approximately 1.3. Mean clearance values observed in Cohort A on Day 1 and 7 (18.04 and 19.52 L/h, respectively) appear to be lower than those observed in Cohort B (24.20 and 25.83, respectively) and C (25.07 and 28.69, respectively). The volumes of distribution ranged from mean values of 24.97 L to 42.48 L. Terminal elimination half-life of doripenem was approximately 1 hour in each cohort. AUCss(0-tau) on Day 7 was approximately the same as AUC(0-inf) on Day 1, suggesting that steady state plasma levels of doripenem were attained for each of the dosing regimens.

Doripenem in Urine

Mean cumulative excretion of doripenem for each treatment cohort is shown in Figure 3, while mean PK parameters for doripenem in urine are presented in Table 4.

Figure 3. Mean (SD) urine doripenem cumulative excretion versus time (linear scale)

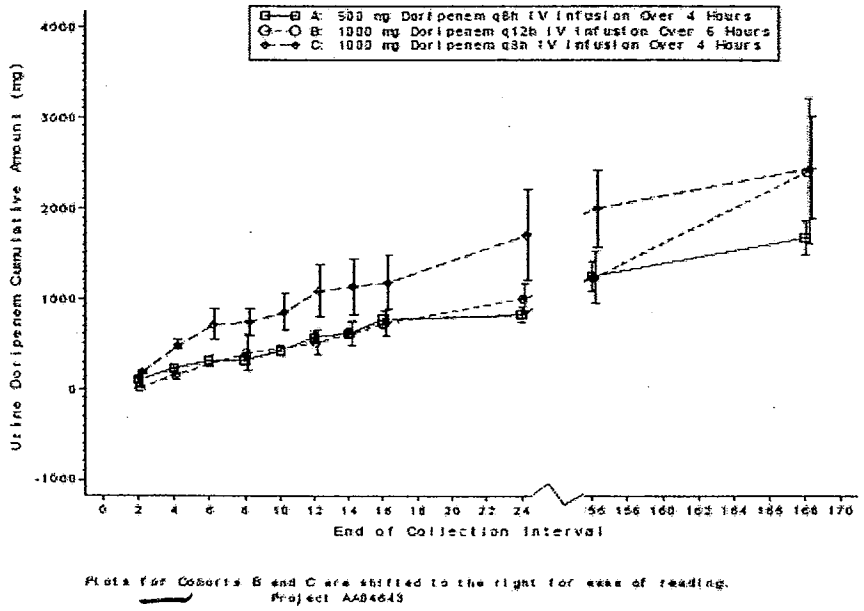


Table 4. Pharmacokinetic parameters of doripenem in urine (N, Mean [SD], Median [Min-Max]

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours	Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours	Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours
Ae(0-tau) (mg)	6 318.74 (61.884) 321.1 (227.2-381.9)	6 506.80 (138.996) 534.2 (249.5-656.9)	6 724.30 (151.070) 715.2 (555.5-975.5)
Ae(0-24) (mg)	6 816.67 (86.094) 816.3 (667.5-911.3)	6 994.24 (155.971) 1048.7 (751.3-1151.6)	6 1682.38 (500.108) 1769.1 (1062.4-2404.7)
Total Ae (mg)	6 1506.10 (443.855) 1651.3 (667.5-1848.6)	6 2398.23 (802.907) 2123.6 (1515.0-3814.5)	6 2420.70 (569.435) 2565.9 (1341.1-3041.0)
RE max (mg/hr)	6 124.015 (58.7960) 111.50 (70.71-231.30)	6 131.967 (56.9229) 111.64 (86.22-235.93)	6 185.187 (42.2313) 178.29 (140.10-250.93)
Tmax (hr)	6 12.022 (4.7678) 14.52 (2.84-14.77)	6 57.393 (80.8252) 7.76 (2.72-161.69)	6 6.088 (3.7270) 4.75 (2.75-10.77)
Fe (%)	6 63.75 (12.377) 64.2 (45.4-76.4)	6 50.68 (13.900) 53.4 (24.9-65.7)	6 72.43 (15.107) 71.5 (55.5-97.6)

The above data indicates that approximately 64 to 72% of a single dose of doripenem is excreted in urine over 8 hours during the first dosing interval when the study drug is administered TID (q8h) over 4 hours (Cohort A and C). This percentage is greater than when doripenem was infused BID (q12h) over 6 hours (approximately 51% of the dose was excreted over 12 hours).

Doripenem-M1 in Plasma

Mean plasma concentration-time curves of doripenem-M1 are presented on linear and log scales in Figures 4 and 5 below. Pharmacokinetic parameter values for doripenem-M1 are shown in Table 5.

Figure 4. Mean (SD) plasma doripenem-M1 concentrations versus time (linear scale)

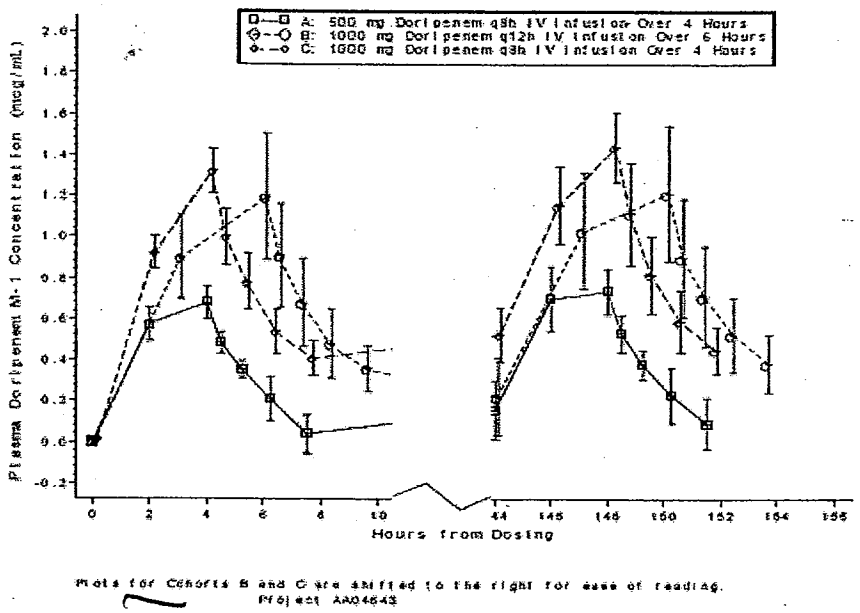


Figure 5. Mean (SD) plasma doripenem-M1 concentrations versus time (log scale)

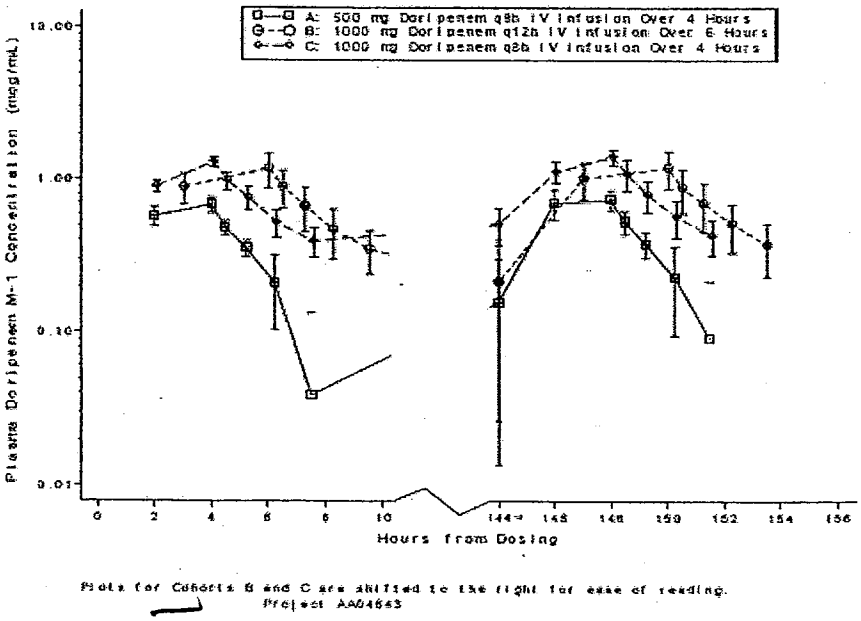


Table 5. Pharmacokinetic parameters of doripenem-M1 in plasma (N, Mean [SD] and Median [Min-Max])

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours		Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours		Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Cmax (mcg/mL)	6 0.6768 (0.07889) 0.680 (0.567-0.778)	5 0.8008 (0.12501) 0.812 (0.665-0.953)	6 1.1827 (0.30670) 1.120 (0.851-1.670)	6 1.1990 (0.32933) 1.195 (0.816-1.710)	6 1.2950 (0.10986) 1.260 (1.170-1.460)	6 1.4150 (0.16920) 1.435 (1.190-1.670)
Tmax (hr)	6 4.014 (0.0143) 4.01 (4.01-4.04)	5 3.608 (0.8987) 4.01 (2.00-4.02)	6 6.013 (0.0100) 6.01 (6.01-6.03)	6 6.010 (0.0007) 6.01 (6.01-6.01)	6 3.999 (0.0013) 4.00 (4.00-4.00)	6 4.001 (0.0005) 4.00 (4.00-4.00)
AUC(0-t) (mcg*hr /mL)	6 2.736 (0.4003) 2.85 (2.04-3.12)	—	6 6.622 (1.6187) 6.42 (4.70-9.31)	—	6 5.525 (0.5296) 5.50 (4.82-6.20)	—
AUC(0-inf) *(mcg*hr /mL)	6 3.443 (0.5426) 3.66 (2.58-4.01)	N/A	6 7.941 (1.7921) 7.71 (5.92-11.09)	N/A)	6 6.904 (0.9224) 6.92 (5.79-8.09)	N/A
AUCss (0-tau) (mcg*hr /mL)	N/A	5 3.609 (0.4948) 3.57 (2.94-4.20)	N/A	6 8.117 (2.4412) 7.66 (5.22-12.41)	N/A	6 7.024 (1.2077) 7.13 (5.32-8.47)
T1/2 (hr)	6 1.9333 (0.75104) 1.629 (1.290-3.317)	5 1.9162 (0.65749) 1.983 (1.023-2.597)	6 2.6084 (0.74117) 2.273 (1.986-3.560)	6 2.5578 (0.63615) 2.351 (2.097-3.814)	6 2.4053 (0.30719) 2.505 (1.858-2.707)	6 2.4369 (0.42078) 2.331 (2.006-3.245)
λz (1/hr)	6 0.3956 (0.11846) 0.427 (0.209-0.537)	5 0.4067 (0.16935) 0.350 (0.267-0.678)	6 0.2823 (0.07046) 0.306 (0.195-0.349)	6 0.2819 (0.05334) 0.295 (0.182-0.331)	6 0.2927 (0.04286) 0.277 (0.256-0.373)	6 0.2906 (0.04298) 0.297 (0.214-0.346)
Cavg (mcg/mL	N/A	5 0.4512 (0.06183) 0.446 (0.367-0.525)	N/A	6 0.6765 (0.20343) 0.638 (0.435-1.034)	N/A	6 0.8780 (0.15096) 0.891 (0.665-1.059)
AUC Ratio*	6 0.1270 (0.01412) 0.125 (0.108-0.150)	5 0.1460 (0.03161) 0.145 (0.105-0.193)	6 0.1974 (0.04100) 0.182 (0.167-0.274)	6 0.2103 (0.03784) 0.203 (0.165-0.269)	6 0.1780 (0.01075) 0.180 (0.157-0.189)	6 0.2408 (0.07610) 0.208 (0.180-0.380)

* Ratio of M1 metabolite to parent compound (corrected for molecular weight)

Comparison of the plasma doripenem-M1 Cmax and AUC(0-t) in Cohorts A and C showed that both parameters increased proportionally with the dose. The terminal elimination half-life of doripenem-M1 was approximately 2 – 2.5 hrs. In each cohort, AUCss(0-tau) on Day 7 was approximately the same as AUC(0-inf) on Day 1, suggesting that steady state plasma concentration levels of doripenem-M1 was attained in each dosing regimen. Comparing the AUC of the parent and metabolite (corrected for molecular weight) showed that after a 4-hour infusion of 500 mg of doripenem (Cohort A), the metabolite exposure was approximately 13% and 15% that of the parent compound on Days 1 and 7, respectively. After infusion of the 1000 mg dose over a 6-hour period, the AUC of doripenem-M1 was approximately 20% and 21% that of doripenem on Days 1 and 7, respectively. Following infusion of the 1000 mg dose over a 4-hour period, the AUC of the metabolite was approximately 18% and 24% that of the parent compound on Days 1 and 7, respectively.

Doripenem-M1 in Urine

Mean cumulative amounts of doripenem-M1 excreted in urine for each treatment is represented in Figure 6. Mean rates of excretion are presented in Table 6.

Figure 6. Mean (S.D.) urine doripenem-M1 cumulative amount versus time (linear scale)

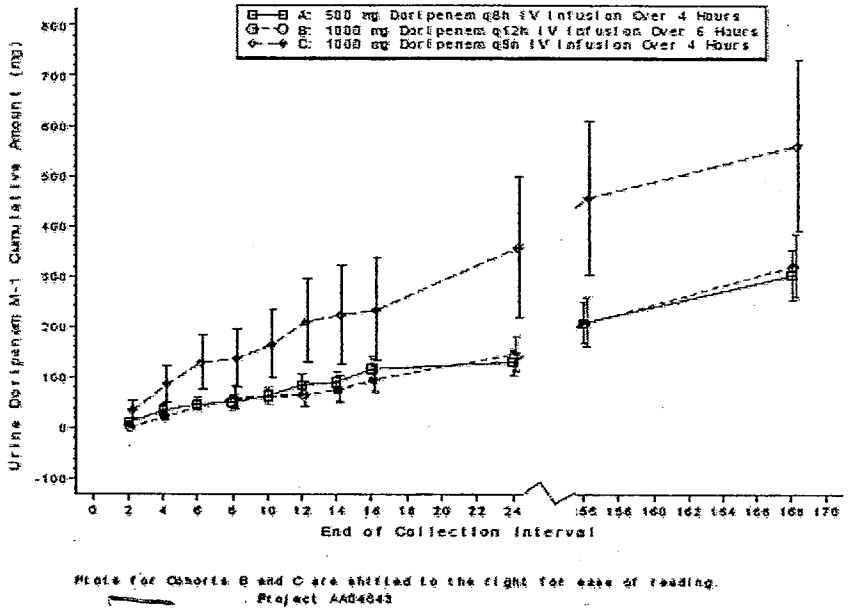


Table 6. Pharmacokinetic parameters of doripenem-M1 in urine (N, Mean [SD], Median [Min-Max])

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours	Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours	Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours
Ae(0-tau) (mg)	6 49.97 (13.435) 47.4 (36.6 - 73.8)	6 64.15 (24.343) 64.7 (37.7 - 92.0)	6 133.36 (57.642) 120.1 (64.7 - 220.1)

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours	Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours	Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours
Ae(0-24) (mg)	6 129.85 (24.608) 130.3 (97.7 - 160.7)	6 144.38 (34.136) 146.4 (82.6 - 181.3)	6 352.38 (139.466) 319.8 (173.8 - 576.1)
Total Ae (mg)	6 276.36 (78.626) 301.4 (144.8 - 347.6)	6 318.63 (62.184) 319.3 (233.1 - 389.3)	6 555.46 (171.207) 558.2 (352.1 - 804.5)
RE max (mg/hr)	6 22.841 (12.3347) 19.71 (11.49 - 41.36)	6 12.652 (1.1947) 13.13 (10.54 - 13.60)	6 26.943 (9.5281) 26.76 (14.29 - 40.56)
Tmax (hr)	6 33.242 (57.4956) 14.52 (2.79 - 150.01)	6 5.748 (4.6581) 4.27 (2.67 - 14.76)	6 7.083 (4.0903) 7.75 (2.73 - 10.77)
Fe* (%)	6 10.43 (2.805) 9.9 (7.6 - 15.4)	6 6.70 (2.541) 6.8 (3.9 - 9.6)	6 13.92 (6.017) 12.5 (6.8 - 23.0)

* Value adjusted for molecular weight

The presented data suggests that approximately 10% to 14% of a single dose of doripenem is excreted in urine as doripenem-M1 within 8-15 hours when the study drug was administered as an IV infusion over 4 hours (Cohort A and C). This percentage is lower (6.7%) when doripenem was infused over 6 hours (Cohort B).

Safety

Seventy-eight post-dose adverse events were reported overall. Six subjects in Cohort A (100%) reported adverse events, and 5 subjects in each of Cohorts B, C and D (83% per cohort) reported adverse events. Of the 78 adverse events, the PI judged 46 (59%) as possibly related to the study drug, and 1 adverse event (1%) as probably related to the study drug (transaminase increase). All adverse events were mild in severity. No dose related trends were seen, except that injection site erythema, the most frequent AE, and headache were reported only by subjects who received active drug. The most frequently reported adverse events were injection site erythema, and injection site swelling, reported by 38% and 29% of subjects, respectively.

In Cohort A, 1 subject had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values that were reported as an adverse event (ALT > 2x ULN), and was judged probably related to the study medication. This adverse event occurred just prior to the start of infusion on Day 7. Elevated ALT levels remained clinically significant until Day 17, and returned to within normal limits by Day 24. Elevated AST levels remained clinically significant until Day 10, and returned to within normal limits by Day 17. Four other subjects had ALT values > ULN (but less than 2x ULN) at least one time post-dose (2 in Cohort A, 1 in Cohort B, 1 in Cohort D).

Sponsor's Conclusions

- Multiple doses of doripenem by prolonged intravenous infusion over a period of 10 days were safe and well tolerated by this group of subjects. All clinically significant laboratory values were transient and reversible, returning to within normal limits by Day 24. Adverse events and abnormal laboratory findings that occurred during this study were consistent with known risks derived from previous studies. All adverse events were mild.
- The half-life of doripenem was approximately 1 hour, its clearance ranged between 15 and 36 L/hr, and its total volume of distribution ranged between 19 and 56 L. The mean doripenem concentration at steady state was approximately 3.3 mcg/mL in Cohorts A and B (500 mg q8h infused over 4 hours, and 1000 mg q12h infused over 6 hours, respectively), whereas Cohort C (1000 mg q8h infused over 4 hours) had a mean concentration at steady state of approximately 4.5 mcg/mL.
- The increase in Cmax and AUC of the parent compound was not proportional to increase in dose (Cohort A vs. C).
- Renal excretion played a significant role in the elimination of doripenem. When 500 mg and 1000 mg of the study drug was infused IV q8h over 4 hours (Cohorts A and C), the percentage of doripenem excreted unchanged in urine ranged between 64 to 72% over the first dosing interval. Approximately 51% of the dose was excreted over the first dosing interval when 1000 mg of the study drug was infused q12h over 6 hours (Cohort B).
- The half-life of doripenem-M1 ranged between 2 to 3 hours. Mean concentration at steady state was approximately 0.45 mcg/mL, 0.68 mcg/mL and 0.88 mcg/mL in Cohorts A, B and C, respectively.
- When 500 mg and 1000 mg of the study drug was infused IV q8h over 4 hours (Cohorts A and C), the percentage of drug excreted in urine as doripenem-M1 ranged between 10 to 14% over the first dosing interval. Approximately 7% of the dose was excreted in urine as doripenem-M1 over the first dosing interval when the drug was infused IV q12h over 6 hours (Cohort B).

Reviewer assessment:

The increase in dose in Cohort C (1000 mg q8h over 4 hours) versus Cohort A (500 mg q8h over 4 hours) did not result in a proportional increase in Cmax and AUC for the parent compound. The ratios of Cmax and AUC were approximately 1.4. This finding is inconsistent with other single-dose and multiple-dose studies of both short and prolonged infusion durations, in which dose proportional increases in doripenem exposure were observed. The exposure of the M1 metabolite, however, did increase proportionally with dose in this study. The Sponsor notes that there were more females in Cohort A (3 males/3 females) than in Cohort C (5 males/1 females), which may have contributed to the findings, since doripenem AUC was found to be 15% higher in females than in males. However, in DORI-NOS-1006, the only PK study to compare exposure between the sexes, the difference was attributed to differences in creatinine clearance, which was 35% greater in the males. The investigators did not report the renal clearance rate of doripenem in this study. However, the total amount of parent compound excreted in urine was actually less than dose proportional for Cohorts A and C.

Mean doripenem CL (18 to 28.7 L/hr) was higher in this study than what was reported in other studies conducted with Western populations (mean CL ranged from 13 to 15.3 L/hr). However, demographic parameters such as age and CL_{CR} were generally similar between the studies. Again, as the investigators did not report doripenem CL_R, it is difficult to explain the reasons for this discrepancy.

The Sponsor used a population PK model using data from DORI-01 to determine the dosing regimens used in this study, with the aim of producing %T >MIC values of at least 40% for more resistant organisms (target MICs 4 – 8 μg/mL). However, the investigators did not related the drug concentration values from this study to any PK/PD targets, such as T > MIC values. As such, attainment of target PD parameters could not be determined for the prolonged infusions.

Study DORI-NOS-1004

A Randomized, Open-label, Three-way Crossover, Phase 1 Study Comparing the Pharmacokinetics of Doripenem After 500 and 1000 mg Singe-dose Infusions in Healthy Adults

Dates: April 2006

Study Sites: [redacted]

Objective:

The primary objective of this study was to compare the AUC of doripenem 500 mg administered as a 4-hour infusion with doripenem 500 mg administered as a 1-hour infusion. The secondary objectives of this study were to examine the dose proportionality of doripenem 500 and 1000 mg doses infused over 4 hours and to further assess the safety and tolerability of the 1- and 4-hour infusion regimens.

Methods:

Study Design

DORI-NOS-1004 was a Phase 1, open-label, 3-way crossover study in which healthy subjects were randomly assigned to receive each of 3 treatments in 1 or 6 unique sequences. Dosing of the 3 treatment periods was separated by a 1 day washout period.

Test Product

The test product was doripenem powder for injection 500 mg (Lot No. CF5049, Exp. Aug 07) and 250 mg (Lot No. CF5023, Exp. Mar 07) reconstituted using Sterile Water for Injection (WFI) USP, and subsequently diluted in normal saline to prepare the following treatments:

Treatment A = Doripenem single-dose 500 mg i.v. infusion administered over 1 hour
Treatment B = Doripenem single-dose 500 mg i.v. infusion administered over 4 hours
Treatment C = Doripenem single-dose 1000 mg i.v. infusion administered over 4 hours

Inclusion criteria

Healthy men or women between 18 and 65 years of age with a body mass index of 18 – 30, healthy by physical exam and laboratory results.

Pharmacokinetic assessment

Blood and urine sample collection was preformed according to the schedule outlined below:

Table 1. Pharmacokinetic Blood and Urine Sample Collection Schedule

Infusion Duration	Days	Volume[a]	Plasma Time[b]		Urine Time (hours) after start of i.v.[c]
1 hour	1, 3, and 5	3 mL	0	predose	0 (predose)[d]
			15 min 30 min 45 min	after the start of the i.v. infusion	0-4 4-8 8-12 Initiate 12-24 h interval collection
			1 h	immediately before the end of the i.v. infusion	
			5 min 10 min 30 min		

Pharmacokinetic Methods

Pharmacokinetic parameters were calculated from doripenem and doripenem-M1 concentrations in plasma using noncompartmental methods. The plasma PK parameters evaluated were Cmax, tmax, AUClast, AUC∞, CL, Vss, t½, and λz.

The following PK parameters were determined for doripenem and the M1 metabolite using individual urine excretion data and actual collection times: total amount of doripenem excreted into urine (AE), the percent of administered dose excreted (AE, % dose) and renal clearance (CL_R).

