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

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Injury, poisoning and procedural Complications	**1 (0.2)**	**0**
Anastomotic leak	1 (0.2)	0
Nervous system disorders	**1 (0.2)**	**1 (0.2)**
Dizziness	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**0**
Respiratory arrest	1 (0.2)	0
Skin and subcutaneous tissue disorders	**1 (0.2)**	**0**
Rash	1 (0.2)	0
Ear and labyrinth disorders	**0**	**1 (0.2)**
Deafness	0	1 (0.2)
Tinnitus	0	1 (0.2)
Immune system disorders	**0**	**1 (0.2)**
Hypersensitivity	0	1 (0.2)
Psychiatric disorders	**0**	**1 (0.2)**
Anxiety	0	1 (0.2)
Confusional state	0	1 (0.2)
Dysphoria	0	1 (0.2)
Vascular disorders	**0**	**1 (0.2)**
Hypertension	0	1 (0.2)

Table 36 from Clinical Summary / Safety Report
Note: At each level of summarization, a subject was counted once if the subject reported one or more events.
AE terms were coded using MedDRA version 9.0.

MO Comment: There was more than double the amount of patients in the doripenem group (1.9%), than in the meropenem (0.9%) group who discontinued therapy due to infections and infestations, 1.9%. Pneumonia was 5 times more common in the doripenem group as a post-operative complication. Pneumonia is an expected post-operative complication in patients with cIAI. However, the reason for the imbalance between the two arms in unclear. Besides being a chance finding it raises the question of whether doripenem exposure can lead to infection due to resistant organisms. It is also difficult to completely exclude a lack of efficacy in the doripenem arm based on this finding.

7.1.3.3 Other significant adverse events

Other adverse events of special interest included study drug therapy intolerability, allergic reaction, seizures, *C dificile* colitis, and phlebitis.

Study Drug Therapy Intolerability

A similar proportion of patients in both treatment arms experienced treatment-emergent adverse events that suggested possible IV study drug therapy intolerability. Adverse events associated with possible study drug therapy intolerability were most often in the GI system organ class and

were reported by 12 (2.5%) patients in the doripenem treatment arm and 8 (1.7%) patients in the meropenem treatment arm. The most frequently reported GI disorder was nausea. With one exception, all reported nausea events were mild or moderate in severity, and related to study drug therapy. There were almost 4 times more reports of nausea in the doripenem treatment arm however (1.5%), than in the meropenem arm (0.4%). Table 37 summarizes the TEAEs reported as drug intolerability.

- Doripenem treated patient 011/02006 experienced severe nausea lasting from Days1-9 after receiving the IV study drug for 6 days.
- Doripenem treated patient 015/12034 experienced nausea associated with dizziness on Day 1. Patient was discontinued from therapy, with dizziness and nausea resolving on Days 2 and 6 respectively.

Table 37: Treatment-Emergent Adverse Events That Were Reported to Represent Study Drug Intolerability
(Pooled Studies: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Total no. subjects with study drug intolerability	**17 (3.6)**	**13 (2.8)**
Gastrointestinal disorders	**12 (2.5)**	**8 (1.7)**
Nausea	7(1.5)	2 (0.4)
Diarrhea	2 (0.4)	4 (0.9)
Vomiting	3 (0.6)	2 (0.4)
Abdominal pain	1 (0.2)	0
Dyspepsia	1 (0.2)	1 (0.2)
Abdominal discomfort	0	1 (0.2)
Abdominal pain upper	0	1 (0.2)
Nervous system disorders	**3 (0.6)**	**1 (0.2)**
Headache	1 (0.2)	1 (0.2)
Dizziness	2 (0.4)	0
Investigations	**1 (0.2)**	**0**
Blood pressure decreased	1 (0.2)	0
General disorders and administration site conditions	**1 (0.2)**	**4 (0.9)**
Rigors	1 (0.2)	1 (0.2)
Application site irritation	0	1 (0.2)
Edema peripheral	0	1 (0.2)
Pyrexia	0	2 (0.4)
Vascular disorders	**1 (0.2)**	**0**
Phlebitis	1 (0.2)	0
Ear and labyrinth disorders	**1 (0.2)**	**0**
Ear discomfort	1 (0.2)	0

Modified Tables 15.3.1.1-3 from DORI-07 and DORI -08 Clinical Study Report
Note: At each level of summarization, a subject was counted once if the subject reported one or more events.
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. AE terms were coded using MedDRA version 9.0. Adverse events were flagged by the investigator on the AE CRF' as possible study drug intolerability.

Possible Allergic Reaction (PAR)

The majority of TEAEs that were considered allergic reactions were all within the skin and subcutaneous tissue disorders system organ class and included pruritus, generalized pruritus, rash, and skin irritation. Table 38 summarizes the TEAEs reported as PAR.

Overall, 8 (1.7%) patents in the doripenem group and 9 (1.9%) patients in the meropenem group experienced a TEAE that was reported by the investigator as a PAR to treatment. In the doripenem group, rash was reported by 4 (0.8 %) patients versus 1 (0.2%) in the meropenem group. All other AEs that were recorded by the investigator as PAR to treatment with study drug therapy were experienced by no more than two subjects in either treatment group.

No cases of Stevens Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis, or anaphylactic shock were reported for subjects receiving doripenem.

Table 38: TEAEs that are reported as Possible Allergic Reaction (Safety Subject Analysis Set)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Total no. subjects with possible allergic reaction	**8 (1.7)**	**9 (1.9)**
Skin and subcutaneous tissue disorders	**7 (1.5)**	**5 (1.1)**
Rash	4 (0.8)	1 (0.2)
Pruritus	1 (0.2)	2 (0.4)
Pruritus allergic	1 (0.2)	0
Pruritus generalized	1 (0.2)	1 (0.2)
Rash papular	1 (0.2)	0
Rash macular	0	1 (0.2)
Skin irritation	0	1 (0.2)
Investigations	**1 (0.2)**	**0**
Body temperature increased	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1 (0.2)
Wheezing	1 (0.2)	0
Dyspnea	0	1 (0.2)
Ear and labyrinth disorders	0	1 (0.2)
Deafness	0	1 (0.2)
Tinnitus	0	1 (0.2)
Gastrointestinal disorders	0	2 (0.4)
Diarrhea	0	1 (0.2)
Nausea	0	1 (0.2)

Sponsor's Clinical Safety Summary Report: Appendix 3.3.25

Note: At each level of summarization, a subject is counted once if the subject reported one or more events. Treatment-emergent adverse events are defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of the study medication and within 30 days after administration of the last dose of the study medication. AE terms are coded using MedDRA version 9.0. Adverse events are flagged by the investigator on the 'Adverse Event CRF' as possible allergic reason.

Seizures
There were no TEAEs that coded to seizure in the doripenem treatment group for cIAI.

C-Difficile Colitis
Two subjects in the doripenem treatment group experienced TEAEs that coded to *C. difficile* colitis in the DORI-07 study:

Subject 01312512 experienced moderate *C. difficile* diarrhea on Day 28 of the study (method of diagnosis unknown). He was treated with metronidazole, and the event resolved. He was treated with approximately 10 days of IV doripenem. The event was considered by the investigator to be possibly related to treatment with study drug therapy.

Subject 02002065 experienced moderate *C. difficile* colitis on Day 8 of the study. He received several concomitant antimicrobials including ampicillin, vancomycin, amoxicillin/clavulanate, piperacillin/tazobactam, levofloxacin, and ciprofloxacin. The event resolved after a 14-day course of treatment with metronidazole. The event was considered by the investigator to be possibly related to treatment with study drug therapy.

Phlebitis
• Although phlebitis was not a predefined AE of interest, during the conduct of the Phase 3 studies, it was observed that the incidence of phlebitis reported as AEs varied by site. Therefore, in an effort to standardize the care of IV catheters across all study sites and to gather additional details on phlebitis as an AE, on 17 May 2005, a summary of the National Institutes for Health guidelines for insertion and maintenance of IV catheters was provided to all sites participating in the ongoing Phase 3 studies. Per the sponsor, only Argentina and Brazil comprised the high incidence sites. After this intervention, the incidence of phlebitis reduced in the high-incidence sites. For pooled analyses of phlebitis as an AE, please see the integrated review of safety by Dr. Alfred Sorbello.

7.1.4 Other Search Strategies

Not Applicable

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

As the protocol allowed for switch from intravenous doripenem/meropenem to oral amoxicillin-clavulanate- if certain pre-specified criteria were met- the safety data on patients treated with IV doripenem alone is fairly limited.

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.

At each level of summarization, a subject was counted once if the subject reported one or more events. TEAEs 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. AE terms were coded using MedDRA version 9.0.

7.1.5.2 Incidence of common adverse events

Commonly reported (>1%) TEAEs for the pooled Phase 3 cIAI studies DORI-07 and DORI-08 are summarized by treatment group in Table 39.

7.1.5.3 Common adverse event tables

Table 39: TEAEs by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group - (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Gastrointestinal disorders	**182 (38.2)**	**166 (35.4)**
Nausea	57 (11.9)	44 (9.4)
Diarrhea	51 (10.7)	52 (11.1)
Vomiting	29 (6.1)	38 (8.1)
Constipation	22 (4.6)	18 (3.8)
Abdominal pain	20 (4.2)	20 (4.3)
Flatulence	19 (4.0)	11 (2.3)
Abdominal distension	12 (2.5)	11 (2.3)
Dyspepsia	12 (2.5)	12 (2.6)
Abdominal pain upper	8 (1.7)	7 (1.5)
Ascites	7 (1.5)	4 (0.9)
Ileus	6 (1.3)	3 (0.6)
Abdominal pain lower	0	6 (1.3)
Infections and infestations	**115 (24.1)**	**103 (22.0)**
Pneumonia	20 (4.2)	7 (1.5)
Wound infection	18 (3.8)	9 (1.9)
Urinary tract infection	16 (3.4)	11 (2.3)
Postoperative wound infection	13 (2.7)	12 (2.6)

Table 39: TEAEs by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Safety Analysis Set - continued)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Urinary tract infection fungal	6 (1.3)	11 (2.3)
Oral candidiasis	5 (1.0)	8 (1.7)
Sepsis	5 (1.0)	7 (1.5)
Abdominal abscess	4 (0.8)	11 (2.3)
Septic shock	4 (0.8)	5 (1.1)
General disorders and administration site conditions	**106 (22.2)**	**95 (20.3)**
Pyrexia	46 (9.6)	44 (9.4)
Edema peripheral	21 (4.4)	15 (3.2)
Asthenia	12 (2.5)	5 (1.1)
Generalized edema	8 (1.7)	3 (0.6)
Pain	5 (1.0)	8 (1.7)
Chills	3 (0.6)	6 (1.3)
Non-cardiac chest pain	2 (0.4)	6 (1.3)
Injection site pain	0	5 (1.1)
Respiratory, thoracic and mediastinal disorders	**80 (16.8)**	**71 (15.1)**
Pleural effusion	19 (4.0)	13 (2.8)
Atelectasis	13 (2.7)	14 (3.0)
Dyspnea	13 (2.7)	17 (3.6)
Cough	8 (1.7)	15 (3.2)
Pharyngolaryngeal pain	7 (1.5)	5 (1.1)
Tachypnea	7 (1.5)	3 (0.6)
Respiratory failure	4 (0.8)	6 (1.3)
Investigations	**72 (15.1)**	**59 (12.6)**
Gamma-glutamyl transferase increased	14 (2.9)	10 (2.1)
Blood creatine phosphokinase increased	11 (2.3)	6 (1.3)
Blood alkaline phosphatase increased	9 (1.9)	4 (0.9)
Platelet count increased	7 (1.5)	2 (0.4)
Blood pressure increased	5 (1.0)	5 (1.1)
White blood cell count increased	5 (1.0)	6 (1.3)
Hepatic enzyme increased	4 (0.8)	8 (1.7)
Injury, poisoning and procedural complications	**69 (14.5)**	**51 (10.9)**
Procedural pain	10 (2.1)	10 (2.1)
Wound complication	10 (2.1)	9 (1.9)
Wound dehiscence	9 (1.9)	6 (1.3)
Post procedural discharge	7 (1.5)	2 (0.4)
Post procedural complication	3 (0.6)	5 (1.1)
Metabolism and nutrition disorders	**69 (14.5)**	**46 (9.8)**
Hypokalaemia	20 (4.2)	12 (2.6)
Hyperglycemia	9 (1.9)	11 (2.3)
Malnutrition	8 (1.7)	4 (0.9)
Dehydration	7 (1.5)	3 (0.6)
Hypomagnesaemia	6 (1.3)	7 (1.5)
Hyponatraemia	6 (1.3)	1 (0.2)
Hypophosphataemia	3 (0.6)	5 (1.1)
Hypocalcaemia	2 (0.4)	6 (1.3)
Vascular disorders	**64 (13.4)**	**66 (14.1)**
Phlebitis	36 (7.5)	26 (5.5)
Hypertension	14 (2.9)	22 (4.7)
Hypotension	9 (1.9)	5 (1.1)

Table 39: TEAEs by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Safety Analysis Set - continued)

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Hematoma	1 (0.2)	6 (1.3)
Pallor	0	5 (1.1)
Skin and subcutaneous tissue disorders	**58 (12.2)**	**42 (9.0)**
Rash	16 (3.4)	5 (1.1)
Pruritus	11 (2.3)	8 (1.7)
Decubitus ulcer	8 (1.7)	2 (0.4)
Hyperhidrosis	6 (1.3)	10 (2.1)
Erythema	3 (0.6)	7 (1.5)
Psychiatric disorders	**55 (11.5)**	**54 (11.5)**
Insomnia	24 (5.0)	22 (4.7)
Anxiety	13 (2.7)	16 (3.4)
Depression	6 (1.3)	2 (0.4)
Agitation	5 (1.0)	6 (1.3)
Confusional state	5 (1.0)	8 (1.7)
Blood and lymphatic system disorders	**54 (11.3)**	**43 (9.2)**
Anemia	46 (9.6)	26 (5.5)
Leukocytosis	8 (1.7)	7 (1.5)
Thrombocythemia	4 (0.8)	6 (1.3)
Nervous system disorders	**47 (9.9)**	**47 (10.0)**
Headache	21 (4.4)	24 (5.1)
Dizziness	15 (3.1)	15 (3.2)
Renal and urinary disorders	**32 (6.7)**	**23 (4.9)**
Dysuria	8 (1.7)	4 (0.9)
Oliguria	8 (1.7)	3 (0.6)
Cardiac disorders	**29 (6.1)**	**30 (6.4)**
Tachycardia	10 (2.1)	5 (1.1)
Atrial fibrillation	7 (1.5)	6 (1.3)
Myocardial infarction	2 (0.4)	5 (1.1)
Musculoskeletal and connective tissue disorders	**24 (5.0)**	**24 (5.1)**
Back pain	7 (1.5)	6 (1.3)

Table 25 from Clinical Summary / Safety Report

The most commonly reported TEAEs in both groups were within the system organ class of GI disorders. Overall, the most commonly reported AEs in the doripenem and meropenem groups were diarrhea (10.7% and 11.1%, respectively) and nausea (11.9% and 9.4%). Anemia was reported for 9.6% of subjects in the doripenem group and 5.5% in the meropenem group. Per the sponsor, the cause of anemia in the vast majority of these cases was post-surgical blood loss. The incidence of phlebitis in the doripenem 500 mg group was 7.5%, compared with 5.5% in the meropenem group.

MO Comments: According to the sponsor's supplemental documents, anemia is due to post – op blood loss and not from medication induced bone marrow suppression. We would expect to see increase blood loss in the cIAI group given the nature of their condition and surgical history; however it is unclear why the doripenem group had almost twice as many adverse events with anemia (12.3% (doripenem) vs. 7.2% (meropenem) in DORI-7, and 7%

(doripenem) vs. 3.9% (meropenem) in DORI-8). We would expect to see a more even distribution of anemia in both groups if anemia was solely due to post op blood loss.

The results of the hematology consult revealed that while the data presented does not directly implicate doripenem as causing hemolytic anemia in this patient population, a number of limitations such as: lack of direct Coombs tests and lack of systematic collection of information about intra-operative and peri-operative blood loss make this assessment difficult. It is also difficult to directly implicate doripenem as a cause of anemia because these patients had: blood transfusions during the study, some had a prior history of anemia, concomitant medications which could be implicated in causing anemia, severe medical illness causing increased phlebotomy requirements, surgical blood loss or bone marrow suppression of red blood cell production which complicates the evaluation and precludes definitive assessment. It was therefore recommended by hematology to request the sponsor to undertake an analysis of doripenem as a possible cause of hemolytic anemia in a Phase 4 Commitment.

For a more detailed analysis of anemia, please refer to Dr. Sorbello's Safety Review.

