dose. Further on, the appropriateness of the recommended 12 mg/kg daptomycin administered as 60-minute infusion for paediatric SAB patients, 1 to <2 years is supported from PK/exposure considerations and safety considerations, including CPK elevations.

In addition, the MAH justified the proposed treatment duration in light of safety. In the context of limited clinical data/study subpopulation, there is no obvious increased risk for specific TEAEs in subjects receiving >14 days of daptomycin as compared to those receiving >14 days of comparator IV antibiotics.

Additional expert consultations

Not applicable

2.5.2. Conclusions on clinical safety

The MAH justified the proposed treatment duration, also in light of safety in the youngest age group 1-6 year of age for which the highest dosing is proposed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 10.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.1 with the following content:

Safety concerns

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

Pharmacovigilance plan

No additional pharmacovigilance activities are planned for the product.

Risk minimisation measures

Safety Concern	**Routine Risk Minimization Measures**	**Additional Risk Minimization Measures**
Important Identified Risk: Severe skeletal muscle toxicity	Section 4.4 Special warnings and precautions for use	Daptomycin dosage card for physicians including paediatric

	Section 4.8 Undesirable effects Relevant preferred terms are included as ADRs in SmPC Section 4.8 Undesirable effects	indications
Important Identified Risk: Reduced susceptibility to daptomycin in *S. aureus*	Section 4.4 Special warnings and precautions for use Section 5.1 PD properties: “Mechanisms of resistance.	Package leaflet for laboratories
Important Identified Risk: Peripheral neuropathy	Sections 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects of the SmPC.	None planned
Important Identified Risk: Severe hypersensitivity reactions (including pulmonary eosinophilia and severe cutaneous reactions)	Sections 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects. Addition of AGEP	None planned
Important Identified Risk: Eosinophilic pneumonia	Section 4.8 Undesirable effects: SOC Respiratory system disorders: Eosinophilic Pneumonia Addition of Organising Pneumonia to list of terms. Section 4.4 Special warnings and precautions for use: Addition of Organising Pneumonia to description of signs/symptoms of eosinophilic pneumonia The MAH has updated the CCSI (see Section 4, Changes to Reference Safety Information) / the Risk Management Plan / the CCSI (see Section 4, Changes to Reference Safety Information) and as proposed to this RMP V10 with this new information included for Organising Pneumonia as part of the important identified risk of Eosinophilic Pneumonia.	None planned
Important Potential Risk: Bone marrow toxicity	Routine pharmacovigilance activities including close monitoring in the PSUR.	None planned
Important Potential Risk: Severe hepatotoxicity	Routine Pharmacovigilance activities including close monitoring in the PSUR	None planned

Important Potential Risk: Dysregulation of *in vivo* coagulation	Routine pharmacovigilance activities including close monitoring in the PSUR	Daptomycin dosage card
Missing Information: Patients with renal impairment*	Section 4.2: Posology and method of administration Section 4.4 Special warnings and precautions for use. Section 5.2 Pharmacokinetic properties	None planned *No longer considered "missing information." As accepted by PRAC Rapporteur assessment for PSUR15. However, MAH will continue to monitor and any new information that arises on renal impairment will be reported in future PSURs and if warranted, RMP will be updated.
Missing Information: Patients with hepatic impairment	Section 4.2: Posology and method of administration Section 5.2 Pharmacokinetic Properties	None planned
Missing Information: Pregnant or lactating women	Section 4.6 Pregnancy, fertility and lactation	None planned

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly.

For details refer to the Product Information adopted by the CHMP on 12 October 2017.

Most important change, extension of indication shown hereafter:

"Adult **and paediatric (1 to 17 years of age)** patients with *Staphylococcus aureus* bacteraemia (SAB) ~~when associated with RIE or with cSSTI~~. **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."**

The full indications for Cubicin will be as follows:

"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."

In addition, the marketing authorisation holder (MAH) took the opportunity to bring the product information in line with the latest QRD template version 10 and to combine the SmPCs for both strengths (350 and 500 mg). The MAH also updated the RMP, from last approved version 9.1 to the current version 10.1.

2.7.1. User consultation

No user consultation with target patient groups on the package leaflet has been performed, nor required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Infections due to resistant Gram-positive bacteria are increasingly common in paediatric patients. Serious infections due to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in particular, are a major health problem worldwide.

3.1.2. Available therapies and unmet medical need

Few antibiotics with activity against MRSA or other serious Gram-positive bacteria are currently available, and fewer still have had their safety and efficacy carefully evaluated in paediatric patients.

Daptomycin, a cyclic lipopeptide antibacterial agent, shows rapid *in vitro* bactericidal activity with concentration-dependent killing for Gram-positive organisms, such as MRSA and methicillin-susceptible *S. aureus* (MSSA).

Clinical trials in adults demonstrated that daptomycin was safe and efficacious in complicated skin and skin structure infections (cSSSI) and bloodstream infections (bacteraemia) caused by *S. aureus*, including right-sided infective endocarditis (RIE). Additionally, in a recently completed clinical trial (DAP-PEDS-07-03), daptomycin was shown to be safe and well tolerated in paediatric subjects (ages 1 to 17 years) with cSSSI caused by Gram-positive pathogens and was similarly effective as standard of care (SOC) therapy.

