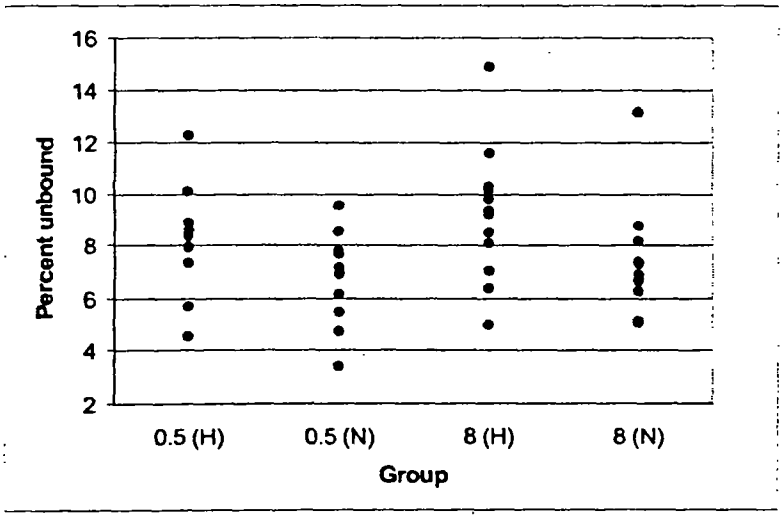
Table 4. Geometric mean ratios (hepatic impairment/normal hepatic function) and 90% confidence intervals for subjects with hepatic impairment and normal hepatic function

	Total		Unbound	
Parameter	Point estimate	90% CI	Point estimate	90% CI
$AUC_{0\text{-}24}$	0.926	(0.830 to 1.035)	1.112	(0.918 to 1.347)
$AUC_{0-\infty}$	0.922	(0.803 to 1.058)	1.106	(0.917 to 1.336)
C_{max}	0.959	(0.856 to 1.074)	1.150	(0.927 to 1.428)
CL_T	1.071	(0.925 to 1.239)	0.876	(0.723 to 1.063)
CL_R	1.261	(0.970 to 1.639)	1.061	(0.791 to 1.422)
Ae_{24}	1.198	(0.930 to 1.543)	---	---

The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$, C_{max}, and CL_T were within 0.80 to 1.25 range based on total daptomycin concentrations but outside of the 0.80 to 1.25 range based on unbound daptomycin concentrations. The differences in the pharmacokinetic parameter estimates based on unbound concentrations were not statistically significantly different between subjects with impaired hepatic function and normal hepatic function. Thus, the magnitude of the difference of the $AUC_{0-\infty}$ and C_{max} between subjects with hepatic impairment and healthy subjects does not warrant a dosage adjustment.

The mean percentage of unbound daptomycin at 0.5 hrs and 8 hrs in subjects with hepatic impairment were 8.13% and 9.20%, respectively. The mean percentage of unbound daptomycin at 0.5 hrs and 8 hrs in healthy subjects were 6.72% and 7.38%, respectively. At 0.5 hrs and 8 hrs, the percent unbound was 21.1% and 16.1% greater, respectively in subjects with hepatic impairment. A comparison of the percentage unbound of daptomycin is shown in figure 2.

Figure 2. Mean individual percent unbound of daptomycin at 0.5 hrs and 8 hrs in subjects with hepatic impairment (H) and normal hepatic function (N)



CONCLUSIONS:

The $AUC_{0-\infty}$ and C_{max} were not statistically significantly different between subjects with impaired hepatic function and normal hepatic function based on total and unbound daptomycin concentrations.

The fraction of unbound daptomycin increased 21.1% at the end of the infusion and 16.1% at 8 hrs after the start of the infusion in subjects with hepatic impairment compared to healthy subjects.

No dosage adjustment of daptomycin is recommended for subjects with hepatic impairment.

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin — ' assay for daptomycin in urine and the — assay for daptomycin in serum (— — and the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the validation report.

A single dose study to evaluate the pharmacokinetics and safety of Cidecin® (daptomycin for injection) in healthy geriatric and younger healthy subjects following a dose of 4 mg/kg total body weight (Protocol DAP-GER-01-11)

Dates: January 7, 2002 to March 6, 2002
Clinical sites:

Analytical site:

RATIONALE:
The pharmacokinetic differences between the young and elderly are generally attributed to physiological and pathophysiological changes that occur more often in the elderly, which can include altered renal function. This study was undertaken to assess the single-dose pharmacokinetics and safety of daptomycin in healthy geriatric subjects compared with younger healthy subjects to determine if pharmacokinetic or safety differences exist between the two populations.

OBJECTIVES:
The primary objective of this study was to evaluate the pharmacokinetics (single dose) of daptomycin in healthy geriatric subjects ≥75 years of age and younger healthy subjects 18 to 30 years of age. The secondary objective was to evaluate the safety of daptomycin in healthy geriatric subjects and younger healthy subjects.

FORMULATIONS:
Daptomycin 500 mg vial (Cubist, Lot No. 680413A)

STUDY DESIGN:
This study was an open-label, single-dose, parallel design, two-center study to evaluate the pharmacokinetics of daptomycin in 12 healthy adult subjects ≥75 years old and 11 healthy young subjects between 18 and 30 years old. Planned enrollment called for 12 geriatric subjects and 12 younger subjects and an attempt was made to enroll an equal number of men and women in each group. All subjects received a single dose of intravenous (IV) daptomycin at 4 mg/kg based on total body weight in 50 mL of normal saline.

Blood samples for determination of daptomycin concentrations were obtained predose, mid-way through the infusion (0.25 hrs), end of the infusion (0.5 hrs), 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hrs from the initiation of the infusion.

Urine samples for determination of daptomycin concentrations were obtained at predose and then at 0-2 hrs, 2-4 hrs, 4-8 hrs, 8-12, 12-16 hrs, and 16 to 24 hrs from the initiation of infusion. Urine was collected for 24 hrs to allow a 24-hr urine creatinine clearance calculation.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Urine	Comments
Concentration range	3.28 to 545 µg/mL	3.36 to 562 µg/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Not stated	Not stated	Unsatisfactory

DATA ANALYSIS:

Plasma daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were determined for plasma daptomycin concentration data: the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), plasma concentration at 24 hrs post-dose (C_{24}), the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), plasma clearance (CL_T), volume of distribution (Vz = CL/Ke), volume of distribution at steady state (V_{SS} = CL × MRT), mean residence time (MRT), and terminal elimination half-life ($t_{1/2}$).

The following parameters were calculated based on daptomycin urine concentration data: the renal clearance (CL_R) and the fraction of dose excreted in urine as parent drug over 24 hrs (Ae).

STATISTICAL ANALYSIS:

Pharmacokinetic parameters were summarized as mean, SD, median, and range. The geometric mean ratios and 90% confidence intervals for daptomycin C_{max}, $AUC_{0-\infty}$, CL_T, CL_R, and Fe were reported.

RESULTS:

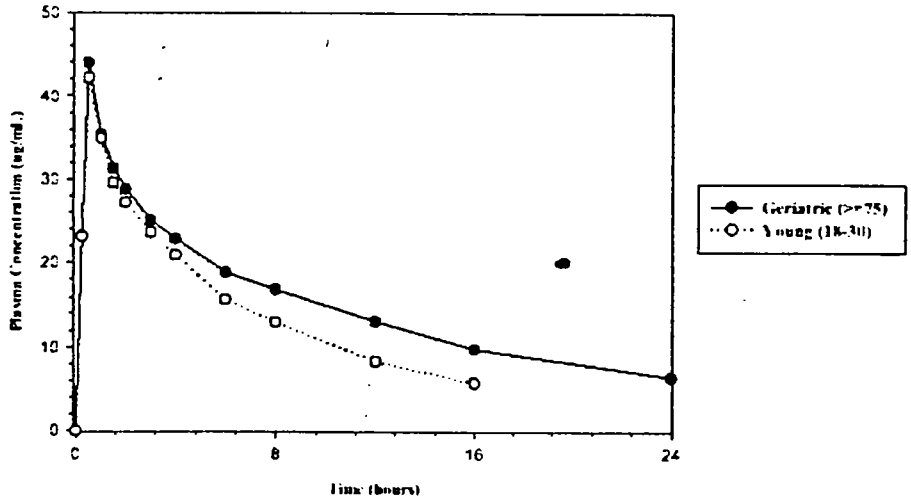
Although 12 healthy elderly and 12 healthy young subjects were enrolled into the study, only 11 healthy young subjects completed the study. Subject 021 was excluded from the pharmacokinetic analysis because this subject received a dose of daptomycin over 8 mg/kg, twice the protocol dose. The mean (SD) demographic data for the 23 subjects who completed the study are shown in Table 1. Most of the subjects were Hispanic (50% of elderly and 100% of young) and the elderly subjects tended to be taller, weight more, and have a lower creatinine clearance.

Table 1. Mean (SD (range) demographics for healthy elderly and healthy young subjects

Group	N	Age (yrs)	Weight (kg)	Height (cm)	Estimated CL_{CR} (mL/min)	Measured CL_{CR} (mL/min)
Healthy elderly	2F/10M	77.3 (2.5)	77.0 (8.2)	164.2 (5.9)	57.6 (12.6)	66.8 (15.1)
Healthy young	6F/5M	23.5 (4.3)	64.8 (10.2)	163.1 (6.7)	94.7 (14.5)	77.9 (17.2)

The mean plasma concentration-time profiles of daptomycin following a single dose of daptomycin IV 4 mg/kg in elderly and young subjects are shown in Figure 1. Although the mean plasma concentrations of daptomycin were similar immediately following administration, plasma concentration were greater in healthy elderly subjects compared to healthy young subjects and may be due to differences in clearance among the two groups of subjects.

Figure 1. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects



The daptomycin pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 4 mg/kg are shown in Table 2. The mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.04-fold, 0.46-fold, and 0.58-fold greater, respectively in elderly subjects than young subjects. The sponsor's estimate of AUC_{0-24} may be an underestimate in young subjects since a plasma concentration of zero was used at 24 hrs (10 of 11 subjects) when the concentration was below the LLOQ. The mean CL_T, CL_R, and Ae were 0.35-fold, 0.41-fold, and 0.19-fold lower in elderly subjects compared to young subjects. The Vz and V_{ss} were 0.13-fold and 0.14-fold greater in elderly subjects. The terminal elimination half-life was 0.74-fold greater.

Table 2. Mean (CV%) daptomycin pharmacokinetic parameter estimates when administered to healthy elderly and healthy young subjects

Parameter	Healthy Elderly (n=12)	Healthy Young (n=11)
AUC_{0-t} (µg*hr/mL)	361 (18%)	248 (13%)
AUC_{0-24} (µg*hr/mL)	361 (18%)	268 (11%)
$AUC_{0-\infty}$ (µg*hr/mL)	474 (23%)	301 (12%)
C_{max} (µg/mL)	44.0 (17%)	42.3 (15%)
C_{24} (µg/mL)	6.4 (29%)	3.4[a]
T_{max} (hrs)	0.5 (7%)	0.5 (28%)
CL_T (mL/hr/kg)	9.86 (25%)	15.09 (16%)
CL_R (mL/hr/kg)	4.27 (40%)	7.20 (24%)
Vz (L/kg)	0.166 (29%)	0.147 (14%)
Vss (L/kg)	0.155 (27%)	0.136 (13%)
Half-life (hrs)	11.86 (19%)	6.80 (8%)
Ae (%)	34.3 (46%)	42.6 (16%)

a - n=1; the plasma concentration was below the LOQ [illegible] by 24 hrs in 10 of 11 healthy young subjects

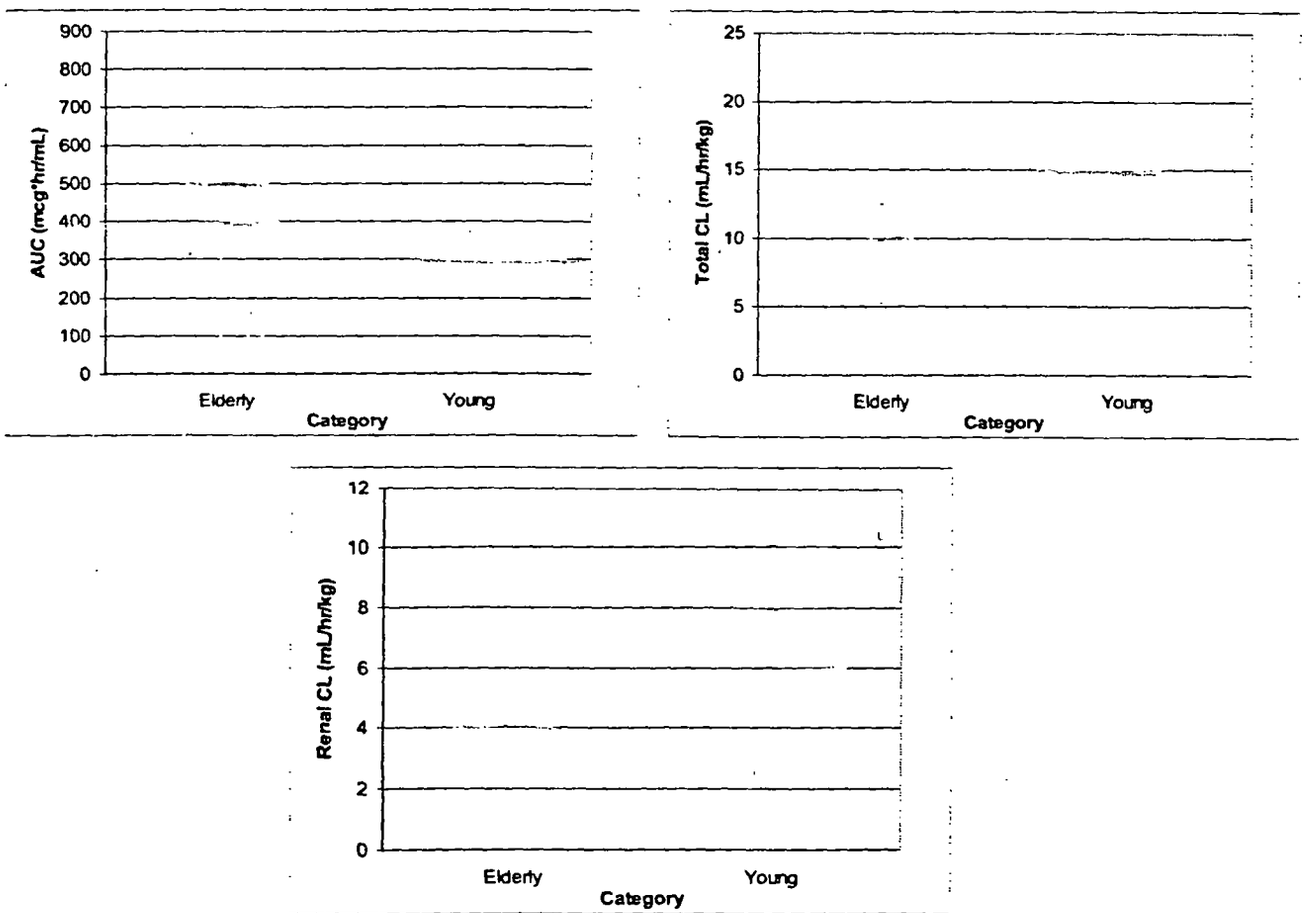
The reviewer calculated the geometric mean ratios (healthy elderly/healthy young) and 90% confidence intervals for daptomycin C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL_T, CL_R and Ae (see Table 3). The AUC_{0-t}, $AUC_{0-\infty}$, CL_T, CL_R and Fe were statistically significantly different between healthy elderly and healthy young subjects. The 90% confidence intervals for daptomycin C_{max} was within the predetermined limits of 0.80 to 1.25 and was not statistically significantly different between the two groups of subjects.

Table 3. Geometric mean ratios and 90% confidence intervals for daptomycin (healthy elderly/healthy young subjects)

Parameter	Point estimate	90% CI
AUC_{0-t}	1.4472	1.3046 - 1.6053
$AUC_{0-\infty}$	1.5517	1.3745 - 1.7518
C_{max}	1.0382	0.9257 - 1.1644
CL_T	0.6427	0.5516 - 0.7489
CL_R	0.5673	0.4496 - 0.7157
Ae	0.7597	0.6194 - 0.9319

Stick plots showing the individual $AUC_{0-\infty}$, CL_T, and CL_R values for daptomycin and aztreonam alone and in combination are shown in Figure 2. Subject #012 had the greatest $AUC_{0-\infty}$ value of 772 µg*hr/mL and the lowest CL_T and CL_R (5.56 mL/hr/kg and 1.62 mL/hr/kg, respectively). Subject #009 had a CL_R (8.86 mL/hr/kg) that exceeded the CL_T (8.07 mL/hr/kg); the CL_T was the third lowest among healthy elderly subjects. The sponsor did not give an explanation for the CL_R value that exceeded CL_T.

Figure 2. Stick plots demonstrating individual $AUC_{0-\infty}$, CL_T, and CL_R values for healthy elderly and young subjects



Although the mean $AUC_{0-\infty}$ increased 0.58-fold in healthy geriatric subjects compared to healthy young subjects, the mean pharmacokinetic parameter estimates from healthy geriatric subjects were similar to healthy subjects from Study DAP-00-02 following administration of the first dose of daptomycin IV 4 mg/kg. The mean (SD) age of the healthy subjects was 33.4 (3.6) yrs in Study DAP-00-02, whereas the mean age of healthy young subjects from Study DAP-GER-01-11 was 23.5 (4.30) yrs. A comparison of the pharmacokinetic parameters from both studies is shown in Table 4.

Table 4. Mean (CV%) daptomycin pharmacokinetic parameter estimates from Study DAP-GER-01-11 and Study DAP-00-02

	Study DAP-GER-01-11		Study DAP-00-02
Parameter	Healthy Elderly (n=12)	Healthy Young (n=11)	Healthy Young (n=6)
AUC_{0-24} (µg*hr/mL)	361 (18%)	268 (11%)	354 (18%)
$AUC_{0-\infty}$ (µg*hr/mL)	474 (23%)	301 (12%)	425 (14%)
C_{max} (µg/mL)	44.0 (17%)	42.3 (15%)	54.6 (10%)
C_{24} (µg/mL)	6.4 (29%)	3.4[a]	6.5 (72%)
T_{max} (hrs)	0.5 (7%)	0.5 (28%)	0.5 (0%)
CL_T (mL/hr/kg)	9.86 (25%)	15.09 (16%)	9.55 (13%)
CL_R (mL/hr/kg)	4.27 (40%)	7.20 (24%)	6.06 (20%)
V_{SS} (L/kg)	0.155 (27%)	0.136 (13%)	0.0925 (12%)
Vz (L/kg)	0.166 (29%)	0.147 (14%)	0.1042 (15%)
Half-life (hrs)	11.86 (19%)	6.80 (8%)	7.39 (12%)
Ae (%)	34.3 (46%)	42.6 (16%)	53.0 (20%)

a - n=1; the plasma concentration was below the LOQ (~~~ µg/mL) by 24 hrs in 10 of 11 healthy young subjects

The mean AUC_{0-24}, $AUC_{0-\infty}$, C_{24}, and CL_T were similar between healthy elderly subjects (Study DAP-GER-01-11) and healthy young subjects from Study DAP-00-02. The lower mean Vz and V_{SS} observed in study DAP-00-02 may have contributed to the greater mean C_{max} and longer elimination half-life in that study. Since the mean measured creatinine clearance from healthy elderly subjects (66.8 ± 15.1 mL/min) was similar to the mean measured creatinine clearance from subjects to mild renal impairment (58.8 ± 7.7 mL/min) in Study MRDI-01-09, no dosage is necessary for elderly subjects ≥75 yrs of age.