7.1.5.4 Identifying common and drug-related adverse events

Table 40 shows the adverse events related to study drug that emerged during therapy in the pooled studies. Study drug-related TEAEs were defined as those AEs with a relationship to study drug of either possibly or probably related, 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 40: Study Drug Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	**Doripenem** (N=477) n (%)	**Meropenem** (N=469) n (%)
Gastrointestinal disorders	**59 (12.4)**	**44 (9.4)**
Nausea*	25 (5.2)	9 (1.9)
Diarrhea*	21 (4.4)	21 (4.5)
Vomiting	9 (1.9)	8 (1.7)
Investigations	**22 (4.6)**	**21 (4.5)**
Gamma-glutamyl transferase increased	6 (1.3)	7 (1.5)
Hepatic enzyme increased*	2 (0.4)	7 (1.5)
Infections and infestations	**21 (4.4)**	**21 (4.5)**
Oral candidiasis*	4 (0.8)	7 (1.5)
Urinary tract infection fungal	2 (0.4)	6 (1.3)
Skin and subcutaneous tissue disorders	**15 (3.1)**	**10 (2.1)**
Rash*	9 (1.9)	0
Pruritus*	2 (0.4)	5 (1.1)
General disorders and administration site conditions	**14 (2.9)**	**17 (3.6)**
Pyrexia	5 (1.0)	8 (1.7)

Table 40: Study Drug Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects (Safety Analysis Set) - continued

Body System or Organ Class Dictionary-derived Term	Doripenem (N=477) n (%)	Meropenem (N=469) n (%)
Nervous system disorders	**13 (2.7)**	**7 (1.5)**
Headache*	6 (1.3)	4 (0.9)
Vascular disorders	**13 (2.7)**	**11 (2.3)**
Phlebitis*	12 (2.5)	10 (2.1)

Table 28 from Clinical Summary / Clinical Safety Report
Note: At each level of summarization, a subject was counted once for the most related event if the subject reported one or more occurrences of the same event. If the relationship of a TEAE was missing, the TEAE was reported as probably related.
AE terms were coded using MedDRA version 9.0.
* Event identified as an ADR or under a similar ADR term of study medication.

In summary of the above table:
• Nausea was the most commonly reported AE in the doripenem (5.2%) group, compared with the meropenem group (1.9%).
•Gastrointestinal disorders in general were frequently reported in all treatment groups. Diarrhea and emesis were reported by 4.4% and 1.9%, in the doripenem group, and 4.5% and 1.7% in the meropenem group.
•Phlebitis was reported by 6.9% of subjects in the doripenem and 5.5% in the meropenem group.
•Pyrexia was reported by 5.5% of subjects in the doripenem, and 9.4% in the meropenem group.
•Specific study drug-related TEAEs were uncommon, with none reported in more than 4.2% of subjects who received doripenem. The only investigator-determined study drug-related TEAEs with a higher incidence in the doripenem 500 mg group versus comparator (other than the marginally higher rate for vomiting) were nausea, headache, and phlebitis.

MO Comments: Rash was more common in the doripenem arm both as an overall AE and as a treatment-related AE. Also, nausea was much more common in the doripenem treatment group than in the meropenem group.

7.1.5.5 Additional analyses and explorations

Adverse reactions with onset during IV doripenem therapy were similar to that observed in the overall population.

Please refer to section 7.1.3.3 for additional information on other adverse events.

7.1.6 Laboratory Findings

The following clinical laboratory tests were performed on all patients. Table 41 shows the time line for obtaining laboratory tests.

Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets.

Serum chemistry: Magnesium, bicarbonate, sodium, potassium, phosphorus, chloride, calcium, alkaline phosphatase, gamma-glutamyltransferase (GGT), ALT, AST, creatine kinase, lactate dehydrogenase, total and indirect bilirubin, total cholesterol, glucose (non-fasting), total protein, albumin, creatinine, blood urea nitrogen (BUN), and uric acid.

Urinalysis: pH, protein, glucose, ketones, bilirubin, urobilinogen, and urine microscopy for RBC, WBC, crystals, and casts.

Table 41	**Time and Events Schedule**							
							EFU	**TOC**
Day	**-1 to 0 (Screen)**	**1**	**2**	**3**	**4-14**	**End of IV**	**(7 to 14 Days)**	**(28 to 42 Days)**
CBC, chemistry, and urinalysis[a]	X		X		X	X	X	
Calculated creatinine clearance	X	X	X	X	X			
Pregnancy test	X						X	
Blood sample for culture[b]	X							
Site of infection sample for culture[c]	X					X	X	X

[a] 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. Safety laboratory tests performed less than 24 hours prior to end of IV study drug therapy were not repeated at the end of IV study drug therapy.
[b] If positive, follow-up blood cultures were taken approximately every 24 hours until 2 consecutive negative culture results were obtained. If the patient was assessed as a clinical failure or signs of sepsis appeared at any time on study, blood cultures were repeated. Every time blood cultures were indicated, 2 sets (each consisting of aerobic and anaerobic bottles) were required.
[c] A sample from the intra-abdominal site of infection was collected for culture at the time of the initial procedure (within 24 hours of enrollment) and as indicated thereafter (e.g., re-intervention, clinical failure).

7.1.6.1 Overview of laboratory testing in the development program

The frequency of laboratory testing appears adequate. There was no pre-specified laboratory testing for hemolytic anemia and hence a detailed analysis of the etiology of anemia is limited.

7.1.6.2 Standard analyses and explorations of laboratory data

1) Hematology

Examination of results from the cIAI studies DORI-07 and DORI-08 indicate that there were no notable differences in hematology results between the doripenem and meropenem groups.

- There were comparable decreases from baseline in WBC count in both groups.

- Platelet counts increased considerably from baseline to Day 14 in both treatment groups, and returned to near baseline values by the LFU visit, consistent with an expected increase in acute phase reactants.
- As expected in post-operative subjects, hemoglobin and hematocrit decreased from baseline to Day 14 in both treatment groups and returned to near baseline values by the LFU visit.
- When hematology parameters were analyzed by shift tables: there were 6 subjects in each treatment group who were grade 4 for WBC, 1 subject in each treatment group with a Grade 4 in hemoglobin, and platelets, and 1 subject in doripenem with Grade 4 for absolute neutrophil count.

MO Comments: There was a difference in anemia between the two groups, with doripenem having a higher incidence of anemia. (Refer to section: 7.1.2). Unclear of the etiology, however, as laboratory markers for hemolytic anemia were not tested.

2) Hepatobiliary Parameters:

The sponsor examined ALT and AST in the following ways:

1) Shifts tables were generated for ALT and AST values using the toxicity grades defined in the PPImDMID Adult Toxicity Tables. They were generated for ALT and AST values using Sponsor-defined severity categories and the regional laboratory's reference range for the ULN
2) All subjects who met the criteria for Hy's High Risk (HHR) classification were identified and evaluated
3) Increases in hepatic enzymes that were reported by the investigators as TEAEs were summarized.

• When hepatobiliary parameters were analyzed by shift tables: there were 3 subjects in each treatment group who were Grade 4 for AST, 2 subjects in doripenem and 3 subjects in meropenem who were Grade 4 in ALT, and 2 subjects in doripenem and 1 subject in meropenem who were Grade 4 for total bilirubin. The highest marker was for GGT with 13 subjects with a Grade 4 in doripenem and 6 subjects with a Grade 4 in meropenem. Significance of this is unclear as there was no equal increase in total bilirubin.

• Evaluation of changes in ALT and AST revealed that the doripenem treatment group had comparable or lower rates of increase of these enzymes compared with the meropenem treatment group.

• Overall, there were 5 patients who met HHR criteria in the doripenem group, and 3 patients who met HHR criteria in the meropenem group; all subjects had confounding medical events that could have contributed to the observed hepatobiliary findings. There were two patients in DORI-07 who were treated with doripenem and met HHR criteria. One met Hy's rule at screening, and had a decrease in AST and total bilirubin the following day while on the study drug. The other patient met Hy's rule at the early follow up visit. In DORI-08, there were three

doripenem treated patients who met the HHR criteria. Two had elevated lab levels on their screening day. The third patient met HHR criteria on day 12 of doripenem therapy.

Below are the narratives of patients meeting Hy's Rule who were treated with doripenem:

DORI-07

Subject 40104517:

- This patient had elevated ALT values at the EFU visit on Day 23 after completing therapy (11 days of IV followed by amoxicillin/clavulanate (875/125 mg), which was completed on Day 15). On day 12, the patient was diagnosed with moderate Addison's disease which was treated with high-dose steroids.

- Laboratory values are summarized in the table. At screening, the patient had a normal ALT value of 29 IU/L, and an elevated AST value of 52 IU/L (normal: less than or equal to 37 IU/L) and elevated total bilirubin of 95 µmol/L (5.6 mg/dl).

- On Day 23, the patient's laboratory values included ALT of 137 IU/L, AST of 48 IU/L, and total bilirubin of 29.2 µmol/L (1.71 mg/dl). On Day 46, the patient's ALT was 227 IU/L, AST was 102 IU/L, and total bilirubin was 11.6 µmol/L (0.68 mg/dl).

This laboratory finding represented a combination of mild hyperbilirubinemia due to acute cholecystitis, which continued to improve after baseline, and a seemingly independent elevation in ALT, which could be related to 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.

Table 42: Laboratory Values

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-07	401/04517	Baseline	5.57	29	52	122
		Day 2	7.39	42	108	140
		Day 5	6.45	31	61	181
		Day 8	2.51	31	63	491
		EOT	2.38	54	87	586
		Day 11	2.16	47	59	520
		Day 14	2.63	59	110	627
		EFU	1.71	137	48	290
		Day 46	0.68	227	102	**

EOT=end of IV therapy. EFU= early follow-up, ** not given

Subject 03502005:

- This patient had elevated AST and ALT values at screening along with an elevated total bilirubin value of 56.4 µmol/L (3.3 mg/dl) thus meeting the HHR classification. Given the high alkaline phosphatase level, the elevated values are most likely due to an obstructive etiology. The patient's medical history included a cholecystectomy just prior

to enrollment in the study. The dosage of IV study drug therapy was adjusted on Days 1 through 8 due to renal impairment. The patient completed 8 days of IV study drug therapy, and then switched to oral study drug therapy with amoxicillin/clavulanate (875/125 mg), which was completed on Day 15.

- Laboratory values are summarized in the table. At TOC, the patient had slightly elevated AST and ALT values of 63 IU/L and 44 IU/L, which did normalize by EFU visit.
- On EFU (Day 22), the patient's laboratory values included an ALT of 23 IU/L, AST of 17 IU/L, total bilirubin of 11.97 µmol/L, and an alkaline phosphatase of 349 IU/L. None of these elevated laboratory values was reported as an adverse event by the investigator.

Table 43: Laboratory Values

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-07	035/02005	Baseline	3.3	225	144	1360
		Day 2	2.5	145	59	1140
		Day 5	1.1	53	26	669
		EOT	1.0	38	31	682
		TOC	0.5	63	44	293
		EFU	0.7	23	17	349

EOT=end of IV therapy, TOC= test of cure, EFU= early follow-up

MO Comment: On review of this information, it is unlikely doripenem had a role in the subjects' abnormal LFTs. In the two cases, there is either no obvious association between treatment and increased LFTs, or there is a concomitant illness such as obstructive biliary disease, that may have caused the increased in LFTs.

DORI-08
Subject 04302050:

- A 39 year old Hispanic male with a history of alcohol use, diverticulitis with a diagnosis of a diverticular abscess.
- He met HHR criteria at baseline, and his values decreased while on IV therapy.
- There were no liver related adverse events during the study.

Table 44: Laboratory Values

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-08	04302050	Baseline	2.1	214	213	269
		Day 2	1.7	151	52	255
		Day 4 (EOT- IV)	0.5	74	15	186
		Day 19 (EFU)	1.2	35	30	94

Subject 3850409:

- A 54 year old Caucasian male with a history of hypertension and cholelithiasis who was diagnosed with a colonic abscess requiring open abdominal surgery.
- This patient also met the HHR criteria at baseline and his LFTs decreased while on IV therapy.

- Doripenem was adjusted for renal impairment
- There was no liver related adverse event while on study IV and oral drug therapy. He was however diagnosed with hepatitis on Day 40 – Day 60 of unknown etiology. It was not felt by the investigator to be study drug related.

Table 45: Laboratory Values

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-08	3850409	Baseline	5.5	130	110	814
		Day 3	2.8	61	31	564
		Day 4 (EOT- IV)	2.2	58	40	587
		Day 40 (TOC)	No data	179	No data	1541
		Day 59	0.36	14	19	364

Subject 43104023:

- This 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.

- Laboratory values are summarized in the table. On Day 5, the patient had markedly elevated AST and ALT values of 950 IU/L and 1759 IU/L. A hepatitis serology was performed but was negative.

- Study drug therapy was ultimately discontinued due to lack of efficacy. The patient subsequently developed septic shock and was treated with multiple antibacterial and cardiotonic therapies (including dobutamine).

- By the EFU visit, the LFTs had decreased and the patient no longer met Hy's rule.

Table 46: Laboratory Values

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-08	43104023	Baseline	0.47	25	23	69
		Day 2	0.47	26	23	68
		Day 5	0.96	1759	950	92
		Day 8	1.62	267	43	76
		Day 11	2.31	150	46	112

MO Comments: The first two cases in the DORI-08 study had abnormal lab values at baseline and improving levels while on therapy. The etiology of the hepatitis in patient 3850409 is unclear. He had received 4 days of IV doripenem, followed by 7 days of oral amoxicillin clavulanate without an elevation in his LFTs. While possible, it is unlikely that the hepatitis was due to doripenem given that the levels of transaminases and bilirubin decreased while on therapy. In the last case, the improvement in liver function tests with continued exposure to doripenem suggests that the drug did not have a contributory role in causing the elevated test values.

3) Other Chemistry Parameters

- In cIAI groups, there was an increase in total protein from baseline to the LFU visit in both treatment groups.
- For the pooled cIAI studies, a blood CPK increase was reported as an AE for 2.3% of subjects in the doripenem group and 1.3% of subjects in the meropenem group.
- Mean CPK, however, decreased from baseline to the LFU visit in both treatment groups. In the doripenem, mean CPK values decreased from 239.9 IU/L at baseline to 62.8 IU/L at the LFU visit. In the meropenem group, CPK decreased from 198.8 IU/L to 73.6 IU/L at the LFU visit.
- When creatinine was analyzed by shift tables: there were 0 subjects in doripenem and 1 subject in meropenem with a Grade 4 shift.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

Vital signs (oral temperature [or equivalent], blood pressure, pulse, and respiration rate) were measured at screening, daily while the patient was receiving IV study drug therapy, and at the EOT (IV), EFU, and TOC visits. Height and weight were measured at screening only.
• There were no notable changes from baseline in mean values for systolic and diastolic blood pressure
• Consistent with recovery from active infections, mean pulse rates, respiration rates, and oral temperatures decreased from baseline values across all treatment groups.

7.1.7.2 Additional analyses and explorations

No additional analysis of vital signs data was performed.

7.1.8 Electrocardiograms (ECGs)

The protocol specified that one baseline ECG was to be administered anytime prior to administration of the first dose of study drug and as medically indicated thereafter. Two copies of each ECG were to be included in the patient's case report form.

In the Phase 3 cIAI studies, ECG data were collected routinely at the Screening Visit only. All events of ventricular arrhythmia were reported.

7.1.8.1 Overview of ECG testing in the development program, including brief review of preclinical results

- In pre-clinical studies, doripenem exhibited no cardiovascular toxicity.
- The negative results of a thorough QT/QTc study designed in accordance with the ICH E14 Guideline supports the cardiac safety of doripenem in healthy subjects.

- Please refer to QT study report by IRT (Interdisciplinary Review Team).

7.1.8.2 Standard analyses and explorations of ECG data

In DORI-08, two subjects in the meropenem treatment arm experienced multiple episodes of ventricular arrhythmia (VA), (i.e. ventricular fibrillation and ventricular tachycardia). No doripenem treated patients had ventricular fibrillation or ventricular tachycardia in either of the cIAI studies.

- Subject 01102516 a 69-year-old woman, experienced three episodes of moderate ventricular tachycardia on Days 2, 5, and 7, which all resolved and were considered by the investigator as not related to treatment with study drug therapy. This patient had an underlying heart issues including an incomplete right bundle branch block and baseline sinus tachycardia. She did not complete the study due to protocol violations (i.e. not meeting the exclusion criteria: open abdominal procedure and history of septic shock prior to receiving study medication). She received only 2 doses of meropenem on study day 1.

- Subject 05401025, a 73-year-old woman, experienced on mild episode of ventricular tachycardia on Day 17, which resolved the same day and was considered by the investigator as not related to treatment with study drug therapy. She withdrew from the study after receiving only 2 doses of meropenem on study day 1.

MO Comments: Subject 01102516 had not only underlying heart abnormalities at baseline, but was also in septic shock which could have been a factor in her arrhythmia. Subject 05401025 received only two doses of meropenem and received those 16 days prior to her singular episode of V-Tach. It is unlikely meropenem was related to there AEs.

7.1.9 Immunogenicity

There was no human immunogenicity data available.

7.1.10 Human Carcinogenicity

There was no human carcinogenicity studies conducted, in humans or animals.

7.1.11 Special Safety Studies

Please refer to the safety review by Dr. Alfred Sorbello, FDA Medical Officer.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

No analyses of withdrawal or rebound effects were performed

7.1.13 Human Reproduction and Pregnancy Data

There was an overall high rate of first trimester miscarriages in the Phase 3 studies. Seven of the 13 pregnancies occurring in all the pooled doripenem Phase 3 studies resulted in first trimester miscarriage/spontaneous abortion. Eight of the above 13 pregnancies occurred after administration of the last dose of study drug. Per the sponsor, given the short half life of doripenem, it is unlikely that it would have affected the outcomes of the pregnancies. Of the three pregnant women who conceived prior to the study and had known exposure to the study drug while pregnant, 2 had pregnancies resulting in spontaneous abortion.

Of the cIAI studies, only two women in DORI-07 study became pregnant in the doripenem treatment arm. One of these pregnancies resulted in a full-term healthy baby and the outcome of the second is unknown:

Subject 37704070 is a 35 year old who conceived prior to enrollment. Positive tests confirming her pregnancy were not available until after she received 2 doses of doripenem. Study drug was discontinued immediately. She delivered a healthy neonate at 39 weeks without obvious physical abnormalities.

