European Medicines Agency

London, 25 July 2007
Product name: **Cubicin**
PROCEDURE NO. EMEA/H/637/II/05

SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

SCIENTIFIC DISCUSSION

1 Introduction

Daptomycin is a novel cyclical lipopeptide derived from a natural product of *Streptomyces roseosporus*.
Cubicin is indicated for the treatment of complicated skin and soft-tissue infections in adults at the recommended dose of 4 mg/kg administered as a single daily dose for 7-14 days or until the infection is resolved.
Daptomycin is active against Gram positive bacteria only. In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

This Type II variation concerns the MAH's proposal to extend the approved therapeutic indication to include the treatment of *Staphylococcus aureus* bacteraemia (SAB), including known or suspected Infective Endocarditis (IE) in adults.

The recommended daily dose for these indications (6 mg/kg once daily) is higher than that currently approved for the treatment of cSSTI (4 mg/kg once daily).

The changes to the SPC include:
Various modifications in 4.1, 4.2 and 5.2 to reflect the two possible doses by indication, an additional warning in 4.4, safety data in 4.8, description of the study in 5.1 and additions to 5.3 to support the higher dose.

In support of this proposal, the MAH provided:

- a completed study report on DAP-IE-01-02 (Pivotal efficacy study). This is dated 17 August 2005 and the study was actually conducted between 28 August 2002 and 16 February 2005. The study enrolled patients at 48 sites across the US, France, Belgium and Germany.
- a final report on a pharmacokinetic study (DAP-ADT-04-02: Phase 1 clinical trial) in healthy subjects who were given up to 12 mg/kg daptomycin daily for two weeks. A preliminary report was previously reviewed during the initial assessment of daptomycin since it provided information on metabolites and included an assessment of nerve conductivity. This final report is presented as supporting safety data for the 6 mg/kg dose used in DAP-IE-01-02.

The application also includes:

- A non-clinical summary that addresses the data that would support the use of a 6 mg/kg dose in man where justified
- 11 reports or articles regarding further data on the microbiological studies performed or completed since the previous submission. Effectively, these reports encompass the information provided almost simultaneously to address FUMs 003 (concerning mechanisms of resistance) and 009 (concerning investigations on S. aureus isolates into patients and organisms that were the subject of daptomycin failures associated with increased MICs in the DAP-IE-01-02). The information from the 11 reports in Module 5 and from FUMs 003 and 009 are summarised together in this assessment report.

2 Clinical aspects

2.1 Pharmacokinetics

2.1.1 Supportive study – DAP-ADT-04-02

2.1.1.1 Description

This was a single centre, randomised and double-blind study in which ascending doses (10 and 12 mg/kg) of daptomycin were administered for 14 days to two cohorts of healthy volunteers. In addition, a third cohort was randomised (1:1) to receive 6 or 8 mg/kg daptomycin for 4 days to establish a pharmacokinetic baseline for comparison.

- The primary objective was to assess the pharmacokinetic profile of multiple doses of 6, 8, 10, and 12 mg/kg/day.
- The secondary objective was to assess the safety and tolerability of once daily IV dosing at 10 and 12 mg/kg for 14 consecutive days.

Up to 36 healthy volunteers between 18 and 45 years of age were to be sequentially enrolled into one of the 3 dosing cohorts. Attempts were to be made to enrol equal numbers of each gender.

In Cohort 1, 12 subjects were to be randomised 3:1 to daptomycin 10 mg/kg or placebo (0.9% sodium chloride) for 14 days. Following Cohort 1, the blinded safety data were to be transferred to the Sponsor for clinical evaluation and then discussed in a teleconference between the Principal Investigator and the Sponsor to reach a decision of whether to proceed to 12 mg/kg/day.
Thus, Cohort 2 subjects were to be randomised 3:1 to daptomycin 12 mg/kg or placebo for 14 days.
In Cohort 3, 12 subjects were to be randomised 1:1 to receive 6 mg/kg or 8 mg/kg once daily for 4 days.

Dosing Cohort	Daily Dose (mg/kg/day)	Total Subjects (n)	Daptomycin subjects	Control Subjects	Maximum # of Dosing Days
1	10	12	9	3	14
2	12	12	9	3	14
3	6 or 8	12	12	0	4

2.1.1.2 Results

All except one subject completed the study dosing and follow-up periods (the subject was in the placebo group of Cohort 2 and withdrew on his own volition.

As shown in the next table, based on data after the first dose, exposure to daptomycin (Cmax and AUC0-∞) increased with dose with Cmax occurring at the end of the infusion (0.5 h) at all dose levels. Half-life ranged from 7.3 to 8.3 h.

Mean (CV%) PK Daptomycin after single doses of 6, 8, 10 and 12 mg/kg – PK Population

Daptomycin Dose (mg/kg)	C_{max} (µg/ml)	$AUC_{0-\infty}$ (µg x hr/ml)	T_{max} (hr)	$T_{1/2}$ (hr)	CLwp (ml/hr/kg)	V_d (ml/kg)
6	95.7 (31.8)	729.8 (32.2)	0.5 (0.5-0.5)	7.5 (10.9)	9.9 (12.5)	105.9 (13.3)
8	106.2 (20.0)	773.3 (20.3)	0.5 (0.5-0.5)	7.3 (18.4)	10.1 (24.0)	102.9 (11.8)
10	129.7 (11.3)	1013.5 (16.2)	0.5 (0.5-0.5)	8.4 (12.0)	9.9 (20.7)	117.2 (11.5)
12	164.8 (7.4)	1269.2 (22.2)	0.5 (0.5-0.5)	7.8 (12.1)	10.0 (23.7)	111.1 (13.7)

Daptomycin was highly bound to plasma protein and the protein binding was independent of drug concentration. The level of plasma protein binding of daptomycin on Day 1 was consistent across dose levels with the unbound fraction (fu) mean values of 0.07 – 0.10.

Daptomycin was excreted mainly in the urine with 37-68% (mean %Fe across all doses and days) of the administered dose being excreted in 24 h as unchanged drug. As a consequence of high plasma protein binding and major excretion by the kidneys, the level of CLwp was relatively low (9.9-10.1 ml/h/kg) and the t1/2 was long (7.3-8.3 h) across the dose groups. Daptomycin had a small Vd (0.1 l/kg) suggesting that the drug remains primarily in the plasma and interstitial fluid.

Repeat daily dosing at all levels resulted in attainment of steady-state conditions by Day 3. The MAH has presented mean PK parameters at steady-state (Day 4) and at Day 14. At steady-state, exposure to daptomycin (Cmax and AUC) increased with dose with Cmax occurring at the end of the infusion (0.5 h) at all dose levels. Again CLwp was relatively low (8.8-9.1 ml/h/kg), the t1/2 was long (7.7-8.3 h) across the dose groups and the Vd was small (0.1 l/kg).

The Cmax and AUC were slightly higher at steady-state (Day 4) than following a single dose for the 8, 10 and 12 mg/kg doses levels of daptomycin. This accumulation was not observed at the 6 mg/kg dose due to very high concentrations on Day 1 for one subject (Cmax = 155 µg/ml). Cmax on Day 14 was similar to that observed at steady-state.

Mean (CV%) PK Parameters of Daptomycin 10 and 12 mg/kg at Day 14 – Pharmacokinetic Population

Daptomycin Dose (mg/kg)	C_{max} (µg/ml)	$AUC_{0\text{-}tau}$ (µg x hr/ml)	T_{max} (hr)	$T_{1/2}$ (hr)	CLwp (ml/hr/kg)	V_d (ml/kg)
10	139.3 (13.9)	1082.1 (15.3)	0.6 (0.5-1.0)	7.9 (6.1)	7.5 (18.6)	85.8 (16.7)
12	181.7 (13.2)	1290.5 (22.0)	0.5 (0.5-0.5)	7.9 (13.8)	9.0 (32.3)	99.2 (18.7)

The MAH has performed the analysis of dose proportionality of AUC0-∞ on Day 1, AUC0-tau on Day 4, Cmax on Days 1 and 4 and Cmin on Day 4 (with natural log transformation prior to analysis). Based on the result of the 90% CI of the slope estimate, the mean AUCs and Cmin of daptomycin were shown to be dose proportional (i.e. included the value of 1.0) while mean Cmax did not meet the dose proportionality criteria.

On both Days 1 and 4 the increase in Cmax with dose was slightly less than dose proportional. The mean Cmax on Day 1 in the 6 mg/kg dose group is inflated by the subject with an unusually high Cmax (155 µg/ml) at that time. The lack of dose proportionality and lack of accumulation for Cmax was less obvious when the median value for the 6 mg/kg dose group was used for comparison on Day 1.

The pharmacokinetic conclusions of the study are as follows:

- Maximum plasma concentrations were reached at the end of the daptomycin infusion (0.5 hours) in all dose groups
- The plasma concentration of daptomycin was slowly eliminated with mean half-lives ranging from 7.29-8.32 hours across the dosing range.
- Plasma protein binding of daptomycin was high across all the dose levels on Day 1 with a mean free drug fraction <0.10. Consistent with this, the mean Vd on Day 1 was approximately 0.1 l/kg.
- Following intravenous infusion, daptomycin was excreted in the urine, with 37-68% (%Fe) of the administered dose being excreted in 24 h as unchanged drug. Glomerular filtration was the major elimination route for daptomycin.
- The steady-state of daptomycin was reached following 3-day repeat doses in all cohorts.
- The mean AUCs and Cmin of daptomycin were dose proportional over the range of 6 to 12 mg/kg; however, the mean Cmax did not meet the dose proportionality requirement as the

90% confidence interval did not encompass 1 (upper bound was 0.973 and 0.964 on Day 1 and 4, respectively).

- T ½ and CLwp at steady-state were similar across dose levels indicating linear pharmacokinetics.

These observations were generally consistent with those reported in the initial assessment report for daptomycin over the range of doses evaluated. The MAH had previously concluded that daptomycin pharmacokinetics were nearly linear and time independent at doses up to 6 mg/kg. Daptomycin 4 mg/kg administered once daily for 7 days achieved steady state concentrations by the third dose.

The safety data from this study do not raise any new issues for daptomycin. With such small denominators per dose group it is not really possible to interpret the small differences in AEs although it remains possible that headache may increase with dose.

The PK results were reflected in section 5.2 of the SPC.

