

changes were observed to be reversible. In repeat dose toxicity studies performed in dogs mild decreases in red blood cell counts, hemoglobin and hematocrit were noted in groups receiving  $\geq 250$ mg/kg/day in one month and 3 month toxicity studies. The no adverse effect level (NOAEL) in dogs was considered to be 125mg/kg/day in one month toxicity studies due to infrequent blood and mucous observed in the feces of these animals. In three month toxicity studies in dogs the NOAEL was 100mg/kg/day again due to occasional blood and mucous observed in the feces. In clinical phase 1 studies anemia was not reported as an adverse event in any of the 208 study subjects. In the single phase 2 study (DORI-03) 2/121 patients had anemia as a treatment emergent adverse event. Dr. Sorbello states that the phase 3 experience based on the four studies described above revealed a signal that was not well explained based on the available data. Dr. Sorbello states that the incidence of anemia in the phase 3 clinical experience can be divided as follows:

- Complicated intra-abdominal infection studies DORI -07 and DORI-08: anemia in the combined Doripenem group was found in 46/477 (9.64%) compared to the combined Meropenem group was 26/469 (5.54%). DORI -07 had 29 patients and DORI - 08 had 17 patients with anemia listed as a treatment emergent adverse event.
- Complicated urinary tract infection study DORI- 05: anemia in the Doripenem treated group was found in 6/375 (1.6%) patients compared to 5/375 (1.08%) patients in the Levofloxacin treated group.
- Complicated urinary tract infection study DORI -06: anemia in Doripenem treated patients was found in 17/450 (3.78%).

Dr. Sorbello reviewed laboratory data on all study subjects who completed IV study drug without receiving the PO switch agent and experienced anemia as a treatment-emergent adverse event. There were 31 Doripenem-treated (9 in the cUTI studies and 22 in the cIAI studies), no Levofloxacin-treated, and 10 Meropenem-treated subjects who completed intravenous (IV) study drug without receiving the oral (PO) switch agent and experienced anemia as a treatment-emergent adverse event in the combined phase 3 clinical trials experience. As depicted in the following table, the median duration of study drug and the median study day of hemoglobin nadir were similar between the Doripenem- and Meropenem-treated subjects who experienced anemia. The median change in hemoglobin was larger in the Meropenem patients with anemia, but more Doripenem-treated subjects received blood transfusions and conversions to a positive direct Coombs test were noted only among subjects treated with Doripenem.

Table 97: Dr. Sorbello's summary of subjects who completed study drug without receiving the PO switch agent and experienced anemia as a treatment-emergent adverse event, Doripenem phase 3 clinical studies, ITT population

	Pooled Doripenem	Meropenem	Levofloxacin
Total # of subjects	31	10	0
Anemia* at baseline	19/28 <sup>†</sup> (68%)	7/8 <sup>†</sup> (88%)	NA
Median duration of IV study drug, days (range)	11 (5-16)	12 (7-15)	NA
Median Study Day of HGB nadir, Study Day # (range)	8 (2-42)	8.5 (1-39)	NA
Median change in HGB from baseline to nadir, G/DL (range)	-1.55 (0.0 to -6.5)	-2.35 (0.0 to -4.0)	NA
# of subjects who received blood transfusions	13 (42%)	3 (30%)	NA
# of subjects who developed positive direct Coombs test <sup>†</sup>	2	0	NA

HGB=hemoglobin, NA=not applicable; HGB <12.5 G/DL; <sup>†</sup>missing data for some subjects

Furthermore, 19 Doripenem-treated subjects (68%) and 7 Meropenem-treated subjects (88%) were anemic at baseline. The median duration of IV study drug was similar between the pooled Doripenem and the Meropenem-treated subjects. The median duration of Doripenem administration was 11 days (range, 11-12) in the patients in the cUTI studies and 10 days (range, 5-16) in the cIAI study subjects. Thirteen (42%) of the Doripenem-treated and four (40%) of the Meropenem-treated subjects experienced their hemoglobin nadir within the first week of IV administration of the drug. It is possible that peri-operative blood loss accounted for the treatment-emergent anemias observed in that subset of study subjects, although no actual or estimated perioperative blood loss data were provided by the Sponsor to support this premise. There was a substantial amount of missing data related to direct Coombs tests. Both of the Doripenem-treated subjects who developed positive direct Coombs tests during study participation had positive results  $\geq 28$  days after completing IV Doripenem therapy and unrelated to the study day of the hemoglobin nadir.

In order to further investigate the underlying pathophysiology of anemia as a treatment-emergent adverse event, Dr. Sorbello reviewed data on those subjects who converted their direct Coombs test results from negative to positive with the test conversion as an indicator of possible immune-mediated hemolytic anemia. Pertinent data is summarized in the table below.

Table 98: FDA Medical Officer's Table of subjects who converted their Direct Coombs Test result from negative to positive during the study (including follow-up) in studies DORI-07 and DORI-08 (ITT population).

Study	Subject ID#	Treatment	Age/Sex	ITT	Study Visit with Negative Result	Study Visit with Positive Result	Anemia as a TEAE	Blood transfusion during study	History of Anemia	Pregnant during study
DORI-07	40204056	Doripenem	20/F	yes	Day 5	EFU	No	No	YES	No
	40204507	Doripenem	93/F	yes	EOT (IV)	RP/UNS SFTY	YES	YES	YES	No
	40204512	Doripenem	78/M	yes	EFU	RP/UNS SFTY	YES	YES	YES	NA
	40204013	Meropenem	41/F	yes	Baseline	EOT (IV)	No	No	YES	No
	40204037	Meropenem	42/M	yes	EOT (IV)	RP/UNS SFTY	YES	YES	YES	NA
	40204041	Meropenem	76/M	yes	RP/UNS SFTY	EFU	No	No	YES	NA
	40204062	Meropenem	42/F	yes	EOT (IV)	EFU	No	No	No	No
	40204504	Meropenem	50/F	yes	EOT (IV)	EFU	No	No	No	No
DORI-08	42603024	Doripenem	33/M	yes	Baseline	EFU	No	No	No	NA
	43004507	Doripenem	56/M	yes	TOC	EFU	YES	No	No	NA