Subject 40104066 is a 24 year old who conceived after study drug therapy was initiated. She also had a history of diabetes mellitus, which further increased her risk for adverse pregnancy outcome. The outcome of her pregnancy is unknown.

MO Comment: Although there were concomitant diagnoses that may have contributed to the high miscarriage rate, the safety of doripenem in pregnant women cannot be established at this time. The women also received comparator medications which to date have not been established as safe in pregnant women.

7.1.14 Assessment of Effect on Growth

Not applicable to this adult study which only enrolled patients over the age of 18.

7.1.15 Overdose Experience

No subjects received > 1g or a total daily dose > 3g which was considered a potential overdose. Therefore the effects of doripenem overdose in humans remains unknown.

7.1.16 Post marketing Experience

Doripenem has been studied by Shionogi in Japan in Phase 3 studies and is approved for the following specific cIAI indications: peritonitis, intraperitoneal abscess, cholecystitis, cholangitis, and hepatic abscess. The dosage is 250 mg IV over 30 – 60 minutes two to three times a day. Duration of treatment is limited to the minimum period required for the treatment of the condition after susceptibility is confirmed.

The Applicant has submitted a report of post-marketing experience which included a cumulative review of the post-marketing experience based on a search of the company's worldwide safety database (SCEPTRE). The search included all spontaneously reported confirmed cases of adverse events reported as of August 31, 2006. There were 49 confirmed cases with doripenem as a suspect drug. Among the 49 cases, there were 29 (59%) serious cases and 20 (41%) non-serious cases. The patient demographics included 30 males, 18 females, and one patient whose gender was not known. The Applicant provided a review of the 49 cases and supports the inclusion of anaphylaxis as an adverse event in the post-marketing section of the product labeling. Although only one case of anaphylactoid reaction was reported, the case describes the event in sufficient detail to conclude that anaphylaxis may occur with the use of doripenem.

The Applicant has subsequently submitted a 4 month updated safety report that has been reviewed by Dr. Alfred Sorbello, FDA Medical Officer. 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.

7.2 Adequacy of Patient Exposure and Safety Assessments

- Within the context of adult patients with cIAI, IV doripenem followed by oral amoxicillin-clavulanate over a period of 14 days was adequate treatment for cIAI. Safety information is however limited as the proportion of patients treated with IV doripenem alone without an oral switch was small (N=74). Please see section 7.2.1.3.
- The exposure based on demographics appears adequate.
- Appropriate clinical tests, including physical exam, ECG, and serum laboratory assessments were carried out adequately.

MO Comment: The majority of patients were switched from IV doripenem to oral amoxicillin-clavulanate, limiting the total time of IV doripenem. The mean exposure of IV treatment in patients eventually switched to an oral medication was 5.8 days (Range 3-13 days). In patients who received only IV doripenem, the mean duration of treatment was 9.6 days (Range 5-16 days). There is potential for more AEs that may manifest with a longer duration of therapy (> 10 days).

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

DORI-07 and DORI-08 were multi-center, randomized, double-blind, double-dummy studies comparing the efficacy of doripenem with that of meropenem in men and women 18 years of age and older with cIAI. Subjects received either doripenem 500 mg as an IV infusion over 1 hour every 8 hours or meropenem 1g as an IV bolus over 3-5minutes every 8 hours for a minimum of 5 (IV alone or IV plus oral) and a maximum of 14 days.

After ≥ 9 doses of IV study drug therapy, patients could have been switched to oral amoxicillin-clavulanate tablets (875mg/125mg PO q12h). The total duration of IV and oral antibiotic therapy was 5 -14 days. The study provided adequate patient exposure and safety assessments for the cIAI indication. The safety analysis included all patients who received at least one dose of study drug. In the combined studies, there were 477 patients who received at least one dose of doripenem and 469 patients who received at least one dose of IV meropenem.

Safety was assessed through the monitoring of AEs, the recording of possible allergic reactions and study drug intolerability, and the collection of conventional laboratory data (chemistry panel, CBC with differential and platelets, and urinalysis). All data were assessed for severity, changes from baseline, outcome, and relationship to treatment with study drug therapy. The tolerability of doses was assessed concurrently with study drug administration, and during the follow-up period.

Please refer to Section 4.2 for a tabular listing and description of the studies conducted.

7.2.1.2 Demographics

Demographic characteristics for patients in the ME at TOC analysis set in Studies DORI-07 and DORI-08 showed that the majority of patients were: Caucasian (68% and 83%, respectively) and male (63% and 64%, respectively). The median ages of study subjects (46 years in DORI-07 and 44 years in DORI-08) were similar between the two studies. Overall, the primary site of infection 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. 50% of who had generalized peritonitis at baseline. There were no noteworthy differences in demographic characteristics between treatment arms in either study except for a higher percentage of Caucasian subjects overall in Study DORI-08 (83%) compared with DORI-07 (68%). Please refer to Tables 10 and Table 11 under Section 6.1.4.1 for full demographic information for Phase 3 cIAI studies.

7.2.1.3 Extent of exposure (dose/duration)

In this trial, 325 patients in the ME at TOC analysis set received IV doripenem [mean = 10.7 days], of which, 251 patients were switched to oral antibiotic therapy [mean = 5.8 days]. The remaining 74 patients received IV therapy alone [mean = 9.6 days). 309 patients received IV meropenem [10.7 days]: 233 were switched to oral antibiotic therapy [mean = 5.7 days] and 86 were treated with IV therapy alone [mean = 9.2 days]. Please refer to Table 14 under section 6.1.4.6.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

For the indication of cIAI, data from DORI-07 and DORI-08 studies were pooled. No other studies were conducted.

7.2.2.2 Post marketing experience

Please refer to section 7.1.16 of this review for further information on post-marketing experience with doripenem.

7.2.2.3 Literature

Please refer to Section 8.6 for literature review

7.2.3 Adequacy of Overall Clinical Experience

Within the context of adult patients with cIAI, IV doripenem followed by oral amoxicillin-clavulanate over a period of 14 days was adequate treatment for cIAI. Safety information is however limited as the proportion of patients treated with IV doripenem alone without an oral switch was small.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal toxicity data and assays for mutagenicity potential were included in the IND submissions (IND 64,416). Please see the reviews by Dr. Amy C. Nostrandt, D.V.M., Ph.D., dated January 22, 2003 and June 27, 2003.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of patients with regard to monitoring vital signs, laboratory testing, and observation of adverse events were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to Clinical Pharmacology Review by Dr. Sarah Robertson.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant adequately evaluated patients for potential drug class-related adverse events, including, but not limited to observing for episodes of seizure, allergies, worsening of renal function, hepatotoxicity, and neutropenia.

MO Comment: We will need to follow up with the Sponsor's planned valproate interaction study.

7.2.8 Assessment of Quality and Completeness of Data

The data available were adequate for conducting the safety review for doripenem.

7.2.9 Additional Submissions, Including Safety Update

The Applicant has submitted a 4-month safety update with data from nosocomial pneumonia studies and additional post-marketing data. Please refer to Dr. Fred Sorbello's Safety Review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

After reviewing the data, the following safety conclusions can be drawn from the two studies in patients with cIAI:

- Doripenem appears to generally safe and well tolerated by patients aged 18 years or older with cIAI.
- Death was seen in 2.7% of the subjects in the doripenem group, and 3.9% in the meropenem group. No death was considered to have been related to the study drug therapy.
- Treatment-emergent serious adverse events were reported in 10.4% of patients in the doripenem treatment arm and 16.2% of patients in the meropenem treatment arm.

- The most frequently reported TEAEs overall (reported in at least 1% of patients in either treatment arm) were sepsis, abdominal abscess, myocardial infarction, peritonitis, and pleural effusion.
- Treatment-emergent adverse events leading to study drug therapy discontinuation in patients who discontinued IV therapy was 4.6% of patients in the doripenem arm and 2.8% of patients in the meropenem treatment arm.
- The most commonly reported TEAEs in both groups were within the GI system organ class. Nausea (11.9% and 9.4%), and diarrhea (10.7% and 11.1%) were the most common in doripenem and meropenem respectively. Anemia was reported for 9.6% of subjects in the doripenem group and 5.5% in the meropenem group.
- Evaluation of changes in ALT and AST revealed that the doripenem treatment group had comparable or lower rates of increase of these enzymes compared with the meropenem treatment group. The percent of subjects meeting the criteria for HHR classification at any time point was similar in the doripenem group (0.4%) than the meropenem group (0.5%); all subjects had confounding medical events that could have contributed to the observed hepatobiliary findings.
- Although seizures are a carbapenem class warning, no seizures were reported in patients treated with doripenem.
- Only one woman had conceived prior to doripenem exposure. The outcome of this pregnancy was a full term healthy infant. The other women conceived after study drug therapy was initiated, and the outcome of her pregnancy is unknown.
- Overall, no unexpected clinically significant changes in vital sign measurements or ECG parameters were observed. There were no QT_C changes associated with doripenem therapy.
- The limitations to the safety of the study include:
    - The higher rates of anemia in the doripenem arm which cannot be explained by post-op blood loss alone. There was no laboratory work up done to assess for the possibility of a drug induced hemolytic anemia. We are currently awaiting a hematology consult.
    - 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 safety 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.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

The Phase 3 efficacy studies (DORI-07 and DORI-08) used identical study designs, so the pooled data was used for analysis.

7.4.2 Explorations for Predictive Factors

• No important differences in the AE profile of doripenem were observed that warrant special precautions for its use with respect to age, sex, or race.
• Dose adjustment of doripenem is required in subjects with moderate (CrCl: 30-50 ml/min) and severe renal impairment (CrCl 10-29 ml/min) to 250mg q8 hours and 250mg q12 hours respectively. Per the sponsor, after such adjustments, the exposure is expected to be similar regardless of renal function and thus the safety profile does not pose an additional safety risk.
• Higher rates of TEAEs were reported in subjects with Child-Pugh scores ≥7 in both treatment groups. Pleural effusion, tachycardia, and tachypnea were reported at higher rates in subjects in both treatment groups with hepatic impairment compared with subjects with normal hepatic function. A greater difference in the rates of these events in subjects with hepatic impairment versus those with normal hepatic function was seen in doripenem treated subjects than meropenem-treated subjects.

7.4.2.1 Explorations for dose dependency for adverse findings

No dose ranging studies were conducted for the cIAI

7.4.2.2 Explorations for drug-demographic interactions

No differences in AEs by age, or sex was noted

7.4.2.3 Explorations for drug-drug interactions

Co-administration of carbapenem antibiotics has been shown to decrease valproic acid levels in serum. Doripenem was shown to increase clearance of sodium valproate in one animal model. We are currently awaiting the planned valproic acid study.

Other possible drug interactions include a contraindication to concomitant administration with probenecid. Probenecid inhibits the tubular excretion of doripenem resulting in a significant increase of serum doripenem levels.

10 APPENDICES

10.1 Review of Individual Study Report

Protocol:
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), although they were conducted at different investigational sites by different investigators. Please refer to Section 6.1.3.1 for the full protocol.

Amendments:
Both DORI-07 and DORI -08 had similar amendment changes. Please refer to Section 6.1.3.8 for those changes.

Post Hoc Changes:
The changes to DORI-07 and DORI -08 were similar. The post-hoc changes made included expanding the follow–up visiting period to up to 60 days, and increasing the sample size population to a target of 236 patients per treatment arm.

Important efficacy and safety results for the individual studies are presented in the following sections:

10.1.1 DORI-07

Efficacy: Table 1 summarizes disposition for all randomized patients. Overall, more patients in the doripenem arm completed study compared to the meropenem arm.

Table 1: Disposition of all Randomized Pateints

	Doripenem	Meropenem	Total
Randomized Patients	237	239	476
Randomized but Not Treated	2 (0.8%)	3 (1.3%)	5 (1.1%)
Patients Who Completed Study	213 (89.9%)	201 (84.1%)	414 (87.0%)
Treated with IV Therapy Only	69 (29.1%)	65 (27.2%)	134 (28.2%)
Treated with IV and Oral Therapy	144 (60.8%)	136 (56.9%)	280 (58.8%)
ME at TOC Treated with IV Therapy Only	45 (19.0%)	53 (22.2%)	98 (20.6%)
ME at TOC Treated with IV and Oral Therapy	118 (49.8%)	103 (43.1%)	221 (46.4%)
Patients Who Did Not Complete Study	24 (10.1%)	38 (15.9%)	62 (13.0%)
And Did Not Receive Study Therapy	2 (0.8%)	3 (1.3%)	5 (1.1%)
And Did Not Complete Study Therapy	14 (5.9%)	20 (8.4%)	34 (7.1%)
Did Not Complete IV Therapy	12 (5.1%)	16 (6.7%)	28 (5.9%)

Table 1: Disposition (All Randomized Patients) continued

	Doripenem	Meropenem	Total
Completed IV But Not Oral Therapy	1 (0.4%)	4 (1.7%)	5 (1.1%)
And Completed Study Therapy	8 (3.4%)	15 (6.3%)	23 (4.8%)
Discontinued from Study Early and Completed TOC Assessment	14 (5.9%)	21 (8.8%)	35 (7.4%)
Follow-up Visits Completed			
Had EFU and TOC	219 (92.4%)	219 (91.6%)	438 (92.0%)
Had EFU but Not TOC	2 (0.8%)	9 (3.8%)	11 (2.3%)
Not EFU nor TOC	8 (3.4%)	8 (3.3%)	16 (3.4%)
Not EFU, but Completed TOC	8 (3.4%)	3 (1.3%)	11 (2.3%)

Table 8 from DORI-07 CSR
Note: Percentages were based on the number of patients randomly assigned to each treatment arm.

- Table 2 summarizes the demographics for patients in DORI-07

Table 2: Demographics (ME at TOC Analysis Set)

	Doripenem (N=163)	Meropenem (N=156)	Total (N=319)
Sex			
Male	106 (65.0%)	94 (60.3%)	200 (62.7%)
Female	57 (35.0%)	62 (39.7%)	119 (37.3%)
Race[a]			
Asian	1 (0.6%)	2 (1.3%)	3 (0.9%)
Black or African Heritage	14 (8.6%)	10 (6.4%)	24 (7.5%)
Caucasian	109 (66.9%)	107 (68.6%)	216 (67.7%)
Hispanic or Latino	39 (23.9%)	37 (23.7%)	76 (23.8%)
Age (years)			
Mean (SD)	46.9 (18.12)	46.4 (17.51)	46.7 (17.80)
Min, Max	18, 93	18, 84	18, 93
Age Categories (years)			
18-44	76 (46.6%)	79 (50.6%)	155 (48.6%)
45-74	76 (46.6%)	65 (41.7%)	141 (44.2%)
< 65	135 (82.8%)	127 (81.4%)	262 (82.1%)
≥ 65	28 (17.2%)	29 (18.6%)	57 (17.9%)
< 75	152 (93.3%)	144 (92.3%)	296 (92.8%)
≥ 75	11 (6.7%)	12 (7.7%)	23 (7.2%)
Height (cm)			
Mean (SD)	170.7 (9.80)	169.2 (9.55)	170.0 (9.70)
Min, Max	150, 196	145, 194	145, 196
Weight (kg)			
Mean (SD)	76.6 (17.04)	77.9 (18.12)	77.2 (17.56)
Median	75.0	74.9	75.0
Min, Max	38.6, 135.5	40.0, 160.0	38.6, 160.0
Region			
North America	42 (25.8%)	48 (30.8%)	90 (28.2%)
South America	81 (49.7%)	67 (42.9%)	148 (46.4%)
Europe	40 (24.5%)	41 (26.3%)	81 (25.4%)

Modified Table 11 from DORI-07 CSR;
Min = minimum; Max = maximum; N = number of patients in the analysis set; SD = standard deviation.
Note: Percentages were based on the number of patients in the given analysis set for each treatment arm. [a] Mixed race was included as "Other."

- Baseline Characteristics for the patients are summarized in Table 3.