SAFETY:

One of 12 subjects in the elderly group experienced one treatment-emergent adverse event and three subjects in the young group experienced three adverse events. Subject #006 in the geriatric group experienced vomiting on the day following dosing that was mild in severity and was not considered to be treatment related. Subject #014 in the young group experienced headache approximately 4 hours after dosing, which persisted until the following day. The event was mild in severity, possibly related to the study drug, and it resolved without treatment. Subject #021 in experienced a rash on her left upper arm the arm (opposite to study drug administration arm) approximately 12 hours following dosing, which persisted for approximately 48 hours. It was considered possibly related to study treatment, although the investigator noted that the rash was characteristic of insect bites. Subject #024 experienced headache as an adverse event approximately 5 hours following dosing. There were no deaths or serious adverse events during the study and none of the subjects discontinued due to an adverse event.

CONCLUSIONS:

The mean $AUC_{0-\infty}$ of daptomycin in healthy elderly subjects was 0.57-fold greater compared with healthy young subjects whereas the CL_T was 0.35-fold less in healthy elderly subjects.

The mean pharmacokinetic parameters of daptomycin in healthy elderly subjects were similar to those from healthy young subjects in Study DAP-00-02.

The safety profile of single-dose daptomycin (4 mg/kg) in healthy elderly subjects was not different from that of healthy young subjects.

Based on the results of the renal impairment study, no dosage adjustment of daptomycin is warranted when administered to elderly patients with normal renal function for their age.

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin —— assay for daptomycin in plasma and urine (— ' the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the complete study report in the future.

2. Even though daptomycin plasma concentrations were below the LLOQ in 10/11 healthy young subjects by 24 hrs, the sponsor reported the AUC_{0-24} for all subjects. The AUC_{0-24} was calculated using a value of zero at 24 hrs. The sponsor is encouraged to calculate AUC_{0-t} in the future rather than assuming a concentration of zero at sampling points in which the plasma concentration is below the LLOQ.

A single dose study to evaluate the pharmacokinetics and safety of Cidecin® (daptomycin for injection) in obese and non-obese matched subjects following a dose of 4 mg/kg total body weight (Protocol DAP-OBSE-01-07)

Dates: January 3, 2002 to February 28, 2002
Clinical site:
Analytical site:

RATIONALE:
Since the pathophysiology of the obese body may affect drug distribution and elimination of daptomycin, this study was designed to assess the single-dose pharmacokinetics and safety of daptomycin in moderately to extremely obese subjects as compared with non-obese subjects that are matched for gender, age, and renal function.

OBJECTIVES:
The primary objective of this study was to evaluate the pharmacokinetics of daptomycin in moderately to extremely obese subjects compared with non-obese subjects that were matched for gender, age, and renal function. The secondary objective of the study was to evaluate the safety of daptomycin in moderately to extremely obese subjects.

FORMULATION:
Daptomycin 500 mg vial (Cubist, Lot No. 680413A)

STUDY DESIGN:
This study was an open-label, single-dose, parallel design, single-center study to evaluate the pharmacokinetics and safety of daptomycin in adult subjects who were moderately or extremely obese and matched non-obese healthy subjects. The sponsor planned to enroll 6 moderately obese subjects (body mass index [BMI] 25-39.9 kg/m^2) and 6 gender, age, and renal function matched non-obese subjects and 6 extremely obese subjects (BMI ≥40 kg/m^2) and 6 gender, age, and renal function matched non-obese subjects. For matched non-obese subjects, the BMI had to be between 18.5 and 24.9 kg/m^2, age had to be within 10 years of the obese subject, and renal function had to be similar (creatinine clearance ≥70 mL/min as calculated by the Cockcroft and Gault equation using total body weight). All subjects received a single dose of intravenous (IV) daptomycin at 4 mg/kg based on total body weight infused over 30 min in 50 mL of normal saline.

Blood samples for determination of daptomycin concentrations were obtained predose, mid-way through the infusion (0.25 hrs), end of the infusion (0.5 hrs), 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hrs from the initiation of the infusion.

Urine samples for determination of daptomycin concentrations were obtained at predose and then at 0-2 hrs, 2-4 hrs, 4-8 hrs, 8-12, 12-16 hrs, and 16 to 24 hrs from the initiation of infusion. Urine was collected for 24 hrs to allow a 24-hr urine creatinine clearance calculation.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Urine	Comments
Concentration range	3.28 to 545 µg/mL	3.36 to 562 µg/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Not stated	Not stated	Unsatisfactory

DATA ANALYSIS:

Plasma daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were determined for plasma daptomycin concentration data: the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), plasma concentration at 24 hrs post-dose (C_{24}), the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), plasma clearance (CL_T), volume of distribution (Vz = CL/Ke), volume of distribution at steady state (V_{SS} = CL × MRT), mean residence time (MRT), and terminal elimination half-life ($t_{1/2}$).

The following parameters were calculated based on daptomycin urine concentration data: the renal clearance (CL_R) and the fraction of dose excreted in urine as parent drug over 24 hrs (Fe).

STATISTICAL ANALYSIS:

Pharmacokinetic parameters were summarized as mean, SD, median, and range. The geometric mean ratios and 90% confidence intervals for daptomycin C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL_T, CL_R, V_{SS}, and Fe were calculated.

RESULTS:

Thirteen obese (6 moderately obese and 7 extremely obese) subjects and 12 non-obese matched controls completed the study. The mean (SD) demographic data for 24 subjects (one extremely obese subject without a matched control was excluded) are shown in Table 1. The majority of subjects were male and Hispanic (6/6 of moderately obese, 5/6 of the moderately obese-matched controls, 4/6 of extremely obese, and 5/6 of the extremely obese-matched controls).

Table 1. Mean (SD) demographics for obese subjects and matched controls

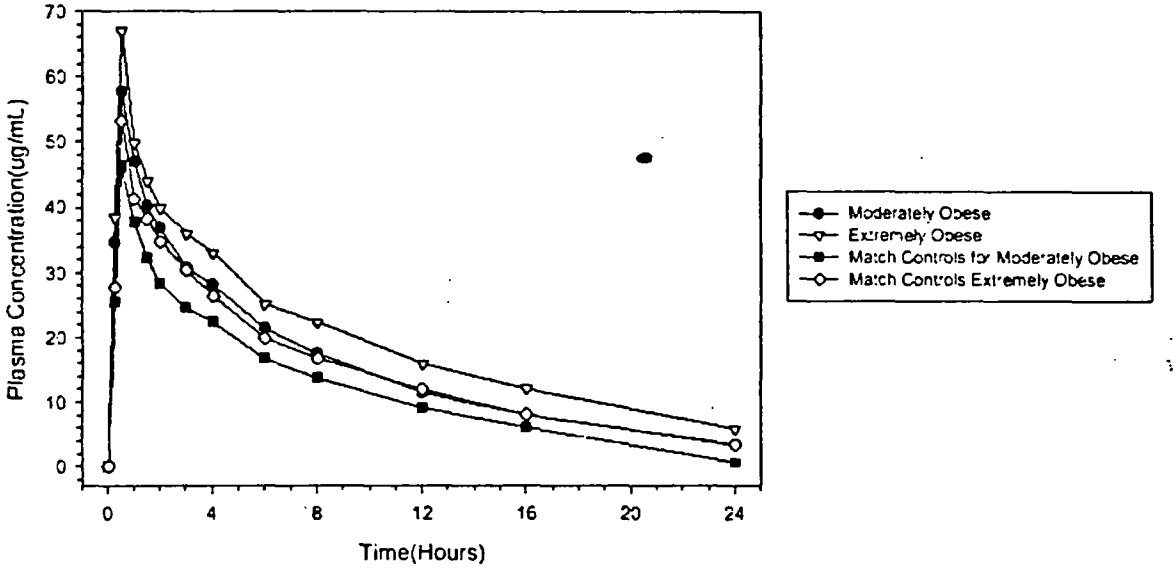
Group	N	Age (yrs)	ABW* (kg)	IBW* (kg)	Height (cm)	Measured CL_{CR} (mL/min)
Moderately obese						
Obese	6F/0M	40.7 (7.3)	85.7 (8.6)	52.8 (4.2)	160.7 (5.0)	107.7 (21.8)
Control	6F/0M	36.5 (8.5)	60.9 (3.8)	49.3 (4.0)	156.8 (4.2)	88.8 (15.4)
Extremely obese						
Obese	2F/4M	38.3 (13.5)	127.5 (18.1)	61.9 (10.5)	166.3 (9.8)	137.1 (45.4)
Control	2F/4M	36.7 (15.4)	67.7 (7.9)	62.7 (10.2)	168.0 (9.1)	82.2 (24.3)

*ABW = actual body weight; IBW = ideal body weight

The mean plasma concentration-time profiles of daptomycin following a single IV 4 mg/kg dose to moderately or severely obese subjects and non-obese matched controls are shown in Figure 1. The mean plasma concentrations of daptomycin were greatest in extremely obese subjects and the lowest in

moderate obesity matched controls. The mean plasma concentrations of daptomycin were similar in moderately obese subjects and extremely obese matched controls.

Figure 1. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects



The mean daptomycin pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 4 mg/kg are shown in Table 2.

Table 2. Mean (CV%) daptomycin pharmacokinetic parameter estimates in obese subjects and matched controls

	Moderately Obese		Extremely Obese	
Parameter	**Obese**	**Control**	**Obese**	**Control**
AUC_{0-t} (µg*hr/mL)	375 (16%)	269 (13%)	473 (17%)	353 (20%)
AUC_{0-24} (µg*hr/mL)	379 (15%)	288 (10%)	473 (17%)	361 (17%)
$AUC_{0-\infty}$ (µg*hr/mL)	421 (16%)	322 (10%)	548 (25%)	419 (25%)
C_{max} (µg/mL)	57.8 (13%)	46.3 (15%)	67.0 (10%)	53.2 (11)
C_{24} (µg/mL)	4.1 (17%)[a]	3.7[b]	5.9 (49)	5.1 (40%)[c]
T_{max} (hrs)	0.50 (0%)	0.50 (0%)	0.50 (0%)	0.50 (0%)
CL_T (mL/hr)	856 (8%)	724 (6%)	1,016 (29%)	696 (34%)
CL_R (mL/hr)	492 (15%)	422 (16%)	500 (32%)	373 (29%)
Vz (L)	9.00 (9%)	7.14 (13%)	11.33 (18%)	7.44 (17%)
Vss (L)	8.10 (12%)	6.60 (11%)	10.82 (15%)	6.78 (17%)
Half-life (hrs)	7.34 (13%)	6.83 (10%)	8.13 (21%)	8.04 (29%)
Fe (%)	51.8 (12%)	52.3 (16%)	42.7 (14%)	48.6 (17%)

[a]plasma concentration below LLOQ in 1/6 subjects; [b]plasma concentration below LLOQ in 5/6 subjects; [c]plasma concentration below LLOQ in 2/6 subjects

In moderately obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 0.25-fold and 0.30-fold greater, respectively in obese subjects than matched controls. The sponsor's estimate of AUC_{0-24} may be an underestimate in matched controls since a plasma concentration of zero was used at 24 hrs in 5/6

moderate obesity-matched controls when the concentration was below the LLOQ. The mean CL_T and CL_R (not corrected by body weight) were 0.18-fold and 0.16-fold greater in moderately obese subjects compared to matched controls.

Table 3. Mean (CV%) daptomycin pharmacokinetic parameter estimates corrected for actual and ideal body weights

	Moderately Obese		Extremely Obese	
Parameter	Obese	Control	Obese	Control
CL_T (mL/hr/kg ABW)	10.07 (12%)	11.89 (5%)	7.82 (20%)	10.19 (33%)
CL_T (mL/hr/kg IBW)	16.24 (6%)	14.72 (7%)	16.40 (30%)	11.09 (35%)
CL_R (mL/hr/kg ABW)	5.81 (20%)	6.94 (15%)	3.83 (22%)	5.44 (23%)
CL_R (mL/hr/kg IBW)	9.35 (15%)	8.57 (14%)	8.06 (34%)	5.88 (21%)
Vz (L/kg ABW)	0.106 (14%)	0.117 (8%)	0.089 (13%)	0.110 (12%)
Vz (L/kg IBW)	0.171 (11%)	0.144 (5%)	0.185 (18%)	0.119 (15%)
Vss (L/kg ABW)	0.095 (13%)	0.108 (9%)	0.085 (10%)	0.100 (14%)
Vss (L/kg IBW)	0.154 (11%)	0.134 (6%)	0.176 (15%)	0.109 (16%)

When corrected for actual body weight (ABW), the mean CL_T and CL_R were 0.15-fold and 0.16-fold lower in moderately obese subjects compared to matched controls (Table 3). In contrast, the mean CL_T and CL_R were 0.10-fold and 0.09-fold greater in moderately obese subjects compared to matched controls when corrected for ideal body weight (IBW). The mean Fe was similar between moderately obese subject and matched controls (51.8% vs. 52.3%, respectively).

The mean Vz and V_{SS} (not corrected for body weight) were 0.26-fold and 0.23-fold greater in moderately obese subjects compared to matched controls. Not surprisingly, the mean elimination half-life was 0.07-fold longer. When Vz and V_{SS} were corrected for actual body weight, the parameters decreased 0.09-fold and 0.12-fold respectively compared to matched controls. In contrast, the mean Vz and V_{SS} were 0.19-fold and 0.15-fold greater in moderately obese subjects compared to matched controls when corrected for ideal body weight.

In extremely obese subjects, the mean C_{max} and $AUC_{0-\infty}$ were 0.26-fold and 0.31-fold greater, respectively in obese subjects than matched controls. Similar to moderately obese subjects, the sponsor's estimate of AUC_{0-24} may be an underestimate in matched controls since a plasma concentration of zero was used at 24 hrs in 2/6 extreme obesity-matched controls when the concentration was below the LLOQ. The mean CL_T and CL_R (not corrected by body weight) were 0.46-fold and 0.34-fold greater in extremely obese subjects compared to matched controls. When corrected for actual body weight (ABW), the mean CL_T and CL_R were 0.23-fold and 0.30-fold lower in extremely obese subjects compared to matched controls. In contrast, the mean CL_T and CL_R were 0.48-fold and 0.37-fold greater in moderately obese subjects compared to matched controls when corrected for ideal body weight (IBW). The mean Fe was 0.12-fold lower in extremely obese subject compared to matched controls.

The mean Vz and V_{SS} (not corrected for weight) were 0.52-fold and 0.60-fold greater in extremely obese subjects compared to matched controls. When Vz and V_{SS} were corrected for actual body weight, the parameters decreased 0.19-fold and 0.15-fold, respectively compared to matched controls. In contrast, the mean Vz and V_{SS} were 0.55-fold and 0.62-fold greater in extremely obese subjects compared to matched controls when corrected for ideal body weight.

The reviewer calculated the geometric mean ratios (obese subjects/matched controls) and 90% confidence intervals for daptomycin C_{max}, AUC, CL_T, CL_R, V_{SS}, and Fe. The geometric mean ratios and 90% confidence intervals are shown in Table 3. For moderately obese subjects, the C_{max} and $AUC_{0-\infty}$ were

outside of the 0.80 to 1.25 predetermined range and were statistically significantly different between moderately obese subjects and matched controls. For extremely obese subjects, the C_{max} and $AUC_{0-\infty}$ were also outside of the 0.80 to 1.25 predetermined range and were statistically significantly different between extremely obese subjects and matched controls. The 90% confidence intervals of the geometric mean ratios were outside of the 0.80 and 1.25 range for all pharmacokinetic parameters.

Table 3. Geometric mean ratios and 90% confidence intervals for daptomycin (obese subjects/ matched controls)

	Moderately obese		Severely obese	
Parameter	Point estimate	90% CI	Point estimate	90% CI
AUC_{0-t} (μg*hr/mL)	1.3886	1.1900 to 1.6204	1.3478	1.1189 to 1.6234
$AUC_{0-\infty}$ (μg*hr/mL)	1.2963	1.1258 to 1.4927	1.3104	1.0400 to 1.6512
C_{max} (μg/mL)	1.2510	1.0812 to 1.4476	1.2599	1.1272 to 1.4083
CL_T (mL/hr)	1.1816	1.0970 to 1.2727	1.4857	0.9730 to 2.2687
CL_T (mL/hr/kg ABW)	0.8423	0.7642 to 0.9284	0.7918	0.5731 to 1.0940
CL_T (mL/hr/kg IBW)	1.1045	1.0311 to 1.1833	1.5065	1.0700 to 2.1211
CL_R (mL/hr)	1.1662	0.9926 to 1.3701	1.3150	0.8840 to 1.9560
CL_R (mL/hr/kg ABW)	0.8313	0.6837 to 1.0107	0.7008	0.5326 to 0.9223
CL_R (mL/hr/kg IBW)	1.0901	0.9310 to 1.2764	1.3333	0.9925 to 1.7912
V_{SS} (L)	1.2260	1.0873 to 1.3823	1.6023	1.3213 to 1.9432
V_{SS} (L/kg ABW)	0.8739	0.7788 to 0.9807	0.8540	0.7522 to 0.9695
V_{SS} (L/kg IBW)	1.1460	1.0398 to 1.2631	1.6247	1.3940 to 1.8936
Fe (%)	0.9950	0.8518 to 1.1622	0.8851	0.7385 to 1.0607

When daptomycin was dosed by actual body weight, the C_{max} and $AUC_{0-\infty}$ were greater in obese subjects compared to non-obese matched controls. The V_{SS} and V_{SS} corrected for IBW were greater in obese subjects compared to non-obese matched controls but not V_{SS} corrected for ABW. These differences may be due to the fact that obese individuals have larger absolute lean body masses as well as masses of adipose tissue compared to non-obese individuals of the same age, gender and height.

The CL_T and CL_T corrected for IBW were greater in obese subjects compared to non-obese matched controls but not CL_T corrected for ABW. The same relationship was true with renal clearance. The differences in daptomycin clearance between obese and matched non-obese controls can be attributed to an increase in daptomycin clearance with increased body mass index. The decreases in daptomycin plasma clearance (mL/hr/kg AB) between obese subjects and matched controls was similar to the decrease in daptomycin renal clearance (mL/hr/kg ABW), suggesting that the observed alteration in daptomycin plasma clearance may be due to differences in renal clearance.

Stick plots showing the individual C_{max} and $AUC_{0-\infty}$ values for daptomycin are shown in Figure 2 whereas individual CL_T and CL_R values for daptomycin are shown in Figure 3.

