This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. SYNOPSIS

SPONSOR COMPANY NAME: Cubist Pharmaceuticals, Inc. **NAME OF FINISHED PRODUCT:** Cubicin® (daptomycin for injection) **NAME OF ACTIVE INGREDIENT:** Daptomycin	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:** **PAGE:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

TITLE OF STUDY:

A Phase 2 Randomized Study Investigating the Safety, Efficacy and Pharmacokinetics of Daptomycin 6 mg/kg and 8 mg/kg versus Comparator in the Treatment of Subjects Undergoing Surgical Standard of Care for Osteomyelitis Associated with an Infected Prosthetic Hip or Knee Joint caused by Staphylococci

INVESTIGATOR(S)/STUDY CENTERS(S):

A total of 22 sites: 14 in the United States [US], 3 in the United Kingdom, and 5 in Russia.

PUBLICATION (REFERENCE):

None at the time of this report.

STUDIED PERIOD:

Study Initiation Date (first subject enrolled): June 26, 2007
Primary Study Completion Date: March 26, 2010
Study Completion Date (last subject completed): June 23, 2010

PHASE OF DEVELOPMENT:

Phase 2

STUDY OBJECTIVES:

The primary objective of this study was to evaluate the safety parameter of creatine phosphokinase (CPK) levels in subjects with prosthetic joint infection (PJI) treated with daptomycin at 6 mg/kg or 8 mg/kg every 24 hours (q24h) versus comparator (vancomycin, teicoplanin, or a semi-synthetic penicillin [SSP]).

Secondary objectives were:

- To evaluate the safety parameters, including vital signs, laboratory analytes and adverse events (AEs) in subjects treated with daptomycin at 6 mg/kg or 8 mg/kg versus those treated with comparator;
- To evaluate the clinical efficacy of daptomycin at 6 mg/kg and 8 mg/kg versus comparator at the Test of Cure (TOC) visit;
- To evaluate the microbiological response rate of daptomycin at 6 mg/kg and 8 mg/kg versus comparator at the TOC visit.
- To assess the pharmacokinetics (PK) of daptomycin at 6 mg/kg versus 8 mg/kg.

METHODOLOGY:

This was a Phase 2, multicenter, randomized (1:1:1), open-label study comparing the safety, efficacy, and PK of intravenous (IV) daptomycin 6 mg/kg and 8 mg/kg administered q24h for 6 weeks (±1 week) with standard antibiotic therapy (IV vancomycin, teicoplanin, or a SSP) administered for 6 weeks (±1 week) in subjects undergoing a two-stage replacement surgery following a diagnosis of PJI.

Subjects were screened within 24 days of first dose of study drug. Screening assessments included medical, medication, and antibiotic history; assessment of the signs and symptoms of PJI; radiography and microbiological culture of the infected joint; physical examination; vital signs; and clinical laboratory tests (hematology, chemistry, urinalysis, pregnancy test [as applicable], and serum CPK). Baseline evaluations, including medication and antibiotic history, signs and symptoms assessment, physical examination, vital signs, clinical laboratory tests and blood culture, were performed within 10 days prior to the first dose of study drug.

Following Surgery #1, empiric antibiotic therapy per standard of care (SOC) was administered for up to 72 hours while awaiting culture results. Eligible subjects who met the inclusion and exclusion criteria were randomized within 72 hours after the end of Surgery #1 unless an exemption was granted by the Medical

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Monitor. Randomization was stratified by anatomical location of surgery (hip versus knee) and by baseline creatinine clearance (CL_{CR}) (<50 mL/min or ≥50 mL/min).

All subjects received 6 weeks (± 1 week) of IV study medication. During the treatment period, subjects were clinically assessed and laboratory parameters were evaluated. Following antibiotic therapy, subjects underwent an End of Therapy (EOT) evaluation followed by an antibiotic-free period of 2 to 6 weeks duration. As per SOC, Surgery #2 for implantation of a new prosthetic device occurred following the antibiotic-free period. The TOC visit was conducted at the time of hospital discharge after Surgery #2 or within 1 to 2 weeks after Surgery #2 if the subject remained hospitalized.