2.2 Clinical efficacy

2.2.1 Main study - DAP-IE-01-02

2.2.1.1 Choice of dose

This application is supported by a single study of efficacy in which daptomycin was administered at 6 mg/kg once daily for the treatment of *S. aureus* bacteraemia and endocarditis. This dose was based upon *in vitro* and *in vivo* pharmacodynamic modelling, animal models of endocarditis, animal toxicology and clinical data from earlier studies.

- Previous PK/PD studies established that for daptomycin Cmax, Cmax/MIC and/or AUC/MIC ratios are most closely correlated with *in vivo* efficacy.

- A series of *in vitro* simulations for treatment of *S. aureus* bacteraemia and simulated endocarditis vegetations were performed using biochambers and infusion pumps to imitate the human PK profiles of different dose regimens. Based on simulated data, it appeared that 6 mg/kg/day produced greater than a 6 log reduction in MRSA and glycopeptide-intermediate *S. aureus* (GISA) in endocarditis.

- A rat model of endocarditis demonstrated that daptomycin at a dose that provided exposures (Cmax and AUC values) consistent with ≤ 6 mg/kg/day in humans produced significant bactericidal activity against *S. aureus*. Two additional models of *S. aureus* endocarditis in rabbits also demonstrated a high degree of efficacy with daptomycin exposures consistent with a daily dose of ≤ 6 mg/kg/day in humans. Moreover, the serum concentrations produced by the 6 mg/kg human equivalent dose were consistently greater than the MIC99 of *S. aureus*.

- Pharmacodynamic studies in mice supported the importance of achieving and maintaining bactericidal concentrations of daptomycin and AUC and Cmax were both shown to be important. In the mouse pharmacodynamic models, the efficacy of daptomycin was not increased by dividing the daily dose (dose fractionation). As already recognised in the initial assessment of daptomycin, animal toxicology studies and data in man indicated that dose fractionation increased muscle toxicity.

- The non-clinical safety profile of daptomycin supported both the safety margin and duration of dosing for 6 mg/kg q24h for treatment of *S. aureus* bacteraemia. No fibrosis or rhabdomyolysis was observed in repeat dose studies up to 150 mg/kg/day in rats and 100 mg/kg/day in dogs, which gave daily AUCs approximately 10- and 6-fold, respectively, the predicted human AUC with 6 mg/kg once daily dosing. The degree of serum muscle enzyme elevations and microscopic myopathy was not increased when treatment once daily was extended from 1 to 6 months,

suggesting that toxicity was not cumulative. Complete reversibility of the muscle lesions was observed within 30 days after cessation of dosing. Non-clinical data relevant to the 6 mg/kg dose support the use of this dose in man.

- In Phase 1 studies in healthy subjects daptomycin was well tolerated at doses up to 8 mg/kg once daily for 14 days (CSR DAP-00-02).

- Two early clinical studies showed that a free daptomycin Cmax value approximately 15 x MIC90 and C6h value approximately 4 to 16 x MIC90 of *S. aureus* could be reached with 6 mg/kg once daily in patients with serious *S. aureus* infections.

- Later studies (9803 and 9804) evaluated 4 mg/kg and 6 mg/kg once daily and 3 mg/kg twice daily for treating bacteraemia and a variety of infections due to Gram-positive bacteria. These data were described previously and their interpretation is hampered by the small numbers and heterogeneity of infections treated. However, in 9803, the efficacy of daptomycin 4 mg/kg once daily was similar to that of the comparators in patients with bacteraemia due to Gram-positive pathogens while 3 mg/kg twice daily seemed to be less effective. Conversely, there was a lower success rate among patients given 6 mg/kg once daily. A review suggested that other confounding clinical factors in the latter group, including delayed surgical drainage and removal of foreign bodies) had had an adverse effect on outcomes. In 9804, a loading dose was used and then doses were adjusted for renal impairment. The 3 mg/kg twice daily regimen and lower and less frequent dosing in the dialysis group seemed to result in lower efficacy.

- Therefore, 6 mg/kg once daily was chosen for study DAP-IE-01-02 with the provision that a Data Safety Monitoring Board (DSMB=DMC below) would evaluate available safety and efficacy data after the first 30 patients were enrolled.

2.2.1.2 Description

Methods
This was a multi-centre, randomised (1:1), open-label study that compared daptomycin with conventional intravenous therapy [either a semi-synthetic penicillin – one of nafcillin, oxacillin, cloxacillin or flucloxacillin – or vancomycin] in patients with IE or bacteraemia due to *S. aureus*.

- **Objectives**

The primary objective was to demonstrate that daptomycin is not inferior to comparator in the treatment of *S. aureus* bacteraemia and IE. The assessment was to be based on outcomes assigned by the Independent External Adjudication Committee (IEAC; see below) outcome at Test of Cure (TOC) in the Intent-to-Treat (ITT) population.
The secondary objectives were:

- To compare clinical success rates between daptomycin and comparator in the treatment of *S. aureus* bacteraemia and IE:
  • at End of Treatment (EOT) in the ITT population
  • at EOT and TOC in the Per Protocol (PP) population
  • at EOT for each of the diagnoses defined by the IEAC in the ITT population
  • at EOT for each of the diagnoses defined by the Investigator in the ITT population
- To compare microbiological eradication rates between daptomycin and comparator
- To demonstrate similar survival rates between daptomycin and comparator in the ITT population
- To evaluate the safety of daptomycin as compared to comparator in the safety population
- To assess the pharmacokinetics of daptomycin.

- **Study Participants**

Inclusion criteria and assignment of diagnosis

Adults (≥18 years) were to have documented *S. aureus* bacteraemia defined as at least one positive blood culture obtained within 2 calendar days prior to the first dose of study medication.

The IEAC assigned the diagnoses at baseline and EOT and the following definitions for the diagnostics at baseline: definite/possible/not IE and at End of Therapy (EOT): left IE, complicated/uncomplicated RIE and complicated/uncomplicated bacteraemia.

The exclusion criteria were clearly defined and included:

- Weighed >150 kg or <50 kg.
- Intravascular foreign material at the time a positive blood culture was drawn (e.g. intracardiac pacemaker wires, percutaneous or implanted venous catheters, vascular grafts) unless the Investigator intended to have the material removed within 4 days after the first dose of study medication. The only exceptions were for vascular stents that had been in place >6 months or permanent pacemakers attached via epicardial leads.
- Prosthetic heart valve.
- Cardiac decompensation and/or valve damage such that there was a high likelihood of requiring valve replacement surgery in the 3 days after randomisation.
- Infected with a pathogen with confirmed reduced susceptibility to vancomycin (MIC >4 µg/ml).
- Creatinine clearance (CLcr) < 30 ml/minute (calculated using the Cockcroft-Gault equation using actual body weight).
- ALT or AST >5 × ULN, total bilirubin ≥3.0 mg/dl, CD4 lymphocytes <0.200×103/µl, absolute neutrophil count <0.500×103/µl or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy.
- Known to have pneumonia, osteomyelitis or a polymicrobial blood infection.

- **Randomisation**

Patients were randomised to daptomycin or conventional therapy based on a centralised computer-generated randomisation schedule designed to achieve a 1:1 ratio of patients, stratified by investigative site.

- **Treatments**

Daptomycin was administered at 6 mg/kg every 24 hours as an intravenous infusion over 30 minutes in 0.9% sodium chloride. The actual dose could be adjusted on a weekly basis if there was a fluctuation of >5% in the patient's weight.

Comparative therapy

Patients were to receive vancomycin or SSP (nafcillin, oxacillin, cloxacillin, or flucloxacillin).

Vancomycin was to be administered as an intravenous infusion over 60 minutes every 12 hours but dosing was to be adjusted based on renal function and plasma levels according to the Investigator's standard practice and local hospital guidelines.

SSPs were to be given 2 g every 4 h and were administered as an intravenous infusion over 15 minutes.

Gentamicin

All patients randomised to conventional treatment and patients with LIE randomised to daptomycin were to receive synergistic gentamicin for the first 4 days (or until blood cultures had been negative for 48 hours). Patients with uncomplicated RIE due to MSSA were to receive gentamicin for the entire 14-day course if short course therapy was deemed appropriate by the principal investigator/treating physicians. Gentamicin (1 mg/kg actual body weight) was to be administered as an intravenous infusion over 30 minutes every 8 hours and dosing was to be adjusted based on renal function according to the Investigator's standard practice and manufacturer's guidelines. Loading doses of gentamicin were allowed.

Other antibacterial agents
Potentially effective non-study anti-staphylococcal antibacterial agents (e.g. rifampicin) were prohibited from the time of enrolment to completion of follow-up unless required to treat failures. Patients requiring treatment for an intercurrent infection may have received aztreonam for Gram-negative organisms or metronidazole for anaerobic organisms or both.

Duration of treatment
This was to be based on the diagnosis as determined by the Investigator and the susceptibility of the *S. aureus* isolate.

- **Sample size**

The original sample size calculation was based on the following assumptions:
• 80% success rate for patients with IE given comparator therapy.
• 80% success rate for patients with IE given daptomycin.
• Significance level of 0.025 (one-sided) to test the null hypothesis that the treatments differed by at least 20%.
Under these efficacy assumptions, the original protocol called for a sample size of 63 RIE patients in each treatment group with 80% power. As part of the original sample size determination, it was anticipated that a target ITT population of 420 patients would be required to achieve these 126 RIE patients.

The protocol was amended in April 2004 to revise the sample size calculation based on the pooled ITT population rather than the RIE subset. In addition, the Sponsor noted that recent reports indicated that with increasing MRSA rates clinical success rates were expected to be approximately 65% in both test and reference populations. Thus, based on the same assumptions for alpha (0.025, one-sided) power (80%), and delta (20%), and assuming 65% efficacy in both treatment groups, a sample size of 90 patients (minimum) per treatment group would be required for the overall ITT (all diagnosis groups pooled) population.

3.2.2.1.3 Results

Of the 246 patients randomised into the study 236, received at least one dose of study drug (120 daptomycin and 116 comparators) at 38 sites in the US and 6 in Europe. In the comparative group 53 received only vancomycin, 59 received SSP with or without initial vancomycin therapy of ≤3 days duration and four received SSP with a longer duration of vancomycin therapy (including three with MSSA had 5, 4 and 8 days of vancomycin prior to switching to nafcillin and one with MRSA received 9 days of nafcillin prior to switching to vancomycin because the organism was isolated at baseline but not recognised until Day 9).