Figure 2. Stick plots demonstrating individual C_{max} and values in obese subjects and non-obese matched controls

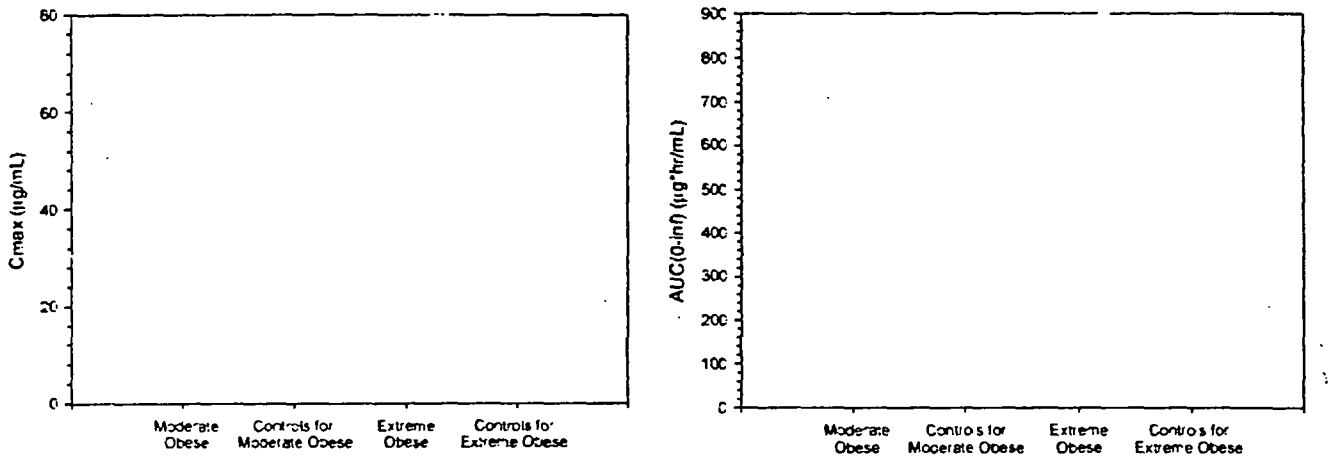
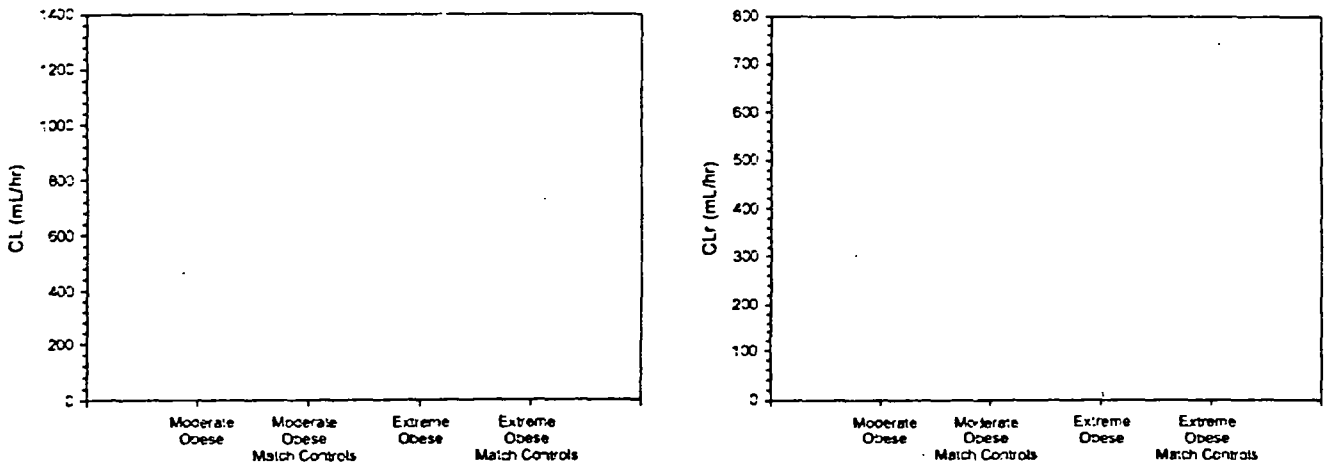


Figure 3. Stick plots demonstrating individual CL_T and CL_R values in obese subjects and non-obese matched controls



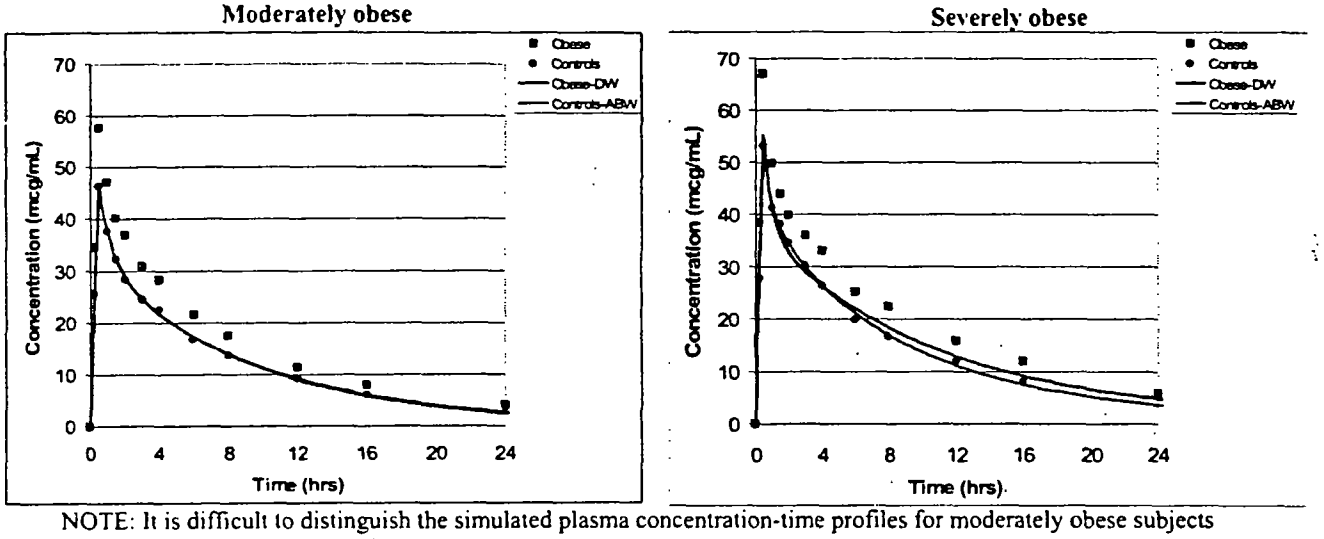
Dosage Adjustment:

The reviewer calculated the weight of each individual subject to "normalize" the apparent volume of distribution between obese subjects and non-obese matched controls. The reviewer termed this weight the dosing weight (DW), which is the body weight (for purposes of dosing) that would result in a similar C_{max} after administration of daptomycin. For moderately obese subjects, the DW=IBW + 0.45(ABW-IBW). For severely obese subjects, the DW=IBW + 0.65(ABW-IBW).

The reviewer fit the measured daptomycin plasma concentration-time profiles from obese subject and non-obese matched control to a 2-cmpt model using WinNonlin (version 4.0, Pharsight) and the

administered dose (4 mg/kg based on ABW). Then, the daptomycin plasma concentration-time profiles for each patient were simulated using a 2-cmpt model and the recommended dosage (4 mg/kg based on DW for obese subjects and ABW for non-obese matched controls) to verify the accuracy of the DW. A comparison of the measured daptomycin plasma concentrations and the simulated concentrations using the DW are shown in Figure 4.

Figure 4. Measured daptomycin plasma concentrations (symbols) and simulated daptomycin plasma concentrations (solid lines) in moderately obese (left) and extremely obese (right) subjects and non-obese matched controls



NOTE: It is difficult to distinguish the simulated plasma concentration-time profiles for moderately obese subjects and non-obese matched controls.

For moderately obese subjects, the simulated daptomycin plasma concentration-time profiles were superimposable for obese subjects and non-obese matched controls when the dosage of obese subjects was based on the DW and non-obese matched controls based on ABW. For severely obese subjects, the simulated daptomycin plasma concentration-time profiles were similar between obese subjects and non-obese matched controls when the dosage of obese subjects was based on the DW. Thus, the DW appears to correct for differences in the apparent volume of distribution between obese and non-obese subjects and may be used to adjust the daptomycin dosage in moderately and severely obese patients. However, due to the modest alteration in daptomycin pharmacokinetic parameters, no dosage adjustment is warranted for patients who are moderately obese or extremely obese.

SAFETY:

One of seven subjects in the extremely obese group experienced three treatment-emergent adverse events; the six moderately obese subjects and the 12 matched control subjects did not experience any adverse events during the study. The subject in the extremely obese group experienced nausea, vomiting, and headache eight or more hours after dosing. The three events were mild in severity and were not considered to be treatment related. There were no deaths or serious adverse events during the study and none of the subjects discontinued due to an adverse event.

CPK concentrations were within normal limits for all subjects at baseline, Day 1, and Day 2.

CONCLUSIONS:

The C_{max} and $AUC_{0-\infty}$ of daptomycin were statistically significantly greater in obese subjects compared to non-obese matched controls when dosed by actual body weight.

The CL_T, CL_R, and V_{SS} of daptomycin were greater in obese subjects compared to non-obese matched controls. When the parameters were corrected for actual body weight, the parameters were lower in obese subjects than non-obese subjects. When the parameters were corrected for ideal body weight, the parameters were greater in obese subjects than non-obese subjects.

Obese individuals probably have a larger absolute lean body masses as well as larger adipose tissue masses compared to non-obese individuals of the same age, gender and height.

For moderately obese subjects, the dosing weight = IBW + 0.45(ABW-IBW). For severely obese subjects, the dosing weight = IBW + 0.65(ABW-IBW).

Due to the modest alteration in daptomycin pharmacokinetic parameters, no dosage adjustment is warranted in moderately and extremely obese patients.

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin — assay for daptomycin in plasma and urine (— the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the complete study report in the future.

2. Even though daptomycin plasma concentrations were below the LLOQ in 10/11 healthy young subjects by 24 hrs, the sponsor reported the AUC_{0-24} for all subjects. The AUC_{0-24} was calculated using a value of zero at 24 hrs. The sponsor is encouraged to calculate AUC_{0-t} in the future rather than assuming a concentration of zero at sampling points in which the plasma concentration is below the LLOQ.

A double-blind, randomized, three-way crossover evaluation of the pharmacokinetics of daptomycin and aztreonam when administered alone and when administered in combination in normal volunteers (Protocol DAP-DI-01-01)

Dates: November 8, 2001 to December 8, 2001
Clinical site:
Analytical sites:

RATIONALE:
Aztreonam is an antibacterial agent with strictly Gram-negative activity; therefore, daptomycin and aztreonam can complement one another when co-administered in the treatment of mixed infections. However, since both drugs are primarily excreted via the kidneys, the potential for a pharmacokinetic interaction may exist based on this common pathway of elimination.

OBJECTIVES:
The primary objective of this study was to evaluate the pharmacokinetics of a single-dose of daptomycin and aztreonam, when administered alone and in combination. The secondary objective was to evaluate the safety of daptomycin when administered in combination with aztreonam.

FORMULATIONS:
Daptomycin 500 mg vial (Cubist, Lot No. 680413A)
Aztreonam 1 gram vial (Bristol-Myers Squibb, Lot No. 1A46483)

STUDY DESIGN:
This study was a randomized, double-blind, single-dose, three-way crossover study to evaluate the pharmacokinetics of daptomycin and aztreonam when administered alone and in combination to 15 healthy adult subjects between 18 and 65 years of age. The treatment schedules were defined as ABC, BCA, and CAB, where each letter represented a specific study drug and the order of administration. The subject's assigned study number determined the order in which each of the treatments was received. Treatment A was 6 mg/kg of daptomycin in 50 mL of normal saline (NS) and 50 mL of NS, administered as two consecutive 35-min (±1 min) IV infusions. Treatment B was 1,000 mg aztreonam in 50 mL of NS and 50 mL of NS, administered as two consecutive 35-min (±1 min) IV infusions. Treatment C was 6 mg/kg of daptomycin in 50 mL NS and 1,000 mg aztreonam in 50 mL of NS, administered as two consecutive 35-min (±1 min) IV infusions. There was a 7-day washout period between each study drug administration with each of the three treatment schedules. When scheduled, daptomycin was always given as the first infusion and aztreonam, when scheduled, was always given as the second infusion. On dosing days, subjects were given a standardized breakfast at least 1 hour prior to drug administration and subjects were allowed water as needed.

Blood samples for determination of daptomycin concentrations were obtained predose, mid-way through the infusion (0.25 hrs), at the end of the infusion (0.5 hrs), and at 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 24.5 hrs from the initiation of the infusion.

Blood samples for determination of aztreonam concentrations were obtained predose, mid-way through the infusion (0.25 hrs), at the end of the infusion (0.5 hrs), and at 1, 1.5, 2.5, 3.5, 5.5, 7.5, 11.5, 15.5, and 24 hrs from the initiation of the infusion.

Urine samples for determination of daptomycin and aztreonam concentrations were obtained at predose and then collected at 0-2 hrs, 2-4 hrs, 4-8 hrs, 8-12, 12-16 hrs, and 16 to 24.5 hrs from the initiation of infusion.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Urine	Comments
Concentration range	3.28 to 562 µg/mL	3.36 to 562 µg/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Not stated	Not stated	Unsatisfactory

AZTREONAM ASSAY METHODOLOGY:

Criterion	Plasma	Urine	Comments
Concentration range	1.00 to 200 µg/mL	9.98 to 4,988.48 µg/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability			Satisfactory

DATA ANALYSIS:

Plasma daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were determined for plasma daptomycin concentration data: the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), plasma clearance (CL_T), renal clearance (CL_R), volume of distribution ($Vz = CL/Ke$), volume of distribution at steady state ($V_{SS} = CL \times MRT$), mean residence time (MRT), fraction of dose excreted in urine as parent drug over 24 hrs (Ae), and terminal elimination half-life ($t_{1/2}$).

STATISTICAL ANALYSIS:

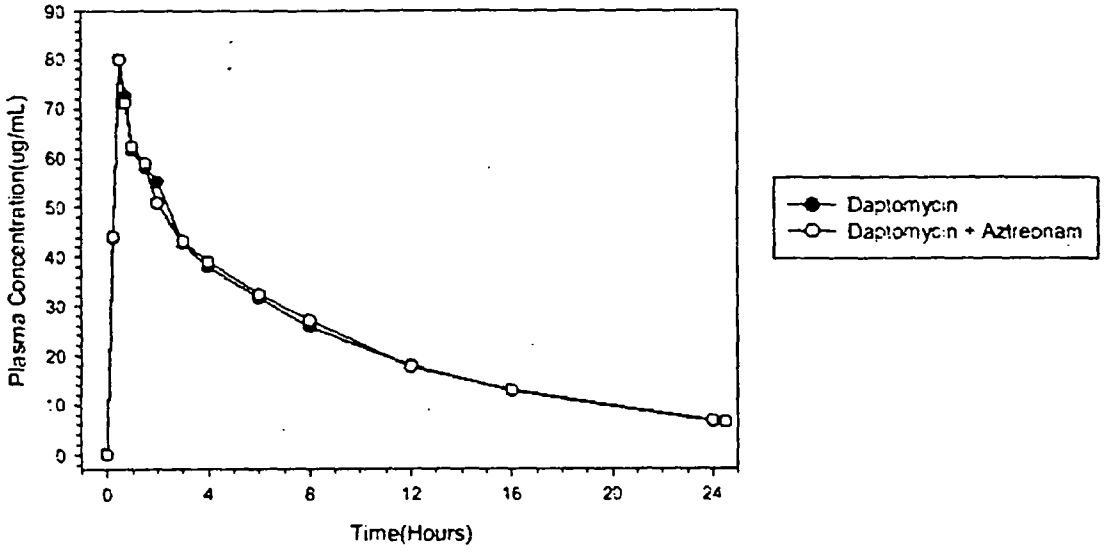
Pharmacokinetic parameters were summarized as mean, SD, median, and range. The geometric mean ratios and the 90% confidence intervals for daptomycin and aztreonam C_{max} and $AUC_{0-\infty}$ were reported alone and combined with the other drug.

RESULTS:

Eighteen subjects were enrolled into the study and fifteen subjects completed all three treatments. Subject 004 received treatments B and C, Subject 012 received only treatment B, and Subject 013 received only treatment C. Of the remaining 15 subjects, four were female and 11 male. The mean (SD) age, weight, and height of the 15 subjects were 44.8 (14.8) yrs, 73.4 (11.7) kg, and 171 (7) cm, respectively.

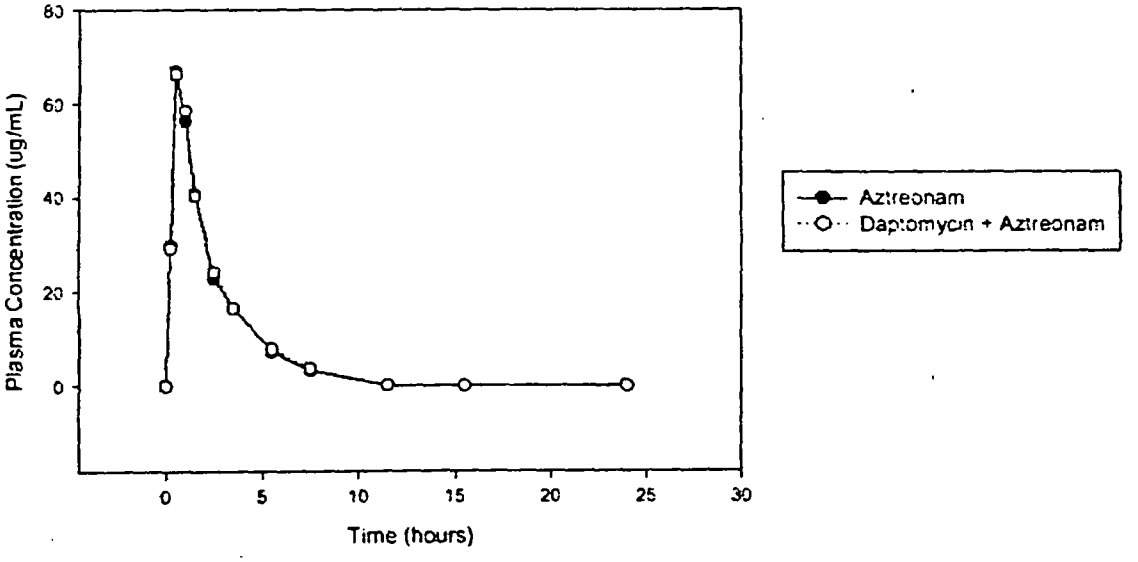
The mean plasma concentration-time profiles of daptomycin following a single dose of daptomycin IV 6 mg/kg alone or in combination with aztreonam IV 1,000 mg are shown in Figure 1. The mean plasma concentrations of daptomycin were similar when administered alone and in combination with aztreonam to healthy subjects.

Figure 1. Mean plasma concentration-time profiles of daptomycin alone (6 mg/kg IV) and in combination with aztreonam (1 gram IV)



The mean plasma concentration-time profiles of aztreonam following a single dose of aztreonam IV 1,000 mg alone or in combination with daptomycin IV 6 mg/kg are shown in Figure 2. The mean plasma concentrations of aztreonam were nearly identical when administered alone and in combination with daptomycin to healthy subjects.

Figure 2. Mean plasma concentration-time profiles of aztreonam alone (1 gram IV) and in combination with daptomycin (6 mg/kg IV)



The daptomycin and aztreonam pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 6 mg/kg and aztreonam IV 1,000 mg alone and in combination are shown in Table 2. When daptomycin was administered with aztreonam, the mean $AUC_{0-\infty}$ of daptomycin was

unchanged and the mean C_{max} decreased 0.01-fold. The mean CL_T of daptomycin was unchanged, although the mean CL_R decreased 0.10-fold. The mean V_{SS} and Vz of daptomycin were similar (decreased 0.03-fold and 0.02-fold, respectively) when administered in combination with aztreonam. The terminal elimination half-life decreased 0.03-fold from 8.77 hrs to 8.51 hrs.

