CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-106

MEDICAL REVIEW(S)

Medical Team Leader Memo

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Application:	NDA 22-106, Doripenem for Injection
Date of Submission:	December 12, 2006
PDUFA Goal Date:	October 12, 2007
Applicant:	Johnson and Johnson Pharmaceutical Research and Development
Drug Class:	Carbapenems
Trade Name:	DORIBAX
Indications:	Complicated Urinary Tract Infections
	Complicated Intra-abdominal Infections
Dosing Regimen:	500 mg every 8 hours intravenously

Recommendation on Regulatory Action:
Based on the data submitted by the Applicant, there is adequate efficacy and safety data to recommend approval of doripenem injection 500 mg every 8 hours for the treatment of complicated urinary tract infections and complicated intra-abdominal infections in patients 18 years of age and older.

Background:
Doripenem is a carbapenem anti-bacterial agent that was discovered by Shionogi and Co., Ltd. Osaka, Japan. In July 2005, doripenem was approved in Japan under the trade name Finibax for the treatment of moderate to severe bacterial infections. In 2003, Peninsula Pharmaceuticals Inc. (PPI) obtained a license for the development and commercialization of doripenem. In July 2005, PPI transferred all Sponsor obligations to Johnson & Johnson Pharmaceutical Research and Development.

Doripenem acts by binding to penicillin-binding proteins and inhibiting cell wall synthesis in both Gram positive and Gram negative bacteria. The *in vitro* activity of doripenem is similar to those of other carbapenems. It is active against methicillin-sensitive staphylococci, streptococci, ampicillin-susceptible *Enterococcus faecalis*, Enterobacteriaceae, *Pseudomonas aeruginosa, Bacteroides* spp., *Peptostreptococcus* spp. and other anaerobes.

Indications:
In the NDA, the Applicant is seeking the approval of doripenem for injection for the following indications:

- Complicated Intra-Abdominal Infections caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus,* ——— *, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros.*
- Complicated Urinary Tract Infections, including ——— ——— pyelonephritis caused by *Escherichia coli* (——— ——— including cases with concurrent bacteremia, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis,* ——— *Acinetobacter baumannii* and ———

EFFICACY

Complicated Intra-abdominal Infections (cIAI):
The Applicant conducted two adequate and well-controlled Phase 3 studies, DORI-07 and DORI-08 in patients 18 years of age or older with cIAI. Both studies were randomized, double-blind, double-dummy, multi-center studies of identical design involving 962 patients (486 doripenem-treated and 476 meropenem-treated). Patients were stratified at the time of randomization by region (North America, South America, Europe), site of infection (complicated appendicitis with localized peritonitis vs. others), and severity of illness (APACHE II score $\leq$ 10 versus > 10). Overall, the study design,

inclusion and exclusion criteria are consistent with those outlined in the IDSA guidelines for evaluation of new anti-infectives for treatment of intra abdominal infections. [1]

Patients could be enrolled either pre or post-operatively as long as they met the inclusion and exclusion criteria outlined in the protocol. Patients received either doripenem 500 mg as an intravenous infusion every 8 hours or meropenem 1 gram as an intravenous bolus every 8 hours for 5-14 days. Dosage regimens were modified in patients with renal impairment based on creatinine clearance. In both studies, patients could be switched to oral amoxicillin-clavulanate after 9 or more doses of IV therapy, if body temperature and WBC decreased (if increased at baseline), if signs and symptoms of cIAI were absent or improved relative to baseline, and if normal bowel function had returned. Concomitant vancomycin was allowed for documented MRSA or enterococcal infections.

Besides a screening visit, patients were evaluated while on treatment, at an early follow up visit (7-14 days after completing therapy) and at the Test of Cure (TOC) visit (28-42 days after completing therapy). For analysis purposes, the visit windows were expanded before breaking the study blind. A surgical review panel consisting of surgeons and interventional radiologists reviewed the adequacy of the surgical source control for all patients classified as failures and for patients classified as failures who underwent a second procedure. The panel members were blinded to treatment assignment and their outcome assessment overruled that of the investigator. Sensitivity analyses were performed by the FDA using the protocol-specified visit windows and using investigator-defined outcomes.

The primary efficacy endpoint was clinical cure rate at the TOC visit. The co-primary populations were the Microbiologically Evaluable (ME) and microbiological modified Intent to Treat (mMITT) populations. Several secondary endpoints were also assessed. The power of the study was increased from 80% to 90% resulting in an increase in sample size from 172 per treatment arm to 236 per arm. This sample size increase was not defined a priori, but was implemented while the study was underway. The pre-defined non-inferiority margin was -15%. A justification for this non-inferiority margin is in Appendix 1.

[1] Solomkin JS, Hemsell DL, Sweet R, et al. Evaluation of new anti-infective drugs for the treatment of intraabdominal infections. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis. 1992;15 Suppl 1:S33-42.

The table below summarizes the number of patients in each of the analysis population for studies DORI-07 and DORI-08 combined:

Table 1: Analysis Populations

Population	Doripenem (N=486)	Meropenem (N=476)
Intent-to-treat	477 (98.1)	469 (98.5)
Microbiological modified ITT	395 (81.3)	375 (78.8)
Clinically evaluable	380 (78.2)	378 (79.4)
Microbiologically evaluable	325 (66.9)	309 (64.9)

Patients were well balanced across both treatment groups with regard to sex, age, and race. Majority of patients in both studies were enrolled outside the US, approximately 24% of patients were enrolled at sites in the US. The primary site of infection was complicated appendicitis with localized peritonitis in 34% of the patients. The appendix was the most common anatomic source of infection (62%) followed by the colon (20%). Only about 6% of patients were bacteremic. Majority of patients (82%) underwent an open surgical procedure.

Seventy-five percent of patients switched to oral therapy. Only 74 patients in the ME population for both studies combined were treated with IV doripenem for the entire course of therapy. The mean (SD) duration of therapy in this group was 9.4 days (3.18), range 5-16. The mean (SD) duration of IV therapy in those who switched to oral therapy was 5.7 days (1.99), range 3-13. Thus data on both efficacy and safety of doripenem used for the entire duration of therapy is limited.

These studies independently met their primary objective of non-inferiority of doripenem to meropenem for the primary efficacy endpoint of clinical cure rate at the TOC visit in ME and mMITT co-primary populations. In both studies, in the ME and mMITT populations, the lower bound of the 95% confidence intervals (CI) was greater than the pre-defined non-inferiority margin of -15% and the 95% CI included the value 0.

- For the pooled studies, the clinical cure in the ME population was 84.6% for the doripenem arm compared to 84.1% in the meropenem arm, (treatment difference 0.5%, 95% CI -5.5% to 6.4%].
- Cure rates in the mMITT population were lower in both treatment arms, 76.2% in the doripenem arm and 77.3% in the meropenem arm (treatment difference -1.1%; 95% CI -7.4% to 5.1%).

The following table summarizes the clinical cure rates for each study and for both studies combined:

Table 2: Clinical cure rates in the co-primary populations

Population	Doripenem n/N (%)	Meropenem n/N (%)	Treatment difference %	95% CI
DORI-07				
Microbiologically Evaluable	140/163 (85.9)	133/156 (85.3)	0.6	-7.7, 9.0
Microbiological modified ITT	152/195 (77.9)	150/190 (78.9)	-1.0	-9.7, 7.7
DORI-08				
Microbiologically Evaluable	135/162 (83.3)	127/153(83.0)	0.3	-8.6, 9.2
Microbiological modified ITT	149/200 (74.5)	140/185 (75.7)	-1.2	-10.3, 8.0
Combined				
Microbiologically Evaluable	275/325 (84.6)	260/309 (84.1)	0.5	-5.5, 6.4
Microbiological modified ITT	301/395 (76.2)	290/375 (77.3)	-1.1	-7.4, 5.1

FDA ME and mMITT populations were defined based on the following criteria:

- Deaths were classified as evaluable failures if patient received at least 3 days of study drug.
- Patients receiving concomitant non-study anti-bacterial medications were re-classified as either evaluable failures or mMITT indeterminate (i.e. failures).
- Misrandomized patients were excluded from the ME population. Misrandomized patients were included in the mMITT population according to the outcome observed assigned to the planned treatment arm.
- The allowable TOC window was 25-45 days (the original protocol window of 28-42 days ± 3 days).

Based on these criteria re-analysis of the primary end-points showed the following results:

Table 3: Clinical cure rates in the FDA-defined co-primary populations

Population	Doripenem n/N (%)	Meropenem n/N (%)	Treatment difference[a] %	95% CI[b]
DORI-07				
Microbiologically Evaluable	130/157 (82.8)	128/149 (85.9)	-3.1	(-11.3; 5.2)
Microbiological modified ITT	143/194 (73.7)	149/191 (78.0)	-4.3	(-12.8; 4.3)
DORI-08				
Microbiologically Evaluable	128/158 (81.0)	119/145 (82.1)	-1.1	(-9.8, 7.8)
Microbiological modified ITT	143/199 (71.9)	138/186 (74.2)	-2.3	(-11.2; 6.6)
Combined				
Microbiologically Evaluable	258/315 (81.9)	247/294 (84.0)	-2.1	(-8.1, 3.9)
Microbiological modified ITT	286/393 (72.8)	287/377 (76.1)	-3.4	(-9.5, 2.8)

a Doripenem minus Meropenem.
b Two-sided 95% CI calculated without continuity correction

Cure rates in the FDA analyses were lower than that obtained by the Sponsor and was more marked in the doripenem arm. In both studies, using the FDA analyses the non-inferiority margin of -15% was met.

Across both treatment arms cure rates were lower in US sites and in patients ≥75 years of age. Cure rates were similar in the two treatment arms in the various subgroups analyzed by age, sex, race, region, APACHE score, infection stratum, and anatomic site of infection.

Patients treated with IV alone represented only a small fraction of the total population enrolled in the cIAI studies. A total of 160 patients, 74 in the doripenem arm and 86 in the meropenem arm were treated with IV antibiotics without an oral switch. The cure rates in the ME population in this group of patients were lower (71.6% (53/74) in the doripenem arm and 77.9 % (67/86) in the meropenem arm) compared to the overall population. Demographic and baseline characteristics in this group such as higher mean age, underlying renal impairment, higher frequency of generalized peritonitis and non-appendiceal infections may account for the lower success rates.

Microbiological cure rates for the pooled data set in the ME population was similar in the two treatment arms, 84.3 % (274/325) in doripenem treated patients and 84.5% (261/309) in meropenem treated patients. The most common pathogens identified were the Enterobacteriaceae (*Escherichia coli, Klebsiella pneumoniae*), *B. fragilis* group and viridans group streptococci. Success rates were similar across treatment arms for the Enterobacteriaceae and *B. fragilis* group. Success rates were lower in the meropenem group for the viridans group streptococci.

The following table summarizes microbiologic outcome by pathogen for the two studies combined:

Table 4: Per-pathogen Microbiological Outcome for DORI-07 and DORI-08 combined in the ME population

	Doripenem			Meropenem		
	N	n	%	N	n	%
Gram-positive, aerobic	176	150	85.2	168	131	78.0
Viridans group strep	109	93	85.3	90	71	78.9
S. constellatus	10	9	90.0	7	5	71.4
S. intermedius	36	30	83.3	29	21	72.4
E. faecalis	20	16	80.0	17	13	76.5
Gram-positive, anaerobic	73	61	83.6	82	62	75.6
P. micros	13	11	84.6	14	11	78.6
Gram negative, aerobic	375	322	85.9	316	265	83.9
Enterobacteriaceae	315	271	86.0	274	234	85.4
E. coli	216	189	87.5	199	168	84.4
K. pneumoniae	32	25	78.1	20	19	95.0
Non-fermenters	51	44	86.3	39	28	71.8
P. aeruginosa	40	34	85.0	32	24	75.0
Gram negative, anaerobic	245	209	85.3	251	210	83.7
Bacteroides fragilis group	173	152	87.9	181	152	84.0
B. caccae	25	23	92.0	19	18	94.7
B. fragilis	67	56	83.6	68	54	79.4
B. thetaiotaomicron	34	30	88.2	36	32	88.9
B. uniformis	22	19	86.4	18	15	83.3
Non-fragilis Bacteroides	14	13	92.9	13	9	69.2
B. vulgatus	11	11	100.0	8	6	75.0

Modified Table 13 from Sponsor's Clinical Summary Report
N=the number of unique baseline isolates; n=the number of pathogens with a favorable microbiological outcome

Additional FDA Analyses:
Additional sensitivity analyses were performed based on errors in randomization, assessment of surgical review panel, expanded visit windows, receipt of concomitant antibiotics. Results were consistent with the primary efficacy analysis. Please refer to the reviews by Dr. Crewalk and Dr. Khedouri for the additional analyses.

Complicated Urinary Tract Infections (cUTI):

To support the indication of cUTI, the Applicant has conducted one Phase 2 dose-ranging study (DORI-03), one Phase 3 randomized, double-blind, comparative study (DORI-05), and one Phase 3, open-label, single arm study (DORI-06) of doripenem wherein the cure rates in the doripenem arm were compared to the levofloxacin treatment arm in DORI-05. The development plan is consistent with the FDA Guidance on Complicated Urinary Tract Infections and Pyelonephritis- Developing Antimicrobial Drugs for Treatment.

DORI-03 was a multi-center, randomized, double-blind, dose finding study of two intravenous (IV) dosing regimens of doripenem (250 mg q8h and 500 mg q8h) for 7 to 14 days in the treatment of cUTI in adults. Of the 121 patients randomized to receive either one of the two doses, 100 patients were evaluable for microbiological assessment. The cure rate in the ME population at TOC was 64.2% (34/53) in the 250 mg q 8h group compared to 68.1% (32/47) in the 500 mg q 8h group.

DORI-05 was a multi-center, double-blind, randomized, Phase 3 study that compared the safety and efficacy of intravenous doripenem 500 mg q8h IV with levofloxacin 250 mg q24h as a 1-hour IV infusion in patients with cUTI or pyelonephritis. After $\geq$ 9 doses of IV therapy, patients could have switched to oral levofloxacin 250 mg q24h if they were afebrile (<37.8 °C oral) for at least 24 hours, if signs and/or symptoms of cUTI were absent or improved relative to those before the start of study drug therapy, and $\geq$ 1 urine culture had been reported with no growth at 24 hours or growth with a colony count of < 10^4 CFU/mL and no subsequent cultures with a colony count of $\geq 10^4$ CFU/mL were observed. The study was conducted at sites in the US and in South America, and Europe. Randomization was stratified by region and within each region by baseline diagnosis.

The primary efficacy endpoint was per patient microbiologic cure rate at the TOC visit 6 to 9 days after completion of study drug therapy in the co-primary ME and mMITT_1 populations. For analysis purposes, before breaking the blind, the Sponsor had extended the visit windows to 5-11 days. The pre-defined non-inferiority margin was -10%. For a justification for this non-inferiority margin please see reviews by Dr. Sorbello and Dr. Deng.

A total of 753 patients were enrolled in the study and 748 received study drug therapy (376 doripenem and 372 levofloxacin). The table below summarizes the number of patients in each of the analysis populations:

Table 5: Analysis Populations

Population	Doripenem	Levofloxacin
Randomized	377	376
ITT	376	372
Microbiological Modified Intent to Treat (MITT_1)	327 (86.7%)	321 (85.4%)
Microbiologically Evaluable (ME)	280 (74.3%)	265 (70.5%)
Clinically Evaluable (CE)	286 (75.9%)	266 (70.7%)

Approximately 60% of patients were female, the median age was 55 years, and 50 % of patients in each group had cLUTI or pyelonephritis. The two treatment arms were fairly similar in terms of demographic characteristics and baseline diagnosis. Only ~6% of patients were enrolled from US sites, with the remainder being enrolled in Europe or South America. Only ~ 8% of patients were bacteremic at study entry.

The following table summarizes the microbiologic cure rates in the ME and mMITT_1 populations:

Table 6: Cure rates in the co-primary populations (DORI-05)

Population	Doripenem	Levofloxacin	Treatment difference (2-sided 95% CI)
ME	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
mMITT_1	259/327 (79.2%)	251/321 (78.2%)	1.0% (-5.6%, 7.6%)

In both the co-primary populations, doripenem was non-inferior to levofloxacin as evidenced by the lower margin of the 95% confidence intervals exceeding the pre-defined margin of -10% and the 95% CI including the value of 0. The clinical cure rate in the CE population was a secondary point. Cure rates in this population in the doripenem arm was 95.1% (272/286) compared to 90.2% (240/266) in the levofloxacin patients (treatment difference 4.9%, 95% CI 0.2% to 9.6%).

Doripenem was microbiologically effective against the major causative pathogens of cUTI. *Escherichia coli* was the most commonly identified organism in both arms followed by *Proteus mirabilis*. Levofloxacin resistance was identified in 20 isolates of E. coli in the doripenem arm and 21 in the levofloxacin a rm. Microbiologic eradication rates were 11/20 (55%) in the doripenem arm and 6/21 (28.6%) in the levofloxacin arm.

The following table summarizes the microbiologic eradication rate by pathogen for selected pathogens in the ME population:

Table 7: The Per-Pathogen Microbiological Outcome in the ME Population

Baseline Uropathogens	**Doripenem (N = 283)** n/NI (%)	**Levofloxacin (N = 266)** n/NI (%)
Enterococcus faecalis	5/7 (71.4%)	1/3 (33.3%)
Escherichia coli	168/199 (84.4%)	184/211 (87.2%)
Levofloxacin-resistant strains	11/20 (55.0%)	6/21 (28.6%)
Levofloxacin-susceptible strains	150/172 (87.2%)	173/185 (93.5%)
ESBL-producing strains	2/3 (66.7%)	1/3 (33.3%)
Non-ESBL-producing strains	159/189 (84.1%)	178/203 (87.7%)
Klebsiella pneumoniae	10/12 (83.3%)	5/8 (62.5%)
Proteus mirabilis	16/23 (69.6%)	13/15 (86.7%)
Acinetobacter baumannii	3/3 (100%)	0/1
Pseudomonas aeruginosa	5/9 (55.6%)	5/7 (71.4%)

ESBL = extended spectrum β-lactamase; n = the number of pathogens eradicated; N = number of patients; NI = number of patients with a baseline pathogen and a follow-up culture at the TOC visit. Modified from Sponsor clinical study report, Table 19.

Cure rates were similar in the two treatment arms in various subgroups based on demographic characteristics or baseline diagnosis. Patients ≥ 65 years of age had lower success rates compared to those < 65 years of age.

Study DORI-06 was a multicenter Phase 3, open-label, single arm study of doripenem administered 500 mg q8h IV in the treatment of cUTI in adults. Doripenem-treated patients in this study were compared to levofloxacin-treated patients in DORI-05. A total of 423 patients with cUTI or pyelonephritis were enrolled from 30 centers. Demographic and baseline characteristics were generally similar between the two studies. In DORI-06 there were more males and more US sites in the doripenem arm compared to the levofloxacin arm in DORI-05.

The following table summarizes the number of patients in each of the analysis populations:

Table 8: Analysis Populations

Population	Doripenem	Levofloxacin
Randomized	426	376
ITT	423	372
Microbiological Modified Intent to Treat (MITT_1)	337 (79.1%)	321 (85.4%)
Microbiologically Evaluable (ME)	250 (58.7%)	265 (70.5%)
Clinically Evaluable (CE)	257 (60.3%)	266 (70.7%)

The following table summarizes the microbiologic cure rate in the co-primary populations (ME and mMITT_1):

Table 9: Cure rates in the co-primary populations

Population	Doripenem	Levofloxacin	Treatment difference (2-sided 95% CI)
ME	209/250 (83.6%)	221/265 (83.4%)	0.2% (-6.6%, 7.0%)
mMITT_1	278/337 (82.5%)	251/321 (78.2%)	4.3% (-2.1%, 10.7%)

Thus, in the co-primary ME and mMITT populations doripenem was non-inferior to levofloxacin using a pre-specified non –inferiority margin of -10%.

The clinical cure rates at the TOC visit in the CE population were similar for the DORI-06 doripenem treatment arm compared to the DORI-05 levofloxacin treatment arm, 93.0% (239/257) for doripenem and 90.2% (240/266) for levofloxacin. The treatment difference was 2.8% with a 2-sided 95% CI of -2.4% to 7.9%. No significant differences were seen in the various sub-groups based on baseline or disease characteristics.

Microbiologic eradication rates for *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Pseudomonas aeruginosa* were 91.8%, 80%, 85.7%, and 77.8%, respectively. Twenty three isolates of *E.coli* were levofloxacin resistant and the cure rates among those isolates were 65.2% (15/23).

Microbiologic eradication rates in the ME population for both studies combined were low for *E. faecalis* and *E. cloacae*. Microbiologic eradication rate for *E. faecalis* was 66.7% (8/12) and for *E. cloacae* was 18/28 (64.3%). Thus, these organisms will not be included in the product label.