Table 3: Baseline Characteristics: (ME at TOC Analysis Set)

	Doripenem (N=163)	Meropenem (N=156)	Total (N=319)
APACHE II Score[c]			
≤ 10	148 (90.8%)	143 (91.7%)	291 (91.2%)
> 10	15 (9.2%)	13 (8.3%)	28 (8.8%)
IVRS Randomization Stratum[d]			
Appendicitis	55 (33.7%)	61 (39.1%)	116 (36.4%)
Other	108 (66.3%)	95 (60.9%)	203 (63.6%)
Anatomic Site[e]			
Biliary-Cholecystitis	11 (6.7%)	11 (7.1%)	22 (6.9%)
Appendix	100 (61.3%)	91 (58.3%)	191 (59.9%)
Colon	32 (19.6%)	32 (20.5%)	64 (20.1%)
Other	20 (12.4.%)	22 (14.1%)	42 (13.1%)
Infectious Process			
Generalized Peritonitis	74 (45.4%)	53 (34.0%)	127 (39.8%)
Single Abscess (with Visceral Perforation)	44 (27.0%)	41 (26.3%)	85 (26.6%)
Localized Infection (with Localized Peritonitis)	38 (23.3%)	54 (34.6%)	92 (28.8%)
Other	7 (4.2%)	8 (5.1%)	15 (4.7%)
Appendix (Anatomic Site) + Generalized Peritonitis	54 (33.1%)	35 (22.4%)	89 (27.9%)
Appendix (Anatomic Site) + Non-generalized Peritonitis	46 (28.2%)	56 (35.9%)	102 (32.0%)
Post-Operative Infection?			
Yes	21 (12.9%)	10 (6.4%)	31 (9.7%)
No	142 (87.1%)	146 (93.6%)	288 (90.3%)
Abdominal Procedure Type[e]			
Percutaneous	18 (11.0%)	17 (10.9%)	35 (11.0%)
Laparoscopy	16 (9.8%)	14 (9.0%)	30 (9.4%)
Open Laparotomy	128 (78.5%)	127 (81.4%)	255 (79.9%)
Other	2 (1.2%)	2 (1.3%)	4 (1.3%)
Bacteremia	4 (2.5%)	8 (5.1%)	12 (3.8%)
Baseline Renal Function			
Calculated Creatinine Clearance (mL/min)[f]			
Normal (80 and above)	122 (74.8%)	124 (79.5%)	246 (77.1%)
Mild Failure (50-80)	34 (20.9%)	23 (14.7%)	57 (17.9%)
Moderate Failure (30-50)	4 (2.5%)	8 (5.1%)	12 (3.8%)
Severe Failure (at most 30)	3 (1.8%)	1 (0.6%)	4 (1.3%)

Modified Table 11 from DORI-07 CSR
APACHE II = Acute Physiology and Chronic Health Evaluation II; IVRS = Interactive Voice Response System; Min = minimum; Max = maximum; N = number of patients in the analysis set; SD = standard deviation.
Note: Percentages were based on the number of patients in the given analysis set for each treatment arm. Baseline value was defined as the last available value before the start of infusion of the first dose of study drug therapy.
[a] Mixed race was included as "Other." [b] Body Mass Index = weight (kg)/height (m)2.; [c] The APACHE II score for patients who were incorrectly stratified in IVRS was tabulated according to the correct stratum; [d] The primary site of infection (Appendix versus Other) for patients who were incorrectly stratified was tabulated according to the correct stratum.; [e] Patients may have had more than 1 anatomic site and type of abdominal procedure; [f] Creatinine clearance was calculated using the Cockroft-Gault formula and the patient's actual body weight.

- Efficacy:

Primary Endpoint: Success rates were similar in the two treatment arms and non-inferiority of doripenem was demonstrated as evidenced by lower bound of 95% CI > -15% which includes a value of 0. Table 4 summarizes clinical success in the co-primary populations:

Table 4: Clinical Cure Rates at the TOC Visit (ME at TOC and mMITT Analysis Sets)

Analysis Set	Doripenem	Meropenem	Difference (2-sided 95% CI[a])
ME at TOC	140/163 (85.9%)	133/156 (85.3%)	0.6% (-7.7%, 9.0%)
mMITT	152/195 (77.9%)	150/190 (78.9%)	-1.0% (-9.7%, .7%)

Table 13 from DORI-07 CSR
CI = confidence interval;
analysis set; ME = microbiologically evaluable; TOC = test-of-cure visit.
[a] The 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions.

Secondary Endpoints: The following table summarizes clinical success in the secondary endpoints.

Table 5: Favorable Clinical Outcomes by Visit and Analysis Set

Visit Analysis Set	Doripenem n Favorable/N (%)	Meropenem n Favorable/N (%)	Difference in %
TOC			
CE at TOC	163/188 (86.7%)	161/186 (86.6%)	0.1%
cMITT	178/226 (78.8%)	183/228 (80.3%)	-1.5%

Modified Table 16 from DORI- 07 CSR
n = number of patients who had a favorable clinical response at that time point in that analysis set; N = all patients in the analysis set at that time point; TOC = test-of-cure visit
[a] Favorable clinical outcomes at the EOT(IV) visit included clinical cure and clinical improvement, whereas the favorable clinical outcome at the EFU and TOC visits was clinical cure.

Additional Analyses: For analyses based on subgroups, and sensitivity analyses please see integrated review in Section 6.

- Safety:

Table 6 below demonstrates an overview of the safety profile, including deaths and adverse events.

Table 6: Overview of Safety (Intent-to-Treat Analysis Set)

Category[a]	Doripenem (N=235)	Meropenem (N=236)
Number (%) of Patients with at Least 1 TEAE[b]	195 (83.0%)	184 (78.0%)
Number (%) of Patients with at Least 1 TEAE Related to Study Drug (including possibly or probably related)	76 (32.3%)	63 (26.7%)
Number (%) of Patients with at Least 1 TESAE	31 (13.2%)	33 (14.0%)
Number (%) of Patients with at Least 1 TESAE Related to Study Drug (including possibly or probably related)	0	0
Number (%) of Patients Who Discontinued Study Drug Therapy or the Study due to Adverse Events[c]	12 (5.1%)	5 (2.1%)
Number (%) of Patients Who Discontinued IV Therapy	5 (2.1%)	3 (1.3%)
Number (%) of Patients Who Discontinued Oral Therapy	3 (1.3%)	0
Number (%) of Patients with AEs Leading to Death	5 (2.1%)	7 (3.0%)

Table 20 from DORI-07 CSR
IV = intravenous; N = number of patients in the analysis set.
a Patients could have been included in more than 1 category.
b All adverse events summarized were treatment-emergent adverse events.
c Patients may have completed IV and oral study drug therapy but discontinued prematurely from the study due to an adverse event.

Overall, the mortality rate was 3% and was comparable between the doripenem and the meropenem treatment arms (5 and 7 patients, respectively); no treatment-emergent SAE resulting in death was considered related to study drug therapy. See Section 7.1.1 for individual summaries of patients who died.

Overall, 14% of ITT patients experienced treatment-emergent SAEs. The incidence of treatment-emergent serious adverse events was similar in both treatment arms (31, doripenem; 33, meropenem). The most frequently reported serious adverse events were in the infections and infestations and GI 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. A total of 11 (5%) doripenem-treated patients and 19 (8%) meropenem-treated ITT patients experienced serious adverse events with onset during IV study drug therapy.

Two doripenem-treated patients with elevated ALT values met the definition of Hy's High Risk (HHR) classification while on study medication.

A total of 12 (5%) and 5 (2%) patients in the doripenem and meropenem treatment arms, respectively, were discontinued prematurely from study drug therapy due to an adverse event. Five of the 12 doripenem-treated patients discontinued study drug therapy due to a study drug related adverse event compared with 3 of the 5 meropenem-treated patients. For both treatment arms, most of the study drug related treatment-emergent adverse events leading to premature study drug therapy included vomiting, dyspepsia, stomatitis, and diarrhea. One patient in each

treatment arm prematurely discontinued study drug therapy due to study drug-related nausea. In both treatment arms, these GI adverse events mostly represented complications of the underlying infection.

10.1.2 DORI-08

Efficacy: Table 7 summarizes disposition for all randomized patients. Overall, slightly more patients in the meropenem arm completed the study compared to the doripenem arm.

- Disposition:

A total of 44 centers (21 in the United States, 10 in Europe, 10 in South America, and 3 in Canada) randomized a total of 486 patients in this study. The table below summarizes the disposition of all randomized patients in this study. Two hundred forty-two of the 249 patients randomly assigned to the doripenem treatment arm received study drug and comprise the ITT analysis set for the doripenem treatment arm; 233 of the 237 patients randomly assigned to the meropenem treatment arm received study drug and were included in the ITT analysis set.

Table 7: Disposition (All Randomized Patients)

	Doripenem	Meropenem	Total
Randomized Patients	249[a]	237	486
Randomized but Not Treated	7 (2.8%)	4 (1.7%)	11 (2.3%)
Patients Who Completed Study	208 (83.5%)	204 (86.1%)	412 (84.8%)
Treated with IV Therapy Only	46 (18.5%)	49 (20.7%)	95 (19.5%)
Treated with IV and Oral Therapy	162 (65.1%)	155 (65.4%)	317 (65.2%)
ME at TOC Treated with IV Therapy Only	32 (12.9%)	33 (13.9%)	65 (13.4%)
ME at TOC Treated with IV and Oral Therapy	130 (52.2%)	120 (50.6%)	250 (51.4%)
Patients Who Did Not Complete Study	41 (16.5%)	33 (13.9%)	74 (15.2%)
And Did Not Receive Study Therapy	7 (2.8%)	4 (1.7%)	11 (2.3%)
And Did Not Complete Study Therapy	17 (6.8%)	20 (8.4%)	37 (7.6%)
Did Not Complete IV Therapy	16 (6.4%)	19 (8.0%)	35 (7.2%)
Completed IV But Not Oral Therapy	1 (0.4%)	1 (0.4%)	2 (0.4%)
And Completed Study Therapy	17 (6.8%)	9 (3.8%)	26 (5.3%)
Discontinued from Study Early and Completed TOC Assessment	12 (4.8%)	10 (4.2%)	22 (4.5%)
Follow-up Visits Completed			
Had EFU and TOC	213 (85.5%)	208 (87.8%)	421 (86.6%)
Had EFU but Not TOC	9 (3.6%)	2 (0.8%)	11 (2.3%)
Not EFU nor TOC	20 (8.0%)	21 (8.9%)	41 (8.4%)
Not EFU, but Completed TOC	7 (2.8%)	6 (2.5%)	13 (2.7%)

Table 8 from DORI-08 CSR
Percentages were based on the number of patients randomized to each treatment arm. Eleven patients were randomly assigned but did not receive study drug therapy. These patients were excluded from all analyses and analysis sets. [a] Patient 428/04109 who was randomly assigned to the meropenem treatment arm but received doripenem for all doses of IV study drug therapy. In an additional analysis, this patient was included in the doripenem treatment arm.

Demographics: Table 8 shows the demographics for the patients in DORI-08.

Table 8: Demographics (ME at TOC Analysis Set)

Category		Doripenem (N=162)	Meropenem (N=153)	Total (N=315)
Sex				
	Male	104 (64.2%)	98 (64.1%)	202 (64.1%)
	Female	58 (35.8%)	55 (35.9%)	113 (35.9%)
Race[a]				
	American Indian or Alaska Native	3 (1.9%)	0	3 (1.0%)
	Asian	1 (0.6%)	1 (0.7%)	2 (0.6%)
	Black or African Heritage	3 (1.9%)	2 (1.3%)	5 (1.6%)
	Caucasian	128 (79.0%)	132 (86.3%)	260 (82.5%)
	Hispanic or Latino	26 (16.0%)	17 (11.1%)	43 (13.7%)
	Other	1 (0.6%)	1 (0.7%)	2 (0.6%)
Age (years)				
	Mean (SD)	44.7 (17.32)	44.8 (17.22)	44.8 (17.24)
	Median	43.5	45.0	44.0
	Min, Max	18, 94	19, 86	18, 94
Age Categories (years)				
	18-44	84 (51.9%)	75 (49.0%)	159 (50.5%)
	45-74	71 (43.8%)	71 (46.4%)	142 (45.1%)
	< 65	137 (84.6%)	129 (84.3%)	266 (84.4%)
	≥ 65	25 (15.4%)	24 (15.7%)	49 (15.6%)
	< 75	155 (95.7%)	146 (95.4%)	301 (95.6%)
	≥ 75	7 (4.3%)	7 (4.6%)	14 (4.4%)
Height (cm)				
	Mean (SD)	169.9 (8.95)	170.5 (9.59)	170.2 (9.25)
	Median	170.0	170.0	170.0
	Min, Max	148, 190	152, 196	148, 196
Weight (kg)				
	Mean (SD)	76.8 (19.22)	74.8 (14.19)	75.8 (16.97)
	Median	73.0	75.9	74.6
	Min, Max	42.0, 165.0	45.5, 130.0	42.0, 165.0
Region				
	North America	48 (29.6%)	41 (26.8%)	89 (28.3%)
	South America	85 (52.5%)	81 (52.9%)	166 (52.7%)
	Europe	29 (17.9%)	31 (20.3%)	60 (19.0%)

Table 11 from DORI-08 CSR
[a] Mixed race was included as "Other."

- Baseline Characteristics

Table 9 demonstrates the baseline characteristics of the patients in DORI-08

Table 9: Baseline Characteristics (ME at TOC Analysis Set)

Category	Doripenem (N=162)	Meropenem (N=153)	Total (N=315)
APACHE II Score[a]			
≤ 10	142 (87.7%)	140 (91.5%)	282 (89.5%)
> 10	20 (12.3%)	13 (8.5%)	33 (10.5%)
IVRS Randomization Stratum[b]			
Appendicitis	57 (35.2%)	42 (27.5%)	99 (31.4%)
Other	105 (64.8%)	111 (72.5%)	216 (68.6%)
Anatomic Site[c]			
Appendix	103 (63.6%)	98 (64.1%)	201 (63.8%)
Colon	33 (20.4%)	30 (19.6%)	63 (20.0%)
Other	26 (16%)	25 (16.3%)	51 (16.2%)
Infectious Process			
Gen. Peritonitis	76 (46.9%)	81 (52.9%)	157 (49.8%)
Single Abscess (with Visceral Perforation)	33 (20.4%)	36 (23.5%)	69 (21.9%)
Localized Infection (with Localized Peritonitis)	46 (28.4%)	30 (19.6%)	76 (24.1%)
Other	7 (4.3%)	6 (3.9%)	13 (4.1%)
Appendix (Anatomic Site) + Generalized Peritonitis	50 (30.9%)	57 (37.3%)	107 (34.0%)
Appendix (Anatomic Site) + Non-generalized Peritonitis	53 (32.7%)	41 (26.8%)	94 (29.8%)
Post-Operative Infection?			
Yes	10 (6.2%)	12 (7.8%)	22 (7.0%)
No	152 (93.8%)	141 (92.2%)	293 (93.0%)
Abdominal Procedure Type[b]			
Percutaneous	12 (7.4%)	10 (6.5%)	22 (7.0%)
Laparoscopy	23 (14.2%)	15 (9.8%)	38 (12.1%)
Open Laparotomy	135 (83.3%)	129 (84.3%)	264 (83.8%)
Other	1 (0.6%)	3 (2.0%)	4 (1.3%)
Bacteremia	10 (6.2%)	15 (9.8%)	25 (7.9%)
Baseline Renal Function Calculated CrCl (mL/min)[c]			
Normal (80 and above)	123 (75.9%)	109 (71.2%)	232 (73.7%)
Mild Failure (50-80)	24 (14.8%)	29 (19.0%)	53 (16.8%)
Moderate Failure (30-50)	11 (6.8%)	9 (5.9%)	20 (6.3%)
Severe Failure (at most 30)	4 (2.5%)	6 (3.9%)	10 (3.2%)

Table 11 from DORI-08 CSR;
APACHE II = Acute Physiology and Chronic Health Evaluation II; IVRS = Interactive Voice Response System; Min = minimum; Max = maximum; N = number of patients in the analysis set; SD = standard deviation.
Note: Percentages were based on the number of patients in the given analysis set for each treatment arm. Baseline value was defined as the last available value before the start of infusion of the first dose of study drug therapy.
[a] The APACHE II score for patients who were incorrectly stratified in IVRS was tabulated according to the correct stratum.; [b] Patients may have had more than 1 anatomic site and type of abdominal procedure; [c]Creatinine clearance was calculated using the Cockroft-Gault formula and the patient's actual body weight.

- Efficacy:

Primary Endpoints: Success rates were similar in the two treatment arms and non-inferiority of doripenem was demonstrated as evidenced by lower bound of 95% CI > -15% and include zero. The following table summarizes clinical success in the co-primary populations:

Table 10: Clinical Cure Rates at the TOC Visit ME at TOC and mMITT Analysis Sets

Analysis Set	Doripenem	Meropenem	Difference (2-sided 95% CI[a])
ME at TOC	135/162 (83.3%)	127/153 (83.0%)	0.3% (-8.6%, 9.2%)
mMITT	149/200 (74.5%)	140/185 (75.7%)	-1.2% (-10.3%, 8.0%)

Table 13 from DORI-08 CSR
a The 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions.

The clinical cure rates in the ME at TOC analysis set were 83.3% in the doripenem treatment arm and 83.0% in the meropenem treatment arm. The difference between the clinical cure rates (doripenem minus meropenem) was 0.3%, with a 2-sided 95% CI of -8.6% to 9.2%. The lower bound of the CI around the difference exceeded the pre-specified non-inferiority margin of -15%, indicating that doripenem was non-inferior to meropenem in the treatment of IAI. In the mMITT analysis set clinical cure rates of 74.5 and 75.7% were observed in the doripenem and meropenem treatment arms, respectively. The difference between the cure rates (doripenem minus meropenem) was -1.2%, with a 2-sided 95% CI of -10.3% to 8.0%. The result from this co-primary analysis set was consistent with that from the ME at TOC analysis set.

Secondary Endpoints: The following table summarizes clinical success in the secondary endpoints:

Table 11: Favorable Clinical Outcomes by Visit and Analysis Set

Analysis Set	Doripenem n Favorable/N (%)	Meropenem n Favorable/N (%)	Difference in %
TOC			
CE at TOC	161/192 (83.9%)	165/192 (85.9%)	-2.1%
cMITT	177/239 (74.1%)	177/226 (78.3%)	-4.3%

Table 16 from DORI-08 CSR
CE = clinically evaluable; cMITT = clinical modified intent-to-treat; CR_1_mMITT = Clinical Response Definition_1 for the microbiological MITT (mMITT) analysis set; CR_2_mMITT = Clinical Response Definition_2 for the mMITT analysis set; EFU = early follow-up visit; EOT(IV) = end of intravenous study drug therapy; ME = microbiologically evaluable; n = number of patients who had a favorable clinical response at that time point in that analysis set; N = all patients in the analysis set at that time point; TOC = test -of-cure visit.