When aztreonam was administered with daptomycin, the mean $AUC_{0-\infty}$ of aztreonam increased 0.03-fold and the mean C_{max} was unchanged. The mean CL_T and CL_R of aztreonam decreased 0.03-fold and 0.05-fold, respectively. The mean V_{SS} and Vz of aztreonam increased 0.03-fold and 0.02-fold, respectively when administered in combination with aztreonam. The terminal elimination half-life increased 0.07-fold from 1.71 hrs to 1.83 hrs.

Table 1. Mean (CV%) daptomycin and aztreonam pharmacokinetic parameters alone and administered in combination

	Daptomycin 6 mg/kg		Aztreonam 1,000 mg	
Parameter	**Daptomycin alone**	**Daptomycin + Aztreonam**	**Aztreonam alone**	**Aztreonam + Daptomycin**
AUC_{0-1} (µg*hr/mL)	561 (13%)	565 (10%)	156 (15%)	160 (16%)
$AUC_{0-\infty}$ (µg*hr/mL)	650 (16%)	648 (13%)	164 (15%)	169 (16%)
C_{max} (µg/mL)	82.1 (18%)	80.9 (13%)	66.9 (13%)	67.1 (16%)
T_{max} (hrs)	0.69 (54%)	0.59 (8%)	0.51 (10%)	0.57 (31%)
C_{24} (µg/mL)	6.65 (23%)	6.79 (22%)	---	---
CL_T (mL/hr/kg)	9.65 (16%)	9.66 (13%)	84.46 (14%)	82.00 (16%)
CL_R (mL/hr/kg)	6.26 (20%)	5.65 (24%)	61.70 (23%)	58.49 (25%)
Vz (L/kg)	0.121 (17%)	0.117 (13%)	0.208 (15%)	0.214 (14%)
Vss (L/kg)	0.109 (15%)	0.106 (11%)	0.189 (11%)	0.192 (13%)
Half-life (hrs)	8.77 (17%)	8.51 (15%)	1.71 (13%)	1.83 (8%)
Ae (%)	56.7 (18%)	51.2 (20%)	72.4 (17%)	70.3 (17%)

The reviewer calculated the geometric mean ratios and 90% confidence intervals for daptomycin (daptomycin + aztreonam/daptomycin) and aztreonam (aztreonam + daptomycin/aztreonam) without period and sequence effects (see Table 2). The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$ and C_{max} were within the predetermined limits of 0.80 to 1.25 for daptomycin and aztreonam and were not statistically significantly different. Although not statistically significantly different, the CL_R of daptomycin and the percent of daptomycin excreted unchanged in the urine were outside of the 0.80 to 1.25 range when administered in combination with aztreonam. Thus, daptomycin and aztreonam do not exhibit a significant drug-drug interaction when administered in combination.

Table 2. Geometric mean ratios and 90% confidence intervals for daptomycin and aztreonam administered alone and in combination

	Daptomycin		Aztreonam	
Parameter	**Point estimate**	**90% CI**	**Point estimate**	**90% CI**
AUC_{0-1}	1.0107	0.9368 - 1.0904	1.0256	0.9219 - 1.1410
$AUC_{0-\infty}$	1.0017	0.9146 - 1.0971	1.0320	0.9262 - 1.1497
C_{max}	0.9923	0.8979 - 1.0966	1.0008	0.9097 - 1.1011
CL_T	1.0048	0.9094 - 1.1101	0.9681	0.8732 - 1.0732
CL_R	0.8936	0.7787 - 1.0255	0.9416	0.8027 - 1.1047
Ae	0.8972	0.7944 - 1.0133	0.9691	0.8575 - 1.0952

Stick plots showing the individual $AUC_{0-\infty}$ and CL_T values for daptomycin and aztreonam alone and in combination are shown in Figures 3 and 4. The geometric mean ratios of $AUC_{0-\infty}$ and CL_T for daptomycin were 1.00 and are supported by the nearly equal distribution of changes shown on the stick plots. The geometric mean ratios of $AUC_{0-\infty}$ and CL_T for aztreonam were 1.03 and 0.97; 11/15 subjects had an $AUC_{0-\infty}$ geometric mean ratio that increased when co-administered with daptomycin and 9/15 subjects had a CL_T geometric mean ratio that decreased when co-administered with daptomycin.

Figure 3. Stick plots demonstrating the $AUC_{0-\infty}$ (left) and total clearance (right) of daptomycin alone and combined with aztreonam

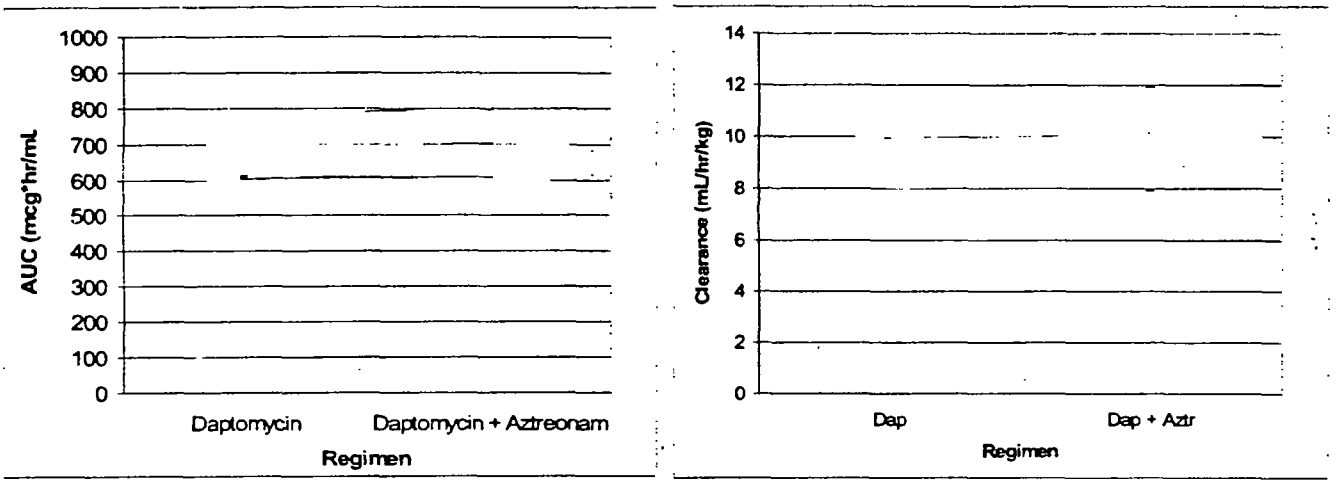
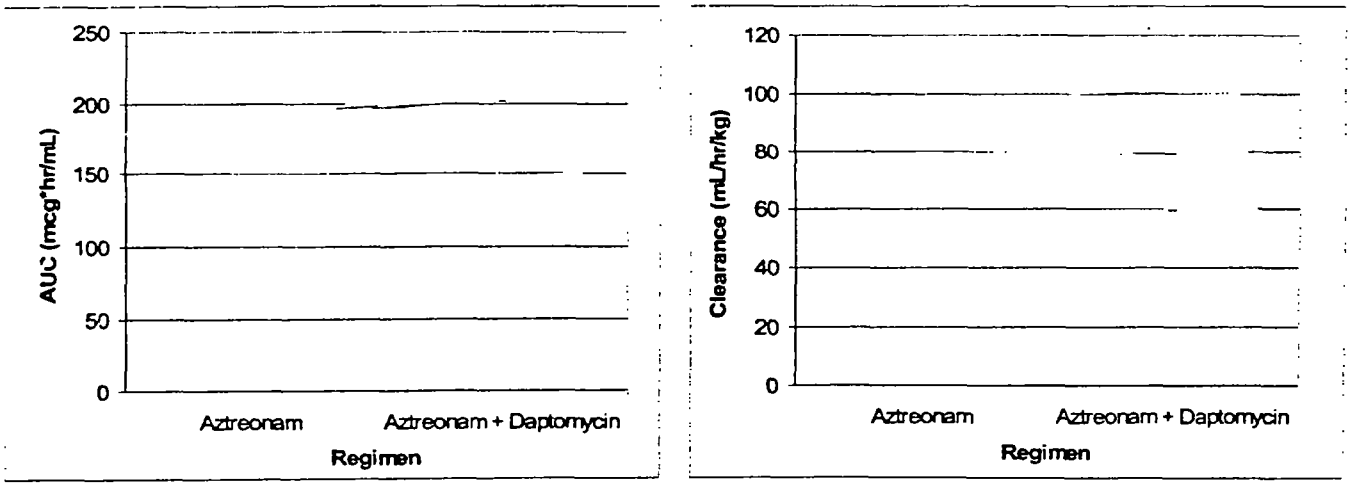


Figure 4. Stick plots demonstrating the $AUC_{0-\infty}$ (left) and total clearance (right) of aztreonam alone and combined with daptomycin



Although the pharmacokinetic parameter estimates of daptomycin were not altered when administered in combination with aztreonam, they were substantially different than those observed in study DAP-00-02 (daptomycin 6 mg/kg IV q24h for 7 days, n=6 healthy subjects). The mean C_{max} and $AUC_{0-\infty}$ were 1.05-fold and 1.08-fold greater, respectively in study DAP-00-02 when the same dose was administered. The

CL_T, CL_R, and Ae (%) were 1.13-fold, 1.37, and 1.20-fold greater in the current study (DAP-DI-01-01. The reviewer was unable to find an explanation for the difference observed between the two populations of subjects.

SAFETY:

There were no apparent differences in the incidence or types of adverse events when subjects received daptomycin 6 mg/kg plus aztreonam 1,000 mg and when they received each drug alone. Three subjects reported 4 adverse events during the study. Two subjects had 3 adverse events following Treatment B (aztreonam 1,000 mg), and one subject had an adverse event following Treatment C (daptomycin 6 mg/kg plus aztreonam 1,000 mg). None of the subjects experienced an AE following daptomycin alone. Adverse events included dyspepsia, groin pain, rigors, and headache. All of the adverse events were mild in severity and only dyspepsia was judged possibly related to treatment (daptomycin plus aztreonam) by the investigator. There were no deaths or serious adverse events during the study. No subject discontinued due to an adverse event.

CONCLUSIONS:

The 90% confidence intervals of the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ of daptomycin (6 mg/kg IV) and aztreonam (1,000 mg IV) were within the 0.80 to 1.25 range and were not statistically significantly different when administered alone and in combination.

No dosage adjustment of daptomycin or aztreonam is warranted when both agents are administered in combination to patients with infections.

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin [redacted] assay for daptomycin in plasma and urine [redacted] the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the complete study report in the future.

APPEARS THIS WAY
ON ORIGINAL

Effects of Cidecin® (Daptomycin for injection) on the pharmacokinetics and pharmacodynamics of warfarin (Protocol DAP-DIW-01-08)

Dates: March 20, 2002 to May 1, 2002
Clinical site:
Analytical sites:

RATIONALE:
Daptomycin is bound to serum proteins in the range of 87-94%; warfarin is both highly and tightly bound to serum protein (97%). The possibility exists that daptomycin may displace warfarin from plasma protein binding sites, thus increasing the unbound fraction of warfarin and the risk of hemorrhage in subjects receiving anticoagulant therapy. This study was undertaken to detect an effect of daptomycin on the pharmacokinetics and pharmacodynamics of warfarin.

OBJECTIVES:
The objective of this study was to evaluate the effects of daptomycin at steady-state on the single dose pharmacokinetics of the R- and S-warfarin enantiomers and pharmacodynamics of warfarin in healthy subjects.

FORMULATIONS:
Daptomycin 500 mg vial (Cubist Pharmaceuticals, Lot no. 680413A)
Coumadin® (warfarin sodium tablets, USP) 5 mg tablets (DuPont Pharma, Lot no. EPN517A)
Coumadin® (warfarin sodium tablets, USP) 10 mg tablets (DuPont Pharma, Lot no. EOJ331A)

STUDY DESIGN:
This study was a randomized, placebo-controlled, double-blind, single-center, two-way crossover study to evaluate the effects of daptomycin at steady-state on the pharmacokinetics and pharmacodynamics of warfarin. Sixteen healthy adult subjects were enrolled into the study to receive two 9-day intravenous treatment periods (Days 1-9 and Days 17-25) separated by a 7-day washout period. Half of the subjects were randomized to receive intravenous daptomycin (6 mg/kg q24h) during the first treatment period and intravenous 0.9% sodium chloride injection, USP (Normal Saline, NS) vehicle during the second treatment period. The other half of the subjects was randomized to receive NS vehicle during the first treatment period and daptomycin (6 mg/kg q24h) during the second treatment period. All subjects received a single oral dose of warfarin 25 mg (2 × 10 mg tablets + 1 × 5 mg tablet) concurrent with the fifth intravenous dose of each treatment period (Days 5 and 21). Daptomycin infusions were administered over 30 minutes. Warfarin was administered with 240 mL of water. Blood was drawn for determination of PT/INR every day except Days 11-15. On dosing days PT/INR was measured prior to dosing; on Day 5 and Day 21, it was measured prior to dosing and 12 hrs following warfarin administration.

Blood samples for determination of daptomycin concentrations were obtained on Days 4 and 20 at predose, mid-way through the infusion (0.25 hrs), at the end of the infusion (0.5 hrs), and at 1, 1.5, 2, 2.5, 3, 4, 6, 12, and 24 hrs following initiation of the infusion. Blood samples for daptomycin trough concentration were obtained at 24, 48, 72, 96, and 120 hrs on Days 6 through 10 and on Days 22 through 26.

Blood samples for determination of warfarin concentrations were obtained on Day 5 and Day 21 prior to daptomycin administration, mid-way through the infusion (0.25 hrs), at the end of the infusion (0.5 hrs), and at 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24, 48, 72, 96, and 120 hrs following the initiation of drug administration.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Comments
Concentration range	3.00 to 500 µg/mL	Satisfactory
LLOQ		Satisfactory
Linearity		Satisfactory
Accuracy		Satisfactory
Precision		Satisfactory
Specificity	Satisfactory	Satisfactory
Stability		Satisfactory

WARFARIN ASSAY METHODOLOGY:

Criterion	R-warfarin	S-warfarin	Comments
Concentration range	5.00 to 1,000 ng/mL	5.00 to 1,000 ng/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability			Satisfactory

DATA ANALYSIS:

Plasma concentration data for daptomycin and the R- and S-warfarin enantiomers were analyzed by non-compartmental pharmacokinetic methods. The following parameters were determined from the plasma concentration data: the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), AUC for the dosing interval ($AUC_{0-\tau}$), AUC from zero to infinity ($AUC_{0-\infty}$), plasma clearance (CL_T for daptomycin and CL_T/F for warfarin), renal clearance (CL_R), volume of distribution ($Vz = CL/Ke$ for daptomycin and Vz/F for warfarin), volume of distribution at steady state ($V_{SS} = CL \times MRT$ for daptomycin and V_{SS}/F for warfarin), mean residence time (MRT), and terminal elimination half-life ($t_{1/2}$).

PHARMACODYNAMIC ANALYSIS:

The pharmacodynamics of warfarin were analyzed by comparison of the following parameters: the International Normalized Ratio (INR = [subject PT/Control PT]^{ISI}), the maximum baseline corrected INR over the entire sampling phase ($INR_{b,max}$), the mean INR from Day -1 to Day 5 (prior to warfarin dosing, INR_c), INR prior to baseline correction (INR_t), the baseline corrected INR ($INR_b = INR_t - INR_c$), and the area under the corrected baseline INR (AUC_{INRb}).

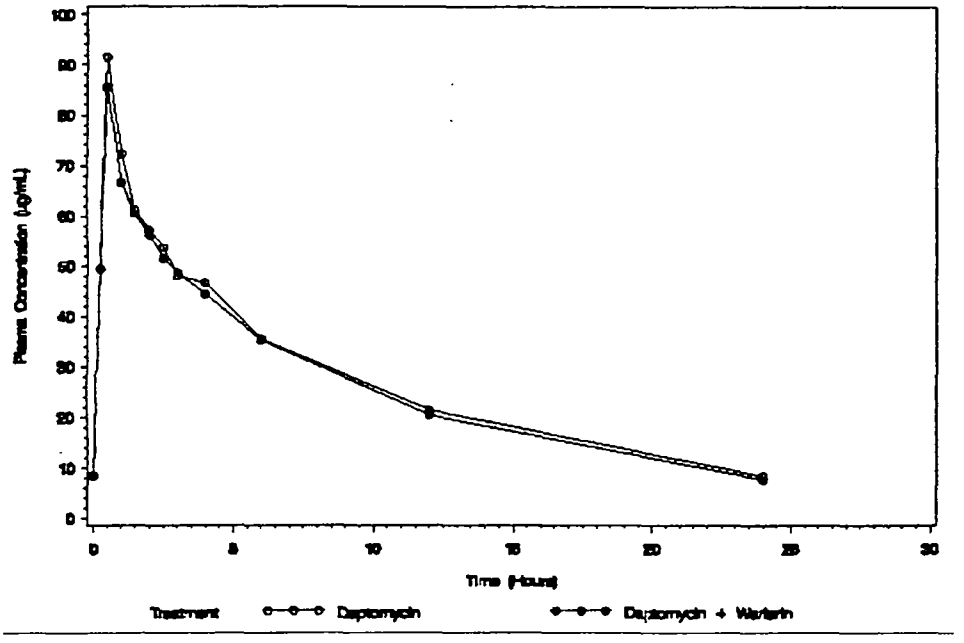
STATISTICAL ANALYSIS:

Pharmacokinetic parameters were summarized as mean, SD, median, and range. The geometric mean ratios and the 90% confidence intervals for daptomycin and R-warfarin and S-warfarin enantiomers pharmacokinetic parameter estimates were also reported.

RESULTS:
Sixteen subjects were enrolled into and completed the study. Most of the subjects were male (75%) and Caucasian (56%). The mean (SD) age, weight, and height of the 16 subjects were 31.2 (8.1) yrs, 71.7 (11.9) kg, and 173 (10) cm, respectively.

The mean plasma concentration-time profiles of daptomycin IV 6 mg/kg q24h on Days 4 and 20 (daptomycin + NS or daptomycin + warfarin) are shown in Figure 1. The mean plasma concentrations of daptomycin were similar when administered alone and in combination with warfarin to healthy subjects.

Figure 1. Mean plasma concentration-time profiles of daptomycin alone and in combination with warfarin



The mean plasma concentration-time profiles of R-warfarin and S-warfarin following a single oral dose of warfarin 25 mg (2 × 10 mg tablets + 1 × 5 mg tablet) alone or in combination with daptomycin IV 6 mg/kg at steady-state are shown in Figures 2 and 3. The mean plasma concentrations of R-warfarin and S-warfarin were both similar when administered alone and in combination with daptomycin to healthy subjects.

The daptomycin, R-warfarin, and S-warfarin pharmacokinetic parameter estimates following the administration of NS or a single dose of warfarin 25 mg to subjects receiving daptomycin IV 6 mg/kg q24h are shown in Table 1. The mean $AUC_{0-\tau}$, C_{max}, V_{SS}, and half-life of daptomycin decreased by 0.04-fold, 0.07-fold, 0.02-fold, and 0.05-fold, respectively, when administered with warfarin. The mean CL_T of daptomycin increased 0.03-fold when administered with warfarin.