Patient disposition was as follows:

	Daptomycin	Comparator	Total
Disposition	**n (%)**	**n (%)**	**n (%)**
Randomised	124	122	246
Randomised but not treated	4	6	10
Safety population	120	116	236
Completed therapy	80 (66.7%)	78 (67.2%)	158 (66.9%)
Prematurely discontinued therapy	40 (33.3%)	38 (32.8%)	78 (33.1%)
Reason for discontinuation of study treatment			
Adverse event	20 (16.7%)	21 (18.1%)	41 (17.4%)
Microbiologic failure	9 (7.5%)	3 (2.6%)	12 (5.1%)
Withdrew consent	1 (<1%)	2 (1.7%)	3 (1.3%)
Discontinued therapy against medical advice	1 (<1%)	2 (1.7%)	3 (1.3%)
Unsatisfactory clinical response	1 (<1%)	1 (<1%)	2 (<1%)
Care transferred to another physician	1 (<1%)	1 (<1%)	2 (<1%)
Other	7 (5.8%)	8 (6.9%)	15 (6.4%)
Completed therapy and study	54 (45.0%)	50 (43.1%)	104 (44.1%)
Completed therapy, prematurely discontinued study Reason for discontinuation of study b	26 (21.7%)	28 (24.1%)	54 (22.9%)
Lost to follow-up	7 (5.8%)	9 (7.8%)	16 (6.8%)
Adverse event	6 (5.0%)	5 (4.3%)	11 (4.7%)
Withdrew consent	1 (<1%)	0	1 (<1%)
Other	12 (10.0%)	14 (12.1%)	26 (11.0%)

The patient populations are shown in the next table.

Population	**Daptomycin n (%)**	**Comparator n (%)**	**Total n (%)**
Safety Population	120 (100%)	116 (100%)	236 (100%)
US	100 (83.3%)	100 (86.2%)	200 (84.7%)
Europe	20 (16.7%)	16 (13.8%)	36 (15.3%)
ITT Population	120 (100%)	115 (99.1%)	235 (99.6%)
Reasons for exclusion from the ITT population			
At risk for LIE prior to Amendment 4A	0	1 (<1%)	1 (<1%)
PP Population	79 (65.8%)	60 (51.7%)	139 (58.9%)
Reasons for exclusion from the PP population			
Missed major evaluation time-point Early termination	36 (30.0%) 29 (24.2%)	40 (34.5%) 34 (29.3%)	76 (32.2%) 63 (26.7%)
Non-compliant with visits	7 (5.8%)	6 (5.2%)	13 (5.5%)
Major inclusion/exclusion violation	12 (10.0%)	14 (12.1%)	26 (11.0%)
Non-evaluable per the IEAC	9 (7.5%)	14 (12.1%)	23 (9.7%)
< 4 days of therapy	9 (7.5%)	9 (7.8%)	18 (7.6%)
Lack of study medication adherence	0	8 (6.9%)	8 (3.4%)
Pharmacokinetic Population	108 (90.0%)	NA	NA
mSSPK Population	106 (88.3%)	NA	NA

Patient demographics were generally similar between groups.
Proportions with certain risk factors and other baseline characteristics were similar between groups except that higher percentages in the daptomycin group had prior surgery within 30 days of onset of the *S. aureus* bacteraemia, pre-existing heart valve disease and positive HIV status.

Systemic Inflammatory Response Syndrome (SIRS) was present in about 75% and over one-third per group had diabetes with ~80% of these patients requiring insulin. It is notable that extravascular foreign material, primarily orthopaedic prostheses, was present in 23.3% and 25.2% per group while permanent intravascular devices were present in 11.7% and 15.7% per group. Also, about 75% had intravascular catheters present at the time of the first positive blood culture (peripheral venous access catheter in ~78% and central catheters in 19.6% and 18.7%). Infection within 30 days (mostly in the skin structure, catheter placement sites and urinary tract) were reported in 73.3% and 74.8% per group and any surgery within 30 days of onset was reported in 40.8% and 31.3%.

Similar results for IEAC Entry and Final diagnostic subgroups were noted in the PP population.

Based on the primary analysis and the MAH's pre-set criteria for non-inferiority, daptomycin was as effective as conventional therapy in the treatment of patients with *S. aureus* bacteraemia with known or suspected endocarditis. That is, in both populations, the lower bound of the 95% CI around the difference in success rates was within the pre-specified delta of -20% for the overall pooled analysis (with and without the continuity correction) and when the results were adjusted for IEAC Entry and Final diagnostic subgroups. In fact, the lower bound of the CIs did not exceed -16.1%.

IEAC Outcome at TOC –Overall and Weighted by IEAC Diagnoses (ITT and PP Populations)

	ITT Population		**PP Population**	
IEAC Outcome at TOC	**Daptomycin (N=120)**	**Comparator (N=115)**	**Daptomycin (N=79)**	**Comparator (N=60)**
Success	53 (44.2%)	48 (41.7%)	43 (54.4%)	32 (53.3%)
Failure	58 (48.3%)	53 (46.1%)	36 (45.6%)	28 (46.7%)
Non-Evaluable a	9 (7.5%)	14 (12.2%)	----	
Difference in Success Rates (95% CI)				
Overall	2.4% (-10.2, 15.1)		1.1% (-15.6, 17.8)	
Overall with continuity correction	2.4% (-9.4, 15.9)		1.1% (-14.2, 19.3)	
Weighted by IEAC Entry Diagnosis b	2.4% (-10.5, 15.2)		0.9% (-16.1, 17.9)	
Weighted by IEAC Final Diagnosis b	2.1% (-10.5, 14.8)		0.9% (-15.5, 17.3)	

a Patients were classified as non-evaluable at TOC if they were classified as non-evaluable at EOT; they are considered Failures in the analysis based on the ITT population.

b Difference in success rates and the associated 95% CI around the difference (daptomycin minus comparator) with adjustment for treatment for IEAC diagnostic subgroup.

In addition, treatment with daptomycin led to generally similar success rates as treatment with conventional therapy regardless of the IEAC Entry diagnostic subgroup. For all IE (definite + possible) daptomycin gave numerically similar success rates as conventional therapy with lower 95% CI of -9.5 for the ITT and -22.2 for the PP populations. However, numbers in ITT and PP populations with definite IE are quite small and the 95% CI are very wide.

Summary of IEAC Success Rates at TOC by IEAC Entry Diagnostic Subgroup (ITT and PP Populations)

Population IEAC Entry Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Differences in Success Rates (95% CI)
ITT Population			
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (-10.2, 15.1)
IE (Definite + Possible)	41/90 (45.6%)	37/91 (40.7%)	4.9% (-9.5, 19.3)
Definite IE	7/17 (41.2%)	8/20 (40.0%)	1.2% (-30.6, 32.9)
Possible IE	34/73 (46.6%)	29/71 (40.8%)	5.7% (-10.4, 21.9)
Not IE	12/30 (40.0%)	11/24 (45.8%)	-5.8% (-32.4, 20.7)
PP Population			
Overall	43/79 (54.4%)	32/60 (53.3%)	1.1% (-15.6, 17.8)
IE (Definite + Possible)	32/62 (51.6%)	24/44 (54.5%)	-2.9% (-22.2, 16.3)
Definite IE	5/13 (38.5%)	5/11 (45.5%)	-7.0% (-46.6, 32.6)
Possible IE	27/49 (55.1%)	19/33 (57.6%)	-2.5% (-24.3, 19.4)
Not IE	11/17 (64.7%)	8/16 (50.0%)	14.7% (-18.7, 48.1)

For patients in the ITT population with an IEAC Final diagnosis of RIE (complicated or uncomplicated), success rates were 42.1% for daptomycin and 43.8% for conventional therapy. However, with such small numbers the 95% CI are wide (-34.6, 31.3). In the PP population, the corresponding rates were 50% in both groups but the denominators are even smaller.

Summary of IEAC Success Rates at TOC by IEAC Final Diagnostic Subgroup (ITT and PP Populations)

Population IEAC Final Diagnostic Subgroup	Daptomycin n/N (%)	Comparator n/N (%)	Differences in Success Rates (95% CI)
ITT Population			
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (-10.2, 15.1)
cRIE + uRIE + cBAC	34/79 (43.0%)	30/77 (39.0%)	4.1% (-11.3, 19.5)
RIE (cRIE + uRIE)	8/19 (42.1%)	7/16 (43.8%)	-1.6% (-34.6, 31.3)
cRIE	5/13 (38.5%)	6/12 (50.0%)	-11.5% (-50.3, 27.2)
uRIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (-33.3, 83.3)
cBAC	26/60 (43.3%)	23/61 (37.7%)	5.6% (-11.8, 23.1)
uBAC	18/32 (56.3%)	16/29 (55.2%)	1.1% (-23.9, 26.0)
LIE	1/9 (11.1%)	2/9 (22.2%)	-11.1% (-45.2, 22.9)
PP Population			
Overall	43/79 (54.4%)	32/60 (53.3%)	1.1% (-15.6, 17.8)
cRIE + uRIE + cBAC	25/51 (49.0%)	18/37 (48.6%)	0.4% (-20.8, 21.5)
RIE (cRIE + uRIE)	6/12 (50.0%)	4/8 (50.0%)	0.0% (-44.7, 44.7)
cRIE	5/10 (50.0%)	4/6 (66.7%)	-16.7% (-65.5, 32.2)
uRIE	1/2 (50.0%)	0/2 (0.0%)	50.0% (-19.3, 119.3)
cBAC	19/39 (48.7%)	14/29 (48.3%)	0.4% (-23.6, 24.5)
uBAC	17/21 (81.0%)	12/17 (70.6%)	10.4% (-17.0, 37.8)
LIE	1/7 (14.3%)	2/6 (33.3%)	-19.0% (-64.8, 26.7)

The 35 patients with a Final IEAC diagnosis of RIE appeared to have had adequate evidence to support this classification. Among these 35 patients 7 patients (20%) experienced possible pneumonia and 2/4 treated with daptomycin compared to 1/3 treated with other therapy also had septic pulmonary emboli present at baseline. In 5 of these 7 patients, including all 4 in the daptomycin group and 1 in the comparator group, no additional antibacterial therapy was administered for the possible

pneumonia. Two of the 4 daptomycin-treated patients and 1 of the 3 comparator-treated patients were reported as successes for the treatment of SAB/IE at TOC by the IEAC.