SAFETY

Safety data from the pooled Phase 1 studies, one Phase 2 study and four Phase 3 studies

comprise the safety database for doripenem. The following table summarizes the number of patients exposed to doripenem in the various studies:

Table 10: Doripenem Safety Population

Study	Number
Pooled Phase 1 studies	164 distinct subjects (138 received 500 mg, 107 received 1000 mg)*
DORI-3, Phase 2 study (dose-ranging study in patients with cUTI	60 patients in each group 250 mg q 8 h or 500 mg q 8 h
Phase 3 cUTI studies	847 (375 DORI-05, 472 DORI-06)
Phase 3 cIAI studies	472 (236 DORI-07, 236 DORI-08)

* excludes patients with renal impairment in studies DORI-02 and DORI-NOS_1005

Overall, the treatment exposure studied in the doripenem phase 3 clinical trials supports the durations of treatment for each proposed indication for the product label by the Applicant. The mean (SD) duration of exposure in patients treated with IV or IV plus oral switch was 9.6 days (3.11), with a range of 1-27 days. In patients treated with IV alone, the mean (SD) duration of therapy was 6 days (2.87) with a range of 1-16 days. However, there is very limited safety data regarding doripenem administered for > 14 days; only 19 patients were treated with IV doripenem alone without an oral (PO) switch for > 14 days.

Adverse Events:
The following table summarizes treatment emergent adverse events for the pooled Phase 2* and 3 studies:

Table 11: Treatment-Emergent Adverse Events

	Doripenem N=1332 n (%)	**Levofloxacin N= 372 n(%)**	**Meropenem n=469 N (%)**
TEAE	955 (71.7)	222 (59.7)	326 (69.5)
Study drug-related TEAE	366 (27.5)	93 (25.0)	110 (23.5)
SAEs	139 (10.4)	15 (4.0)	76 (16.2)
Study-drug related SAE	2 (0.2)	0	0
Deaths	17 (1.3)	0	18 (3.8)
Discontinuation due to AEs	36 (2.7)	14 (3.8)	13 (2.8)

* excludes doripenem 250 mg group from DORI-03

There were a total of 17 (1.3%) deaths in doripenem treated patients and 18 (3.8%) deaths in meropenem treated patients. There were no deaths in levofloxacin-treated patients. In the doripenem treated patients, 10.4% had Serious Adverse Events (SAEs) compared to 4.0% in the levofloxacin arm and 16.2% in the meropenem arm. SAEs were more common in the doripenem arm for the System Organ Classes of Renal and Urinary Disorders (13 vs. 0) and Blood and Lymphatic System Disorders (5 vs.0).

Overall, in the pooled Phase 2 and 3 studies, headache was the most commonly reported AE. Headache was reported by 12.6%, 14.5%, and 5.1% of patients in the doripenem, levofloxacin, and meropenem treatment arms, respectively. The incidence of headache

was higher in subjects in the cUTI safety analysis set (9.2%, doripenem 250 mg; 17.2%, doripenem 500 mg; 14.5%, levofloxacin) compared to the cIAI safety analysis set (4.4%, doripenem; 5.1%, meropenem). No subjects discontinued study drug therapy prematurely due to headache. However, because of the frequency with which headache was reported in the cUTI studies, this was included as an Adverse Drug Reaction (ADR).

Diarrhea was reported in 7.9%, 10.2%, and 11.1% of subjects in the doripenem, levofloxacin, and meropenem treatment arms, respectively. Most episodes of diarrhea were mild or moderate in severity; one doripenem-treated patient and 4 levofloxacin-treated patients reported severe diarrhea, which resulted in study drug discontinuation for the levofloxacin-treated patients.

Nausea was reported in 6% to 9% of patients across the three treatment arms. Most episodes of nausea were mild or moderate in severity, and generally resolved within 1 to 2 days. Two doripenem-treated patients experienced severe nausea and discontinued study drug therapy prematurely, in addition to 1 meropenem-treated patient with moderate nausea. Both diarrhea and nausea were included as ADRs by the Applicant.

Anemia was reported at similar rates in the doripenem and meropenem arms (5.3% and 5.5%, respectively). It was more common in the doripenem arm in the cIAI studies and similar in the two arms in the cUTI studies. Reports of anemia were evaluated by the Sponsor as not being plausibly related to doripenem use and clinical laboratory evaluations did not reveal any different trends among the treatment arms. Thus, anemia was not included as an ADR by the Applicant. Please see Sections 7.1.5.5 and 7.1.7.5 of Dr. Sorbello's review for a detailed analysis of anemia cases.

No seizures were reported in any doripenem-treated or meropenem-treated patients in the Phase 1, 2 and 3 studies. One levofloxacin-treated patient (DORI-05) experienced a generalized seizure. Preclinical data suggest a reduced risk for seizures associated with doripenem compared with other carbapenems, based upon its low affinity for displacing 3H-muscimol from GABA receptors in mouse brain synaptic membrane in *in vitro* studies.

Urinary tract related infections were commonly reported as adverse events in DORI-06. Asymptomatic bacteriuria and urinary tract infection were each reported in 30 (7%) patients, and pyelonephritis was reported in 1 additional patient. Urinary tract infection was reported as an SAE in 6 (1%) patients while pyelonephritis was reported as a serious adverse event in 1 additional patient. These cases more likely represent lack of efficacy rather than a safety signal. Patients with reports of UTI outcomes as adverse events are discussed in greater detail in Section 7.1.4 of Dr. Sorbello's safety review.

Study drug-related AEs with a higher incidence in doripenem-treated patients versus levofloxacin-treated patients and meropenem-treated patients (other than the marginally higher rate for vomiting), included headache (4.2% versus 2.7% and 0.9%), phlebitis (4.1% versus 3.0% and 2.1%), and nausea (3.4% versus 1.6% and 1.9%), respectively.

There were no reported cases of erythema multiforme, toxic epidermal necrolysis, Stevens Johnson Syndrome, agranulocytosis, or hepatic necrosis among the 1,276 doripenem-treated subjects in the combined safety population in the four Phase 3 clinical trials.

The Applicant defined ADR as an undesirable effect reasonably associated with the use of doripenem based on its pharmacologic action, timing of event relative to doripenem administration, and whether the AE is was known to be caused by drugs in the same class. The Applicant has provided the algorithm used for making this determination. Using the Applicant's criteria, the most common ADRs occurring in $\geq$ 5% of patients were headache, nausea, diarrhea, rash, and phlebitis.

Anemia and renal failure/renal impairment were analyzed in further detail to determine any association of these adverse events with doripenem. In the pooled cIAI data, anemia was observed in 9.6% of doripenem-treated patients and in 5.5% of meropenem-treated patients . In the comparative cUTI study it was seen in 1.5% of doripenem-treated patients compared to 2.8% and 1.1% of levofloxacin and meropenem-treated patients respectively.

Nineteen renal treatment emergent AEs were reported by 17 patients (16 doripenem-treated and 1 meropenem-treated). One patient each in DORI-06 and DORI-07 had two separate renal AEs. Nine of the events were considered SAEs and two were considered study-drug related. Baseline creatinine clearance (CrCL) in these patients was as follows: >80 ml/min = 4, 50-80 ml/min = 6, 30-50 ml/min = 6, < 30 ml/min =1.

The timing of the renal AE varied from study day 1-study 32. In five patients (4 doripenem-treated and 1 meropenem treated), abnormal baseline creatinine values decreased without discontinuing therapy. In seven patients the renal AE occurred 6-26 days post-treatment. Five patients in whom renal AEs occurred while on therapy had significant underlying co-morbidities that could contribute to renal impairment. For narratives on these patients please see Dr. Sorbello's review. Overall, based on the cases of renal AEs reported in this NDA it is difficult to establish a causal link between renal AEs and doripenem administration. It is certainly possible that in patients with significant underlying illness that compromise renal function, doripenem administration can further aggravate the renal dysfunction. Post marketing surveillance of this adverse event is important.

Laboratory tests

Laboratory parameters were assessed adequately during the studies. Laboratory abnormalities were classified using the toxicity grades defined by the Division of Microbiology and Infectious Diseases which were slightly modified by the Applicant to include a normal grade and to remove clinical manifestations. For examination of potential hepatic injury, Hy's High Risk (HHR) classification defined as an alanine amino transferase (ALT) > 3 x upper limit of normal (ULN) and a total bilirubin > 1.5 x ULN at the same time point was utilized.

Hepatobiliary:
Eleven patients in the pooled doripenem Phase 3 studies fulfilled HHR criteria at time points ranging from baseline to the late follow up visit. Five patients fulfilled HHR criteria at screening: one levofloxacin-treated patient in DORI-05 (#03103074), three doripenem-treated patients [two in DORI-08 (#04302050 and #38504049) and one in DORI-07 (#0502005)] and one meropenem-treated patient (# 38103013) in DORI-08. The levofloxacin-treated patient withdrew consent after receiving four days of levofloxacin. The other four patients successfully completed study drug and study participation.

Six patients (four doripenem-treated and 2 meropenem-treated) fulfilled HHR criteria at some point post-baseline. Of the four doripenem-treated patients, one met HHR criteria at the end of IV therapy and three met HHR criteria at early or late follow up visit. Brief summaries of these four patients is described here, for detailed narratives, please see Dr. Sorbello's review.

1. DORI-06, ID 35000106: 37-year old with history of gallstone had screening GGT.ULN. At the end of IV therapy on day 3, both AST and ALT were >10 ULN with bilirubin elevation to >1.5ULN. AST and ALT values decreased by day 8, GGT and bilirubin remained elevated. On day 31, GGT remained elevated to >5xULN. Hepatitis B and HIV serology were negative, Mycoplasma IgM was positive. Persistently elevated GGT seem to suggest a cholestatic liver injury. However, as AST and ALT peaked at the end of IV therapy and improved after stopping doripenem, it is likely that doripenem contributed to some hepatocellular damage resulting in elevated transaminases.

2. DORI-06, ID 45000084: 81-year old, male with multiple co-morbidities had screening ALT, AST, and GGT >2xULN, and Alkaline Phosphatase (ALP) >ULN. Laboratory tests on day 3 met HHR, ALT>4xULN, AST >6xULN, bilirubin 1.8xULN. GGT and ALP were also elevated. On day 7, patient died of cardiac arrest. No other follow up serum chemistries are available. Without follow up laboratory values after the abnormal value on day 3 it is not possible to comment on whether the levels continued to rise or decrease on therapy. However, given underlying Chagas cardiomyopathy and congestive heart failure and elevation of GGT and ALP, it is difficult to assess causality.

3. DORI-07, ID 40104517: This patient met the definition of HHR classification at the EFU visit. At screening, the patient had a normal ALT value of 29 IU/L, an elevated AST value of 52 IU/L, elevated indirect bilirubin of 18 µmol/L (normal range: 3.42 to 13.68 µmol/L), and elevated total bilirubin of 95 µmol/L (normal range: 3.42 to 17.1 µmol/L). During doripenem therapy, the patient had ALT values of 42, 31, and 54 IU/L, and AST values of 108, 61, 63, and 87 IU/L. After completing 11 days of IV study drug therapy the patient was switched to oral amoxicillin/clavulanate which was completed on Day 15. On Day 23, the patient had ALT of 137 IU/L, AST of 48 IU/L, and total bilirubin of 29.24 µmol/L. On

Day 46, the patient's ALT was 227 IU/L, AST was 102 IU/L, and total bilirubin was 11.63 μmol/L. The elevation in ALT coincided with the diagnosis of Addison's disease and the introduction of steroid therapy. The hyperbilirubinemia had already declined from baseline levels when the patient met the criteria for Hy's rule. The investigator considered this event unlikely to be related to study drug therapy. Underlying Addison's disease and steroid therapy are the most likely cause of elevation in ALT and is unlikely to be related to doripenem as the elevated values occurred after doripenem was discontinued.

4. DORI-08, ID 43104023: This doripenem-treated patient was an 80-year-old Hispanic female who was enrolled with generalized peritonitis following a perforated appendix. Baseline bilirubin and LFT values were normal and while on therapy she developed a sudden increase in ALT peaking to 1759IU/L. Study drug was discontinued due to lack of efficacy. The patient subsequently developed septic shock and was treated with multiple antibacterial and cardiotonic therapies. At the EOT she met criteria for HHR classification, though ALT had decreased to 267 while the bilirubin had increased to 28 mol/L. By the TOC visit, the LFTs had decreased and the patient no longer met criteria for HHR classification. The underlying cIAI and septic shock could have contributed to increase in LFTs.

Hematologic: Mean change in most hematology parameters were similar across the treatment arms. The mean (SD) change in hemoglobin in g/L was 3.2 (13.89), 3.4 (11.53), and 3.3 (15.38) in the doripenem, levofloxacin and meropenem treated patients respectively. Five doripenem-treated patients had Grade 4 hemoglobin values post-baseline and in two patients represented a ≥ 2 Grade change of. Two meropenem-treated patients had Grade 4 hemoglobin values post-baseline and in one patient it represented a ≥ 2 Grade change. No levofloxacin-treated patient had a Grade 4 hemoglobin value. A hematology consult was obtained to assess anemia as a treatment -emergent adverse event and to assess the likelihood of an association between doripenem administration and development of anemia. In their assessment there was insufficient evidence to establish a link between doripenem and development of hemolytic anemia. They recommended that the Sponsor assess doripenem as a cause of hemolytic anemia as a phase 4 commitment. Please see consult review by Dr Andrew Dmytrijuk M.D.

Conclusions:
Based on the data submitted by the Applicant, there is adequate efficacy and safety data to recommend approval of doripenem injection 500 mg every 8 hours for the treatment of complicated urinary tract infections and complicated intra-abdominal infections in patients 18 years of age and older.

In the pivotal study for complicated urinary tract infections doripenem was non-inferior to levofloxacin. Results of the non-comparative study were supportive. For the complicated intra-abdominal infections indication, in both the active-controlled studies doripenem was non-inferior to meropenem. In both indications, oral switch was allowed

after patients met protocol-specified criteria of clinical improvement, hence only limited data is available on patients treated with intravenous doripenem alone.

In the overall safety population, doripenem was generally well -tolerated. The most common adverse reactions identified were headache, nausea, diarrhea, rash, and phlebitis. An important limitation of the safety database is that only a small number of patients were treated with doripenem alone, hence the safety assessment is confounded by the oral switch regimens for both the cUTI and cIAI indications. Also, safety data on treatment-durations exceeding 14 days is very limited. No clear association between doripenem administration and development of anemia could be established in this data,. However as hemolytic anemia has been reported with carbapenem class of drugs, the Sponsor should monitor for this adverse event post-marketing. Also, monitoring for renal adverse events including worsening of pre-existing renal disease and seizures is warranted. As a phase 4 commitment, anemia, renal failure/impairment, and seizures should be monitored, preferably with a registry being set up of patients treated with doripenem. Additionally, surveillance data should be collected to monitor for development of resistance.

Appendix 1

Justification of Non-Inferiority Margin for Complicated Intra-Abdominal Infections

This document outlines the approach used to justify the non-inferiority margin for complicated intra-abdominal infections (cIAI). A summary of the Sponsor's response is provided followed by the Agency's approach. This review was conducted by Sumathi Nambiar MD MPH, Medical Team leader DAIOP and Scott Komo DrPH, Statistical reviewer OB/DBIV.

Overview of Sponsor's Approach

The following steps outline the Sponsor's justification of the non-inferiority margin for cIAI:

1. A literature search was performed using several databases (PubMed, Embase, Medline, Biosis) to assess the spontaneous resolution rate with surgery alone (placebo cure rate) for cIAI based on the following:

   - Clinical trials involving antibiotics for this indication with a placebo control.
   - Clinical trials involving antibiotics for surgical prophylaxis.
   - Clinical trials involving antibiotics for this indication reporting results of delayed treatment or inappropriate treatment.

   As no placebo controlled trials were identified for the treatment of cIAI, the Sponsor reviewed studies of antibiotic prophylaxis in patients undergoing abdominal surgeries. Using the proportion of patients with appendiceal vs. non-appendiceal infections in the current submission as weights, a weighted point estimate of the complication rate was computed. The estimated placebo cure rate was computed as the complement of the complication rate, i.e. 1-complication rate. Thus, the putative placebo cure rate was estimated as no greater than 62.0%. Note, neither intra- nor inter-study variability was accounted for in the estimate.

2. The cure rate of meropenem, the comparator in both Studies DORI-07 and DORI-08, and corresponding variability of this estimate was estimated from seven published studies of meropenem for the treatment of cIAI in a meta-analysis using a random-effects model, i.e. DerSimonian-Laird method. The pooled estimate of the cure rate and corresponding two-sided 95% confidence interval for meropenem was 96.749 (94.963-98.535)

3. Literature was reviewed for studies of delayed/inappropriate therapy in intra-abdominal infections. The aim was to examine the effect of a delay in receipt or nonreceipt of effective therapy on clinical outcomes. Results of these studies were not included in the calculation of the putative placebo rate.

4. The lower bound of the 95% confidence interval for the active comparator cure rate and the point estimate of the putative placebo cure rate were then used to calculate the largest difference between meropenem and placebo that would still

preserve 50% of the benefit of meropenem. The most conservative estimated value for Δ50 obtained from the two-sided 95% CI is 16.5%.

Agency's Approach

The overall approach by the Sponsor and the Agency were similar. One of the studies used by the Sponsor to support the placebo cure rates were excluded from the Agency's analysis as all patients in the study who had perforated appendicitis received post-operative antibiotics. This discrepancy and others noted in the data provided by the Sponsor to compute the placebo rates was brought to the Sponsor's attention and the numbers presented above represent the numbers reported by the Sponsor after deleting data from the Gottrup study and revising other discrepancies. [1] This revised calculation was submitted by the Applicant on September 4, 2007.

Estimation of placebo rates:

The following sources of information were used to estimate placebo cure rate:

- Placebo-controlled trials in patients with cIAI
- Placebo-controlled prophylaxis trials in patients undergoing abdominal surgery
- Inappropriate therapy studies

No placebo controlled studies were identified in the treatment of complicated intra-abdominal infections.

The putative placebo cure rates were indirectly estimated from the placebo controlled studies for pre-operative prophylaxis in patients undergoing abdominal surgery.[2-5] This approach in estimating the placebo cure rates has the following limitations:

- Patients in these studies do not have cIAI and are only at risk of infection. So, the placebo effect seen with prevention of infections will certainly be higher than that seen in patients with cIAI.
- Some of these studies assessed prevention of wound infection or prevention of IAI. Again, the estimate of placebo rates in the prevention of wound infections will be much higher than that expected in the treatment of cIAI.
- The preponderance of evidence is from studies in patients with appendicitis and may not represent all types of cIAI. However, as a conservative approach among patients with appendicitis, only data from patients with gangrenous/perforated appendicitis was used as they tend to be sicker and more likely to have poorer outcomes. This was combined with data from patients undergoing colo-rectal surgeries.

The following table summarizes the complication rates (wound infection/intra-abdominal) in placebo and antibiotic groups from the prophylaxis trials (appendiceal and non-appendiceal):

Table 1: Complication rates from placebo-controlled prophylaxis trials

Author	Type of Surgery	Placebo, (%[n/N])	Antibiotic (%)
Donovan et al.	Perforated appendix	78% (7/9)	44%
Bauer et al.	Gangrenous Appendix	30.6% (22/72)	8.3%
Gomez-Alfonso et al.	Colorectal surgery	48.4% (15/31)	17.1 %
Hojer et al.	Colorectal Surgery	45% (27/60)	12.1 %

A summary of the five studies used by the Sponsor to estimate the placebo cure rates (includes Gottrup study) are summarized in the following table.

Table 2: Summary of placebo-controlled prophylaxis trials

Author/Year	Treatment	Source (n)	No in study	Infection rate Antibiotic group	Infection rate Placebo group	Type of infection prevented	Time assessed	Comments
Gottrup/1979	Flagyl	Appy	426 200 (Flagyl) 206 (Placebo)	0	3/79 (Phleg) 8/33 (Gangrenous) 15/33 (Perf)	Wound/intra-abdominal infection	f/u for 3 months after surgery	Pts. In perf. group received abx x 5days (PCN/SM), so placebo rates not useful
Donovan (1979)	Clinda/cefoxitin	Appy	238, 72 (P), 81 (Clinda), 85 (Cefoxitin)	8/18 (44%) clinda, 20/25 (80%) cefazolin	7/9 (78%)	Wound infection	2-3 weeks post op	Only 52 were gang/perf, only 9 in pl gp. Placebo rate in normal/acutely inflamed 30%; placebo and cefazolin rates similar in gangrenous
Bauer/1988	Cefoxitin 3-5 mins. before surgery	Non-perf appy	1735, 845 cefoxitin, 890 placebo; Gangrenous: 109 (C), 72 (P)	9/109 (8.3%) Wound infection 1/109 (0.9%) IA abscess	22/72 (30.6%) Wound infection 2/72 (2.8%) IA abscess	Wound/intra-abdominal infection	Upto 4 weeks post-op	Only non-perforated appy. Patients with perforated appy were excluded
Alonso/1984	GM+Flagyl 2 hrs prior and q 8 hr/24-72 hours	Appy/Colo rectal (CR) surgery	188 (122 appy, 66 CR)	4.9% (A)	34.4%	Wound/intra-abdominal infection	?	Not all CR surgeries in patients with perforation, only 7 perforated. In most patients, reduction in wound infection rather than reduction in intra-abd abscess. See graph
				6/35 (17.1%) (CR)	15/31 (48.4 %)			
				9.4% (both)	39.1%			
Hojer/1977	Doxycycline	CR surgery-resection/transaction of colon. No. CR perf. not provided.	118, 58 (Doxy), 60 (P)	7/58 (12.06%)	27/60 (45%)	Wound/intra-abdominal infection	30 days post-op	Most had wound infection.