EOT (IV)=End of IV Therapy; EFU=Early follow-up; RP/UNS SFTY=repeat unscheduled safety lab assessment; TOC=Test of Cure; NA=not applicable; TEAE=treatment-emergent adverse event

Direct Coombs tests were not reported for subjects in DORI-5 and DORI-06. Direct Coombs results were reported for 53 subjects in DORI-07 and 74 subjects in DORI-08. The reason for such testing only among select patients in the cIAI studies is uncertain, but may relate to the need for peri-operative type and cross-matching done in the event that blood transfusions were required for some of the surgical patients.

In total, five Doripenem-treated subjects and five Meropenem-treated subjects with negative direct Coombs tests converted to a positive test during the study or follow-up periods. Four of the 10 subjects had anemia as a TEAE, including three Doripenem-treated and one Meropenem-treated subject. Six of the 10 subjects had a history of anemia. Six were taking concomitant drugs (captopril) and many had received concomitant antibiotics (cephalosporins, other beta-lactams) that can be associated with hemolytic anemia. Three subjects had received a blood transfusion during the study. There were no pregnancies among the female subjects. Graphic patient profiles were examined for each subject, but there was missing data for time points beyond early follow-up (EFU) for some subjects.

The following series of tables summarizes Dr. Sorbello's review of the data on the incidence of various treatment-emergent adverse events (TEAEs) as derived from the electronic datasets. Tables 40 and 41 summarize the TEAEs with incidence of  $\geq 2\%$  for patients treated with Doripenem and comparator stratified by clinical trial and treatment group regardless of whether the subject received oral switch agent or not. Tables 50, 51, and 47 summarize the incidence of treatment-emergent adverse events ( $\geq 1\%$  frequency) for subjects who completed IV Doripenem therapy without PO switch, in an effort to eliminate potential confounding of causality assessment by the oral switch agent. All of the tables are derived from the safety population (ITT).

Table 40: FDA Medical Officer Summary Table of Incidence (%) of treatment-emergent adverse events reported with a frequency of  $\geq 2\%$  for patients treated with Doripenem and comparator stratified by clinical trial and treatment group in the Doripenem phase 3 cUTI studies (ITT Population)

Adverse Events	DORI-05 Doripenem (n=376)	DORI-05 Levofloxacin (n=372)	DORI-06 Doripenem (n=423)
Abdominal pain	1.86	3.49	3.07
Abdominal pain upper	4.52	3.49	3.07
Anemia	1.6	1.08	4.02
Anxiety	1.6	2.15	1.89
Asymptomatic bacteriuria	3.72	1.08	7.09
Back pain	2.13	4.57	3.07
Constipation	5.85	4.84	4.02
Diarrhea	5.59	9.95	6.38
Dizziness	2.39	2.69	4.49
Dyspepsia	2.66	0.54	1.18
Dyspnea	1.86	1.61	2.60
Edema peripheral	1.86	0.81	3.78
Flatulence	1.06	1.61	2.36
Headache	15.69	14.52	18.91
Hypertension	1.33	1.34	2.36
Hypokalemia	2.13	3.49	2.60
Insomnia	3.72	2.96	5.67
Nausea	4.26	5.91	7.80
Phlebitis	3.72	4.03	9.22
Pyrexia	1.6	1.61	4.96

Urinary tract infection	3.72	1.61	6.62
Vomiting	5.05	4.30	8.04

Table 41: FDA Medical Officer Summary Table of Incidence (%) of treatment-emergent adverse events reported with a frequency of  $\geq 2\%$  for patients treated with Doripenem and comparator stratified by clinical trial and treatment group in the Doripenem phase 3 cIAI Studies (ITT Population)

Adverse Events	DORI-07 Doripenem (n=235)	DORI-07 Meropenem (n=236)	DORI-08 Doripenem (n=242)	DORI-08 Meropenem (n= 233)
Abdominal pain	4.26	4.24	4.13	4.29
Abdominal pain upper	2.13	0.85	1.24	1.29
Anemia	12.34	7.2	7.02	3.86
Anxiety	2.55	2.97	2.89	3.86
Asymptomatic bacteriuria	0.0	0.0	0.0	0.0
Back pain	2.13	1.69	0.83	0.86
Constipation	4.26	4.66	4.96	3.0
Diarrhea	13.19	11.86	7.44	7.73
Dizziness	4.26	4.24	2.07	0.0
Dyspepsia	2.98	2.12	2.07	3.0
Dyspnea	2.98	3.81	2.48	3.43
Edema peripheral	5.11	2.97	3.72	3.43
Flatulence	5.53	3.81	2.48	0.86
Headache	5.53	8.05	3.31	2.15
Hypertension	3.4	6.36	2.48	3.0
Hypokalemia	5.11	2.12	3.31	3.0
Insomnia	6.38	3.81	3.72	5.58
Nausea	14.47	9.32	9.5	9.44
Phlebitis	10.64	7.63	4.55	3.43
Pyrexia	13.62	13.98	5.79	4.72
Urinary tract infection	5.53	2.54	1.24	2.15
Vomiting	5.53	9.32	6.61	6.87

Table 50: FDA Medical Officer table of treatment-emergent adverse events with frequency  $\geq 5\%$  among subjects in either treatment arm who completed IV study drug without exposure to PO switch agent, Phase 3 cUTI Studies, ITT Population