For those patients with IEAC Final diagnoses of either complicated or uncomplicated bacteraemia success rates were at least as high for daptomycin as for comparative therapy and the lower 95% CI were all within -25%.

With only 18 patients (9 per treatment group) with an IEAC Final diagnosis of LIE the small number of patients and few positive outcomes means that use cannot be supported.

At CHMP's request a retrospective analysis was conducted in which patients were categorised according to any identifiable baseline foci of infection (i.e. microbiologically confirmed sites of *S. aureus* infection at study entry). This review showed that 150/235 (63.8%) patients [78/120 (65%) daptomycin; 72/115 (62.2%) comparator] had bacteraemia with no documented foci of infection at baseline. However, the IEAC Final diagnoses for the 150 patients identified retrospectively as having no identifiable focus of infection at baseline were:

- Bacteraemia (total complicated or uncomplicated) in 109 patients (58 daptomycin and 51 comparative therapy)
  - Complicated bacteraemia was the IEAC Final diagnosis in 75/109 patients - 39 daptomycin and 36 in the comparative group
  - Uncomplicated bacteraemia was the IEAC Final diagnosis in 34/109 patients - 19 and 15 patients in respective treatment groups
- IT (RIE or LIE) in 41 patients (20 daptomycin and 21 comparative therapy); of these 13 had LIE, 20 had cRIE and 8 had uRIE with similar distributions between treatment groups.

Thus, it can be deduced from these listings that:
- 116/150 patients with no identifiable focus of infection at baseline based on this retrospective review went on to have a focus of infection identified after initiation of therapy (IE or cBAC)
- 34/150 did not have a focus of infection discovered after initiation of therapy and had an IEAC Final diagnosis of uBAC.
- 34/61 ITT patients with a Final diagnosis of uBAC had no identifiable focus of infection at baseline but this means that the other 27 uBAC patients must have had a focus of infection identified at baseline.

The success rates at TOC were similar between treatment groups as shown below. In particular, patients with bacteraemia only at baseline had similar success rates whether treated with daptomycin (34/78; 43.6%) or comparator (31/72; 43.1%) [Δ 0.5%, 95% CI: -15.3%, 16.4%].

IEAC outcome of success at TOC by baseline focus of infection

	Daptomycin n/N (%)	**Comparator n/N (%)**
All patients	53/120 (44.2%)	48/115 (41.7%)
Bacteraemia only	34/78 (43.6%)	31/72 (43.1%)
Catheter	9/16 (56.2%)	5/10 (50.0%)
Skin/wound	5/17 (29.4%)	7/24 (29.2%)
Other	2/4 (50.0%)	3/7 (42.9%)
Multiple	3/5 (60.0%)	2/2 (100%)

Baseline focus of infection groups were used to evaluate outcomes in the 182 patients (77.4% of the total 235 enrolled; 92 in the daptomycin group and 90 in the comparative therapy group) who had an IEAC Final diagnosis of bacteraemia (uBAC [61] **or** cBAC [121]). The distribution by baseline focus of infection varied slightly between the treatment groups, mainly for SSTI/wound foci.

Patients who were in the bacteraemia only category at baseline and had a final IEAC diagnosis of uBAC or cBAC had generally similar success rates whether they were treated with daptomycin (27/58; 46.6%) or with comparative therapy (24/51; 47.1%) [Δ -0.5%, 95% CI: -19.3%, 18.3%].

IEAC outcome of success by baseline focus of infection for patients with final IEAC diagnosis of bacteraemia (complicated or uncomplicated)

Patients with IEAC diagnosis of bacteraemia	44/92 (47.8%)	39/90 (43.3%)
Bacteraemia only	27/58 (46.6%)	24/51 (47.1%)
Catheter	8/15 (53.3%)	5/10 (50.0%)
Skin/wound	5/12 (41.7%)	7/23 (30.4%)
Other	2/3 (66.7%)	1/4 (25.0%)
Multiple	2/4 (50.0%)	2/2 (100%)

The next table shows IEAC outcomes at TOC for ITT patients with bacteraemia only at baseline based on the retrospective review and with an IEAC Final diagnosis of cBAC or uBAC. Denominators are small but the table suggests slightly higher success with daptomycin in the subset finally classified as cBAC and the opposite for those with uBAC.

IEAC Outcome at TOC	Daptomycin (N=120) n (%)	Comparator (N=115) n (%)
cBAC		
N	39	36
Success	19 (48.7%)	15 (41.7%)
Failure	18 (46.2%)	17 (47.2%)
NonEvaluable	2 (5.1%)	4 (11.1%)
uBAC		
N	19	15
Success	8 (42.1%)	9 (60.0%)
Failure	10 (52.6%)	5 (33.3%)
NonEvaluable	1 (5.3%)	1 (6.7%)

For cBAC: Difference = 7.1%; 95% CI -15.4, 29.5
For uBAC: Difference = -17.9% 95% CI -51.2, 15.4)

The antibacterial activity of daptomycin would not be affected by expression of methicillin resistance in staphylococci. However, due to the expected complexity of patients with MRSA rather than MSSA it might be expected that success rates would be lower in the former subgroup. However, the overall success rates with daptomycin in the ITT population were actually identical in patients with MSSA (44.6%) or MRSA (44.4%). In contrast, the success rates in the comparator group were 48.6% for patients with MSSA and 31.8% for patients with MRSA.

Treatment group was not a significant factor for IEAC outcome at TOC in any of the logistic regression analyses. Increased age, persistent fever at 72 hours and decreased creatinine clearance were associated with poorer outcome in the ITT population.

In the overall PP population, baseline creatinine clearance and IEAC Final diagnostic subgroup (uncomplicated bacteraemia) were significant factors.

In a sensitivity analysis, the overall IEAC outcomes at TOC were analysed excluding the 18 patients with LIE the success rates were 46.8% and 43.4% in the daptomycin and comparator groups, respectively, with a lower 95% CI within -20%. Also, after excluding 26 patients (14 daptomycin and 12 comparator group) with TOC evaluations conducted outside of the protocol-defined visit the success rates were 49.2% and 50.0%, respectively, and the lower 95% CI was within -20%.

IEAC outcomes at EOT evaluation show that daptomycin was as effective as conventional therapy in the treatment of patients with *S. aureus* bacteraemia, including those with known or suspected endocarditis.

Pathogen eradication rates at TOC were mainly based on the 1215 isolates that were received by the Central Laboratory yielding a *S. aureus* recovery rate of 83.3%. All Baseline Infecting Pathogens that were methicillin-resistant were *mecA* positive. Pathogen eradication rates at TOC for all *S. aureus* show that daptomycin appeared to be similarly effective at eradicating *S. aureus* from the blood as conventional therapy with eradication rates at TOC of 52.1% in the daptomycin group and 50.0% in the comparator group. For patients with infections caused by MRSA, the eradication rate in the daptomycin group was 51.1% compared to 37.2% for vancomycin.

In the PP population at TOC, *S. aureus* eradication rates overall were 65.8% for daptomycin and 61.7% in the comparator group. For MSSA eradication rates were 68.9% and 69.0% and for MRSA eradication rates were 61.8% and 44.4% in respective groups.

For those patients with an IEAC Entry diagnosis of definite or possible IE, *S. aureus* eradication rates were 53.3% and 47.3% in the daptomycin and comparator groups, respectively, as shown below. Eradication rates for patients who were judged by the IEAC not to have IE at study entry were 48.3% in the daptomycin group and 60.9% in the comparator group, which reflects a lower eradication rate in the daptomycin group for patients with MSSA (45.0%) relative to the comparator group (64.7%).

S. aureus eradication rates at EOT for the ITT population were 77.3% and 74.6% in the daptomycin and comparator groups, respectively, compared to 83.5% and 90.0% for the PP population. All IEAC microbiological failures due to persistent or relapsing *S. aureus* bacteraemia at EOT had documented positive blood cultures. One patient who was an IEAC success at EOT had a persistent *S. aureus* with a positive blood culture on Day 3 post-therapy so was assessed as a microbiological failure at TOC.

A review of *S. aureus* susceptibility data over time showed that 8 patients had *S. aureus* isolates that demonstrated increasing daptomycin MICs on study. Of these, 7 had received daptomycin and one had received vancomycin. As shown in the table below IEAC Final diagnoses among the 7 treated with daptomycin were complicated bacteraemia in four, LIE in two and complicated RIE in one. Five of these seven had MRSA and the other two had MSSA. Cmax daptomycin was below the median for the population as a whole in 3/7 and above the median in the remaining four and similar results were noted for AUC.

Six of the 7 daptomycin-treated patients infected with organisms that showed increasing MICs were considered failures at TOC due to persisting or relapsing bacteraemia.

The next table shows the PK data from these patients, which are considered to be within the range seen for other patients who were clinical successes.

	Age	Sex	Organism	Diagnosis	Cmin	Cmax	AUC
Daptomycin							
009-212	54	Male	MRSA	cBAC	3.2	188	442
010-152	34	Female	MSSA	cRIE	7.72	69.7	537
015-105	60	Male	MRSA	cBAC	9.28	76.7	651
017-037	67	Female	MRSA	LIE	6.77	41.3	413
027-183	82	Male	MRSA	LIE	36.8	171	1420
088-172	36	Female	MSSA	cBAC	5.36	1070	1100
324-136	40	Male	MRSA	cBAC	21.0	59.7	713
Comparator							
004-193	30	Female	MRSA	cRIE	NA	NA	NA

The seven isolates with elevated daptomycin MICs and their respective daptomycin-susceptible parent isolate were also tested in the neutropenic mouse thigh model. Drug exposures required to attain a 3 $\log_{10}$ reduction in bacterial CFU in the non-susceptible isolates were generally higher than for the

parental isolates. However, in all cases the AUC achieved in each patient exceeded the exposure predicted to provide adequate treatment from the neutropenic mouse test.

When the AUC/MIC ratio for each individual isolate in the mouse thigh model was compared with those calculated from patient AUC data the AUC/MIC ratio in the seven patients was, in all cases, higher than that in the mouse model indicating that drug exposure should have been adequate for treating baseline and non-susceptible isolates.

Therefore, the microbiological investigations did not reveal an explanation for PRSA in these patients. The one unifying feature of these patients was the lack of adjunctive care for deep-seated infections.