Statistical Methods

Only subjects who completed all 3 treatments were included in the statistical analysis of AUC_{last} and AUC_{∞}. The analysis was performed on the natural logarithm (ln) of dose-normalized AUC_{last} and AUC_{∞}. Mixed effects models were used to fit the data with the dose-normalized ln-transformed AUC_{last} and AUC_{∞} as the dependent variable, treatment sequence group, period, and treatment (A, B, and C) as the fixed effects, and subject as a random effect. Testing for the treatment sequence group effect was carried out at a 10% level of significance and testing for the period effect was carried out at a 5% level of significance. The estimated least-squares means (LSM) and the intra-subject variance from the mixed effects model were used to construct 90% confidence intervals (CIs) for the difference in means on the log scale for the following pairs of treatments:

500 mg 4-hour i.v. infusion (B) vs. 500 mg 1-hour i.v. infusion (A)
1000 mg 4-hour i.v. infusion (C) vs. 500 mg 4-hour i.v. infusion (B)

The statistical analysis of doripenem Cmax was restricted to data from the 1000 mg 4-hour i.v. infusion (C) and the 500 mg 4-hour i.v. infusion (B). The analysis was performed on the natural logarithm of dose-normalized Cmax. Mixed effects models were fit to the data with the dose-normalized ln-transformed Cmax as the dependent variable, treatment sequence group, period, and treatment (B, C) as fixed effects, and subject as a random effect. Testing for the treatment sequence group effect was carried out at a 10% level of significance and testing for the period effect was carried out at a 5% level of significance. The estimated LSM and intra-subject variance from the mixed effects model was used to construct 90% CIs for the difference in means on the log scale between the 1000 mg 4-hour i.v. infusion (C) and 500 mg 4-hour i.v. infusion (B).

Results:

Study Population

All 24 enrolled subject completed study participation and were included in the final PK analysis. Of the 24 subjects, 2 were female, the mean age was 34.7 years (range 21 – 37) and the mean weight was 81.6 kg (range 59.8 – 96.4 kg). Complete subject demographic characteristics are described below.

Table 2. Subject Demographics

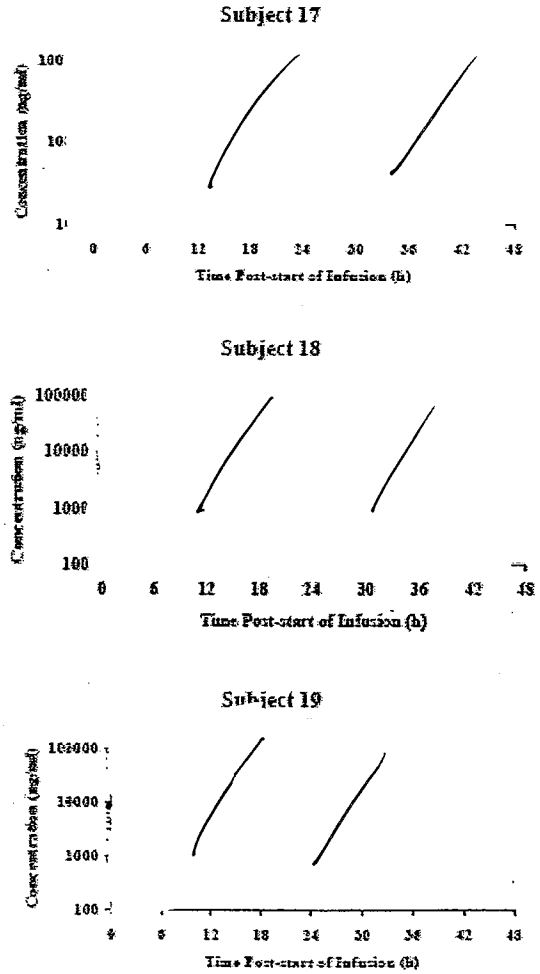
	---- Total ---- (N=24)
Race, n (%)	
N	24
American Indian or Alaskan Native	1 (4)
Black or African American	13 (54)

infusion. Visual assessment of plasma doripenem concentration-time profiles in end-stage renally-impaired subjects (post-dialysis infusion) indicated that this assumption was valid. There was an estimated 48 to 62% reduction in systemic doripenem concentrations in end-stage renally-impaired subjects following dialysis. The rebound in plasma concentrations observed immediately post-end of dialysis reflects the re-distribution back into plasma.

Table 4. Estimated reduction in systemic doripenem exposure by dialysis.

Subject	Time PSOI (h)	Concentration (ng/ml) Observed	Predicted	Reduction (%)
17	2.10			62.3
18	1.88			48.5
19	1.63			48.1

Figure 3. Estimated reduction in systemic doripenem by dialysis following intravenous administration (Group C)



- Vertical dotted lines represent start and end of dialysis, respectively.

- Diagonal dotted line represents the linear regression of post-end of dialysis doripenem concentrations, back-extrapolated to the time at which pre-dialysis samples were taken.

- Subjects 17 and 19 plasma samples at end of dialysis were BLQ, considered anomalous and excluded from the figure and PK analysis.

Urinary Excretion

The urinary recovery of doripenem is illustrated in Figure 4 by renal impairment group. The proportion of dose recovered in the urine and renal clearance estimates are summarized in Table 5. Estimates of urinary excretion and renal clearance could not be determined for Group C (pre-dialysis) due to lack of urine sample prior to and during dialysis.

Figure 4. Geometric mean urinary recovery profiles of doripenem following 500 mg I.V. dose: Groups A to D

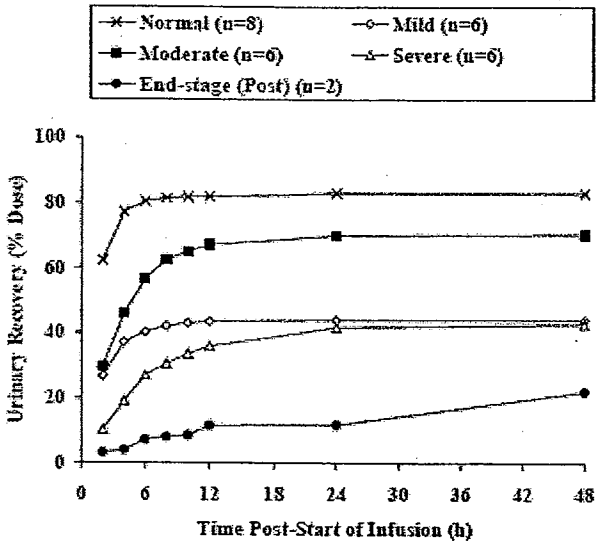


Table 5. Urinary excretion and renal clearance of doripenem (Geometric Mean [CV%])

Renal impairment [Group]	Fe (% Dose)	CL_R (ml/min)
Mild (n=6) [A]	44.0 (63.9)	59.8 (73.9)
Moderate (n=6) [B]	70.3 (19.2)	56.1 (28.1)
Severe (n=6) [D]	42.7 (20.3)	19.0 (23.2)
End-stage (Post) (n=2) [C]	22.0 (71.4)	4.71 (42.5)
Normal (n=8) [A-D]	83.0 (6.22)	185 (18.8)

Estimated over a 48-hour period

Urinary recovery of doripenem approached completion approximately 6 hours post-start of infusion for the pooled normal controls. The time taken to reach complete urinary recovery appeared to increase with increased renal impairment, from approximately 6 hours (normal controls) to 48 hours for end-stage renal impairment. The urinary recovery of doripenem in normal control subjects was, on average, approximately 80%. With the exception of Group B, urinary recovery decreased with increased renal impairment. Although urinary recovery of doripenem in Group B (moderate) was less than that observed in normal controls, it was considerably greater than that observed in Group A (mild). This finding may be due to the large variability observed in excretion rates among the mild impairment subjects (Group A). Subjects 1 and 4 (mild impairment) had urinary recovery rates of 78.4 and 110 %, respectively, which

	---- Total ---- (N=24)
White	10 (42)
Ethnicity, n (%)	
N	24
Hispanic or Latino	4 (17)
Not Hispanic or Latino	20 (83)
Sex, n (%)	
N	24
Female	2 (8)
Male	22 (92)
Age (years)	
N	24
Mean (SD)	34.7 (8.98)
Median	34.0
Range	(21;53)
Weight (kg)	
N	24
Mean (SD)	81.57 (11.049)
Median	85.00
Range	(59.8;96.4)
Height (cm)	
N	24
Mean (SD)	175.7 (6.64)
Median	173.5
Range	(166;187)
Body mass index (kg/m2)	
N	24
Mean (SD)	26.37 (2.706)
Median	27.00
Range	(20.9;29.8)

Analytical Performance

Pharmacokinetic Analysis

The mean (SD) plasma doripenem and doripenem-M1 concentration-time curve are presented in Figures 1 and 2 below. Tables of PK parameter values derived from plasma and urine concentrations follow.

Figure 1. Mean (SD) plasma concentration-time curves: Doripenem

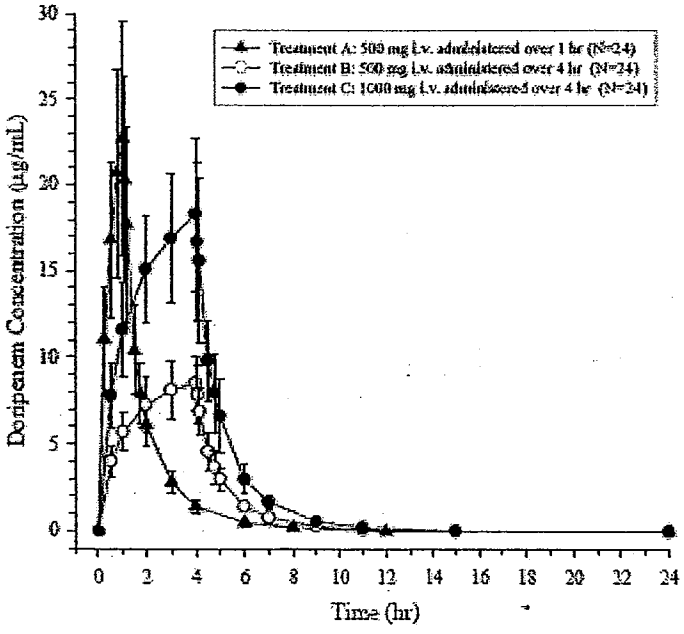


Figure 2. Mean (SD) plasma concentration-time curves: Doripenem-M1

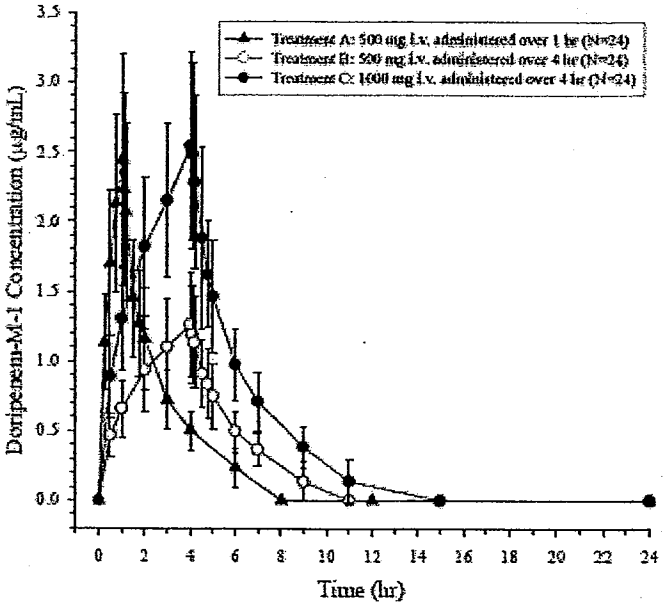


Table 3. Mean (SD) pharmacokinetic parameters of doripenem

PK Parameters	500 mg Doripenem x 1 hr N=24	500 mg Doripenem x 4 hr N=24	1000 mg Doripenem x 4 hr N=24
Cmax (µg/mL)	23.0 (6.61)	8.69 (1.73)	18.8 (4.95)
tmax[a] (hr)	0.92 (0.75-1.17)	3.92 (3.00-4.08)	3.92 (2.00-4.17)
AUC_{last} (µg.hr/mL)	37.4 (10.9)	35.7 (7.12)	74.9 (16.0)
AUC∞ (µg.hr/mL)	36.3 (8.77)[b]	35.6 (6.95)[b]	75.4 (16.0)
CL (L/hr)	14.6 (3.61)[b]	14.6 (3.17)[b]	13.8 (2.88)
Vss (L)	16.8 (5.50)[b]	18.0 (4.03)[b]	18.0 (5.44)
Half-life (hr)	1.20 (0.104)[b]	1.23 (0.214)[b]	1.53 (1.58)
λz (hr-1)	0.582 (0.0511)[b]	0.587 (0.146)[b]	0.556 (0.116)
AE (µg)	349008 (111282)	349138 (87355)	735138 (264229)
AE, % Dose	69.8 (22.3)	69.8 (17.5)	73.5 (26.4)
CL_R (L/hr)	10.3 (4.19)[b]	10.3 (3.94)[b]	10.3 (4.82)

[a] Represented by median (range).
[b] n=23

Table 4. Mean (SD) pharmacokinetic parameters of doripenem-M1

PK Parameters	500 mg Doripenem x 1 hr N=24	500 mg Doripenem x 4 hr N=24	1000 mg Doripenem x 4 hr N=24
Cmax (μg/mL)	2.47 (0.755)	1.27 (0.367)	2.64 (0.774)
tmax[a] (hr)	0.92 (0.75-1.12)	3.92 (3.90-4.17)	3.93 (3.92-4.50)
AUClast (μg.hr/mL)	5.56 (1.80)	5.77 (1.90)	12.2 (3.37)
AUC∞ (μg.hr/mL)	6.61 (1.63)[c]	6.71 (1.91)[d]	13.1 (3.39)
Half-life[b] (hr)	1.99 (0.377)	2.11 (0.358)	2.20 (0.439)
λz (hr-1)	0.361 (0.0717)	0.337 (0.0532)	0.326 (0.0557)
AE (μg)	81316 (31061)	81078 (23401)	169134 (68971)
AE, % Dose	16.3 (6.21)	16.2 (4.68)	16.9 (6.90)
CL_R (L/hr)	12.7 (5.14)[c]	12.6 (4.82)[d]	13.8 (6.03)

a Represented by median (range).
b Apparent t1/2
c n=22
d n=23

Mean doripenem C_{max} and median t_{max} values for the 500 mg x 4-hour infusion were 38% of and 3 hours longer than those respective values for the 500 mg x 1-hour infusion. No meaningful differences in doripenem CL, CL_R, and Vss for the 500 mg x 1-hour, 500 mg x 4-hour, and 1000 mg x 4-hour infusions were observed, with mean parameters differing by less than 7% between the 3 treatments. Mean doripenem half-life was similar for the 500 mg x 1-hour and 500 mg x 4-hour infusions, but was approximately 25% higher for the 1000 mg x 4-hour infusion. This finding appears to be due to a very high half-life for one subject (t1/2 = 8.93 hours) after the 1000 mg x 4-hour infusion. Excluding the half-life value for this subject, mean (SD) half-life for the 1000 mg x 4-hour infusion was 1.21 (0.12) hours. The total amount of doripenem recovered in urine as a percentage of the administered dose was consistent across treatments at 69.8% – 73.5%.

The AUCs of doripenem-M1 were consistent between the 500 mg treatments and approximately doubled with a doubling of the doripenem dose to 1000 mg. Mean apparent doripenem-M1 $t_{1/2}$ and CL_R were similar across the 3 treatments. Approximately 17% to 18% of doripenem was converted to doripenem-M1 for all 3 treatments, as indicated by molecular weight corrected mean AUC_{last} ratios. The total amount of doripenem-M-1 recovered in urine as a percentage of the administered dose was consistent across treatments at 12.7% – 13.8%.

Doripenem and doripenem-M1 AUC_∞ and AUC_{last} for the 500 mg x 4-hour infusion were equivalent to those respective values for the 500 mg x 1-hour infusion, as evidenced by 90% confidence intervals (CI) for the geometric mean ratios contained within 80% and 125% (Table 5).

Table 5. Geometric mean ratios (GMR) for doripenem and doripenem-M1 exposure following 1-hour and 4-hour infusions of 500 mg

Parameter	N	G. Mean 500 mg x 4-hr (Test)	G. Mean 500 mg x 1-hr (Reference)	GMR (%) Test/ Reference	90% CI for Ratio
Doripenem					
AUC∞	22	35.18	35.12	100.15	(92.42, 108.53)
AUClast	24	35.03	35.99	97.34	(89.59, 105.76)
Doripenem-M-1					
AUC∞	22	6.66	6.45	103.32	(96.49, 110.63)
AUClast	24	5.47	5.24	104.44	(96.05, 113.56)

Dose-normalized doripenem and doripenem-M-1 AUC_{∞}, AUC_{last}, and C_{max} for the 1000 mg x 4-hour infusion were equivalent to those respective values for the 500 mg x 4-hour infusion, as evidenced by 90% confidence intervals (CI) for the geometric mean ratios contained within 80% and 125% (Table 6).

Table 6. Geometric mean ratios (GMR) for dose-normalized doripenem and doripenem-M1 exposure following 4-hour infusions of 500 mg and 100 mg

Parameter	N	G. Mean 1000 mg x 4 hr (Test)	G. Mean 500 mg x 4 hr (Reference)	(%) Test / Reference	90% CI for Ratio
Doripenem					
AUC∞	22	37.22	35.18	105.82	(97.63, 114.7)
AUClast	24	36.63	35.03	104.58	(96.25, 113.64)
Cmax	24	9.10	8.52	106.83	(97.34, 117.23)
Doripenem-M-1					
AUC∞	22	6.49	6.66	97.35	(90.92, 104.24)
AUClast	24	5.87	5.47	107.16	(98.56, 116.52)
Cmax	24	1.27	1.23	103.51	(94.69, 113.15)

Safety

Six (25%) of 24 subjects reported at least 1 adverse event during the study. One or more adverse events were experienced by 2 (8%) of 24 subjects treated with doripenem 500 mg infused over 1 hour, compared to 3 (13%) of 24 subjects treated with doripenem 500 mg infused over 4 hours, and 3 (13%) of 24 subjects treated with doripenem 1000 mg infused over 4 hours. There was no trend in distribution of adverse events between all 3 treatment groups. The Investigator considered 1 adverse event (dysgeusia) probably related to study drug, 1 adverse event possibly related (headache), and all other adverse events doubtfully or not related to study drug. The most frequently reported adverse event in this study was headache, reported in 3 (13%) of 24 subjects. No clinically significant clinical laboratory abnormalities occurred in this study.

Sponsor's Conclusions

- Doripenem AUC for the 500 mg x 4-hour infusion was bioequivalent to that for the 500 mg x 1-hour infusion. As expected, doripenem Cmax was lower and tmax prolonged for the 500 mg x 4-hour infusion relative to the 500 mg x 1-hour infusion. No meaningful differences in doripenem CL, CLR, Vss, and t1/2 were observed between the 2 treatments. In addition, doripenem-M1 AUC demonstrated equivalence for the 500 mg x 4-hour vs. 500 mg x 1-hour infusions.
- For the 1000 mg x 4-hour and 500 mg x 4-hour infusions, dose proportionality was concluded as dose-normalized Cmax and AUC were equivalent for the 2 treatments. No meaningful differences in doripenem CL, CLR, Vss, and t½ were observed between the 2 treatments. Doripenem-M1 Cmax and AUC also were shown to be equivalent for the 1000 mg x 4-hour and 500 mg x 4-hour infusions.
- Single doses of doripenem 500 mg i.v. infusion administered over 1 and 4 hours, and single doses of doripenem 1000 mg i.v. infusion administered over 4 hours appeared to be safe and well tolerated in the healthy adult subjects enrolled in this study. No differences or trends among treatments were observed with respect to subject safety.

Reviewer assessment:
The Sponsor's conclusions regarding the pharmacokinetics of 1-hour and 4-hour infusions of doripenem 500 mg and 1000 mg are appropriate based on the study results.

The investigators did not conduct any pharmacodynamic analyses, such as determination of T > target MIC values. As such, comparison of PK/PD targets could not be performed for the three dosing regimens.

Study 940R1412
S-4661 Phase I Clinical Study, Single-dose Administration (Dose Response Correlation)

Dates: February – April 1994

Study Sites: [redacted]

Objective:
To evaluate the tolerability and pharmacokinetics (PK) of doripenem after single dose administration of 125, 250, 500 and 1000 mg in healthy adults, in order to demonstrate dose proportionality, as well as to investigate the serum-protein binding rate and evaluate the presence of metabolites.

Methods:
Study Design
This was a phase I dose-escalation study of single-dose doripenem conducted in 24 healthy adult subjects. Single intravenous doses of 125 mg – 1000 mg doripenem were administered, followed by frequent blood sampling for determination of doripenem PK parameters. Additional blood samples were collected for measurement of serum-protein binding rate and determination of metabolites in blood. Urine samples were also collected for drug concentration analysis and to investigate metabolites.

Test Product
Content: Each vial contained 250 or 500 mg (potency) of S-4661
Form: Injectable vial formulations
Manufacturing No.: CP3045 (250 mg) and CP3046 (500 mg)
Storage: stored in a refrigerator, protected from light

Study	Dose	Conditions	Number of subjects
Study 2-1	125 mg	Fasting	6
Study 2-2	250 mg	Fasting	6
Study 2-3	500 mg	Fasting	6
Study 2-4	1000 mg	Fasting	6

Inclusion criteria
Healthy adult males between 20 and 50 years of age, within 20% of the standard body weight were enrolled in the study.

Pharmacokinetic assessment
Blood and urine samples were collected according to the following schedule:

Blood samples	
Pharmacokinetics (4 mL each)	Pre- and 0.5 (at the end of infusion), 0.75, 1, 1,5, 2, 4, 6, 8 and 12 hours post-start of infusion
Serum-protein binding rate (3 mL each)	0.5 (at the end of infusion) and 2 hours post-start of infusion

Metabolite in blood (2 mL each)	Pre- and 0.5 (at the end of infusion), 0.75, 1, 1,5, 2 and 4 hours post-start of infusion

Each blood sample was collected in a heparinized sample tube and immediately centrifuged at 3000 rpm for 15 min. at 4°C. The resulting plasma was divided into 1 mL samples for bioassay and 1 mL samples for HPLC, then stored frozen at – 70°C until analysis. To determine the serum-protein binding rate, blood was collected and immediately centrifuged at 3000 rpm for 15 min. at 4°C. The resulting serum was stored in a refrigerator until measurement using ultrafiltration at 37°C. To investigate metabolites in blood, blood was collected in a heparinized sample tube and immediately centrifuged at 3000 rpm for 15 min. at 4°C. The resulting plasma was stored frozen until analysis. Part of the plasma for pharmacokinetic analysis was used for metabolite analysis samples.

Urine was pooled over 24-hours before the infusion of doripenem and at the following intervals: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24 hours. During follow-up, urine was collected 3 and 7 days after infusion, in the morning.

After the urinary volume was determined, urine was divided into 2 mL samples for bioassay and 2 mL samples for HPLC, both for drug concentration analysis, as well as 10 mL samples for investigation of metabolites, and stored frozen at – 70°C until analysis.

Analytical Methods

Plasma concentrations were measured by bioassay and by HPLC.

Pharmacokinetic and Statistical Methods

PK parameters Ke, Vc, $t_{1/2}$ and AUC were calculated from plasma concentration data using a 2-compartment model. Parameters Cmax, $AUC_{0\text{-}12}$, CL_T, CL_R and Fe were calculated by non-compartmental analysis using WinNonlin (Ver 2.1). The relationship between PK parameters (Cmax and AUC) and dose were analyzed by linear regression. Differences between CL_T, $t_{1/2}$, Fe and CL_R were analyzed by Tukey's multiple comparison test.

PK parameters of doripenem-dicarboxylate (the ring-opened) metabolite were calculated by non-compartmental analysis.

Results:

Study Population

All 24 Japanese male subjects enrolled in the study completed participation and were included in the primary and secondary analyses. Demographic characteristics are described below.