Preferred Term	Doripenem DORI-05 N=36 n/%	Doripenem DORI-06 N=72 n/%	Levofloxacin DORI-05 N=42 n/%
Urinary tract infection	2 (5.6)	10 (13.9)	0 (0)
Asymptomatic bacteriuria	3 (8.3)	8 (11.1)	0 (0)
Anemia	1 (2.8)	8 (11.1)	0 (0)
Headache	3 (8.3)	7 (9.7)	2 (4.8)
Insomnia	1 (2.8)	6 (8.3)	2 (4.8)
Pyrexia	1 (2.8)	6 (8.3)	1 (2.4)
Edema peripheral	1 (2.8)	5 (6.9)	0 (0)
Constipation	2 (5.6)	4 (5.6)	0 (0)
Diarrhea	1 (2.8)	2 (2.8)	6 (14.3)

Table 51: FDA Medical Officer table of treatment-emergent adverse events with frequency  $\geq 5\%$  among subjects in either treatment arm who completed IV study drug without exposure to PO switch agent, Phase 3 cIAI Studies, ITT Population

Preferred Term	Doripenem Combined DORI-07 and DORI-08 N=135 n,%	Meropenem Combined DORI-07 and DORI-08 N=128 n,%
Anemia	22 (16.3)	10 (7.8)

Preferred Term	Doripenem Combined DORI-07 and DORI-08 N=135 n,%	Meropenem Combined DORI-07 and DORI-08 N=128 n,%
Pyrexia	20 (14.8)	13 (10.1)
Nausea	18 (13.3)	15 (11.7)
Urinary tract infection	13 (9.6)	6 (4.7)
Edema peripheral	13 (9.6)	5 (3.9)
Diarrhea	13 (9.6)	17 (13.3)
Wound Infection	13 (9.6)	4 (3.1)
Pleural Effusion	12 (8.9)	8 (6.3)
Insomnia	10 (7.4)	4 (3.1)
Hypokalemia	9 (6.7)	7 (5.5)
Constipation	8 (5.9)	6 (4.7)
Vomiting	8 (5.9)	16 (12.5)
Dyspnea	7 (5.2)	5 (3.9)
Abdominal pain	6 (4.4)	7 (5.5)
Hypertension	5 (3.7)	10 (7.8)

Table 47: FDA Medical Officer's compilation of the treatment-emergent adverse events ( $\geq 1\%$  frequency) for subjects who completed IV Doripenem therapy without PO switch, Phase 3 Clinical Studies, ITT Population

Preferred Term	Doripenem DORI-05 (N=36) (n,%)	Doripenem DORI-06 (N=72) (n,%)	Doripenem DORI-07 (N=78) (n,%)	Doripenem DORI-08 (N=58) (n,%)	Doripenem Total (N=244) (n,%)
Anemia	1 (2.8)	8 (11.1)	17 (21.8)	5 (8.6)	31 (12.7)
Pyrexia	1 (2.8)	6 (8.3)	13 (16.7)	7 (12.1)	27 (11.1)
Urinary tract infection	2 (5.6)	10 (13.9)	10 (12.8)	3 (5.2)	25 (10.2)
Nausea	1 (2.8)	4 (5.6)	10 (12.8)	8 (13.8)	23 (9.4)
Edema peripheral	1 (2.8)	5 (6.9)	8 (10.3)	5 (8.6)	19 (7.8)
Insomnia	1 (2.8)	6 (8.3)	7 (9.0)	3 (5.2)	17 (7.0)
Diarrhea	1 (2.8)	2 (2.8)	9 (11.5)	4 (6.9)	16 (6.6)
Constipation	2 (5.6)	4 (5.6)	4 (5.1)	4 (6.9)	14 (5.7)
Headache	3 (8.3)	7 (9.7)	2 (2.6)	2 (3.4)	14 (5.7)
Wound Infection	0 (0)	0 (0)	13 (16.7)	0 (0)	13 (5.3)

Dr. Sorbello states that the analyses of the data on anemia are limited by the following:

- Lack of direct Coombs test information on patients in DORI-05 and DORI-06 and for a large number of patients in studies DORI-07 and DORI-08.
- Lack of systematic collection of information about intraoperative and perioperative blood loss.
- Lack of uniform collection of blood transfusion data.
- Missing data for time points beyond early follow-up.

The sponsor reports that the safety profile of Doripenem does not appear to adversely affect any particular body system. The profile of the adverse events in the phase 2 and phase 3 studies generally reflected complications anticipated within the respective indications under study. Headache was the most common adverse event reported in 12.6% of patients. Diarrhea was reported at rates typical of broad-spectrum antibiotics, according to the sponsor, in 7.9% of patients. Other adverse events that occurred in  $> 5\%$  of patients who received 500 mg other Doripenem included: nausea, phlebitis, anemia,

vomiting and pyrexia. In the pooled phase 2 and 3 studies the overall incidence rate of adverse events considered by the investigator as probably or possibly related to treatment with study drug therapy was comparable across treatment groups (23.5%-27.5%). Specific study drug related adverse events were uncommon with none reported in more than 4.2% of patients who received Doripenem. Study drug related adverse events with a higher incidence in subjects who received Doripenem compared to the comparator treatment included: headache, phlebitis and nausea. Adverse drug reactions with an incidence > 10% in patients who received Doripenem or were determined by the sponsor to have a plausible relationship to Doripenem after review of numerous representative cases included: *Clostridium difficile* colitis, diarrhea, headache, hepatic enzyme elevation, hypersensitivity reactions, nausea, oral candidiasis, phlebitis, pruritus, rash and vulvomyocytic infection. The sponsor found no notable differences in the incidence of adverse drug reactions in subgroups by age, sex or race. In phase 1 studies no deaths or treatment emergent serious adverse events were reported in healthy subjects or in renally impaired patients. Although patients in the phase 2 and 3 studies had serious complicated infections, the mortality rate was 1.3% for Doripenem treated patients compared to 0% for Levofloxacin treated patients compared to 3.8% for Meropenem treated patients. None of the serious adverse events resulting in death were considered by the investigator to be study drug related. All adverse events leading to death were considered related to the underlying disease or illness that developed while the patient was enrolled in the study. In phase 2 and 3 studies the rate of study drug therapy discontinuations due to adverse events was comparable across treatment groups. No specific adverse events led to the discontinuation from study drug therapy for more than 0.5% of patients who received Doripenem. Since Doripenem is predominantly eliminated by renal excretion, dose adjustment is required in patients with moderate and severe renal impairment. After such adjustments, the exposure was similar in renally impaired patients compared to non-renally impaired patients.