In addition to these four studies, one additional study was used to estimate the placebo cure rates.[6] This was a retrospective study in 300 children with gangrenous or perforated appendicitis at the Hospital for Sick Children, Toronto from 1975-1980. Patients were grouped according to their antibiotic regimen as follows:

Group A: Received ampicillin, gentamicin, and clindamycin
Group B: Received ampicillin and/or gentamicin
Group C: Received no antibiotics

Data from this study is limited in that it is not a prospective randomized trial. However as there are sufficient number of patients with gangrenous or perforated appendicitis who did not receive antibiotics it was considered that including this data was meaningful. As a conservative estimate, only data from patients who developed post-operative intraperitoneal abscess with stage III disease were used in estimating placebo rates.

Mean age of children in this study was 8.9 years. Of the 300 patients, 30 had gangrene of the appendix (stage I), 143 had local perforation (stage II), and 127 had generalized peritonitis.

The incidence of post operative wound infections and the incidence of post-operative intraperitoneal abscess by stage of appendicitis and treatment group are presented in the following two graphs.

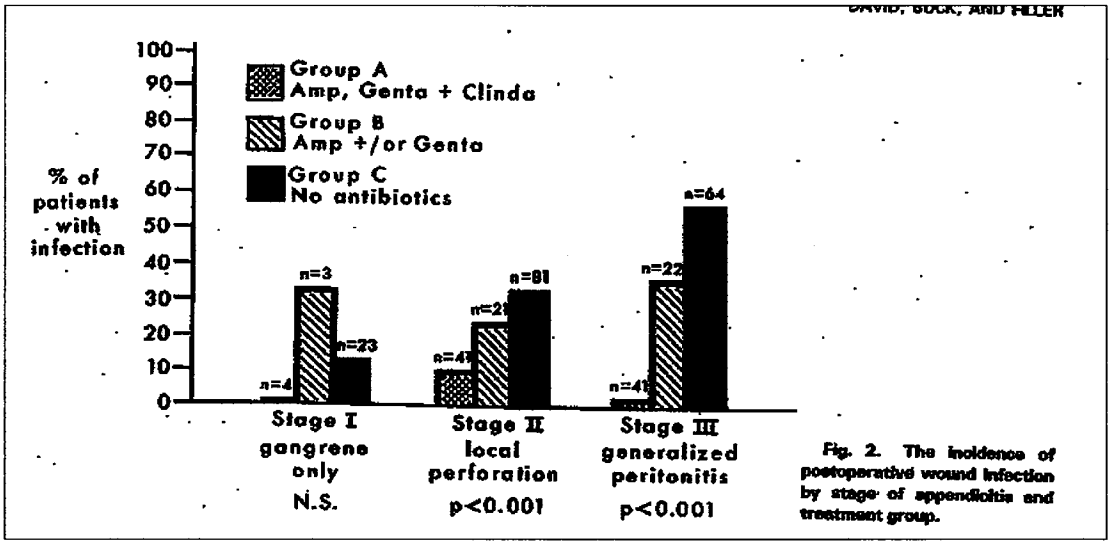

Fig. 2. The incidence of postoperative wound infection by stage of appendicitis and treatment group.

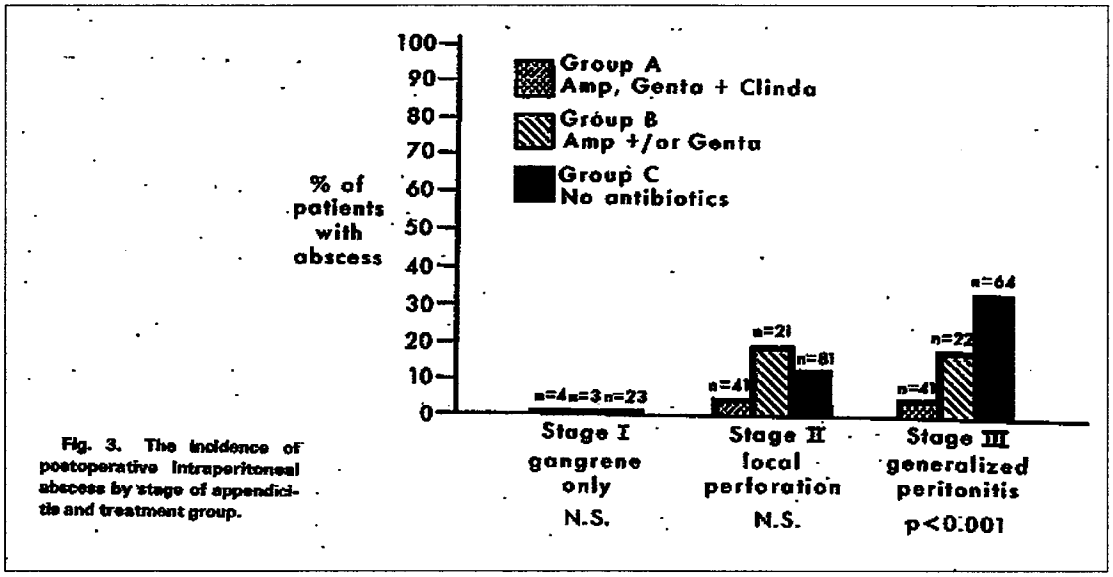

Fig. 3. The incidence of postoperative intraperitoneal abscess by stage of appendicitis and treatment group.

Additionally, a recent Cochrane review of antibiotic prophylaxis for prevention of post-operative complications in patients undergoing appendectomy was reviewed. This review showed that antibiotic prophylaxis was effective in. prevention of wound infection (Odds ratio (OR): 0.31; 95% CI: 0.24-0.42) and intra-abdominal abscess (OR: 0.35; 95% CI: 0.13-0.91) for all types of appendicitis combined. For perforated appendicitis, the antibiotic effect for prevention of wound infections was (OR: 0.47; 95% CI: 0.22-1.00) and for prevention of intra-abdominal abscess was (OR: 0.28; 95% CI: 0.08-0.91).[7]

Delayed treatment/inappropriate treatment

The following four epidemiologic studies were reviewed. Overall, data from these studies were not very helpful and were not used to compute the putative placebo rate.

1. Bare et al. 2006- Patients with community acquired cIAI were studied. Appropriateness of therapy defined based on literature (no specific criteria listed). Out of 376 cases, 51 received inappropriate therapy. This was associated with need for a second-line antibiotic.[8]
2. Krobot et al. 2004- 425 patients with community-acquired cIAI (38 % perforated appendicitis, 27% colon, 22% gastro-duodenal) were studied. In patients with documented pathogen on blood culture/intraabdominal swab, inappropriate therapy was defined as one or more bacteria isolated at baseline that were resistant regardless of whether regimen was subsequently changed. For those with no culture or negative culture appropriate therapy included coverage for beta-lactamase positive gram negative bacteria, *S. aureus*, and *B. fragilis*. 54 patients received inappropriate treatment. Clinical success was higher in the appropriate therapy group, 79% (74-84) vs. 53 (41-69).[9]
3. Sturkenboom et al. 2005- This was a population based retrospective cohort study of 175 cases of IAI. Inappropriate was defined as regimen that did not cover

facultative and aerobic gram negative bacteria plus anaerobes. ~ 50% had perforated appendicitis, 147 (84%) had received appropriate therapy and 28 received inappropriate therapy. Risk of clinical failure was 3.4 fold (1.3-9.1) with inappropriate therapy.[10]

4. Manes et al. 2006. This was a randomized controlled trial of early vs. delayed treatment in patients with pancreatitis. 108 patients were started on meropenem 500 mg tid within 1.07 +/- 0.6 days compared to 4.56+/- 1.2 days. Pancreatic infection occurred in four patients in group A and nine in group B. Extra-pancreatic infection, need for surgery and length of hospitalization was higher in group B.[11]

The following steps outline the Agency's method used to define the non-inferiority margin:

I. Estimating placebo cure rate

A. Using 4 antibiotic prophylaxis trials provided by the Sponsor and an additional trial identified by the Agency, we computed the placebo complication rate using a fixed-effects model for gangrenous/perforated appendicitis and nonappendiceal disease separately. The complication rate for gangrenous/perforated appendicitis was 45.6% with a 95% confidence interval (CI) of (37.3%, 54.2%). For nonappendiceal disease, the complication rate was 46.2% with a 95% CI of (36.2%, 56.4%).

B. An overall complication rate of 44% was computed as a weighted average, with weights based on the proportion of patients seen in the Sponsor's phase III studies (60% appendiceal disease; 40% nonappendiceal disease). The weighted complication rate was 45.8% with a 95% CI of (39.5%, 52.2%).

C. The placebo cure rate was assumed to be 1 – complication rate (from Step I (B)). The weighted placebo cure rate was 54.2% with a 95% CI of (47.8%, 60.5%)

II. Estimating active comparator cure rate

Though other publications using meropenem for treatment of cIAI were reviewed, only three of the studies provided by the Sponsor contained results for the ITT population. Remainder of the studies had data for the evaluable population only. We used results based on the ITT population because they provide a conservative estimate and are protected by randomization. A fixed-effects model was used to compute both a point estimate and the corresponding confidence 95% interval for the active comparator (meropenem) clinical cure rate. The estimated clinical cure rate was 80.9% with a 95% CI of (75.4%, 85.3%).

The following table summarizes results form the three studies used to calculate the meropenem clinical cure rates:

Table 3: Studies used in the Estimation of the Meropenem Cure Rate

Authors	Timing of endpoint assessment	Type of study	Cure rates	Comments
Brismar et al 1995 [12]	1-2 weeks and 4-6 weeks post-therapy	Open label	94% meropenem, 85% imipenem/cilastatin	Not clear if success rates are at 1-2 weeks/4-6 weeks post therapy
Condon et al. 1995 [13]	4-14 days and 28-42 days post therapy	Double-blind	62/88 (70%) meropenem, 58/89 (65%) clindamycin/tobramycin	Not clear if success rates are at 4-14 days/28-42 days post therapy
Zanetti et al. 1999 [14]	End of therapy and 2 weeks post therapy	Open-label	82.1% meropenem, 86.1% imipenem/cilastatin	Results for ITT are at end of therapy, no data for ITT at the 2 week post therapy visit

Estimating the non-inferiority margin

Summarizing the cure data from Steps I (B and C) and II provides the following information:

- Weighted placebo complication rate of 45.8% with a 95% CI of (39.5 %, 52.2%)
- Assuming the response rate was the complement of the complication rate, the weighted placebo cure rate was estimated to be 54.2% with a 95% CI of (47.8%, 60.5%)
- Active comparator (meropenem) cure rate of 80.9% with a 95% CI of (75.4%, 85.3%).
- The putative placebo clinical cure rate, obtained from placebo cure rate for prophylaxis of cIAI was at best about 60.5% (using the upper bound of the 95% CI for the estimated placebo prophylaxis cure rate). The conservative estimate of the clinical cure rate for meropenem was 75.4% (using the lower bound of the 95% CI for the estimated meropenem cure rate). This estimate was similar to the observed meropenem clinical cure rates based on the current submission (NDA22-106), which were 78.0% and 74.2% in the microbiological ITT population for Studies DORI-07 and DORI-08 respectively. Therefore, the conservative estimate of the active control (meropenem) over the placebo is 14.9% (75.4%-60.5%) which provides an estimate of 14.9% for M1. Considering that the M1 was computed based on the placebo rate for prophylaxis rather than for treatment of cIAI, it is likely that M1 is larger than 14.9%.
- A limitation of this estimation is that no fraction of M1 was preserved. However, it is felt that the estimated placebo cure rate for treatment of

cIAI will be much lower than that estimated based on the placebo cure rate for prophylaxis. Firstly, patients in these studies do not have cIAI and are only at risk of infection. Secondly, some of these studies assessed prevention of wound infection rather than prevention of IAI. Placebo cure rates for prevention of wound infection are likely to be higher than that seen for prevention of IAI. Thirdly, the preponderance of evidence was from studies in patients with appendicitis and thus does not represent all types of cIAI.

- Additionally we used conservative estimates for the placebo cure rate, using the upper bound of the 95% CI, and for the comparator cure rates, using the lower bound of 95% CI in the ITT population. Also, as a conservative approach among patients with appendicitis, only data from patients with gangrenous/perforated appendicitis was used as they tend to be sicker and more likely to have poorer outcomes. This was combined with data from patients undergoing colo-rectal surgeries.

Hence, an M2 of 15% would preserve an unknown but positive fraction of the meropenem treatment effect for the treatment cIAI. Therefore, a 15% noninferiority margin is justifiable given all of the information summarized above with the caveats provided.

It should be noted that the acceptability of a 15% non-inferiority margin using meropenem as the active control for cIAI is based on the limited information currently available. However, this margin could be subject to change in the future based on availability of additional information on the placebo and control effect.

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/s/

Sumathi Nambiar
10/10/2007 05:56:29 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	022106
Submission Code	000
Letter Date	12/12/06
Stamp Date	12/13/06
PDUFA Goal Date	10/12/07
Reviewer Name	Julie-Ann Crewalk, MD
Review Completion Date	10/11/07
Established Name	Doripenem for Injection
(Proposed) Trade Name	Doribax
Therapeutic Class	Carbapenem
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Priority Designation	S
Formulation	IV
Dosing Regimen	500 mg every 8 hours
Indication	Complicated Intra-abdominal Infections
Intended Population	≥ 18 years

Table of Contents

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Complicated Intra-abdominal Infections (cIAI), caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus, ; Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros.*

6.1.1 Methods

The primary clinical data which were used in this efficacy review to support the proposed indication were collected from two nearly identically designed Phase III studies, DORI-07 and DORI-08. The case report forms, datasets, and the sponsor's study reports were reviewed. Sections of this report have been excerpted from the Clinical Study Reports of DORI-07 and DORI-08, and the Sponsor's Clinical Summary Report. The Medical Officer's (MO) Comments will be bolded and in italics.

The Division requested that the Applicant submit a 10 % random sample of the doripenem and meropenem case report forms (CRFs) from study DORI-07 and 08. The CRFs were reviewed for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of the protocol, and accuracy in reporting of results. The results were then compared to those of the Applicant. Seventy-two CRFs were examined for each study.

During the review, there was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer. However, there was a discrepancy present for the following CRF. This discrepancy is summarized as follows:

Study and Patient ID	Comments
DORI-07 01502045	Patient was treated with doripenem and evaluated as a cure. However, there was no abdominal exam done at the follow up visit. CT scan demonstrated an intra-abdominal abscess. It is therefore unclear how this patient can be a cure with what appears to be limited evaluation for clinical improvement. Should be called indeterminate.

There was also discrepancies with regards to using concomitant antibiotics which are mentioned in more detail in Section 6.1.4.3.

6.1.2 General Discussion of Endpoints

The co-primary efficacy endpoints in both studies were:

1) Clinical cure rates for the microbiologically evaluable (ME) at test of cure (TOC) analysis set.

2) Clinical cure rates for the microbiological modified intent to treat (mMITT) at TOC analysis set

The primary analysis for both studies tested the hypothesis of non-inferiority of intravenous (IV) doripenem to IV meropenem in both the ME at TOC analysis set and the mMITT population. Non-inferiority was concluded if the lower bound of the 2-sided 95% confidence interval (CI) around the difference in the clinical cure rates (doripenem minus meropenem) was $\geq$ -15%.

The secondary efficacy endpoints:

1) Clinical cure or improvement rates at the end of IV therapy [EOT (IV)] visit
2) Clinical cure rates at the early follow up (EFU) visit
3) Microbiological endpoints at the TOC visit examined in two ways:
a. Per-patient microbiological cure rates
(i.e., eradication or presumed eradication of all baseline pathogens)
b. Per-pathogen microbiological outcomes
(i.e., eradication or presumed eradication at the EFU and TOC visits).

Visit Windows:

For the purpose of evaluability assessments and data analyses, and before breaking the study blind, the protocol-defined visit windows for the EFU (7 to 14 days) and TOC (28 to 42 days) visits were expanded to 6 to 20 days and 21 to 60 days, respectively, after the final dose of study drug therapy (IV alone, or IV plus oral). The TOC visit window was expanded to allow inclusion of subjects who were otherwise evaluable but had TOC visits inadvertently scheduled from the end of IV therapy, rather than the end of oral study drug therapy, or who missed their originally scheduled TOC visit. The expanded TOC visit window was consistent with the final assessment window of 4- to 6- weeks after entry into the study, as specified in the Infectious Disease Society of America (IDSA) general guidelines for the evaluation of new anti-infective drugs for the treatment of intra-abdominal and pelvic infections. Per the sponsor, although the late follow up (LFU) visit was considered the TOC visit, the EFU visit is an important endpoint in this indication because the clinical outcome following surgery and antibacterial therapy is not anticipated to change beyond 2 weeks post-therapy. There are also fewer drop-outs at this visit than at the later LFU (TOC) visit. The EOT (IV) assessment is an especially important time point because it represents the outcome closest to the end of treatment with the IV study drug therapies being evaluated in these studies.

MO Comments: ***The expanded visit windows are acceptable and consistent with the IDSA guidelines for the evaluation of new anti-infective drugs for the treatment of intra-abdominal and pelvic infections[1]. However, as these visit windows were not defined in the protocol, sensitivity analyses were preformed using both protocol-specified and expanded visit windows. Please refer to section 6.1.4.8 for sensitivity analyses based on the change in visit windows.***

6.1.3 Study Design

6.1.3.1 Overview

The two Phase III studies for complicated intra-abdominal infections (DORI-07 and DORI-08) were identical, multi-center, randomized, double-blind, studies comparing doripenem (500 mg infused over 1 hour q8h) with meropenem (1 g IV bolus q8h). They were, however, conducted at different investigational sites by different investigators.

MO Comments: ***As the two studies were identical in design and conduct, integrated analyses based on pooled data from the two studies will be presented in this section. For results of individual studies, please see Appendix in Section 10.***

A total of 962 subjects were enrolled and randomized on a 1:1 basis to receive either doripenem (N= 486) or meropenem (N= 476). Subjects were stratified at the time of randomization by region (North America, South America, and Europe); primary site of infection (complicated appendicitis with localized peritonitis versus diagnosis of other sites of cIAI); and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score $\leq$ 10 versus > 10). Subjects with generalized peritonitis, regardless of the origin (i.e., even if originating from the appendix), were stratified to the "other" group during randomization.

Subjects received a minimum of 3 days IV treatment before being eligible for transition to oral (PO) antibiotic therapy with amoxicillin-clavulanic acid at a dose of 875 mg IV every 12 hours. Patients were treated for a minimum of 5 days and a maximum of 14 days with either IV medication or a combination of IV and PO medication. Follow up consisted of an EFU visit 7-14 days after the last dose of study drug, and a TOC visit 28-42 days after the last dose of study drug.

6.1.3.2 Inclusion criteria and Exclusion Criteria:

Inclusion Criteria:

1. Male or female at least 18 years of age.

2. Patient had provided informed consent. If the patient was unable to provide the consent him/herself, the patient's legally acceptable representative may have provided written consent, as approved by institutional-specific guidelines.

3. Patient had a requirement for surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of study entry.

4. Pathogen(s) isolated prior to study entry from patients enrolled with a post-operative infection or with failure of a prior regimen was (were) susceptible to both study drugs.