The secondary efficacy analyses showed favorable clinical responses comparable between the 2 treatment arms and support the conclusions drawn from the primary efficacy analyses. In particular, both study drug therapies exhibited clinical cure/improvement rates greater than 90% at the EOT(IV) visit.

- **Safety:**

Table 12 below demonstrates an overview of the safety profile, including deaths and adverse events.

Table 12: Overview of Safety (Intent-to-Treat Analysis Set)

Category[a]	Doripenem (N=242)	Meropenem (N=233)
Number (%) of Patients with at Least 1 TEAE[b]	162 (66.9%)	142 (60.9%)
Number (%) of Patients with at Least 1 TEAE Related to Study Drug (including possibly or probably related)	37 (15.3%)	47 (20.2%)
Number (%) of Patients with at Least 1 TESAE	41 (16.9%)	44 (18.9%)
Number (%) of Patients with at Least 1 TESAE Related to Study Drug (including possibly or probably related)	0	0
Number (%) of Patients Who Discontinued Study Drug Therapy or the Study due to Adverse Events[c]	10 (4.1%)	8 (3.4%)
Number (%) of Patients Who Discontinued IV Therapy	7 (2.9%)	7 (3.0%)
Number (%) of Patients Who Discontinued Oral Therapy	3 (1.2%)	1 (0.4%)
Number (%) of Patients with AEs Leading to Death	8 (3.3%)	11 (4.7%)

IV = intravenous; N = number of patients in the analysis set.
[a] Patients could have been included in more than 1 category; [b] All adverse events summarized were treatment-emergent adverse events.
[c] Patients may have completed IV and oral study drug therapy but discontinued prematurely from the study due to an adverse event.

Overall, the mortality rate was 3.3% and was comparable between the doripenem and the meropenem treatment arms (8 and 11 patients, respectively); no treatment-emergent serious adverse event resulting in death was considered related to study drug therapy. See Section 7.1.1 for individual summaries.

Overall, 16.9% of ITT patients experienced treatment-emergent serious adverse events. The incidence of treatment-emergent serious adverse events was similar in both treatment arms (41, doripenem; 44, meropenem). The number of patients with any treatment-emergent adverse event or any study drug related treatment-emergent adverse event was 67 and 15%, respectively in the doripenem treatment arm compared with 61 and 20%, respectively in the meropenem treatment arm. Ten and eight patients in the doripenem and meropenem treatment arms, respectively, discontinued study drug therapy due to treatment-emergent adverse events, few of which were related to study drug therapy.

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 was prematurely discontinued due to nausea associated with dizziness, and 1 patient from each treatment arm was prematurely discontinued due to abdominal pain.

10.1.3 Summary

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%).

The clinical cure rate in the primary (ME at TOC) population was consistent in both studies with only a slightly higher rate in DORI-07. 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. 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 that doripenem is non-inferior to meropenem in the treatment of cIAI.

Although number of deaths was fairly similar between the two studies, there were a higher percentage of patients with a TEAE in the doripenem treatment group in DORI-07 (83%) than in DORI-08 (66.9%). In DORI-07 most of the study drug related treatment-emergent adverse events leading to premature study drug therapy included vomiting, dyspepsia, stomatitis, and diarrhea. In DORI -08 the most frequent study drug related treatment-emergent adverse event leading to premature study drug therapy discontinuation was pneumonia.

10.2 FDA Table on Re-Classified Subjects:

DORI-07 Patient ID	Planned Arm	Sponsor ME at TOC (SRP and Mis Rand)	FDA ME at TOC	Sponsor mMITT	FDA mMITT	Comments
04602510 20206503	Doripenem	Excluded	Failure	Failure	Failure	Death (3 days of study drug received)
40204519	Meropenem					
00102003 04701037 37204081	Doripenem	Excluded	Failure	Cure	Failure	M.O. Reclassification (Failure)
20406027	Meropenem					
00102068 01801503 10106030 10106040 37303004	Doripenem	Excluded	Excluded	Cure	Failure	M.O. Reclassification (mMITT Indeterminate)
37704068	Meropenem					
37104010	Meropenem	Included in Doripenem arm	Excluded	Cure (Doripenem)	Cure (Meropenem)	Patient Misrandomized (Received Doripenem)
18 Patients	Doripenem	Cure	Excluded	N/A	N/A	Patient Evaluated Outside of Allowable TOC Window
15 Patients	Meropenem	Cure	Excluded			
3 Patients	Meropenem	Failure	Excluded			

FDA Table on Re-Classified Subjects (continued)

DORI-08 Patient ID	Planned Arm	Sponsor ME at TOC (SRP and Mis Rand)	FDA ME at TOC	Sponsor mMITT	FDA mMITT	Comments
00502515 00502519 05402526 12606026	Doripenem	Excluded	Failure	Failure	Failure	Death (3 days of study drug received)
02202501 43004512 43104513	Meropenem	Excluded	Failure	Failure	Failure	
05402523	Doripenem	Excluded	Failure	Cure	Failure	
06012306	Doripenem	Excluded	Failure	Cure	Failure	M.O. Reclassification (Failure)
06001043 12606035 12606038	Doripenem	Excluded	Excluded	Cure	Failure	M.O. Reclassification (mMITT Indeterminate)
01102031 23006030 38503011	Meropenem	Excluded	Excluded	Cure	Failure	
42804109	Meropenem	Included in Doripenem arm	Excluded	Cure (Doripenem)	Cure (Meropenem)	Patient Misrandomized (Received Doripenem)
12 Patients	Doripenem	Cure	Excluded	N/A	N/A	Patient Evaluated Outside of Allowable TOC Window
3 Patients		Failure	Excluded			
8 Patients	Meropenem	Cure	Excluded			
3 Patients		Failure	Excluded			

2 Page(s) Withheld

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CLINICAL REVIEW

Application Type: NDA
Submission Number: 22,106
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Reviewer Name: Alfred Sorbello, DO, MPH
Through: Sumati Nambiar, MD, MPH (Team Leader)
Review Completion Date: October 4, 2007

Established Name: Doripenem
(Proposed) Trade Name: Doribax
Therapeutic Class: carbapenem
Applicant: Johnson & Johnson

Priority Designation: S

Formulation: Intravenous
Dosing Regimen: 500 mg every 8 hours
Indication: Complicated urinary tract infections and Complicated intra-abdominal infections
Intended Population: Adults

Table of Contents

List of Tables:

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Doripenem is an injectable, synthetic, broad-spectrum carbapenem in the beta-lactam (β-lactam) class of antibacterial agents. It binds to penicillin-binding proteins and inhibits cell wall synthesis in both gram-positive and gram-negative bacteria. This mode of action results in bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria commonly encountered in complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The drug's *in vitro* spectrum includes *E. coli*, other Enterobacteriaceae, and *B. fragilis*. Additional *in vitro* activity includes methicillin-susceptible staphylococci, streptococci, ampicillin-susceptible *Enterococcus faecalis*, *Pseudomonas aeruginosa*, ceftazidime-susceptible *Acinetobacter* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Clostridium* spp., and other gram-positive anaerobes. The drug has not been marketed in the United States, although it is marketed in Japan.

The Sponsor has conducted various phase 1 and 2 studies to provide data in support of four phase 3 clinical trials related to the use of doripenem in the treatment of adult patients with cUTI and cIAI. The cUTI efficacy and safety database consisted of one adequate and well-controlled Phase 3 clinical trial (DORI-05), one single arm, non-comparative Phase 3 clinical trial (DORI-06), and one Phase 2 study of doripenem in hospitalized subjects with cUTI (DORI-03). The cIAI efficacy and safety database consisted of two adequate and well-controlled clinical trials, DORI-07 and DORI-08. Based on the results of the Phase 3 clinical trials, doripenem 500 mg intravenously every 8 hours was demonstrated to be non-inferior to levofloxacin in the treatment of cUTI and non-inferior to meropenem in the treatment of cIAI.

The drug appears to be safe for its intended use. The most common adverse reactions attributable to doripenem were nausea, diarrhea, headache, rash, and phlebitis. Indication-specific differences in the incidence of certain treatment-emergent adverse events (TEAEs) were observed, involving asymptomatic bacteriuria, UTI, headache, and anemia. In addition, there was a relative imbalance in the number of renal failure/renal impairment-related TEAEs between the doripenem- and comparator-treated groups in the Phase 3 studies.

Based on evidence from the pivotal, comparative, controlled Phase 3 clinical trials conducted by the Sponsor, there is adequate efficacy and safety data to recommend approval of this new molecular entity for the indications of cUTI and cIAI in adult patients aged 18 years and older from a clinical perspective. The data are sufficient to provide adequate directions for use. The route of elimination is via renal excretion, and dose adjustment is necessary for patients with renal impairment.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The FDA Medical Officer recommends that the incidence of the following adverse events be monitored as part of a post-marketing surveillance program for the product:

- Anemia
- Renal Failure
- Seizure

1.2.2 Required Phase 4 Commitments

The FDA Medical Officer recommends

The FDA Medical Officer also recommends that the Sponsor conduct a study and analysis of doripenem-treated subjects for the development of hemolytic anemia, renal failure, and seizures, possibly in the form of a post-marketing patient registry.

1.2.3 Other Phase 4 Requests

The FDA Medical Officer does not have any additional phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

- Product name: Doripenem for Injection
- Drug class: carbapenem (beta-lacatam class of antibacterial agents)
- Route of administration: parenteral (intravenous only)
- Indications proposed by the Sponsor:
    - 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

including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii* and

- Populations studied: Doripenem was studied only in adult patients; no pediatric clinical studies have been conducted.
    - Phase 1 studies: Healthy adults, elderly adults, and adults with renal impairment were studied.
    - Phase 2 study: Adults with cUTIs were studied.
    - Phase 3 studies: Adults with cIAIs and cUTIs were studied.
- Number of pivotal efficacy and safety trials: There were four pivotal phase 3 clinical trials conducted by the sponsor: Studies DORI-05 and DORI-06 involved patients with cUTI. Studies DORI-07 and DORI-08 involved patients with cIAI. Three of the trials were randomized, controlled, comparative studies (DORI-05, DORI-07, and DORI-08), whereas the remaining trial was a single arm non-comparative study (DORI-06). Results of these four phase 3 clinical trials supported by the phase 1 and phase 2 studies were intended to demonstrate the efficacy and safety of doripenem in adults with the following infections:
    - Complicated urinary tract infections infections
    - Complicated intra-abdominal infections
- Number of patients enrolled in the primary trials: There were a total of 1,276 doripenem-treated and 841 comparator-treated (372 levofloxacin and 469 meropenem) patients in the pooled phase 3 doripenem trials in the intent-to-treat (ITT) population. In the cUTI studies, there were 376 doripenem-treated and 372 levofloxacin-treated subjects in DORI-5 and 423 doripenem-treated in DORI-06. There were a total of 477 doripenem-treated subjects and 469 meropenem-treated subjects in the combined cIAI studies.
- Overall number of patients and extent of exposure in the safety database: There were 216 patients enrolled in the pooled phase 1 studies, 121 in the single phase 2 study, and 2,117 in the four phase 3 studies (which involved 841 comparator-treated and 1,276 doripenem-treated subjects). Overall, the treatment exposure studied in the doripenem phase 3 clinical trials supports the durations of treatment recommended for each proposed indication by the Sponsor. However, there is very limited human safety data regarding doripenem administered for a treatment duration beyond 14 days, especially when the clinical evidence of exposure is restricted to the subgroup of subjects treated with intravenous (IV) doripenem without an oral (PO) switch
- Other clinical data sources: Potential sources of data for the review included foreign post-marketing safety data (the drug is marketed only in Japan), consultations with other Divisions within the Agency but outside of the primary review team, and case reports in the medical literature.

1.3.2 Efficacy

Complicated Urinary Tract Infections (cUTI):
The applicant completed one Phase II dose-finding study (DORI-03), one Phase III randomized, double-blind, comparative study (DORI-05), and one Phase III, open-label,

single arm study of doripenem (DORI-06). The first study, 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. The Applicant designed the cUTI development program to consist of one statistically adequate and well-controlled study establishing safety and efficacy in this indication (DORI-05) and a second non-comparative study (DORI-06) establishing statistical equivalence to the success rate of the approved agent in the first cUTI study. Thus, the levofloxacin treatment arm in DORI-05 was compared with the doripenem arm in DORI-06 to assess the comparability of efficacy, demographics and baseline characteristics, inclusion/exclusion criteria, and patient evaluability criteria.

Study DORI-05 was a multi-center, double-blind, randomized, Phase 3 study to compare the safety and efficacy of intravenous doripenem and levofloxacin in cUTI or pyelonephritis. The study was designed to compare a 1-hour IV infusion of doripenem (500 mg q8h) with a 1-hour IV infusion of levofloxacin (250 mg q24h) in the treatment of cUTI caused by susceptible gram-negative or gram-positive bacteria. Of the 753 patients enrolled in the study, 748 received study drug therapy with 376 in the doripenem treatment arm and 372 in the levofloxacin treatment arm. The primary objective was to establish non-inferiority of doripenem to levofloxacin with respect to per-patient microbiological cure at the Test-of-Cure visit, which was 6 to 9 days after the completion of study drug therapy following a 10-day treatment regimen. This determination was made by comparing the microbiological evaluable at test-of-cure (ME at TOC) and the microbiological modified intent-to-treat (mMITT_1) at TOC populations with those groups in the levofloxacin treatment arm. Non-inferiority was concluded if the lower bound of the 2-sided 95% confidence interval (CI) around the treatment difference (doripenem minus levofloxacin) was greater than or equal to -10%.

There were 280 doripenem patients and 265 levofloxacin patients in the ME at TOC group. Among the mMITT_1 group, there were 327 doripenem patients and 321 levofloxacin patients. The microbiological cure rate for the ME at TOC population was 82.1% (230/280) for the doripenem arm compared to 83.4% (221/265) for the levofloxacin arm. The treatment difference between the two groups was -1.3% and the 2-sided 95% confidence interval (CI) around this difference was [-8.0% to 5.5%]. Since the lower bound of this interval is greater than -10%, the pre-defined non-inferiority margin and the 95% CI includes the value 0, the results show doripenem to be non-inferior to levofloxacin in the treatment of these infections.

The microbiological cure rate for the mMITT_1 group at the TOC visit was 79.2% (259/321) for the doripenem patients and 78.2% (251/321) for the levofloxacin patients. The treatment difference was 1% with a 2-sided 95% CI around the difference of [-5.6% to 7.6%], which was consistent with the results obtained from the ME at TOC analysis set.

One of the secondary objectives was the clinical response at the TOC visit. The clinical cure rate for patients in the doripenem arm (clinical evaluable at test-of-cure population, CE at TOC) was 95.1% (272/286) compared to 90.2% (240/266) for the levofloxacin patients. The treatment difference was 4.9% in favor of the doripenem arm with a 2-sided

95% CI of [0.2% to 9.6%]. The clinical results establish that doripenem is non-inferior to levofloxacin for the treatment of clinical symptoms of cUTI and supports the microbiological results of this study.

Among the 280 ME at TOC patients in the doripenem treatment arm, the cure rate for patients with cUTI was 75.9% (110/145) and the cure rate for patients with pyelonephritis was 88.9% (120/135). In the levofloxacin treatment arm with 265 patients, the cure rates for cUTI and pyelonephritis were 75.6% (99/131) and 91.0% (122/134), respectively.

Doripenem was microbiologically effective against the major causative pathogens of cUTI as shown by the eradication rates of such pathogens as *Escherichia coli* (84.4%), *Klebsiella pneumoniae* (83.3%), and *Proteus mirabilis* (69.6%). Doripenem was not superior to levofloxacin in eradicating *E. coli* in this study. Levofloxacin had an eradication rate of 87.2% for this organism.

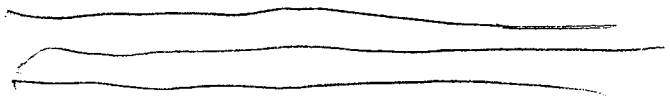
Study DORI-06 was a multicenter Phase 3, prospective, open-label, single arm study of doripenem administered as a 1-hour IV infusion (500 mg q8h) in the treatment of cUTI in adults. DORI-06 involved 423 patients (ITT population) with cUTI or pyelonephritis enrolled at 30 centers. The study was designed to provide independent confirmation of the response rate for doripenem observed in the double-blind, levofloxacin-controlled study in cUTI (DORI-05). The microbiological cure rate for the doripenem patients was 83.6% (209/250), while the cure rate in the DORI-05 levofloxacin treatment arm was 83.4% (221/265). The treatment difference was 0.2%, with a 2-sided 95% CI of [-6.6% to 7.0%]. The results show that the lower bound of the 95% CI around the difference in the cure rates was greater than -10% which meets the protocol definition of non-inferiority.

In the mMITT analysis set, the microbiological cure rate was higher among the patients who received doripenem compared to those in the DORI-05 levofloxacin treatment arm. The microbiological cure rate was 82.5% (278/337) for the doripenem patients and 78.2% (251/321) for DORI-05 levofloxacin patients. Again, the treatment difference between the two cure rates showed non-inferiority with a difference of 4.3% and a 2-sided 95% CI of [–2.1% to 10.7%].

The clinical cure rates at the TOC visit were similar for the DORI-06 doripenem treatment arm compared to the DORI-05 levofloxacin treatment arm for patients in the CE at TOC population, 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%]. Again, the results show that the lower bound of the 2-sided 95% CI around the treatment difference was greater than -10%, which demonstrates non-inferiority.

Among the 250 ME at TOC patients in the DORI-06 study, the cure rate for doripenem patients with cUTIs was 73.5% (97/132) and for pyelonephritis was 94.9% (112/118).