For the phase 2 and 3 studies hematology tests included hemoglobin, hematocrit, erythrocyte count, leukocyte count, neutrophil count, erythrocyte count, monocyte count, eosinophil count, basophil count, platelet count, mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were to be obtained according to protocol. No immunologic tests were specified in the protocols.

#### **Summary of relevant materials:**

Doripenem is an injectable, sterile, synthetic, broad-spectrum carbapenem (beta-lactam) antibacterial drug. The bactericidal mode of action of Doripenem and other beta-lactam's involves binding to penicillin binding proteins and inhibiting the biosynthesis of the bacterial cell wall in both gram-positive and gram-negative bacteria. The proposed indications for Doripenem are for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) including \_\_\_\_\_ pyelonephritis. These infections can be caused by different gram-positive and gram-negative aerobic and anaerobic bacteria. Combined intra-abdominal infections are commonly encountered in general surgery and require both operative drainage and treatment with broad-spectrum antibiotics. Urinary tract infections are associated with a

high risk of morbidity especially in the elderly population. Complicated lower urinary tract infections occur in patients with functionally, metabolically or anatomically abnormal urinary tracts. These infections range from cystitis to life-threatening urosepsis. Some predisposing conditions alter the urinary tract and can promote urinary tract infection such as indwelling catheters, increased residual urine volume and obstructive uropathies.

Drugs may cause immune hemolytic injury of red blood cells by three mechanisms. These types of red blood cell injuries are classified by the end effector mechanisms of the hemolysis, since the induction mechanisms of antibody formation are generally poorly understood.<sup>1</sup> The hapten/drug adsorption mechanism involves covalent binding of drug to red blood cell membranes and attachment of antidrug antibody to the membrane bound drug which opsonizes the cells for destruction by splenic macrophages. The ternary complex mechanism is characterized by formation of a trimolecular immune complex consisting of drug, red blood cell membrane bound antigen and an antibody that recognizes that compound neoantigen formed by drug and membrane antigen. Red blood cell destruction occurs intravascularly by activation of the whole complement sequence. The antibodies involved in the hapten/drug adsorption and ternary complex mediated hemolysis are drug dependent since the drug must be present with the red blood cell and antibody *in vivo* or *in vitro* for the antibody to cause red blood cell hemolysis. In sharp contrast to these mechanisms, some drugs induce formation of true autoantibodies indistinguishable from the autoantibodies seen in autoimmune hemolytic anemia. T-lymphocyte immunomodulation may play a role in this mechanism of drug-induced hemolysis. However in this autoimmune hemolytic anemia mechanism the drug is not necessary for red blood cell hemolysis to occur. The hemolysis with drug-related immune mechanisms is generally mild but severe and sometimes fatal hemolysis can be seen in cases mediated by the ternary complex mechanism and in patients with chronic lymphocytic leukemia with autoantibodies induced by purine analogues. Specifically, patients with the hapten/drug adsorption hemolytic mechanism, e.g., penicillin and autoimmune mechanism, e.g., alpha-methyldopa exhibit mild to moderate red blood cell destruction with insidious onset of symptoms developing over a period of days to weeks. In contrast, patients with hemolysis mediated by the ternary complex mechanism, e.g., cephalosporins or quinidine may have sudden onset of severe hemolysis with hemoglobinuria. In patients with the ternary complex mechanism hemolysis can occur after only one dose of the drug if the patient has been previously exposed to the drug. Acute renal failure may accompany severe hemolysis by the ternary complex mechanism. Cephalosporins are drugs that can cause severe, even fatal, hemolysis by the ternary complex mechanism. Withdrawal of the offending drug is usually the only treatment required. However, for patients with severe hemolytic anemia prednisone therapy may be necessary. Furthermore, in patients with G6PD (glucose-6-phosphate-dehydrogenase) deficiency hemolytic anemia may be caused by an oxidative process due to the lack of the important hexose monophosphate shunt enzyme G6PD. In addition, patients with G6PD deficiency may have infection induced hemolysis again due to an oxidative process related to the infection. In fewer than 5% of patients who receive cephalosporin antibiotics positive antiglobulin reactions due to nonspecific adsorption of plasma proteins to red blood cell membranes may occur. This may occur within a day or two

after the drug has been administered. Multiple plasma proteins including immunoglobulins, complement, albumin, fibrinogen and other proteins may be detected on red cell membranes in such cases. Hemolytic anemia due to this mechanism has not been reported. The clinical importance of this phenomenon is its potential to complicate crossmatch procedures unless the drug history is taken into account. As noted above cephalosporin antibiotics also may induce red cell injury by the hapten/drug mechanism or the ternary complex mechanism. These later reactions are more serious but apparently occur less frequently than the nonimmunologic reaction.

The clinical features of drug-induced hemolytic anemias are as follows:

- History of drug exposure.
- Anemia.
- Reticulocytosis.
- Positive direct Coombs test.
- Leukopenia and thrombocytopenia may be noted in cases of ternary complex mediated hemolysis.
- Hemoglobinemia or hemoglobinuria suggests the ternary complex mechanism of hemolysis.
- The table below shows the major mechanisms of drug-related hemolytic anemia and immunologic findings that can occur in each mechanism.