5. Patient required antibacterial therapy, in addition to surgical intervention, for the following eligible diagnoses (in which there was evidence of intraperitoneal infection) including:

- Cholecystitis (including gangrenous cholecystitis) with rupture, perforation, or progression of the infection beyond the gallbladder wall;
- Diverticular disease with perforation or abscess;
- Appendiceal perforation or periappendiceal abscess;
- Acute gastric and duodenal perforations, only if operated more than 24 hours after perforation had occurred;
- Traumatic perforation of the intestines, only if operated more than 12 hours after perforation had occurred
- Peritonitis due to perforated viscus, post-operative or other focus of infection (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites);
- Inflammatory bowel disease or ischemic bowel disease with bowel perforation;
- Intra-abdominal abscess (including liver and spleen)

6. If patient was enrolled pre-operatively, the patient had to have evidence of a systemic inflammatory response, with at least 1 of the following:

- Fever (oral temperature greater than 100.4°F/38°C) or hypothermia (core body temperature less than 95°F/35°C);
- Elevated WBC count (greater than 10,500 cells/mm^3);
- Decrease in blood pressure (however, systolic blood pressure should not have been less than 90 mm Hg and patient should not have required continued pressor support);
- Increased pulse and respiratory rates;
- Hypoxemia;
- Altered mental status

7. If pre-operative, the patient had to have physical findings consistent with IAI, defined as at least 1 of the following:

- Abdominal pain and/or tenderness; Localized or diffuse abdominal wall rigidity;
- Mass;
- Ileus

8. A patient enrolled as a failure of a prior antibacterial treatment regimen had to have:

- Required surgical intervention;
- Had a positive culture (from an intra-abdominal site)

Such patients could have been enrolled before the results of the culture were known but if the culture was negative, the patient was removed from study drug therapy.

Exclusion criteria:

1. Women who were pregnant, nursing, or if of childbearing potential, not using a medically accepted, effective method of birth control (e.g., condom, oral contraceptive, indwelling intrauterine device, or sexual abstinence).

2. Diagnosis of abdominal wall abscess; small bowel obstruction or ischemic bowel disease without perforation; traumatic bowel perforation with surgery within 12 hours; perforation of gastroduodenal ulcers with surgery within 24 hours (these were considered situations of peritoneal soiling before infection had become established); or other intra-abdominal processes in which the primary etiology was not likely to have been infectious.

3. Simple cholecystitis; gangrenous or suppurative cholecystitis without rupture or extension beyond the bladder wall; simple appendicitis; acute suppurative cholangitis; infected, necrotizing pancreatitis, or pancreatic abscess.

4. Managed by Staged Abdominal Repair or open abdomen technique.

5. Known at study entry to have an IAI caused by pathogen(s) resistant to the study antimicrobial agents.

6. APACHE II score greater than 30.

7. Considered unlikely to survive the 6- to 8-week study period.

8. Any rapidly progressing disease or immediately life-threatening illness (including acute hepatic failure, respiratory failure and septic shock).

9. The need for concomitant systemic antibacterial agents (other than vancomycin) in addition to study drug(s).

10. Severe impairment of renal function including a calculated creatinine clearance (CrCl) of less than 10 mL/min; requirement for peritoneal dialysis, hemodialysis or hemofiltration; or oliguria (less than 20 mL urine output per hour over 24 hours).

11. The presence of hepatic disease:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than four times the upper limit of normal (ULN);
- Total bilirubin greater than 2 times the ULN;
- Alkaline phosphatase greater than 4 times the ULN. (Patients with values greater than 4 times the ULN and less than 5 times the ULN were eligible if this value was historically stable);
- Patients with acute hepatic failure or acute decompensation of chronic hepatic failure

12. Hematocrit of less than 25% or hemoglobin of less than 8 g/dL

13. Neutropenia with absolute neutrophil count of less than 1000 cells/mm^3 (Patients with neutrophil counts as low as 500 cells/mm^3 were permitted if the reduction was due to the acute infectious process.)

14. Platelet counts less than 75,000 cells/mm^3 (Patients with platelet counts as low as 50,000 cells/ mm^3 were permitted if the reduction was historically stable).

15. Immunocompromising illness, including known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), organ (including bone marrow) transplant recipients, and hematological malignancy, and immunosuppressive therapy, including use of high-dose corticosteroids (e.g., greater than 40 mg prednisone or equivalent per day for greater than 2 weeks)

16. History of hypersensitivity reactions to carbapenems, penicillins, other β-lactam antibiotics, or β-lactamase inhibitors (Patients with a history of mild skin rash, documented not to have been caused by previous β-lactam use, were permitted to enroll).

17. Participation in any investigational drug or device study within 30 days prior to study entry

18. Use of systemic antibiotic therapy for cIAI for 24 or more hours in the 48-hour period prior to first dose of IV study drug therapy, unless there was a documented lack of response to such therapy

19. No more than 1 dose of an active non-study antibacterial regimen was given post-operatively. (For patients enrolled pre-operatively, including those enrolled as failures of prior antibacterial therapy, no post-operative non-study antibacterial therapy was allowed).

20. Patients who had previously received doripenem

21. Patients who had previously received meropenem for the current infection

MO Comments: The study design conforms to the IDSA guidelines on evaluation of new anti-infective drugs for the treatment of intra-abdominal and pelvic infections. The inclusion and exclusion criteria are acceptable. Meropenem is an acceptable comparator based on its broad spectrum of antimicrobial coverage and approved indication for cIAI. Amoxicillin-clavulanic acid, while an acceptable step down antibiotic in regards to coverage, is not specifically approved for cIAI.

6.1.3.3 Study Treatment

Patients were to be randomized to receive either doripenem (500 mg), administered as a 1-hour IV infusion every eight hours, or meropenem (1gm), administered as a 5 minute IV bolus every eight hours. Tables 1 and 2 are modified tables from Table 4 of the individual Clinical Study Reports that show the proposed study drug schedule for each treatment arm. In order to maintain the blind, patients on each study arm received an active drug and a placebo as follows:

Table 1: Randomized to Active IV Doripenem

Patients randomly assigned to active IV Doripenem received the following:

1st dose	Meropenem placebo	Doripenem Active (500 mg q8h)
2nd dose	Meropenem placebo	Doripenem Active (500 mg q8h)
3rd dose	Meropenem placebo	Doripenem Active (500 mg q8h)

Table 2: Randomized to Active IV Meropenem

Patients randomly assigned to active IV Meropenem received the following:

1st dose	Meropenem active (1gm IV q8h)	Doripenem placebo
2nd dose	Meropenem active (1gm IV q8h)	Doripenem placebo
3rd dose	Meropenem active (1gm IV q8h)	Doripenem placebo

After a minimum of 9 doses of IV study drug therapy (or equivalent number of doses if adjustments for renal impairment were made), the investigator was permitted to switch subjects from IV study drug therapy to oral amoxicillin/clavulanate therapy (875 mg/125 mg q12h). The following criteria for clinical improvement had to be met to allow for the oral switch:

1) A decrease in body temperature and white blood cell (WBC) count relative to the values before dosing on Day 1 (if increased at baseline),
2) Absence or relative improvement of signs/symptoms of cIAI compared to Day 1, and
3) Normal return of bowel function.

MO Comments: ***Although the switch from IV to oral study drug therapy was required to improve the feasibility of the cIAI studies, this could have potentially confounded interpretation of the efficacy results. Therefore, analyses were performed to address potential concerns regarding the contribution of the oral portion of study drug therapy to the overall outcome of subjects in the cIAI studies. This included outcome analyses at EOT [IV] and outcome analyses in subjects who received IV study drug therapy alone. Please refer to Section 6.1.4.6 in the FDA subgroup analyses.***

According to the protocol Amendment 1 dated September 22, 2004, if patients were allergic to amoxicillin-clavulanate, or the abdominal pathogen was felt to be resistant to amoxicillin-clavulanate, patients were allowed an alternative oral switch. According to the Sponsor's response on September 14, 2007, there were a total of 52 patients who were classified as receiving alternative oral therapy. It was later confirmed that 22 patients did receive amoxicillin–clavulanic acid with 20 of these 22 patients receiving Optamox another trade name for amoxicillin –clavulanic acid.

The remaining 30 patients actually received an alternative oral agent other than amoxicillin – clavulanic acid. Of the 30 patients, there were 20 in the doripenem treated group and 10 in the meropenem treated group who received an alternative oral antibiotic. In DORI-07 there were 12 doripenem and 8 meropenem treated patients who received alternative oral antibiotics, compared

to DORI-08 where there were 8 doripenem and 2 meropenem treated patients who received alternative oral antibiotics.

There were 12 patients who used only one alternative oral therapy, and 18 patients who used two alternative oral antibiotics concomitantly. The alternative antibiotics included: Metronidazole (56.7%), Ciprofloxacin (56.7%), Levofloxacin (23.3%), Clindamycin (10%), Trimethoprim Sulfamethoxazole (6.7%), and Cefpodoxime (3.3%). The mean duration of oral treatment was 7.4 days with a range of 3-12 days.

Of the 30 patients treated with an alternative oral medication: 16 subjects had a baseline organism resistant to amoxicillin-clavulanate, 10 patients were allergic or unable to tolerate amoxicillin-clavulanate, 3 patients did not have a resistant organism, but susceptibility results were not available or differed from Sponsor's laboratory result, and 1 patient received an alternative oral therapy in error. Baseline organisms which were considered resistant to amoxicillin-clavulanate in the above 16 patients included: *E.coli, M. morganni, E. cloacae, and H. alvei.*

MO Comment: The antibiotics chosen were most likely for gram negative and anaerobic coverage. It is unfortunate that the 30 patients received an alternative antibiotic as this could have potentially confounded interpretation of the efficacy results. However, we can assume based on the protocol that the patients were improving while on IV therapy to have been eligible for the oral switch. It is unclear as to why more doripenem treated patients were switched to an alternative oral medication.

Vancomycin therapy was permitted if required for documented Methicillin Resistant *Staphylococcus aureus* (MRSA), or *Enterococcus* infection. Empirical therapy with vancomycin was permitted if MRSA was suspected in patients enrolled with post-operative infections. However, vancomycin therapy was discontinued if cultures did not grow MRSA.

Patients with renal impairment had their study drug therapy dosage adjusted as indicated in Tables 3 and 4 for doripenem and meropenem, respectively. The most recent serum creatinine value, obtained from the local laboratory, was used to calculate CrCl. Patients with severe renal impairment [defined as a calculated CrCl of less than 10 mL/min; requirement for peritoneal dialysis, hemodialysis, or hemofiltration; or oliguria (less than 20 mL urine output per hour over 24 hours)] were excluded from this study. Any patient who required dialysis was also removed from study drug therapy.

Table 3: Doripenem Dosage Adjustment

Doripenem for Injection (All Doses Infused over 1 Hour)

Creatinine Clearance [a] (mL/min)	Doripenem Dose (Volume) and Interval	Doripenem Placebo (Volume) and Interval
> 50	500 mg (100 mL) q8h	(100 mL) q8h
30 to 50	250 mg (50 mL) q8h	(50 mL) q8h
10 to 29	250 mg (50 mL) q12h	(50 mL) q12h
< 10	Excluded or removed from study	

Table 5 from DORI -7 Clinical Study Report;
q8h = every 8 hours; q12h = every 12 hours;
[a]Estimated using the Cockcroft-Gault formula.

Table 4: Meropenem Dosage Adjustment
Meropenem for Injection (All Doses Given as IV Bolus over 3 to 5 Minutes)

Creatinine Clearance [a] (mL/min)	Meropenem Dose (Volume) and Interval	Meropenem Placebo (Volume) and Interval
> 50	1 g (20 mL) q8h	(20 mL) q8h
26 to 50	1 g (20 mL) q12h	(20 mL) q12h
10 to 25	0.5 g (10 mL) q12h	(10 mL) q12h
< 10	Excluded or removed from study	

Table 6 from DORI -7 Clinical Study Report
q8h = every 8 hours; q12h = every 12 hours; [a] Estimated using the Cockcroft-Gault formula.

Patients with renal impairment who were eligible for switching from IV study drug therapy to oral study drug therapy with amoxicillin/clavulanate also required dosage adjustment as presented in Table 5.

Table 5: Amoxicillin/Clavulanate Dosage Adjustment
Amoxicillin/Clavulanate Tablets

Creatinine Clearance (mL/min) [a]	Dose and Interval
> 30	875/125 mg q12h
< 30 and ≥ 10	500/125 mg q12h
< 10	500/125 mg qd

Table 7 from DORI -7 Clinical Study Report
qd = once daily; q12h = every 12 hours. [a] Estimated using the Cockcroft-Gault formula.

6.1.3.4 Study Procedures and Time Outline

Table 6: Summary of the Study Visits

SCREENING Day –1 to 0 (24 hours prior to randomization)	TREATMENT Day 1 to End of Therapy (Days 1 to 5 through 14)	EARLY FOLLOW-UP 7 to 14 Days After Final Dose of Study Drug Therapy	TEST-OF-CURE 28 to 42 Days After Final Dose of Study Drug Therapy
Diagnosis of cIAI was established **Stratification by region (North America, South America, Europe), by site of infection (complicated appendicitis with localized peritonitis versus other sites of cIAI), and by disease severity (APACHE II ≤ 10 versus > 10).** **Randomization to study drug therapy**	**Doripenem IV infusion 500 mg (over 1 hour) q8h or meropenem IV bolus 1 g (over 3 to 5 min) q8h** **Optional switch to oral therapy with amoxicillin/clavulanate therapy after 9 IV doses. Total study drug therapy (IV and oral) was 5 to 14 days.** **Vancomycin therapy was added if Enterococcus or MRSA infection was suspected or isolated at baseline.**	**Patient returned to study center for assessment of microbiological and clinical response and safety.**	**Patient returned to study center for assessment of microbiological recurrence or clinical relapse and final safety.**

Figure 1 from DORI-7 Clinical Study Report
APACHE II = Acute Physiology and Chronic Health Evaluation II; q8h = every 8 hours; MRSA = Methicillin-Resistant *Staphylococcus aureus*.

Table 7: Summary of the Study Procedures for the Pooled Studies

Time and Events Schedule								
Day	**-1 to 0 (Screen)**	**1**	**2**	**3**	**4-14**	**End of IV[a]**	**EFU (7 to 14 days)[b]**	**TOC (28 to 42 days)[b]**
Informed consent	X							
Medical history	X							
APACHE II score	X							
Child-Pugh score	X							
General physical examination	X					X	X	X
Assessment of abdominal signs/symptoms and wound	X	X	X	X	X	X	X	X
Oral temperature	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X
CBC, chemistry, and urinalysis[c]	X		X		X	X	X	
Calculated creatinine clearance	X	X	X	X	X			
Pregnancy test	X						X	
Blood sample for culture[d]	X							
Site of infection sample for culture[e]	X							
Radiological examination[f]	X							
Description of operative procedures and operative note[g]	X							
Randomization	X							
12-lead ECG[h]	X							
Adverse events		X	X	X	X	X	X	X
Clinical response						X	X	X
Doripenem IV or meropenem IV or amoxicillin/clavulanate orally[i]		X	X	X	X			
Determination of need for continued therapy					X			

Table 2 DORI-7 Clinical Study Report
APACHE II = Acute Physiology and Chronic Health Evaluation; CBC = complete blood count; ECG = electrocardiogram; EFU = early follow-up; IV = intravenous; TOC =test -of-cure.
a Day of premature withdrawal, day of failure, or last day IV study drug therapy was administered.
b Days after the last dose of study drug therapy (IV and oral).
c If the patient was assessed as a treatment failure and IV study drug therapy was stopped, follow-up laboratory tests were required at the TOC visit only and not at the EFU visit. Laboratory tests performed < 24 hours prior to end of IV study drug therapy were not repeated at the end of IV drug therapy.
d. If positive, follow-up blood cultures were taken approximately every 24 hours until 2 consecutive negative culture results were obtained.
e A sample from the intra-abdominal site of infection was also as indicated thereafter (e.g., re-intervention, clinical failure).
f Radiological examinations were not required for the study but if these were done as part of the diagnosis, the results were recorded.
g At study entry and for each subsequent procedure.
h One baseline ECG was obtained any time prior to administration of the first dose of IV study drug therapy.
i Patients remained on study drug therapy (IV only or IV followed by oral) for a minimum of 5 days (unless clinical failure occurred earlier) and a maximum of 14 days.

A surgical review panel (SRP) consisting of 9 surgeons and 2 interventional radiologists assessed the adequacy of the initial surgical or interventional radiology procedure for subjects with intra-abdominal infections classified as clinical failures and for subjects whose deaths met criteria to

be classified as clinically indeterminate. The purpose of this review was to attempt to distinguish between true antibiotic failures versus an inadequate initial procedure which could preclude any chance of antibiotic success.

The SRP was blinded to study drug therapy and reviewed the adequacy of surgical source control for all subjects assessed as a clinical failure. The SRP also determined whether there was evidence of clinical failure at the time of a second surgical procedure in subjects determined to be clinical cures who had a second surgical procedure performed prior to the TOC assessment. All subjects considered for review were identified before the database was un-blinded. For those cases in which the clinical outcome of the surgical review panel differed from that of the investigator, the clinical outcome assessment by the surgical review panel prevailed. Subjects assessed by the surgical review panel to have had an inadequate initial infection source control were made non-evaluable for efficacy, and were excluded from the ME and clinically evaluable [CE] analysis sets.

MO Comments: ***The overall approach to reviewing cases by the SRP seems appropriate. The charter for the SRP was submitted by the Sponsor, and reviewed. However, as these re-classifications were done post-hoc, a sensitivity analysis was performed using investigator assessment. Please refer to our results section regarding analyses of patient re-classification by the SRP.***

6.1.3.5 Patient Populations

Intent-to-Treat (ITT): This analysis set consisted of all randomized subjects who received any dose or partial dose of study medication whether or not they met all study inclusion/exclusion criteria. This analysis set was used only for safety analyses.

Microbiological Modified Intent-to-Treat (mMITT): This analysis set consisted of all randomized subjects who received any dose or partial dose of study medication and met the minimal disease definition of IAI (i.e. any intra-abdominal or pelvic infectious process that required antibiotic therapy, whether complicated or uncomplicated) and had a bacterial pathogen identified at baseline regardless of susceptibility to study agents.

Clinically Evaluable at Test-of-Cure (CE at TOC): The CE at TOC analysis set consisted of all randomized subjects who met the protocol-specified disease definition of cIAI and received an adequate course of study drug therapy, and for whom sufficient information was available to determine the subject's clinical outcome at the TOC visit.

Microbiologically Evaluable at Test-of-Cure (ME at TOC): The ME at TOC analysis set was a subset of the CE at TOC. In addition to the criteria for inclusion into the CE at TOC analysis set, subjects had at least 1 baseline bacterial pathogen, susceptible to both IV study drug therapies, isolated from an intra-abdominal culture at baseline.

Clinically Evaluable at Early Follow-up (CE at EFU): The criteria for inclusion in this analysis set were similar to those for the CE at TOC analysis set. However, unlike the CE at

TOC analysis set, an outcome assessment (other than "indeterminate") was required at the EFU, but not necessarily at the TOC visit.

Microbiologically Evaluable at Early Follow-up (ME at EFU) : The ME at EFU analysis set was a subset of the CE at EFU analysis set. In addition to the criteria for inclusion in the CE at EFU analysis set, subjects in the ME at EFU analysis set had at least 1 baseline bacterial pathogen, susceptible to both IV study drug therapies, isolated from an intra-abdominal culture

6.1.3.6 Outcome Criteria

Clinical Response Definitions:

• Clinical Cure - Complete resolution or significant improvement of signs or symptoms of the index infection, such that no additional antibacterial therapy or surgical or percutaneous intervention was required for the treatment of the current infection.

• Clinical Improvement - Complete resolution or significant improvement of signs or symptoms of the index infection.
(Note: This outcome was only allowed at the EOT [IV] visit.)

• Clinical Failure - Patients were classified as a clinical failure based on:

- Death related to IAI at any time point;
- Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively;
- Post-surgical wound infection, defined as an open wound with signs of local infection, such as purulent exudate, erythema, or warmth that require additional antimicrobial therapy and/or non-routine wound care (such as incision and drainage or re-opening of the wound); OR
- Treatment with additional antibiotics for ongoing symptoms of IAI during the study period.

(Note: In the event of an enterocutaneous fistula, a closure procedure was not considered a failure, and failures were documented by obtaining an appropriately performed wound or deep site culture).

• Indeterminate - Study data were not available for evaluation of efficacy for any reason, including: death occurred during the study period and the index infection was clearly non-contributory or extenuating circumstances precluded classification as cure or failure.

Microbiological Response Definitions:

- Eradication - absence of causative organism from an appropriately obtained specimen at the site of infection

- Presumed eradication - absence of material to culture in a patient who had responded clinically to treatment
- Persistence - presence of the original pathogen in cultures of an appropriately obtained specimen from the site of infection
- Persistence acquiring resistance - continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, and the pathogen that was susceptible to study drug therapy pre-treatment was now resistant to study drug therapy after treatment
- Presumed persistence - absence of material to culture in a patient who was assessed as a clinical failure
- Indeterminate
  - Entry culture either not obtained or no growth
  - Assessment not possible because of protocol violation
  - Any other circumstance that made it impossible to define the microbiological response

Emergent Infections:

- Superinfection- isolation of a pathogen, other than the original baseline pathogen(s), from an intra-abdominal specimen taken while the patient was on study drug therapy in a patient who had signs and symptoms of infection
- New infection- isolation of a non-baseline pathogen from a post-treatment culture in a patient with signs or symptoms of infection

6.1.3.7 Statistical Consideration

Determination of Final Sample Size:

The hypotheses of interest were:

- null hypothesis H0: $\pi 2 - \pi 1 < -0.15$, versus
- alternative hypothesis H1: $\pi 2 - \pi 1 \geq -0.15$

The primary efficacy analysis was to test the hypothesis of non-inferiority of IV doripenem to IV meropenem. Non-inferiority was concluded if the lower limit of the 2-sided 95% CI for the difference (doripenem minus meropenem), in the proportion of patients who were classified as clinical cures, was greater than or equal to -15%. In the ME and mMITT populations, the CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method).