Reasons for Treatment Failure

The IEAC reported that 134 ITT patients were failures or non-evaluable (67/120 [55.8%] daptomycin and 67/115 [58.3%] in the comparator group). The IEAC reasons for each failure or non-evaluable case showed no differences between treatment groups for proportions that received non-study antibacterial agents that may have influenced outcome (16.7% and 13.9%) or in the number of deaths (10.8% and 11.3%). Patients in the daptomycin group were more likely to be reported by the IEAC as failures at TOC due to persisting or relapsing bacteraemia (15.0% compared to 8.7%) while failures in the comparator group were more likely to reflect premature discontinuation due to AEs (6.7% and 14.8%).

18 (15.0%) daptomycin and 10 (8.7%) comparator group patients were assessed as microbiological failures by the IEAC due to persisting or relapsing bacteraemia and one additional patient in each treatment group was considered to have failed due to a positive culture for *S. aureus* from a non-blood source (e.g. abscess). Thus, 30 patients (19 +11 per group) were reviewed as microbiological failures. The 19 daptomycin patients include the six with pathogens that showed reduced susceptibility to daptomycin during treatment.

There were 21 (17.5%) and 14 (12.2%) patients in respective groups who were considered to be clinical failures by the IEAC and 17 and 10 of these were also determined to be microbiological failures.

In fact, there were no major differences in characteristics that might explain the overall difference in failure rates between treatments. While a higher proportion in the daptomycin group had complicated bacteraemia, the previous analyses did not show a disadvantage for daptomycin in this diagnostic subgroup.

Outcomes by other patient characteristics

While daptomycin appeared to be more successful in males than females at the same time there was no notable disadvantage for daptomycin in treating females as far as the denominators allow for interpretation. Regarding age, the numbers in the ≥ 75 years group are too small for any reliable interpretation of the apparent difference between treatments. Regarding renal function, again numbers with lower creatinine clearance values are small but there does seem to be trend for daptomycin to be less effective as CrCl declines. As previously mentioned the summary of the logistic regression analysis shows that all final models include age or creatinine clearance but not both, giving the impression that the age effect is probably mediated through renal clearance. However, in this study dose adjustment would not have been instituted except for persons with CrCl < 30 ml/min as per the US package insert and so a potential under-dosing due to unnecessary dose adjustment is not the explanation. The MAH was requested to further explore this observation. Therefore, the MAH has present data on the association between age and creatinine clearance in this study by cross tabulations and/or scatter plots. In the logistic regression analysis treatment group was not a significant factor for IEAC outcome at TOC. Increased age, persistent fever at 72 hours and decreased creatinine clearance were associated with poorer outcomes in the ITT population. The answer to this request indicates that the negative effects of age and CrCl on outcomes cannot be distinguished.

Pharmacokinetic data and PK/PD evaluations

A review of DAP-IE-01-02 indicated that the previous PK/PD model that was derived for the purposes of the initial application for licensure of daptomycin was applicable to this population. Exposure to daptomycin in patients with IE or bacteraemia as assessed by AUC was lower than in healthy subjects at the same dose at steady-state. In patients with infections, the Vss (l/kg) was markedly increased and the total CL (ml/hr/kg) higher but Cmax, T1/2 and trough (C24,ss) values were generally similar to those in healthy subjects given the same dose.

In the population analysis conducted to determine PK parameters at steady-state in 108 patients with SABIE and treated with 6 mg/kg q24h the results were stratified by varying degrees of renal function.

Mean (SD) daptomycin (6 mg/kg) population pharmacokinetic parameters at steady state in *S. aureus* bacteraemia and endocarditis patients with varying degrees of renal function

Renal Function	$AUC_{0-\infty}$ (µg*h/ml)	$t_{1/2}$ (h)	V_{ss} (l/kg)	CL_T (ml/h/kg)	C_{max} (µg/ml)	C_{min} (µg/ml)
CL_{CR} >80 ml/min (N=62)	545 (296)	9.0 (2.86)	0.15 (0.07)	13.2 (5.0)	108 (143)	6.90 (3.54)
CL_{CR} 50-80 ml/min (N=29)	637 (215)	12.0 (2.26)	0.17 (0.04)	10.5 (3.5)	80.1 (41.1)	12.4 (5.57)
CL_{CR} 30-<50 ml/min (N=15)	868 (349)	16.1 (3.62)	0.17 (0.05)	8.2 (3.6)	114 (124)	19.0 (9.03)
CL_{CR} <30 ml/min (N=2)	1050, 892	25.8, 16.0	0.2, 0.015	5.7, 6.7	96.8, 82.6	25.4, 21.4

- On comparing with the population PK analysis in the initial dossier (i.e. based on 4 mg/kg in cSSTI patients) plasma clearance (CL_T), elimination half-life ($t_{1/2}$), and volume of distribution (V_{ss}) were similar in patients with cSSTI compared to those with SABIE.
- Plasma clearance (CL_T) decreased with decreasing renal function.
- Exposure to daptomycin (AUCss) was nearly two-fold and T1/2 nearly three-fold higher in patients with severe renal impairment (CrCL < 30 ml/min) compared to patients with normal renal function (CrCL > 80 ml/min).
- Mean Cmin increased about 2-fold in mild and 3-fold in moderate impairment compared to normal renal function. Means but not SDs were below the 25 ug/ml threshold identified for risk of muscle toxicity.
- Cmax was not affected by changes in renal function or CL_T.
- Mean AUC increased 1.2-fold and 1.6-fold in SABIE patients with mild and moderate renal impairment, respectively, compared to those with CL_{CR} >80 ml/min. Total exposure (AUC) in the moderately impaired SAB/IE patients after 6 mg/kg doses (868) was similar to that seen with an 8 mg/kg dose in adult healthy volunteers (858) in study DAP-ADT-04-02. This is in keeping with AUC values after 4 mg/kg doses in patients with cSSTI that were on average 13 to 24% lower compared to matched healthy subjects.

The comparisons of population PK between 4 mg/kg and 6 mg/kg doses showed AUCs in such patients of 560 (SD 258) with 4 mg/kg and 868 (SD 349) with 6 mg/kg. Taking into account the SD, at least some patients with CrCl 30-50 ml/min could achieve Cmin values at or above the 25 µg/ml threshold that has been estimated to be associated with elevations of CK. However the MAH has provided further analyses and proposed no dose adjustment to 6 mg/kg daily doses until CrCl was < 30 ml/min.

The next table shows a summary of the PK data available from the SABIE study according to renal function.

Summary of PK Parameters for DAP-IE-01-02 Patients by Baseline CrCl Category

Renal Function (Number of patients with PK data in each category of CrCl)	Cmax,ss* µg/ml	Cmin, ss µg/ml	AUCss µg*hr/ml
CrCl > 80 ml/min (N=62)	108 (143)	6.90 (3.54)	545 (296)
CrCl 50 - 80 ml/min (N=29)	80.1 (41.1)	12.4 (5.57)	637 (215)
CrCl 30 -< 50 ml/min (N=15)	114 (124)	19.0 (9.03)	868 (349)
CrCl < 30 ml/min (N=2)	96.8, 82.6	25.4, 21.4	1050, 892

*All results presented as Mean (SD) except in CrCl < 30 ml/min presented as actual values

The MAH has presented the actual values for the 15 patients with CrCl in the range 30-50 ml/min. These data demonstrate a notable variability in values and show that the two successes had plasma daptomycin levels that overlapped with the failures.

Additionally, simulations based on the final population PK model were carried out to determine the typical daptomycin exposure values in non-dialysis patients with varying degree of renal function, as shown in the next table.

Predicted daptomycin mean PK at steady state in patients (70 kg) by renal function

Renal Function	Dosing Regimen	$C_{max,ss}$ µg/ml	$C_{min, ss}$ µg/ml	AUC_{ss} µg*hr/ml
CrCl=50	6 mg/kg QD	84.1	14.3	734
CrCl=30	6 mg/kg QD	93.3	22.9	968
CrCl=30	6 mg/kg Q48	76.9	6.23	968
CrCl=20	6 mg/kg Q48	81	10	1208

The simulations based on a population PK model that was developed as an extension of the one initially derived for cSSTI so that it included data from the DAP-IE-01-02 study and two additional daptomycin studies (DAP-SST-98-01B, DAP-REN-02-03). Thus the final population PK database included data from ten Phase 1 and eight Phase 2/3 clinical trials.

Thus among patients with CrCl 30 - < 50 ml/min, the mean C_{min} observed at steady state (6 mg/kg once daily) was 19 µg/ml while the predicted values fall between 14.3 and 22.9 µg/ml. Daptomycin exposure in patients with CrCl 30-50 ml/min dosed at 6 mg/kg once daily was within the range of that seen in subjects with normal renal function when given daptomycin in doses of 8-12 mg/kg daily over 2 weeks. The comparison between studies was proposed to support no alteration in the daptomycin dose or dose regimen in patients whose calculated creatinine clearance is ≥ 30 ml/min.

For the two patients with CrCl < 30 ml/min who were dosed at 6 mg/kg once daily, the actual C_{min} values at steady state were 25.4 and 21.4 µg/ml while the predicted C_{min} at steady state for the dose of 6 mg/kg administered once every other day ranged between 6.23 and 10 µg/ml. Therefore, the MAH claimed that the proposed regimen of 6 mg/kg once every 48 hours for patients with CrCl < 30 ml/min ensures adequate patient safety.

When PK parameters were evaluated by IEAC Final diagnosis results were generally similar for patients with final diagnoses of complicated and uncomplicated bacteraemia and with LIE. Cmax and AUC were lower in patients with RIE although numbers in these subgroups were small and the variability was large. Nevertheless, patients with RIE were younger (38.9 years *vs* 54.6 years in the other patients) and had higher CrCl (12/17 *vs* 50/91 >80 ml/min), which would result in a higher predicted CL. Also, patients with RIE were more likely to have intravenous drug users (IVDU) as a risk factor (88.2%) compared to the patients with LIE and bacteraemia (8.8%), and this alone may account for an increase in clearance in this subgroup.

A trend towards increasing CPK with increasing exposure to daptomycin as measured by AUC(ss) and Cmin(ss) was noted. However, this trend was observed for CPK levels within the normal range and the number of observations of CPK above the upper limit was limited.

2.2.1.4 Discussion

Dose regimen
It appears that 4 mg/kg is potentially an insufficient dose for treating RIE and that doses higher than 6 mg/kg would not be likely to be more efficacious. In general, the safety profile of daptomycin at 6 mg/kg in SABIE patients was similar to that for comparative treatments except for the anticipated excess of AEs associated with increased CK with daptomycin. Therefore, 6 mg/kg once daily can be viewed as a conservative regimen for patients with RIE and CrCl >50 ml/min.