Table 1. Demographic Details by Treatment Group

Study	Dose	Infusion time (h)	Case No.	Initials	Age (years)	Height (cm)	Weight (kg)
Study 2-1	125mg	0.5	1	KK	45	165	65.0
			2	SM	36	173	65.5
			3	SO	33	170	63.0
			4	YM	32	176	66.0
			5	JI	30	176	69.0
			6	KS	26	177	67.0
Study 2-2	250mg	0.5	1	KI	43	168	58.5
			2	KI	28	172	66.0
			3	SS	28	170	61.0
			4	EK	27	173	68.0
			5	KO	28	173	78.0
			6	TM	29	173	59.0
Study 2-3	500mg	0.5	1	MD	41	163	65.0
			2	TK	32	180	75.0
			3	TO	30	177	70.0
			4	MI	28	168	70.0
			5	TS	28	172	66.0
			6	SH	28	170	61.0
Study 2-4	1000mg	0.5	1	NM	42	177	71.0
			2	SS	29	181	81.0
			3	SK	27	172	66.5
			4	MK	26	177	61.5
			5	MK	31	177	72.5
			6	KT	37	167	66.5

Analytical Performance

Pharmacokinetic Analysis

Doripenem

The plasma concentration data based on bioassay analysis are presented below (Figure 1). The mean doripenem plasma concentrations at the end of infusion (equivalent to the C_{max}) were 8.09, 18.1, 33.1 and 63.0 μg/mL at doses of 125, 250, 500 and 1000 mg, respectively. The elimination half-life ranged from 0.85 to 0.98 hr by bioassay and from 0.83 to 1.16 hr by HPLC, and was independent of dose. Both the Cmax and AUC increased dose-proportionally, demonstrating linearity of doripenem pharmacokinetics (Figures 3 and 4). Within 24 hours after infusion, the mean urinary excretion rate ranged from 74.5 to 76.7% for the 4 dose levels.

Figure 1. Mean plasma concentration data of doripenem following single-dose infusion (results of bioassay)

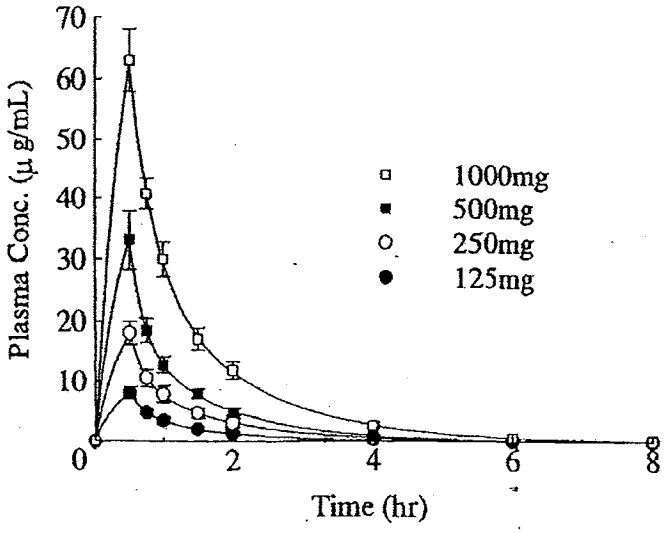


Table 2. Pharmacokinetic parameters of doripenem in plasma and urinary excretion rate

Dose (mg)	Subject N=6	Method	C_{max} (μg/mL)	AUC (μg·h/mL)	$t_{1/2}$ (h)	Urine (0-24h) (%)
125	Mean	Bioassay	8.09	8.71	0.85	76.7
		HPLC	8.33	8.96	0.83	76.9
250	Mean	Bioassay	18.1	20.26	0.90	74.5
		HPLC	16.1	18.71	1.16	75.4
500	Mean	Bioassay	33.1	34.38	0.86	74.5
		HPLC	30.7	32.36	0.90	76.1
1000	Mean	Bioassay	63.0	75.52	0.98	74.9
		HPLC	60.4	70.97	1.01	73.3

Figure 2. Cumulative urinary excretion of doripenem following single-dose infusion (results of bioassay)

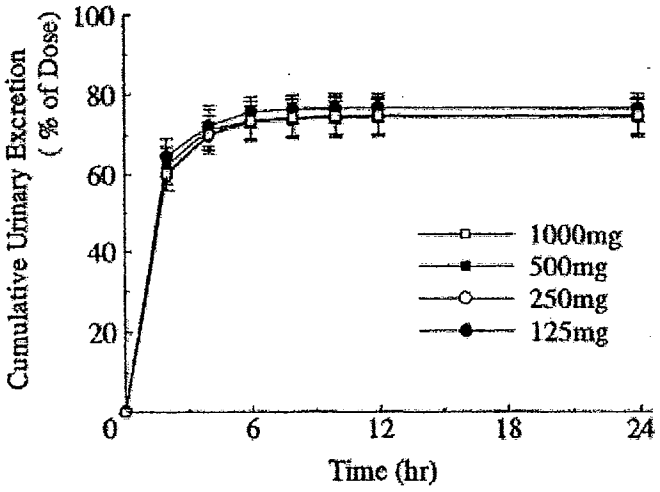
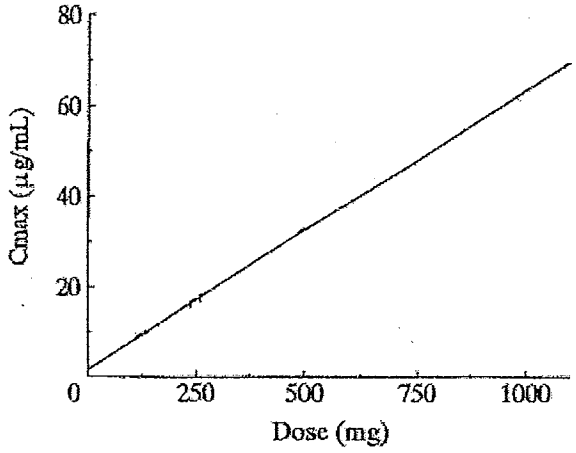
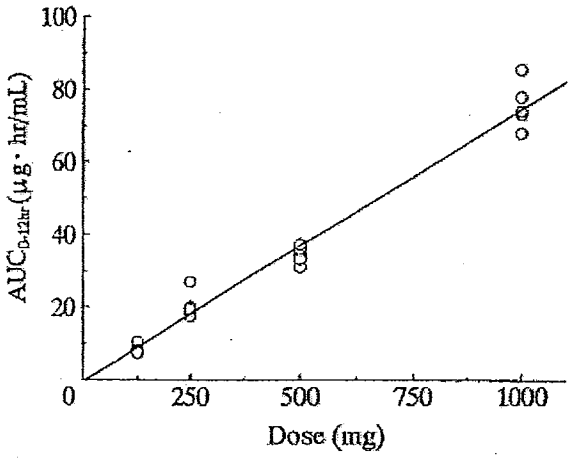


Figure 3. Dose dependence of Cmax (results of bioassay)



*** Confidence Interval of Intercept: -1.03 – 4.23**

Figure 4. Dose dependence of $AUC_{0\text{-}12}$ (results of bioassay)



*** Confidence Interval of Intercept: -3.38 – 2.34**

Evaluation of active metabolites

To examine for any active metabolites of doripenem in plasma and urine, TLC- bioautography was performed after a single administration of 1000 mg. The results reveal the only antibacterial fraction is attributable to doripenem, and thus no active metabolites were detected in plasma or urine.

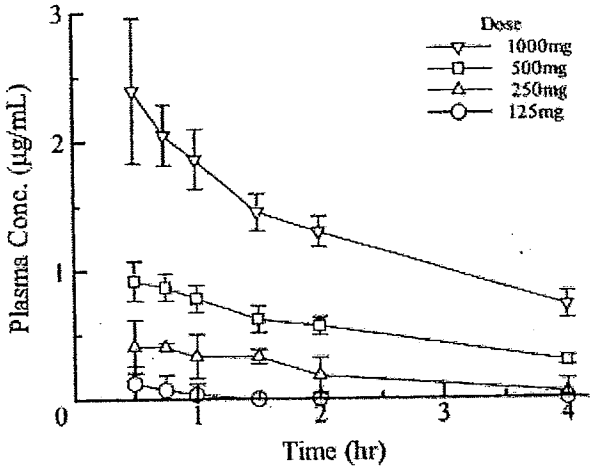
Doripenem-M1

HPLC was used to determine the concentrations of the metabolite (dicarboxylic acid derivative of doripenem) in plasma and urine following single dose administration. At all doses evaluated only a trace amount of the metabolite was detected in plasma. The plasma concentration curve is

illustrated in Figure 5. The Cmax and AUC_{0-12} of the metabolite were less than 5% and 8% of the respective values for the parent compound.

Within 24 hours of infusion, the mean urinary excretion rate of the metabolite was 12.7%, 12.1%, 15.5% and 17.2% at doses of 125, 250, 500 and 1000 mg, respectively. The mean combined urinary excretion of doripenem and the metabolite was 87.5 to 91.6% for the 24-hour collection period.

Figure 5. Mean plasma concentration of doripenem-M1 following single-dose infusion of doripenem (N = 6 each)



Serum protein binding
Serum protein binding of doripenem was approximately 5 – 10% for the four concentrations at the two time points studied (table 3 below).

Table 3. Mean serum protein-binding rate of doripenem at two time points

	Protein binding rate (%)	
Dose (mg)	0.5 h	2.0 h
125	10.3	--
250	5.84	5.65
500	7.89	7.92
10000	8.76	7.28

Safety
No abnormal subjective symptoms or objective findings, or no abnormal physical findings were observed in any subject. Clinical laboratory tests revealed mild changes (occult blood in urine and increased GGT and WBC), but no abnormal changes attributed to doripenem administration.

Sponsor's Conclusions
Adverse effects related to doripenem administration were not observed in any of the 24 subjects with respect to subjective symptoms, objective findings, or physical examination. Slight variations were observed in some of the parameters of laboratory tests, but none of them were considered to be attributable to doripenem.

Doripenem C_{max} values were 8.09, 18.1, 33.1 and 63.0 μg/mL, and AUC were 8.71, 20.17, 34.38 and 75.56 μg*hr/mL, respectively. Both PK parameters increased proportionally with dose. The elimination half-life was about 1 hour, regardless of dose. The urinary excretion rate for doripenem following 24-hour collection was about 75% for all doses studied. The existence of active metabolites was examined by the TLC bio-autography using the urine and blood samples obtained following administration of 1000 mg. The only positive result identified was derived from unchanged doripenem found in the samples, suggesting there was no active metabolites. The amount of the metabolite (β-lactam ring cleavage derivative) detected in plasma was very small. The amounts of the metabolite detected in urine were 12.7%, 12.1%, 15.5% and 17.2%, respectively, at 125 mg, 250 mg, 500 mg and 1000 mg.

Reviewer assessment:
The assay validation and details of analytical performance for HPLC were incomplete. As such, the performance of the assay could not be fully assessed.

PK parameter values (including CL_T, CL_R, $t_{1/2}$, and Fe) were generally similar to results from studies conducted with Western populations. In Western populations the mean plasma doripenem-M1 to doripenem AUC ratio (18.3%) was slighter higher than the 8% reported in this study. However, plasma sampling for determination of plasma M1 concentrations was limited to a 4-hour collection period; as such, the plasma exposure of M1, and subsequently the AUC ratio, is likely underestimated

Study DORI-NOS-1007

An Open-label, Single-Center Study to Investigate the Metabolism and Excretion of Doripenem After a Single Intravenous Infusion of a 500 mg Dose in Healthy Men

Dates: June - August 2006

Study Sites: Johnson & Johnson Pharmaceutical Research & Development, Clinical Pharmacology Unit, Antwerp, Belgium

Objective:

The primary objective of this study was to characterize the metabolism and excretion of doripenem in healthy men after a single i.v. dose of ^{14}C-doripenem 500 mg given as a 1-hour infusion. Safety and tolerability were also assessed.

Methods:

Study Design

DORI-NOS-1007 was a Phase 1, open-label, single-center study designed to characterize the excretion of doripenem and to elucidate the metabolic pathway and structures of doripenem's predominant metabolites. The study was performed in 8 healthy men. The subjects received a single i.v. infusion of ^{14}C-doripenem 500 mg over 1 hour on Day 1 of the study. Serial blood, urine and feces samples were collected up to Day 8. Concentrations of doripenem and its primary metabolite, doripenem-M1, were determined by analytical methods in urine and plasma samples. Total radioactivity of ^{14}C was measured in blood, plasma, urine and feces. Metabolic profiling, including quantitative and qualitative identification, was planned for plasma, urine and feces. Based on the study results, metabolite profiling was conducted in urine only.

Test Product

^{14}C-doripenem, labeled on the 2-position of the azabicycloheptene of doripenem, batch #2010, was diluted with unlabeled doripenem. A total 250 mL of prepared solution was infused over 1 hour, representing a 500 mg doripenem dose and 1.85 MBq of radioactivity.

Inclusion criteria

Men 18 to 45 years of age, inclusive, with a body mass index of 18 – 30 kg/m^2, inclusive, and healthy by physical exam and laboratory results.

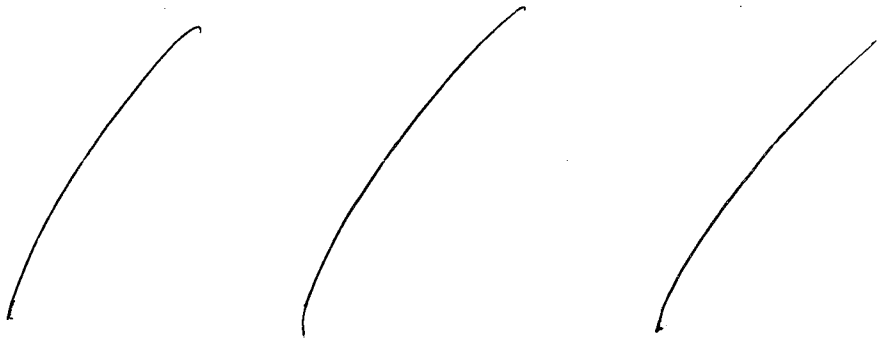
Pharmacokinetic assessment

Blood, urine and feces were collected for 7 days after dosing (ie. until Day 8), with the potential for additional collection up to Day 15 if the radioactivity in the 24-hour urine collections on Day 6 or Day 7 accounted for $\geq$ 2% of the total administered dose, or if less than 7 post-dose feces samples had been obtained by Day 8.

Plasma samples were collected for determination of doripenem concentration and total radioactivity at the following time points: 0 (pre-dose), 15, 30 and 45 min., 1, 1.08, 1.17, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose. Plasma samples were also collected for total radioactivity at 72, 96, 120, 144, and 168 hours post-dose. Blood samples were drawn for metabolite profiling and total radioactivity at 0 (pre-dose), 1, 2, 4, 8 and 24 hours post-dose. Urine was collected in 4-hour intervals for the first 16 hours, then 16 – 24, 24 – 36, 36 – 48, 48 – 72, 72 – 96, 96 – 120, 120 – 144 and 144 – 168 hours post-dose.

Analytical Methods

Concentrations of doripenem and doripenem-M1 were determined in plasma using a validated LC-MS/MS method at [redacted]. Concentrations of doripenem and doripenem-M1 were determined in urine using a validated LC-MS/MS method at [redacted]



Results:

Study Population

Eight healthy male subjects were enrolled in the study and completed participation. Baseline characteristics are shown below in Table 1.

Table 1. Subject Demographics

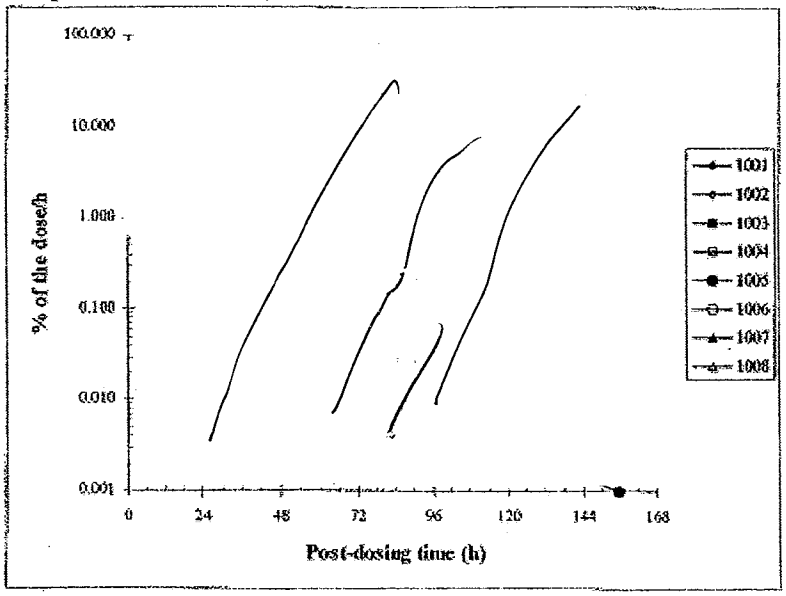
	---- Total ---- (N=8)
Race, n (%)	
N	8
White	8 (100)
Sex, n (%)	
N	8
Female	0
Male	8 (100)
Age (years)	
N	8
Mean (SD)	23.0 (8.96)
Median	20.5
Range	(18 – 45)
Weight (kg)	
N	8
Mean (SD)	79.1 (14.88)
Median	87.5
Range	(55 – 93)
Height (cm)	
N	8
Mean (SD)	185.5 (11.3)
Median	182.0
Range	(170 – 202)
Body mass index (kg/m2)	

N	8
Mean (SD)	22.9 (3.24)
Median	22.5
Range	(19 – 28)

Doripenem Radioactivity

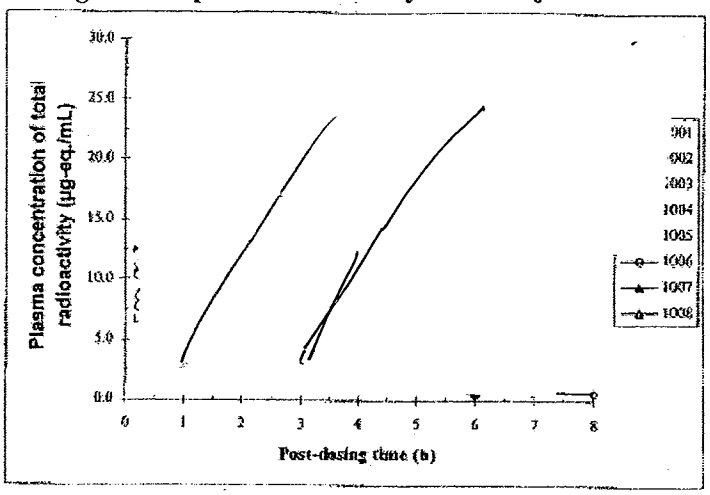
^{14}C-doripenem-related radioactivity was almost exclusively excreted in urine; the largest fraction was excreted in urine within 4 hours post-dose (mean 85.1%). At 12-hours post-dose an average of 93.4% of the dose was excreted in the urine. After 1 week, the mean cumulated excretion of radioactivity in urine and feces was 95.3% and 0.72%, respectively. Urinary excretion of total radioactivity is shown below in Figure 1.

Figure 1. Urinary excretion rate of total radioactivity after a single i.v. dose of 500 mg ^{14}C-doripenem in 8 healthy male subjects



The concentration-time profiles of total radioactivity in plasma are shown in Figure 2. The Cmax of total radioactivity in plasma was attained around 1 hour after the start of infusion. Doripenem and doripenem-M1 accounted for 86 – 101% of the AUC of total radioactivity. Unchanged doripenem accounted for an average of 80.7% of plasma radioactivity AUC_{∞}, while doripenem-M1 accounted for an average of 12.7% of plasma radioactivity AUC_{∞}. The blood to plasma concentration ratio of total radioactivity ranged from 0.47 to 0.60 across all time points, indicating that neither doripenem nor its metabolites were retained by cellular components of blood.

Figure 2. Plasma concentration-time profiles of total radioactivity after a single i.v. dose of 500 mg ^{14}C-doripenem in 8 healthy male subjects



Plasma and Radioactive PK Parameters

Doripenem concentration-time profiles in plasma paralleled those of total radioactivity in plasma, indicating that unchanged drug is the major circulating component in plasma. The ratio of AUC_∞(doripenem)/AUC_∞(total ^{14}C) was 0.807. Pharmacokinetic parameters for doripenem and doripenem-M1 are shown below in Table 2.

Table 2. Mean (SD) Pharmacokinetic Parameters of ^{14}C-Labelled Moiety in Plasma and Whole Blood and Doripenem and Doripenem-M1 in Plasma Following a Single IV Dose of 500 mg ^{14}C-Doripenem

PK Parameters		Doripenem Plasma (n=8)	Doripenem-M-1 Plasma (n=8)	Total Radioactivity in Plasma (n=8)	Total Radioactivity in Whole Blood (n=8)
C_{max}	(µg/mL)	22.9 (2.37)	1.56 (0.24)	22.1 (3.34)[b]	13.2 (2.35)[b]
t_{max}	(h)[a]	1.02 (1.00-1.02)	1.01 (0.75-1.02)	1.02 (1.00-1.02)	1.02 (1.00-1.02)
AUC_{last}	(µg.h/mL)	31.5 (4.51)	4.03 (0.427)	37.5 (5.55)[c]	20.2 (3.71)[c]
AUC_∞	(µg.h/mL)	31.8 (4.50)	4.98 (0.389)	39.5 (5.47)[c]	NAs
$t_{1/2}$	(h)	1.07 (0.125)	2.54 (0.264)	1.59 (0.133)	NAs
λ_z	(h^{-1})	0.657 (0.0747)	0.275 (0.0284)	0.438 (0.0356)	NAs
CL	(L/h)	16.0 (2.23)	NAs	NAs	NAs
Vss	(L)	24.8 (5.80)	NAs	NAs	NAs
AUC_∞	Ratio[d]	0.807 (0.0510)	0.127 (0.0117)		

NAs - Not Assessable

[a] Median (range); [b] Unit = µg-eq/mL; [c] Unit = µg-eq.h/mL

[d] Ratio of AUC_∞ for unchanged doripenem or doripenem-M-1 to total radioactivity in plasma.

Metabolic Profiling

Unchanged drug and 7 radioactive compounds (either metabolites or degradation products) were identified in urine by LC-MS/MS. Metabolite 5 was also identified by co-chromatography with a

mixture of unlabelled authentic compounds. Four metabolites, 1, 3, 4 and 5, were identified as genuine metabolites. Metabolite 5 (doripenem-M1) results from cleavage of the β-lactam ring of doripenem, while metabolites 3 and 4 were identified as the taurine and glycine conjuages of doripenem dicarboxylic acid. Metabolite 1 was identified as an oxidized metabolite of doripenem-M1. The cluster of metabolites 3, 4 and 5 accounted for the largest fraction of excreted radioactivity in urine (an average of 30.9% in 0-24 hours). Metabolites 3, 4 and 5 accounted for an average of 0.46%, 3.12% and 23.9% of total radioactivity in urine at 0-4 hours. Using a validated LC/MS/MS assay and samples of urine stored at -70°C, it was determined that an average of 97.2% of the dose was excreted in urine as doripenem (78.7%) and doripenem-M1 (18.5%) over 24 hours.

Urine sample stored for metabolite profiling were improperly stored at -18°C for 4.5 months, as opposed to -70°C. Doripenem has been shown to be significantly more stable when stored at -70°C versus -20°C. The improper storage conditions likely accounts for the formation of degradation products and the higher fraction of acid metabolite as measured by radio-HPLC assay versus the LC/MS/MS assay.

Analytical Performance

Safety

Treatment-emergent adverse effects were reported in 3 of the 8 subjects. Two subjects experienced gastrointestinal discomfort on Day 1 and one subject experienced dizziness on Day 2. No subject had any clinically relevant abnormal laboratory values during or at the end of study participation.

Sponsor's Conclusions

- Approximately 81% of total radioactivity in plasma reflected doripenem levels, rather than that of metabolites. The inactive metabolite, doripenem-M1, represented approximately 12.7% of total radioactivity in plasma.
- A total of 96% of the administered radioactivity was recovered in urine and feces over 7 days. Excretion was mainly via urine, with about 95.3% of the radioactivity recovered in urine. Fecal excretion accounted for less than 1% of the radioactive dose.
- Due to the suboptimal storage of urine samples that were utilized for metabolite profiling, the quantification of metabolites in urine are not considered to be fully quantitative. However, based on the 97.2% dose recovery of doripenem and doripenem-M1 by bioanalytical assay, the other metabolites identified collectively represent less than 3% of the administered dose in urine.
- PK results for doripenem and doripenem-M1 in plasma and urine are consistent with results obtained in previous Phase I studies.