Adjustments to the Original Study Sample Size:

One adjustment to the original study sample size was done in order to increase study power from 80 to 90% as a result of the re-evaluation of the development plan that occurred when Peninsula Pharmaceuticals, Inc. was acquired by J&JPRD on 01, July 2005. An overview of relevant

details regarding assumptions for the sample size justification in the original protocol and amendment is provided in Table 8:

Table 8: Adjustment to Sample Size Population

Protocol Version[a]	Cure Rate	Evaluability Rate	Study Power[b]	Total Sample	Total Evaluable
Original (04 December 2003)	80%	65%	80%	346	224
Amend. 2 (24 August 2005)	80%	65%	90%	472	306

Page 53 from DORI-7 Clinical Study Report
a Protocol amendments in which a sample size adjustment was included are listed.
b Type I error = 2.5%.

The following definitions were applied to the patient populations based on the sample size adjustments:

Original Population: Patients who were enrolled in the study as part of the initial planned sample size.

Subsequent Population: Patients who were enrolled in the study after the initial sample size was attained.

Final Population: All patients who were enrolled in the study.
(Final Population = Original Population + Subsequent Populations).

MO Comment: Adjustment to sample size was not defined a priori and was done while the study was underway. Per the Sponsor, the re-estimation was based on the blinded observed evaluability rate and hence is acceptable. Analyses were performed by the Sponsor and the Agency to determine if sample size changes affected the efficacy data. See section 6.1.4.8.

Efficacy Analyses:

Primary Efficacy Analyses:

Clinical cure rates for:
a. ME at TOC analysis set
b. mMITT at TOC analysis set

For each endpoint, a sensitivity analysis was also conducted by adjusting for the effects of the baseline diagnosis (complicated localized appendicitis versus diagnosis of other sites of IAI) and severity of illness (APACHE II score less than or equal to 10 or greater than 10). This was conducted via a continuity-adjusted Cochran-Mantel-Haenszel (CMH)-type approach weighted by the sample sizes.

Secondary Efficacy Analyses:

1) Clinical cure or improvement rates at the EOT (IV) visit
2) Clinical cure rates at the EFU visit
3) Microbiological endpoints at the TOC visit examined in two ways:
    a. Per-patient microbiological cure rates
    (i.e., eradication or presumed eradication of all baseline pathogens)
    b. Per-pathogen microbiological outcomes
    (i.e., eradication or presumed eradication at the EFU and TOC visits).

6.1.3.8 Protocol Amendments and Changes

Two amendments were made to the original protocol. These changes are summarized below:

DORI-07

Amendment 1 (22, September 2004)

The following changes were made under this amendment:

- Study centers in South America and Europe were added.
- Clarification was given regarding the timing of safety assessments and the clinical outcomes for patients who were early treatment failures/withdrawals from IV study drug therapy. In addition, the outcome of clinical failure at EOT (IV) was to be carried forward to the TOC clinical outcome.
- The secondary study objectives were expanded to include the determination of clinical and microbiological response at EOT (IV).
- An alternative oral antibacterial agent was permitted in cases of patient intolerance or bacterial resistance to amoxicillin/clavulanate.
- The inclusion criteria were revised to clarify pre-operative, intra-operative, and post-operative requirements.
- The exclusion criteria were revised to define the severity of renal impairment; to remove exclusion based on coagulation tests and predisposition to seizures; to clarify which type of hypersensitivity to antibiotics was permitted; and to clarify the use of non-study antibacterial agents prior to the start of IV study drug therapy.
- Clarification was given regarding patients with negative culture results; study drop-outs prior to TOC; study drug therapy compliance calculation; use of concomitant therapies; and document requirements for the expert SRP.
- Dose adjustments of doripenem, meropenem, and their respective placebos for patients with renal impairment were revised based on data from Phase 1 and 2 studies (doripenem [active/placebo]) and for consistency with meropenem and Augmentin product labels.
- Clarification was given that all serious adverse events, regardless of relationship to study drug therapy, were to be followed to resolution or stabilization.

Amendment 2 (29, November 2005) in CSR 24 August

This amendment was implemented to improve the power of the study and re-estimate the sample size based on the overall blinded observed evaluability rate.

- The study power was increased from 80 to 90%. This resulted in a target sample size increase from 172 to 236 patients per treatment arm to provide 153 evaluable patients per treatment arm.

Amendment 3 (20, October 2005) CSR 05, Oct
The following changes were made under this amendment:

- The procedure for reporting of pregnancies was added.
- A J&JPRD medical monitor was added.

DORI-08

Similar changes were made to the DORI-08 study on the following dates:

Amendment 1 (22, September 2004):
Amendment 2 (20, October 2005):

6.1.4 Efficacy Findings

6.1.4.1 Disposition of Patients

A total of 46 centers (23 in the United States; 7 in Argentina; 5 in Brazil; 5 in Germany; 5 in Poland; and 1 in Canada) randomized a total of 476 patients in the DORI-07 Study. In the DORI-08 Study there were a total of 44 centers (21 in the United States, 10 in Europe, 10 in South America, and 3 in Canada) which randomized a total of 486 patients. Table 9 summarizes the disposition of all randomized patients by analysis set.

Table 9: Randomized Patients and Analysis Populations in the Pooled Data Set (All Randomized Subjects Analysis Set)

	Doripenem N (%) (N=486)	Meropenem N (%) (N=476)	Total N (%) (N=962)
Intent-to-treat (ITT)	477 (98.1)	469 (98.5)	946 (98.3)
Microbiological modified ITT	395 (81.3)	375 (78.8)	770 (80.0)
Clinically evaluable at test-of-cure	380 (78.2)	378 (79.4)	758 (78.8)
Microbiologically evaluable at test-of-cure	325 (66.9)	309 (64.9)	634 (65.9)
Clinically evaluable at early follow-up	377 (77.6)	371 (77.9)	748 (77.8)
Microbiologically evaluable at early follow-up	322 (66.3)	302 (63.4)	624 (64.9)

Table 3 from Sponsor's Clinical Summary

Demographic characteristics for subjects in the ME at TOC analysis set in Studies DORI-07 and DORI-08 combined are shown in Table 10. A summary of the findings is as follows:

• The majority of subjects between the two treatment groups were male (64.6% and 62%, respectively) and Caucasian (72.9% and 77.3%, respectively). Approximately half of the subjects in both studies (51.1% and 47.9%) were from South America. The median age of study subjects

were similar between the two studies. The proportion of subjects 65 and 75 years of age or older were approximately 16.3% and 17.2% in the doripenem and meropenem treatment groups respectively.

Table 10: Demographic Characteristics for the Pooled Analysis Set (Studies ME at TOC Analysis Set)

	DORIPENEM (N=309)	MEROPENEM (N=325)	TOTAL (N=634)
Sex, n (%)			
Female	115 (35.4)	117 (37.9)	232 (36.6)
Male	210 (64.6)	192 (62.1)	402 (63.4)
Age (years)			
Mean (SD)	45.8 (17.73)	45.7 (17.35)	45.7 (17.53)
Median	45.0	45.0	45.0
Range	(18-94)	(18-86)	(18-94)
Age, n (%)			
<65	272 (83.7)	256 (82.8)	528 (83.3)
≥65	53 (16.3)	53 (17.2)	106 (16.7)
<75	307 (94.5)	290 (93.9)	597 (94.2)
≥75	18 (5.5)	19 (6.1)	37 (5.8)
Race, n (%)			
White	237 (72.9)	239 (77.3)	476 (75.1)
Black	17 (5.2)	12 (3.9)	29 (4.6)
Hispanic	65 (20.0)	54 (17.5)	119 (18.8)
Other	6 (1.8)	4 (1.3)	10 (1.6)
Region, n (%)			
North America	90 (27.7)	89 (28.8)	179 (28.2)
US	76 (23.4)	73 (23.6)	149 (23.5)
South America	166 (51.1)	148 (47.9)	314 (49.5)
Europe	69 (21.2)	72 (23.3)	141 (22.2)

Table 6 from Sponsor's Clinical Summary Report
Note: Race is classified as "Other" if subject is not any of the stated race categories or more than 1 race was checked on CRF.

Baseline disease characteristics for subjects in the ME at TOC analysis set in the pooled data are shown in Table 11. There were no noteworthy differences in baseline disease characteristics between treatment arms in either study. In summary, the findings are as follows:

• A small percentage (9.6%) of subjects in the two studies had an APACHE II score >10.

• Overall, the primary site of infection, i.e., infection stratum in Table 11, was complicated appendicitis with localized peritonitis for 34% of subjects; it was "other site of infection" for 66% of subjects.

• The anatomic source of a subject's infection was the appendix in 62% of subjects overall. Approximately 45% of subjects in the two studies had generalized peritonitis as their infectious process at baseline.

• Eighty-two percent of subjects overall had an open procedure to treat their intra-abdominal infection.

• In DORI-07, 9.7% of subjects had a post-operative infection compared to 8.4% of subjects in DORI-08.

• Bacteremia was present in 6% of subjects overall.

• Mild, moderate, and severe renal failure was seen in 17%, 5%, and 2% of subjects, respectively.

Table 11: Baseline Disease Characteristics for the Pooled Data Set (ME at TOC Analysis Set)

	Doripenem (N=325)	Meropenem (N=309)	Total (N=634)
Stratum, APACHE II Score, n (%)			
APACHE II score ≤10	290 (89.2)	283 (91.6)	573 (90.4)
APACHE II score >10	35 (10.8)	26 (8.4)	61 (9.6)
Infection Stratum, n (%)			
Complicated appendicitis with localized peritonitis	112 (34.5)	103 (33.3)	215 (33.9)
Other Sites	213 (65.5)	206 (66.7)	419 (66.1)
Infectious Process, n (%)			
Generalized peritonitis	150 (46.2)	134 (43.4)	284 (44.8)
Localized infection[a]	84 (25.8)	84 (27.2)	168 (26.5)
Single abscess[b]	77 (23.7)	77 (24.9)	154 (24.3)
Multiple abscess	11 (3.4)	11 (3.6)	22 (3.5)
Other	3 (0.9)	3 (1.0)	6 (0.9)
Anatomic Site of Infection, n (%)			
Appendix	203 (62.5)	189 (61.2)	392 (61.8)
Biliary-cholangitis	0	1 (0.3)	1 (0.2)
Biliary-cholecystitis	17 (5.2)	15 (4.9)	32 (5.0)
Colon	65 (20.0)	62 (20.1)	127 (20.0)
Parenchymal (liver)	6 (1.8)	6 (1.9)	12 (1.9)
Parenchymal (spleen)	1 (0.3)	1 (0.3)	2 (0.3)
Small Bowel	17 (5.2)	15 (4.9)	32 (5.0)
Stomach/duodenum	11 (3.4)	12 (3.9)	23 (3.6)
Other	11 (3.4)	15 (4.9)	26 (4.1)
Post-operative Infection, n (%)			
No	294 (90.5)	287 (92.9)	581 (91.6)
Yes	31 (9.5)	22 (7.1)	53 (8.4)
Procedure Type, n (%)			
Laparoscopic	39 (12.0)	29 (9.4)	68 (10.7)
Open	263 (80.9)	256 (82.8)	519 (81.9)
Percutaneous	30 (9.2)	27 (8.7)	57 (9.0)
Other	3 (0.9)	5 (1.6)	8 (1.3)
Bacteremia at Baseline, n (%)			
No	311 (95.7)	286 (92.6)	597 (94.2)
Yes	14 (4.3)	23 (7.4)	37 (5.8)
Baseline Creatinine Clearance (μmol/L) Group, n (%)			
Normal (≥80)	245 (75.4)	233 (75.4)	478 (75.4)
Mild Renal Failure (> 50 - < 80)	58 (17.8)	52 (16.8)	110 (17.4)
Moderate Renal Failure (> 30 - ≤ 50)	15 (4.6)	17 (5.5)	32 (5.0)
Severe Renal Failure (≤30)	7 (2.2)	6 (1.9)	13 (2.1)
Missing[c]	0	1 (0.3)	1 (0.2)

Table 7 from Clinical Summary Report

[a] includes localized peritonitis

[b] includes visceral perforation

[c] Subjects with unknown creatinine clearance at baseline were categorized into the severe renal failure group in each of individual study reports. This imputation was not done in the summaries presented in this table. Therefore, the distribution of baseline renal function may be different from those presented in the individual study reports.

6.1.4.2 Protocol Violations

DORI-7 Study:

The type and incidence of protocol deviations were generally similar in both treatment arms. The major protocol deviations in the ME at TOC, and the cMITT analysis set are summarized as follows:

• Overall, the most common protocol deviation in the ME at TOC and cMITT analysis sets was the TOC visit clinical assessment performed outside of the protocol-specified 28- to 42-day post-therapy window. This protocol deviation was reported in 10% and 7% of doripenem- and meropenem-treated patients, respectively, in the ME at TOC and cMITT analysis sets. As a result of the TOC window expansion, patients who deviated from the protocol-specified 28- to 42-day assessment window were nevertheless counted as evaluable if their TOC visit was within the expanded window (i.e., 21 to 60 days after the last dose of study drug therapy [IV or oral]).

• Two patients had dosing errors. One patient (Patient 371/04010), who was randomly assigned to the meropenem treatment arm, received doripenem for all doses of IV study drug therapy; therefore, this patient was included in the doripenem treatment arm for the ITT analysis set. The other patient (Patient 047/01037), who was randomly assigned to the doripenem treatment arm, received meropenem for at least 1, but not all, doses of IV study drug therapy. This patient was excluded from the primary efficacy analysis, but was included in the doripenem treatment arm in the cMITT and mMITT analysis sets.

• The treatment assignment of 1 patient (Patient 102/06059) in the doripenem treatment arm was accidentally unblinded. The hospital discharge letter and source documents provided details of the study drug therapy administration. Further clarification was not available. In the opinion of the investigator, the study pharmacist did not follow blinding procedures as outlined in the Pharmacy Manual and the nurses and clinical team were unblinded to the patient's treatment arm. The patient completed the EFU visit, but did not complete the study and was lost to follow-up.

DORI-8 Study:

The type and incidence of protocol violations were generally similar in both treatment arms. The major protocol deviations in the ME at TOC and the cMITT analysis set are summarized as follows:

• Overall, the most common protocol deviation in the ME at TOC and cMITT analysis sets was EFU clinical assessment outside the protocol specified 7- to 14-day post therapy window. This deviation was reported in 9% and 12% of doripenem- and meropenem-treated patients, respectively, in the ME at TOC analysis set, and in 8% and 12% of doripenem- and meropenem-treated patients, respectively, in the cMITT analysis set.

• The next most common protocol deviation was TOC clinical assessment outside the protocol specified 28- to 42-day post therapy window for both the ME at TOC and cMITT analysis sets. This deviation was reported in 10% of patients in each treatment arm in the ME at TOC analysis set, and in 8 and 10% of doripenem- and meropenem-treated patients, respectively, in the cMITT analysis set.

• Approximately 8% of all randomized patients did not meet one or more inclusion or exclusion criteria. Some violations of inclusion or exclusion criteria rendered the patients non-evaluable for the ME at TOC analysis set, but others, which did not affect either the diagnosis or outcome assessment, did not necessarily disqualify patients from the ME at TOC analysis set.

• Five patients had dosing errors. Four patients (3 in the doripenem arm [Patients 040/01021, 045/02062, and 428/04064] and 1 in the meropenem arm [Patient 428/04065]) received at least 1 dose (but not all) of the incorrect study drug therapy. These 4 patients were excluded from the evaluable analysis sets (ME at EFU, ME at TOC, CE at EFU, and CE at TOC) but were included in both the cMITT and mMITT analysis sets. The fifth patient (Patient 428/04109), was randomly assigned to the meropenem treatment arm, but received doripenem for all doses of IV study drug therapy; therefore, for efficacy and safety analyses, this patient was included in the doripenem treatment arm.

• Three patients were unblinded during the study, all at Site 127. Patients 127/05003 and 127/06005 were accidentally unblinded by the nurse and the anesthesiologist, respectively. Patient 127/06003 was intentionally unblinded by a surgeon (who was not involved in study) to aid in a treatment decision for the patient's adverse event of bilateral pneumonia.

MO Comment: The number of patients who received erroneous medication appears high compared to most studies. Unclear as to why such a high number received the wrong medication. Of the patients mentioned, 2 were from US sites and 3 were from Brazil sites. Please see Section 6.1.4.9 for FDA analyses.

6.1.4.3 Concomitant Antibacterial Medication

• Concomitant antibacterial therapy given for treatment of clinical failure did not disqualify patients from the ME at TOC analysis set as described in the SAP. In addition, a small number of patients who were still considered evaluable for the ME at TOC analysis set received an antibacterial agent considered "non-active" (e.g., a topical antibacterial agent).

• The rationale for inclusion into the primary ME population in patients with concomitant non-study antibiotic use is as follows:

1) Antibiotic was not systematically active, e.g. oral vancomycin or topical administration.
2) Antibiotic was not active against Gram negative enterics or anaerobes, so therefore not considered active against pathogens causing cIAI, e.g., narrow spectrum agents such as vancomycin or linezolid.

3) Antibiotic was used as prophylaxis for surgery procedure. (Up to 24 hours of prophylactic therapy was allowed).
4) Antibiotic was the allowed study oral switch medication (amoxicillin clavulanic acid), which was erroneously captured on the Concomitant Therapy CRF.
5) Permitted alternative oral switch therapy (The use of alternative therapy was allowed based on the pathogen susceptibility or patient hypersensitivity to amoxicillin clavulanic acid).
6) Antibiotic therapy < 24 hours prior to study
7) One dose of prior therapy given in error after enrollment
8) Error in database, no concomitant antibiotic given

• The use of non-study antibiotic therapy did not affect inclusion into the co-primary mMITT population, so no rationale for inclusion was provided for patients who were in the mMITT population, but not the ME population.

• Overall, the most common concomitant antibacterial medications received by patients in the ITT analysis set were metronidazole (9.5%), vancomycin (6.5%), ciprofloxacin (5.5%), and piperacillin with tazobactam (4.5%).

• The Agency requested the sponsor to submit additional data on all patients who received concomitant antibiotics before the TOC visit and were considered cures. The data was submitted by the Sponsor on August 31, 2007. For the combined studies there were 31 patients in the doripenem treated arm, and 30 patients in the meropenem treated arm who received concomitant antibiotics. Of these patients, 16 and 13 in the doripenem and meropenem arms respectively were included in the ME at TOC analysis group by meeting the above rationale, and were considered cures at the TOC visit. There was no rationale given for one patient in the doripenem treated arm, but it appears the concomitant antibiotic given was for less than 24 hours. There were 15 and 17 patients in the doripenem and meropenem arms respectively who were considered non ME and were included in the mMITT population only.

MO Comment: On review of the data, it is the MO's opinion that there were 8 patients in the doripenem treatment arm and 4 patients in the meropenem treatment arm who should have been indeterminate in the mMITT population. This decision was based on the fact that the patients who received the concomitant antibiotic did so for a range 4-15 days, and the antibiotics used had overlapping activity which may have influenced the final outcome.

Of those patients assessed by the Sponsor as not being microbiologically evaluable, but considered successes in the mMITT population, there were 4 doripenem treated patients and 2 meropenem treated patients who should have been assessed as ME failures. This determination is due to continued clinical signs of IAI such as continued discoloration or drainage from wound site, continued abdominal pain, and increasing white blood cell count.

FDA analyses revealed no major differences in cure rates based on re-classifying the above patients. Table 12 lists the doripenem and meropenem treated patients who were re-classified by the FDA, and the rationale for the re-classification.