TABLE 57-2. MAJOR MECHANISMS OF DRUG-RELATED HEMOLYTIC ANEMIA

	HAPTEN/DRUG ADSORPTION	TERNARY COMPLEX FORMATION	AUTOANTIBODY BINDING	NONIMMUNOLOGIC PROTEIN ADSORPTION
Prototype drug	Penicillin	Quinidine	$\alpha$ -Methylidopa	Cephalothin
Role of drug	Binds to red cell membrane	Forms ternary complex with antibody and red cell membrane component	Induces formation of antibody to native red cell antigen	Possibly alters red cell membrane
Drug affinity to cell	Strong	Weak	None demonstrated to intact red cell but binding to membranes reported	Strong
Antibody to drug	Present	Present	Absent	Absent
Antibody class predominating	IgG	IgM or IgG	IgG	None
Proteins detected by direct antiglobulin test	IgG, rarely complement	Complement	IgG, rarely complement	Multiple plasma proteins
Dose of drug associated with positive antiglobulin test	High	Low	High	High
Presence of drug required for indirect antiglobulin test	Yes (coating test red cells)	Yes (added to test medium)	No	Yes (added to test medium)
Mechanism of red cell destruction	Splenic sequestration of IgG-coated red cells	Direct lysis by complement plus splenic-hepatic clearance of C3b-coated red cells	Splenic sequestration	None

From: Beutler, E. et al. *William's Hematology sixth edition. 2001.*

*Reviewer comment: Hemolytic anemia is not listed as a specific adverse event in the product label for Imipenem. Carbapenems appear to be among the beta-lactam antibiotic agents that are not readily associated with hemolytic anemia as an adverse event. In a review of 3470 patients treated with Imipenem/Cilastatin, the authors found one patient with a positive direct Coombs test result but zero patients with hemolysis.<sup>2</sup>*

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**Discussion:**

Dr. Alfred Sorbello from the Division of Anti-Infective and Ophthalmology Products requests a consult to obtain assessment of anemia as a treatment emergent adverse event and to rule out drug-induced hemolytic anemia for the carbapenem Doripenem for the NDA 22-106.

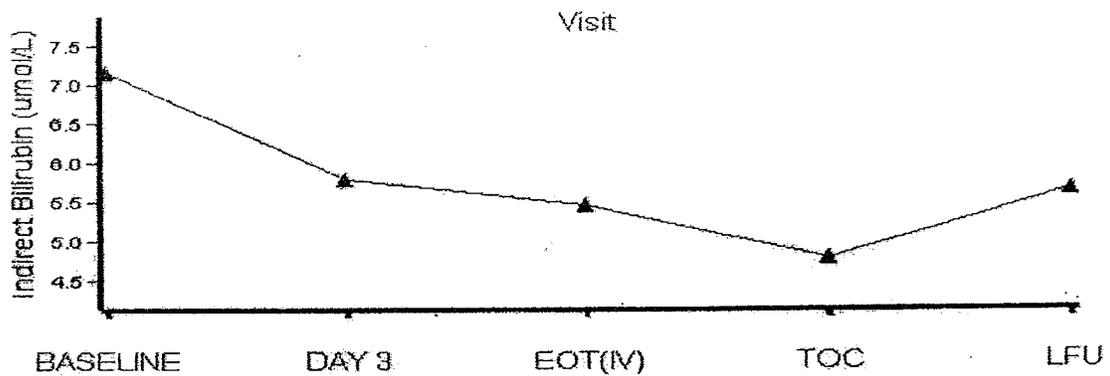
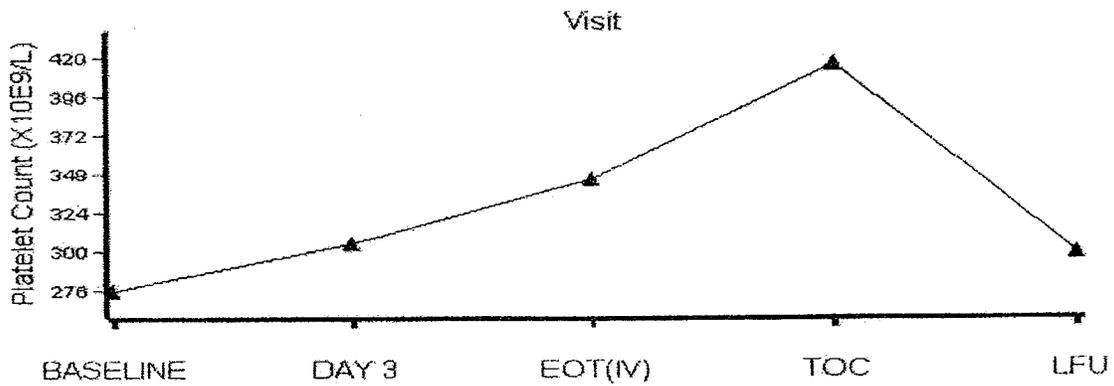
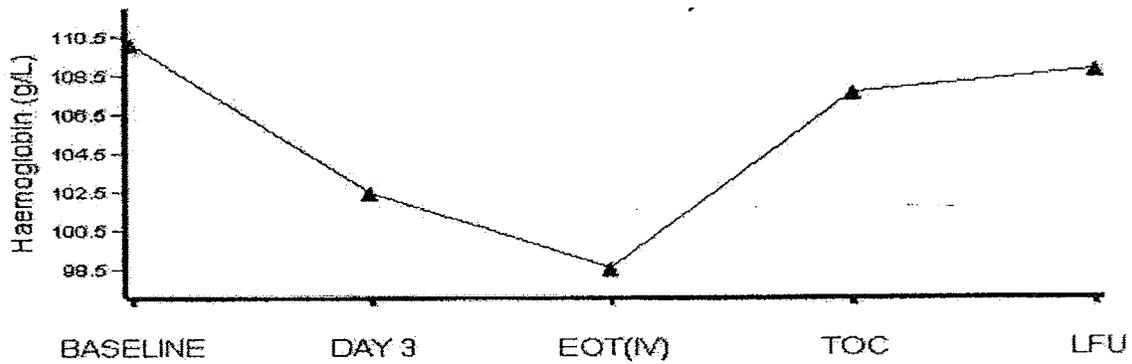
Hemolytic anemia is not listed as a specific adverse event in the product label for Imipenem or Meropenem. Carbapenems appear to be among the beta-lactam antibiotic agents that are not readily associated with hemolytic anemia as an adverse event. Positive direct antiglobulin (Coombs') test results, without clinical or laboratory evidence of hemolysis, have been reported in about 2% of patients receiving imipenem and cilastatin sodium.<sup>3</sup>