Subjects who were considered a success at TOC were clinically assessed at a follow-up visit 3 to 4 months after Surgery #2.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

72 planned: 24 subjects in each of the 3 treatment groups

74 subjects were treated, including 25, 24 and 25 subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. All subjects received treatment as randomized.
68 subjects had a baseline infecting pathogen, including 24, 23 and 21 subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively; 6 subjects were randomized and treated but did not have two confirmatory cultures positive for a staphylococcal infecting pathogen at baseline.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Hospitalized male or female subjects 18 to 80 years of age inclusive, with a diagnosis of PJI in a hip or knee joint which had never previously been totally revised because of an infection and for which the subject was anticipated to undergo a two-stage replacement surgery, with one of the following microbiological identifiers of PJI: (1) 2 confirmatory deep intra-operative cultures obtained at Surgery #1 from 4 or more independent surgical sites for staphylococci (e.g., *Staphylococcus aureus* or coagulase-negative staphylococcus [CoNS]); (2) 1 culture positive for staphylococci (e.g., *S. aureus* or CoNS) from affected joint synovial fluid aspirate obtained within 6 weeks prior to Surgery #1 with a confirmatory positive culture from 1 or more deep intra-operative surgical sites within 72 hours of Surgery #1; (3) in the event intra-operative cultures were negative or remained pending after 72 hours, a subject could be considered for study participation if 2 Gram-stains showed Gram-positive pathogens or histopathological evidence of staphylococci was obtained within 72 hours following Surgery #1; or (4) 2 positive blood cultures for staphylococci (e.g., *S. aureus* or CoNS) were obtained from 2 independent peripheral sites within 48 hours prior to Surgery #1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER(S):

Daptomycin for injection, 6 mg/kg or 8 mg/kg, administered by IV infusion over 30 minutes q24h for 6 weeks (±1 week).

Lot number of daptomycin: [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER(S):

Investigators were to select one of the following comparator agents based on local availability and normal treatment practice; comparator agents were to be obtained from commercial sources:

- Vancomycin, 1 gm, administered by IV infusion twice a day (BID) or as per SOC for 6 weeks (±1 week).
- Teicoplanin, 6 mg/kg, administered by IV infusion q24h or as per SOC for 6 weeks (±1 week).
- Semi-synthetic penicillins (nafcillin, oxacillin or flucloxacillin), 1 to 2 gm, administered by IV infusion q4h or as per SOC for 6 weeks (±1 week).

DURATION OF TREATMENT:

6 weeks (±1 week)

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CRITERIA FOR EVALUATION:

EFFICACY:

Efficacy analyses were conducted on the Intent-to-treat (ITT), modified ITT (mITT), and Per protocol (PP) populations.

- ITT population: comprised all subjects who were randomized and received 1 or more doses of study medication. Subjects were analyzed according to the treatment group to which they were randomized.
- mITT population: comprised of subjects in the ITT population who had at least one staphylococcal Baseline Infecting Pathogen (methicillin-resistant *S. aureus* [MRSA], methicillin-susceptible *S. aureus* [MSSA], methicillin-resistant CoNS [MRCoNS], and/or methicillin-susceptible CoNS [MSCoNS]).
- PP population: the subset of evaluable ITT subjects who received the drug to which they were randomized, who had no major deviations from inclusion and exclusion criteria, who received a minimum of 5 days of study treatment (or were withdrawn for AE of clinical/microbiological failure), and who were not deemed non-evaluable at TOC.

Clinical assessment of the signs and symptoms of infection was conducted at screening, baseline, EOT, pre-operatively on the day of Surgery #2, and at the follow-up visit for subjects with a successful outcome at TOC. In addition, radiography of the infected prosthetic joint was conducted as part of screening, EOT, during the antibiotic-free period, pre- and post-operatively on the day of Surgery #2, at TOC, and at the follow-up visit for subjects with a successful outcome at TOC. Based on serial assessment of both the clinical signs and symptoms of infection and radiographic results, the Investigator determined clinical response at TOC as cured, improved, non-evaluable, or failure. Subjects who were considered cured or improved at TOC were evaluated for possible relapse at a follow-up visit 3 to 4 months after Surgery #2.

All microbiological cultures taken and any organisms recovered within 6 weeks of Surgery #1 were recorded. During Surgery #1, intra-operative cultures were obtained at the time the pseudocapsule was opened. During the treatment and antibiotic-free periods through Surgery #2, all unscheduled microbiological cultures taken and any organisms recovered were reported. During Surgery #2, the same microbiological evaluations were conducted as performed for Surgery #1. Any microbiological cultures obtained through the TOC visit also were recorded. Microbiological response was assessed on both a pathogen and subject level by the Sponsor based on a blinded review of all available culture results. Pathogen-level responses included eradicated, documented persistent, non-evaluable, and not applicable (pathogen other than staphylococci). Subject-level responses included success, failure, non-evaluable, and not applicable.