Figure 2. Mean plasma concentration-time profiles of R-warfarin alone and in combination with daptomycin

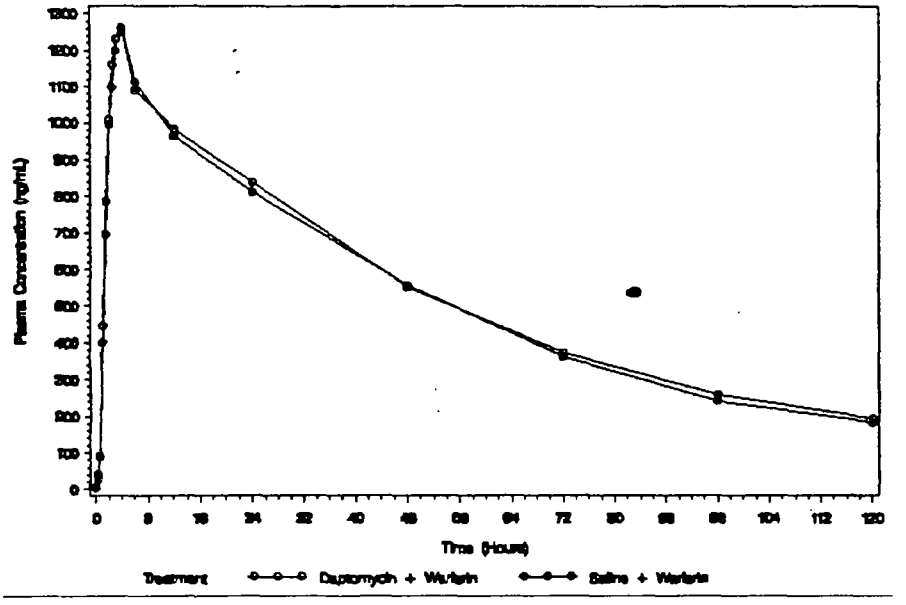
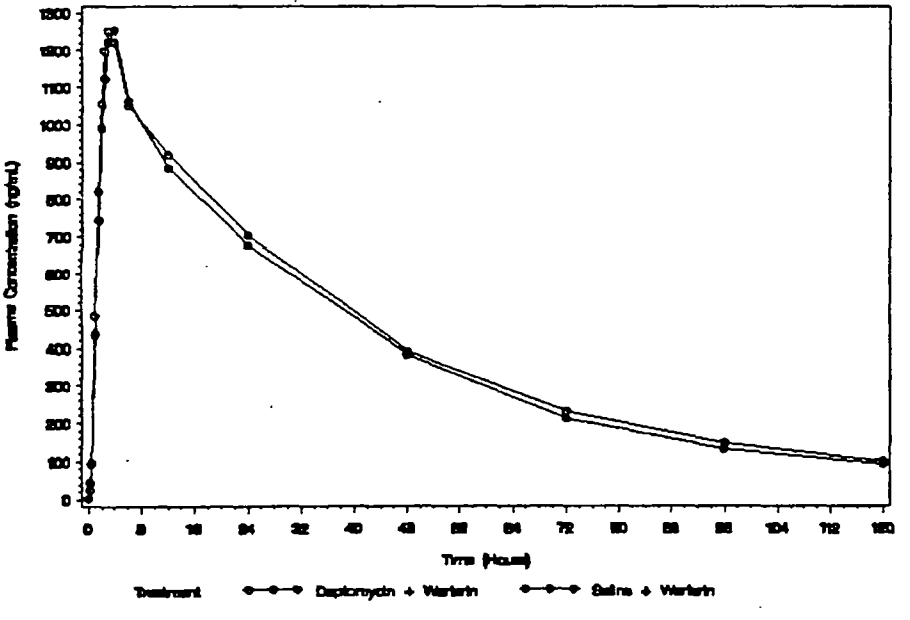


Figure 3. Mean plasma concentration-time profiles of S-warfarin alone and in combination with daptomycin



The mean $AUC_{0-\infty}$, V_{SS}/F, and half-life of R-warfarin increased by 0.04-fold, 0.02-fold, and 0.04-fold, respectively, when administered with daptomycin, whereas the mean C_{max} and CL_T/F of R-warfarin decreased by 0.04-fold and 0.03-fold, respectively when administered with daptomycin.

The mean $AUC_{0-\infty}$ of S-warfarin increased by 0.04-fold when administered with daptomycin, whereas the mean CL_T/F, V_{SS}/F, and half-life of S-warfarin decreased by 0.04-fold, 0.03-fold, and 0.01-fold, respectively when administered with daptomycin. The mean C_{max} of S-warfarin was unchanged.

Table 1. Mean (CV%) daptomycin and warfarin pharmacokinetic parameters alone and administered in combination

	Daptomycin		R-Warfarin		S-Warfarin	
Parameter	Daptomycin	Daptomycin + Warfarin	R-Warfarin	R-Warfarin + Daptomycin	S-Warfarin	S-Warfarin + Daptomycin
AUC_{0-t} (µg*hr/mL)	---	---	62.2 (18%)	63.5 (17%)	47.3 (26%)	49.3 (27%)
$AUC_{0-\tau}$ (µg*hr/mL)	658 (15%)	635 (16%)	---	---	---	---
$AUC_{0-\infty}$ (µg*hr/mL)	764 (18%)	727 (18%)	75.6 (23%)	78.6 (24%)	53.0 (31%)	55.4 (33%)
C_{max} (µg/mL)	91.5 (12%)	85.5 (12%)	1.39 (20%)	1.34 (17%)	1.38 (18%)	1.38 (17%)
T_{max} (hrs)	0.58 (2%)	0.54 (8%)	3.50 (38%)	3.81 (63%)	2.75 (39%)	2.91 (26%)
CL_T (mL/hr/kg)*	9.56 (17%)	9.85 (18%)	5.03 (32%)	4.86 (32%)	7.29 (31%)	7.02 (30%)
Vz (L/kg)	0.10 (10%)	0.10 (12%)	0.33 (17%)	0.33 (16%)	0.38 (16%)	0.36 (19%)
V_{SS} (L/kg)*	0.10 (13%)	0.10 (11%)	0.31 (14%)	0.31 (12%)	0.33 (13%)	0.32 (11%)
Half-life (hrs)	8.56 (13%)	8.14 (14%)	48.2 (20%)	50.2 (24%)	38.1 (24%)	37.7 (22%)

The geometric mean ratios and 90% confidence intervals for daptomycin (daptomycin + warfarin/daptomycin), R-warfarin (warfarin + daptomycin/warfarin), and S-warfarin (warfarin + daptomycin/warfarin) are shown in Table 2. The 90% confidence intervals of the geometric mean ratios for the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were within the predetermined limits of 0.80 to 1.25 for daptomycin and warfarin (S-warfarin and R-warfarin) and were not statistically significantly different. Thus, co-administration of daptomycin and warfarin does not statistically significantly effect the pharmacokinetics of either daptomycin, R-warfarin, or S-warfarin.

Table 2. Geometric mean ratios and 90% confidence intervals for daptomycin, R-warfarin, and S-warfarin administered alone and in combination

	Daptomycin		R-Warfarin		S-Warfarin	
Parameter	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC_{0-t}	---	---	1.0227	1.0001 - 1.0459	1.0402	1.0184 - 1.0626
$AUC_{0-\tau}$	0.9629	0.9415 - 0.9847	---	---	---	---
$AUC_{0-\infty}$	---	---	1.0372	0.9985 - 1.0774	1.0421	1.0150 - 1.0699
C_{max}	0.9350	0.9103 - 0.9604	0.9669	0.8946 - 1.0451	0.9996	0.9469 - 1.0553

Pharmacodynamics:
The mean baseline corrected INR (INR_b) vs. time profiles and mean INR prior to correction (INR_t) vs. time profiles are shown in Figure 4. The results support the absence of a pharmacodynamic interaction between warfarin and daptomycin when a single dose of warfarin is administered with daptomycin at steady-state. The reviewer found no substantial difference between INR vs. time when either the INR_b or INR_t was used.

Stick plots showing the individual maximum INR_t (INR_{tmax}) and maximum INR_b (INR_{bmax}) values when warfarin was administered with daptomycin or NS is shown in Figure 5. The geometric mean ratios (warfarin + daptomycin/warfarin) of INR_{tmax} (left) and INR_{bmax} (right) were both 1.05. The change in individual INR_{tmax} and INR_{bmax} values when warfarin was administered with daptomycin compared to NS ranged from -0.5767 to 0.4634 and -0.5672 to 0.4606 (a negative values depicts a decrease in the INR when warfarin was administered with daptomycin).

Figure 4. Mean baseline corrected INR (INR_b) and mean INR prior to correction (INR_t) vs. time profiles for subjects receiving warfarin + NS and warfarin + daptomycin

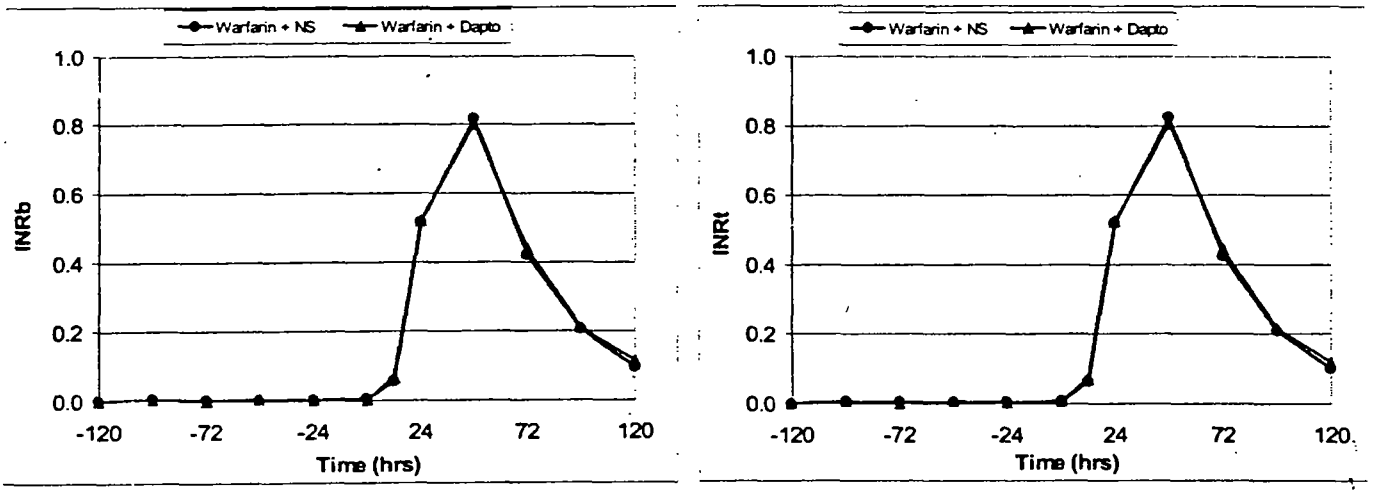
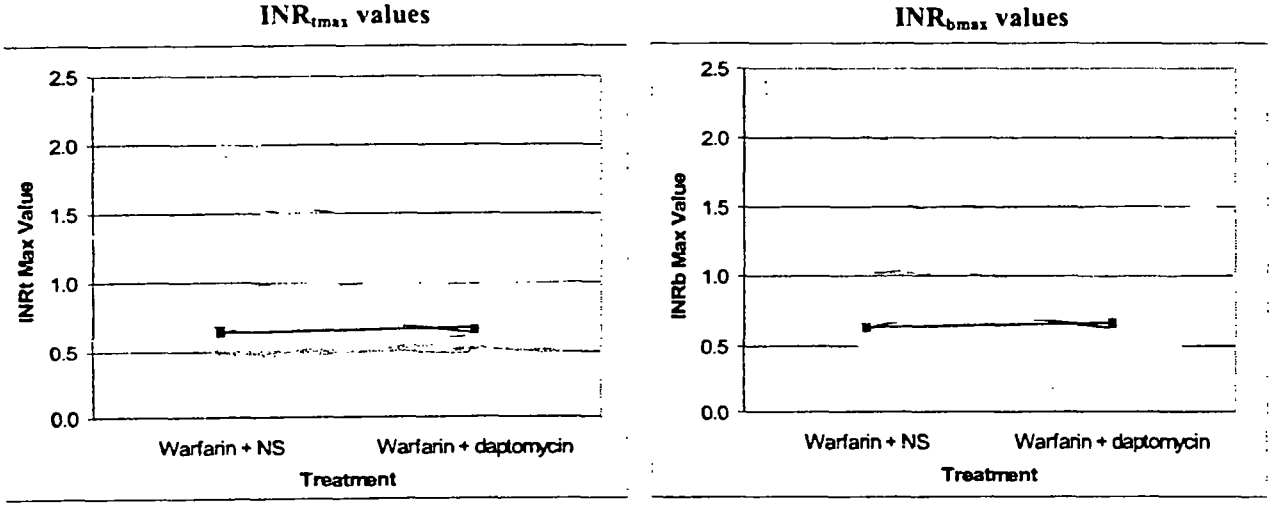
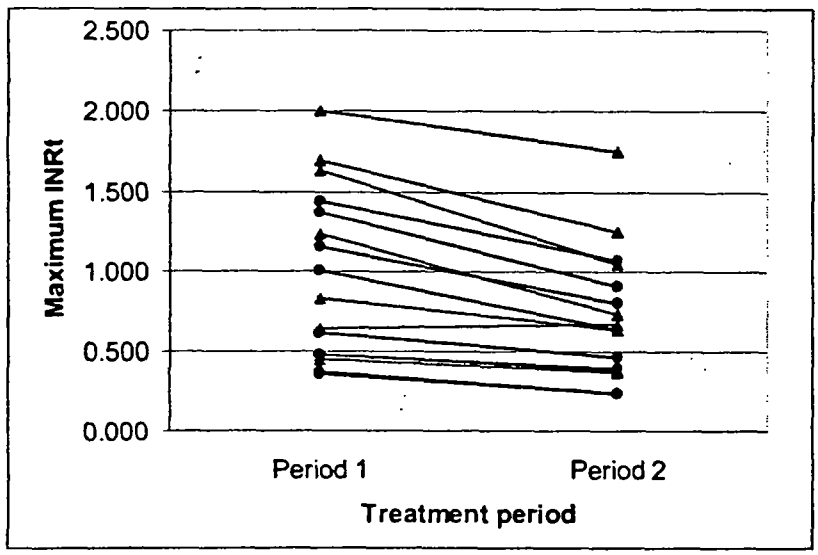


Figure 5. Stick plot demonstrating the individual INR_{tmax} and INR_{bmax} values of warfarin + NS and warfarin + daptomycin (bold red line represents the geometric mean)



The reviewer observed a substantial period effect of the INR_{tmax} and INR_{bmax} values that were independent of the administered treatment (daptomycin vs. NS). As shown in Figure 6, the circles represent subjects who received warfarin + daptomycin in Period 1 and warfarin + NS in Period 2, where the triangles represent subjects who received warfarin + NS in Period 1 and warfarin + daptomycin in Period 2. The INR_{tmax} was greatest Period 1 for 15/16 subjects and greatest in Period 2 for 1/16 subjects receiving NS.

Figure 6. INR_{max} values for Period 1 and Period 2 (▲ = subjects receiving warfarin + NS in Period 1; ● = subjects receiving warfarin + daptomycin in Period 1)



SAFETY:
Twelve of the 16 subjects reported 48 adverse events during the daptomycin + warfarin treatment period; 9 subjects reported 18 adverse events during treatment with vehicle (NS) + warfarin. Of the 48 AEs during treatment with daptomycin + warfarin, 44 were mild in severity and 4 were moderate. Similarly, during NS + warfarin treatment, 15 AEs were mild and 3 were moderate in severity. There were no severe AEs during either treatment period. Five AEs that occurred during the daptomycin + warfarin treatment period were considered possibly treatment related including diarrhea, nausea, fatigue, and headache, which occurred twice in one subject. None of the AEs during NS + warfarin treatment were considered possibly or probably treatment related.

CONCLUSIONS:
The administration of a single dose of warfarin to subjects at daptomycin steady-state does not alter the pharmacokinetic of daptomycin.

Daptomycin does not alter the pharmacokinetics of R-warfarin or S- warfarin when a single dose of warfarin is administered to subjects receiving daptomycin at steady-state.

Although the administration of daptomycin was not associated with an increase in the INR values, a substantial period effect was observed.

Since the impact of daptomycin administration on subjects at steady-state with warfarin was not assessed, the INR should be frequently monitored when daptomycin is administered to subjects who are currently receiving warfarin.

A randomized, double-blind study to evaluate the safety profile of multiple dose Cidecin® (Daptomycin for injection) in subjects on Zocor® (Simvastatin) (Protocol DAP-STAT-01-10)

Dates: January 7, 2002 to February 11, 2002
Clinical site:
Analytical sites:

RATIONALE:
Skeletal muscle has been identified as a primary site of daptomycin toxicity. Elevations in serum CPK concentrations have been associated with daptomycin administration. In addition, elevations in CPK concentrations have a prevalence of 5% to 10% with HMG CoA reductase therapy. Since both drugs can have an effect on skeletal muscle and CPK concentrations, this study was conducted to assess the safety profile of simvastatin with and without daptomycin.

OBJECTIVES:
The primary objective of this study was to evaluate the safety of daptomycin when administered once daily for 14 consecutive days to subjects on a stable daily dose of 40 mg of simvastatin. The secondary objective was to evaluate and compare the trough concentrations of daptomycin with those observed in other daptomycin clinical studies.

FORMULATIONS:
Daptomycin 500 mg vials (Cubist, Lot No. 680413A)
Normal saline (Braun, Lot no. J1P901)
Zocor® (simvastatin) 40 mg tablets (Merck & Co, Inc., Lot no. L1214)

STUDY DESIGN:
This study was a randomized, double-blind, controlled, multiple-dose, in-patient study to assess the safety of daptomycin treatment in adult subjects (≥30 years of age) already on a stable daily dose of 40 mg simvastatin. Twenty subjects were randomized in a 1:1 ratio to receive daptomycin or normal saline (NS) administered intravenously (IV) over approximately 30 minutes, daily for 14 days, at a dose of 4 mg/kg of total body weight. All subjects continued to take a single, oral 40-mg simvastatin tablet once daily in the evening, as recommended in the Zocor® package insert.

At 8:00 PM on Day -1, subjects were given one 40-mg simvastatin tablet with 240 mL water. Subjects were fed a standardized dinner consistent with American Heart Association (AHA) guidelines. On Day 1, subjects were given a standardized breakfast and lunch (consistent with AHA guidelines and without grapefruit or grapefruit juice) at approximately 7:00 AM and 12:00 PM, respectively. At approximately 1:00 PM on Day 1, 4 mg/kg of daptomycin or NS was administered IV over approximately 30 minutes.

Blood samples for the determination of daptomycin and simvastatin trough concentrations were conducted only on Days 1, 5, 9, and 14 one hr prior to daptomycin administration.

A 24-hour urine collection was performed on Day 5 for the calculation of creatinine clearance.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Comments
Concentration range	3.28 to 545 µg/mL	Satisfactory
LLOQ		Satisfactory
Linearity		Satisfactory
Accuracy		Satisfactory
Precision		Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Not stated	Unsatisfactory

SIMVASTATIN ASSAY METHODOLOGY:

Criterion	Simvastatin	Simvastatin Acid	Comments
Concentration range	0.100 to 50 ng/mL	0.100 to 50 ng/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability			Satisfactory

DATA ANALYSIS:

The plasma daptomycin, simvastatin, and simvastatin acid trough concentration data on Days 1, 5, 9, and 14 were analyzed by descriptive statistics.