Table 12: Doripenem and Meropenem Treated Patients Re-Classified Based on Concomitant Antibiotic Use

Patient #	Baseline Pathogen	Concomitant Medication	Days of therapy	Sponsor Decision	FDA Decision	Rationale
DORIPENEM						
SUBJID# 00102003	*E. coli* *S. aureus* *S. intermedius*	Vancomycin IV Metronidazole IV Cefotetan IV	0 6 6	Included only in mMITT, but not ME population	Should be ME failure	Received concomitant antibiotics for abdominal infection
SUBJID# 04701037	*E. coli*	Piperacillin IV Ticarcillin IV Piperacillin IV	0 2 2	Included only in mMITT, but not ME population	Should be ME failure	Received concomitant antibiotics for relapse of abdominal pain
SUBJID# 37204081	*B. distasonis* *B. thetaiotamicron* *E. coli ; S. bovis* *P. aeruginosa*	Amox/Clav.	2	Included only in mMITT, but not ME population	Should be ME failure	Received concomitant antibiotics for serous secretion from surgical site
SUBJID# 06012036	*C. freundii* *K. oxytoca*	Clavulin PO	7	Included only in mMITT, but not ME population	Should be ME failure	Concomitant-antibiotics for redness at umbilicus
SUBJID# 00102068	*B. thetaiotamicron* *Strep Group F* *S. intermedius*	Moxifloxacin PO	15	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	Completed 15 days of concomitant antibiotics just prior to TOC
SUBJID# 01801503	*C. youngae* *K. pnemoniae* *Lactobacillus sp.*	Metronidazole IV	5	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotitcs for total duration of IV study drug
SUBJID# 10106030	*Bacillus sp.* *B. ovatus* *E. coli* *P. vulgaris* *P. aeruginosa*	Ciprofloxacin PO	6	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On antibiotics for UTI which may have influenced results
SUBJID# 10106040	*B. fragilis* *B. thetaiotamicron* *E. faecalis; E. coli* *K. oxytoca* *P. mirabilis*	Ciprofloxacin PO	4	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics which may have influenced results
SUBJID# 37303004	*E. coli* *P. acnes*	Ciprofloxacin	13	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics which may have influenced results
SUBJID# 06001043	*B. caccae* *B. thetaiotamicron* *E. coli*	Metronidazole IV	4	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics which may have influenced results
SUBJID# 12606035	*E. faecalis*	Ciprofloxacin IV	9	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics which may have influenced results
SUBJID# 12606038	*B. fragilis* *E. avium*	Metronidazole PO	6	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics which may influence final results

Patient #	Baseline Pathogen	Concomitant Medication	Days of therapy	Sponsor Decision	FDA Decision	Rationale
MEROPENEM						
SUBJID# 20406027	*E. coli* *P. aeruginosa*	Ciprofloxacin IV Metronidazole IV	2 2	Included only in mMITT, but not ME population	Should be ME failure	Concomitant antibiotics given for increase in white blood cell count, abdominal pain, and jaundice
SUBJID# 37704068	*B. thetaiotamicron* *C. freundii; E. coli* *K. pneumoniae* *S. marcescens* *S. intermedius*	Norfloxacin PO	6	Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	On concomitant antibiotics for UTI 1 week before TOC
SUBJID# 01102031	*B. thetaiotamicron* *S. anginosus* *Strep Group C*	Ciprofloxacin PO	7	None given - Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	Concomitant antibiotic may have influenced final results
SUBJID# 23006030	*C. perfringens*	Metronidazole PO Amoxicillin PO	6 0	None given - Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	Concomitant antibiotics may have influenced final results
SUBJID# 38503011	*E. aerogenes*	Duocid PO	6	None given - Included only in mMITT, but not ME population	Should be mMITT indeterminate, not cure	Concomitant antibiotic may have influenced final results

6.1.4.5 Reasons for Exclusion from Efficacy

A summary of the findings is as follows:

• The subjects excluded from the ME at TOC analysis set were similar between the doripenem and meropenem treatment arms in both studies.

• The principal reasons for exclusion from the ME at TOC analysis set in both studies included an absence of a qualifying IAI culture result at baseline (20%) and an absence of a valid TOC visit (9%).

Table 13: Reasons for Exclusion From the ME at TOC Analysis Set for the Pooled Data Set

(Intent-to-Treat Analysis Set)

	Doripenem	Meropenem	Total
	(N=477)	(N=469)	(N=946)
No Qualifying IAI Baseline Culture	88 (18.4)	102 (21.7)	**190 (20.1)**
Not CE at TOC	97 (20.3)	91 (19.4)	**188 (19.9)**
Concomitant antibiotic violation	42 (8.8)	28 (6.0)	70 (7.4)
No valid TOC assessment	41 (8.6)	41 (8.7)	82 (8.7)
Non compliant with study drug therapy	34 (7.1)	35 (7.5)	69 (7.3)
Confounding medical event	20 (4.2)	23 (4.9)	43 (4.5)
No IAI diagnosis as per protocol	17 (3.6)	26 (5.5)	43 (4.5)
Prior antibiotic violations	14 (2.9)	15 (3.2)	29 (3.1)
Subjects received both IV study drug therapies	4 (0.8)	1 (0.2)	5 (0.5)
Overruled by surgical review panel	3 (0.6)	3 (0.6)	6 (0.6)

Source: Table 4 from Clinical Summary
Note: Individual subjects may have had more than 1 reason for exclusion
Key: IAI=intra-abdominal infection; TOC=test-of-cure

MO Comment: The reasons for exclusion from the ME population is similar in the two treatment arms. The percentage of patients with no baseline pathogen is consistent with that seen in other studies of cIAI.

6.1.4.6 Drug Exposure

Compliance with IV therapy was documented by recording the start/stop times of each infusion on the study drug therapy record. All subjects were required to receive study drug therapy (IV only or IV plus oral) for a minimum of 5 to a maximum 14 days (unless clinical failure occurred earlier). During oral study drug therapy, subject compliance was documented by tablet count.

• Exposure to study drug therapy (IV or oral) was similar between treatment arms.

• Overall, 17% (110/ 634) of subjects received treatment beyond the protocol-specified maximum therapy duration of 14 days. As the formula for calculating duration of therapy counted partial days of therapy as full days, the duration of therapy in some subjects would appear to be longer.

• Overall, a total of 474 (75%) of 634 subjects were switched to oral therapy during the study.

• For subjects who were switched to oral study drug therapy, the mean duration of IV study drug therapy was 6 days before switching to oral therapy and the total mean duration of total therapy was approximately 11 days.

MO Comment: Overall, there were 110 (14%) patients who received 14 days of therapy and 13(1.7%) patients who received > 14 days of treatment. The distributions of study duration categories were largely similar among doripenem and meropenem arms. In DORI-07, the

mean treatment duration was 9.65 days for both treatment arms. In DORI-08, the mean treatment duration was approximately 8.9 days for both doripenem and meropenem.

Table 14: Extent of Exposure to Study Drug for Pooled Data Set: ME at TOC Analysis Set

Category,	Doripenem	Meropenem	Total
IV or IV and Oral Therapy (Total Study Drug Therapy)			
N	(N=325)	(N=309)	(N=634)
Days, n (%)			
4 – 7	56 (17.2)	57 (18.4)	113 (17.8)
8 – 10	103 (31.7)	96 (31.1)	199 (31.4)
11 - 14	107 (32.9)	105 (34.0)	212 (33.4)
> 14	59 (18.2)	51 (16.5)	110 (17.4)
Mean (SD)	10.7 (3.2)	10.7 (3.1)	10.7 (3.2)
Range	(5; 27)	(5; 18)	(5; 27)
IV Therapy in Subjects Who Received IV Therapy Only			
N	(N=74)	(N=86)	(N=160)
Category, n (%)			
≤ 5	3 (4.1)	4 (4.7)	7 (4.4)
6 – 7	21 (28.4)	29 (33.7)	50 (31.3)
> 7	50 (67.6)	53 (61.6)	103 (64.4)
Mean (SD)	9.6 (3.3)	9.2 (3.1)	9.4 (3.2)
Range	(5;16)	(5;15)	(5;16)
IV Therapy in Subjects Who Were Switched to Oral Therapy			
N	(N=251)	(N=223)	(N=474)
Category, n (%)			
< 4	8 (3.2)	5 (2.2)	13 (2.7)
4 – 7	198 (78.9)	179 (80.3)	377 (79.5)
8 – 10	32 (12.7)	34 (15.2)	66 (13.9)
11 – 14	13 (5.2)	5 (2.2)	18 (3.8)
Mean (SD)	5.8 (2.1)	5.7 (1.9)	5.7 (2.0)
Range	(3;13)	(3;12)	(3;13)

Table 9 from Clinical Summary – Modified from Sponsor's to incorporate only combined studies

6.1.4.7 Efficacy

Primary Endpoint:

The clinical cure rates at TOC in the ME and mMITT groups (co-primary populations) for the individual studies and the pooled studies are listed below in Table 15:

Table 15: Clinical Cure Rates for Complicated Intra-Abdominal Infections (ME at TOC and mMITT Analysis Sets)

Study/Analysis Set	Doripenem			Meropenem			Diff[a] 95%	CI[b]
	N	n	(%)	N	n	(%)		
Study DORI-07								
ME at TOC	163	140	(85.9)	156	133	(85.3)	(0.6)	(-7.7; 9.0)
mMITT	195	152	(77.9)	190	150	(78.9)	(-1.0)	(-9.7; 7.7)
Study DORI-08								
ME at TOC	162	135	(83.3)	153	127	(83.0)	(0.3)	(-8.6; 9.2)
mMITT	200	149	(74.5)	185	140	(75.7)	(-1.2)	(-10.3; 8.0)
Pooled Data from DORI-07 and DORI-08								
ME at TOC	325	275	(84.6)	309	260	(84.1)	(0.5)	(-5.5; 6.4)
mMITT	395	301	(76.2)	375	290	(77.3)	(-1.1)	(-7.4; 5.1)

From Table 10 of Sponsor's Clinical Summary Report
[a] Doripenem minus Meropenem.
[b] 2-sided 95% confidence interval (CI) was based on the normal approximation to the difference of 2 binomial proportions with continuity correction.
Key: N was the number of subjects in each treatment arm; n was the number of subjects who were clinically cured;

6.1.4.8 Sensitivity Analyses

Primary Endpoints:

Tables 16 and 17 provide the results of the primary efficacy endpoints using the original population and subsequent population, respectively in DORI-07 and DORI-08. Clinical cure rates in the co-primary analysis sets are presented for the patients in the following 3 sample size groups: original population, subsequent population, and final population.

• In DORI-07, in the ME at TOC analysis set, the clinical cure rates were largely un- changed in the subsequent population (84.8%, 86%) compared to the original population (86.3%, 85%) in the doripenem and meropenem arm respectively. In the mMITT population, there was a higher success rate post amendment in the doripenem arm, but no significant change in the meropenem arm. Treatment differences in clinical cure rates for patients in the original population were similar to those of the final population in the ME at TOC and mMITT analysis sets. Consistent with the results in the final population, the results in the original population also demonstrated that doripenem was non-inferior in efficacy to meropenem in the treatment of cIAI for the pre-defined non-inferiority margin of -15%.

• In DORI-08, clinical cure rates in the subsequent population, increased in the meropenem treatment arm from the original populations for both the ME at TOC and mMITT analysis sets. For the doripenem treatment arm, the clinical cure rates were largely unchanged in the subsequent population for the ME at TOC analysis set and slightly greater for the mMITT analysis set. Consistent with the results in the final population, the results in the original population also demonstrated that doripenem was non-inferior in efficacy to meropenem in the treatment of cIAI for the pre-defined non-inferiority margin of -15%.

Table 16: Clinical Cure Rates of Co-Primary Analysis Sets for the 3 Sample Size Populations: Original Population, Subsequent Population, Final Population (Study DORI-07)

	Doripenem	Meropenem	Difference (2-sided 95% CI[a])
ME at TOC Analysis Set			
Original	101/117	96/113	1.4%
	(86.3%)	(85.0%)	(-8.6%, 11.3%)
Subsequent[b]	39/46	37/43	-1.3%
	(84.8%)	(86.0%)	(-18.2%, 15.6%)
Final	140/163	133/156	0.6%
	(85.9%)	(85.3%)	(-7.7%, 9.0%)
mMITT Analysis Set			
Original	108/141	110/139	-2.5%
	(76.6%)	(79.1%)	(-13.0%, 7.9%)
Subsequent[b]	44/54	40/51	3.1%
	(81.5%)	(78.4%)	(-14.2%, 20.3%)
Final	152/195	150/190	-1.0%
	(77.9%)	(78.9%)	(-9.7%, 7.7%)

Modified Table 14 from DORI-07 and DORI-08 CSR
a 2-sided 95% CI for difference in cure rates using the normal approximation to the difference between 2 binomial distributions with continuity correction.
b "Subsequent Population" is equivalent to "Beyond The Original Sample Size Population" in source tables.

Table 17: Clinical Cure Rates of Co-Primary Analysis Sets for the 3 Sample Size Populations: Original Population, Subsequent Population, Final Population (Study DORI-08)

	Doripenem	Meropenem	Difference (2-sided 95% CI[a])
ME at TOC Analysis Set			
Original	94/113	91/114	3.4%
	(83.2%)	(79.8%)	(-7.6%, 14.3%)
Subsequent[b]	41/49	36/39	-8.6%
	(83.7%)	(92.3%)	(-24.2%, 7.0%)
Final	135/162	127/153	0.3%
	(83.3%)	(83.0%)	(-8.6%, 9.2%)
mMITT Analysis Set			
Original	103/140	101/137	-0.2%
	(73.6%)	(73.7%)	(-11.2%, 10.9%)
Subsequent[b]	46/60	39/48	-4.6%
	(76.7%)	(81.3%)	(-21.8%, 12.7%)
Final	149/200	140/185	-1.2%
	(74.5%)	(75.7%)	(-10.3%, 8.0%)

a 2-sided 95% CI for difference in cure rates using the normal approximation to the difference between 2 binomial distributions with continuity correction.
b "Subsequent Population" is equivalent to "Beyond The Original Sample Size Population" in source tables.

Secondary Endpoints:

1. Clinical cure rate (CE at TOC) and Microbiological cure rate (ME at TOC): Analyses of these two secondary endpoints are presented below:

Table 18: Clinical and Microbiologic Cure in the CE and ME at TOC Analysis Sets (Pooled Studies)

	Doripenem			Meropenem			Difference in %
Outcome/Analysis Set	**N**	**n**	**(%)**	**N**	**n**	**(%)**	**Dori /Mero**
Clinical cure							
CE at TOC	380	324	85.3	378	326	86.2	-1.0 (-6.2; 4.3)
Microbiological cure							
ME at TOC	325	274	84.3	309	261	84.5	-0.2 (-6.1; 5.8)

Table 10 from Sponsor's Clinical Summary Report
N = all patients in the analysis set at that time point;
n = number of patients who had a favorable clinical response at that time point in that analysis set;

2. Favorable per-pathogen microbiological outcome (eradication or presumed eradication) rates: The per pathogen microbiologic outcome for the pooled data in the ME at TOC analysis set are presented in Table 19. Data are presented only for those baseline pathogens isolated from ≥10 subjects in the doripenem treatment arm. The results show that doripenem was microbiologically effective at the TOC visit against the major causative pathogens of cIAI, including *E. coli, K. pneumoniae, P. aeruginosa, B. fragilis, B. thetaiotaomicron, B. caccae, B. uniformis, B. vulgatus, E. faecalis, S. intermedius, S. constellatus*, and *P. micros*.

Table 19: Favorable Per-pathogen Microbiological Outcome for Pathogens Isolated in ≥10 Subjects in the Pooled Data (ME at TOC Analysis Set)

	Doripenem			Meropenem			Diff[a] (%)
	N	**n**	**%**	**N**	**n**	**%**	**95% CI[a]**
Gram-positive, aerobic	176	150	85.2	168	131	78.0	7.3 (-1.5; 16.0)
Viridans group strep	109	93	85.3	90	71	78.9	6.4 (-5.3; 18.2)
S. constellatus	10	9	90.0	7	5	71.4	18.6
S. intermedius	36	30	83.3	29	21	72.4	10.9 (-12.5; 34.4)
E. faecalis	20	16	80.0	17	13	76.5	3.5
Gram-positive, anaerobic	73	61	83.6	82	62	75.6	8.0 (-5.9; 21.8)
P. micros	13	11	84.6	14	11	78.6	6.0
Gram negative, aerobic	375	322	85.9	316	265	83.9	2.0 (-3.7; 7.7)
Enterobacteriaceae	315	271	86.0	274	234	85.4	0.6 (-5.4; 6.6)
E. coli	216	189	87.5	199	168	84.4	3.1 (-4.1; 10.3)
K. pneumoniae	32	25	78.1	20	19	95.0	-16.9
Non-fermenters	51	44	86.3	39	28	71.8	14.5 (-4.8; 33.7)
P. aeruginosa	40	34	85.0	32	24	75.0	10.0 (-11.5; 31.5)

Table 19: Favorable Per-pathogen Microbiological Outcome for Pathogens Isolated in ≥10 Subjects in the Pooled Data (ME at TOC Analysis Set) - continued

	Doripenem			Meropenem			Diff[a] (%)
	N	n	%	N	n	%	95% CI[a]
Gram negative, anaerobic	245	209	85.3	251	210	83.7	1.6 (-5.1; 8.4)
Bacteroides fragilis group	173	152	87.9	181	152	84.0	3.9 (-3.9; 11.7)
B. caccae	25	23	92.0	19	18	94.7	-2.7
B. fragilis	67	56	83.6	68	54	79.4	4.2 (-10.4; 18.7)
B. thetaiotaomicron	34	30	88.2	36	32	88.9	-0.7 (-18.4; 17.1)
B. uniformis	22	19	86.4	18	15	83.3	3.0
Non-fragilis Bacteroides	14	13	92.9	13	9	69.2	23.6
B. vulgatus	11	11	100.0	8	6	75.0	25.0

Table 13 from Sponsor's Clinical Summary Report
[a] 2-sided 95% CI is based on the normal approximation to the binomial distribution with continuity correction;
CI presented only for those pathogens isolated in ≥30 subjects in either treatment arm
Key: N=the number of unique baseline isolates; n=the number of pathogens with a favorable microbiological outcome

6.1.4.9 FDA Analyses

1. Primary Analysis:

Table 20 represents the clinical cure rates in the FDA defined ME and mMITT co-primary analysis sets. Data for this re-analysis were based on patients in the DORI-07 and DORI-08 studies in which Sponsor and FDA evaluations of the primary efficacy outcome differed in the ME and/or mMITT populations. They differed based on the following four criteria:

- FDA classification of patient deaths as evaluable failures if patient received at least 3 days of study drug.
- FDA Medical Officer re-classification of patients receiving concomitant non-study anti-bacterial medications. Patients listed in the tables were re-classified in the FDA analysis as either evaluable failures or mMITT indeterminate. See section 6.1.4.3.
- FDA exclusion of mis-randomized patients from the ME population. Mis-randomized patients were included in the mMITT population according to the outcome observed assigned to the planned treatment arm.
- FDA allowable TOC window of 25-45 days (the original protocol window of 28-42 days ± 3 days).

Table 20: FDA Re-Analysis of Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets

Study Visit/Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95% CI[b]) (%)
DORI-07			
Clinical Cure at TOC (ME)[c]	130/157 (82.8)	128/149 (85.9)	-3.1 (-11.3; 5.2)
Clinical Cure (mMITT)[c,d]	143/194 (73.7)	149/191 (78.0)	-4.3 (-12.8; 4.3)
DORI-08			
Clinical Cure at TOC (ME)[c]	128/158 (81.0)	119/145 (82.1)	-1.1 (-9.8; 7.8)
Clinical Cure (mMITT)[c,d]	143/199 (71.9)	138/186 (74.2)	-2.3 (-11.2; 6.6)
DORI-07 and DORI-08			
Clinical Cure at TOC (ME)[c,e]	258/315 (81.9)	247/294 (84.0)	-2.1 (-8.1, 3.9)
Clinical Cure (mMITT)[c,d,e]	286/393 (72.8)	287/377 (76.1)	-3.4 (-9.5, 2.8)

FDA Table
[a] Doripenem minus Meropenem.
[b] Two-sided 95% CI calculated without continuity correction
[c] Co-primary endpoints as defined by Sponsor
[d] Comparisons assume actual treatment received and re-evaulation for mis-randomization
Note that pooled analyses were not included in the primary analysis.

MO Comments: Cure rates in the FDA analyses were lower than that obtained by the Sponsor and was more marked in the doripenem arm in both studies. In both studies, using the FDA analyses, the non-inferiority margin of -15% was met.

The list of patients who were re-classified is in the Appendix, Section: 10.2

2. Surgical Review Panel Reassessments:

As mentioned in section 6.1.3.4, an independent expert SRP, assessed the adequacy of surgical interventions in all patients who were clinical failures and evaluated whether second procedures in patients assessed as cures actually represented failures. In Study DORI-07, approximately 11% of all randomized patients met the criteria for review by the SRP. Following their blinded review, the panel changed the clinical response from clinical cure to failure in only 1 patient (in the meropenem treatment arm) and assessed 4 patients (2 in each treatment arm) as non-evaluable because of inadequate initial infection source control. In Study DORI-08, the SRP reviewed the outcomes in approximately 12% of all randomized patients. Following their blinded review, the panel assessed 2 patients (1 in each treatment arm), previously classified as evaluable, to be non-evaluable because of inadequate initial infection source control. This panel changed the clinical response in 9 patients (5, doripenem; 4, meropenem) from clinical cure to failure. Below is Table 21 with Clinical Cure rates without SRP Re-classification for the pooled studies.