Reviewer assessment:

The results of the mass-balance study are in agreement with previously conducted PK studies which identified urinary excretion as the primary route of doripenem elimination. The inactive metabolite, doripenem-M1, represented about 13% of total radioactivity in plasma; this is consistent with a mean plasma doripenem-M1/doripenem AUC ratio of 0.183 from Phase I studies.

4.2.3. Intrinsic Factors

Study DORI-02

A Phase 1 open label controlled study to evaluate the safety, tolerability, and pharmacokinetics of doripenem administered intravenously to subjects with renal impairment.

Dates: August 2002 – September 2003

Study Sites: [redacted]

Objective:

The purpose of the study was to assess the safety, tolerability and pharmacokinetics of doripenem administered intravenously in subjects with mild, moderate, severe and end-stage renal impairment (ESRI), categorized via the Cockroft-Gault formula.

Methods:

Study Design

This was a Phase 1, open-label, single-dose controlled study. Subjects were allocated to 4 groups of 8 subjects according to degree of renal impairment – mild, moderate, severe and end-stage renal impairment (ESRI). In each group, renally impaired subjects were matched in a ratio of 3:1 with control subjects who had normal renal function, matched for age (+/- 5 years of age), gender, and weight (+/- 20% body weight). Groups were treated sequentially, beginning with Group A (mild renal impairment/ matched controls). All subjects received a single dose of 500 mg doripenem over 30 min. on Day 1. In the ESRI group, 3 subjects were administered doripenem prior to dialysis, and 3 subjects after completion of dialysis. The safety and tolerability of study drug administration in each group were assessed when at least three subjects in that group had completed the Day 7 evaluations. The investigator reviewed safety data from each group prior to treating the next group.

Group	Degree of Renal Impairment	Creatinine Clearance
A	Mild (n=6)	51-79 ml/min
B	Moderate (n=6)	31-50 ml/min
C	End-stage: Pre-dialysis infusion (n=3) and Post-dialysis infusion (n=3)	Dialysis dependent
D	Severe (n=6)	≤ 30 ml/min
A-D	Normal matched control (n=2 per group)	≤ 80 ml/min

Test Product

Drug product was manufactured by Shionogi & Co. Ltd., Osaka Japan, and drug product supply was controlled by Peninsula Pharmaceuticals, Inc. The drug product was analyzed and released according to the specifications of Shionogi. The drug product, Doripenem for Injection, was available as a sterile powder in a single-dose, clear glass vial that was reconstituted with Water for Injection USP/EP immediately prior to administration. Each vial supplied for the clinical study contained 250 mg sterile doripenem; no excipients were included in the formulation. The lots used in this study are as follows: CF2033 (Exp. March 2003), CF3015 (Exp. February 2004)

Inclusion criteria

Males or females with mild, moderate or severe renal impairment, as defined by Cockroft-Gault formula, were included in the study. Only males or females with ESRI on hemodialysis (HD) were included in Group C. All subjects were between the ages of 18 and 75 years, inclusive, with a body mass index (BMI) of 18-35 kg/m^2. Control subjects were to have normal renal function (creatinine clearance 80 mL/min or greater).

Pharmacokinetic assessment

Plasma samples

Venous blood samples of approximately 7 mL each were drawn during the study for PK evaluation of doripenem. Except for the pre-dialysis infusion group, blood samples were obtained on Day 1 at pre-dose, and at post-start of infusion times of 15, 30, and 45 minutes, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, 18 and 24 hours. Blood samples were also obtained at 36 hours (Day 2) and 48 hours (Day 3) post-start of infusion. For the pre-dialysis infusion subjects in Group C, samples were drawn pre-infusion, 15 minutes following infusion, pre-dialysis; venous and dialysate samples were drawn at 1, 2, and 3 hours into dialysis, followed by standard venous samples at 8, 12, 16, 18 and 24 hours post-start of infusion.

Urine samples

Total urine collections were done according to the following schedule:
Day 1: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, and 12-24 hours from the start of the infusion.
Day 2: 24 - 48 hours from the start of the infusion.

Dialysate samples

On Day 1, dialysate samples for doripenem concentrations were taken from subjects who received a pre-dialysis infusion of doripenem; the nominal collection time-points were 1, 2, and 3 hours post-start of dialysis. All subjects on dialysis also had a 5 mL sample of their dialysate fluid collected at each occurrence of dialysis during the week of the study.

Analytical Methods

Plasma, urine and dialysate doripenem concentration data were provided by [redacted] A previously validated LC-MS/MS assay, using [redacted] detection by tandem mass spectrometry was used to quantify doripenem levels in the study samples. The limit of quantification was established at [redacted] g/ml.

Pharmacokinetic Methods

Non-compartmental analysis

Pharmacokinetic parameter values were estimated, where appropriate, by non-compartmental analysis using WinNonlin Pro® Version 4.0.1. Pharmacokinetic parameters included: C_{inf} (plasma concentration at end of infusion), CL_R (renal clearance of doripenem), CL_{CR} (creatinine clearance calculated from Cockroft-Gault), A_e (amount of doripenem recovered in each collection interval), and F_e (fraction of administered dose excreted in urine).

Compartmental analysis

Plasma concentration-time profiles of doripenem after single intravenous administration were described by exponential functions using WinNonlin Pro® Version 4.0.1. Mono-exponential and bi-exponential functions were fitted to the individual plasma doripenem concentration-time data. The most representative model was selected using an F-test (at the 5% level of significance) and the selected exponential function was applied to all subjects.

Statistical Methods

Creatinine clearance values calculated using the Cockroft-Gault formula were plotted against the primary PK parameter (AUC0-∞) to visually assess the differences in the pharmacokinetics of doripenem in subjects with different stages of renal impairment and subjects with normal renal function.

An ANOVA model was fitted to the log-transformed primary PK parameters (Cinf and AUC0-∞), using SAS version 8.1, with a fixed effect term for stage of renal impairment (normal, mild, moderate, severe, end-stage). All 8 normal subjects were pooled together assuming there was no period effect due to the different dates on which these subjects received their dose of doripenem. The model was used to estimate the ratio of each stage to normal renal function with 90% confidence intervals. A confidence interval which excludes 1 would give evidence of a statistical difference in the pharmacokinetics of doripenem in subjects with different stages of renal impairment compared to the normal matched controls. The differences between subjects with normal renal function and those with each stage of renal impairment were discussed in terms of statistical significance.

Results:

Study Population

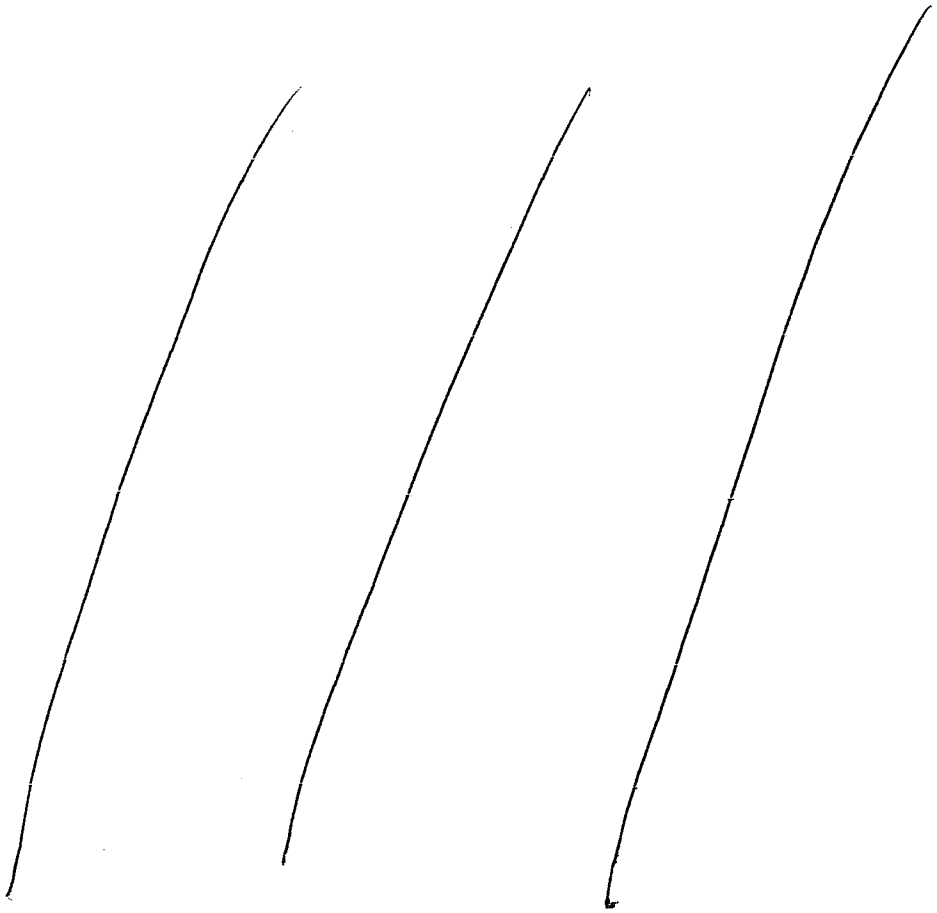
All 32 subjects who enrolled in the study completed participation. Of the 32 subjects, 27 were male and 5 were female. Four of the 5 female subjects were in the mild renal impairment group, and 1 was in the moderate group; there were no female subjects in the severe, ESRI or control groups.

Table 1. Demographic Details by Group

Variable	Renal impairment					
Statistic or Category	Mild (n=6)	Moderate (n=6)	Severe (n=6)	ESRI pre-dialysis (n=3)	ESRI post-dialysis (n=3)	Control (n = 8)
Age (years)						
Mean	53.3	45.2	50.5	60.3	47.0	45.3
SD	10.84	16.28	8.12	18.58	23.07	11.55
Height (m)						
Mean	1.647	1.760	1.752	1.720	1.733	1.745
SD	0.0720	0.1135	0.0679	0.0693	0.1007	0.0487
Weight (kg)						
Mean	69.55	77.53	79.57	84.63	74.03	80.54
SD	17.505	16.723	13.881	17.591	16.483	13.611
BMI (kg/m2)						
Mean	25.3	25.0	25.8	28.7	24.3	26.4
SD	4.59	4.05	3.49	5.51	4.04	3.81
CrCl (mL/min)						
Mean	68.2	40.8	19.1	11.8		104
SD	9.01	3.94	2.76	3.66		15.9
Race						
White	5	4	5	3	2	7
Black	1	2	1	0	1	1

Variable Statistic or Category	Renal impairment					
	Mild (n=6)	Moderate (n=6)	Severe (n=6)	ESRI pre-dialysis (n=3)	ESRI post-dialysis (n=3)	Control (n = 8)
Gender						
Male	2	5	6	3	3	8
Female	4	1	0	0	0	0

Analytical Performance



Pharmacokinetic Analysis

All 32 subjects who completed participation were included in the PK analyses. Mean plasma concentration-time profiles of doripenem following IV administration of 500 mg over 30 min. are detailed in the tables and figures below. Data is categorized by degree of renal impairment.

Figure 1. Arithmetic mean plasma concentration-time curves following 500 mg single dose doripenem.

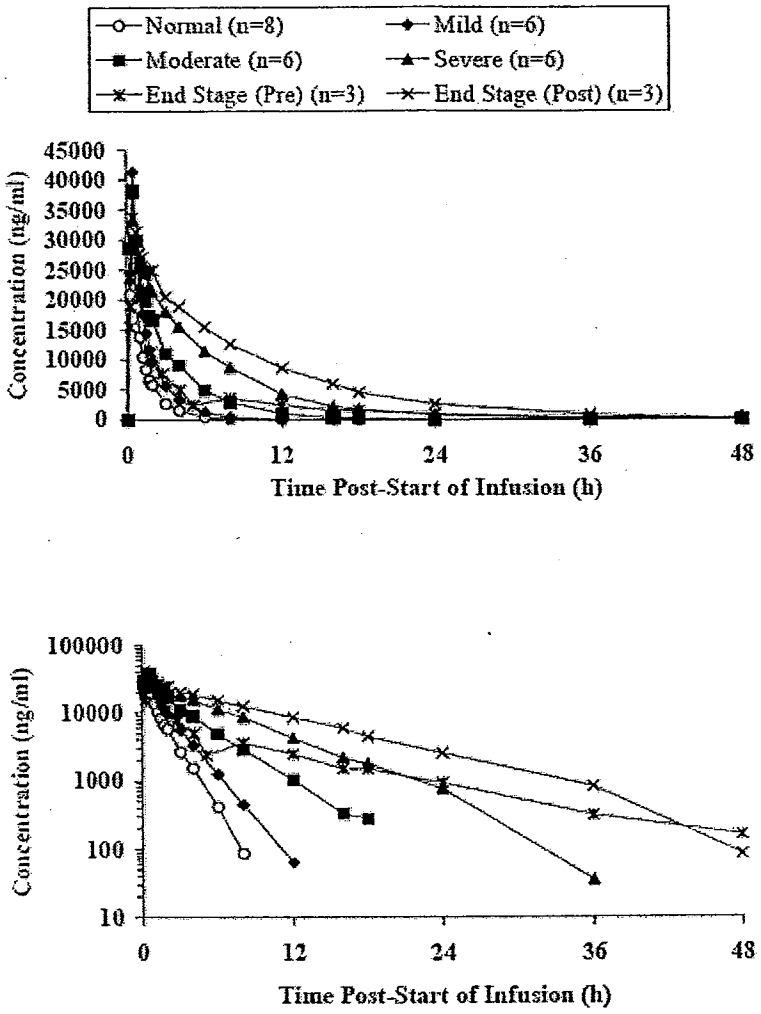


Table 2. Pharmacokinetic parameters of doripenem in renally-impaired and matched control subjects (geometric mean [CV%])

Parameter	Group A Mild	Group B Moderate	Group C End-stage (Pre)	Group C End-stage (Post)	Group D Severe
n	6	6	3	3	6
Cinf (ng/ml)	40267 (22.8)	37671 (15.7)	NC	33458 (16.3)	32771 (19.1)
Cmax (ng/ml)	40267 (22.8)	38127 (15.4)	NC	33458 (16.3)	35926 (17.3)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.25-0.5)	0.25 (0.25-0.25)[b]	0.5 (0.5-0.5)	0.5 (0.25-0.75)
AUC0-∞ (ng·h/ml)	59455 (29.4)	104505 (17.6)	99659 (8.46)	269541 (41.1)	188409 (13.9)
t1/2 (h)	1.27 (28.8)	2.60 (23.9)	8.77 (17.9)	6.20 (17.6)	4.60 (10.7)
CL (ml/min)	140 (23.8)	79.7 (15.4)	83.6 (8.48)	30.9 (45.6)	44.2 (14.6)
Vss (ml)	12673 (38.2)	15399 (21.2)	51195 (17.6)	16630 (21.7)	16610 (16.5)

[a] Median (min-max) data
[b] Underestimate, no samples were taken at end of infusion
Pre = pre-dialysis infusion, Post = post-dialysis infusion

	Normal Matched Controls				
Parameter	Group A	Group B	Group C	Group D	All Groups
n	2	2	2	2	8
Cinf (ng/ml)	38487 (45.5)	27180 (4.51)	31688 (5.99)	27056 (3.04)	30774 (29.1)
Cmax (ng/ml)	38487 (45.5)	27180 (4.51)	31688 (5.99)	27056 (3.04)	30774 (29.1)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)
AUC0-∞ (ng·h/ml)	37362 (25.3)	33601 (16.2)	39843 (14.0)	37181 (6.77)	36929 (14.4)
t1/2 (h)	0.926 (2.96)	1.24 (14.1)	1.07 (29.6)	1.16 (9.19)	1.09 (17.3)
CL (ml/min)	223 (25.3)	248 (16.2)	209 (14.0)	224 (6.77)	226 (14.5)
Vss (ml)	13792 (29.9)	20729 (1.59)	13476 (12.4)	17763 (2.43)	16174 (21.6)

[a] Median (min-max) data

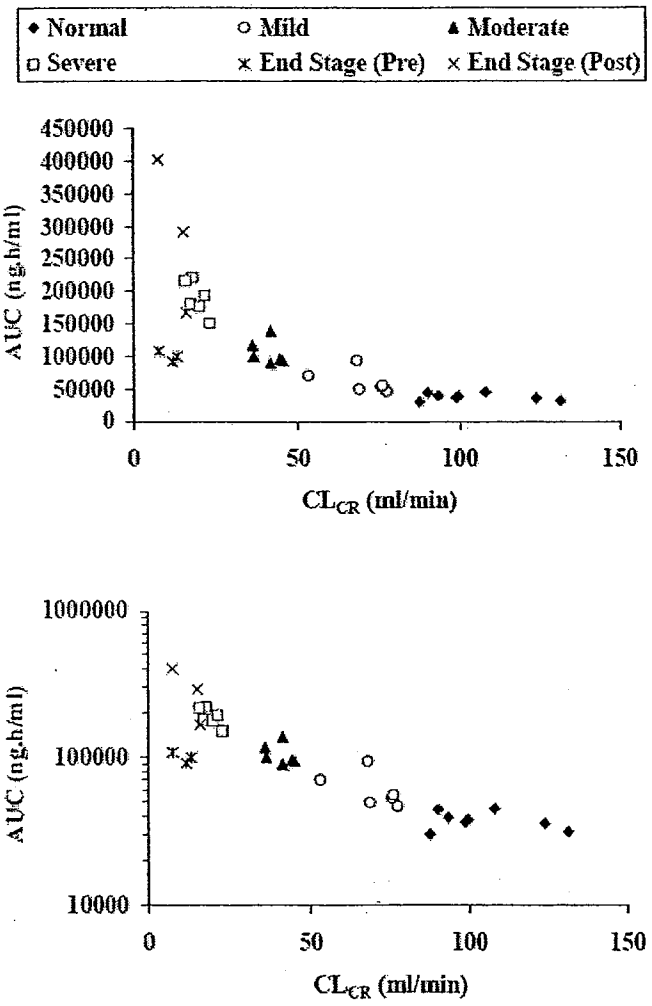
Following single intravenous administration of doripenem to subjects with normal or impaired renal function, maximum plasma concentrations were generally attained at the end of the infusion, i.e., at 0.5 h post-start of infusion. Thereafter, plasma doripenem concentrations appeared to decline in a bi-phasic manner. The mean apparent terminal elimination half-life appeared to increase with reduced renal function; mean values ranged from approximately 1 h (normal) to 5 h (severe). Estimates for subjects dependent on chronic dialysis (end-stage) were approximately 6 h (post-dialysis infusion) and 9 h (pre-dialysis infusion).

The apparent volume of distribution of doripenem at steady state did not appear to change appreciably with renal impairment. Estimates of Vss ranged from approximately 13 to 21 L in all subjects. The exception was for end-stage subjects that received a pre-dialysis infusion, where the Vss was approximately 51 L, likely due to the additional volume of the hemodialyser. The short apparent terminal elimination half-life observed in subjects with normal renal function, relative to those with renal impairment, is primarily a function of the higher clearance in these normal subjects, since Vss was generally similar across subjects. However, subjects that received

dialysis following the infusion of doripenem exhibited a longer apparent terminal elimination half-life due to a high volume of distribution.

Creatinine clearance (CL_{CR}) estimates were calculated from individual subjects' baseline creatinine concentration and demographic data. Figure 2 illustrates the relationship between the degree of renal impairment (as measured by CL_{CR}) and systemic exposure ($AUC_{0-\infty}$) of doripenem.

Figure 2. Relationship between creatinine clearance and $AUC_{0-\infty}$



A statistical assessment of the pharmacokinetic parameters C_{inf} and $AUC_{0-\infty}$ in relation to the degree of renal impairment is presented in the table below.

Table 3. Effect of renal impairment on systemic exposure following single intravenous administration of 500 mg doripenem.

Parameter	Renal impairment [Group]	Geo. Mean	Ratio of Geometric Least Square Means (Renal impairment /Normal) Estimate	90 % CI	p-value
C_{inf}	Normal [A-D]	30774	.	.	.
	Mild [A]	40267	1.31	(1.07, 1.59)	0.0287
	Moderate [B]	37671	1.22	(1.00, 1.49)	0.0929
	Severe [D]	32771	1.06	(0.87, 1.30)	0.5914
	End Stage (Post) [C]	33458	1.09	(0.85, 1.39)	0.5691
$AUC_{0-\infty}$	Normal [A-D]	36929	.	.	.
	Mild [A]	59455	1.61	(1.33, 1.95)	0.0003
	Moderate [B]	104505	2.83	(2.33, 3.43)	<.0001
	Severe [D]	188409	5.10	(4.20 6.19)	<.0001
	End Stage (Pre) [C]	99659	2.70	(2.12 3.44)	<.0001
	End Stage (Post) [C]	269541	7.30	(5.73 9.30)	<.0001

Estimates of doripenem C_{inf} in renally impaired subjects were, on average, generally not appreciably different to those observed in normal control subjects. Since the length of the infusion (0.5 h) was short relative to the apparent terminal elimination half-life for the different stages of renal impairment, steady state was not achieved at the end of infusion. $AUC_{0-\infty}$, on the other hand, is a more reliable index of systemic exposure to doripenem. Least square geometric means of doripenem $AUC_{0-\infty}$ were significantly higher than that of normal controls for all degrees of renal impairment. The extent of systemic exposure of doripenem in the mild, moderate, severe and end-stage (post-dialysis infusion) renal impairment groups were, on average, 1.6, 2.8, 5.1 and 7.3-fold greater than in the normal controls.

Dialysis

The effect of dialysis on the systemic exposure of doripenem was assessed in subjects with end-stage renal impairment that are dependent on chronic dialysis for renal function. The extent of systemic exposure ($AUC_{0-\infty}$) in subjects that were administered doripenem prior to dialysis (Subjects 17, 18 and 19), was on average, 2.7-fold lower than that in subjects that were administered doripenem after the completion of dialysis. The reduction in systemic concentrations of doripenem following dialysis were estimated in ESRD subjects (pre-dialysis infusion) by linear regression and back-extrapolation of the post-end of dialysis doripenem plasma concentrations to obtain a predicted pre-dialysis concentration (Table 4 and Figure 3 below). This estimation assumed that the plasma concentrations of doripenem declined in a mono-exponential manner post-start of dialysis, i.e. approximately 2 h post-start of the doripenem

were similar to the normal controls. By contrast, subjects 2, 3, 5 and 6 (mild renal impairment) had urinary recovery estimates ranging from 10.6 to 60.6 %. Renal clearance of doripenem in pooled, normal control subjects was, on average, 185 ml/min.

Compartmental PK Analysis
A bi-exponential function best represented the plasma doripenem concentration-time data. The derived PK parameters are reported below in Table 6.