An overall outcome was determined by the Sponsor based on a blinded review of clinical, microbiological, and radiological outcomes. The Sponsor-defined overall outcome at TOC was classified as Success, Failure, or Non-evaluable. Subjects were considered a success if both clinical and microbiological responses were success. A subject who failed to respond clinically or microbiologically was categorized as a failure. If microbiological response was non-evaluable and/or clinical evaluation at TOC was not performed, the subject was deemed non-evaluable.

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SAFETY:

Analyses of CPK were conducted on the CPK Safety population, which included subjects who received a minimum of 3 days of dosing with study drug, had a baseline CPK value, and a minimum of 1 further CPK assessment between Day 3 and Day 7 post-dose (Day 7P). CPK was evaluated at screening; baseline; pre-dose on Day 1; Days 3, 5, 7, 10 and 14; and weekly thereafter until EOT; at EOT, 4-days post-EOT; 7-days post-EOT; and at the TOC visit. If a subject experienced a CPK level of >1000 U/L, isoenzymes, serum and urinary myoglobin were to be obtained at the time of the CPK increase; CPK was then checked daily until the CPK results were within the local laboratory normal range.

Other safety parameters, including AEs, serious adverse events (SAEs), laboratory examinations, vital signs, concomitant medications, and physical findings, were assessed throughout the study. These safety analyses were conducted on the Safety population which included all subjects who received study treatment; analyses were based on actual treatment received.

PHARMACOKINETICS:

Pharmacokinetic analyses were conducted on the PK Population defined as subjects randomized and dosed with daptomycin for a minimum of 4 days. Blood samples were collected on Day 1, pre-dose and on Day 4 prior to start of daptomycin infusion (0 hour) and at 0.5 hour (end of infusion), 1-1.5, 3-5, 8-12 and 24 hours after the start of daptomycin infusion.

STATISTICAL METHODS:

Inferential statistical analyses were not conducted; the study was not powered to detect statistically significant differences between the treatment groups for either safety or efficacy parameters.

The primary endpoint was the occurrence of elevated CPK (defined as any CPK value >500 U/L in the CPK Safety population at any time from Day 3 through Day 7P). These data were summarized for the 3 treatment groups overall and by baseline CL_{CR} strata (CL_{CR} <50 or ≥50 mL/min). In addition to the observed number and percentage of subjects with any CPK >500 U/L for each treatment group, a 90% confidence interval (CI) around the observed rate for each of the 3 treatment groups and a 90% CI around pairwise differences among the treatment groups were calculated. Other threshold levels of CPK elevations (>250, >1000, >2000, >5000 and <10,000 U/L) were evaluated in the same manner. In order to assess the duration of the CPK elevations, an additional summary was conducted in which a sustained abnormality was defined as CPK >500 U/L for 2 consecutive evaluations based on results obtained from both the central and local laboratories.

The key efficacy endpoint in this study was the Sponsor-defined overall outcome at the TOC visit. The Sponsor-defined overall outcome success rate was calculated as the proportion of subjects in a population who had an outcome of success compared with the total population analyzed. The 90% CIs around the success rates for each treatment group were calculated using Fisher's exact test. A comparison of the success rates was conducted by calculating a 90% CI around the difference in rates among the 3 treatment groups (each daptomycin group minus comparator and 8 mg/kg daptomycin minus 6 mg/kg daptomycin) using Fisher's exact test.

Clinical success rates based on Investigator evaluation of subjects' response to treatment were calculated as the proportion of subjects in a population with an outcome of success relative to the total population analyzed, where success was defined as cured or improved. Confidence intervals on the point estimates and on the differences in success rates were determined as described for Sponsor-defined overall outcome.

Pathogen-level microbiological success rates were calculated for each pathogen subgroup as the proportion of subjects in a population with that pathogen and susceptibility who had an outcome of success (i.e., eradicated) relative to the mITT population. Subject-level microbiological success rates were calculated as the proportion of subjects with an outcome of microbiological success compared with the mITT population. Confidence intervals on the point estimates and on the differences in pathogen-level and subject-level microbiological

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success rates were determined as described for Sponsor-defined overall outcome.