Table 21: Clinical Cure Rates (%) in the ME and mMITT Populations without Surgical Review Panel (SRP) Re-classifications for Pooled Studies

Population	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95% CI[b]) (%)
ME at TOC	280/328 (85.4)	265/312 (84.9)	0.4 (-5.1, 6.0)
mMITT at TOC	305/395 (77.2)	295/375 (78.7)	-1.5 (-7.3, 4.4)

Modified Table 20 from Statistician Report
[a] Doripenem minus Meropenem.
[b] Two-sided 95% CI calculated using StatXact 5

MO Comments: The clinical success rates in those patients who were not re-classified by the SRP are overall similar to those patients who were re-classified.

3. Randomization errors:

Table 22: Comparison of Clinical Cure Rates (%) in the ME and mMITT Populations in Patients According to Planned versus Actual Treatment Randomization[a]

Population	Doripenem n/N (%)	Meropenem n/N (%)	Diff[b] (95% CI[c]) (%)
Planned Treatment			
ME at TOC	277/324 (85.5)	268/315 (85.1)	0.4 (-5.1; 6.0)
mMITT at TOC	303/393 (77.1)	297/377 (78.8)	-1.7 (-7.5, 4.2)
Actual Treatment			
ME at TOC (ME)	275/325 (84.6)	260/309 (84.1)	0.5 (-5.5; 6.4)
mMITT at TOC	301/395 (76.2)	290/375 (77.3)	-1.1 (-7.4; 5.1)

[a] Patients treated according to planned randomization were also without SRP Re-classification.
[b] Doripenem minus Meropenem.
[c] Two-sided 95% CI without continuity correction computed using StatXact 5

MO Comments: There were no major differences in clinical cure rates in the doripenem or meropenem group based on planned vs. actual treatment.

Table 23 below addresses the possible confounding issue with regards to the expanded visit windows for the pooled studies.

4. Visit Windows:

Table 23: Clinical Cure Rates (%) in the ME Population at TOC Using Original Visit Windows vs. Extended Visit Windows - continued

Window Period	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95%CI [b]) (%)
FDA Defined TOC Window of 25-45days (28-42 Days ± 3 days)			
DORI-07	131/153 (85.6)	128/147 (87.1)	-1.5 (-9.4; 6.5)
DORI-08	129/153 (84.3)	119/142 (83.8)	0.5 (-7.9; 9.1)
DORI-07 & DORI-08[c]	260/306 (85.0)	247/289 (85.5)	-0.5 (-6.2, 5.3)

Source: FDA Table
a Doripenem minus Meropenem; b Two-sided 95% confidence intervals computed using StatXact 5 without continuity correction

MO Comments: The differences in clinical cure rates based on TOC window of 25-45 days (doripenem 85%, meropenem 85.5%)were largely consistent among treatment groups. It is unlikely that the change in visit windows affected the study findings.

5. Renal Impairment:

Renal impairment was defined as mild (CrCl: 30 to 50), moderate (CrCl: 10 to 29) and severe (CrCl: < 10, or on hemodialysis). Table 24 demonstrates clinical cure rates in patients with renal failure.

Table 24: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients with Renal Impairment for Pooled Studies

Analysis Sets	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95% CI [b])
ME [c] at TOC	12/17 (70.6)	11/20 (55.0)	15.6 (-16.8; 46.7)
mMITT [c] at TOC	12/27 (44.4)	13/26 (50.0)	-5.6 (-31.1; 20.7)

Table 25 from FDA Statistician's report
a Doripenem minus Meropenem.
b 2-sided 95% confidence interval (CI) computed using StatXact 5 exact test
c Co-primary endpoints as defined by Sponsor

MO Comments: The number of patients were almost equal among the treatment groups, however, meaningful statistical inferences cannot be made due to the small number of subjects with renal impairment in each study.

6. Concomitant antibiotics:

In both cIAI studies, prior antibacterial use was common. The proportion of patients in the ME population who used concomitant medications prior to the scheduled TOC visit was high in both the doripenem and meropenem treatment arms at approximately 88/163 (54.0%) and 74/156 (47.4%) respectively in DORI-O7 and 83/162 (51.2%) and 71/153 (46.4%) respectively in DORI-08.

Table 25: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients Using/Not Using Anti-Bacterial Concomitant Medications before TOC Date in Pooled Population

Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95% CI) [b] (%)
Patients Using Concomitant Medications Prior to TOC date			
ME at TOC	132/171 (77.2)	106/145 (73.1)	4.1 (-5.4; 13.8)
mMITT at TOC	150/228 (65.8)	132/200 (66.0)	-0.2 (-9.2, 8.8)
Patients Not Using Concomitant Medications Prior to TOC date			
ME at TOC	143/154 (92.9)	154/164 (93.9)	-1.0 (-7.0, 4.7)
mMITT at TOC	151/167 (90.4)	158/175 (90.3)	0.1 (-6.4; 6.6)

Modified Table 26 from Statistician's FDA report
a Doripenem minus Meropenem.
b 2-sided 95% confidence interval (CI) computed using StatXact 5 exact test

MO Comments: Statistical analyses showed that although lower cure rates were observed in patients using concomitant medications prior to the TOC date, treatment differences remained generally consistent when observing overall results for patient included or excluded from this subgroup.

6.1.4.10 Subgroup Analyses

The clinical cure rates by subgroups are listed below. Table 26 summarizes clinical cure by demographic characteristics, and Table 27 by patient characteristics. Tables 28 and 29 evaluate clinical cure rates in patients receiving: IV plus PO therapy versus IV therapy alone.

Table 26: Clinical Cure Rate by Demographic Characteristics
Pooled Data Set
(ME at TOC Analysis Set)

	Doripenem			Meropenem				
	N	n	%	N	n	%	Diff[a] (%)	95% CI[b]
Sex								
Female	115	94	81.7	117	96	82.1	-0.3	(-11.1; 10.5)
Male	210	181	86.2	192	164	85.4	0.8	(-6.6; 8.1)
Age (Years)								
<65	272	232	85.3	256	220	85.9	-0.6	(-7.0; 5.7)
≥65	53	43	81.1	53	40	75.5	5.7	(-11.9; 23.2)
<75	307	262	85.3	290	246	84.8	0.5	(- 5.5; 6.6)
≥75	18	13	72.2	19	14	73.7	-1.5	
Race								
White	237	202	85.2	239	198	82.8	2.4	(-4.6; 9.4)
Black	17	14	82.4	12	11	91.7	-9.3	
Hispanic	65	56	86.2	54	48	88.9	-2.7	(-16.3; 10.8)
Other	6	3	50.0	4	3	75.0	-25.0	
Region								
NA	90	66	73.3	89	67	75.3	-1.9	(-15.9; 12.0)
US	76	56	73.7	73	56	76.7	-3.0	(-18.2; 12.2)
SA	166	148	89.2	148	131	88.5	0.6	(-7.0; 8.3)
Europe	69	61	88.4	72	62	86.1	2.3	(-10.1; 14.7)
APACHE II Score								
≤10	290	250	86.2	283	242	85.5	0.7	(-5.4; 6.8)
>10	35	25	71.4	26	18	69.2	2.2	
Infection Stratum								
Complicated Appendicitis with Localized Peritonitis								
	112	100	89.3	103	89	86.4	2.9	(-6.8; 12.6)
Other Sites of IAI								
	213	175	82.2	206	171	83.0	-0.9	(-8.6; 6.9)
Infectious Process								
Generalized Peritonitis								
	150	130	86.7	134	119	88.8	-2.1	(-10.5; 6.2)
Localized Infection								
	84	74	88.1	84	71	84.5	3.6	(-8.0; 15.1)
Single Abscess								
	77	60	77.9	77	60	77.9	0.0	(-14.4; 14.4)
Multiple Abscesses								
	11	8	72.7	11	9	81.8	-9.1	

Modified Table 15 from Sponsor's Clinical Summary report

Table 27: Clinical Cure Rate by Patient Characteristics in the Pooled Data Set (ME at TOC Analysis Set)

	Doripenem			Meropenem			
	N	n	%	N	n	%	Diff[a] (%) 95% CI[b]
Anatomic Site of Infection							
Stomach/duodenum	11	9	81.8	12	11	91.7	-9.8
Biliary-cholecystitis	17	17	100	15	14	93.3	6.7
Biliary-cholangitis	0	0		1	1	100	
Small Bowel	17	12	70.6	15	10	66.7	3.9
Appendix	203	180	88.7	189	169	89.4	-0.7 (-7.4; 5.9)
Colon	65	49	75.4	62	43	69.4	6.0 (-11.1; 23.1)
Parenchymal (Liver)	6	4	66.7	6	58	3.3	-16.7
Parenchymal (Spleen)	1	1	100	1	1	100	0.0
Other	11	9	81.8	15	10	66.7	15.2
Bacteremia at Baseline							
No	311	263	84.6	286	243	85.0	-0.4 (-6.5; 5.7)
Yes	14	12	85.7	23	17	73.9	11.8
Reduced IV Study Drug Because of Renal Impairment							
No	300	257	85.7	286	248	86.7	-1.0 (-7.0; 4.9)
Yes	25	18	72.0	23	12	52.2	19.8

Modified Table 15 from Sponsor's Clinical Summary report
N= number of patients in each treatment arm; n=number of patients clinically cured; NA=North America; US = United States; SA= S. America; a doripenem - meropenem
[b] 2-sided 95% Ci is based on the normal approximation to binomial distribution with continuity correction; CI presented only for those pathogens isolated in ≥30 subjects in either treatment arm.

Table 28: Clinical Cure Rate by Antibiotic Therapy in the Pooled Data Set (ME at TOC Analysis Set)

	Doripenem			Meropenem				
	N	n	%	N	n	%	Diff[a] (%)	95% CI[b]
Switched to Oral Therapy								
No	74	53	71.6	86	67	77.9	-6.3	(-21.0; 8.5)
Yes	251	222	88.4	223	193	86.5	1.9	(-4.5; 8.3)

Modified Table 15 from Sponsor's Clinical Summary report
N= number of patients in each treatment arm: n=number of patients who were clinically cured; NA=North America; US = United States; SA= South America
a doripenem - meropenem
[b] 2-sided 95% Ci is based on the normal approximation to binomial distribution with continuity correction; CI presented only for those pathogens isolated in ≥30 subjects in either treatment arm.

Table 29: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients Receiving IV Therapy Only

Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff[a] (95% CI[b])
ME at TOC [c.]			
DORI-07& 08	53/74 (71.6)	67/86 (77.9)	-6.3 (-19.9; 7.1)
mMITT [c.]			
DORI-07&08	66/123 (53.7)	76/123 (61.8)	-8.1 (-20.2; 4.2)

Modified Table 18 from Statistician's Report
a Doripenem minus Meropenem.
b Two-sided 95% CI computed using StatXact 5 without continuity correction
c Co-primary endpoints as defined by Sponsor

MO Comments: Success rates were lower in both arms for patients treated with IV alone, which can be expected with this group as they were likely to be sicker and hence needed more IV treatment. However, the difference seems larger in the doripenem group. No inferences can be drawn as the numbers are small and these are subgroup analyses. In general, subjects who were not switched to oral therapy (i.e., were treated with IV therapy only) had lower cure rates than subjects who were switched to oral therapy. This difference was expected, as the pre-condition for switching to oral therapy was evidence of improvement at the EOT (IV) visit.

A summary of the results is as follows:

• The clinical cure rates in each of the subgroups were generally comparable between treatment arms.

•Clinical cure rates were lower in North American subjects than in subjects from other regions. Per the sponsor, the difference in cure rates may be explained by differences in demographic and baseline disease characteristics of North American subjects compared with subjects in Europe or South America. These differences (North America versus Europe and South America, respectively) include higher proportions of North American subjects who:
– were older (median age: 53 years vs. 48 and 38 years)
– were female (43% vs. 36% and 33%)
– had APACHE II scores >10 (15% vs. 8% and 7%)
– had a colon infection (36% vs. 27% and 8%)
– underwent laparoscopic surgery (21% vs. 4% and 8%)
– had percutaneous drainage (20% vs. 4% and 5%)

MO Comment: It is unclear how the last two baseline disease characteristics would decrease cure rates. Patients undergoing laparoscopic surgery tend to be less acutely ill than those undergoing open surgery, and I would expect to see higher cure rates in this population. I would also expect that patients with a percutaneous drain would actually have higher cure rates given the added benefit of actively draining an infection.

• Clinical cure rates were lower in subjects who had at least one dose of IV study therapy reduced due to renal impairment compared to subjects with no renal dose adjustment (72.0% vs. 85.7% in the doripenem group; 52.2% vs. 86.7% in the meropenem arm). Of note, only 25 subjects (7.7%) in the doripenem arm and 23 subjects (7.4 %) in the meropenem arm had any IV study dose reduction because of renal impairment. The Sponsor stated that this group had older patients and higher percent with APACHE scores >10, hence success rates were lower.

6.1.5 Clinical Microbiology

6.1.5.1 Baseline Susceptibilities

A tabular summary of in vitro susceptibility to study therapy for intra-abdominal pathogens isolated at baseline in the pooled data is provided in Table 30. Per the sponsor, susceptibility definitions for doripenem were susceptible(S), intermediate (I) or resistant(R) if the MIC level was ≤4μg/mL, = 8 μg/mL or ≥16 μg/mL, respectively.

• The distribution of baseline intra-abdominal pathogens overall was similar between the treatment arms.

• Overall, the most common pathogens isolated in both the doripenem and meropenem arms included *E. coli* (250 and 226, respectively), *B. fragilis* (77 and 81), *P. aeruginosa* (46 and 35), *B. thetaiotaomicron* (43 and 41), *S. intermedius* (43 and 37), *K. pneumoniae* (41 and 27), *E. faecalis* (33 and 26), *B. caccae* (30 and 21), and *B. uniformis* (23 and 22). Other less common pathogens that were isolated in ≥10 subjects in either the doripenem or meropenem arm included *S. aureus*, *S. constellatus*, *E. avium*, *E. faecium*, *S. agalactiae*, *C. perfringens*, *S. anginosis*, *E. lentum*, *P. micros*, *C. freundii*, *E. cloacae*, *K. oxytoca*, *P. mirabilis*, *B. distasonis*, and *B. vulgatus*.

• Baseline resistance to doripenem or meropenem was rare among gram-negative organisms. Resistance in doripenem was seen with *P. aeruginosa* (1/44), *B. fragilis* (1/71), and *P. bivia* (1/4). Resistance in meropenem was seen with *A. baumannii* (1/3), *S. maltophilia* (1/1), *B. fragilis* (2/72). No resistance to doripenem or meropenem was observed at baseline for any Enterobacteriaceae isolate, including *E. coli*, *K. pneumoniae*, and *P. mirabilis*.

• The most frequently isolated baseline intra-abdominal pathogens were gram-negative aerobes (447 for doripenem and 380 for meropenem), the most common of which were Enterobacteriaceae (374 for doripenem and 330 for meropenem).

• Other frequently isolated baseline intra-abdominal pathogens included gram-negative anaerobes (288 for doripenem and 290 for meropenem), the most common of which belonged to the *Bacteroides fragilis* group (204 for doripenem and 210 for meropenem), and gram-positive aerobes (278 for doripenem and 277 for meropenem).

• The overall resistance of gram-positive aerobes to doripenem was 18/244. As the breakpoints for meropenem are not defined for many of these pathogens, comparative susceptibility statements cannot be made. For *E. faecalis,* 90% (28/31) of the isolates were susceptible to doripenem with only 10% (3) in the intermediate range. No resistance to doripenem or meropenem was observed for isolates of viridans streptococci, including members of the *Streptococcus anginosus* group (*S. anginosus*, *S. constellatus*, *S. intermedius*).

•Baseline resistance to doripenem or meropenem was not observed among gram-positive anaerobes, including *P. micros*.

• Overall (i.e. irrespective of treatment group) baseline susceptibility to doripenem and meropenem was 100% for most of the major causative pathogens of cIAI including Enterobacteriaceae, *B. thetaiotaomicron*, *S. intermedius*, *K. pneumoniae*, *B. caccae* and *B. uniformis*. Susceptibility to doripenem and meropenem for *B. fragilis* was 98 and 99%, and for *P. aeruginosa* it was 99 and 97%, respectively. Among the enterococci, none of the *E. faecalis* isolates were resistant to doripenem, whereas 45% of *E. faecium* isolates were resistant. Comparative data for meropenem were not generated because meropenem susceptibility criteria for enterococci were not defined.

• In general, overall baseline susceptibility to ampicillin/sulbactam was demonstrated for most of the major causative pathogens of cIAI. In particular, virtually all members of the *B. fragilis* and non-fragilis *Bacteroides* groups were uniformly susceptible to ampicillin/sulbactam at baseline (99 and 100% respectively). Among the Enterobacteriaceae, 82% of all *E. coli* and 89% of *K. pneumoniae* were susceptible to ampicillin/sulbactam at baseline.

Table 30: In Vitro Susceptibility of Baseline Intra-abdominal Pathogens for the Pooled Data Set
(mMITT Analysis Set)

	Doripenem				Meropenem			
	Total	Susceptibility, n (%)			Total	Susceptibility, n (%)		
	NI/NT	Suscept.	Intermed.	Resist.	NI/NT	Suscept.	Intermed.	Resist.
Gram positive, aerobic	**278/244**	**219(90%)**	**7(3%)**	**18(7%)**	**277/161**	**158(98%)**	**1(1%)**	**2 (11%)**
Staphylococcus aureus	15/15	14(93%)	0	1(7%)	20/19	16 (84%)	1(5%)	2 (11%)
Viridans group streptococci	135/127	127(100%)	0	0	119/100	100(100%)	0	0
Other gram positive aerobic	128/102	78(76%)	7(7%)	17(17%)	138/42	42(100%)	0	0
Gram positive, anaerobic	85/64	63 (98%)	1(2%)	0	103/12	12(100%)	0	0
Gram negative, aerobic	447/412	410(100%)	1(0%)	1(0%)	380/351	349 (99%)	0	2(1%)
Enterobacteriaceae	374/346	346(100%)	0	0	330/311	311(100%)	0	0
Non-fermenters	57/55	53(96%)	1(2%)	1(2%)	43/38	37(97%)	0	1(3%)
Haemophilus	8/6	6(100%)	0	0	1/0	0	0	0
Other	8/5	5(100%)	0	0	6/2	1(50%)	0	1(50%)
Gram negative, anaerobic	288/254	249(98%)	3(1%)	2(1%)	290/198	194(98%)	2(1%)	2(1%)
Bacteroides fragilis group	204/188	185(98%)	2(1%)	1(1%)	210/182	179(98%)	1(1%)	2(1%)
Non-fragilis Bacteroides	18/13	13(100%)	0	0	16/8	8(100%)	0	0
Other	66/53	51(96%)	1(2%)	1(2%)	64/8	7(88%)	1	0

Table #8 from Sponsor's Clinical Summary – has been modified to include only most common organisms under each main category.
Key: NI= the number of subjects with the specified baseline isolate; NT=the number of subjects with the specified baseline isolate tested for which an interpretation of susceptibility results was available.
(Note: For doripenem, susceptibility definitions were Susceptible (S), Intermediate (I) or Resistant (R) if the MIC level is = 4µg/mL, = 8 µg/mL or =16 µg/mL, respectively. For meropenem, the number Susceptible, Intermediate or Resistant is defined according to the Clinical and Laboratory Standards Institute (CLSI) recommendations).

6.1.6 Efficacy Conclusions

DORI-07and DORI-08 were international, randomized, multi-center, Phase 3 studies involving 962 patients with complicated intra-abdominal infections enrolled at 46 centers. Patients were enrolled and randomized on a 1:1 basis to receive either doripenem (N= 486) or meropenem (N= 476). Subjects were stratified at the time of randomization by region, site of infection, and severity of illness (APACHE II score $\leq$ 10 versus > 10).

The objective of the trial was to compare the efficacy and safety of doripenem (500 mg given as an IV infusion over 1 hour every 8 hours) with that of meropenem (1gm given as an IV bolus every 8 hours). Based on the evaluation of data provided by the sponsor, the following conclusions can be made:

1) Patients were well balanced across both treatment groups with regard to sex, age, and race, except for a higher percentage of Caucasian subjects in DORI-08 (83%) compared to DORI-07 (68%). There were a higher percentage of males (63.4%) in both studies, and the majority of patients were Caucasian (75%). Mean age of patients was 45.7 years and approximately 83% of patients were < 65 years of age. Approximately 24% of patients were enrolled at sites in the US and 50% of patients were enrolled in South American centers. The primary site of infection was complicated appendicitis with localized peritonitis for 34% of the randomized patients.