In amendment 0020 the sponsor states that in study DORI-03, a phase 2 complicated urinary tract infection study, the indirect Coombs test was positive in only 1/53 patients tested. The result was positive at baseline and remained positive throughout the study. In study DORI- 04, a phase 1 study in healthy volunteers (n = 24), both direct and indirect Coombs tests were negative in all patients at baseline, day 10 (23 subjects) and follow up 22-26 days later (24 subjects).

Changes in hemoglobin, indirect bilirubin, platelet counts and other parameters are not suggestive of drug effects among patients who received Doripenem. The composite graphs below display hemoglobin, platelet count and indirect bilirubin changes in all 23 complicated urinary tract infection patients with reported anemia.

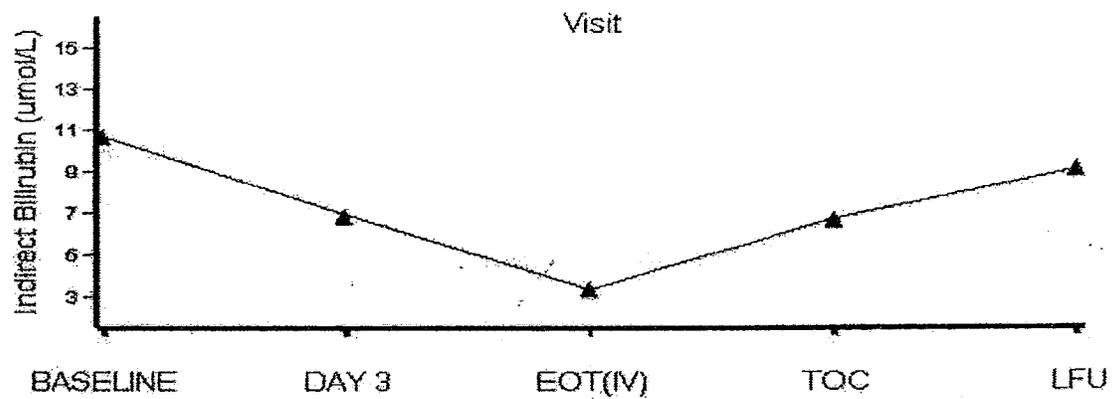
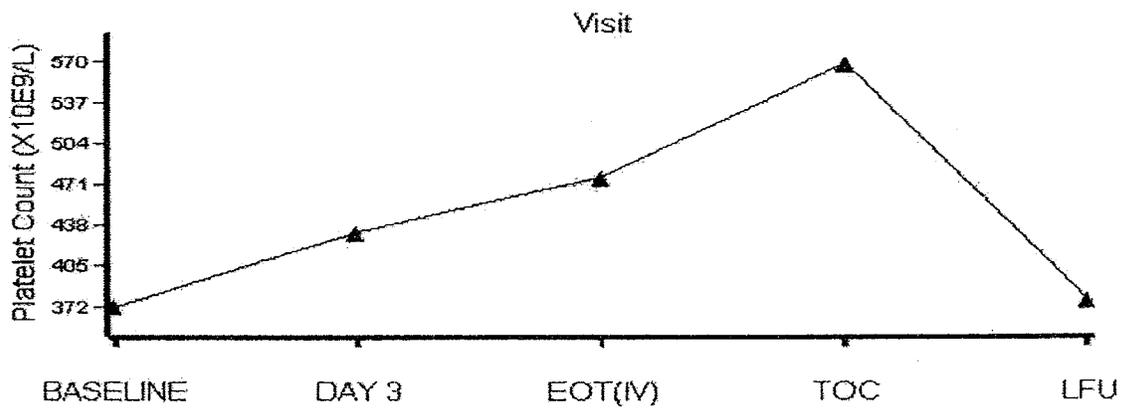
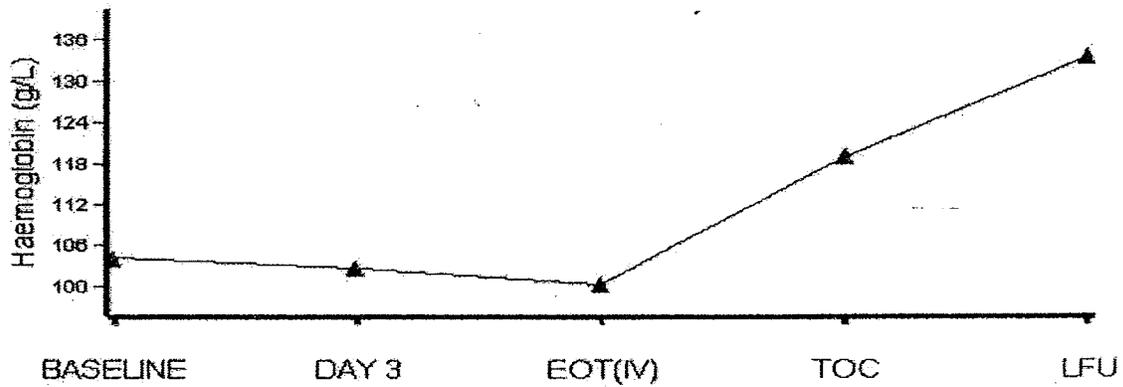
**APPEARS THIS WAY  
ON ORIGINAL**

Doripenem: Response to FDA - Anemia in cUTI and Pooled cUTI and eIAI studies  
**ALL DORI SUBJECTS (Dori 500 mg 1-h inf q8h)**



Sponsor figures from NDA 22-106 amendment 0019.