The data from Study DORI-06 show doripenem to be effective in eradicating *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Pseudomonas aeruginosa* with eradication rates of 91.8%, 80%, 85.7%, and 77.8%, respectively.



The data from Studies DORI-05 and DORI-06 show doripenem to be both microbiologically and clinically effective in the treatment of cUTI (including pyelonephritis) and non-inferior to i.v. levofloxacin.

Complicated Intra-abdominal Infections (cIAI):
DORI-07and DORI-08 were international, multi-center, double-blind Phase 3 clinical trials of identical design involving 962 patients with complicated intra-abdominal infections who were randomized (1:1) to receive either doripenem 500 mg i.v. every 8 hours (N= 486) or meropenem 1 gram i.v. every 8 hours (N= 476). In both studies, patients could be switched to oral amoxicillin-clavulanate after nine or more doses of i.v. therapy if body temperature and white blood cell (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 methicillin-resistant Staphylococcus aureus (MRSA) or enterococcal infections. Study subjects were stratified at the time of randomization by region (North America, South America, and Europe), site of infection (complicated appendicitis with localized peritonitis versus other sites), and severity of illness (APACHE II score ≤ 10 versus > 10). The overall design of the studies and the endpoints selected were consistent with the published *General Guidelines for the Evaluation of new Anti-Infective Drugs for the Treatment of Intra-abdominal Infections.*

In both studies, the primary efficacy endpoint was clinical cure rate at the TOC visit, 28-42 days after completing therapy. The co-primary analysis populations were the microbiologically evaluable (ME) and microbiological modified intent-to-treat (mMITT) populations. 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 failure and for patients classified as failures who underwent a second procedure. The panel members were blinded to treatment assignment and their outcome assessment over-ruled that of the investigator. Sensitivity analyses were performed by the FDA using the protocol-specified windows and using investigator-defined outcomes.

Patients were well-balanced across both treatment groups with regard to sex, age, and race. The majority of patients in both studies were enrolled outside of the United States (US), whereas approximately 24% of patients were enrolled at sites in the US. The primary site of infection was complicated appendicitis with localized appendicitis noted in 34% of the patients. Anatomically, the appendix was the most common source of infection (62%) followed by the colon (20%). Only about 6% of the study patients were bacteremic. The majority of patients (82%) underwent an open surgical procedure. Seventy-five percent of all patients were switched from i.v. study drug to oral therapy with amoxicillin-clavulanate.

Both studies independently met the primary objective of demonstrating the non-inferiority of doripenem compared to meropenem in the treatment of adults with cIAIs. Doripenem

was both clinically and microbiologically effective in the treatment of cIAI. The clinical cure rates in the ME at TOC population were 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 rates for the mMITT population at TOC were 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%]. As the lower bound of the 95% CIs was greater than the pre-defined non-inferiority margin of -15% in both populations and the 95% CI included the value 0, doripenem was non-inferior to meropenem in the treatment of cIAI.

One of the secondary objectives of both clinical trials was to assess the clinical response in the clinically evaluable at test-of-cure (CE at TOC) population. The clinical cure rate for patients in the doripenem arm (CE at TOC) was 85.3% compared to 86.2% for the meropenem group. The treatment difference was -1.0 % with a 2-sided 95% CI of [-6.2% to 4.3%]. These results support the findings noted in the microbiologically defined study populations.

Success rates were similar in the two treatment arms for various sub-groups based on demographics, sites of infection, and other disease characteristics. Overall, cure rates were lower in both treatment arms in patients treated with i.v. antibiotics alone, in those >65 years of age, and in those patients with renal impairment.

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%) and *S. constellatus* (90%); Gram positive anaerobes such as *P. micros* (84.6%).

As a switch to oral amoxicillin-clavulanate was permissible after three days of i.v. study drug in both treatment groups, only a small subpopulation of patients received i.v. doripenem therapy alone for the entire treatment duration (N= 74, in the ME at TOC population). The small size of this subgroup limited assessment of the efficacy of doripenem for this indication that was not confounded by the followup oral switch agent. However, as the antimicrobial spectrum of amoxicillin-clavulanate and doripenem are fairly similar and patients were switched to oral agents only after clinical improvement was noted, it is likely that doripenem administered for the full treatment duration would be as effective as doripenem followed by an oral switch antibiotic.

1.3.3 Safety

The data reviewed in this report support the conclusion that doripenem is safe for its intended use in subjects with cUTI and cIAI. The safety database consisted of the four pivotal Phase 3 clinical trials supported by six Phase 1 studies in healthy subjects, two

Phase 1 studies in patients with renal impairment, and one Phase 2 study in hospitalized subjects with cUTI. Laboratory testing in the four doripenem phase 3 clinical studies included hematology, chemistry, urinalysis, and pregnancy tests. Laboratory tests were performed serially beginning at screening/baseline, during the study at specified visits, and during the post-treatment follow-up period. Abnormal findings were usually followed until resolution or until they were trending into the normal range.

The most frequently reported adverse drug reactions in patients receiving doripenem were headache, nausea, diarrhea, rash, and phlebitis. However, indication-specific differences in the incidence rates of asymptomatic bacteriuria, UTI, headache, and anemia as treatment-emergent adverse events (TEAEs) were observed. Asymptomatic bacteriuria and urinary tract infections were reported as TEAEs with an incidence of >5% in the cUTI studies. However, asymptomatic bacteriuria was not reported among any of the doripenem-treated subjects in both cIAI studies, and UTI was reported as a TEAE in only 3.35% of doripenem-treated patients in those studies. Further review and analysis of the UTI-related TEAEs revealed that many of the patients were microbiological failures or had indeterminate microbiological outcomes, such that the data indicated a lack of drug efficacy rather than a novel safety signal. Additionally, exploratory analysis of the incidence of TEAEs stratified by body mass index (BMI) in the two Phase 3 cUTI studies revealed a clear dose-response relationship in that doripenem-treated patients with the lowest BMI had the highest rates of headaches, whereas this trend was not observed in the cIAI studies. Anemia was observed in 9.64% of the pooled doripenem-treated subjects in the cIAI trials in contrast to the low incidence observed in the pooled meropenem group (5.54%) and in the comparative cUTI study (1.6% in DORI-05). The reasons for the indication-specific differences in incidence of TEAEs among the studies for the cUTI and cIAI indications are uncertain, but may include inherent differences in the study populations evaluated for the individual indications, differential reporting of TEAEs by investigators at the diverse study sites, different patterns of concomitant medication use (such as pain medications), and lack of uniformity in the frequency of laboratory testing.

Anemia and renal failure/renal impairment were identified as TEAEs that required further scrutiny during the course of the safety review by the FDA Medical Officer. Exploratory analyses involving the subgroup of patents treated with i.v. study drug without a follow-up oral switch revealed a higher incidence of anemia in doripenem-treated subjects compared to the comparator groups. Although peri-operative blood loss could potentially account for some of the anemia cases reported in the cIAI studies, there was insufficient data to exclude drug-induced anemia. A consult with Hematology was obtained as part of the assessment. In relation to renal failure-related TEAEs, there was a striking imbalance noted between the high incidence of such events in the pooled doripenem-treated patients compared to the minimal incidence in comparator-treated subjects in the three comparative phase 3 studies. The disparity in the overall incidence of renal failure/renal impairment as a TEAE between doripenem and comparator groups raised concerns about possible drug-induced nephrotoxicity. However, based on further analysis of the laboratory data, sponsor narratives, and risk factors identified in the patients' medical histories, it was evident that underlying intravascular volume depletion, pre-renal azotemia, and pre-existing renal insufficiency may enhance the subject's susceptibility to develop acute renal failure/renal

impairment following exposure to doripenem and that such patients should have their renal function monitored while receiving the drug.

There were no reported cases of seizure, 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. Doripenem appears to be less neurotoxic compared to other carbapenem class agents based upon preclinical animal studies. However, the doripenem phase 3 clinical program is not of sufficient size or statistical power to detect rare adverse events that occur with a frequency of less than one in 425 (approximately 3/1,276 by the Rule of Three).[1] Although not the primary suspect drug, there were spontaneous post-marketing adverse event reports of Stevens Johnson Syndrome, toxic epidermal necrolysis, hypotension, agranulocytosis, and fulminant hepatitis in which doripenem was a concomitant medication. Assessement of causality in some of those cases was confounded by other concurrent medications and co-morbid conditions. Further surveillance for such rare adverse events should be an integral part of the post-marketing surveillance program for this drug.

1.3.4 Dosing Regimen and Administration

The Sponsor's proposed dosing regimens for the treatment of cUTIs and cIAIs are provided below:

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
cIAI	500 mg	q8h	1	5-14 days*
cUTI,including pyelonephritis	500 mg	q8h	1	10 days*§

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.
§ Duration can be extended up to 14 days for patients with concurrent bacteremia.

In patients with moderate renal impairment (CrCl $\geq$ 30 to $\leq$ 50 mL/min), the dosage of doripenem should be 250 mg every 8 hours by intravenous infusion over one hour. In patients with severe renal impairment (CrCl > 10 to < 30 mL/min), the dosage of doripenem should be 250 mg every 12 hours by intravenous infusion over one hour.

There is sufficient human safety data from the four phase 3 clincial studies to support the Sponsor's proposed dosing regimens and administration of the drug for the treatment of cUTI and cIAI in which IV doripenem is initiated and then followed by an oral switch antibiotic. However, there is insufficient safety data related to durations of doripenem that extend beyond 14 days.

1.3.5 Drug-Drug Interactions

Co-administration of doripenem with probenecid decreases the renal clearance of doripenem. This product is not metabolized by the P450 enzyme system; therefore, pharmacokinetic interactions of doripenem are not expected with drugs that induce, inhibit or are metabolized by cytochrome P-450 or other liver enzyme systems. Various reports in

the medical literature have described an interaction between carbapenem antibiotics and sodium valproate (valproic acid) in which patients administered both drugs concomitantly experienced an increased risk of seizure. In order to assess the potential for similar interaction involving doripenem, the Sponsor plans to conduct a Phase 1 study to evaluate changes in plasma valproic acid levels when the drug is co-administered with doripenem.

1.3.6 Special Populations

Efficacy: cIAI Studies

Two special populations were evaluated for efficacy in the cIAI studies: the elderly (defined as patients aged ≥ 65 years [106 subjects]; or ≥ 75 years [37 subjects]), and subjects with renal impairment requiring dose adjustments (48 subjects) in the pooled ME at TOC analysis set. Pediatric patients with cIAI were not studied.

In both treatment arms, the clinical cure rates at the TOC visit were lower in patients ≥ 65 years of age and ≥ 75 years of age compared to patients <65 years old. The cure rates for patients aged ≥ 65 years was 81.1% (43/53) in the doripenem arm and 75.5% (40/53) in the meropenem arm. Similar clinical cure rates were seen in both treatment arms for subjects aged ≥ 75 years (72.2% [13/18], doripenem; 73.7% [14/19], meropenem) in the pooled ME at TOC analysis set. These differences are expected and are likely the result of more co-morbidities and delayed clinical presentation of infection in the elderly population. No dosage adjustments are recommended for elderly subjects with normal age-appropriate renal function.

A total of 48 (7.6%) subjects in the pooled ME at TOC analysis population had renal impairment and required study drug dose adjustment. In this subgroup, clinical cure rates were lower compared to subjects who did not require a dose adjustment (85.7% versus 72.0% in the doripenem treatment arm, and 86.7% versus 52.2% in the meropenem treatment arm, respectively). This subgroup had a greater prevalence of high risk factors: 69% were aged > 65 years compared with 17% in the overall population, and 46% had APACHE II scores > 10 compared with 10% in the overall study population. The lower clinical cure rates in the renally impaired subgroup may be related to concurrent risk factors and co-morbidities in this population rather than representing a reduced treatment effect due to a downward adjustment in the dose of study drug necessitated by underlying renal insufficiency.

Safety

In adults treated with doripenem, there were no definitive safety issues identified with respect to age, race, renal impairment, or hepatic impairment that would impact dosing and administration. Indication-specific trends that were observed in the phase 3 clinical trials included the following: an increased risk for headache among subjects with low body mass index (BMI) in the phase 3 cUTI studies, an increased risk for asymptomatic bacteriuria in elderly subjects in the cUTI studies, and an increased risk for anemia and pyrexia among Black subjects in the cIAI studies. As pediatric populations (subjects aged <18 years old) were not studied, no specific recommendations regarding efficacy and safety in children can be provided.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Doripenem is an injectable, synthetic, broad-spectrum carbapenem in the beta-lactam (β-lactam) class of antibacterial agents. The mode of action results in its bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria commonly encountered in cIAIs such as *E. coli*, other Enterobacteriaceae, and *B. fragilis*. It binds to penicillin-binding proteins and inhibits cell wall synthesis in both gram-positive and gram-negative bacteria. Additional *in vitro* activity includes methicillin-susceptible staphylococci, streptococci, ampicillin-susceptible *Enterococcus faecalis*, *Pseudomonas aeruginosa*, ceftazidime-susceptible *Acinetobacter* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Clostridium* spp., and other gram-positive anaerobes. The drug has not been marketed in the United States, although it is marketed in Japan.

- Generic Name: Doripenem monohydrate
- Proposed Trade Name: Doribax
  This proprietary name was found to be acceptable by the Division of Medication Errors and Technical Support (DMETS). The Division of Drug Marketing, Advertising, and Communications (DDMAC) found the proprietary name to be acceptable from a promotional perspective.
- Chemical class: New Molecular Entity
- Pharmacological class: Carbapenem class of β-lactam antibacterial agents.
- Proposed indications, dosing regimens, age groups: The proposed indications are for the treatment of cIAI and cUTI in adults using a dosage of 500 mg i.v. every 8 hours for subjects whose creatinine clearance is >50 mL/min (see Section 1.3.1). Dosage adjustment is necessary in renal impairment: In moderate renal impairment (creatinine clearance ≥30 to ≤50 mL/min), the dosage is 250 mg every 8 hours. In severe renal impairment (creatinine clearance >10 to <30 mL/min), the dosage is 250 mg every 12 hours by intravenous infusion over one hour. No dosage adjustment is necessary based on age or hepatic impairment.

2.2 Currently Available Treatment for Indications

There are multiple antibacterial medications available currently for the treatment of cUTI, including ciprofloxacin (Cipro®), ertapenem (Invanz®), levofloxacin (Levaquin®), cefepime (Maxipime®), norfloxacin (Noroxin®), and gatifloxacin (Tequin®).

The following medications are labeled for the indication of cIAI: ciprofloxacin (Cipro®), ertapenem (Invanz®), and cefepime (Maxipime®). Antimicrobial agents that have been approved for the indication of intra-abdominal infections include ceftazidime (Fortaz®),

cefotaxime (Claforan®), imipenem-cilastatin (Primaxin®), ceftriaxone (Rocephin®), ticarcillin-clavulanate (Timentin®), ampicillin-sulbactam (Unasyn®), piperacillin-tazobactam (Zosyn®), and meropenem (Merrem®).

2.3 Availability of Proposed Active Ingredient in the United States

Doripenem is a new molecular entity. It is an investigational agent that has been marketed only in Japan. The product was launched there on September 16, 2005 under the tradename Finibax® for the treatment of moderate to severe bacterial infections.

2.4 Important Issues With Pharmacologically Related Products

Doripenem is a carbapenem in the beta-lactam (β-lactam) class of antibacterial agents and is anticipated to have a similar adverse event profile to other members of that class, including hypersensitivity, rash, and cross-reactions to other beta-lactams.

2.5 Presubmission Regulatory Activity

The presubmission regulatory history and milestones related to the current NDA submission are summarized in the following table:

Table 1: FDA Medical Officer Summary of the Pre-submission Regulatory Activity

Meeting/Milestone	Date	Major Issues from the Sponsor	Agency Agreements and Recommendations
End of Phase 2 Meeting	May 3, 2004	•Discussion of the phase 3 cUTI and cIAI studies, including a proposed delta of 15% for the cIAI study	•The cUTI study design proposed by the Sponsor was acceptable. •Future discussions with the Sponsor regarding the delta for cIAI were planned.
Orphan Drug Status	July 16, 2004		•The Agency granted doripenem orphan drug status for the treatment of bronchopulmonary infections in patients with cystic fibrosis who are colonized with *P. aeruginosa* and *B. cepacia*.
Meeting to review	February 28,		

drug development plan following IND acquisition by Johnson & Johnson	2006		
Discussion of doripenem toxicology program	April 28, 2006 teleconference	•The Sponsor committed to conducting a 2-week bridging dog toxicology study with the less soluble dry powder form of doripenem (including a Coombs assay).	•The Division recommended a 2-week dog bridging study.
Pre-NDA Meeting	July 27, 2006	•Sponsor stated intent to submit one NDA as a standard review for the indications of cUTI and cIAI in December, 2006 •Sponsor to provide 4-month safety update related to deaths, SAEs, and discontinuations that occurred during the time period 8/31/2006 to 12/31/2006 in a blinded manner. •Sponsor discussed breakpoint data submission and filing strategy	•The Division planned to request a random sample of about 10-15% of treatment-blinded CRFs for inclusion in the initial NDA submission. •The Division granted a deferral of pediatric studies until after approval of doripenem use in adults. •The Division concurred with the Sponsor's plan to submit drug product stability data within 7 months of the cUTI/cIAI NDA submission. •The Sponsor agreed to submit a 2-week dog bridging toxicology study. •The 4-month safety update was acceptable.
Meeting to discuss ISS/ISE requirements	October 27, 2006 teleconference	•The Sponsor discussed the FDA submission format for the ISS and ISE and for Modules 2.7.3 and	•It was agreed that splitting of the Body from the Supporting Data (appendicies and Attachments) for the ISS and ISE was acceptable.