Regarding the proposal that 6 mg/kg should be used to treat cSSTI when accompanied by bacteraemia rather than the 4 mg/kg dose currently approved for cSSTI the need for the higher dose cannot be established unequivocally. However, use of the higher dose would provide a conservative approach and there is no major reason to reject this proposal provided that the SPC is worded carefully to avoid over-use of the higher dose in cSSTI patients.

Concerning treatment of **RIE** and cSSTI when accompanied by bacteraemia the MAH proposed that for a 6 mg/kg once daily regimen no dose adjustment is recommended for patients with creatinine clearance ≥ 30 ml/min. This issue was extensively discussed by the CHMP in particular concern was raised regarding:

- Whether or not a dose reduction was needed in patients with CrCl in the range 30 - <50 ml/min. The comparisons of population PK between 4 mg/kg and 6 mg/kg doses showed AUCs in such patients of 560 (SD 258) with 4 mg/kg and 868 (SD 349) with 6 mg/kg. Based on the standard deviation, at least some patients with CrCl 30-50 ml/min dosed at 6 mg/kg once daily could achieve Cmin values at or above the 25 µg/ml threshold that has been estimated to be associated with elevations of CK. Therefore, it was considered that 6 mg/kg once daily should be recommended only for patients with CrCl of at least 50 ml/min.
  Although a reduction to 4 mg/kg daily was suggested when CrCl is in the range 30 - <50 ml/min there was concern that this dose could be inadequate for treating *S. aureus* bacteraemia.
- The lack of safety and efficacy data with respect to 6 mg/kg every 48 h in those with CrCl <30 ml/min. This was especially of concern given the observations made in the initial application dossier that unduly cautious dose reduction in the cSSTI studies was associated with poor efficacy.
- The observation that daptomycin group patients with decreased renal function (especially when CrCl was 30 to <50 ml/min) were more likely to experience SAEs. No such difference was noted in the comparator group. Patients with decreased renal function had higher exposures to daptomycin. Despite this fact there was also an excess of failure associated with PRSA in these patients.

Therefore, 6 mg/kg once daily can be viewed as a conservative regimen for patients with RIE or cSSTI associated with S*taphylococcus aureus* bacteraemia and CrCL> 50 ml/min.
Furthermore, a statement informing that there are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteraemia whose creatinine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min should be introduced in the SPC.

Therapeutic indications

Following the adoption of Major Objections by the CHMP in October 2006, the following question was posed to the Scientific Advisory Group (SAG), which was considered on 7 December 2006**:**

"In the light of the data provided in study DAP-IE-01-02 does the SAG consider that if the MAH can satisfactorily address the CHMP list of questions, then the following indications might be considered?

- Right sided endocarditis (RIE) due to *Staphylococcus aureus*
- *Staphylococcus aureus* bacteraemia with no identifiable focus of infection"

The SAG made the following recommendations to the CHMP

- If reassurance for RIE is provided (in particular, reassurance that patient groups are comparable) and that the small dominator is emphasised in the SPC, this indication may be supportable.
- The indication complicated bacteraemia is not supported
- The feasibility of the diagnosis uncomplicated bacteraemia has to be re-considered. Concern was expressed that this diagnosis does not exist, because condition might be due to undiagnosed cryptogenic infection.

The CHMP considerations for each indication are discussed below.

Right-sided infective endocarditis

The CHMP was concerned that a final IEAC diagnosis of RIE pertained to only 35 patients. While efficacy appeared to be very similar between daptomycin and comparative therapy the 95% CI are inevitably wide although evenly distributed around zero. However it was also recognised that accumulating such patients is not easy, as demonstrated by the total finally identified from the number enrolled into this study in which all patients had staphylococcal bacteraemia at enrolment. Overall, the CHMP considered that an indication for use in RIE due to *S. aureus* is approvable as long as the SPC carefully reflects the limitations of the data and that the RMP was amended appropriately to cover the new dose and indication (see section 3.5).

Bacteraemia without infective endocarditis

With regard to the majority of the patients in this study, with a final IEAC diagnoses other than IE (including 121 with complicated bacteraemia and 61 with uncomplicated bacteraemia) it appears that the population was very heterogeneous with regard to exactly what was being treated in addition to the bacteraemia.

The definition of uncomplicated *S. aureus* bacteraemia included the requirement that there should be no metastatic foci of infection or infection of prosthetic material (not including intravascular foreign material removed by Day 4). The definition of complicated bacteraemia included those with *metastatic foci and infection involving prosthetic material, including intravascular foreign material not removed by Day 4*.

In order for the CHMP to consider any possible indication for the treatment of *S. aureus* bacteraemia not associated with IE the MAH was requested to provide an analysis based on the sites of *S. aureus* infection that were known or very likely to be present at study entry. Thus, the MAH was asked to estimate how many patients had bacteraemia in association with specific infections and how many had a truly cryptogenic bacteraemia.

The retrospective review found that 150/235 (63.8%) of the total patients enrolled had bacteraemia with no documented foci of infection at baseline. These patients with bacteraemia only at baseline had similar success rates whether treated with daptomycin (34/78; 43.6%) or comparator (31/72; 43.1%) [Δ 0.5%, 95% CI: -15.3%-16.4%]. However, only 34/150 had an IEAC Final diagnosis of uBAC, which means that the majority (116/150) of these patients had a diagnosis of IE and/or metastatic foci of infection identified only after initiation of therapy. Correspondingly 27/61 ITT patients with a Final diagnosis of uBAC had no identifiable focus of infection at baseline but must have had a focus of infection identified at baseline. Overall the study was not designed to assess the efficacy of daptomycin in patients with and without identifiable foci of S. aureus infection either at baseline or

discovered later. The CHMP considered that an unqualified indication for use in S. aureus bacteraemia was completely untenable since this would imply that daptomycin could be used to treat any focus of *S. aureus* infection that was identified before or after discovery of the bacteraemia when in fact the drug has only been shown to be efficacious in cSSTI and RIE. The retrospective review also made it untenable to consider an indication for use in patients with no identifiable focus of infection since it was clear from the study that the population with no focus found throughout the study period was small and that many of the 150 with no focus known at baseline were later found to have (primary and/or secondary) foci during treatment. Based on these considerations the CHMP considered that the evidence for the use of daptomycin in the treatment of *S. aureus* bacteraemia (other than when associated with cSSTI or RIE) remained difficult to interpret and was inadequate to support the indication proposed.

The MAH acknowledged the CHMP opinion that the study DAP-IE-01-02 results do not fully support an indication of daptomycin in the treatment of *S. aureus* bacteraemia other than when associated with cSSTI or RIE. The MAH consequently withdrew this indication for the requested extension of indication.

The MAH's decision not to pursue an indication for *S. aureus* bacteraemia other than when associated with the approved indications resolves the Major Objection that was raised during the procedure.

Granting a specific indication for use in *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI is a departure from the usual CHMP stance regarding endorsement for use in concurrent bacteraemia and does set a precedent. However, this is the first application in which very substantial data on the use of an antibacterial agent to treat infections with concurrent bacteraemia have been provided and therefore in this instance a specific endorsement for such use is considered to be appropriate.

Other issues

The rate of IEAC failure due to persistent or relapsing infection SAB (PRSA) at TOC was numerically higher in the daptomycin group but there remained no clear explanation for this observation in terms of any particular factors that might have given rise to different response rates. Regarding patients with reduced creatinine clearance, the MAH has demonstrated that there is no interaction on a multiplicative scale, i.e. that the relative risk of failure due to PRSA is not different between daptomycin and comparator treated patients. However, the risk of failure is higher in the daptomycin group and therefore an identical relative risk leads to a higher absolute increase in risk, which is potentially problematic. The fact that there was a significant effect of age for PRSA in the daptomycin group supported this concern.

The SPC already contained information on the six daptomycin-treated patients with isolates that showed increasing MICs who were considered failures at TOC due to PRSA and so contribute to the overall picture. The CHMP recommended that an expanded section on Information from clinical studies should be inserted into section 5.1 of the SPC along with details of these PRSA failure rates since these data are relevant to cSSTI.

2.3 Clinical safety

Data relevant for the assessment of the clinical safety stem for the main study DAP-IE-01-02 are detailed below. The results of the supportive study DAP-ADT-04-02 did not bring any relevant results to this discussion and are therefore not described.

2.3.1 Main study – DAP-IE-01-02

2.3.1.1 Patient exposure

Among the 120 daptomycin patients the mean daily dose administered was 5.9 ± 0.30 mg/kg with a median of 6.0 mg/kg. Only one patient in the daptomycin group had a dose adjustment for renal failure. The mean total daily daptomycin dose administered was 487 ± 116.2 mg/day with a median of 478 mg/day.

Total Adverse Events
There were no notable differences between the treatment groups with regard to the incidence of TEAEs by MedDRA SOC except that more patients in the comparator group had AEs mapped to General Disorders and Administration Site Conditions. This reflected the higher rates of oedema, pain and discomfort, febrile disorders, asthenic conditions and injection and infusion site reactions. The most commonly reported events in the daptomycin group were anaemia and gastro-intestinal AEs but these were not more common than in the comparator group. The incidence of pharyngolaryngeal pain was higher in the daptomycin group (8.3%) than in the comparator group (1.7%).

AEs judged by the Investigators to be severe or marked in intensity were reported in 45.8% daptomycin and 45.7% comparator group patients. The most common severe event was sepsis, reported in 5.0% and 2.6% in respective groups.

Failure Due to AEs
A higher proportion of patients in the comparator group (14.8%) were assessed by the IEAC as treatment failures due to AEs compared to the daptomycin group (6.7%), as shown in the next table.

In the comparator group, the most common AEs reported as the reason for treatment failure were hypersensitivity type events, including rash, red man syndrome and anaphylaxis (6 patients), and renal toxicities (5 patients). In the daptomycin group, the most commonly reported events were rash (2 patients), increased CPK (2 patients) and gastrointestinal events (2 patients).