Table 6. Pharmacokinetic parameter estimates of doripenem by compartmental analysis (Geometric Mean [CV%]

Parameter	Group A Mild	Group B Moderate	Group C End-stage (Post)	Group D Severe
N	5	4	2	5
Cmax (ng/ml)	39929 (23.7)	41278 (8.96)	35217 (20.9)	34515 (20.8)
$AUC_{0-\infty}$ (ng.h/ml)	60115 (31.2)	104650 (20.1)	254103 (60.5)	186699 (14.2)
t1/2 (h)	0.732 (30.9)	1.24 (33.6)	4.35 (52.8)	3.24 (18.6)
Vss (ml)	13345 (36.0)	14899 (7.39)	16969 (22.0)	16620 (18.3)
A (ng/ml)	37045 (37.3)	30205 (30.4)	13192 (10.4)	12257 (57.8)
B (ng/ml)	17864 (43.0)	27234 (7.92)	27096 (18.7)	27024 (21.9)
α (/h)	2.19 (50.0)	3.11 (7.95)	1.25 (96.9)	1.47 (69.1)
β (/h)	0.465 (24.3)	0.291 (18.8)	0.111 (42.6)	0.154 (7.22)

	Normal matched controls				
Parameter	Group A	Group B	Group C	Group D	All Groups
N	2	2	2	2	8
Cmax (ng/ml)	36224 (37.4)	25869 (1.18)	36151 (0.490)	28115 (0.228)	31240 (23.7)
$AUC_{0-\infty}$ (ng.h/ml)	36503 (31.2)	33996 (14.7)	38749 (13.7)	35234 (4.71)	36078 (15.4)
t1/2 (h)	0.175 (55.4)	0.618 (15.5)	0.245 (50.6)	0.501 (10.9)	0.340 (51.3)
Vss (ml)	13128 (19.3)	22411 (8.48)	12080 (0.933)	16675 (1.13)	15603 (27.8)
A (ng/ml)	122684 (27.9)	27747 (21.7)	80672 (72.4)	27095 (15.4)	52228 (78.5)
B (ng/ml)	21687 (18.5)	9161 (57.7)	27521 (27.9)	21642 (15.7)	18547 (39.8)
α (/h)	15.1 (101)	2.26 (13.8)	12.1 (107)	4.96 (55.2)	6.72 (119)
β (/h)	0.800 (29.0)	0.448 (15.7)	0.889 (1.79)	0.736 (2.10)	0.696 (27.8)

The PK parameters (Cmax, $AUC_{0-\infty}$ and V_{ss}) derived from bi-exponential function were similar to those obtained following non-compartmental analysis. The apparent terminal elimination half-life of doripenem was, in general, estimated to be shorter than that obtained by non-compartmental analysis.

Safety
In total, 23 treatment-emergent adverse events were reported by 14 subjects (44% of the study population) during the course of the study. Of the 14 subjects reporting adverse events, 9 (28% of the study population) experienced at least one treatment-emergent adverse event (11 adverse

events in total) that was considered possibly related to treatment with doripenem. The remaining 12 treatment-emergent adverse events were classified as either unrelated or unlikely to be related to treatment; no adverse events were considered probably related. The treatment-emergent adverse events that were considered possibly related to treatment were: headache (4 occurrences), drowsiness (2 occurrences), eye strain (1 occurrence), constipation (1 occurrence), diarrhea (1 occurrence), and nausea (2 occurrences). The majority of adverse events were mild in severity. It does not appear that subject incidence of adverse events correlated with the degree of renal impairment.

Abnormalities in laboratory data were consistent with subjects' medical histories, and were not thought to be related to administration of doripenem. No abnormalities were considered to be clinically significant. There were no apparent clinically relevant changes in liver function parameters in this study.

Sponsor's Conclusions

Safety

- Single doses of 500 mg doripenem appeared to be safe and well-tolerated when administered intravenously to the renally impaired and control subjects in this study.
- The subject incidence of adverse events did not appear to have any correlation with the degree of renal impairment.
- There were no clinically significant abnormalities in laboratory test results, including liver function tests, physical examinations, vital sign measurements or ECG recordings. There were no apparent trends in safety parameters over time, and there were no apparent differences between subjects with differing degrees of renal impairment.

Pharmacokinetics

- Following single intravenous administration of doripenem to subjects with normal or impaired renal function, maximum plasma concentrations were generally attained at the end of the infusion period. Thereafter, plasma doripenem concentrations declined in a bi-phasic manner.
- The mean apparent terminal elimination half-life appeared to increase with reduced renal function, ranging from 1 h (normal controls) to 5 h (severe renal impairment). Estimates of the mean apparent terminal elimination half-life for end-stage renal impaired subjects were approximately 6 h (post-dialysis infusion) and 9 h (pre-dialysis infusion).
- Plasma clearance estimates tended to decrease with decreased renal function ranging from, on average, 140 mL/min (mild) to 30.9 mL/min (end-stage, post-dialysis).
- The apparent volume of distribution of doripenem at steady state (approximately 13000 to 21000 mL) approximated the extracellular fluid of man and did not tend to change appreciably with renal impairment. The exception was for end-stage subjects that received a pre-dialysis infusion (Vss = approximately 51000 mL), which most likely represents the additional volume of the hemodialyser.
- Given that the apparent volume of distribution did not appear to change considerably in renally impaired subjects, the longer elimination half-life for these subjects was a result of reduced plasma clearance.
- The extent of systemic exposure ($AUC_{0-\infty}$) of doripenem in mild, moderate, severe and ESRD groups were, on average, 1.6, 2.8, 5.10 and 7.3-fold greater than in the pooled normal controls. The 90% confidence intervals for the ratios indicate statistical significance.

- The extent of systemic exposure ($AUC_{0-\infty}$) of doripenem in subjects administered doripenem prior to dialysis was, on average, 2.7-fold lower than in subject administered doripenem after dialysis.
- Urinary excretion appeared to be complete by 6 h post-start of infusion in normal controls. Renal clearance in normal subjects was, on average, 185 mL/min, which is similar to glomerular filtration rate in man. Renal clearance decreased with increasing renal impairment.
- Plasma doripenem concentration vs time profiles were best represented by a bi-exponential function with uniform weighting. PK parameter values derived from the bi-exponential function were similar to those obtained from the non-compartmental analysis.

Reviewer assessment:
The investigators did not analyze plasma or urine samples for the M1 (open-ring) metabolite. The urinary recovery of doripenem in normal controls reported in this study (83%) was higher than that reported in other healthy volunteer studies (generally 60 – 70%), as was the renal clearance (11.3 L/h, as compared to 9.5 – 10.3 L/hr). It is unclear what may have contributed to this finding.

Plasma, urine and dialysate specimens were stored frozen at - 70°C for a maximum of 13 months prior to completion of analysis (based on dates provided in the study report). Long-term stability of doripenem in urine and plasma has been demonstrated only up to 9 months at –70 °C. Doripenem-M1 stability in urine has been established for only 59 days at –70 °C, and doripenem and M1 stability in dialysate fluid has been established for 98 days and 114 days, respectively, at –70 °C. The effect of longer storage periods on specimen stability is unknown. However, the variability in exposure between subjects in this study (%CV) was similar to the variability reported in other studies, suggesting significant loss of analytes likely did not occur during storage.

Study DORI-NOS-1005

An Open-label Pharmacokinetics Study of Doripenem in Healthy Subjects and Subjects with End-Stage Renal Disease Receiving Hemodialysis

Dates: May – June 2006

Study Sites: [redacted]

Objective:

To characterize the pharmacokinetics of doripenem and its metabolite (doripenem M1) after a single 500-mg infusion before and after dialysis to ESRD subjects. Pharmacokinetics of ESRD and normal subjects were compared, and the percent of study drug removed by dialysis was determined. Safety was also assessed.

Methods:

Study Design

A total of 12 subjects, 6 with ESRD on hemodialysis (HD), and 6 healthy subjects with normal renal function were enrolled. The study had 3 phases: a 20-day pretreatment screening phase; a 3-day, open-label treatment phase for subjects with normal renal function, or two 3 day treatment periods separated by a 7- to 14-day washout period for subjects with ESRD, and a post-treatment phase (end-of-study procedures). Doripenem was administered as a single-dose of 500 mg over 60 min to all subjects. Normal subjects received only 1 single doripenem dose, while ESRD subjects received a single 500 mg infusion 2 hours before the start of HD in Period 1, and a single 500 mg infusion 1 hour after the HD session in Period 2.

Test Product

Doripenem 250 mg and 500 mg were reconstituted with sterile water for injection (10 mL per vial). The resultant solution was further diluted with 276 mL of normal saline for infusion of the 500-mg dose. The 500-mg doripenem solution was administered as a constant-rate i.v. infusion given over 60 minutes in this study. The lot numbers and expiration dates for both doripenem doses are: 250 mg, Lot CF5023, March, 2007, and 500 mg, Lot CF5049, August 2007.

Inclusion criteria

- Men or women between 18 and 75 years of age, inclusive
- Body mass index (BMI) between 18 to 38 kg/m2, inclusive
- • Healthy subjects were comparable in mean age (± 20 years) and mean weight (±30%) to subjects with renal impairment;
- Good health, as confirmed by investigator after review of screening physical examination, medical history, vital signs, 12-lead ECG, and clinical laboratory tests
- Normal renal function (CrCl ≥ 80 mL/min) calculated by Cockroft-Gault formula, using actual body weight
- Subjects selected for the group with ESRD: Stable physical condition consistent with ESRD based on finding of screening physical examination, medical history, vital signs, 12-lead ECG, and results of clinical laboratory tests

Pharmacokinetic assessment

Blood was collected for determination of doripenem and doripenem-M1 plasma concentrations at the following time points: 0 (pre-dose), and at 15 min, 30 min, 45 min, 1 h, 1.25, 1.5. 1.75, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, and 48 hours post-start of infusion. For ESRD subjects, additional 3 mL samples of arterial (pre-dialyzed) samples.

Urine was collected pre-dose at 0, 0-4, 4-8, 8-12, 12-24, and 24-48 hours post-start of infusion.

Dialysate was collected at 2-2.5, 2.5-3, 3-3.5, 3.5-4, 4-4.5, 4.5-5, 5-5.5, and 5.5-6 hours post-start of infusion (for ESRD subjects receiving test drug prior to dialysis only).

Analytical Methods

Doripenem and doripenem-M1 were measured in plasma, urine and dialysate by validated LC-MS/MS methods. The LLOQ for doripenem and doripenem-M1 in plasma and dialysate were [redacted] µg/mL, respectively. The LLOQ for the two analytes in urine was [redacted] µg/mL.

Pharmacokinetic Methods

Pharmacokinetic parameters were calculated from doripenem and its microbiologically inactive metabolite, doripenem-M1, from plasma concentrations by non-compartmental methods using WinNonlin® (Pharsight Corp, Cary, NC). The plasma PK parameters evaluated were ER, AUClast, AUC∞, CL, Vss, t½, and λz. Additionally, CL_R, CL_{HD}, Ae, Ae% and %DIAL (% of administered dose recovered in dialysis fluid) were determined for doripenem and doripenem-M1 based on the individual subject urinary excretion data and dialysate concentrations.

Statistical Methods

All estimated plasma, urine, and dialysate pharmacokinetic parameters of doripenem and doripenem-M-1 were summarized per subject group with mean, median, geometric mean, minimum value, maximum value, standard deviation, and coefficient of variation (%).
The primary parameters of interest for the statistical analysis were AUC and Cinf. The analysis was performed on log-transformed estimated PK parameters and was restricted to data from healthy subjects and ESRD post-dialysis only. Analysis of variance models were fit to the logarithm of the selected PK parameters with group (healthy, ESRD-post-dialysis) as a factor. Using the least square means and inter-subject SD from the model, the estimated difference in means and 90% confidence intervals for the difference in means between ESRD-post-HD and healthy subjects were obtained. The results were back-transformed using anti-logarithm to obtain the estimated ratio of mean PK parameters and 90% confidence intervals for the ratio of means. Similar ANOVA models were used to compare mean Cinf and AUCs of doripenem and doripenem-M1 by restricting to data from the healthy subjects and ESRD-pre-HD only.

Results:

Study Population

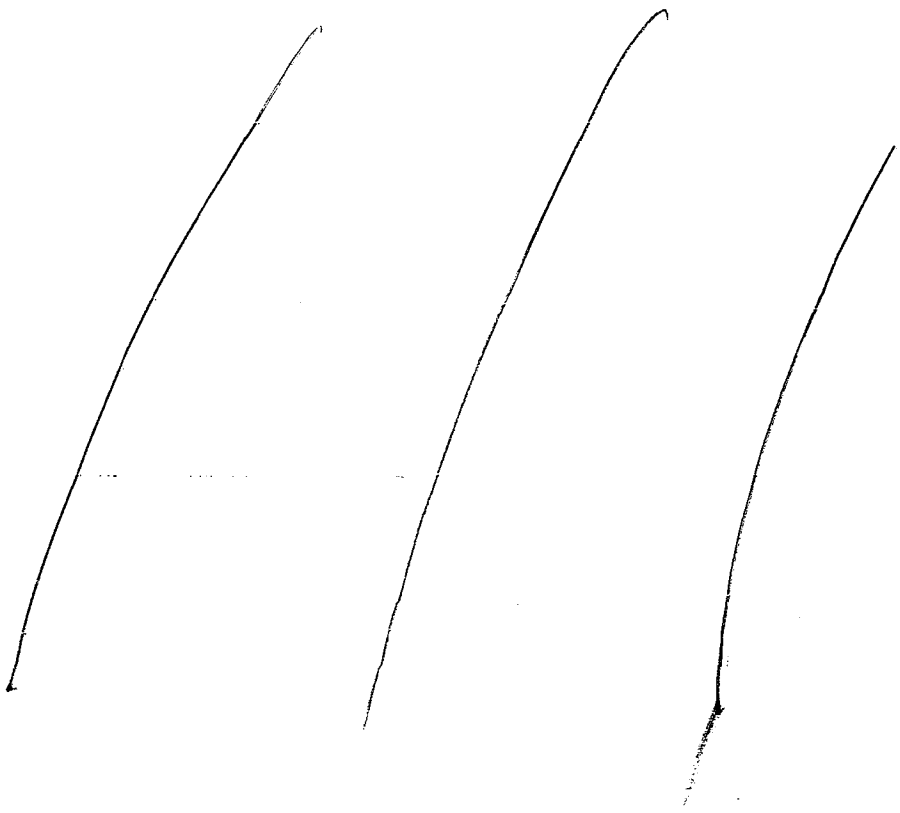
A total of 12 subjects (6 healthy subjects and 6 ESRD) enrolled in the study, received study treatment, and completed participation. Complete demographic details are presented below.

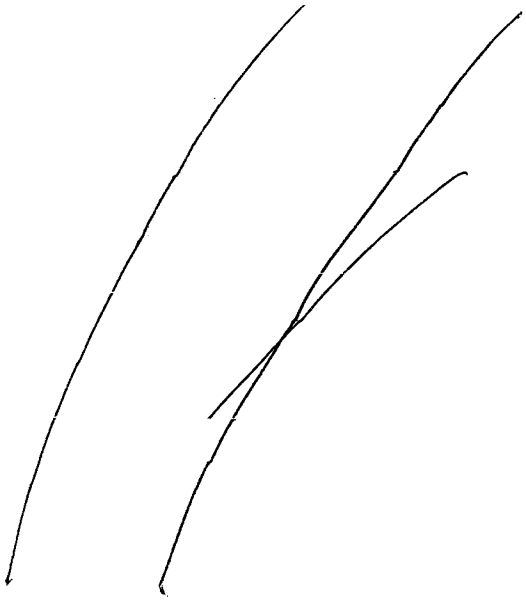
Table 1. Demographic Details by Group

Subjects	Healthy (N=6)	ESRD subjects (N=6)	Total (N=12)
Race, n (%)			
White	1 (17)	0	1 (8)
Black or African American	3 (50)	4 (67)	7 (58)
Hispanic or Latino	2 (33)	2 (33)	4 (33)
Ethnicity, n (%)			
Hispanic or Latino	2 (33)	2 (33)	4 (33)
Sex, n (%)			
Female	1 (17)	1 (17)	2 (17)
Male	5 (83)	5 (83)	10 (83)

Subjects	Healthy (N=6)	ESRD subjects (N=6)	----- Total ---- (N=12)
Age (years)			
Mean (SD)	40.7 (8.66)	46.0 (6.36)	43.3 (7.76)
Median	44.0	43.5	43.5
Range	(28-49)	(40-54)	(28-54)
Weight (kg)			
Mean (SD)	85.7 (19.19)	92.3 (23.29)	89.0 (20.63)
Median	84.5	94.8	85.3
Range	(64-116)	(60-121)	(60-121)
Height (cm)			
Mean (SD)	172.2 (11.54)	173.9 (6.22)	173.0 (8.89)
Median	169.6	171.5	170.6
Range	(160-189)	(167-183)	(160-189)
Body mass index (kg/m2)			
Mean (SD)	28.7 (3.97)	30.3 (6.43)	29.5 (5.16)
Median	29.6	31.7	30.3
Range	(24-33)	(21-37)	(21-37)

Analytical Performance





Pharmacokinetic Analysis

Plasma Data

Linear plots of doripenem and doripenem-M1 plasma concentrations for hours 0 – 48 and 0 – 12 (doripenem only) are presented in Figures 1 - 3 below. Mean PK parameters for the two analytes are listed in Table 2.

Figure 1. Mean doripenem plasma concentration time profiles for 0-48 hours

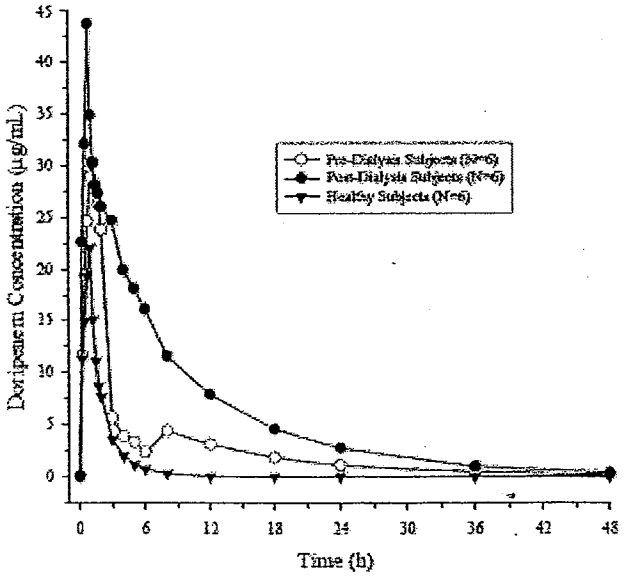


Figure 2. Mean doripenem plasma concentration time profiles for 0-12 hours

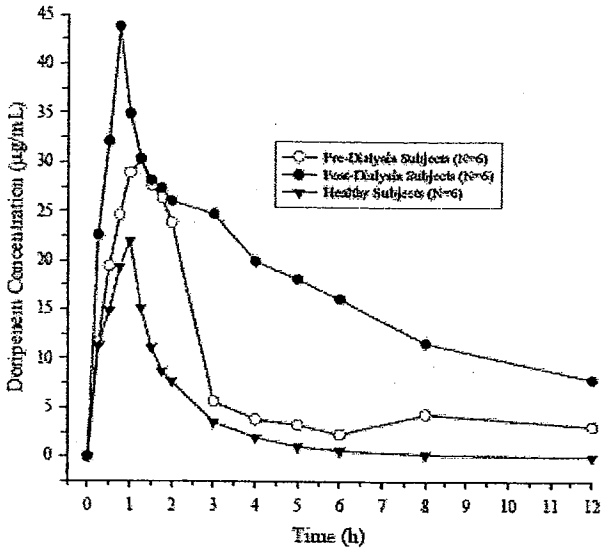


Figure 3. Mean doripenem-M1 plasma concentration time profiles for 48 hours.

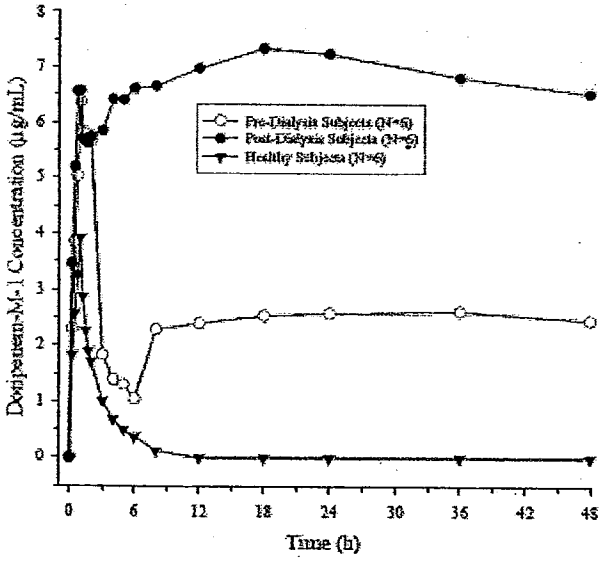


Table 2. Mean (SD) pharmacokinetic parameters of doripenem in ESRD and healthy subjects

PK Parameters	ESRD Subjects Pre-Dialysis (N=6)	ESRD Subjects Post-Dialysis (N=6)	Healthy Subjects (N=6)
Cinf (µg/mL)	28.9 (7.04)	34.9 (10.3)	22.0 (4.54)

PK Parameters	ESRD Subjects Pre-Dialysis (N=6)	ESRD Subjects Post-Dialysis (N=6)	Healthy Subjects (N=6)
Cmax (μg/mL)	31.4 (7.41)	49.6 (32.99)	22.0 (4.54)
tmax[a] (hr)	1.13 (1.00-1.25)	1.00 (0.67-1.25)	1.00 (1.00-1.02
AUClast (μg.hr/mL)	127 (22.2)	297 (75.9)	38.3 (6.29)
AUC∞ (μg.hr/mL)	129 (23.1)	302 (76.4)	38.7 (6.24)
t1/2 (hr)	7.94 (1.70)	7.81 (1.53)	1.30 (0.238)
λz (hr-1)	0.0911 (0.0215)	0.0919 (0.0195)	0.548 (0.0848)
CL (L/hr)	3.99 (0.822)	1.76 (0.492)	13.2 (1.98)
Vss (L)	33.1 (9.06)	16.8 (4.89)	17.5 (4.82)
Ae (μg)	NAs	NA	362092 (145032)
Ae, %Dose	NA	NA	72.4 (29.0)
CLCR (mL/min)	NA	NA	133 (24.3)
CLR (L/hr)	NA	NA	9.66 (4.19)

NA – Not assessable

[a] Data represent Median (range)

For both ESRD and healthy subjects, maximum doripenem plasma concentrations were generally attained at the end of the infusion (i.e. 1 hour post-start of infusion). The highest concentrations were found in ESRD subjects during the post-dialysis treatment and were markedly different from those observed for healthy subjects, as demonstrated in Figure 1 above. For ESRD subjects given doripenem pre-dialysis, the mean plasma concentration of doripenem at 2 hours post-start of infusion (start of dialysis) was 23.8 μg/mL. After termination of the dialysis (at 6 hours) the mean plasma concentration was 2.31 μg/mL -- which represents a 90% decrease in doripenem concentration. However, mean plasma doripenem levels rose rapidly immediately after the dialysis session, suggesting redistribution into the plasma.

Doripenem-M-1 appeared rapidly in plasma, indicating a fast metabolism of doripenem to doripenem-M-1 in healthy and ESRD subjects. Similar to doripenem, the concentrations of the metabolite in plasma for ESRD subjects during the post-dialysis treatment were markedly higher than those for healthy subjects. Similar to doripenem, doripenem-M1 AUC_{last} for the pre-dialysis treatment group was on average 37% of that for the post-dialysis treatment.

A 4-h dialysis session starting 1 hour after the end of the doripenem infusion reduced plasma levels of doripenem-M1 by about 82%, as compared to at the start of dialysis (5.66 μg/ml vs. 1.04 μg/ml). Similar to doripenem, a rebound in doripenem-M1 plasma concentrations were observed immediately post-end of dialysis. One of the 6 ESRD subjects (Subject # 100005) had a measurable pre-dose doripenem-M1 concentration (0.222 μg/ml) during post-dialysis treatment (Period 2). In the remaining 5 ESRD subjects, the pre-dose doripenem-M1 concentrations were below quantifiable limit during Period 2.

Compared with the mean plasma clearance of doripenem in healthy subjects (13.2 + 1.98 L/hr), that of subjects with ESRD was reduced by 87% (1.76 + 0.49 L/hr) for post-dialysis infusion and by 70% (3.99 + 0.82 L/hr) for pre-dialysis infusion subjects. Compared with the mean terminal half-life value for healthy subjects, the value increased by approximately 6-fold in ESRD subjects

regardless of dialysis group. The mean Vss values were similar between healthy subjects and in subjects that were administered doripenem after the completion of dialysis, versus a Vss value of approximately twice that observed for pre-dialysis treatment. The inter-subject variability (CV%) on the pharmacokinetic parameters in healthy subjects, pre-dialysis and post-dialysis infusion periods varied from approximately 16%-40%, 18%-27% and 20%-67%, respectively.