RESULTS:

Twenty subjects were enrolled and completed the study. The mean (SD) demographic parameters are shown in Table 1. The majority of subjects were Caucasian (7/10 in the daptomycin group, 8/10 in the NS group) an male.

Table 1. Mean (SD) demographics of subjects in the daptomycin and placebo groups

Group	N	Age (yrs)	Weight (kg)	Height (cm)	BMI (kg/m^2)
Daptomycin	2F/8M	51.4 (5.4)	80.7 (10.6)	170.4 (4.2)	27.7 (2.9)
NS	4F/6M	51.8 (8.7)	75.9 (11.6)	167.9 (6.8)	26.9 (3.5)

The individual plasma daptomycin concentrations are shown in Table 2. Trough concentrations of daptomycin were between 3 µg/mL and 7µg/mL for all subjects except Subject 010. The measured creatinine clearance of subject 010 was 93.0 mL/min, whereas the mean (SD) creatinine clearance of all subjects receiving daptomycin was 99.1 (11.2) mL/min and ranged from 86 to 118 mL/min. The effect of co-administration of simvastatin and daptomycin on the pharmacokinetics of daptomycin is unknown since each subject was previously on a stable dose of simvastatin 40 mg daily. In previous studies in which 4 mg/kg was administered, the mean C_{24} ranged from 5.25 to 6.47 µg/mL (Study DAP-00-02) and was less than 3.28 µg/mL (Study DAP-GER-01-11). It ranged from 4.69 to 5.18 µg/mL in the current study and thus, within the ranges reported in other studies.

Table 2. Daptomycin trough concentrations (µg/mL) on Days 1, 5, 9, and 14

Subject	Daptomycin concentration (µg/mL)			
	Day 1	Day 5	Day 9	Day 14
001	BLOQ			
002	BLOQ			
005	BLOQ			
007	BLOQ			
010	BLOQ	BLOQ	BLOQ	3.37
012	BLOQ			
014	BLOQ			
015	BLOQ			
017	BLOQ			
018	BLOQ			
Mean (SD)	—	**5.03 (1.03)**	**5.18 (1.06)**	**4.69 (2.03)**

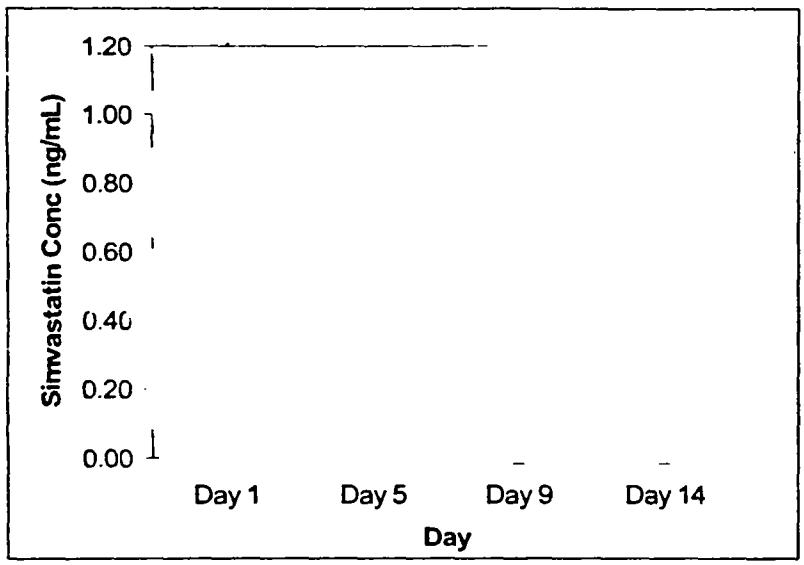
BLOQ - below lower limit of quantitation (= µg/mL)

The mean and geometric mean simvastatin and simvastatin acid plasma trough concentration data are shown in Table 3 for subjects that received daptomycin IV 4 mg/kg q24h or NS (placebo) for 14 days. The mean plasma trough concentration of simvastatin between subjects receiving daptomycin or NS were similar. However, it appears that mean plasma trough concentrations of simvastatin acid decreased following administration of daptomycin or NS and remained below Day 1 concentrations in the daptomycin group to a greater extent than the NS group. Although these observations may represent a decreased production of the active metabolite (simvastatin acid) when simvastatin is administered with daptomycin, the observations are based on plasma trough concentrations only and may not reflect accurate changes in the 24 hr AUC.

Table 3. Mean (SD) and geometric mean (range) plasma simvastatin and simvastatin acid trough concentration data on Days 1, 5, 9, and 14 for subjects receiving daptomycin or NS

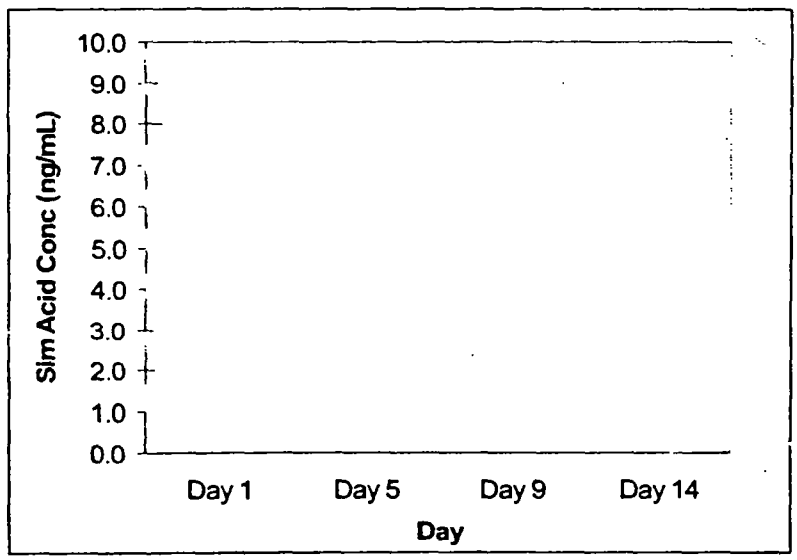
Analyte	Concentration (ng/mL)			
	Day 1	Day 5	Day 9	Day 14
Mean (SD)				
Simvastatin				
Daptomycin Group	0.35 (0.17)	0.34 (0.22)	0.42 (0.29)	0.38 (0.23)
NS Group	0.42 (0.31)	0.41 (0.20)	0.52 (0.32)	0.43 (0.16)
Simvastatin Acid				
Daptomycin Group	2.68 (1.60)	1.06 (0.85)	1.97 (1.52)	2.04 (2.86)
NS Group	2.42 (2.62)	1.42 (2.34)	2.40 (2.53)	2.05 (2.37)
Geometric Mean				
Simvastatin				
Daptomycin Group	0.31	0.28	0.34	0.32
NS Group	0.33	0.36	0.43	0.40
Simvastatin Acid				
Daptomycin Group	2.31	0.88	1.46	1.12
NS Group	1.67	0.76	1.65	1.28

Figure 1. Stick plots of simvastatin (top) and simvastatin acid (bottom) plasma trough concentrations on Days 1, 5, 9, and 14 for subjects receiving daptomycin (circles) or NS (triangles)



Simvastatin

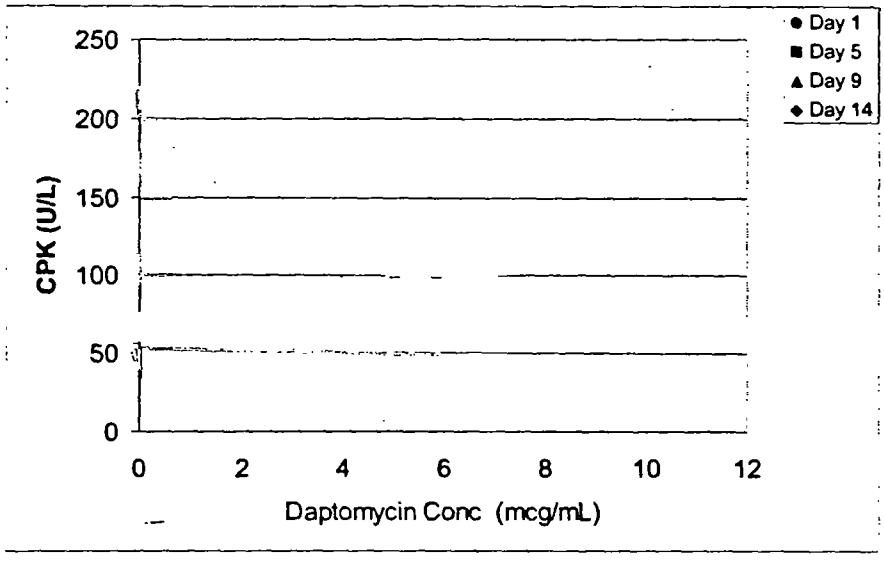
Note: concentrations depicted as zero are below the lower limit of quantitation



Simvastatin Acid

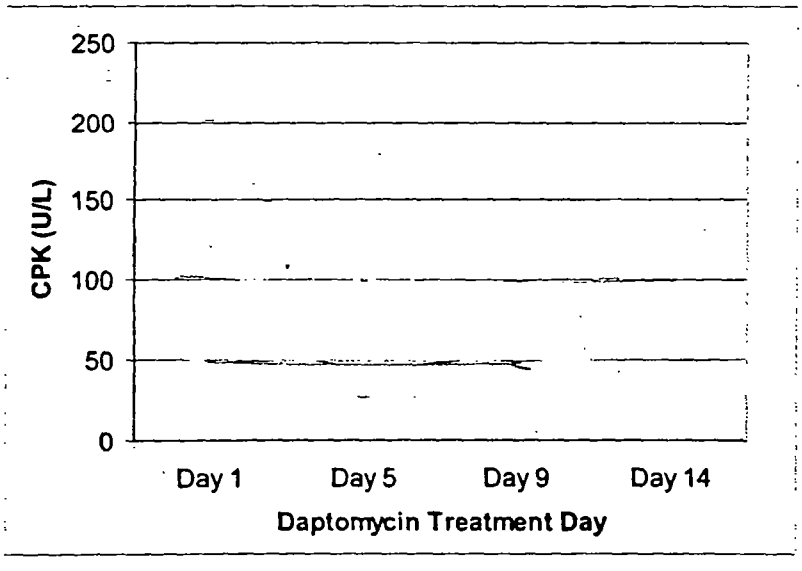
The reviewer assessed the relationship between the plasma daptomycin trough concentration and the CPK concentration (U/L) on Days 5, 9, and 14 (see Figure 2). There was no apparent relationship between daptomycin trough concentration and CPK concentration. None of the CPK values exceeded the upper limit of normal. Subject 012 had CPK values of 204, 213, 229, and 235 U/L on Days 1, 5, 9, and 14. The CPK value on Day 1 (prior to daptomycin administration) exceeded all other CPK values on that day.

Figure 2. Relationship between plasma daptomycin trough concentration and CPK concentration on Days 1, 5, 9, and 14



The reviewer also assessed the variability in CPK concentrations over 14 days for subjects receiving daptomycin and NS. As shown in Figure 3, CPK concentrations remained below the upper limit of normal over 14 days of daptomycin administration. The CPK values for subject 012 (daptomycin group) was 204 U/L on Day 1 and steadily increased to 235 U/L on Day 14. The CPK values for Subject 015 (daptomycin group) was 164 U/L on Day 1 and decreased to 120 U/L on Day 5. The CPK concentrations for the other subjects remained relatively constant over the course of the study.

Figure 3. CPK concentrations Days 1, 5, 9, and 14 for subjects receiving daptomycin (circles) and NS (triangles)



SAFETY:
One subject in the daptomycin group experienced hypertension (Subject 002) and another experienced hypertension and hyperglycemia (Subject 007). Subject 002 had no history of hypertension and his blood pressure at baseline was 134/78. This subject's blood pressure was 158/100 mmHg 8 hrs after infusion of daptomycin on Day 9 and resolved on Day 13. The AE was mild in severity and considered not related to study drug treatment by the investigator.

Subject 007 had a history of hypertension and was receiving fosinopril sodium and clonidine as therapy; he was also a type II diabetic receiving insulin (Humulin N and Humulin R). His blood pressure at baseline was 140/82. This subject's blood pressure was 152/90 mmHg pre-dose on Day 2 when the AE started and resolved on Day 5. These two AEs were mild in severity. Hypertension was considered possibly treatment related and hyperglycemia was not.

One subject each in the normal saline group (Subject 006) experienced hyperglycemia, dizziness (Subject 013), and cellulitis of the right hand (Subject 020). The three events were mild in severity. Dizziness was considered possibly treatment related and cellulitis and hyperglycemia were not related.

CONCLUSIONS:
Co-administration of daptomycin IV 4 mg/kg q24h for 14 days and simvastatin 40 mg daily was not associated with a higher incidence of adverse events than co-administration of normal saline and daptomycin.

CPK concentrations on Days 5, 9, and 14 did not appear to be associated with plasma daptomycin trough concentrations in subject receiving simvastatin 40 mg daily.

COMMENTS:
1. The sponsor has not provided data to support the stability of the daptomycin — assay for daptomycin in plasma ,
· stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the complete study report in the future.

A randomized, double-blind, placebo-controlled assessment of peripheral nerve function and cardiac repolarization in normal volunteers administered daptomycin intravenously once daily for 14 days (Protocol DAP-QTNC-01-06)

Dates: November 29, 2001 to March 7, 2002
Clinical site: [redacted]

RATIONALE:
Since pre-clinical studies have shown the possibility of muscle and peripheral nerve effects with daptomycin administration, the current study was undertaken to address the safety profile of daptomycin using formal neurophysiological testing of motor and sensory nerves using objective and subjective methods. The study was also designed to assess the development of daptomycin-induced effects on the cardiac action potential.

OBJECTIVES:
The primary objective of this study was to assess peripheral nerve function and cardiac repolarization in normal volunteers who were administered either intravenous (IV) daptomycin 6 mg/kg or 0.9% sodium chloride for injection, USP (NS) once every 24 hours for 14 consecutive days. The secondary objective was to assess the overall safety and tolerability of IV daptomycin 6 mg/kg administered once every 24 hours for 14 consecutive days to normal volunteers.

FORMULATIONS:
Daptomycin 500 mg vial (Cubist Pharmaceuticals, Lot no. 680413A)

STUDY DESIGN:
This study was a randomized, placebo-controlled, double-blind, single-center study to assess and compare peripheral nerve function and cardiac repolarization in normal adult volunteers administered either IV daptomycin 6 mg/kg or NS once every 24 hours for 14 consecutive days. Half of the subjects were to be between 30 and 49 years old and half between 50 and 65 years old, with equal percentages of men and women in both dosing groups. Subjects received either IV daptomycin 6 mg/kg in 50 mL of NS, or 50 mL of NS control, once every 24 hours over approximately 30 minutes for 14 consecutive days.

On the day prior to dosing (Day -1), before administration on Day 14, and two weeks after the end of the 14-day treatment period (Day 28 subjects underwent a battery of assessments to quantify peripheral nerve function. The battery consisted of three parts:

1) Electrophysiological measurement of the median nerve motor function (distal motor latency [DML], amplitude of the compound muscle action potential [CMAP], and F-wave latency) of the non-dominant hand. All electrophysiological data were recorded using the [redacted] combined with a median nerve biosensor.

2) Vibratory perception thresholds to assess large fiber sensory nerve function (VPT) were tested in the non-dominant great toe using the [redacted]

3) Completion of an unvalidated neurological questionnaire (the Symptoms and Functional Deficits Questionnaire). The questionnaire consisted of 20 questions, each scored on a 0-4 scale (0=not present and 4=most severe deficit). Questions were designed to assess distal sensory and motor function in both the hands and feet, as well as on difficulties in everyday activities known to be early manifestations of neuropathy or myopathy.

Subjects also had 12-lead ECG tracings recorded at various time points (pre-dose, 30, 60, and 90 min and 2, 6, and 12 hrs after the end of infusion of study drug) on Days -1, 1, and 7. A single ECG was obtained at 24 hrs on Day 1 and 7. A series of eight ECGs were recorded over a 24-hour period. A single ECG was recorded at pre-dose on Day 14. In order to control for diurnal variation and drug effect on the QT interval, the ECGs were recorded at specific times relative to the 24-hour clock and end of infusion of the test article. In addition, ECGs were not collected within 2 hours of meals in order to control for post-prandial effects. QT interval measurements were corrected for heart rate using Bazett's correction factor.

Blood samples for determination of daptomycin plasma concentration were obtained at 30 min and 6 hrs after the end of infusion on Day 1 and Day 7 as well as pre-dose on Day 2 and Day 7.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Comments
Concentration range	3.28 to 545 µg/mL	Satisfactory
LLOQ		Satisfactory
Linearity		Satisfactory
Accuracy		Satisfactory
Precision		Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Not stated	unsatisfactory

DATA ANALYSIS:
The QTc interval was corrected for heart rate using Bazett's (QTc) correction factor ($QTc = QT/[RR]^{1/2}$). The change in the QTc interval (Δ QTc) from baseline was calculated using the pre-dose QTc value at baseline as well as using the time-corresponding QTc value at baseline to account for diurnal variation.

STATISTICAL ANALYSIS:
Differences across treatment groups for each of the continuous neurologic endpoints (i.e., DML, F-wave latency, CMAP, QST, Symptoms and Deficits) were analyzed with rank analysis of covariance (ANCOVA), while, between treatment groups differences in frequency of abnormal values were analyzed with a nonparametric logistic regression (e.g., Wald Test). Regression models included as covariates any demographic characteristic (e.g., age, gender, race) that differed between treatment groups at baseline. Change from baseline analyses also included the baseline assessment as a covariate. Alpha levels were set at 0.05.

RESULTS:
A total of 120 subjects were enrolled and 115 subjects completed the study. Four subjects in the daptomycin group discontinued due to elevated CPK values (n=2), the development of facial Bell's palsy (n=1), or withdrew consent on Day 11 (n=1). One subject in the NS group discontinued due to elevated CPK values. The mean (SD) demographics of the 120 subjects enrolled in the daptomycin and NS treatment groups are shown in Table 1. There were no statistically significant differences between the daptomycin and NS groups with regard to mean age, sex, or race.

Table 1. Mean (SD) demographics by treatment group

Group	N	Age (yrs)	Weight (kg)	Height (cm)	CL_{CR} (mL/min)
Daptomycin	30M/30F	47.1 (8.1)	73.3 (9.1)	165.0 (8.5)	86.6 (13.0)
NS	30M/30F	47.7 (9.0)	73.9 (8.6)	165.2 (8.8)	85.1 (12.7)

Distal Median Motor Latency (DML)

The DML is principally sensitive to the slowing of conduction in distal motor neurons due to either demyelination or axonopathy. The measure is an absolute latency (msec), but it reflects maximal conduction velocity in the largest myelinated axons innervating the abductor pollicis brevis muscle of the hand. An increase in DML provides objective evidence for an induced neuropathy.

The mean (SD) DML values are shown in Table 2. The DML were similar at baseline, Day 14, and Day 28 for either group. No statistically significant differences were observed in a comparison of change from baseline.