Five of the 17 patients in the comparator group who were failures due to AEs died compared to one patient in the daptomycin group. In 3/5 deaths in the comparator group the IEAC Final diagnosis was complicated bacteraemia. SAEs seen in these five were cardiovascular collapse, sepsis, gastrointestinal haemorrhage with renal and respiratory failure and cerebral infarction plus septic shock. The other two patients had an IEAC Final diagnosis of LIE with SAEs of hemorrhagic stroke associated with heparin therapy and cerebral infarction plus septic shock. The daptomycin patient who died had an IEAC Final diagnosis of complicated bacteraemia with an SAE of worsening hypoxia.

Drug-related AEs
These were reported in 35.0% daptomycin and 42.2% comparator group patients. The most commonly reported drug-related AE was diarrhoea but the incidence was 1.7% and 9.5% in respective groups. Other drug-related events reported in ≥ 5% of patients in either treatment group included CPK increased (5.0% and 0% per group), renal failure (1.7% and 6.0%) and nausea (1.7% and 5.2%).

Rates for severe drug-related AEs were 6/120 (5.0%) for daptomycin and 13/116 (11.2%) for comparator group patients.

In the daptomycin group these included two patients with renal failure and two with rash. There were also single cases of blood phosphorus increased and vomiting, atrial flutter and atrial fibrillation, cardiac arrest and hallucinations.
In the comparator group, these included 5 reports of renal disorders (renal failure acute, renal tubular necrosis) and 4 reports of drug-allergy type events (hypersensitivity reaction, dermatitis medicamentosa, red man syndrome, anaphylactic reaction). Others included pyrexia, nausea with diarrhoea, pulmonary infarction and abnormal liver function tests.

AEs of special note

The overall incidence of infections was slightly higher in the daptomycin group (54.2% and 48.3%) while the incidence of severe infections was 21.7% and 19.8% in respective groups. In addition, 6.7% daptomycin and 1.7% comparator group patients had an infection that was assessed as drug-related by the Investigators.

Among 13 daptomycin patients with sepsis, bacteraemia or septic shock the infection occurred during treatment or 1 day post-treatment in 8 patients and occurred more than one week post-treatment in the remaining 5. None of events of sepsis or bacteraemia were assessed as drug-related by the Investigator in either treatment group.

There was no excess of respiratory tract TEAEs, renal tract TEAEs or incidence of *C. difficile* enterocolitis in the daptomycin group. Despite the known association between daptomycin and raised CPK, with or without symptoms, musculoskeletal or connective tissue TEAEs were reported in 29.2% in the daptomycin group and in 36.2% in the comparator group. One event in the daptomycin group (myalgia) and 4 events in 2 patients in the comparator group (2 of arthralgia and one each of neck pain and pain in extremity) were assessed as drug-related by the Investigators. Severe musculoskeletal and connective tissue disorders were reported in 2.5% and 1.7% of patients in the daptomycin and comparator groups, respectively. Nevertheless, as expected, the incidence of raised CPK was 6.7% in the daptomycin group (8 patients) and <1% (one patient) in the comparator group (discussed below).

In both treatment groups, the overall incidence of AEs was higher in females but incidences within gender were similar between treatments. The incidence of cardiac disorders, gastrointestinal disorders, infections and infestations, skin and respiratory disorders was higher in females compared to males in both the daptomycin and comparator groups but did not appear to be substantially different between treatments.

In both treatment groups the overall incidence of AEs was higher in patients aged ≥65 years but rates within the age groups were similar between treatments. The incidence of cardiac disorders, gastrointestinal disorders, infections and infestations and respiratory disorders was higher in patients aged ≥65 years. The incidence of blood and lymphatic system, eye and skin disorders was higher in older patients in the daptomycin group. The incidence of general disorders and musculoskeletal system disorders was higher in younger patients than older patients within the daptomycin group but rates were not higher than seen with comparators.

Deaths

Thirty-seven (15.7%) of the 236 patients died during the study or in post-study follow-up. These included 18/120 (15.0%) in the daptomycin group and 19/116 (16.4%) comparator-treated patients. Death occurred within 30 days of the last dose in 14 (11.7%) and 12 (10.3%) per group and varied by IEAC final diagnosis.

Among 18 deaths in the daptomycin group 15 (83.3%) patients were aged ≥65 year including 10 aged ≥75 years. One death, which was a cardiac arrest reported in an 87-year-old female while being treated with daptomycin, was judged to be possibly related to treatment by the Investigator. However, review of the narrative does not suggest that daptomycin likely contributed to death.

Serious Adverse Events

Overall 114/236 patients experienced at least one SAE including 62/120 (51.7%) daptomycin and 52/116 (44.8%) in the comparator group. There were no statistically significant differences between the treatment groups for SAEs within any MedDRA SOC except that serious renal and urinary disorders were reported at a higher incidence in the comparator group and the incidence of serious infections was higher in the daptomycin group.

Serious events in both treatment groups were most commonly reported in the infections and infestations SOC and the most commonly reported were in the HLT of sepsis, bacteraemia and viraemia (8.3% daptomycin group and 6.0% in the comparator group).

The majority of SAEs were assessed as unrelated to study treatment but 3 in the daptomycin group (2.5%) and 6 in the comparator group (5.2%) experienced SAEs that were reported by the Investigators as drug-related. Possibly related SAEs in the daptomycin group included an elevation in CPK that resolved within 6 days, atrial flutter/fibrillation and renal failure in a patient who entered the study with renal insufficiency and the cardiac arrest leading to death as detailed above. In the comparator group, drug-related SAEs included renal failure or renal tubular necrosis in four patients and one patient each with antibiotic-associated diarrhoea and anaphylaxis.

In the daptomycin group, patients with decreased renal function (especially when CLcr was 30 to < 50 ml/min) were more likely to experience SAEs. No such difference was noted in the comparator group.

Patients with AEs and SAEs of Infections Potentially Related to SAB/IE

Events mapped to the Infections and Infestations SOC that were potentially related to *S. aureus* bacteraemia or IE were identified by the medical monitor based on 34 preferred terms. For any AE and any SAE, the incidence of these events was higher in the daptomycin group.

In order to assess the possible relationship of these reported events to the failure of study treatment, an analysis was conducted to evaluate the IEAC outcome at TOC and EOT for this patient subset.

The failure rate in this patient subset was higher than that observed in the total population in both treatment groups. The failure rate at TOC for patients with SAEs potentially related to SAB/IE was higher in the comparator group but the rate at EOT was higher in the daptomycin group.

Also, 11 (9.2%) daptomycin and 13 (11.2%) comparator patients experienced at least one event potentially related to *S. aureus* pneumonia. In 14/24 the IEAC Final diagnosis was IE, including 7 with RIE and 7 with LIE, while 8 had a final diagnosis of complicated bacteraemia and two had uncomplicated bacteraemia. In four and seven per group no additional antibiotic therapy was associated with the event. None of these AEs was assessed as drug-related by the Investigators and all were reported as resolved. One patient in the daptomycin group was discontinued from the study due to pneumonia. Eighteen of the 24 patients, including 9 in each treatment group, were reported as failures at TOC by the IEAC

Discontinuations Due to Adverse Events

Overall 41/236 patients discontinued study treatment due to AEs including 20 (16.7%) daptomycin and 21 (18.1%) in the comparator group. In 10 and 13 in respective groups the AEs that led to treatment discontinuation were considered drug-related. In the daptomycin group these included three reports of increased CPK, three of rash and one report each of vomiting, renal failure, thrombocytopenia and cardiac arrest. In the comparator group, drug-related AEs leading to treatment withdrawal included rashes and hypersensitivity reactions in 7 patients, four with renal toxicity and two with pyrexia.

Laboratory data

There were no clinically meaningful or statistically significant differences between the treatment groups for changes from baseline in haematology parameters except that mean haemoglobin increased from baseline to EOT by 1.4 g/l in the daptomycin group and decreased from baseline to EOT by -1.7 g/l in the comparator group. This difference was statistically significant but was not thought to be clinically meaningful. Mean values at EOT for haemoglobin were 109.3 g/l and 105.6 g/l in the daptomycin and comparator groups, respectively. Changes in coagulation parameters were also similar overall between treatments.

Mean changes from baseline to EOT in ALT and AST (see below) were statistically significant between groups but again not thought likely to be clinically meaningful.

There were no statistically significant differences between the treatment groups for changes from baseline in CPK to any on-study time point with the exception of Day 14 when mean changes were -11.2 u/l for daptomycin and -53.1 u/l for comparator patients. At the EOT visit, mean changes from baseline showed an increase (by 37.1 u/l) in the daptomycin group and a decrease (-32.2 u/l) in the

comparator group. In contrast, corresponding median changes were -5.5 and -11.5 u/l in the daptomycin and comparator groups, respectively, which was mainly due to three outliers with mean increases of >2,000 u/l from baseline to EOT.

With regard to measures of renal function, mean changes from baseline in serum creatinine were statistically significantly higher in the comparator group at most time points. This may reflect synergistic gentamicin given with vancomycin and SSPs. At EOT, mean changes from baseline were 6.6 µmol/l for daptomycin and 21.2 µmol/l in the comparator group while actual mean creatinine values were 102.9 and
121.9 µmol/l.

The most common of these in the daptomycin group was an INR >2.0. The elevations in INR were sporadic in most patients but were not unexpected given that heparin products were administered concomitantly in 81.7% (98) of daptomycin and 77.6% (90) of comparator group patients and warfarin was administered to 15.8% (19) and 10.3% (12) in respective groups. However, platelet counts were <50 x 109/l in 5.0% and 1.7% per group. Despite this, serious gastrointestinal haemorrhage was reported in four in the comparator group but none in the daptomycin group. CVA was reported as a SAE in two per group and worsening bleeding disorder in one in the comparator group. Only one of these patients (daptomycin) with serious bleeding events had a clinically notable INR value and platelet count reported during the study.

The most commonly reported laboratory AE was anaemia (in 12.5% and 15.5% per group). Other laboratory AEs reported in >5% of patients in either treatment group included hypokalaemia (9.2% and 12.9%), hyperkalaemia (5.0% and 8.6%) and increased blood CPK (6.7% and <1%).

Mean changes in vital signs during the study were generally small and there were no statistically significant differences between the treatment groups for changes from baseline to any time point for any vital signs parameter. There were no notable differences between treatment groups in the maximum weekly temperatures during weeks 1 through 6. In both groups, the maximum weekly temperature was higher at Baseline than during any study week.

There were 10 patients (4 daptomycin) with normal or not clinically significantly abnormal baseline ECG results who had a shift to an abnormal, clinically significant finding during or post-treatment. All ECG abnormalities reported as AEs occurred in only one or 2 patients in either treatment group and there were no apparent differences between the treatment groups for the types of abnormalities reported.