		2.7.4 with Ken Edmunds of the FDA Office of Business Process Support	Recommendations related tot eh Modules were also discussed.
NDA Filing	February 6, 2007		The Division filed the cUTI/cIAI NDA as a standard review.
Pediatric Development Program Meeting	March 12, 2007		

cUTI=complicated urinary tract infections, cIAI=complicated intra-abdominal infections, NDa=new drug application, SAE=serious adverse event, , CRF=case report forms

ISS=integrated summary of safety, ISE=integrated summary of efficacy

2.6 Other Relevant Background Information

According to the product label isued in Japan, the concomitant use of carbapenems and sodium valproate is contraindicated. Coadministration of the drugs decreases blood concentrations of valproic acid, which could result in seizure recurrence.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to the report of Dr. Lin Qi for full details of the CMC review. In brief, the application is recommended for approval from a Chemistry prespective. The drug substance is synthesized through . Adequate information is provided on the synthesis and process controls, drug substance characterization, characterization of impurities, specification, container closure system, and stability studies. The drug product is manufactured by adequate information is provided on manufacturing process and process controls, container closure system, and stability studies.

3.2 Animal Pharmacology/Toxicology

Critical aspects of the animal pharmacology/toxicology review for doripenem have been reproduced from the report of Dr. Wendelyn Schmidt, Ph.D. Please refer to her report for full details. The application is recommended for approval from the Pharmacology/Toxicology perspective.

The pharmacokinetics of doripenem has been investigated in multiple species including mouse, rat, dog, rabbit, and monkey. No gender differences were noted. No accumulation with multiple doses was observed. Exposure was relatively linear with dose. The half life was generally less than 1 hour. Doripenem has relatively little binding to plasma proteins. Doripenem is widely distributed in both rat and dog. The majority of drug in both species was found in the kidney, and subsequently, in urine. A secondary site was the bone. The highest concentration of doripenem in the fetus was seen in the kidney.

Acute intravenous toxicity studies were conducted in the rat, rabbit, and dog. The major targets of toxicity were the kidney, hematologic cells (primarily white blood cells), gastrointestinal tract (vomiting in dogs, hemorrhage/erosion), and possibly liver. Subchronic dosing was conducted in the rat and dog. The major targets of toxicity in those studies were the kidney, hematologic cells, and gastrointestinal tract.

The cardiac effects of doripenem were tested both *in vitro* (hERG, Purkinje fibers) and in the *in vivo* dog. While all of the safety pharmacology studies were negative, the toxicology studies (1 and 3 month dog studies) showed significant changes in the QT interval. It should be noted that the maximum dose in the single dose safety pharmacology study was at 100 mg/kg while the 30 or 90 dose toxicology studies were conducted at 500 and 250 mg/kg. No QT prolongation has been associated with other penems at this time.

One of the class effects of the penems is the increase in seizures. With doripenem, no seizures or convulsions were noted during the general toxicology studies with doses up to 2000 mg/kg in the single dose rat and dog.

Mutagenicity of doripenem was investigated in both bacterial (Ames at up to 5 ug/plate) and mammalian (Chinese Hamster Ovary at up to 5000 ug/mL) cells. Both systems were negative. Doripenem was negative for clastogenicity in the Chinese Hamster Lung cell assay. Doripenem was also negative in the *in vivo* mouse micronucleus assay at 2000 mg/kg. No carcinogenicity studies were required based on the short-term, intermittent use of doripenem.

Studies have been conducted in the rat and rabbit to investigate the potential of doripenem to cause reproductive toxicity. The preliminary dose-ranging studies were conducted at the same doses (up to 1000 mg/kg/day i.v.) as the definitive studies and showed no significant effects on the feti or on other reproductive parameters (e.g. maternal toxicity, placental weights, implantation sites, abortions etc). Additionally, doripenem did not affect fertility in male or female rats at doses up to 1000 mg/kg/day.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary sources of clinical data for review of this NDA application involved electronic submissions of datasets and case report forms for subjects enrolled in four Phase 3 studies that had been conducted by the Sponsor: three clinical trials were double blind, randomized, comparative studies and one was a single arm, open label study. These studies were supported by eight Phase 1 studies and one Phase 2 study. Study DORI-03 was the single phase 2 double-blind clinical study comparing two doses of doripenem (250 mg and 500 mg) in subjects with cUTI. The phase 3 studies DORI-05 and DORI-06 were clinical trials of doripenem in subjects with cUTI, whereas DORI-07 and DORI-08 were comparative clinical trials of doripenem in subjects with cIAI. Additional information was available from multiple spontaneous post-marketing adverse event reports related to the use of the drug in Japan.

4.2 Tables of Clinical Studies

Table 2: Summary Table of doripenem Phase 1, 2, and 3 Clinical Studies

Study	Design and Dosage	Number of Subjects Treated
Completed Phase 1:	Pharmacokinetic and Safety	Studies in Healthy Subjects
DORI-01:	Randomized, DB, ascending MD, placebo-controlled study of safety, tolerability, and PK in healthy adult subjects of either sex Doripenem I.V. infusion: 500 mg over 30 min q12h or q8h; or 1,000 mg over 1 hour q12h or q8h (7 days [13 doses]); Six doripenem-treated and 2 placebo-treated subjects per cohort	N = 32 Doripenem 500mg q12h, N=6 500 mg q8h, N=6 1gm q12h, N=6 1gm q8h, N=6 Placebo, N=8 (2/cohort)
DORI-04:	Randomized, DB, ascending MD, placebo-controlled, dose finding study of PK, safety, and tolerability of doripenem prolonged infusions in healthy adult subjects of either sex Doripenem I.V. infusion: 500 mg over 4 hours q8h; 1,000 mg over 6 hours q12h; or 1,000 mg over 4 hours q8h (10 days). Six doripenem-treated and 2 placebo-treated subjects per cohort	N = 24 Doripenem: 500 mg, 4h, q8h, n=6; 1,000 mg, 6h, q12h, n=6 1,000 mg, 4h, q8h, n=6; Placebo, n=6 (2/cohort)
DORI-NOS-1001	Randomized, DB, MD, placebo- and positive-controlled, 4-way CO study of ECG intervals in healthy adult subjects receiving I.V. doripenem	N=60 All subjects received doripenem (or placebo) 500 mg over 1 hour q8h, 1,000 mg over 1 hour q8h, and oral moxifloxacin (or placebo), 400 mg

	Doripenem I.V. infusion: 500 mg or 1,000 mg or matching placebo infused over 1 hour q8h; SD oral moxifloxacin (400 mg); or matching placebo (sequence dependent on randomization)	once
DORI-NOS-1004	Randomized, OL, SD, 3-way CO, PK study of 500 mg and 1,000 mg infusions of doripenem in healthy adult subjects Doripenem I.V. 500 mg infused over 1 hour; 500 mg infused over 4 hours, and 1,000 mg infused over 4 hours (sequence dependent on randomization)	N = 24 All subjects received doripenem 500 mg over 1 hour once, 500 mg over 4 hours once, and 1,000 mg over 4 hours once.
DORI-NOS-1006	OL, SD, PK study of doripenem in healthy elderly and non-elderly adult subjects. Doripenem I.V. 500 mg infused over 1 hour	N=24 (12 elderly/12 nonelderly) All subjects recceived Doripenem 500 mg over 1 hour once.
DORI-NOS-1007	Open-label, single dose, PK study of the metabolism and excretion of doripenem in healthy men. Safety and tolerability were also assessed.	N = 8 healthy subjects All subjects received 14C-doripenem 500 mg over one hour, once.
Completed Phase 1	**Pharmacokinetic and Safety**	**Studies in the Renally Impaired**

DORI-02	OL, SD, controlled PK and safety study in subjects with mild, moderate, severe, or end-stage renal disease; two control subjects with normal renal function per cohort
	
	Doripenem I.V. 500 mg infused over 30 minutes
		N=32
		mild impairment, n=6;
		moderate impairment, n=6;
		severe impairment, n=6;
		end-stage disease, n=6;
		normal, n=8 (2/cohort)

DORI-NOS-1005	OL, PK, study of doripenem and doripenem-M-1 in hemodialysis-dependent subjects and healthy adult subjects. Doripenem I.V. 500 mg infused over 1 hour; 2 doses in hemodialysis-dependent subjects, and 1 dose in healthy adult subjects	N=12 (6 healthy/6 with end stage renal disease on dialysis) Doripenem 500 mg over 1 hour
Completed Phase 2 Efficacy and Safety Study		
DORI-03	Multicenter, randomized, DB, study of efficacy, safety, and PK of 2 dosages of doripenem in subjects with cUTI including pyelonephritis Doripenem I.V. 250 or 500 mg infused over 1 hour q8h for 7 to 14 days	N = 121 Doripenem: 250 mg, n=65; 500 mg, n=56
Completed Phase 3 Efficacy and Safety Study		
DORI-05	Multicenter, DB, double-dummy, randomized, comparison study of safety and efficacy of I.V.	N = 750

	doripenem and I.V. levofloxacin in subjects with cUTI, including pyelonephritis Doripenem I.V., 500 mg infused over 1 hour q8h or Levofloxacin I.V., 250 mg infused over 1 hour q24h; 10 days (I.V. + oral) (up to 14 days for subjects with concurrent bacteremia at study entry), with option to switch to oral levofloxacin (250 mg q8h) after at least 9 doses of I.V. therapy.	Doripenem; n=375 Levofloxacin: n=375
DORI-06	Multicenter, OL, comparison study of safety and efficacy of I.V. doripenem in subjects with cUTI including pyelonephritis Doripenem I.V., 500 mg infused over 1 hour q8h; 10 days (I.V. + oral) (up to 14 days for subjects with concurrent bacteremia at study entry), with option to switch to oral levofloxacin (250 mg q24h) after at least 9 doses of I.V. therapy.	N = 450
DORI-07 DORI-08	Multicenter, DB, double-dummy, randomized comparison study of safety and efficacy of I.V. doripenem and I.V. meropenem in subjects with cIAI Doripenem I.V., 500 mg infused over 1 hour q8h or Meropenem, I.V. bolus (3 to 5 min) 1 g q8h; 5 to 14 days (I.V. + oral), with option to switch to oral amoxicillin/clavulanate tablets (875 mg/125 mg) after Day 3	DORI-07: N=471 Doripenem: n=235 Meropenem: n=236 DORI-08: N=475 Doripenem: n=242 Meropenem: n=233

cIAI = Complicated intra-abdominal infection: cUTI - Complicated urinary tract infection;
DB = Double-blind, I.V. = Intravenous; OL =Open label;
PK = Pharmacokinetic; q8h = every 8 hours; q6h = every 6 hours; q24h = every 24 hours;

4.3 Review Strategy

The FDA review for this NDA was a joint effort involving the following Medical Officers:

- Alfred Sorbello, DO, MPH conducted the safety review and was the lead Medical Officer for the joint efficacy and safety report.
- James Blank, PhD conducted the efficacy review for the cUTI studies.
- Julie-Ann Crewalk, MD conducted the efficacy review for the cIAI studies.

The primary sources of data that were utilized for the efficacy and safety review for the

indications of cUTI and cIAI were the four doripenem Phase 3 clinical trials. The efficacy and safety analysis were conducted so that the rates of adverse events were examined for each study individually and also for pooled study data. Where there were substantial differences in assessment when the analyses were conducted using individual study data compared to pooled data, the differences were identified.

For data validation from the efficacy perspective, the FDA Medical Officers (Drs. Blank and Crewalk) conducted an independent review of a random sample of case report forms corresponding to 10% of all enrolled patients in the four doripenem Phase 3 clinical trials. The case report forms were blinded to subject identity and treatment group.

Safety information derived from the Phase 1 and 2 studies was used in support of the safety data from the four pivotal doripenem Phase 3 clinical trials in conducting the integrated safety analysis. For data validation, the FDA Medical Officer (Dr. Sorbello) conducted reviews of individual case report forms for subjects in the doripenem Phase 3 clinical trials who died or had selected serious adverse events. Case report forms and patient profiles were also assessed with respect to anemia and renal failure/renal impairment as treatment emergent adverse events in various exploratory safety analyses. In addition, case reports from the medical literature providing evidence of medically significant drug-drug interactions were accessed. This approach to the safety review provided evidence of a substantial interaction involving carbapenem antibiotics and sodium valproate, resulting in decreased serum valproic acid levels and heightened risk for seizure recurrence.

The justification for the non-inferiority margin used in Study DORI-05 comparing doripenem to levofloxacin in the treatment of complicated urinary tract infections was performed by Yunfan Deng, PhD and Alfred Sorbello, DO, MPH, and is included as an appendix to this report. The justification for the non-inferiority margin used in Studies DORI-07 and DORI-08 comparing doripenem to meropenem in the treatment of complicated intra-abdominal infections was performed by Scott Komo, PhD and Sumati Nambiar, MD, MPH and is included in Dr. Nambiar's report.

4.4 Data Quality and Integrity

For each of the proposed indications, the FDA Medical Officers reviewed a random sample of treatment-blinded case report forms to assess the conduct of the trial, ensure compliance with inclusion and exclusion criteria, and to verify the investigators' clinical and microbiological endpoint assessments.

The Division of Scientific Investigation (DSI) conducted audits of selected domestic and international study investigators and a review of the Sponsor's monitoring of studies conducted by those investigators. The inspections audited Protocol #s DORI-05, DORI-07, and DORI-08. Studies conducted by the following clinical investigators were assessed:
Kallol Chauduri, MD, Ph.D. – USA – DORI-08
Jose Cipullo, MD, Ph.D. – Brazil – DORI-05

Jorge Corral, MD	– Argentina – DORI-08
Clovis da Cuhna, MD	– Brazil – DORI-05
Antonio Freire, MD	– Brazil – DORI-07
Abel Jasovich, MD	– Argentina – DORI-07
Christopher Lucasti, MD	– USA – DORI-07
Osvaldo Malafaia, MD	– Brazil – DORI-08
Claudia Rodriguez, MD	– Argentina – DORI-05

FDA issued a Form FDA 483 to one clinical investigator, who provided written responses and a corrective action plan. FDA also issued a one-item Form FDA 483 to the Sponsor, who provided the requested documentation. The overall assessment of data integrity by DSI was that the Sponsor adequately conducted the studies and the data generated in support of this NDA appeared acceptable. Please refer to the report of the Division of Scientific Investigation for further details.

4.5 Compliance with Good Clinical Practices

According to the Sponsor, the clinical studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCPs), and any applicable regulatory requirements. An institutional review board (IRB) or independent ethics committee (IEC) reviewed the study protocol, including all amendments, the patient informed consent form, and all relevant supporting data. In addition, the studies were conducted in compliance with the International Conference on Harmonisation (ICH) E6(R) GCP pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, patients or their legally acceptable representatives gave their written dated informed consent to participate in the study after having been informed about the nature and purpose of the study, participation/discontinuation conditions, and risks and benefits of treatment. A copy of the signed informed consent document was provided to the patient or the patient's legally acceptable representative. If applicable, the informed consent document was translated into the native language and provided to non-English speaking patients.

Based on a review by the FDA Medical Officers, minor protocol violations were identified at various study centers. However, they were considered minor in nature and did not compromise the integrity of the NDA submission.

4.6 Financial Disclosures

The Sponsor submitted financial disclosures using continuation of Form FDA 3454 Part A listing clinical investigators who hold none of the disclosable financial arrangements with Peninsula Pharmaceuticals as defined in 21 CFR 54.2(a)(b)(c) and (f). In addition, the Sponsor submitted continuation of Form FDA 3454 Part B listing clinical investigators who participated in support of the NDA application was not obtainable because no response was received or no forwarding address was available. The principal investigators

included in the Form FDA 3454 Part B submission are listed below:

Study	Site #	Investigator
DORI-05	110	Donn, Folkert PD Dr Rehnert, Nicola Dr Abmad, Fatima Renning, Eckhard
	102	Hacker, Axel Dr. Shah, Wiebke Mrs.
	109	Adams, Christel
	013	Cortese, Florian M. MD, FACG Sironi, Rindo MD
	106	Lutge, Marco Milekic, Mumira
DORI-06	350	Zurueta, Jimena Maria MD
	641	Venkateswaralu, Venukonda Bhasker MD
	152	Razmaria, Aria Dr. med.
	153	Reissigl, Andreas Prim. Prof. Dr. Obwexer, Stefan Dr. med.
DORI-07	371	Franco, Monica Andrea, RN
	100	Schoning, Tilman Ehmann, Martin Walk, Stefanie Schwald, Martina Geierhaus, Jurgen Schimpf, Dorothea Nguyen, Hang Backhaus, Jurgen Schwartz, Anke Veit, Adrian Dr. med.
	200	Synator, Hanna Winiecka, Bozena
	374	Brito, Ruth MD
	041	Bergeron, Eric Dr. Mailloux, Armande RN Provost, Louise RN
	101	Hermann, Prof. Dr. Kramann, Prof. Dr.
	102	Moser, Christian Mr.
	024	Uppal, Baljeet MD Singares, Eduardo Smith MD
	103	Mootz, Richard Dr. Domsel, Georg Schmitz, Martina Kaempfer, R. Dr.
DORI-08	014	Bongard, Frederick MD
	126	Oesinghaus, Ulf Dr. Brugge, Andreas DR. Rambow, Frank Schulze, Brigitte Aumuller, Annemarie Hildebrandt, Philip Dr.
	227	Robakowska, Barbara Dr.
	133	Neuhaus, Peter Prof. Dr. med. Schoning, Wenzel Dr. med.