Table 2. Mean (SD) DML score (msec) at baseline, Day 14, and Day 28 for subjects receiving daptomycin IV 6 mg/kg × 14 days or placebo (based on the ITT population)

Assessment	N	Daptomycin	N	NS	p-value
Baseline	56	3.50 (0.43)	59	3.51 (0.38)	0.675
Day 14					
Actual	56	3.47 (0.38)	60	3.49 (0.41)	
Δ from baseline	56	-0.034 (0.197)	60	-0.051 (0.185)	0.692
Day 28					
Actual	56	3.48 (0.43)	60	3.48 (0.38)	
Δ from baseline	56	-0.025 (0.181)	60	-0.051 (0.204)	0.639

At baseline, five subjects in the daptomycin group and 4 subjects in the NS group demonstrated a DML in the abnormal range (>97.5th percentile of data provided by the instrument manufacturer) but not significantly different across groups. At Day 14, the number of subjects demonstrating an abnormal DML in the NS group (n=8) was more than double the number in the daptomycin group (n=3). None of the differences were statistically significant ($p \geq 0.207$). A review of the 8 subjects in the NS group found that none of these subjects had abnormal F-wave latency or CMAP amplitude at the same time point (Day 14).

F-Wave Latency

The F-wave latency is a measure that includes conduction in both the distal and proximal portions of the median nerve. The measure of latency at the muscle is principally sensitive to slowing in conduction, induced by changes in myelin and axon integrity. The F-wave may be sensitive to early signs of neuropathy; it is insensitive to the effects of a myopathy. An increase in the F-wave latency provides evidence for an induced neuropathy.

The mean values for the F-wave latency demonstrated small changes across time points for either group (Table 3). A comparison of change from baseline values revealed no statistically significant differences across groups.

Table 3. Mean (SD) F-wave latency (msec) at baseline, Day 14, and Day 28 for subjects receiving daptomycin IV 6 mg/kg × 14 days or placebo (Based on the ITT population)

Assessment	N	Daptomycin	N	NS	p-value
Baseline	56	27.1 (2.34)	59	27.0 (2.10)	0.805
Day 14					
Actual	56	26.8 (2.29)	59	26.9 (1.78)	
Δ from baseline	56	-0.325 (1.256)	59	-0.144 (1.741)	0.300
Day 28					
Actual	56	27.3 (2.55)	59	27.1 (1.79)	
Δ from baseline	56	0.213 (1.913)	59	0.095 (1.606)	0.759

At baseline, the incidence of abnormal F-wave latencies (>97.5th percentile of data provided by the instrument manufacturer) was elevated in the daptomycin group (n=4) relative to the NS group (n=2). Similar differences were evident at Day 14 (n=2 for the daptomycin group, n=1 for the NS group) and Day 28 (n=5 for the daptomycin group, n=2 for the NS group). However, none of the differences were statistically significant (p ≥0.264).

Compound Muscle Action Potential (CMAP) Amplitude (mV)

The CMAP amplitude reflects the summation of nearly synchronous action potentials evoked in a muscle following supramaximal stimulation of the associated nerve. The amplitude of the CMAP is principally sensitive to the number and synchrony of activated motor neurons, the integrity of neuromuscular transmission, and the density of innervated muscle fibers. Because this endpoint is affected by both muscle and nerve, an evoked change in CMAP amplitude could be due to a neuropathy, a myopathy or a combination. However, a change in CMAP amplitude in the absence of slowing of DML from the same motor nerve provides strong evidence for a primary myopathy. A lower CMAP value indicates a worse deficit.

The mean values for the CMAP amplitude measure demonstrated small changes across time points for both groups as shown in Table 4. A comparison of change from baseline values revealed no statistically significant differences across groups.

Table 4. Mean (SD) compound muscle action potential amplitude (mV) at baseline, Day 14, and Day 28 for subjects receiving daptomycin IV 6 mg/kg × 14 days or placebo (Based on the ITT population)

Assessment	N	Daptomycin	N	NS	p-value
Baseline	56	1.21 (0.38)	59	1.19 (0.44)	0.584
Day 14					
Actual	56	1.27 (0.44)	60	1.19 (0.41)	
Δ from baseline	56	0.053 (0.348)	59	0.005 (0.328)	0.274
Day 28					
Actual	56	1.17 (0.37)	60	1.25 (0.53)	
Δ from baseline	56	-0.043 (0.304)	59	0.066 (0.386)	0.139

At baseline, one subject in the NS group had an abnormal CMAP value. At Day 14, two subjects had abnormal values (n=1 for the daptomycin group, n=1 for the NS group) and four subjects had abnormal value on Day 28 (n=1 for the daptomycin group, n=3 for the NS group). None of the differences were statistically significant (p ≥0.619).

Vibratory Perception Threshold (VPT)

The VPT provides a direct measure of sensory perception. The VPT is a semi-objective measure since it requires the subject's active participation, but it is a sensitive index of distal sensory neuropathies affecting larger diameter axons. This measure is entirely insensitive to myopathy. A higher value is indicative of worse deficit.

The mean values for VPT amplitude were similar groups at baseline and subsequent time points as shown in Table 5. Although the inter-subject variability was large, a comparison of change from baseline values revealed no statistically significant differences across groups.

Table 5. Mean (SD) compound muscle action potential amplitude (mV) at baseline, Day 14, and Day 28 for subjects receiving daptomycin IV 6 mg/kg × 14 days or placebo (Based on the ITT population)

Assessment	N	Daptomycin	N	NS	p-value
Baseline	58	3.48 (1.78)	60	3.36 (1.57)	0.968
Day 14					
Actual	58	3.55 (1.69)	60	3.26 (1.49)	
Δ from baseline	58	0.07 (0.830)	60	-0.11 (0.699)	0.214
Day 28					
Actual	58	3.46 (1.76)	60	3.19 (1.48)	
Δ from baseline	58	-0.02 (0.785)	60	-0.17 (1.017)	0.461

Numerous VPT abnormalities (>97.5th percentile) were present in both groups at all time points. The number of subjects in the daptomycin group with abnormal VPT values at baseline, Day 14, and Day 28 were 18, 16, and 14, respectively. The number of subjects in the NS group with abnormal VPT values at baseline, Day 14, and Day 28 were 16, 15, and 13, respectively. However, the number of subjects with abnormal VPT values between the two groups were not statistically significantly different ($p \geq 0.686$).

Questionnaire for Symptoms and Functional Deficits

The 20 questions included in this measure were intended to focus on distal sensory and motor function in both the hands and feet, as well as on difficulties in everyday activities known to be early manifestations of neuropathy or myopathy. Analysis parameters were created from the questionnaire to assess the Total Score (sum of all 20 questions), Neuropathy Measures (sum of scores on the subset of items most likely related to the presence of a neuropathy), and Myopathy Measures (sum of scores on the subset of items most likely related to the presence of a myopathy).

Out of a possible score of 80, the mean scores ranged from 0.4 to 1.8 across treatment groups and time points. Total Scores at baseline ranged from 0 to 12 with means (SD) of 0.7 (1.42) and 1.1 (2.31) in the daptomycin and NS groups, respectively. Four subjects (1 in the daptomycin group and 3 in the NS group) reported Total Scores of 6 or more at baseline.

The mean changes in Total Score from baseline revealed only one statistically significant difference ($p = 0.024$) that occurred at Day 28 with scores in the daptomycin group showing a greater increase from baseline than scores in the NS group (see Table 6). The mean change in the subset of questions that were most consistent with neuropathy demonstrated a statistically significant difference between groups at Day 28. There are no statistically significant differences with the findings for the subset of questions most consistent with myopathy.

The original criterion specified in the Statistical Analysis Plan defined an abnormal score as a change from baseline of 2 or more in at least 2 out of 20 questions. Three subjects in the daptomycin group had

an abnormal finding in the Total Score on Day 14 and Day 28, compared to no subjects in the NS group. An additional blinded evaluation using an even more conservative post hoc scoring system identifying all subjects with a total score elevation of 4 or more (without regard to how the values were distributed across the 20 questions) was performed. A total of 8 subjects in the daptomycin group and 5 subjects in the NS group met this new criterion on either Day 14 or Day 28. The results of this analysis are shown in Table 7.

Table 6. Mean (SD) symptoms and deficits total score at baseline, Day 14, and Day 28 (Based on the ITT population)

Symptoms and Deficits Total Score					
Assessment	**N**	**Daptomycin**	**N**	**NS**	**p-value**
Baseline	59	0.7 (1.42)	60	1.1 (2.31)	0.513
Day 14					
Actual	59	1.8 (3.97)	60	0.9 (1.66)	
Δ from baseline	59	1.1 (3.40)	60	-0.2 (2.11)	0.154
Day 28					
Actual	59	1.5 (3.70)	60	0.4 (0.96)	
Δ from baseline	59	0.7 (3.64)	60	-0.6 (2.27)	0.024
Symptoms and Deficits Questions Consistent With Neuropathy					
Baseline	59	0.4 (0.99)	60	0.5 (1.10)	0.982
Day 14					
Actual	59	1.0 (2.26)	60	0.4 (0.93)	
Δ from baseline	59	0.6 (2.35)	60	-0.1 (1.02)	0.109
Day 28					
Actual	59	1.0 (2.26)	60	0.3 (0.61)	
Δ from baseline	59	0.5 (2.28)	60	-0.2 (0.98)	0.048
Symptoms and Deficits Questions Consistent With Myopathy					
Baseline	59	0.2 (0.66)	60	0.3 (0.69)	0.419
Day 14					
Actual	59	0.4 (1.35)	60	0.2 (0.89)	
Δ from baseline	59	0.2 (1.32)	60	-0.1 (0.74)	0.173
Day 28					
Actual	59	0.4 (1.13)	60	0.1 (0.33)	
Δ from baseline	59	0.2 (1.30)	60	-0.2 (0.75)	0.164

Although the sponsor's blinded reviewer stated that there was no clear, consistent evidence for a treatment-related increase in either treatment group in the incidence of symptoms or deficits using either the a priori or post hoc definition of abnormal values, it appears to the reviewer that subjects in the daptomycin group had more abnormal findings than subjects in the NS group. However, the statistical significance of these findings is not known.

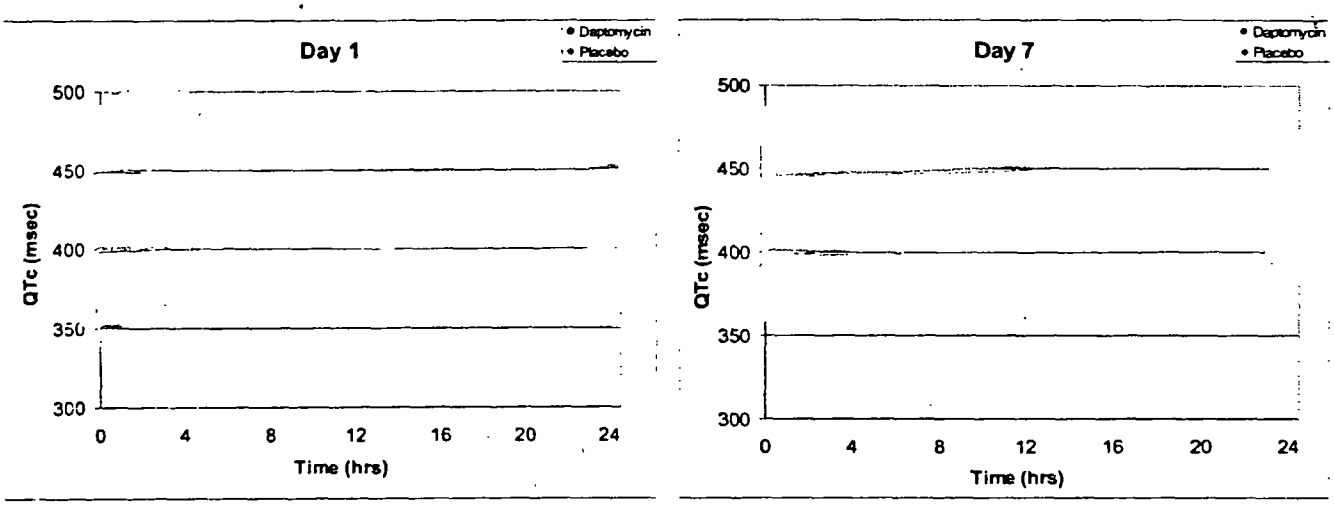
Table 7. Distribution of elevated symptoms/deficits (change of 1 or more) by subject at any time during follow-up in subjects with change from baseline in Total Score of 4 or more

	Daptomycin Group Subjects								NS Group Subjects				
Symptom	**#9**	**#27**	**#30**	**#67**	**#78**	**#90**	**#95**	**#98**	**#28**	**#61**	**#69**	**#85**	**#109**
Neuropathy	3	4	1	5	5	4	4	3	1	0	1	0	1
Myopathy	0	3	0	3	4	4	0	0	1	2	0	1	1
Neuropathy/ Myopathy	1	0	1	3	3	1	1	1	1	0	0	0	2
Total Symptoms	**4**	**7**	**2**	**11**	**12**	**9**	**5**	**4**	**3**	**2**	**1**	**1**	**4**

ECG Measurements

The QTc values (using Bazett's correction factor) following the administration of daptomycin IV 6 mg/kg or NS infused over 30 min for all subjects on Day 1 and Day 7 are shown in Figure 1. Based on the Committee for Proprietary Medicinal Products (CPMP) Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular medicinal Products criteria for male and female subjects, the QTc interval was prolonged (>450 msec for males and >470 msec for females) for numerous subjects receiving daptomycin and NS. In the daptomycin group, the QTc interval was prolonged for 15 male (3.6%) and 12 female (2.9%) subjects at baseline, 7 male (1.5%) and 8 female (1.7%) subjects on Day 1, and 7 male (1.5%) and 7 female (1.5%) subjects on Day 7. In the NS group, the QTc interval was prolonged for 7 male (1.7%) and 12 female (2.9%) subjects at baseline, 8 male (1.7%) and 5 female (1.0%) subjects on Day 1, and 2 male (0.4%) and 10 female (2.1%) subjects on Day 7. The range of QTc values was similar between subjects receiving daptomycin and NS. There were no statistically significant differences in the mean QTc values at any time point.

Figure 1. Individual QTc values by treatment group on Day 1 (left) and Day 7 (right) at pre-dose, 0.5, 1, 1.5, 2, 6, 12, and 24 hrs for daptomycin and NS groups



The Δ QTc values corrected for baseline (using the corresponding time at baseline) are shown in Figure 2. In the daptomycin group, the Δ QTc was 30-60 msec for 12 subjects (2.9%) on Day 1 and 14 subjects (3.4%) on Day 7. The Δ QTc exceeded 60 msec for one subject on Day 1 (at 2 hrs) and no subjects on Day 7. In the NS group, the Δ QTc was 30-60 msec for 13 subjects (3.1%) on Day 1 and Day 7. The QTc exceeded 60 msec for no subjects on Day 1 and two subjects on Day 7 (at pre-dose and 12h hrs). There were no statistically significant differences between the treatment groups with respect to mean change from baseline. The mean and median Δ QTc values for daptomycin and NS on Days 1, 7 and 14 are shown in Table 8.

The reviewer also calculated the Δ QTc values corrected using the pre-dose baseline only. In the daptomycin group, the Δ QTc was 30-60 msec for 20 subjects at baseline, 16 subjects on Day 1, and 23 subjects on Day 7. The Δ QTc exceeded 60 msec for one subject at baseline and no subjects on Day 1 or Day 7. In the NS group, the Δ QTc was 30-60 msec for 25 subjects at baseline, 20 subjects on Day 1, and 20 subjects and Day 7. The QTc exceeded 60 msec for no subjects at baseline, one subject on Day 1, and no subjects on Day 7.

The reviewer assessed the relationship between plasma daptomycin concentration and Δ QTc corrected for baseline using the corresponding time at baseline. The relationship between Δ QTc and plasma concentration is shown in Figure 3. There was no apparent relationship between daptomycin plasma concentration and Δ QTc. In addition, there appeared to be no relationship between Δ QTc and day of assessment (Day 1 or Day 7) as well as the time of assessment on each day (0.5 hrs or 6 hrs post infusion).

Figure 2. Individual Δ QTc values by treatment group on Day 1 (left) and Day 7 (right) at pre-dose, 0.5, 1, 1.5, 2, 6, 12, and 24 hrs for daptomycin and NS groups

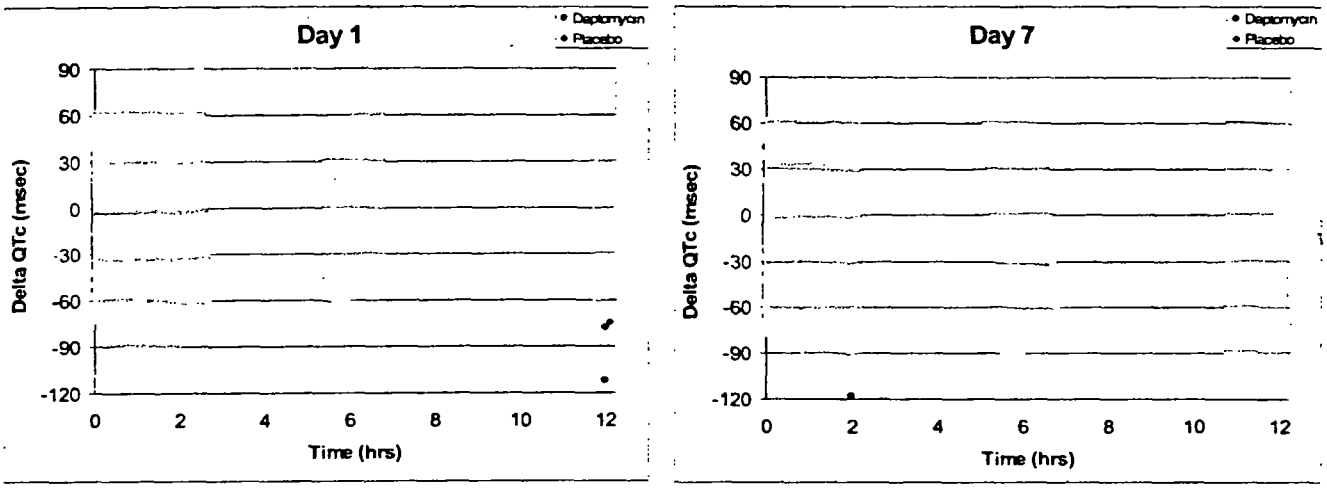


Figure 3. Individual Δ QTc values vs. daptomycin plasma concentration on Day 1 and Day 7 (Δ QTc corrected for baseline using the corresponding time at baseline)

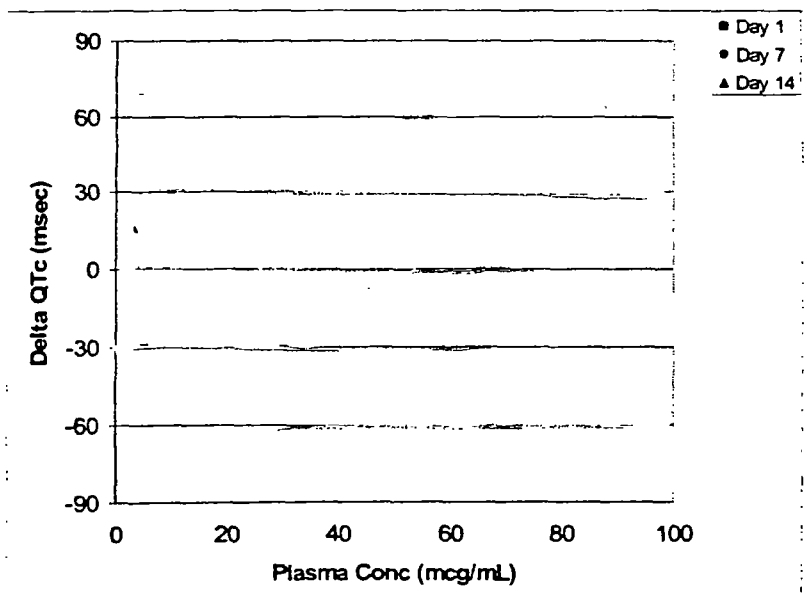


Table 8. Median (range) Δ QTc values (corrected for baseline using the corresponding time at baseline) for daptomycin and NS on Days 1, 7, and 14

	Daptomycin	NS
Day 1		
pre-dose	-3	-6
0.5 hrs	-8	-2
1 hrs	-8	-6
1.5 hrs	-9	-9
2 hrs	-11	-11
6 hrs	-6	-7
12 hrs	-5	-3
Day 7		
pre-dose	-5	-6
0.5 hrs	-5	1
1 hrs	-4	-5
1.5 hrs	-9	-9
2 hrs	-2	-6
6 hrs	-2	-4
12 hrs	-4	2
Day 14		
pre-dose	5	3

SAFETY:

Three subjects were discontinued from the study due to elevated CPK concentrations. Subject 115 was a 57 year-old Black female randomized to daptomycin with CPK values within the normal range on Day 3 and Day 7. CPK values were elevated above normal beginning on Day 10 (1098 U/L), reaching 14,693 on Day 13. Study medication was discontinued on Day 13 after the subject received 13 doses. Additional testing on Day 14 showed that the CPK isoenzymes were entirely from skeletal muscle (MM band isoenzyme = 100 %; BB isoenzyme band = 0%; MB isoenzyme band = 0%).