Doripenem: Response to FDA - Anemia in cUTI and Pooled cUTI and cIAI studies  
**ALL LEVO SUBJECTS (Levo 250 mg 1-h inf q24h)**



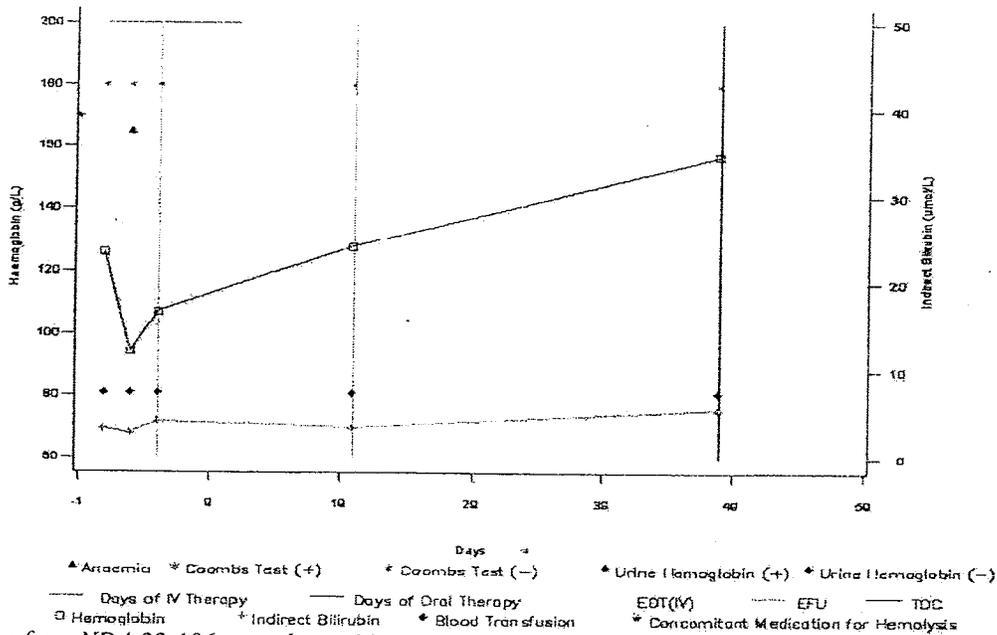
Sponsor figures from NDA 22-106 amendment 0019.

The graphs above show decreases in mean hemoglobin from baseline correlated with similar decreases in mean indirect bilirubin and do not support anemia due to red blood cell destruction or hemolysis. The changes in platelets shown above may be due to a number of possibilities such as return of platelet count back to baseline after an acute phase reaction due to treatment of infection or other stress.

In amendment 0020 the sponsor states that information was provided to the review division consisting of additional data on Coombs testing from sites participating in studies DORI-05, DORI-06, DORI-07 and DORI-08 in all patients for whom anemia was reported as an adverse event. In three patients for whom Coombs test were available both prestudy and on study, two patients had negative test results throughout (patient ID 01302 513 in DORI-07, one prestudy test and one on study test; patient ID 43104023 in DORI-08, one prestudy test and four on study tests). One patient in study DORI-08 (patient ID 01002002) had a positive Coombs test at prestudy followed by three negative tests while on study. It would appear from the available data in patients with an adverse event of anemia in the phase 3 studies that no patient developed a positive Coombs test that would suggest hemolysis following initiation of study drug therapy.

The graphs below show the hematology related laboratory outcomes for three Doripenem treated patients who had anemia listed as a treatment emergent adverse event in study DORI-07 or DORI-08 who are listed in Dr. Sorbello's review as patients who converted their direct Coombs test result from negative to positive during the study.

PENDOR08-43004507 (Dori 500 mg 1-h inf q8h)  
with Anemia



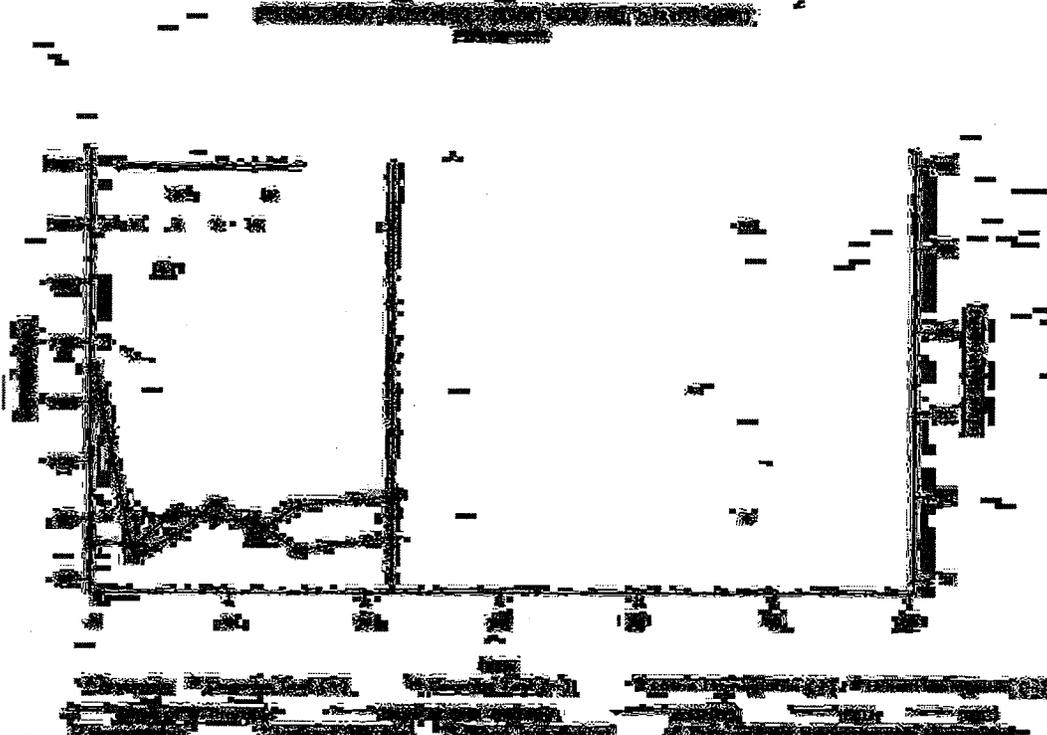
Sponsor figure from NDA 22-106 amendment 0019.