The purpose of this submission is to support the efficacy and safety of daptomycin in the treatment of *S. aureus* bacteraemia (SAB) in paediatric patients (1 to 17 years of age).

3.1.3. Main clinical study

A prospective, 2:1 randomized paediatric Phase 4 study ([DAP-PEDBAC-11-02] was performed, wherein the safety, efficacy, and PK of age-specific, weight-based dosing of intravenous (IV) daptomycin was specifically evaluated in 82 paediatric subjects with SAB, including 55 subjects who received daptomycin. Comparators included intravenously administered medications as follows: vancomycin, clindamycin, semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin], or first-generation cephalosporins.

The study in paediatric patients aged 1 to 17 years aimed to confirm the safety of daptomycin at exposures similar to those reported for adults treated for bacteraemia (90% of adult subjects had mean steady state systemic exposures [AUC] between 270 to 1151 µg*h/mL; mean AUC 622 µg*h/mL; median AUC 543 µg*h/mL). In paediatric pharmacokinetic (PK) studies, children showed progressively higher daptomycin clearance and higher volume of distribution with decreasing age compared to that of adult subjects. Thus, to achieve similar exposures in children to those seen in adults, different doses (mg/kg) were evaluated by age groups.

3.2. Favourable effects

In the mMITT population at TOC clinical success were obtained in 45 (88.2%) in the daptomycin group and 17 (77.3%) in the comparator group. The majority were defined as “cured” in both treatment groups. At end of IV treatment (EOIV) 48 (91. 4%) patients in the daptomycin group were categorised as clinical success, defined as “cure” or “improved”. Of these 14 (27.4%) were cured. In the comparator group 19 (95%) patients obtained clinical success of which only 4 (18.2%) patients were being defined as cured.

3.3. Uncertainties and limitations about favourable effects

The enrolled population is heterogeneous with regard to primary infection, and only a limited number of enrolled patients belong to the cSSTI category. Furthermore, the efficacy at TOC/safety visit in the mMITT population is based on variable duration of daptomycin treatment (range 1-44 days), as well as, different subsequent oral treatments. Moreover, no patients below the age of two years have been included.

The study population in each of the paediatric studies was quite small, with even smaller numbers in the sub groups and therefore some caution would be advisable. However the dosing regimens are supported by both PK modelling and clinical data, which is reassuring. There were also a high number of major protocol violations but these were considered not to have influenced the interpretation of the results. There is still a lack of data in renal impairment (flagged in SmPC).

3.4. Unfavourable effects

No new adverse events have been identified and the safety profile for daptomycin in children appears to be in line with what has been previously reported. The need for monitoring the potential increase in creatine phosphokinase is mentioned in the SmPC and administration in children below 1 year age is not recommended due to adverse effects seen in neonatal dogs.

3.5. Uncertainties and limitations about unfavourable effects

For the proposed posology, the safety profile in patients below 2 year of age is unknown but the recommended 12 mg/kg daptomycin dosage administered as 60-minute infusion for paediatric SAB patients, 1 to <2 years is supported from PK/exposure considerations and safety considerations, including CPK elevations. Data for the recommended maximum treatment duration is limited and, hence,

for the requested indication of SAB with cSSTI in paediatric population, the duration of therapy should be in accordance with available official recommendations.

3.6. Benefit-risk assessment and discussion

Infections due to resistant Gram-positive bacteria are increasingly common in paediatric patients. Serious infections due to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), in particular, are a major health problem worldwide. Few antibiotics with activity against MRSA or other serious Gram-positive bacteria are currently available, and fewer still have had their safety and efficacy carefully evaluated in paediatric patients. Hence, there is an undisputable medical need for further treatment options for the paediatric patient population.

The submitted documentation offers very limited data on the clinical efficacy for the applied indication (SAB in association with cSSTI). Due to uncertainties of the main study, the interpretation of the results is somewhat hampered. Although study DAP-PEDBAC-11-02 was not powered to demonstrate efficacy in the applied indication, exposure (AUC) matching with adults was demonstrated for all age groups. Consequently, the efficacy previously shown for treatment of SAB in adults can be extrapolated to the paediatric population based on PK data.

No new adverse events of concern have been identified. The safety data from the paediatric patients in this study were consistent with the known safety profile of daptomycin.

3.7. Conclusions

These data support an extension to the approved prescribing information for Cubicin to include paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In paediatric patients, use in bacteraemia should be associated with cSSTI.

In line with requirements outlined in the guidance document on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 2), a Phase II environmental risk assessment (ERA) should be submitted as a post authorisation measure (REC) by end of March 2019.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are

updated. The Package Leaflet is updated accordingly.

In addition, the marketing authorisation holder (MAH) took the opportunity to bring the product information in line with the latest QRD template version 10 and to combine the SmPCs for both strengths (350 and 500 mg). The MAH also updated the RMP, from last approved version 9.1 to the current version 10.1.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

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

Scope

Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly.

In addition, the marketing authorisation holder (MAH) took the opportunity to bring the product information in line with the latest QRD template version 10 and to combine the SmPCs for both strengths (350 and 500 mg). The MAH also updated the RMP, from last approved version 9.1 to the current version 10.1.

Summary

Please refer to the Scientific Discussion – Cubicin II-61.