Urinary Excretion
In healthy subjects, urinary recovery of doripenem was completed within 24 hours post-start of infusion. About 72% of the dose was recovered as unchanged drug in urine by 24 hours, while approximately 63% of the dose was recovered in urine as unchanged drug during the first 4 hours. In contrast, the urinary recovery of doripenem-M1 was not completed by 48 hours post-start of infusion (9.8% within 0-24 h and 0.2% within 24-48 h); about 10% of the administered dose was eliminated in urine as the metabolite doripenem-M-1 within 48 h. Overall, approximately 82% of the dose was recovered in urine as doripenem and doripenem-M-1.

Effect of Dialysis
The HD extraction ratio and clearance for doripenem and the M1 metabolite are summarized in Table 3 below.

Table 3. Mean (SD) doripenem and doripenem-M1 extraction ratio (ER) and HD clearance (CL_{HD}) in ESRD subjects receiving pre-dialysis treatment

Analyte Time	ER	CL_{HD} (L/hr)
Doripenem		
3 hr (N=6)	0.585 (0.0684)	7.44 (0.825)
4 hr (N=6)	0.594 (0.0807)	7.52 (0.508)
5 hr (N=5)	0.568 (0.0680)	7.40 (0.601)
6 hr (N=6)	0.493 (0.206)	6.26 (2.55)
Total (N=23)	0.560 (0.121)	7.15 (1.43)
Doripenem-M1		
3 hr (N=6)	0.506 (0.0903)	6.41 (0.929)
4 hr (N=6)	0.517 (0.0840)	6.55 (0.807)
5 hr (N=5)	0.502 (0.0838)	6.54 (0.935)
6 hr (N=6)	0.439 (0.136)	5.57 (1.63)
Total (N=23)	0.490 (0.0998)	6.25 (1.13)

A 4-hour HD session starting 1 hour after the end of infusion reduced plasma levels of doripenem by about 90% (Range: 81% to 95%); accordingly, doripenem was detected in the dialysate at mean concentrations of about 3.51 µg/ml (Range: [illegible] µg/ml) at the beginning and 0.90 µg/ml (range: [illegible] µg/ml) at the end of the dialysis session. Similarly, doripenem-M-1 was detected in the dialysate at mean concentrations of about 0.285 µg/ml (range: BLQ – [illegible] µg/ml) at the beginning and 0.198 µg/ml (range: BQL – [illegible] µg/ml) at the end of dialysis session.

The doripenem extraction ratios remained fairly constant throughout the 4-hour HD session, with an overall mean extraction ratio of 0.560, thus verifying the removal of doripenem during HD. The mean HD clearance of doripenem was 7.15 L/hr, and the amount of doripenem removed by HD was 231 mg (46% of the dose). Similarly the mean overall extraction ratio for doripenem-M1 was 0.490 and the mean HD clearance of doripenem-M-1 was 6.25 L/hr. The mean recovery

of doripenem-M-1 in the dialysate was 28 mg (5.6% of the dose). The mean total recovery of doripenem and doripenem-M-1 in the dialysate during the 4-hour HD session was 259 mg (52% of the dose).

Safety
Three subjects (25%) experienced at least 1 treatment-emergent adverse event. Of these, 2 healthy subjects each had one drug-related adverse event; one was considered moderate (diarrhea) and one (headache), mild in severity. One ESRD subject had 3 adverse events that were not considered drug related. Two (nausea and vomiting) were considered moderate and one (headache) mild in severity. All adverse events resolved without sequelae.

Sporadic changes in hematology, serum chemistry, and urinalysis results among healthy and ESRD subjects occurred during the study. Except for decreases in sodium levels in ESRD subjects, which were likely related to HD, all other results were single events that were probably not related to study drug.

Sponsor's Conclusions
Renal CL in healthy subjects was 9.66 L/hr, and 72% of administered dose was excreted unchanged in the urine within 24 hours, which is consistent with results obtained for healthy volunteers in the previous renal impairment study (DORI-02). Approximately 10% of the dose was excreted as metabolite doripenem-M1 within 48 hours in healthy subjects.

The increase in maximum concentration of doripenem in plasma seen in patients with ESRD (post-dialysis treatment) is mainly explained by the lack of renal elimination, as differences in Vss were not observed. The high and persistent concentrations of circulating metabolite (doripenem-M1) observed in ESRD subjects may be due to (a) lack of renal elimination of doripenem in ESRD subjects, (b) lack of renal elimination of doripenem-M1 (c) increased metabolism to M1, and (d) very little to no subsequent metabolism of doripenem-M1 based on its flat concentration-time profile.

During post-dialysis treatment (Period 2), the pre-dose doripenem-M1 concentrations were below the quantifiable limit in the majority of ESRD subjects (n=5/6). Only one of the 6 ESRD subjects had a measurable pre-dose doripenem-M-1 concentration (0.222 µg/ml) during Period 2. Since ESRD subjects had 2 additional HD sessions between treatment periods, these data suggest that doripenem-M1 is removed by HD.

The mean AUC∞ of doripenem in ESRD subjects (post-dialysis infusion) increased to 7.8 times the respective values obtained with healthy subjects, and t1/2 for these patients were prolonged to 6 times those for subjects with normal renal function. These results are consistent with data from the previously conducted renal impairment study (DORI-02). The extent of systemic exposure (AUClast) of doripenem-M1 in these patients increased to 39 times the respective values obtained with healthy subjects. The mean AUC∞ in subjects that were administered doripenem after the completion of dialysis was 2.3-fold lower than in subjects that were administered doripenem prior to dialysis.

The hemodialysis CL of doripenem calculated from the blood flow rate and doripenem concentrations in plasma of both arterial and venous lines was 7.15 L/hr during HD. Hemodialysis significantly removed plasma doripenem, but half-life during HD was still six times longer than that reported in subjects with normal renal function. Moreover, AUC∞ in pre-dialysis infusion subjects was still three times higher than in subjects with normal renal function.

Following a 500 mg one hour infusion of doripenem, HD removed approximately 231 mg (46% of the dose) of doripenem and 28 mg (5.6% of the dose) of its metabolite during a standard 4-hour session. After a single dialysis session, approximately 52% of the total administered dose of doripenem was recovered in the dialysate. Immediately after HD, the plasma doripenem and doripenem-M-1 level increased due to redistribution back into plasma.

Adverse events among healthy and ESRD subjects were uncommon, and only 6 events (either headache or gastrointestinal events) were reported by 3 subjects. Sporadic changes in hematology, serum chemistry, and urinalysis results among healthy and ESRD subjects occurred during the study, but none was considered clinically meaningful.

Reviewer assessment:

The Sponsor's conclusions are appropriate based on the data presented in the study report.

Study DORI-NOS-1006

An Open-label Pharmacokinetics Study of Doripenem in Healthy Elderly and Non-Elderly Adults

Dates: April - May 2006

Study Sites: [redacted]

Objective:

The primary objective was to evaluate the effect of age on the pharmacokinetics (PK) of doripenem, comparing healthy elderly subjects and healthy non-elderly subjects. The secondary objectives were to evaluate the differences in doripenem PK between men and women and to assess the safety and tolerability of a doripenem 500 mg infusion in all subjects.

Methods:

Study Design

This was an open-label, single-center study. Following a 21-day screening period 24 healthy elderly and non-elderly subjects received a single 500 mg dose of doripenem infused over 1 hour. Twelve (6 men and 6 women) healthy non-elderly adults and 12 healthy elderly adults (6 men and 6 women) were enrolled. At least 3 men and 3 women from the elderly group were 75 years or older. Elderly subjects were enrolled first. Non-elderly men and women were then matched by body weight to within ± 20% of the mean value for the elderly men and women, respectively

Test Product

The following test products were reconstituted using Sterile Water for Injection (WFI) USP, and subsequently diluted in normal saline to prepare the test treatment. The test treatment was a single 500 mg dose of doripenem administered intravenously as a 1-hour infusion.

Doripenem for injection 500 mg vials
Lot Number: CF5049
Expiration Date: Aug-2007
Manufacturer: Shionogi & Co., Ltd.

Doripenem for injection 250 mg vials
Lot Number: CF5023
Expiration Date: Mar-2007
Manufacturer: Shionogi & Co., Ltd.

Inclusion criteria

Non-elderly adults were enrolled if aged 18 through 45 years, inclusive, and healthy by physical exam, medical history and laboratory screening. The elderly adults were aged 65 years and older, with at least 3 men and 3 women age 75 years or older, and age-appropriately healthy as evaluated. Non-elderly men and women matched to the elderly by body weight to within ± 20% of the mean value for the elderly men and women, respectively. Other inclusion criteria included a BMI between 18 and 30 kg/m^2, inclusive, and normal renal function (elderly $CL_{CR} \geq 55$ mL/min; non-elderly $CL_{CR} \geq 80$ mL/min) as determined by Cockcroft-Gault equation.

Pharmacokinetic assessment

Blood samples (3 mL) were drawn for determination of PK parameters at the following time points: 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.08, 1.17, 1.5, 1.75, 2, 3, 4, 6, 8, 12 and 24 hours post-

start of infusion. Urine samples were collected for PK determinations at 0-4, 4-8, 8-12, and 12-24 hours following the start of infusion.

Analytical Methods

Plasma concentrations of doripenem and doripenem-M-1 were determined using validated LC-MS/MS assays by

Urine concentrations of doripenem and doripenem-M1 were determined using validated LC-MS/MS assays.

Pharmacokinetic Methods

Pharmacokinetic parameters were calculated from doripenem and its microbiologically inactive metabolite, doripenem-M1, from plasma concentrations by non-compartmental methods using WinNonlin® (Pharsight Corp, Cary, NC). The plasma PK parameters evaluated were Cmax, tmax, AUClast, AUC∞, CL, Vss, t½, and λz. Additionally, CL_R, Ae, and %Ae were determined for doripenem and doripenem-M1 based on the individual subject urinary excretion data. Non-renal clearance (CL_{NR}) also was determined. Creatinine clearance (CL_{CR}) was determined based on 12-hour serum creatinine concentration and 24-hour urinary excretion data.

Statistical Methods

Descriptive statistics were analyzed for plasma doripenem and doripenem-M1 concentrations and PK parameters by age group and by sex. The PK parameters (AUClast, AUC∞, and Cmax) were statistically analyzed using mixed effects models. Each model was fit to the data using natural log (ln)-transformed AUClast, AUC∞, and Cmax as the dependent variable, and age group, sex, and age group by sex interaction as the fixed effects. The 90% confidence intervals (CIs) for the difference in the least-squares (LS) means of the ln-transformed AUClast, AUC∞, and Cmax were constructed, then reverse-transformed to obtain 90% CIs for the ratio of the geometric mean AUClast, AUC∞, and Cmax. In addition, the effects of CL_{CR} and body weight on doripenem and doripenem-M1 PK parameters were evaluated via linear regression.

Results:

Study Population

A total of 24 subjects (12 elderly and 12 non-elderly) enrolled in the study, received study treatment, and completed participation. The mean age for elderly subjects was 74 years (range 66-84), versus 19.8 years (range 18-29) for non-elderly. Complete demographic details are presented below.

Table 1. Demographic Details by Group

	Non-Elderly (N=12)	Elderly (N=12)	Male (N=12)	Female (N=12)	Total (N=24)
Race, n (%)					
N	12	12	12	12	24
White	12 (100)	11 (92)	12 (100)	11 (92)	23 (96)
Asian	0	1 (8)	0	1 (8)	1 (4)

	Non-Elderly (N=12)	Elderly (N=12)	Male (N=12)	Female (N=12)	Total (N=24)
Age (Years)					
N	12	12	12	12	24
Mean (SD)	19.8 (3.07)	74.1 (7.04)	47.4 (28.53)	46.5 (29.15)	47.0 (28.21)
Median	19.0	73.0	47.5	43.5	47.5
Range	(18;29)	(66;84)	(18;84)	(18;84)	(18;84)
Weight (kg)					
N	12	12	12	12	24
Mean (SD)	72.7 (11.21)	75.9 (15.74)	82.6 (11.71)	65.9 (9.44)	74.3 (13.46)
Median	70.3	74.0	82.3	68.5	70.8
Range	(56;92)	(46;102)	(69;102)	(46;79)	(46;102)
Height (cm)					
N	12	12	12	12	24
Mean (SD)	172.4 (8.50)	168.1 (11.91)	178.3 (4.11)	162.3 (8.24)	170.3 (10.36)
Median	175.5	169.0	180.0	162.0	172.5
Range	(158;181)	(146;185)	(172;185)	(146;176)	(146;185)
Body Mass Index (kg/m2)					
N	12	12	12	12	24
Mean (SD)	24.4 (2.86)	26.7 (3.63)	26.0 (3.72)	25.0 (3.12)	25.5 (3.40)
Median	24.3	26.7	26.4	25.2	25.4
Range	(21;30)	(20;33)	(21;33)	(20;31)	(20;33)

Analytical Performance

Pharmacokinetic Analysis

Mean doripenem and doripenem-M1 plasma concentration-time profiles for elderly vs. non-elderly and male vs. female subjects are shown in Figures 1 and 2 below. Tables 2 and 3 contain a summary of PK parameters for doripenem and the M1 metabolite by age group and sex.

Elderly vs. Non-elderly

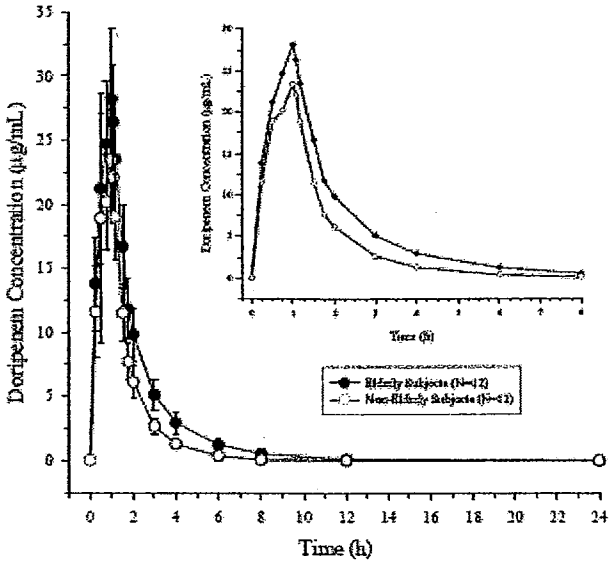
Mean t½ was approximately 0.5 hours longer in elderly subjects compared to non-elderly subjects (1.53 hours and 0.997 hours, respectively). Total body clearance of doripenem in elderly subjects was approximately 33% lower compared to non-elderly subjects (9.31 L/hr and 13.9 L/hr, respectively), and CL_R of doripenem in elderly subjects was approximately 30% lower compared to non-elderly subjects (6.69 L/hr and 9.56 L/hr, respectively). Doripenem exposure, as assessed by AUC, was approximately 1.5-fold greater in elderly subjects. CL_{NR} was 40% lower in elderly compared to non-elderly subjects. Doripenem Vss (approximately 14 L) was essentially the same between elderly and non-elderly subjects. Creatinine clearance was 32% lower in elderly compared to non-elderly subjects.

Doripenem and the M1 metabolite reached C_{max} values at 1 hour for both elderly and non-elderly subjects. Doripenem-M1 C_{max} and $AUC\infty$ were approximately 2-fold greater in elderly subjects as compared to non-elderly subjects. The apparent $t_{1/2}$ of doripenem-M1 was approximately 0.9 hours longer in elderly vs. non-elderly subjects. Doripenem-M1 CL_R in elderly subjects was approximately 70% lower compared to non-elderly subjects (3.06 L/hr and 10.3 L/hr, respectively), and the percentage of the dose recovered in urine as doripenem-M1 was 28% lower in the elderly compared to the non-elderly.

Male vs. Female

Mean t½ was approximately 0.2 hours shorter in female subjects compared to male subjects (1.17 hours and 1.36 hours, respectively). Doripenem CL, CL_R, and CL_{NR} in females were 12%, 11%, and 15% lower, respectively, than in males. Creatinine clearance was 26% lower in females than in males (79 mL/min vs 107 mL/min). Doripenem Vss in females was 26% lower than in males. Overall exposure of doripenem, as assessed by mean AUC_∞, was only slighter greater in females – 48.3 µg.hr/mL versus 43.7 µg.hr/mL. However, evaluation of the geometric mean ratio (GMR) indicates a statistically significant difference of 12% (Table 4). Doripenem-M1 C_{max} was similar in females and males, while AUC was 15% lower compared to males. Renal clearance and urinary recovery of doripenem-M1 were approximately 15% and 24% lower, respectively, in females compared to males. Similar reductions in CL_R and Ae for females vs. males were seen within each age group.

Figure 1. Mean (SD) doripenem and doripenem-M1 plasma concentration-time profiles for elderly vs. non-elderly subjects



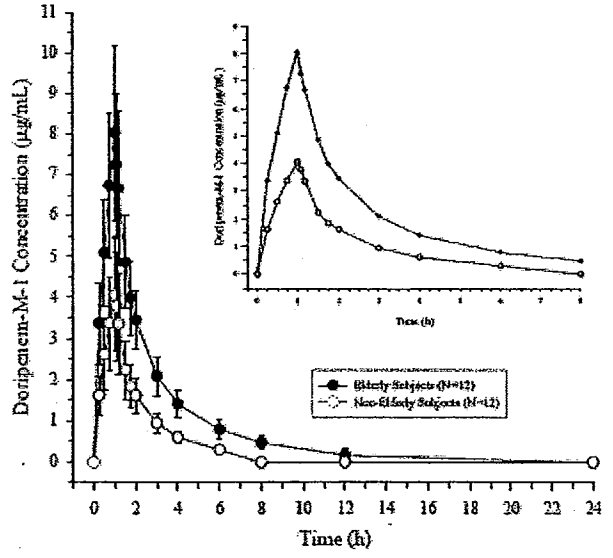
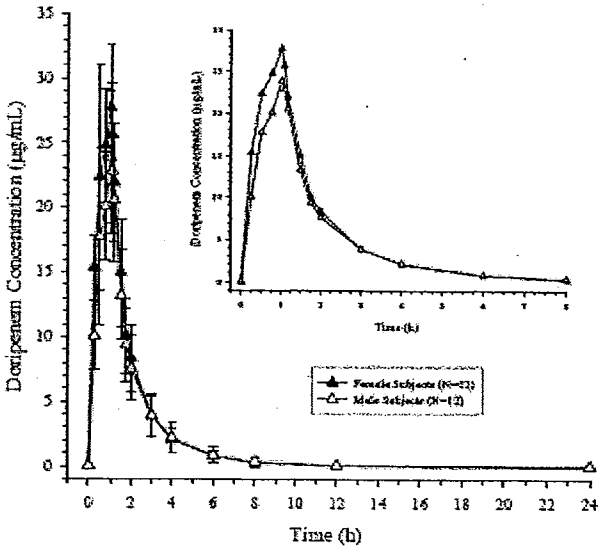


Figure 3. Mean (SD) doripenem and doripenem-M1 plasma concentration-time profiles for male vs. female subjects



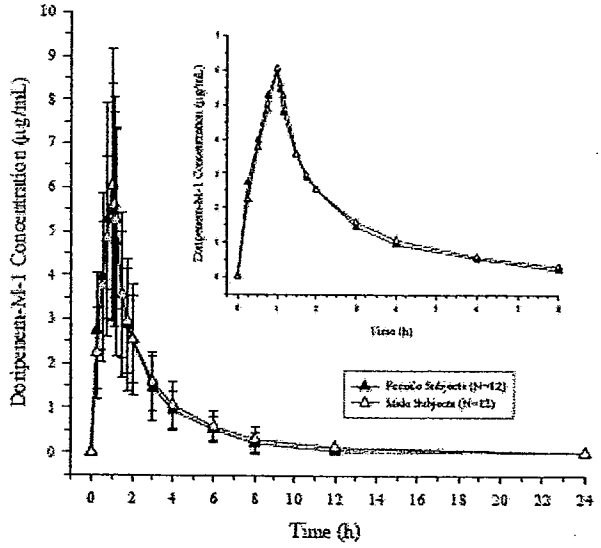


Table 2. Mean (SD) pharmacokinetic parameters of doripenem for elderly, non-elderly, male and female subjects

PK Parameters	Elderly Subjects	Non-Elderly Subjects	Male Subjects	Female Subjects
N	12	12	12	12
Cmax (μg/mL)	30.6 (3.98)	25.7 (8.07)	26.1 (5.74)	30.1 (7.25)
tmax [a] (hr)	1.00 (0.50-1.18)	1.00 (0.50-1.08)	1.01 (0.50-1.18)	1.00 (0.50-1.10)
AUC_{last}	54.4 (8.14)	36.7 (6.41)	43.2 (12.40)	48.0 (10.6)

PK Parameters	Elderly Subjects	Non-Elderly Subjects	Male Subjects	Female Subjects
(μg.hr/mL)				
AUC_∞ (μg.hr/mL)	55.0 (8.27)	37.0 (6.35)	43.7 (12.62)	48.3 (10.7)
CL (L/hr)	9.31 (1.63)	13.9 (2.62)	12.4 (3.60)	10.9 (2.62)
Vss (L)	14.1 (2.76)	14.0 (3.57)	16.1 (2.73)	12.0 (2.01)
t1/2 (hr)	1.53 (0.326)	0.997 (0.130)	1.36 (0.409)	1.17 (0.302)
λz (hr-1)	0.471 (0.0974)	0.704 (0.0764)	0.549 (0.149)	0.626 (0.140)
Ae (μg)	356697 (101238)	343248 (37202)	345649 (71401)	354296 (81197)
Ae, %Dose	71.3 (20.2)	68.6 (7.44)	69.1 (14.3)	70.9 (16.2)
CL_{CR} (mL/min)	76.0 (18.9)	111 (28.4)	107.3 (29.3)	79.2 (22.9)
CL_R (L/hr)	6.69 (2.39)	9.56 (2.02)	8.61 (3.00)	7.64 (2.18)
CL_{NR} [b] (L/hr)	2.62 (1.81)	4.37 (1.28)	3.77 (1.81)	3.22 (1.78)

[a] Mean (range)
[b] CL_{NR} - Non-renal clearance ($CL_{NR} = CL - CL_r$)

Table 3. Mean (SD) pharmacokinetic parameters of doripenem-M1 for elderly, non-elderly, male and female subjects

PK Parameters	Elderly Subjects	Non-Elderly Subjects	Male Subjects	Female Subjects
N	12	12	12	12
Cmax (μg/mL)	8.12 (2.12)	4.08 (1.36)	6.12 (2.40)	6.08 (3.08)
tmax [a] (hr)	1.02 (0.75-1.18)	1.00 (1.00-1.08)	1.00 (1.00-1.18)	1.00 (0.75-1.08)
AUClast (μg.hr/mL)	19.0 (3.8)	7.97 (2.33)	14.0 (6.38)	13.0 (6.75)
AUC∞ (μg.hr/mL)	20.2 (4.1)	8.66 (2.30)	15.0 (6.74)	13.9 (6.97)
t1/2 (hr)	2.65 (0.720)	1.74 (0.151)	2.37 (0.791)	2.02 (0.544)
λz (hr-1)	0.281 (0.0805)	0.400 (0.0364)	0.322 (0.0975)	0.360 (0.0722)
Ae (μg)	60436 (14086)	83715 (22658)	81765 (21654)	62386 (18267)
Ae, %Dose	12.1 (2.82)	16.7 (4.53)	16.4 (4.33)	12.5 (3.65)
CL_{CR} (mL/min)	76.0 (18.9)	111 (28.4)	107 (29.3)	79.2 (22.9)
CL_R (L/hr)	3.06 (0.812)	10.3 (3.87)	7.18 (5.09)	6.14 (4.18)

[a] Mean (range)

The slope of the regression line for CL_{CR} was found to be statistically significant at a 5% level of significance for doripenem CL (see figure below), as well as for CL_R. The slope of the regression line for weight was not statistically significant for doripenem CL. The slope of the regression line for body weight was statistically significant at a 5% level of significance for Vss.