Subject 118 was a 51 year-old Caucasian female randomized to daptomycin with CPK values on Day 3 and Day 7 within the normal range. CPK values were elevated above normal beginning on Day 10, reaching a maximum of 1940 U/L on Day 14. The study medication was discontinued on Day 13 after the subject had received a total of 13 doses.

Subject 117 was a 53 year-old Caucasian female randomized to normal saline with CPK values on Day 3 and Day 7 within the normal range. CPK values were elevated above normal beginning on Day 10 (4439 U/L), reaching a high of 11,430 U/L on Day 14. Study medication was discontinued on Day 13 after the subject had received a total of 13 doses.

CONCLUSIONS:

Based upon the results of assessments to quantify peripheral nerve function (distal motor latency, amplitude of the compound muscle action potential, F-wave latency, and vibratory perception thresholds to assess large fiber sensory nerve function), there were no significant differences in mean values for these measures and no consistent pattern of incidence across groups.

Daptomycin administration was associated with an increase in the number of affirmative responses to the neurological questionnaire. However, there were no statistically significant or clinically meaningful differences in the set of objective measures defined in the statistical analysis plan as the primary evidence of a sensory neuropathy, in the pattern of adverse events, or in laboratory findings.

There were no statistically or clinically significant differences in the mean QTc values or mean change from baseline (Δ QTc) at any time point on any treatment day.

The proportion of subjects with increases in Δ QTc of 30-60 msec or >60 msec did not differ between the daptomycin and NS (negative control) treatment groups.

There appears to be no apparent temporal relationship to administration of study drug (Day 1 vs. Day 7) or time of sampling to an increase in Δ QTc among subjects receiving daptomycin or placebo (NS).

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin [redacted] assay for daptomycin in plasma and urine. [redacted] the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the complete study report in the future.

2. In the current study, the sponsor compared the QTc interval as well as the QTc interval corrected for baseline (Δ QTc) using daptomycin (active-treatment) and NS (negative-control). Although the sponsor did not include a positive-control to substantiate prolongation of the QTc interval when corrected for baseline, the lack of any statistically significant and clinically significant difference between daptomycin and NS reduces the need for a positive-control in order to interpret a positive response.

An open-label, phase I study to assess the pharmacokinetics and concentration of Cidecin® in cantharides-induced skin blisters following intravenous infusion of a single 4 mg/kg dose in healthy volunteers (Protocol DAP-00-04)

Dates: August 15, 2000 to September 6, 2000
Clinical site: Department of Medical Microbiology, City Hospital NHS Trust, Birmingham, UK
Analytical site: Department of Medical Microbiology, City Hospital NHS Trust, Birmingham, UK
[daptomycin plasma, inflammatory fluid, and urine concentrations]

RATIONALE:
This study was performed to evaluate the concentration of daptomycin in blister fluid and plasma as well as provide an indication of the tissue penetration of daptomycin relative to plasma concentrations.

OBJECTIVES:
The objectives of this study were 1) to assess the pharmacokinetics and concentrations of daptomycin in cantharides-induced skin blisters over a period of 24 hrs after intravenous infusion of a single 4 mg/kg dose in healthy volunteers; 2) to assess the pharmacokinetics and concentrations of daptomycin in plasma over a period of 24 hrs after intravenous infusion of a single 4 mg/kg dose in healthy volunteers; and 3) to assess the percentage of urinary recovery of daptomycin.

FORMULATION:
Daptomycin 250 mg vial (lot no. 800654)

STUDY DESIGN:
This study was an open-label, Phase I study conducted in healthy male volunteers to evaluate the pharmacokinetics of daptomycin in cantharides-induced skin blisters and plasma over a period of 24 hrs. A single dose of daptomycin IV 4 mg/kg was to be administered intravenously by infusion pump over a 30 min period. On Day -1 approximately 14 hrs prior to study drug administration, two or three 1.5 cm^2 plasters, impregnated with 0.2% cantharides, were to be placed on the forearm of each subject in order to induce blistering of the skin. The subjects were asked to return to the study site the following day.

Samples of blister fluid were obtained by puncturing the blister with a sterile needle and aspirating the fluid with a sterile micropipette. Skin blister fluid samples were obtained at 30 min, and 1, 1.5, 2, 4, 6, 8, 12, and 24 hours after the start of the infusion. Blister samples were not collected at 15, 35, and 45 min. Blisters were to be resealed after aspiration using a plastic spray dressing.

Blood samples for daptomycin concentration determination were to be obtained at pre-dose, 15, 30, 35 and 45 min and 1, 1.5, 2, 4, 6, 8, 12 and 24 hrs after the start of the infusion.

Urine samples were collected during the following intervals from each subject: 0-4, 4-8, 8-12, and 12-24 hrs after the end of the infusion.

DAPTOMYCIN ASSAY METHODOLOGY:

The concentrations of daptomycin in the blister fluid, serum and urine were determined using a microbiological assay diffusion method performed at the study center employing an Isotonic Sensitivity Test agar supplemented with 50 mg/L Ca^{+2}. The indicator organism, *Staphylococcus aureus* F1445, was incorporated into the agar in order to achieve semi-confluent growth.

Standards for plasma, blister fluid and urine were prepared by diluting daptomycin in human serum, 70% human serum in phosphate buffer (pH 7), and phosphate buffer (pH ≈7.0), respectively.

Criterion	Serum	Urine	Blister Fluid	Comments
Concentration range	2 to 32 µg/mL	2 to 32 µg/mL	2 to 32 µg/mL	Satisfactory
LLOQ				Satisfactory
Linearity				Satisfactory
Accuracy				Satisfactory
Precision				Satisfactory
Specificity	Satisfactory	Not specified	Not specified	Unsatisfactory
Stability	Not stated	Not stated	Not stated	Unsatisfactory

DATA ANALYSIS:

Plasma and skin blister inflammatory fluid daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were determined for plasma and skin blister fluid concentration data: the maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), and the area under the plasma concentration-time curve from zero to 24 hrs (AUC_{0-24}). In addition, the percentage urinary recovery between 0 and 24 hrs post-infusion was determined.

STATISTICAL ANALYSIS:

Pharmacokinetic parameters were summarized as mean, standard deviation, and coefficient of variation.

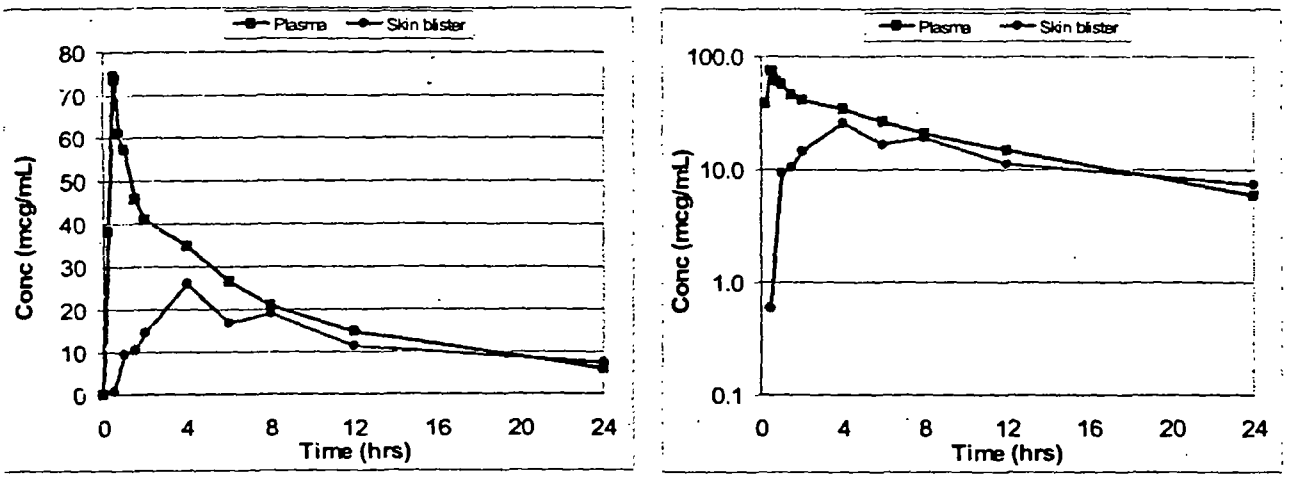
RESULTS:

Six of the seven enrolled subjects completed the study as planned. Subject 002 was withdrawn from the study due to severe adverse events (diarrhea, vomiting and fainting) that were reported as serious by the investigator. The subject continued to be monitored for safety but a pharmacokinetic analysis was not performed.

The mean (SD) age, weight, and height for the six subjects were 23.3 (2.7), 78.5 (9.0), and 179.8 (8.0), respectively. All subjects were male and 4/6 subjects were Caucasian.

The mean plasma and skin blister fluid concentration-time profiles for the six subjects following a single dose of daptomycin IV 4 mg/kg are shown in Figure 1.

Figure 1. Mean daptomycin plasma and skin blister fluid concentrations following a single dose of daptomycin IV 4 mg/kg (n=6)



The pharmacokinetic parameters calculated by the sponsor following administration of daptomycin IV 4 mg/kg to healthy male subjects are shown in Table 1. The mean C_{max} of daptomycin in plasma was 77.5 µg/mL and observed at the end of the 30 minute infusion. The mean C_{max} of daptomycin in skin blister fluid was 27.6 µg/mL and observed approximately 3.7 hrs after the start of the infusion. The mean skin blister fluid AUC_{0-24} was 318 µg*hr/mL and represents 68.4% of the mean plasma AUC_{0-24} (468 µg*hr/mL).

Table 1. Mean (CV%) pharmacokinetic parameters for daptomycin in plasma and skin blister fluid

Parameter	Sponsor's results		Reviewer's results
	Plasma (n=6)	Skin blister fluid (n=6)	Skin blister fluid (n=4)
C_{max} (µg/mL)	77.5 (11%)	27.6 (34%)	22.7 (31%)
T_{max} (hrs)	0.54 (8%)	3.7 (22%)	3.5 (29%)
AUC_{0-24} (µg*hr/mL)	468 (3%)	318 (27%)	287 (26%)
$AUC_{0-\infty}$ (µg*hr/mL)	530 (2%)	—	—
V_{ss} (L/kg)	0.082 (15%)	—	—
Vz (L/kg)	0.078 (12%)	—	—
CL_T (mL/min)	9.84 (3%)	—	—
CL_T (mL/hr/kg)	7.60 (12%)	—	—
Half-life (hrs)	7.74 (8%)	16.9 (64%)	ND
Ae (%)	59.7 (17%)	—	—
Penetration (%)	—	68.4 (29%)	61.0 (28%)

ND - the reviewer was unable to characterize the terminal elimination phase

Although the sponsor stated that skin blister samples were not collected at 15, 35, and 45 min, the concentration of daptomycin in skin blister fluid was missing from various time points for several subjects. Subject 001 was missing skin blister concentrations at 0.5, 1, 1.5, 2, and 8 hrs; subject 003 was missing skin blister concentrations at 0.5, 1.5, 2, and 12 hrs; subject 004 was missing a skin blister concentration at 6 hrs. Thus, the reviewer calculated the AUC_{0-24} and % penetration of daptomycin into skin blister fluid using the data from subjects 004, 005, 006, and 007 (shown as the right column in Table 1). The mean C_{max}, T_{max}, AUC_{0-24}, and % penetration were 22.7 µg/mL, 3.5 hrs, 287 µg*hr/mL, and

61.0%, respectively. The penetration of daptomycin into skin blister fluid decreased from 68.4% to 61.0% when subjects 001 and 003 were excluded.

Compared to the pharmacokinetic parameters estimates from Study DAP-00-02, the V_{SS} and Vz were less than previously reported (0.0925 L/kg and 0.0960 L/kg, respectively) and the CL_T was also less than previously reported (9.55 mL/hr/kg). Although the sponsor calculated the half-life of daptomycin in skin blister fluid, the reviewer was unable to accurately characterize the terminal elimination phase and half-life of daptomycin in skin blister fluid.

CONCLUSIONS:
Daptomycin penetrated cantharides-induced skin blister with a C_{max} in skin blister fluid that was 29% of the C_{max} in plasma and a delay in the T_{max} (3.5 hrs vs. 0.54 hrs).

Based on the AUC_{0-24} skin blister fluid/AUC_{0-24} plasma ratio, the percent penetration of daptomycin into skin blister fluid was 61.0 %. It is assumed that the penetration of daptomycin into inflammatory exudate fluid will be similar to skin blister fluid.

COMMENTS:
1. The study was previously published (Antimicrob. Agents Chemother. 2002;46:31-33). Analytical validation data were submitted to the Agency upon request. Although the analytical method is acceptable based on accuracy and precision, it appears that the calibration standards and QC samples were prepared in serum and used to determine daptomycin concentration from plasma samples.

2. The sponsor used a microbiological assay validated with serum to determine the concentration of daptomycin from plasma. No data were submitted to demonstrate the cross-validation of the microbiological assay in serum and plasma. It is known that anticoagulants can alter the *in vitro* protein binding of highly protein bound drugs and thus, impact the results of a microbiological assay. Since the concentration of daptomycin from study DAP-00-04 was greater than any previous Phase 1 study in which healthy subjects received the same dose, the results of this study were deemed unacceptable for labeling purposes.

Appendix C. Published Literature Reviews

Tobramycin and Daptomycin Disposition When Co-Administered to Healthy Volunteers

Woodworth JR, Nyhart EH, Wolny JD, LeBrier G, Black HR. Tobramycin and Daptomycin Disposition When Co-Administered to healthy Volunteers. J. Antimicrob. Chemother. 1994;33:655-659.

The authors present the results from six healthy male subjects (20 to 45 yrs of age) who received daptomycin IV 2 mg/kg, tobramycin IV 1 mg/kg, and daptomycin IV 2 mg/kg plus tobramycin IV 1 mg/kg in combination infused over 30 min. All treatments were separated by 3 days.

Frequent blood samples were obtained for 24 hrs after the start of the infusion for each treatment. Urine was collected pre-dose (-1 to 0) and 0 to 6, 6 to 12, and 12 to 24 after dosing. Daptomycin concentrations in plasma and urine were determined using a microbiological assay with *Sarcina lutea* ATCC 9341 as the indicator organism. A commercial EMIT assay was used to determine tobramycin concentrations from plasma and urine. Urine was also analyzed for alanine aminopeptidase (AAP) and N-acetyl-β-d-glucosaminidase (NAG) excretion, two renal tubular brush border enzymes. Non-compartmental methods were used to estimate pharmacokinetic parameters. Differences in pharmacokinetic parameters between treatments were tested with a one-way analysis of variance.

RESULTS:

An infusion pump malfunctioned during the antibiotic combination treatment; thus, results from six subjects who received individual drugs and five who received the combination are presented. The plasma concentration-time profiles of daptomycin alone, tobramycin, and daptomycin plus tobramycin in combination are shown in Figure 1.

Figure 1. Mean plasma concentration-time profiles for daptomycin, tobramycin, and daptomycin plus tobramycin in combination

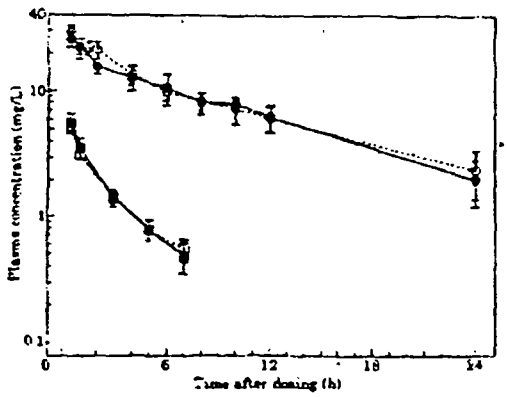


Figure. Mean plasma concentrations of daptomycin (2 mg/kg administered) alone (●), tobramycin (1 mg/kg administered) alone (■), daptomycin when in combination with tobramycin (○), and tobramycin when in combination with daptomycin (□). Bars represent standard deviations.

The mean pharmacokinetic parameters of daptomycin, tobramycin, and daptomycin plus tobramycin are shown in Table 1. The mean C_{max} and $AUC_{0-\infty}$ of daptomycin increased 12.7% and 8.7%, respectively when administered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin decreased 10.7% and 6.6%, respectively when administered with daptomycin. No significant differences in any of the pharmacokinetic parameters were detected between the individual and combination treatments of the two agents.

Table 1. Mean (SD) pharmacokinetic parameters for daptomycin, tobramycin, and daptomycin plus tobramycin in combination

Treatment	N	C_{max} (µg/L)	$t_{1/2}$ (hrs)	$AUC_{0-\infty}$ (µg*hr/mL)	CL_T (mL/min/kg)	CL_R (mL/min/kg)	V_β (L/kg)
Daptomycin							
Alone	6	26.0 (3.7)	7.40	205.5 (37.8)	0.168 (0.034)	0.103 (0.018)	0.108 (0.014)
Combination	5	29.3 (4.0)	8.27	223.4 (57.7)	0.159 (0.044)	0.081 (0.019)	0.113 (0.005)
Tobramycin							
Alone	6	5.6 (0.88)	2.26	13.7 (1.7)	1.23 (0.142)	0.83 (0.25)	0.24 (0.065)
Combination	5	5.0 (0.20)	2.13	12.8 (1.9)	1.33 (0.201)	0.75 (0.11)	0.24 (0.028)

Each of the drug treatments resulted in significantly greater excretion of both NAG and AAP when compared to baseline values ($p < 0.05$). Comparisons between the different drug treatments showed no differences. Despite the increased enzyme excretion, the induced injury is considered negligible for all treatments, which is consistent with previous observations for short-term treatment.

COMMENTS:

The results suggest that there is no need to alter the present aminoglycoside dosing regimen if tobramycin is co-administered with daptomycin. However, the dose of daptomycin is less than the proposed therapeutic dose (4 mg/kg) for the treatment of complicated skin and skin-structure infection and the dose of tobramycin is less than the customary dose. Although the renal injury sustained with both drugs was no more than tobramycin alone, the potential of both drugs in combination to inflict renal injury following administration of therapeutic doses as well as with multiple dosing is unknown.