2) Doripenem was both clinically and microbiologically effective in the treatment of cIAI. Treatment with doripenem was shown to be non-inferior to treatment with IV meropenem. Based on the Sponsor's results, the cure rate in the primary (ME at TOC) population was 84.6% for the doripenem arm compared to 84.1% in the meropenem arm. The treatment difference between the two groups was 0.5% and the 2-sided 95% confidence interval (CI) around this difference was [-5.5% to 6.4%]. The clinical cure for the mMITT population at TOC was 76.2% in doripenem and 77.3% in meropenem. The treatment difference between the two groups was -1.1% and the 2-sided 95% confidence interval (CI) around this difference was [-7.4% to 5.1%]. Since the lower bound of this interval is greater than -15%, the pre-defined non-inferiority margin and the 95% CI includes the value 0, the results show doripenem to be non-inferior to meropenem in the treatment of cIAI. Overall, results were consistent in the FDA defines populations though cure rates were lower in the doripenem arm in both studies.

3) Given the ability to switch to oral therapy, only a small population of patients received IV doripenem therapy alone, for the entire treatment regimen (N= 74, in the ME at TOC population). Thus only limited assessment can be made regarding the efficacy of doripenem when used for the entire course of therapy. However, as the antimicrobial spectrum of amoxicillin-clavulanate and doripenem are fairly similar and patients were switched to oral only after clinical improvement was noted, it is likely that doripenem will be effective as IV alone.

4) One of the secondary objectives was the clinical cure rate response in the CE at TOC population. Per the Sponsor, the clinical cure rate for patients in the doripenem arm (CE at TOC) was 85.3% compared to 86.2% for the meropenem patients. The treatment difference was -1.0 % in favor of the doripenem arm with a 2-sided 95% CI of [-6.2% to 4.3%]. The clinical results establish that doripenem is non-inferior to meropenem for the treatment of clinical symptoms of cIAI and supports the microbiological results of this study.

5) The microbiological cure rate for ME at the TOC visit was 84.3% for the doripenem patients and 84.5% for the meropenem patients. The treatment difference was -0.2% with a 2-sided 95% CI around the difference of [-6.1% to 5.8%], which was consistent with the results obtained from the clinical cure rate of ME at TOC analysis set.

6) Doripenem was microbiologically effective against the major causative pathogens of cIAI including: **Gram negative anaerobes** such as: *B. vulgatus* (100%), *B. caccae* (92%); *B. thetaiotaomicron (88.2%), B. fragilis* (87.9%), and *B. uniformis* (86.4%) **Gram negative aerobes** such as: *E. coli* (87.5%), *P. aeruginosa* (85%), *E. faecalis* (80%), and *K. pneumoniae* (78.1%) **Gram positive, aerobes** such as: *S. intermedius* (83.3%), *S. constellatus* (90%), and **Gram positive, anaerobes** such as: *P. micros* (84.6%).

7 INTEGRATED REVIEW OF SAFETY

MO Comment: ***In this section only safety, from the two cIAI studies, is reviewed. For the overall safety review of doripenem, which includes the results from studies DORI-03, DORI-05, DORI-06, DORI-07, and DORI-08, please see the safety review by Dr. Alfred Sorbello, FDA Medical Officer***

7.1 Methods and Findings

The safety analysis set in Study DORI-07 and DORI-08 includes all patients in the ITT population who received at least one dose of study drug. Of the randomized patients, 946 received study drug therapy (477 doripenem and 469 meropenem).

Safety was assessed throughout the study by monitoring of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements (oral temperature, pulse, blood pressure, and respiration rate), and physical examination findings. Any serious adverse events persisting at the end of the study were followed until resolution or until a clinically stable endpoint was reached.

Adverse events included any side effect, injury, toxicity, sensitivity reaction, inter-current illness, or sudden death (whether or not it was considered study drug related) that occurred during a patient's study participation. Adverse events were to be reported by the patient or the investigator from the time of the first study related procedure through the last study visit.

Serious adverse events (SAEs) were defined as adverse events that were fatal, were life threatening, required hospitalization or prolonged inpatient hospitalization, caused a persistent or significant disability/incapacity, or were a congenital anomaly/birth defect. All SAEs were reported to the Applicant within 24 hours of the investigational site's knowledge of the occurrence.

Table 31 shows the overall summary of Treatment-Emergent Adverse Events (TEAEs) for the combined cIAI studies.

Table 31: Overall Summary of TEAEs
Safety Analysis Set

	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Any TEAE	357 (74.8)	326 (69.5)
Any study drug-related TEAE[a]	113 (23.7)	110 (23.5)
Any serious TEAE	72 (15.1)	76 (16.2)
Deaths	13 (2.7)	18 (3.8)
Discontinuation due to TEAEs	22 (4.6)	13 (2.8)
Discontinuation due to[a] a study drug-related TEAE	7 (1.5)	6 (1.3)

Table 21 from Sponsor's Summary of Clinical Safety
[a]Includes possibly and probably related TEAEs.

7.1.1 Deaths

All deaths that occurred during Phase 3 cIAI clinical trials were reviewed. Narratives, case report forms, and data from datasets were reviewed in detail. In the pooled studies there were a total of 31 deaths: 13 (2.7%) and 18 (3.9%) deaths in doripenem and meropenem respectively. Refer to Tables 32 and Table 33 for summary of deaths, and adverse events (AEs) leading to deaths.

Table 32: Number of Deaths (Intent to Treat Analysis Set)

	Treatment	
Category	**Doripenem**	**Meropenem**
DORI -7		
Number of Patients who received study drug	235	236
Number (%) of patients who died	5 (2.1%)	7 (3.0%)
Deaths:		
During study drug therapy[a]	1	4
During follow up	4	3
Deaths due to treatment-emergent adverse events related to study drug therapy[b]	0	0

Table 32: Number of Deaths (Intent to Treat Analysis Set - continued)

Category DORI – 8	Treatment Doripenem	Meropenem
Number of Patients who received study drug	242	233
Number (%) of patients who died	8 (3.3%)	11 (4.7%)
Deaths:		
During study drug therapy[a]	1	1
During follow up	7	10
Deaths due to treatment-emergent adverse events related to study drug therapy[b]	0	0

Table 24 from DORI 7 and DORI 8 Clinical Study Report
[a] Onset during IV study drug therapy administration
[b] Study drug related events included possibly and probably related events

Table 33: Adverse Events Leading to Death (Safety Analysis Set)

Site Number/ Pt. ID	Age/Sex	Preferred Term	Day of Study When Death Occurred	Total Days of Study Drug Therapy
DORI-7			**(mg)**	**(days)**
Doripenem				
046/02510	61/F	Staphylococcal Sepsis	22	6
047/02519	74/M	Sepsis	1	1
202/06503	72/F	Multi-Organ Failure	30	5
204/06002	33/F	Gastric Cancer	100	5
372/04503	77/M	Sepsis	2	1
Meropenem				
040/02509	72/F	Duodenal Ulcer Perf.	36	10
101/06007	75/M	Multi-Organ Failure	6	6
101/06501	88/F	Peritonitis	3	3
203/06504	75/F	Pneumonia	10	10
401/04518	59/F	Intestinal Ischemia	32	3
402/04509[a]	68/M	Sepsis	2	1
402/04519	67/M	Sepsis	10	10
DORI-8				
Doripenem				
005/02060	80/F	ARDS	28	15
005/02515	60/F	ARDS	26	13
005/02519	85/F	Enterococcal sepsis	13	9
054/02058	49/F	Multi-organ failure	39	8
054/02523	83/F	Respiratory failure	25	8
054/02526	86/F	Respiratory arrest	7	7
126/06026	69/F	Renal insufficiency	53	6
431/04023	79/F	Pneumonia	25	12
Meropenem				
003/02508	53/F	Hepatic failure	3	2

Modified Table 25 from DORI-07 & DORI-08 Clinical Study Report
M = male; F = female; ARDS = Acute Respiratory Distress Syndrome.
Note: The day of the last dose of study drug therapy was the same as the number of total days of study drug therapy. In addition, the total days of study drug therapy included IV only and IV plus oral study drug therapy.
All events that resulted in death were assessed as unrelated to study drug therapy.
[a] Patient 431/04509 died prior to receiving the first dose of IV study drug therapy.

A summary of the narratives of death are as follows:

There were five deaths among the doripenem-treated subjects (ITT) in study DORI-07:

- Subject ID# 04602510 was a diabetic patient who was treated with six days of study drug status post small bowel resection for a small bowel abscess. She developed pneumonia on Day 6 followed by an enterococcal UTI, staphylococcal bacteremia, pancreatitis, myocardial ischemia, and renal insufficiency during the eight days following completion of study drug. She died on Day 22 from staphylococcal sepsis.

- Subject ID# 04702519 was an elderly male who was enrolled in the study with a perforated cecum and probable carcinoma of the hepatic flexure. He developed sepsis and died on Day 1 of the study.

- Subject ID# 20206503 was a 72 year old female enrolled with a perforated duodenal ulcer, multiple intra-abdominal abscesses, and damage to the bladder wall. She developed severe sepsis beginning on Day 1, which prompted study drug discontinuation on Day 5. Her course was complicated by peritonitis, pneumonia, and later multi-organ failure, which proved fatal.

- Subject ID# 20406002 was a 33 year old female diagnosed with gastric cancer on Day 8 of the study. About 2 weeks later, surgery was performed for an anastomotic fistula, gastrectomy, pancreoduodenectomy, splenectomy, and right hemicolectomy. Three months later, the patient experienced additional complications, including massive gastrointestinal bleeding, cholestasis, epilepsy, paraneoplastic syndrome, left jugular vein thrombosis, and constricted choleduochojejunostomy. She died on Day 100 from an acute respiratory arrest.

- Subject ID# 37204503 was a 77 year old male with peritonitis and dehiscence of an esophagojejunal anastomosis following a total gastrectomy for stomach cancer performed on Day -5. He developed septic shock on Day 1 and died the following day.

There were eight deaths among the doripenem-treated subjects (ITT) in study DORI-08:

- Subject ID# 00502060 was an 80 year old female status-post sigmoid colectomy and Hartmann's procedure for perforated sigmoid diverticulitis, who was treated with study drug for 15 days for complicated IAI. She developed pneumonia due to MRSA on Day 10. She experienced hypotension, tachycardia, and acute respiratory distress over the following two weeks. Life support was withdrawn on Day 28, and she died later that day.

- Subject ID# 00502515 was a 60 year old female with cIAI from a perforated sigmoid colon. She had been diagnosed previously with metastatic cancer to bone of unknown primary on Day -10. She developed ARDS on Day 6 and required a tracheostomy on Day 21. Life support was withdrawn on Day 26, and she died later that day.

- Subject ID# 00502519 was an 85 year old female who had a right hemicolectomy with primary anastomosis, right oophorectomy, and cholecystectomy on Day -1. She developed a bacteremia due to *Enterococcus faecium* on Day 9 and developed progressive sepsis on Day 11. Life support was withdrawn on Day 13, and she died later that day.

- Subject ID# 05402058 was a 49 year old female with Crohn's disease, perforated duodenum and jejunum, sepsis, ARDS, and renal failure who developed pneumonia on Day 1. She developed a UTI on Day 11 as well as a gastrointestinal bleed that required surgical repair on Day 27. She required repeat surgical repair for recurrent gastrointestinal bleeding on Day 34, and she experienced a cardiac arrest, ARDS, and multi-organ failure. Gastrointestinal bleeding recurred again on Day 37. Life support was withdrawn on Day 39, and she died later that day.

- Subject ID# 05402523 was an 83 year old female with multiple medical problems.. She had a perforated viscus, gastrointestinal bleed, ischemic bowel, postoperative stroke, acute pericarditis, mediastinal hematoma, pericardial effusion, septic shock, and staphylococcal pneumonia prior to entering the study. On Day -1, she had a sigmoid resection with end colostomy. She had a cardiac arrest on Day 12, but developed pleural effusions with atelectasis on Day 14. She died on Day 25.

- Subject ID# 05402526 was an 86 year old female with peritonitis whose gastrostomy tube eroded through her stomach on Day 1. She developed septic shock on Day 2 with anemia, atrial fibrillation, generalized edema, and abdominal wound and catheter complications noted during Days 2 – 7. Life support was withdrawn on Day 7, and she died later that day.

- Subject ID# 12606026 was a 69 year old female enrolled in the study with abdominal surgeries for a perforated sigmoid colon with peritonitis prior to study enrollment. Her course was complicated by bacteremia, pneumonia, respiratory failure necessitating tracheostomy and mechanical ventilation, two surgeries to repair an anastomotic leak, sepsis, recurrent pneumonia, pancreatitis, gall bladder necrosis, and renal failure. The patient died on Day 53.

- Subject ID# 43104023 was a 79 year old diabetic female with peritonitis from a perforated appendix who was treated with 12 days of doripenem. She experienced septic shock on Day 4, ventilator-associated pneumonia (VAP) on Day 12, wound dehiscence on Day 18, recurrent VAP on Day 21, and atrial fibrillation on Days 2-4 and on Day 22. She died on Day 25 from pneumonia.

MO Comment: In examining the timing of the 13 deaths among the doripenem treated patients in both studies, one death occurred prior to doripenem administration, 3 deaths occurred during the time of administration of the drug, and 9 deaths occurred after doripenem administration had been completed such that there was not a clear temporal relationship between doripenem exposure and the fatal event. In five cases, lack of drug efficacy could not be excluded as a contributing factor to infectious complications

(bacteremia, pneumonia). In two patients, doripenem lacked in vitro activity against the infectious organism (i.e. E. faecium, and MRSA).

7.1.2 Other Serious Adverse Events

Table 34 summarizes treatment-emergent serious adverse events (TESAEs) by preferred term.
• Overall, 15.6% of ITT patients experienced TESAEs.
The incidence of TESAEs was similar in both treatment arms (72, doripenem; 76, meropenem).
• The most frequently reported serious adverse events were in the infections and infestations and gastrointestinal system organ classes
• The most frequently reported treatment-emergent serious adverse events overall (reported in at least 1% of patients in either treatment arm) were sepsis, abdominal abscess, myocardial infarction, peritonitis, and pleural effusion.

Table 34: Treatment-Emergent Serious Adverse Events (TESAE) (Intent-to-Treat Analysis Set)

SOC Preferred Term	Doripenem (N=477)	Meropenem (N=469)	Total (N=946)
Number of Patients with at Least 1 TESAE	**72 (15.1%)**	**76 (16.2%)**	**148 (15.6%)**
Blood and lymphatic system disorders	**4 (0.8%)**	**0**	**4 (0.4%)**
Anemia	3	0	3
Cardiac disorders	**5 (1.0%)**	**8 (1.7%)**	**13 (1.4%)**
Myocardial infarction	2	4	6
Gastrointestinal disorders	**22 (4.6%)**	**25 (5.3%)**	**47 (5.0%)**
Peritonitis	4	3	7
General disorders and administration site conditions	**2 (0.4%)**	**2 (0.4%)**	**4 (0.4%)**
Hepatobiliary disorders	**1 (0.2%)**	**3 (0.6%)**	**4 (0.4%)**
Infections and infestations	**34 (7.1%)**	**37 (7.9%)**	**71 (7.5%)**
Abdominal abscess	4	9	13
Sepsis	3	6	9
Septic shock	2	5	7
Injury, poisoning and procedural complications	**13 (2.7%)**	**7 (1.5%)**	**20 (2.1%)**
Wound dehiscence	3	2	5
Metabolism and nutrition disorders	**1 (0.2%)**	**2**	**3 (0.3%)**
Neoplasms benign, malignant and unspecified	**1 (0.2%)**	**0**	**1 (0.1%)**
Nervous system disorders	**2 (0.4%)**	**1 (0.2%)**	**3 (0.3%)**
Psychiatric disorders	**0**	**1 (0.2%)**	**1 (0.1%)**
Renal and urinary disorders	**4 (0.8%)**	**0**	**4 (0.4%)**
Respiratory, thoracic and mediastinal disorders	**9 (1.9%)**	**9 (1.9%)**	**18 (1.9%)**
Pleural effusion	1	3	4
Skin and subcutaneous tissue disorders	**1 (0.2%)**	**0**	**1 (0.1%)**
Surgical and medical procedures	**2 (0.4%)**	**0**	**2 (0.2%)**
Vascular disorders	**1 (0.2%)**	**2 (0.4%)**	**3 (0.3%)**

Modified Table 27 from Sponsor's Clinical Study Report combining data from DORI-7 and DORI-8.
Not all TEAE subsets are listed
N = number of patients in the analysis set; SOC = system organ class
Note: Both fatal and non-fatal treatment-emergent serious adverse events are presented.

MO Comments: The number of patients with TESAEs was equally distributed between the two treatment groups. The top two were infections and infestations with 7.1% in the doripenem arm, and 7.9% in the meropenem arm. Gastrointestinal disorders were second with 4.6% and 5.3% in the doripenem and meropenem arms respectively. While overall equally distributed,

there did appear to be less significant infections (abscess, sepsis, and shock) in the doripenem group than in the meropenem group. It is not clear, however, with regards to blood system disorders why there were more patients with anemia in the doripenem group.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of those subjects who did not complete the studies, the most common reason for discontinuation in Study DORI-07 was loss to follow-up (3%) and in Study DORI-08 the most common reason for discontinuation was adverse event(s) (3%).

Table 35: Study Completion and Discontinuation Information (Intent-to-Treat Analysis Set)

	Doripenem N (%)	Meropenem N (%)
	(N=477)	(N=469)
Subj. completed study per protocol	421 (88)	405 (86)
Subj. did not complete study per protocol	56 (12)	64 (14)
Secondary to:		
Adverse event	12 (3)	11 (2)
Treatment failure	3 (1)	4 (1)
Need for additional antibacterial therapy	6 (1)	3 (1)
At request of subject, investigator, sponsor	5 (1)	6 (1)
Death	9 (2)	14 (3)
Non-compliance	4 (1)	1 (<1)
Lost to follow up	10(2)	14 (3)
Other	7 (1)	11 (2)

Table 10 from Sponsor's Summary of Clinical Safety
Note: Percentages were calculated with the number of subjects in each group as the denominator. Only the primary reason for discontinuation is presented in this table. Therefore, the number of subjects that discontinued due to death in each group may not be the same as the actual number of deaths during the study in each group.

7.1.3.2 Adverse events associated with dropouts

• A total of 12 (3%) and 11 (2%) patients in the doripenem and meropenem treatment arms, respectively, were discontinued prematurely from study drug therapy due to an adverse event.

• In DORI-07, most of the study drug related treatment-emergent adverse events leading to premature study drug therapy discontinuation were in the GI system organ class, and included vomiting, dyspepsia, stomatitis, and diarrhea. One patient in each treatment arm prematurely discontinued study drug therapy due to study drug-related nausea.

• In DORI-08, for both treatment arms, the most frequent study drug related treatment-emergent adverse event leading to premature study drug therapy discontinuation was pneumonia, reported in 4 doripenem-treated patients and 1 meropenem-treated patient. One doripenem-treated patient

(Patient 015/12034) was prematurely discontinued due to nausea associated with dizziness, and 1 patient from each treatment arm was prematurely discontinued due to abdominal pain.

Table 36 shows the TEAE leading to discontinuation of the study drug for the pooled studies. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy.

Table 36: Treatment-Emergent Adverse Events Leading to Discontinuation from Study Drug
(Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem N=469) n (%)
Total no. subjects who discontinued due to TEAEs	**22 (4.6)**	**13 (2.8)**
Infections and infestations	**9 (1.9)**	**4 (0.9)**
Pneumonia	5 (1.0)	1 (0.2)
Sepsis	2 (0.4)	0
Abdominal abscess	1 (0.2)	1 (0.2)
Bacteremia	1 (0.2)	0
Vulvovaginal mycotic infection	1 (0.2)	0
Peritoneal abscess	0	1 (0.2)
Septic shock	0	1 (0.2)
Gastrointestinal disorders	**5 (1.0)**	**6 (1.3)**
Nausea	2 (0.4)	1 (0.2)
Abdominal pain	1 (0.2)	1 (0.2)
Dyspepsia	1 (0.2)	1 (0.2)
Vomiting	1 (0.2)	1 (0.2)
Abdominal discomfort	0	1 (0.2)
Diarrhea	0	1 (0.2)
Femoral hernia	0	1 (0.2)
Small intestinal obstruction	0	1 (0.2)
Small intestinal perforation	0	1 (0.2)
Stomatitis	0	1 (0.2)
General disorders and administration site conditions	**2 (0.4)**	**1 (0.2)**
Injection site reaction	1 (0.2)	0
Pyrexia	1 (0.2)	0
Asthenia	0	1 (0.2)
Investigations	**2 (0.4)**	**0**
Hematocrit decreased	1 (0.2)	0
White blood cell count increased	1 (0.2)	0
Blood and lymphatic system disorders	**1 (0.2)**	**0**
Anemia	1 (0.2)	0
Hepatobiliary disorders	**1 (0.2)**	**1 (0.2)**
Cholecystitis	1 (0.2)	0
Hepatic failure	0	1 (0.2)