All patients received at least one concomitant medication during the study and the types of commonly administered medications were similar between treatments. The most commonly reported classes were anilides (82.5% and 80.2%), heparin group (81.7% and 77.6%) and natural opium alkaloids (72.5% and 77.6%). Proportions who may have been receiving agents that could potentially interact with daptomycin to increase the risk of increased CPK, with or without symptoms, are not discussed in the study report. However, it should be noted that 20% in the daptomycin group and 17.2% in the comparator group were on HMG CoA reductase inhibitors.

2.3.2 Supportive study – DAP-ADT-04-02

There were no deaths, SAEs or discontinuations due to AEs in this study. There are no new relevant findings on safety concerning this study.

2.3.3 Discussion

In general, and referring to the results on safety of the main study, the safety profile of daptomycin at 6 mg/kg was similar to that for comparative treatments except for the anticipated excess of increased CPK with daptomycin.

In the daptomycin group, patients with decreased renal function (especially when CLcr was 30 to < 50 ml/min) were more likely to experience SAEs. No such difference was noted in the comparator group.

The excess of SAEs in the infections and infestations SOC is in keeping with, and is probably driving, the overall finding in this study that the incidence of serious infections was higher in the daptomycin group. In fact, the pattern reflects in turn the higher incidence of PRSA in the daptomycin group.
It was previously recognised that failure rates were higher in patients with impaired renal function. However, since this study required daptomycin dose adjustment only when CrCl fell below 30 ml/min and since so few patients were in this category, inadvertent under-exposure to the drug was not the explanation in the daptomycin group.

It remains unclear why there was a higher rate of SAEs (including SAEs relating to failures) in patients with CrCl below 50 ml/min in the daptomycin group (see discussion on dose regimen in section 3.2.2.1.4).

All patients received at least one concomitant medication during the study. In fact 20% in the daptomycin group and 17.2% in the comparator group were on HMG CoA reductase inhibitors. The overall picture pointed towards an increasing risk of raised CK when daptomycin was given with an HMG Co-A reductase inhibitor. However, the SPC already states the following in 4.4:
CPK should be measured more frequently than once weekly in patients who are at higher risk of developing myopathy. These patients include those with severe renal insufficiency (creatinine clearance < 30 ml/min) and patients taking other medications known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
Until such time as it may come to light that clinically important increases in CK are more likely to occur during co-administration there does not seem to be a need to amend the current warning. This issue has been included in the Risk Management Plan and will continue to receive special attention in the PSURs.

3 Pharmacovigilance system

3.1 Risk Management Plan

The CHMP considered that the MAH should update the RMP to reflect use of the higher dose (6 mg/kg once daily) for RIE and the safety data associated with this.

The MAH has supplied a revised RMP in which reference is made in several sections to the use of a 6 mg/kg/day dose.

A summary of the risk management plan for daptomycin highlighting the safety concerns with daptomycin is presented below:

Summary of the risk management plan for Cubicin

Safety concerns	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks		
Musculoskeletal	- analysis of on-going study to further characterize the effects of daptomycin on skeletal muscle and possible mechanism - Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Detailed review in PSURs	- Warning in the section 4.4 of the SPC - Listed as ADR in section 4.8 of the SPC
Renal insufficiency	- Renal study on PK, safety and efficacy of daptomycin in patients with Cr Cl<50ml/min. - Study in elderly with complicated skin and soft tissue infections and/or SAB when associated with RIE or CSSTI in EU -Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Detailed review in PSURs	- Specific dosing recommendation in section 4.2 of the SPC - Warning in section 4.4 of the SPC - Listed as ADR in section 4.8 of the SPC
Elderly patients	-Study in elderly with complicated skin and soft tissue infections and/or SAB when associated with RIE or CSSTI in EU - Safety evaluation of ongoing clinical trials as well as spontaneous post marketing report	- Specific dosing recommendation in section 4.2 of the SPC - Management recommendation in section 5.2 of the SPC
Microbiological resistance	-Surveillance studies (US and EU) -Mechanism of resistance studies	- Knowledge to date provided in section 5.1 of the SPC - Surveillance communication: prescribers/physicians to be informed if significant new findings emerge - Information package on susceptibility testing for microbiologists to be distributed
Potential safety concerns		
Peripheral neuropathy and related terms	-Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Close monitoring and detailed review in PSURs	- Warning in the section 4.4 of the SPC - Paraesthesiae listed as ADR in section 4.8 of the SPC
Hepatitis (including hypersensitivity hepatitis), liver failure, jaundice and bilirubin increase	-Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Close monitoring and detailed review in PSURs	- Specific dosing recommendation in section 4.2 of the SPC - Listed as ADR in section 4.8 of the SPC - Management recommendation in section 5.2 of the SPC
Bone marrow toxicity	-Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Close monitoring and detailed review in PSURs	- Thrombocythaemia, anaemia, eosinophilia listed as ADRs in section 4.8 of the SPC
Dysregulation of in	-Safety evaluation of ongoing clinical trials	- Issue of coagulation measurement

vivo coagulation	as well as spontaneous post marketing reports - Close monitoring and detailed review in PSURs	described in section 4.5 of the SPC
Hypersensitivity reactions including pulmonary eosinophilia	-Safety evaluation of ongoing clinical trials as well as spontaneous post marketing reports - Close monitoring and detailed review in PSURs	- Hypersensitivity including pulmonary eosinophilia described in section 4.8 of the SPC

The RMP needs to be further revised taking into consideration the following points:
-The RMP should be updated according to the EU-RMP template
-The Safety Specification refers to > 319,000 US patients exposed as of March 2007. This denominator should be updated when the revisions to the RMP are finalised.
-The sections on renal insufficiency should reflect the final EU SPC to result from this variation.
-The additions regarding 6 mg/kg/day should reflect the uncertainties that still surround the safety profile of this dose.

The MAH as committed to provide a revised RMP by the next PSUR submission on 11 November 2007.

4 Overall discussion and Benefit/Risk Assessment

In line with the CHMP *Note for Guidance*, there is sufficient evidence to allow an indication specific to the treatment of RIE due to *Staphylococcus aureus*. The revised SPC resulting from this variation clearly states the limited data on which this indication is based. Previously, some concerns were raised that due to the poor efficacy of daptomycin in CAP, which is associated with chemical interaction between the drug and surfactant, RIE patients might be at higher risk of infectious pulmonary complications. The numbers are too small to draw definite conclusions on this point but the data are not alarming and the SPC already mentions lack of efficacy in pneumonia.

The application did not contain sufficient evidence to support an indication for use in *S. aureus* bacteraemia with no identifiable focus. However, the data would support a specific endorsement for use in *S. aureus* bacteraemia strictly when associated with the indications to be approved (i.e. cSSTI and RIE only). This is, in itself, a departure from the more usual approach to mentioning use in concurrent bacteraemia in the SPC and should be viewed as an exception that has been considered only because the SABIE study has supplied data specific to patients with *S. aureus* bacteraemia, resulting in numbers of patients treated that goes far beyond that usually encountered in applications concerning antibacterial agents.

The selection of 6 mg/kg to treat *S. aureus* bacteraemia and endocarditis in patients with CrCl ≥ 50 ml/min is accepted to be an appropriately conservative regimen that may also be applied to patients with cSSTI who have concomitant bacteraemia.

There has been a detailed exploration of the fact that the rate of IEAC failure due to persistent or relapsing infection SAB (PRSA) at TOC was numerically higher in the daptomycin group. The CHMP considered that *Information from clinical studies* on section 5.1 of the SPC should be expanded to include details of the PRSA failure rates.

5 Changes to the product information

SPC
Section 4.1 "Therapeutic indication"
The MAH's initially proposed to extend the approved indication to *Staphylococcus aureus* bacteraemia (SAB), including known or suspected Infective Endocarditis (IE) in adults.
Based on the submitted data the CHMP considered that there is sufficient evidence to allow an indication specific to the treatment of RIE due to *Staphylococcus aureus.* However the CHMP considered that the study DAP-IE-01-02 results do not fully support an indication of daptomycin in the treatment of *S. aureus* bacteraemia other than when associated with cSSTI or RIE. The MAH acknowledges the CHMP position and submitted a revised wording which was agreed with, as follows:

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

- *Complicated skin and soft-tissue infections (cSSTI)*
- ***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.***
- ***Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI.***

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

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

Section 4.2 "Posology and method of administration"
The MAH proposed to revise section 4.2 to reflect the two possible dosing regimens by indication. This section was further updated to reflect the indications agreed above.

Furthermore, this section was revised to introduce detailed recommendations concerning dose adjustments in patients with renal insufficiency by indication and creatinine clearance.
It was highlighted that there are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteraemia whose creatinine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min.

Section 4.4 "Special warnings and precautions for use"
The MAH's initially proposed changes to section 4.4 were discussed and the CHMP proposed new revisions.
A paragraph was added to advise prescribers to consider instituting alternative antibacterial therapy for adjunctive treatment.
A paragraph was added to reflect the limited clinical data to treat RIE due to *Staphylococcus aureus* and a warning was introduced concerning the lack of data for prosthetic valve infections.
The MAH proposed a revised wording that was agreed with by the CHMP.

Section 4.8 "Undesirable effects"
The MAH initially proposed to slightly update this section to reflect additional data in the denominators and rates. The CHMP considered that the introductory paragraph should be revised to state how many patients have been treated with 4 or 6 mg/kg with the indication mentioned and to make clear that the totals mentioned included both health volunteers and patients with infections.
The MAH proposed a revised wording that was agreed with by the CHMP.

Section 5.1 “Pharmacodynamic properties”
The MAH’s initially proposed wording introduced the results of the main study. The CHMP proposed the revision of this section to reflect the results obtained for the patients treated with daptomicyn who met the criteria for RIE.

Section 5.2 “Pharmacokinetic properties”
The MAH has proposed a minor change to this section based on the PK results and to reflect the two doses. The initial wording was slightly revised.

Section 5.3 “Preclinical safety data”
The MAH proposed to revise preclinical safety data concerning myotoxicity and neurotoxicity to support the higher dose. The MAH has introduced the changes proposed by the CHMP.

Annex IIB
Annex II was updated to mention that an updated RMP should be provided as per CHMP guideline on the risk management systems for medicinal products for human use.

PL
The PL was updated in accordance with the changes proposed to the SPC.