		Uhl, Inge
	047	Olivencia-Yurvati, Albert DO
	131	Bonsch, Stefan Gerken, Heike Keiyzer, Silvia

5. CLINICAL PHARMACOLOGY

The critical aspects of the pharmacokinetics, pharmacodynamics, and exposure-response relationships for doripenem have been reproduced from the report of Sarah Robertson, Pharm.D. in this section of the report. Please refer to Dr. Robertson's review for full details.

5.1 Pharmacokinetics

Doripenem is administered intravenously and exhibits linear and time-dependent pharmacokinetics. Doripenem has demonstrated linear pharmacokinetics over a dosage range of 125 mg to 1000 mg. Dose proportionality was confirmed for 1-hour and 4-hour infusions of 500 mg and 1000 mg doses of doripenem. No evidence of accumulation of doripenem was observed at any of the dose levels studied upon repeat dosing. Clearance of doripenem appears to remain constant at the range of doses studied.

The median (range) doripenem volume of distribution at steady-state (Vd_{ss}) in healthy Western subjects was 16.6 L (8.09 – 55.5L), similar to the extracellular fluid volume in humans. No relationship between Vd_{ss} and doripenem dose was observed. *In vitro* protein binding of doripenem in human plasma was 8.1% at a concentration of 100 μg/mL. Doripenem exposure in various body tissues and fluids was evaluated in Phase 2 and 3 Japanese studies.

Key aspects of the metabolism of doripenem are summarized below:
• Doripenem undergoes no metabolism (CYP450-mediated or otherwise) based on the results of *in vitro* studies conducted with pooled human liver microsomes (HLM) in the presence and absence of NADPH. Further, doripenem had no effect on the modulation of CYP enzymes or UDP-glucuronosyltransferase (UGT) enzymes in HLM and human hepatocytes.
• Based on two Japanese studies involving the application of TLC-bioautography, no active metabolites of doripenem in plasma or urine were found following single doses of 25 mg to 1000 mg.
• *In vitro* studies have confirmed the role of dehydropeptidase-1 (DHP-1) in the metabolism of doripenem to doripenem-M1 (doripenem dicarboxylic acid), the inactive ring-opened metabolite. After incubating doripenem, meropenem and imipenem in purified murine DHP-1 for 90 min., residual concentrations of the respective agents were 82.4%, 78.1% and 23.2%, indicating that doripenem has a similar rate of hydrolysis as meropenem. Like meropenem, doripenem should be administered without the addition of a DHP-1 inhibitor.

Important aspects of the excretion of the drug are the following:
• Doripenem has a renal route of elimination, primarily. It concentrates well in the urine, exceeding plasma concentrations by an average of 600-fold for 4 hours postinfusion.
• Doripenem is excreted mainly unchanged. Across pooled studies conducted in Western populations, approximately 70% and 15% of doripenem doses (500 mg and 1000 mg) were excreted as the parent drug and doripenem-M1, respectively.
• The mean renal clearance of doripenem across healthy Western populations administered 500 mg and 1000 mg single- and multiple-doses is 170 mL/min. This value exceeds normal rates of glomerular filtration in healthy adults, indicating a contribution from active tubular secretion (ATS) to renal excretion. Results of a drug interaction study conducted with probenecid confirm the role of ATS in doripenem renal elimination.
• Doripenem does not appear to undergo hepatic metabolism or biliary excretion. Although the effect of hepatic impairment on the pharmacokinetics of doripenem has not been assessed, doripenem pharmacokinetics are not expected to be affected by changes in hepatic function. Further, as doripenem is only minimally protein bound (approximately 8%), the effect of varying serum albumin concentrations is not expected to have a significant impact on doripenem distribution.

In terms of drug-demographic interactions, the following features were noted:
• In a study evaluating the effects of age on doripenem PK, elderly subjects had a 33% lower total body clearance than non-elderly subjects. Doripenem exposure in elderly subjects was approximately 1.5 times that of younger subjects. Renal clearance was 30% lower in the elderly, roughly equivalent to the difference in creatinine clearance, which was 32% lower. The observed increase in doripenem exposure in the elderly is primarily due to reduced renal function, as opposed to age.
• No significant gender-related differences in doripenem pharmacokinetics were observed.
• The effect of race on doripenem PK was examined in the population PK analysis, which determined there is no clinically relevant difference in doripenem PK between Caucasians, Hispanic/Latino, African American and Asian subjects. Comparison of doripenem exposure across Western and Japanese studies did not reveal any marked differences between the two populations.

In terms of drug-drug interactions, the following features were noted:
• *In vitro* data from human liver microsomes suggest a low probability of drug-drug interactions between doripenem and drugs that are metabolized by cytochrome P450 enzymes.
• Concomitant administration of probenecid, an inhibitor of renal organic anionic transporters (OATs), resulted in a 75% increase in doripenem $AUC_{0\text{-}12}$, a 15% increase in C_{max} and a 53% increase in half-life. The increase in doripenem exposure observed in this study is less than what has been observed with the 1000 mg dose of doripenem administered alone. However, experience with the 1000 mg dose in humans is extremely limited, particularly multiple dosing. Based on the lack of safety data at the higher anticipated doripenem exposure, the Sponsor's recommendation to avoid probenecid co-administration with doripenem is appropriate.
• A clinically significant reduction in serum valproic acid (VPA) concentrations has been

reported for other carbapenem antibiotics. *In vitro* studies evaluating the effect of doripenem on VPA metabolism demonstrated doripenem's inhibition of VPA-glucuronide hydrolysis. Studies conducted in rats and monkeys confirmed that doripenem inhibits VPA-glucuronide hydrolysis *in vivo*. However, in these animal studies VPA serum concentrations were not significantly lowered. A study evaluating the effect of doripenem on VPA exposure has not been conducted in humans. Serum concentrations of VPA should be monitored during coadministration with doripenem therapy.

The Sponsor has not provided any information regarding the use of doripenem in pregnant or lactating humans.

5.2 Pharmacodynamics

No dose-limiting adverse events have been identified for doripenem. A small study conducted in Japan attempted to examine the relationship between drug exposure and abnormal hepatobilliary laboratory results. No relationship was identified, though limitations in study design and a small number of subjects with elevated enzymes limits the interpretation of these results. In an ascending, multiple-dose PK study conducted in Western healthy volunteers, there was an apparent dose-response trend for an increase in hepatic enzymes following repeated doripenem administration. The trend was most pronounced at the highest dose – 1000 mg q8h. However, evaluation of doripenem PK parameters in the 5 subjects with elevated liver enzymes reveals no apparent relationship between elevated enzymes and increased drug exposure within the ascending dosage cohorts.

Administration of doripenem at doses of 500 mg over 1 hour q8h (x 4 doses) and 1000 mg over 1 hour q8h (x 4 doses) demonstrated no signal of any effect on cardiac repolarization. There was no signal of any relationship between the plasma concentration of doripenem and change in QTc from baseline.

5.3 Exposure-Response Relationships

The exposure-response relationship for doripenem has been evaluated using *in vitro* time-kill studies, *in vivo* animal models of infection, Monte Carlo simulations, efficacy results from Phase 3 studies, and exploratory PK/PD analyses.

The main exposure-response relationships are summarized below:
• Animal models of infection established time above the minimum inhibitory concentration (T > MIC) as the primary PK/PD parameter related to efficacy. Efficacy studies for doripenem in the neutropenic mouse thigh infection model were conducted with penicillin-susceptible (PSSP), penicillin-resistant (PRSP) and quinolone-resistant strains of *S. pneumoniae*, methicillin-susceptible and –resistant strains of *S. aureus*, and cephalosporin and ESBL-producing strains of Gram-negative bacilli (GNB). The %T>MIC required to produce a static effect ranged from of 2.3 to 38% among the individual pathogens studied.

GNB and *S. aureus* required the longest %T>MIC for a static effect, with mean values of 29%. For *S. pneumonia* the mean %T>MIC for a static effect was 12.4%.
• There was no major difference in %T>MIC determinations for PSSP, PRSP and quinolone resistant strains of *S. pneumoniae*. Nor did the presence of methicillin-resistance or ESBL production impact the magnitude of %T>MIC necessary for efficacy.
• Simulations based on a target %T>MIC of at least 35% support the use of a 500 mg x 1-hour infusion every 8 hours (q8h) in subjects with normal renal function for target pathogens with doripenem MICs $\leq$ 2 μg/mL.
• Plasma concentration sampling was not performed in any of the Phase 3 clinical trials of cUTI or cIAI. As such, a dose/concentration-response relationship could not be determined for clinical and microbiological outcomes in the clinical trials.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The relevant data sources for the safety assessment for this NDA consisted of various electronic submissions from the Sponsor of individual study safety data, integrated safety data across the various studies, and the four-month safety update report. Safety data was derived from eight completed phase 1 studies (DORI-01, DORI-02, DORI-04, DORI-NOS-1001, DORI-NOS-1004, DORI-NOS-1005, DORI-NOS-1006, and DORI-NOS-1007; DORI-NOS-07 was included in the four month safety update), one phase 2 study (DORI-03), and four phase 3 studies (DORI-05, DORI-06, DORI-07, and DORI-08). The phase 1 studies involved single and multiple dose trials of varying design (double blind or cross-over). Study DORI-03 was a phase 2 double-blind, dose-ranging clinical study of doripenem in subjects with complicated urinary tract infections (cUTI). The phase 3 studies DORI-05 and DORI-06 were clinical trials of doripenem in subjects with cUTI, whereas DORI-07 and DORI-08 were clinical trials of doripenem in subjects with complicated intra-abdominal infections (cIAI). The following tables summarize the key features of the various studies, including the study design, dosages, and number of subjects treated. Adverse events were assessed at each visit throughout the studies.

Table 3: Sponsor Summary Table of Completed Phase 1 Pharmacokinetic and Safety Studies in Healthy Subjects (adapted from Table 1, Module 2.5 – Clinical Overview)

Study	Design and Dosage	# Subjects Treated
DORI-01	Randomized, DB, ascending MD, placebo-controlled study of safety, tolerability, and PK in healthy adult subjects of either sex Doripenem i.v. infusion: 500 mg over 30 min q12h or q8h; or 1,000 mg over 1 hour q12h or q8h (7 days [13 doses]); Six doripenem-treated and 2 placebo-treated subjects per cohort	N=32 Doripenem: 500 mg q12h, n=6; 500 mg q8h, n=6; 1,000 mg q12h, n=6; 1,000 mg q8h, n=6; Placebo, n=8 (2/cohort)
DORI-04	Randomized, DB, ascending MD, placebo-controlled, dose finding study of PK, safety, and tolerability of doripenem prolonged infusions in healthy adult subjects of either sex Doripenem i.v. infusion: 500 mg over 4 hours q8h; 1,000 mg over 6 hours q12h; or 1,000 mg over 4 hours q8h (10 days). Six doripenem-treated and 2 placebo-treated subjects per cohort	N=24 Doripenem: 500 mg, 4h, q8h, n=6; 1,000 mg, 6h, q12h, n=6; 1,000 mg, 4h, q8h, n=6; Placebo, n=6 (2/cohort)
DORI-NOS-1001	Randomized, DB, MD, placebo- and positive-controlled, 4-way CO study of ECG intervals in healthy adult subjects receiving i.v. doripenem Doripenem i.v. infusion: 500 mg or 1,000 mg or matching placebo infused over 1 hour q8h; SD oral moxifloxacin (400 mg); or matching placebo (sequence dependent on randomization)	N=60 All subjects received doripenem (or placebo) 500 mg over 1 hour q8h, 1,000 mg over 1 hour q8h, and oral moxifloxacin (or placebo), 400 mg once
DORI-NOS-1004	Randomized, OL, SD, 3-way CO, PK study of 500 mg and 1,000 mg infusions of doripenem in healthy adult subjects Doripenem i.v. 500 mg infused over 1 hour; 500 mg infused over 4 hours, and 1,000 mg infused over 4 hours (sequence dependent on randomization)	N=24 All subjects received doripenem 500 mg over 1 hour once, 500 mg over 4 hours once, and 1,000 mg over 4 hours once.
DORI-NOS-1006	OL, SD, PK study of doripenem in healthy elderly and non-elderly adult subjects Doripenem i.v. 500 mg infused over 1 hour	N=24 (12 elderly/12 nonelderly) All subjects recceived Doripenem 500 mg over

cUTI=complicated urinary tract infections; CO=crossover; DB=double-blind; ECG=Electrocardiogram; i.v.=intravenous; MD=multiple dose; OL=open-label; PK=pharmacokinetic; q8h=every 8 hours; q12h=every 12 hours; SD=single-dose.

Table 4: Sponsor Summary Table of Completed Phase 1 Pharmacokinetic and Safety Studies in Renal Impaired Subjects (adapted from Table 1, Module 2.5 – Clinical Overview)

Study	Design and Dosage	# Subjects Treated

DORI-02	OL, SD, controlled PK and safety study in subjects with mild, moderate, severe, or end-stage renal disease; two control subjects with normal renal function per cohort
	
	Doripenem i.v. 500 mg infused over 30 minutes
		N=32
		mild impairment, n=6;
		moderate impairment, n=6;
		severe impairment, n=6;
		end-stage disease, n=6;
		normal, n=8 (2/cohort)

DORI-NOS-1005	OL, PK, study of doripenem and doripenem-M-1 in hemodialysis-dependent subjects and healthy adult subjects Doripenem i.v. 500 mg infused over 1 hour; 2 doses in hemodialysis-dependent subjects, and 1 dose in healthy adult subjects	N=12 (6 healthy/6 with end stage renal disease on dialysis) Doripenem 500 mg over 1 hour

cUTI=complicated urinary tract infections; CO=crossover; DB=double-blind; ECG=Electrocardiogram; i.v.=intravenous; MD=multiple dose; OL=open-label; PK=pharmacokinetic; q8h=every 8 hours; q12h=every 12 hours; SD=single-dose.

Table 5: Sponsor Summary Table of Completed Phase 2 Efficacy and Safety Study (adapted from Table 1, Module 2.5 – Clinical Overview)

Study	Design and Dosage	# Subjects Treated
DORI-03	Multicenter, randomized, DB, study of efficacy, safety, and PK of 2 dosages of doripenem in subjects with cUTI including pyelonephritis Doripenem i.v. 250 or 500 mg infused over 1 hour q8h for 7 to 14 days	N=121 Doripenem: 250 mg, n=65; 500 mg, n=56

Table 53: FDA Medical Officer table of treatment-emergent adverse events with frequency ≥5% among subjects in either treatment arm who did not complete IV study drug and did not receive PO switch agent, Phase 3 cUTI Studies, ITT Population

Preferred Term	Doripenem DORI-05 (n=41)	Levofloxacin DORI-05 (n=66)	Doripenem DORI-06 (n=63)
Headache	6 (14.6)	4 (6.1)	8 (12.7)
Constipation	3 (7.3)	5 (7.6)	4 (6.3)
Vomiting	2 (4.9)	3 (4.5)	8 (12.7)
Nausea	1 (2.4)	2 (3.0)	6 (9.5)
Insomnia	1 (2.4)	1 (1.5)	4 (6.3)
Abdominal pain	1 (2.4)	0 (0)	4 (6.3)
Back pain	1 (2.4)	1 (1.5)	4 (6.3)
Hypokalemia	1 (2.4)	5 (7.6)	2 (3.2)
Diarrhea	0 (0)	10 (15.2)	7 (11.1)
Anemia	0 (0)	1 (1.5)	4 (6.3)
Dyspnea	0 (0)	3 (4.5)	4 (6.3)
Edema peripheral	0 (0)	0 (0)	4 (6.3)
Hypotension	0 (0)	1 (1.5)	4 (6.3)
Urinary tract infection	0 (0)	2 (3.0)	4 (6.3)

As depicted in the table above, the most frequent treatment-emergent adverse events in the doripenem group of subjects in DORI-05 and DORI-06 who did not complete IV study drug and did not receive PO switch were headache and gastrointestinal disorders (nausea, vomiting, constipation, and abdominal pain), whereas diarrhea was the most common such adverse event in the levofloxacin group. Overall, treatment-emergent adverse events appeared more frequent in DORI-06 compared to DORI-05. The reason for the disparity is uncertain, but may reflect the heterogeneity of the study population in DORI-06 as a single arm, non-comparative study and the loss of the effect of random patient allocation in conducting the subgroup analysis.

Table 54: FDA Medical Officer table of treatment-emergent adverse events with frequency ≥5% among subjects in either treatment arm who did not complete IV study drug and did not receive PO switch agent, Phase 3 cIAI Studies, ITT Population

Preferred Term	Doripenem Combined DORI-07 And DORI-08 (N=29) n, %	Meropenem Combined DORI-07 and DORI-08 (N=34) n, %
Nausea	6 (20.7)	2 (5.9)
Vomiting	4 (13.8)	1 (2.9)
Anemia	3 (10.3)	4 (11.8)
Dyspnea	2 (6.9)	3 (8.8)
Pyrexia	2 (6.9)	5 (14.7)
Edema peripheral	1 (3.4)	3 (8.8)

In subjects who did not complete IV study drug and did not receive PO switch in DORI-07 and DORI-08, the most frequent treatment-emergent adverse events in the combined doripenem group were nausea and vomiting, whereas anemia, peripheral edema, and pyrexia were the most common such events in the combined meropenem group.

Thus, based on the combined experience regarding the subgroup of patients who received only i.v. study drug without the PO switch drug and the subgroup of patients who did not