Treatment-emergent adverse events (TEAE) were coded and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1 system organ class and preferred term overall and by CL_{CR} strata, severity of the event (mild, moderate, and severe) and relationship to study drug (related, not related). Serious adverse events also were tabulated. Adverse events leading to treatment discontinuation or withdrawal from the study were listed.

Descriptive statistics for baseline, post baseline, and change from baseline values were tabulated for alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and CPK for study visits for which these data were collected. Renal toxicity was assessed by the number and percentage of subjects who had at least 1 creatinine value greater than the upper limit of normal between Day 2 and pre-operatively for Surgery #2, inclusive. The number and percentage of subjects with notable laboratory abnormalities (i.e., those parameters that reached the panic level as defined by the central laboratory) were summarized by treatment group.

The primary PK endpoint was the assessment of the steady state (Day 4) PK of daptomycin at 6 mg/kg and 8 mg/kg.

SUMMARY AND CONCLUSIONS:

SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

In general, the demographic and baseline characteristics of the 74 subjects in the Safety/ITT population were comparable across the 3 treatment groups. Mean ages were 63.5, 60.4 and 61.2 years in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. Across the treatment groups, 56.0%, 41.7% and 44.0% of subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg, and comparator groups, respectively, were female. The majority of subjects (73 of the 74) were White. Mean CL_{CR} was 96.2, 104.4 and 113.0 mL/min in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. Only 5 subjects had baseline CL_{CR} <50 mL/min, including 2, 2 and 1 subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. Most subjects in all treatment groups had PJI of the knee (60.0%, 54.2% and 60.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively).

Mean and median time from diagnosis to Surgery #1 was considerably longer in the daptomycin 6 mg/kg group (124.0 and 71.0 days, respectively) compared to the daptomycin 8 mg/kg (41.5 and 12.0 days, respectively) and the comparator group (50.1 and 15.0 days, respectively). Median duration from Surgery #1 to first dose was shortest in the daptomycin 6 mg/kg group (68.9 hours); with median durations of 70.5 and 71.5 hours in the daptomycin 8 mg/kg and comparator groups, respectively.

Among the 68 subjects included in the mITT population, PJI was caused by *S. aureus* (including MRSA and MSSA) in 58.3%, 60.9%, and 47.6% of subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg, and comparator groups, respectively, and by CoNS (including MRCoNs and MSCoNS) in 33.3%, 39.1% and 33.3% of subjects, respectively. A higher proportion of subjects in the daptomycin 8 mg/kg group had infections caused by MRSA (30.4%) compared to the 6 mg/kg (12.5%) and comparator (14.3%) groups. MRCoNS infections were equally distributed across the treatment groups (25.0%, 21.7% and 28.6% of subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively).

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SUMMARY OF EFFICACY:

The Sponsor-defined overall success rates for the mITT population at TOC were higher in the daptomycin groups relative to the comparator group with success rates of 54.2% and 56.5% in the daptomycin 6 mg/kg and 8 mg/kg groups, respectively, compared to 38.1% in the comparator group. Daptomycin was similarly effective in both PJI located in the hip and the knee. For PJI of the hip, the Sponsor-defined overall success rates were 50.0%, 60.0% and 40.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively and for PJI of the knee, success rates were 57.1%, 53.8% and 36.4%, respectively. For infections caused by *S. aureus*, including both MRSA and MSSA, overall Sponsor-defined outcome success rates were 57.1%, 57.1% and 40.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively, and for infections caused by CoNS, including MRCoNS and MSCoNS, success rates were 50.0%, 55.6% and 42.9%, respectively. Overall outcome success rates were also evaluated based on methicillin-susceptibility of the baseline infecting pathogen and comparator agent administered. For MRSA, overall outcome success rates were 33.3%, 42.9%, and 22.2% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and vancomycin/teicoplanin groups, respectively and for MSSA, were 63.6%, 71.4%, 100% (1 of 1 subject) and 33.3% for subjects who received daptomycin 6 mg/kg, daptomycin 8 mg/kg, SSP, and vancomycin/teicoplanin, respectively. Note that all subjects with CoNS randomized to the comparator arm received vancomycin/teicoplanin, regardless of susceptibility.