Figure 3. Individual subject doripenem CL vs. measured creatinine clearance

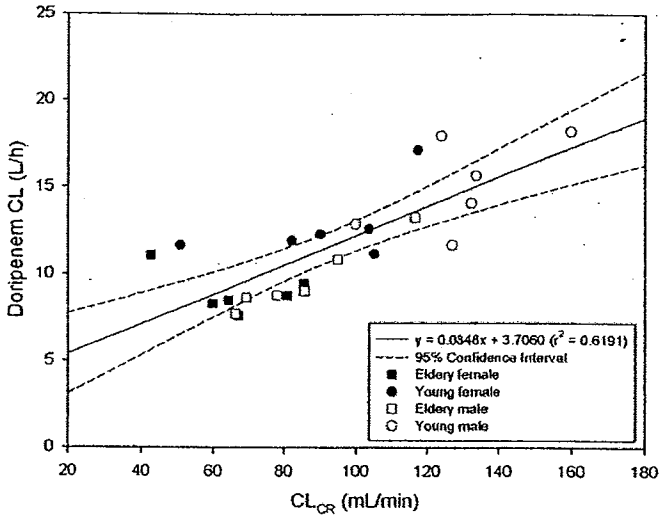
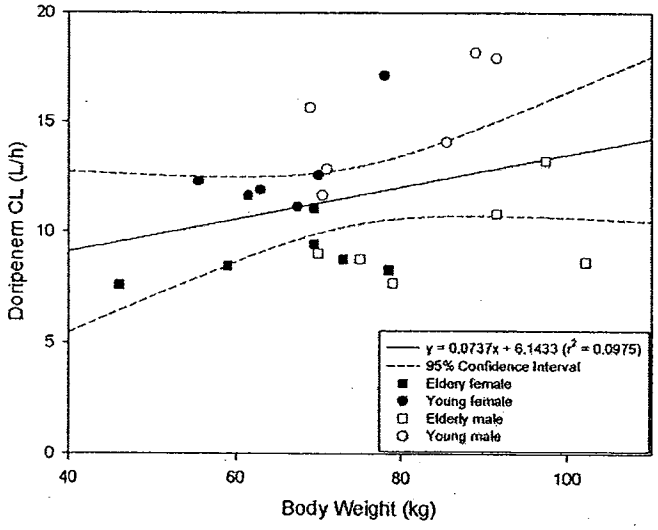


Figure 4. Individual subject doripenem CL vs. body weight



Evaluation of the full statistical model with interactions, the age group by sex interaction effect was not statistically significant for any of the doripenem PK parameters (AUClast, AUC∞, and Cmax). Therefore, the reduced models were fitted to the data without the interaction term. The geometric mean ratios and 90% confidence intervals for the comparison of AUCs and Cmax for the two age groups and two sexes are presented in the following table:

Table 4. Geometric mean ratios (GMR) and 90% CI for AUC and Cmax

		Geo. Mean	Geo. Mean	GMR (%)	90% CI
		Elderly	Non-Elderly	Test/	
Parameter	N	(Test)	(Reference)	Reference	
Doripenem					
AUC∞	24	54.38	36.47	149.11	(132.87, 167.32)
AUClast	24	53.80	36.16	148.78	(132.52, 167.03)
Cmax	24	30.32	24.75	122.51	(106.33, 141.14)
		Female	Male		
AUC∞	24	47.22	41.99	112.45	(100.21, 126.18)
AUClast	24	46.85	41.53	112.80	(100.48, 126.65)
Cmax	24	29.39	25.54	115.08	(99.89, 132.59)

Doripenem AUC and Cmax in elderly subjects were approximately 49% and 23% higher, respectively, compared to those respective values in non-elderly subjects. Doripenem AUCs and Cmax in female subjects were approximately 13% and 15% higher, respectively, compared to those respective values in male subjects.

Safety

Four (17%) of 24 subjects (2 elderly and 2 non-elderly subjects) reported 1 adverse event each during the study. All 4 adverse events were mild in severity. Dizziness was reported by 2 non-elderly subjects; 1 occurrence was considered very likely related to study drug and the second was considered possibly related. Of the two remaining adverse events, one (diarrhea) was considered possibly related, and the other adverse event (mild fungal infection) was considered not related to study drug. All adverse events resolved by the end of the study.

All mean hematology and chemistry results (for all subjects combined) were within reference ranges, and changes from baseline were minor. No trends were observed in mean hematology and chemistry results over time.

Sponsor's Conclusions

The results of this study showed that doripenem Cmax, AUC, and t1/2 increased in elderly subjects relative to non-elderly subjects, primarily due to a reduced clearance in the elderly. Renal clearance represents 70% and CL_{NR} [metabolism to doripenem-M1 and elimination by other unidentified pathway(s)] represents the other 30% of doripenem total systemic clearance. Similar reductions in doripenem CL and CL_R were observed in the elderly. Positive correlations were observed between doripenem CL and CL_{CR} and between doripenem CL_R and CL_{CR}.

In addition to reduced doripenem CL_R in the elderly, CL_{NR} of doripenem was decreased by 40% compared to non-elderly subjects. The lower urinary recovery of doripenem-M1 in the elderly (28% lower than in the non-elderly) suggests that formation of this metabolite was reduced in the elderly. Reduced CL_{NR} of two other carbapenems (meropenem and ertapenem) has been reported in the elderly, and it was postulated that the reduction in CL_{NR} in the elderly was likely due to reduced metabolism by DHP-1. However, doripenem-M1 Cmax, AUC∞, and apparent t1/2 increased 99%, 133%, and 52% in the elderly compared to non-elderly subjects, greater than that expected based on a 70% reduction in doripenem-M1 CL_R. These findings suggest that other elimination pathway(s) [e.g., metabolic] of doripenem-M-1 are somewhat reduced in the elderly.

With respect to gender-related differences, doripenem Cmax and AUC were slightly higher (<15%) in females than in males. The small observed differences in exposure between females and males are likely related to differences in CL_{CR} between the genders (79 vs 103 mL/min). Doripenem Vss was 26% lower in females compared to males and is reflective of a lower body weight in females.

The lower urinary recovery of doripenem-M1 in females relative to males suggests a lower conversion of doripenem to doripenem-M1 in females. Mean (SD) doripenem AUC and t1/2 in elderly subjects are similar to those respective values in subjects with mild (CLCR 51-79 mL/min) renal impairment. No dosage adjustment is required for subjects with mild renal impairment. The highest dose of doripenem tested in clinical trials is 1000 mg. In 106 healthy subjects who received a 1000 mg dose in Phase 1 trials, doripenem was considered to be safe and well tolerated. Relative to steady-state Cmax and AUCτ values for the 1000 q 8 hour dose, doripenem Cmax and AUC∞ after a single 500 mg dose infused over 1-hour in the elderly were 30% and 20% lower, respectively; doripenem-M-1 Cmax and AUC∞ in the elderly were 17% and 5%, lower, respectively. Based on these findings and the safety results in the present study, no dosage adjustment is recommended for the elderly with normal (for their age) renal function. Based on the small differences in exposure between females and males (< 15%), no dosage adjustment is recommended based on gender.

Reviewer assessment:

The Sponsor's recommendation for no dosage adjustment in the elderly, in the absence of impaired renal function, is appropriate based on the findings from this study.

However, the Sponsor's assertion that lower urinary recovery of doripenem-M1 in the elderly suggests that formation of this metabolite is reduced in the elderly is not consistent with the observed 99% and 133% increase in doripenem-M1 Cmax and AUC∞ in the elderly. While a reduction in the renal clearance of doripenem-M1 is likely related, the increase in M1 exposure is greater than what would be expected based on a 70% reduction in doripenem-M1 renal clearance. As noted by the Sponsor, these findings suggest that other elimination pathway(s) of doripenem-M-1 are somewhat reduced in the elderly.

4.2.4. Extrinsic Factors

Study 0117R1416
Pharmacokinetics of Doripenem Co-administered with Probenecid

Dates: February – March 2002

Study Sites: [redacted]

Objective:
The objective of this study was to investigate the renal excretion of doripenem following a dose of doripenem (single dose, 250 mg) alone and following the dose of doripenem when co-administered with probenecid to healthy adult male volunteers.

Methods:
Study Design
This study was conducted on healthy adult male volunteers at a single trial site using an open-label, crossover design in which a single dose of doripenem 250 mg was administered alone and with probenecid. Nine blood samples and urine samples were collected up to 12 h after each administration for the measurement of doripenem in plasma and urine for determination of pharmacokinetic parameters.

Test Product
Doripenem: Powder containing 250 mg of doripenem per vial (S-4661 intradermal test drug: doripenem 300μg per ampule) (Solvent for S-4661 intradermal test drug/control solution: physiological saline 1.3 mL per ampule)

Lot numbers (manufacturing numbers)
Doripenem 250 mg (potency): CF0063
Doripenem intradermal test drug: CF0065
Probenecid: I15370

After it was confirmed that the results of the doripenem intradermal test were "negative," the drugs were administered as follows:

Group I (Single dose doripenem first):

Period 1: Single dose of 250 mg of doripenem by intravenous infusion (over 30min)

Period 2:

1) Oral dose of 1 g probenecid (4 tablets) with 100 mL of water 2 h before doripenem
2) One dose of 250 mg doripenem by intravenous infusion (over 30min)
3) Oral dose of 0.5 g probenecid (2 tablets) with 100 mL of water immediately after end of intravenous infusion

Group II (concomitant probenecid administered first):

Period 1:

1) Oral dose of 1 g probenecid (4 tablets) with 100 mL of water 2 h before doripenem
2) One dose of 250 mg doripenem (over 30 min)

3) Oral dose of 0.5 g probenecid (2 tablets) with 100 mL of water immediately after end of infusion

Period 2: Single dose of 250 mg doripenem infusion (over 30 min)

Inclusion criteria

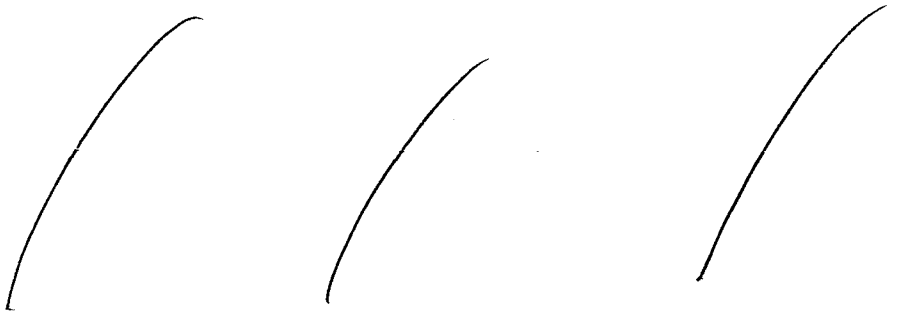
Subjects were healthy adult male volunteers aged ≥ 20 but ≤ 40 years old, weighing ≥ 50 but ≤ 80 kg, with a BMI of 18 – 27 (inclusive), and no significant medical history or current medication use.

Pharmacokinetic assessment

Evaluation of plasma concentration parameters calculated from data taken before drug administration and 0.5, 0.75, 1, 2, 4, 6, 8, and 12 h after the start of the infusion. Evaluation of excretion rate by urine collection at intervals of 0-2, 2-4, 4-6, 6-8, 8-10, and 10-12 h after administration.

Analytical Methods

Doripenem concentrations in plasma and urine were determined by microbiological assay by the band-culture method.



Pharmacokinetic Methods

For the evaluation of the plasma concentration of doripenem in each subject and the mean plasma concentration at each time point, the AUC up to 12 h after the start of administration was obtained ($AUC_{0\text{-}12}$) using the trapezoidal method, and the measured value at the completion of the intravenous infusion was used as Cmax. In addition, an analysis was performed using the 2-compartment model, and the AUC and elimination half-life ($t1/2(\beta)$) were calculated. The concentration of doripenem in the urine was measured, and the cumulative urinary excretion rate (Fe) from the start of administration until 12 h after administration was based on the urine volume and urine concentration in each subject. The urinary excretion clearance (renal clearance, CL_R) was calculated from the $AUC_{0\text{-}12\ hr}$. The mean values and standard deviations were calculated for the above parameters, and a comparison was made between data obtained when doripenem was administered alone and when co-administered with probenecid using a crossover analysis of variance. A two-tailed level of significance of 5% was set for the statistical tests.

Results:

Study Population

Eight subjects were enrolled in and completed the study. Table 1 shows the distribution of baseline characteristics.

Table 1. Demographic Details by Group

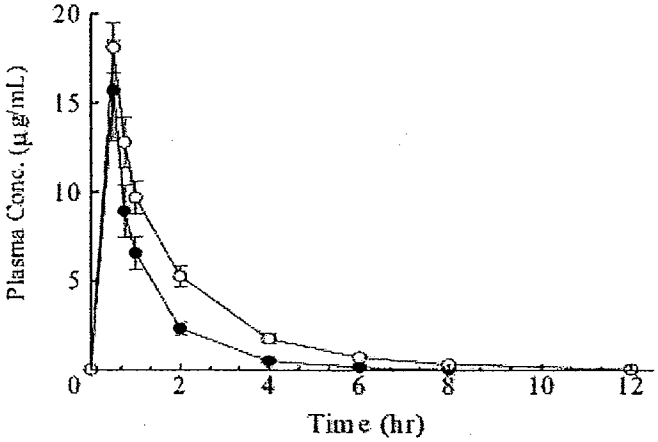
Item	Category	Screening	Period 1: Day before administration	Period 2: Day before administration
Age (category)	≥20 but <30	4		
	≥30 but <40	4		
Age (years)	No. of subjects	8		
	Mean	28.38		
	Standard deviation	6.95		
	Minimum	20.00		
	Median	30.00		
	Maximum	38.00		
Height (category)	≥160 cm but <170 cm	5	5	5
	≥170 cm but <180 cm	3	3	3
Height (cm)	No. of subjects	8	8	8
	Mean	169.23	168.98	169.13
	Standard deviation	5.42	5.51	5.45
	Minimum	161.80	161.20	161.50
	Median	169.05	168.95	169.05
	Maximum	178.00	177.60	177.80
Weight (category)	≥50 kg but <60 kg	3	2	3
	≥60 kg but <70 kg	4	5	4
	≥70 kg	1	1	1
Weight (kg)	No. of subjects	8	8	8
	Mean	62.63	62.98	63.03
	Standard deviation	5.76	5.91	5.91
	Minimum	54.60	54.80	54.50
	Median	62.50	62.65	62.90
	Maximum	71.10	72.50	72.40
BMI	No. of subjects	8	8	8
	Mean	21.85	22.06	22.01
	Standard deviation	1.71	1.70	1.65
	Minimum	19.60	20.20	20.50
	Median	21.80	22.00	21.80
	Maximum	24.50	24.80	24.60
History of drug allergy	Yes	0	0	0
	No	8	8	8

Analytical Performance

Pharmacokinetic Analysis

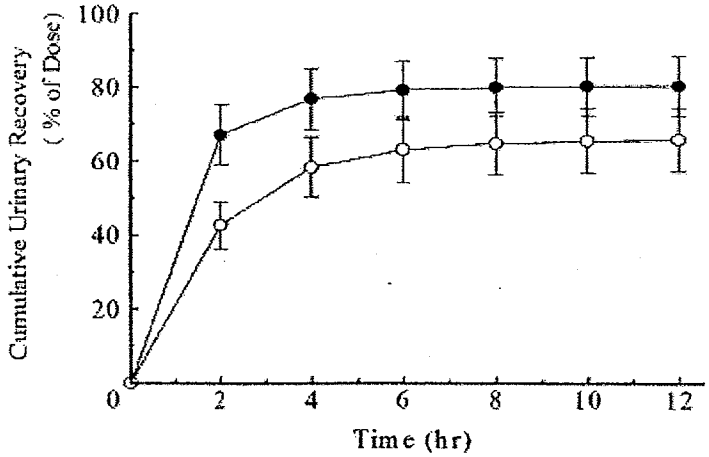
Mean doripenem plasma exposure was increased and the cumulative urinary excretion rate decreased when doripenem was co-administered with probenecid (Figures 1 and 2). The following PK parameters were significantly different following administration with probenecid: C_{max} increased by 15%, $AUC_{0\text{-}12hr}$ increased by 75%, CL_T decreased by 44%, t1/2(β) increased by 53%, Fe decreased by 18%, and CL_R decreased by 54% (Table 2).

Figure 1. Mean plasma concentration vs. time of doripenem alone and after co-administration with probenecid



(n=8, •: administration of S-4661 alone; ○: coadministration of S-4661 with probenecid; mean values ± standard deviations)

Figure 2. Mean cumulative urinary excretion of doripenem alone and after co-administration with probenecid



(n=8, •: administration of S-4661 alone; ○: coadministration of S-4661 with probenecid; mean values ± standard deviations)

Table 2. Mean PK parameters of doripenem administered alone and with probenecid

Dose : 250mg

		Cmax[1] (μg/mL)	AUC[2] (μg.hr/mL)	AUC_{0-12hr}[3] (μg.hr/mL)	CL_T[4] (L/hr)	$t_{1/2}(\beta)$[2] (hr)	Fe[5] (%)	CL_R[6] (L/hr)
S-4661 alone	Mean	15.7	16.59	17.10	14.91	0.94	80.4	12.00
	S.D.	2.8	2.43	2.56	2.22	0.16	8.0	2.21
S-4661 with Probenecid	Mean	18.1	28.93	29.86	8.41	1.44	65.8	5.52
	S.D.	1.4	2.05	2.10	0.58	0.11	8.6	0.71
	Ratio[7]	1.15	1.74	1.75	0.56	1.53	0.82	0.46
	p-value	0.0091	0.0000	0.0000	0.0000	0.0002	0.0017	0.0001
	test	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05

1) Cmax : observed values at 0.5hr
2) AUC, $t_{1/2}(\beta)$: estimated by model parameters
3) AUC_{0-12hr} : calculated by trapezoidal method
4) CL_T : calculated by Dose / AUC_{0-12hr}
5) Fe : urinary recovery from 0 to 12 hours
6) CL_R : urinary (renal) clearance estimated by CL_T x Fe / 100
7) Ratio : calculated by mean value of S-4661 with Probenecid / mean value of S-4661 alone

Safety

Throughout Period 1 and Period 2, adverse events were seen in 1 of 8 subjects. Cough, malaise, and feeling hot (each "mild" in severity, causal relationship to doripenem: "not related") were reported after doripenem was administered alone. Following co-administration with probenecid, there were 3 events of queasiness, decreased appetite, and headache (each "mild" in severity, causal relationship to doripenem: "not related"). Abnormal changes in clinical laboratory test results of leukocytosis, neutrophilia, and lymphocytopenia (each "mild" in severity, causal relationship: "not related") were observed in the one subject who experienced adverse events when doripenem was administered alone. No other clinically abnormal changes were seen in the physical examinations or clinical laboratory test results.

Sponsor's Conclusions

The pharmacokinetic parameters of doripenem after concomitant administration with probenecid clearly show that the elimination of doripenem from the plasma is significantly delayed and the renal excretion rate is significantly lower. More specifically, in comparison with the administration of doripenem alone, after co-administration with probenecid the pharmacokinetic parameters changed as follows: Cmax increased by 15%, AUC_{0-12} increased by 75%, CL_T decreased by 44%, $t_{1/2}(\beta)$ increased by 53%, Fe decreased by 18%, and CL_R decreased by 54%. These findings suggest that renal tubule secretion is involved in the mechanism of excretion of doripenem via the kidneys.

Among the adverse events that appeared during the study period, there were 3 events of abnormal symptoms consisting of cough, malaise, and feeling hot in 1 of 8 cases after doripenem was administered alone, and in the clinical laboratory test results of the same case leukocytosis, neutrophilia, and lymphocytopenia were seen. These findings were attributed to a common cold and the causal relationship with the investigational product was judged to be "not related." After co-administration with probenecid, there were 3 events of headache, queasiness, and decreased appetite in 1 of 8 cases (the same case as above). These findings were attributed to the effects of probenecid.

Reviewer assessment:
Probenecid's propensity to interfere with the tubular secretion of co-administered drugs via inhibition of active transport proteins is well appreciated. Its anticipated effect on doripenem renal excretion is confirmed in this study by the significant increase in doripenem exposure and significant decrease in clearance. The findings support the proposed mechanism of doripenem excretion – glomerular filtration plus active tubular secretion.

The Sponsor has added the following statement to the product label: "Coadministration of probenecid with TRADENAME is not recommended." Based on the 75% increase in AUC and 15% increase in Cmax observed in this study, the exposure that is expected to result from co-administration of probenecid with 500 mg of doripenem is less than that observed with 1000 mg alone, based on the dose-proportionality of doripenem. However, experience with the 1000 mg dose in humans is limited, particularly multiple dosing. Based on the lack of safety data at the higher anticipated doripenem exposure, the Sponsor's recommendation is appropriate.

4.2.5. Patient Studies/Exploratory PK/PD Analyses

Study 9502R142A
Early Phase II Study of S-4661

Dates: April 1995 – March 1996

Study Sites: [redacted]

Objective:
The primary objective is to evaluate efficacy and safety of doripenem in various disease states, including chronic respiratory tract infections, complicated urinary tract infections (cUTI) and surgery. In addition, drug concentrations are to be measured in various body fluids and tissues to assist in the evaluation of drug efficacy.

Methods:
Study Design
This was an early Phase 2 open-label study to assess the efficacy and safety of various doses of doripenem in various disease states. Indications to be studied included:

- Internal Medicine: Chronic respiratory tract infection (acute exacerbation of chronic bronchitis, infection accompanied by bronchiectasis, and secondary infection due to chronic respiratory disease), with the exception of diffuse panbronchiolitis
- Urology: Complicated urinary tract infection (excluding patients with a catheter or who underwent prostate surgery within 6 months)
- Surgery and Obstetrics/Gynecology (study of measurement of drug concentrations in body fluids and tissues): Infected or postoperative patients requiring treatment with antibacterial drugs

Patients received an intravenous infusion (30 to 60 min.) of doripenem at a dose of 125 or 250 mg, 2 or 3 times daily, or 500 mg twice daily. Treatment duration was to last at least 3 but no more than 14 consecutive days. The planned sample size was 80 patients with infections related to the field of internal medicine and 10 patients each in the fields of surgery and obstetrics/gynecology.

Test Product
Lot Numbers:
S-4661 250 mg: CP4183, 500 mg: CP4184
S-4661 for intradermal test: CP4185 and CP6003

Inclusion criteria
Male or female inpatients aged 20 to 69 years (inclusive) with definitive findings or symptoms of a moderate infection. Patients with serious symptoms or a poor prognosis or underlying cardiac, hepatic or renal disease were excluded.

Clinical assessment

Clinical efficacy was to be evaluated based on the time course of subjective symptoms and objective and laboratory findings. For urinary tract infections, clinical efficacy was additionally rated according to the "Jpn. UTI criteria (3rd edition)". Microbiologic efficacy was to be evaluated based on changes in the presence of causative baseline pathogens.

Pharmacokinetic assessment

The study plans included measurement of concentrations in body fluids and tissues, such as blood, urine, sputum, bile, and retroperitoneal fluid, gallbladder tissue and uterus/uterine appendages, whenever possible. After an intravenous infusion (30 to 60 min.) at a dose of 125, 250, or 500 mg, samples were collected over time or at 1 time point during surgery. Sampling time was determined at the time of collection by investigators, with consideration for subject conditions and type of body fluid or tissue.

Analytical Methods

Concentrations of doripenem in plasma and tissue and fluid samples were determined by the band-culture method. Certain specimens were also analyzed at the same time by HPLC.

Results:

Study Population

A total of 107 patients were enrolled. In violation of the age restriction of "under 70 years old," 15 patients aged 70 years or older were treated with the investigational product, but excluded from evaluations. Six patients with diseases other than chronic respiratory tract infection and complicated urinary tract infections that were treated with the investigational product were also excluded from evaluations. The most common regimen was 250 mg twice daily used by 58.9% of patients, followed by 250 mg × 3 daily by 15.0%. In addition, 125 mg twice daily and 500 mg twice daily were assessed. No patients received the investigational product in a regimen of 125 mg × 3 daily. Duration of treatment was 1 week or less in approximately 80%, followed by approximately 10 and 14 days.

Table 1. Demographic Details

Baseline characteristic	Classification	Number of patients (% of the population)	
Total number of patients		**107**	
Sex	Male	64	(59.8)
	Female	43	(40.2)
Age	20 - 29	3	(2.8)
	30 - 39	6	(5.6)
	40 - 49	11	(10.3)
	50 - 59	15	(14.0)
	60 - 69	57	(53.3)
	70 -	15	(14.0)
Diagnosis	Acute exacerbation of chronic bronchitis	15 (14.0)	
	Infection accompanied by bronchiectasis	19 (17.8)	

Baseline characteristic	Classification	Number of patients (% of the population)	
Total number of patients		**107**	
Diagnosis	Bronchial asthma + infection	4 (3.7)	
	Old pulmonary tuberculosis + infection	10 (9.3)	
	Emphysema + infection	3 (2.8)	
	Complicated cystitis	30 (28.0)	
	Complicated pyelonephritis	20 (18.7)	
	Other	6 (5.6)	
Daily dosage	125 mg × 2	12	(11.2)
	250 mg × 2	63	(58.9)
	250 mg × 3	16	(15.0)
	500 mg × 2	16	(15.0)
Duration of treatment	3 - 4	1	(0.9)
	5 - 6	47	(43.9)
	7 - 8	36	(33.6)
	9 - 11	11	(10.3)
	12 - 13	4	(3.7)
	14 - 15	8	(7.5)
History of allergy	Yes	1	(0.9)
	No	106	(99.1)
Pre-treatment chemotherapy	Yes	26	(24.3)
	No	81	(75.7)

Analytical Performance

Details of the performance of the bioassay and HPLC assay are not provided.

Pharmacokinetic Analysis

Urine concentrations were not measured in any of the patients.

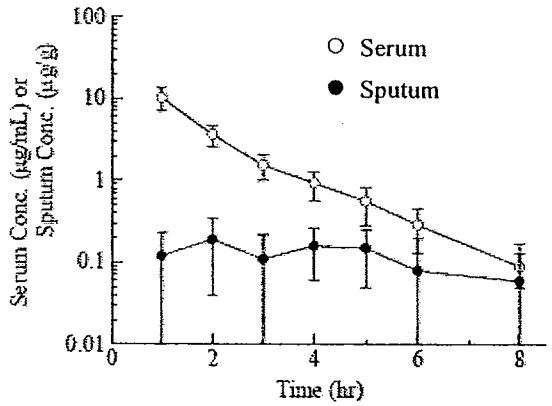
Sputum concentrations were measured in 7 patients; however, 2 of the 7 were excluded from evaluation due to age restrictions (subjects were > 70 years of age). After an intravenous infusion of doripenem at a dose of 250 mg over 60 min., maximum sputum concentrations ranged from 0.14 to 0.40 μg/g, with a maximum distribution ratio (maximum sputum concentration/maximum serum concentration) of 1.1 - 4.9%.

Table 2. Sputum/serum concentration ratio (%) of doripenem after i.v. infusion of 250 mg over 60 min.

		Ratio (%)						
SubjectNo.	Pre-dose	1hr	2hr	3hr	4hr	5hr	6hr	8hr
00001A	-1)							
00002A	-1)							
00003A	-1)							
00004A	-1)							
00005A	-1)							
Mean		1.5	5.9	6.6	20.1	36.5	42.4	48.7
S.D.		1.4	5.8	7.9	14.5	30.9	69.5	84.4

1) No sputum sample
Zero values (0.0) - Sputum concentration < 0.10 μg/g

Figure 1. Mean serum and sputum concentrations of doripenem following 250 mg i.v. infusion over 60 min.



Gallbladder tissue/bile concentrations of doripenem were measured in 10 pre-operative patients. After an intravenous infusion of a 250 mg dose over 30 min, gallbladder concentrations ranged from < 0.1 to 1.87 μg/g and bile concentration ranged from < 0.16 to15.4 μg/mL.

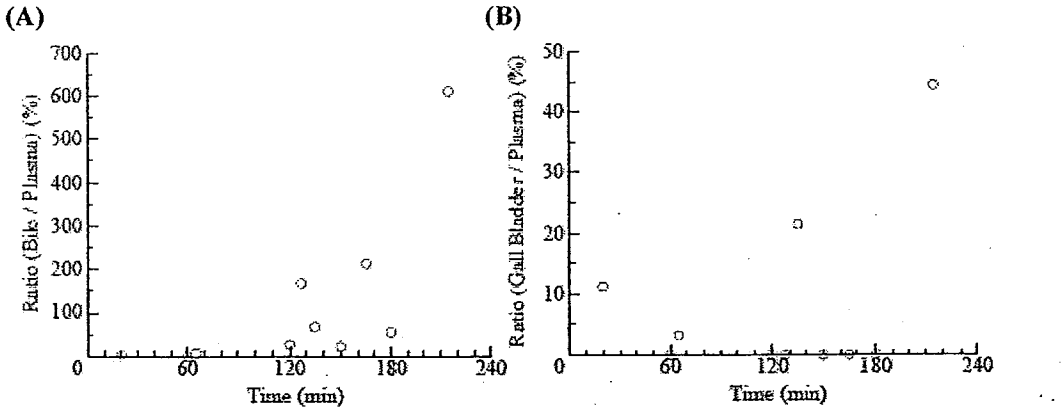
Table 3. Gall Bladder and plasma concentrations of doripenem in pre-operative patients administered a 250 mg dose over 30 min.

	Plasma							
Subject No.	Time[1] (min)	Conc. (μg/mL)	Tissue Time[1] (min)	Bile Conc. (μg/mL)	Gall Bladder Conc. (μg/g)	Bile Ratio (%)	Gall Bladder Ratio[2] (%)
30001A	180		180			54.9	0.0
30002A	215		215			611.1	44.4
30003A	165		165			212.6	0.0

Subject No.	Plasma Time[1] (min)	Plasma Conc. (µg/mL)	Tissue Time[1] (min)	Bile Conc. (µg/mL)	Gall Bladder Conc. (µg/g)	Bile Ratio (%)	Gall Bladder Ratio[2] (%)
30004A	60		60			0.0	0.0
30005A	65		70			7.6	3.2
30006A	20		20			3.1	11.2
30007A	60		----			----	----
	135		180			67.1	21.4
	240		----			----	----
30008A	127		145			166.7	0.0
30009A	120		135			26.2	0.0
30010A	150		210			21.8	0.0
		Mean				**117.1**	**8.0**
		S.D.				**188.0**	**14.6**
		Minimum				**0.0**	**0.0**
		Maximum				**611.1**	**44.4**

[1] Sampling time – from start of infusion
[2] Ratio of tissue conc./ plasma conc. x 100%
N.D. – Not determined (fluid conc < 0.16 µg/mL or tissue conc < 0.10 or <0.20 µg/g)

Figure 2. Doripenem concentration ratios for individual subjects for (A) bile/plasma or (B) gallbladder tissue/plasma



The distribution of doripenem in the uterus/uterine appendages was assessed following the infusion of 250 mg over 30 min. in 10 pre-operative patients.

Table 4. Tissue/plasma concentration ratios of doripenem following 250 mg infusion over 30 min. in pre-operative gynecologic patients

Subject	Sampling Time (min)	Plasma in Uterine Artery(%)	Myometrium (%)	Cervix Uteri (%)	Portio Vaginalis (%)	Endometrium (%)	Oviduct (%)	Ovary (%)
40005A	75							
40006A	40							

Subject	Sampling Time (min)	Plasma in Uterine Artery(%)	Myometrium (%)	Cervix Uteri (%)	Portio Vaginalis (%)	Endometrium (%)	Oviduct (%)	Ovary (%)
40007A	45							
40008A	165							
40009A	45							
40011A	65							
40013A	75							
40018A	40							
40019A	360							
40020A	60							
Mean		99.1	55.7	57.3	53.8	60.8	50.5	41.1
S.D.		7.0	23.1	27.8	27.4	17.3	36.3	19.8
Minimum								
Maximum								

1) No sample

Retroperitoneal and plasma concentrations of doripenem were assessed in 10 patients administered either 250 mg or 500 mg i.v. doripenem (over 30 min.) pre-operatively. Retroperitoneal exposure peaked at approximately 1 to 1.5 hours, with mean peak concentrations of 5.76 µg/mL and 12.0 µg/mL following 250 mg and 500 mg infusions, respectively.

Table 5. Concentrations of doripenem in retroperitoneal fluid following 250 mg and 500 mg pre-operative infusions (over 30 min.)

Subject No.		Conc. in Retroperitoneal Fluid (µg/mL)							
	pre-dose	0.25hr	0.5 hr	1 hr	1.5 hr	2.5 hr	4.5 hr	6.5 hr	8.5 hr
250mg / 30min infusion									
40001A	NS								
40002A	NS								
40003A	NS								
40004A	NS								
40016A	NS								
40017A	0.04								
Mean	**0.04**	**0.63**	**3.38**	**6.69**	**5.76**	**3.71**	**1.12**	**0.27**	**--**
S.D.	**--**	**0.56**	**1.97**	**2.78**	**2.42**	**1.45**	**0.37**	**0.15**	**--**
500mg / 30min infusion									
40010A	NS								
40012A	NS								
40014A	NS								
40015A	NS								
Mean	**--**	**1.08**	**4.27**	**10.6**	**12.0**	**9.51**	**3.67**	**1.27**	**--**
S.D.	**--**	**1.44**	**3.88**	**2.1**	**1.9**	**1.74**	**1.18**	**0.62**	**--**

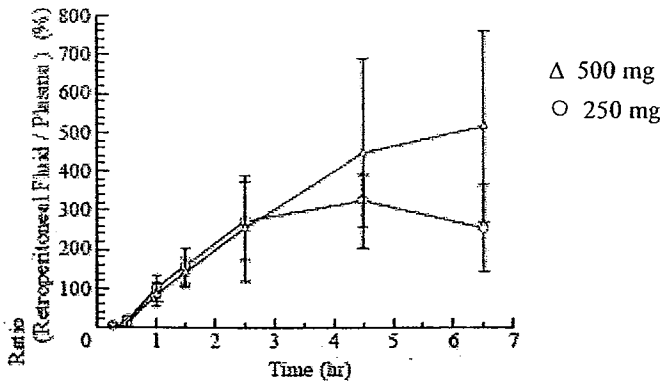
[1] NS – No sample
[2] < 0.03 µg/mL
[3] < 0.016 µg/mL

Table 6. Ratio of retroperitoneal fluid / plasma concentrations of doripenem following 250 mg or 500 mg pre-operative infusion (over 30 min.)

Subject No.	before	Ratio (%) 0.25hr	0.5hr	1hr	1.5hr	2.5hr	4.5hr	6.5hr	8.5hr
250mg / 30min infusion									
40001A	ND								
40002A	ND								
40003A	ND								
40004A	ND								
40016A	ND								
40017A	ND								
Mean		**4.1**	**16.9**	**100.5**	**157.8**	**273.0**	**325.4**	**254.3**	
S.D.		**4.0**	**11.9**	**33.3**	**44.5**	**99.4**	**67.2**	**111.8**	--
500mg / 30min infusion									
40010A	ND								
40012A	ND								
40014A	ND								
40015A	ND								
Mean		**3.3**	**10.1**	**84.1**	**141.0**	**253.9**	**447.4**	**515.8**	--
S.D.		**3.7**	**7.5**	**30.5**	**37.7**	**135.1**	**242.9**	**245.2**	

ND – Not determined

Figure 3. Ratio of retroperitoneal fluid / plasma concentrations of doripenem after single 250 mg or 500 mg infusions (over 30 min.) pre-operatively



Safety

Adverse drug reactions (symptoms) related to the investigational product were reported in 3 patients, with a frequency of 2.8%, including rash (moderate), numbness of tongue (mild), and headache (mild). All these reactions occurred within 3 days after the start of treatment and resolved completely. Adverse laboratory values occurred in 17 patients (27.4%) at a daily dosage of 250 mg × 2 daily and 1 patient (6.7%) at a daily dosage of 500mg × 2 daily. The most common adverse drug reaction was increased ALT (11 events), followed by eosinophilia (7),

increased AST (6) and increased alkaline phosphatase (6). In addition, abnormal changes in laboratory parameters unrelated to the investigational product were observed in 11 patients.

Sponsor's Conclusions
In general, the sputum concentrations after administration of doripenem at a dose of 250 mg were [redacted]. In addition, concentrations in the gallbladder tissue/bile, uterus/uterine appendage, and retroperitoneal fluid demonstrated that it was distributed well to these body fluids and tissues, suggesting potential clinical application for infections like biliary tract infection and obstetric/gynecological infections.

Reviewer assessment:
The study report is lacking in several important details. For instance, it is unclear what the diagnosis or indication for surgery was in the 30 subjects who had tissue or fluid concentrations assessed pre-operatively, including those patients undergoing gynecologic procedures and those subjects who had gallbladder tissue/bile fluid and retroperitoneal concentrations measured. The demographic data provided in the study report accounts only for those subjects with "chronic respiratory tract infections" or cUTIs, as well as "6 patients with diseases other than chronic respiratory tract infection and cUTI" which were excluded from evaluations. In addition, it is not stated how many doses of doripenem the surgical patients received, though one might assume it was only a single pre-operative dose. Also not stated, is whether sputum concentrations were assessed following single or multiple-dose administration of doripenem.

The analytical report for the bioassay and HPLC assay of doripenem in human plasma, tissue and fluids is dated November 1999, with a revision date of June 2003. The study synopsis indicates the last date of drug administration was March 1996, a full 44 months prior to the analytical report date. The analytical report indicates a study completion date of June 13, 2003. The report does not provide the actual date of analyses, nor total duration of sample storage. The analytical report does not contain any details about the performance of the bioassay or HPLC analysis, nor does it specify which samples were analyzed by bioassay versus HPLC.

Only 4 gall bladder samples concentrations were determined – at 215, 65, 20 and 135 minutes. The remaining 6 samples had exposures reported as either < 0.20 or <0.10 μg/g. It is unclear why there are two lower limits of quantitation for the same data set. Due to the limited number of quantified samples and the variability in sampling times, little can be concluded from this study about doripenem's distribution into gall bladder tissue. Doripenem exposure in bile appears to increase as time progresses following the end of infusion, with levels as high as 15.4 μg/mL at 215 minutes and 5.85 μg/mL at 135 minutes in two individuals. The bile/plasma ratio ranged from zero at 60 min. to 611% at 215 min. post-infusion. This limited data suggests doripenem is well distributed to bile.

Doripenem also appears to be extensively distributed to retroperitoneal fluid, with a mean exposure of 4.3 μg/mL and 3.4 μg/mL at 0.5 hours for the 500 mg and 250 mg infusions, respectively. Retroperitoneal concentrations appear to be dose-proportional, with peak exposure occurring at approximately 0.5 to 1 hour after the end of infusion. The mean retroperitoneal concentration at 4.5 hours was 3.67 μg/mL (range 2.70 to 5.27 μg/mL) following a 500 mg infusion. This would suggest that doripenem exposure exceeds MICs of ≤ 2 in the retroperitoneum for over half of the q8h dosing interval.

Study 9634R142D
Late phase II study of S-4661 – Open label study (urology)

Dates: February 1997 – March 1998

Study Sites:

Objective:
This study was conducted to evaluate the efficacy and safety of doripenem and assess the indications and dosages in patients with infections in the field of urology as defined in the protocol. The safety of doripenem was also evaluated by examining the relationship between doripenem concentrations and laboratory parameters of hepatic function during the treatment period.

Methods:
Study Design
This non-blinded, non-controlled, non-randomized multi-center study was conducted in 46 subjects (planned sample size: 90). After confirmation of the negative result of an intradermal skin test of doripenem, subjects received an intravenous infusion (30 to 60 min.) of the investigational product at one of the following dosages, based on the treating clinician's selection: 125 mg × 2 daily; 250 mg × 2 daily; 250 mg × 3 daily; and 500 mg × 2 daily. The investigational product was administered for at least 3 but not more than 14 consecutive days.

Individuals with the following infections and with evidence or estimation of Gram-positive or negative bacteria sensitive to doripenem in urine or expressed prostatic secretion were enrolled: complicated cystitis, pyelonephritis (acute uncomplicated or complicated), acute bacterial prostatitis, and bacterial epididymitis

Test Product
(1) Investigational product: S-4661 250 mg (potency)/vial and 500 mg (potency)/vial

(2) Dosage and mode of administration: The subjects received an intravenous infusion (30 to 60 min.) of the investigational product at one of the following dosages if an intradermal skin test showed no allergic reaction to doripenem:

(i) 250 mg (potency) × 2 daily
(ii) 250 mg (potency) × 3 daily
(iii) 125 mg (potency) × 2 daily
(iv) 500 mg (potency) × 2 daily

(3) Lot number (manufacturing number):
S-4661 250 mg (potency)/vial: CF6009, S-4661 500 mg (potency)/vial: CF6010
S-4661 300 μg (potency)/ampule for intradermal skin test: CF6015

Inclusion criteria
Male or female inpatients aged 20 to 79 years (inclusive) were included. Patients with pre-existing medical conditions, including hepatic or renal dysfunction, were excluded from participation.

Pharmacokinetic assessment
A single plasma concentration of doripenem was to be collected on Day 3 of treatment at the end of infusion for the purpose of evaluating the relationship between plasma concentrations and adverse drug reactions in hepatic function, as assessed by laboratory values.

Analytical Methods
Not provided.

Results:
Study Population
Of 45 subjects enrolled in this study, 32, 40, 39, 40, and 34 subjects were included in the efficacy evaluation, the safety evaluation in terms of adverse drug reactions (symptoms), adverse drug reactions (laboratory values) and overall safety, and the usefulness evaluation, respectively.

In the efficacy analysis set, male subjects were predominant over female subjects (25 male and 7 female subjects), and the mean age was 62.1 years (range: 23 - 79). A dosage of 250 mg × 2 daily was used in 24 of 32 subjects. In particular, most subjects with complicated pyelonephritis and complicated cystitis (19 of 20 subjects) received the investigational product at a dosage of 250 mg × 2 daily. In acute bacterial prostatitis and bacterial epididymitis, on the other hand, over half of subjects received the investigational product at a dosage of 250 mg × 3 daily or 500 mg × 2 daily.

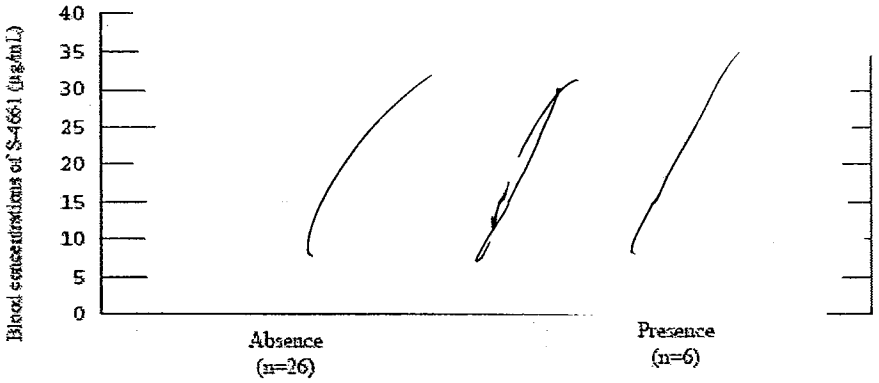
Table 1. Subject characteristics by disease state

Baseline characteristic		All diseases	Acute uncomplicated pyelonephritis	Complicated urinary tract infection			Acute bacterial prostatitis	Bacterial epididymitis
				Pyelo-nephritis	Cystitis	Subtotal		
Number of subjects		32	1	9	11	20	6	5
Sex	Male	25	0	5	9	14	6	5
	Female	7	1	4	2	6	-	-
Age (year)	Mean	62.1	-	63.4	62.1	62.7	59.7	-
	Standard deviation	15.2	-	12.2	15.5	13.8	15.9	-
	Maximum	79.0	-	77.0	77.0	77.0	74.0	79.0
	Median	67.5	72.0	67.0	66.0	66.5	63.0	70.0
	Minimum	23.0	-	40.0	33.0	33.0	33.0	23.0
Underlying Disease	No	6	1	0	0	0	3	2
	Yes	26	0	9	11	20	3	3
Pre-treatment Chemotherapy	No	27	1	7	10	17	5	4
	Yes	5	0	2	1	3	1	1
Daily dosage (mg × times/day)	250 mg × 2	24	1	8	11	19	2	2
	250 mg × 3	5	0	0	0	0	2	3
	500 mg × 2	3	0	1	0	1	2	0
Duration of Treatment	≤ 2 days	0	0	0	0	0	0	0
	≥ 3, ≤ 6 days	20	0	8	9	17	2	1
	≥ 7, ≤ 8 days	11	1	1	2	3	3	4
	≥ 9, ≤ 15 days	1	0	0	0	0	1	0

Pharmacokinetic Analysis

The plasma concentrations of doripenem were determined in 37 of the 39 subjects included in the evaluation of adverse drug reactions (laboratory values). Of these subjects, the plasma concentration of doripenem was below the detection limit (<0.06μg/mL) in 1 subject (Subject No. 7) and thus not used in the evaluation. In addition, blood sampling was not performed as scheduled in the protocol (at the end of infusion) in 4 subjects (Subject No. 6, 12, 36, and 41), who were also excluded from the evaluation. Therefore, 32 subjects were included in the evaluation. The plasma concentrations of doripenem at the end of infusion were compared between subjects with and without abnormal hepatobilliary laboratory values (SGOT, SGPT, Alk Phos, total bilirubin, or γ-GTP) during the treatment period. The number of subjects with and without abnormal laboratory values, as described above, was 6 and 26, respectively. The mean plasma concentrations of doripenem in subjects with and without abnormal hepatic laboratory results were 9.1 ± 4.1 μg/mL and 12.1 ± 7.4 μg/mL, respectively (*t* test, $p = 0.3498$).

Figure 1. Plasma concentrations of doripenem in the presence or absence of abnormal hepatobilliary laboratory values



Safety

Adverse events (symptoms) were observed in 3 of 40 subjects, and included rash, eruption, and malaise. All symptoms were considered as adverse drug reactions (symptoms) whose causal relationship with the investigational product could not be ruled out. They were mild in severity, and improved or resolved immediately after the discontinuation or completion of treatment. Adverse events (laboratory values) were reported in 10 of 39 subjects (18 events), including abnormal changes in hepatic enzymes. Among these 18 adverse laboratory events, 16 events in 8 subjects were considered to be adverse drug reactions (laboratory values), with an incidence of 20.5% (8/39). They included SGOT increases (6 events), SGPT increases (6), γ-GTP increases (2), Alk Phos increase (1), and eosinophilia (1). All of these abnormal laboratory values were mild or moderate in severity. Following the discontinuation or completion of treatment, improvements of adverse drug reactions (laboratory values) were confirmed in all subjects.

Sponsor's Conclusions

Adverse drug reactions (symptoms and laboratory values) observed at dosages of 250 mg × 2 daily, 250 mg × 3 daily, and 500 mg × 2 daily in this study were comparable to those of commercially available carbapenem antibiotics, including no serious reactions. Most subjects in this study received the investigational product at a dosage of 250 mg × 2 daily, revealing no

certain dose dependency between the incidence of adverse drug reactions (symptoms and laboratory values) and the dosages.

The concentrations of doripenem were determined in almost all subjects during the treatment (mainly on Day 3) to evaluate the relationship between the blood concentrations and the adverse drug reactions (laboratory values) in hepatic function, revealing no obvious relation.

Reviewer assessment:
The absence of a relationship between observed increases in hepatobilliary parameters and doripenem exposure cannot be concluded based on the results of this study. The number of assessable subjects with plasma concentration data is limited (32 total; 6 with abnormal hepatobilliary laboratory results). Further, there is no information regarding the day on which blood collection for PK determination took place (other than a statement that most were done on Day 3). In addition, a relationship between concentration and adverse events is difficult to ascertain as most patients in the study received the same dose of 250 mg twice daily, with only a limited number of subjects receiving the higher doses of 250 mg 3x/daily and 500 mg twice daily. The limited range of dosages restricts the utility of the analysis, as most subjects had relatively low exposures.

Details regarding the analytical method were not provided; as such, analytical performance could not be assessed.