Clinical success rates for the mITT population based on Investigator evaluations at TOC were 58.3% and 60.9% in the daptomycin 6 mg/kg and 8 mg/kg groups, respectively, compared to 38.1% in the comparator group. For infections caused by *S. aureus*, the clinical success rates were 57.1% in both daptomycin groups and 40.0% in the comparator group. For infections caused by CoNS, the clinical success rates were 50.0% and 66.7% in the daptomycin 6 mg/kg and daptomycin 8 mg/kg groups, respectively, and 42.9% in the comparator group.

Microbiological eradication rates for *S. aureus*, at the TOC visit were 68.8%, 50.0% and 46.7% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively, and for infections caused by CoNS, the eradication rates were 58.3%, 63.6% and 86.7%, respectively. For MRSA, eradication rates were 60.0%, 42.9% and 40.0% for subjects who received daptomycin 6 mg/kg, daptomycin 8 mg/kg, and vancomycin/teicoplanin, respectively. Eradication rates for infections caused by MSSA were 72.7% in the daptomycin 6 mg/kg group, 55.6% in the daptomycin 8 mg/kg group, 100% (1 of 1 pathogen) for subjects who received SSP, and 44.4% for subjects who received vancomycin/teicoplanin.

Superinfections, defined as a Gram-positive pathogen other than the baseline infecting pathogen, that was isolated while on therapy through to and including the TOC visit, occurred in 3 (12.5%) of 24 subjects in the daptomycin 6 mg/kg group and 6 (28.6%) of 21 subjects in the comparator group.

Microbiological success on the subject-level was observed in 50.0%, 52.2% and 38.1% of subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. For subjects with infections caused by *S. aureus*, the microbiological success rates were 50.0%, 50.0% and 40.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively, with similar rates noted for subjects with infections caused by CoNS (50.0%, 55.6% and 42.9%, respectively). By methicillin-susceptibility, microbiological success rates in subjects with MRSA infections were 33.3% in the daptomycin 6 mg/kg group, 42.9% in the daptomycin 8 mg/kg group, and 33.3% for subjects who received vancomycin/teicoplanin. For subjects with MSSA infections, microbiological success rates were 54.5% in the daptomycin 6 mg/kg group, 57.1% in the daptomycin 8 mg/kg group, 100% (1 of 1 subject) for subjects who received SSP, and 33.3% for subjects who received vancomycin/teicoplanin.

SUMMARY OF SAFETY:

A higher proportion of subjects in both the daptomycin 6 mg/kg group (16.0%) and 8 mg/kg group (21.7%) had CPK >500 U/L between Days 3 and 7P relative to the comparator group (8.0%) based on review of central

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laboratory data. Three subjects had CPK elevations >1000 U/L between Days 3 and 7P, including 1 subject (4.0%) in the daptomycin 6 mg/kg group and 2 subjects (8.7%) in the daptomycin 8 mg/kg group. Two of these 3 subjects, including 1 each in the 6 mg/kg and 8 mg/kg groups, had rhabdomyolysis reported by the Investigators as serious events; maximum CPK elevations in these subjects were 11,429 U/L and 3,471 U/L, respectively. The subject in the 6 mg/kg group also reported muscle pain in both forearms; the subject in the 8 mg/kg group was asymptomatic. Both subjects were discontinued from treatment for the events and recovered within 7 days of onset with no residual effects.

Sustained elevations of CPK >500 U/L (those occurring on 2 or more consecutive measurements based on either central or local laboratory data) occurred in 5 subjects, including 2 in the daptomycin 6 mg/kg group and 3 in the daptomycin 8 mg/kg group. With the exception of the one subject with rhabdomyolysis who reported concurrent muscle pain in both forearms, none of the other subjects with sustained elevations in CPK had concurrent musculoskeletal symptoms.

The majority of subjects in all treatment groups experienced at least 1 TEAE. The overall incidence of any TEAE was 92.0%, 79.2%, and 88.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg group and comparator groups, respectively. TEAEs reported in 10% or more of subjects in any treatment group are provided in the following table. In general, there were no clinically meaningful differences across the treatment groups in the incidence of any of these commonly reported events.

Treatment-Emergent Adverse Events Reported in 10% of More of Subjects in Any Treatment Group (Safety Population)

MedDRA Preferred Term	Daptomycin 6 mg/kg (N=25)	Daptomycin 8 mg/kg (N=24)	Comparator (N=25)
Nausea	5 (20.0)	3 (12.5)	4 (16.0)
Pyrexia	4 (16.0)	2 (8.3)	4 (16.0)
Urinary Tract Infection	4 (16.0)	1 (4.2)	4 (16.0)
Oedema Peripheral	2 (8.0)	2 (8.3)	4 (16.0)
Constipation	4 (16.0)	2 (8.3)	1 (4.0)
Deep vein Thrombosis	4 (16.0)	1 (4.2)	1 (4.0)
Blood CPK Increased	3 (12.0)	2 (8.3)	1 (4.0)
Pruritus	1 (4.0)	3 (12.5)	2 (8.0)
Rash	1 (4.0)	3 (12.5)	2 (8.0)
Hypotension	1 (4.0)	2 (8.3)	3 (12.0)
Headache	3 (12.0)	0	2 (8.0)
Dyspnoea	1 (4.0)	0	3 (12.0)

The majority of TEAEs were assessed as unrelated to study treatment; drug-related AEs were reported in 24.0%, 29.2% and 36.0% of subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively.

Most TEAEs were assessed as mild to moderate in severity. Events of severe intensity were reported with similar incidence across the treatment groups (20.0%, 16.7% and 24.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively). The most common investigator-reported event of severe intensity was blood CPK increased, reported in 2 subjects overall, including 1 subject each in the daptomycin 6 mg/kg and comparator groups. All other severe events were reported in 1 subject each.

There were no deaths during the study. Serious adverse events were reported in 32.0%, 16.7% and 32.0% of

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subjects in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. All SAEs were reported in 1 or 2 subjects within a treatment group with no differences noted in the incidence of any SAE across the groups. The most commonly reported SAEs were urinary tract infection (UTI) (4.0%, 0% and 8.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively) and deep vein thrombosis (4.0%, 4.2% and 4.0%, respectively). Treatment-related SAEs were reported in 5 subjects and included rhabdomyolysis in 2 subjects and rash, hypersensitivity and device-related in infection in 1 subject each.

Adverse events leading to discontinuation of study drug were reported in 8.0%, 16.7% and 16.0% in the daptomycin 6 mg/kg, daptomycin 8 mg/kg and comparator groups, respectively. The most common events leading to discontinuation of study drug were blood CPK increased, reported in 2 subjects in the daptomycin 8 mg/kg group and rhabdomyolysis, reported in 2 subjects, including 1 subject each in the daptomycin 6 mg/kg and 8 mg/kg groups. One case of rhabdomyolysis reported by the Investigator was severe in intensity and accompanied by muscle pain; the other report was mild in intensity with no accompanying symptoms. All other events leading to withdrawal from treatment were reported in 1 subject each.

There were no clinically meaningful differences observed across the treatment groups for mean changes from baseline to EOT for ALT or AST. Mean change from baseline to EOT for creatinine was higher in the comparator group (24.3 µmol/L) relative to the daptomycin 6 mg/kg and 8 mg/kg groups (-2.3 and -4.3 µmol/L, respectively). Consistent with this finding, more subjects in the comparator group with baseline creatinine values within the normal range had shifts to values outside the normal range (32.0%) compared to the daptomycin 6 mg/kg and 8 mg/kg groups (8.0% and 0%, respectively).

SUMMARY OF PHARMACOKINETICS:

Plasma concentrations of daptomycin increased rapidly following the start of infusion and achieved median maximum plasma concentration (C_{max}) values of 59.1 and 92.3 µg/mL following the administration of the 6 mg/kg and 8 mg/kg doses, respectively. The corresponding median area under the concentration-time curve at steady state (AUC_{ss}) values also increased with dose (498 and 821 µg•hr/mL, respectively, for the 6 and 8 mg/kg doses). The steady state volume of distribution and clearance appeared to be dose-independent indicating a linear PK profile.

CONCLUSIONS:

Treatment with daptomycin at doses of 6 mg/kg or 8 mg/kg was safe when administered over 6 weeks to subjects with PJI and there were no apparent differences observed in the safety profile of the 2 daptomycin doses.

Daptomycin at doses of 6 mg/kg and 8 mg/kg was effective in the treatment of subjects with microbiologically-confirmed PJI of the hip and knee caused by susceptible strains of staphylococci, including methicillin-resistant and methicillin-susceptible strains. There was a trend for improved efficacy results with daptomycin compared with those observed with standard of care.

DATE OF THE REPORT: 6 January 2011