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The figures above show that the laboratory parameters evaluated do not follow a temporal pattern that would be expected for evidence of drug-induced hemolysis as the cause of anemia.

In addition, from the patients listed as those who converted their direct Coombs test result from negative to positive during the study, one patient (patient ID 43004507, DORI-08 study) is of particular interest because this patient not only had a conversion of his direct Coombs test but had anemia listed as a treatment emergent adverse event. This patient also had no prior history of anemia and no blood transfusion during the study according to Dr. Sorbello's communication. Each of these factors would be expected to possibly complicate the analysis of anemia in these studies. This patient is a 56-year-old Caucasian man with a history of hypertension, ischemic heart disease treated by a myocardial revascularization, ischemic stroke, carotid stent placement, asthenia and diabetes. This patient presented with constipation, anorexia, malnutrition, nausea, vomiting, chills and oliguria. The patient received prophylactic ampicillin, cefazolin, ceftriaxone and metronidazole for greater than 24 hours prior to surgery. He had abdominal surgery with a splenectomy for a splenic capsular abscess. No transfusions were given during surgery. Prior to randomization he was also on amiodarone, captopril, glibenclamide, heparin and isosorbide in addition to transient treatment with metoprolol, nifedipine and propranolol. He was also receiving treatment with tramadol and received one day of insulin. At the time of his admission the patient had hemoglobin of 12.6 mg/L with a mean cell volume of 99 FL. The patient's serum albumin was low at 2.8 g/dL. The patient had a trace amount of hemoglobin in the urine and a negative direct Coombs test and a normal indirect bilirubin at the time of admission. However, the patient's narrative states that he did indeed receive a blood transfusion and had a moderate transfusion reaction from which he recovered without treatment or interruption of the transfusion. On day five the patient developed atrial flutter which was considered life-threatening but not associated with hypotension. Amlodipine was added to the amiodarone with the resolution of the atrial flutter in three days. His direct Coombs test was negative at baseline, day three and at the end of intravenous therapy on day five. On day 20, 15 days after the last dose of Doripenem his direct Coombs test was positive but it was not associated with evidence of hemolysis from the data available. The indirect bilirubin was normal, urine hemoglobin was negative and the hematologic parameters were improving. On day 48 the patient's direct Coombs test reverted to negative. Over the course of his hospitalization his serum albumin improved from 2.1 g/dL after surgery to 4.6 g/dL on day 48 as did his anemia. The table below shows this patient's relevant hematologic laboratory parameters.

Day	Hg (g/L)	HCT (V/V)	Platelet Count (x10 <sup>9</sup> /L)	Indirect Bilirubin (µmol/L)	Urine Hg	Direct Coombs	PRBC Transfusion
Baseline (Day 1)	126	0.4	352	3.42	Negative	Negative	
Day 3	94	0.3	252	2.907	Traces	Negative	
Day 4							Received
Day 5 End IV	107	0.33	350	4.275	Negative	Negative	
Day 20 (EFU)	128	0.41	603	3.591	Negative	Positive	
Day 48 (TOC)	157	0.47	328	5.643	Negative	Negative	
Normal range	133-175	0.39-0.50	150-450	<15.39*	Negative	Negative	

EFU=early follow-up; HCT=hematocrit; Hg=hemoglobin; N=no data; TOC=test of cure

\* For Days 1-20; on Day 48, the normal range was 3.42-13.68 µmol/L.

Sponsor table from NDA 22-106 amendment 0029.

I found no other cases of possible hemolytic anemia in my review of the data presented. Analysis of the available patient narratives for the patients listed above that had converted their direct Coombs test from negative to positive after exposure to Doripenem revealed no clear direct correlation between Doripenem exposure and the possible adverse event of hemolytic anemia. From the data presented it does not appear that Doripenem can be directly implicated in causing hemolytic anemia in this patient population. However, the number of patients evaluated with Coombs tests is inadequate and overall the available information is insufficient to make a meaningful conclusion as to whether or not Doripenem could potentially cause hemolytic anemia in these patients. A number of deficiencies in data collection during the studies limit evaluation of Doripenem as a possible cause of hemolytic anemia - these include:

- Lack of direct Coombs test information on patients in DORI-05 and DORI-06 and for a large number of patients in studies DORI-07 and DORI-08.
- Lack of systematic collection of information about intraoperative and perioperative blood loss.
- Lack of uniform collection of blood transfusion data.
- Missing data for time points beyond early follow-up.

From the data that is available it is difficult to directly implicate Doripenem as a cause of anemia and in particular to implicate Doripenem as the cause of hemolytic anemia in patients who converted from a negative direct Coombs test to a positive direct Coombs test. These patients had:

- Blood transfusions during the study.
- 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.

However, since the possibility of Doripenem causing hemolytic anemia cannot be fully ruled out due to the limitations of the database listed above and because Doripenem is a member of a drug class for which Coombs test positivity can be a potential signal for

hemolysis, it is not unreasonable for the review division to recommend that the sponsor undertake an analysis of Doripenem as a possible cause of hemolytic anemia as a phase 4 commitment.

**Recommendations:**

The following recommendations should be forwarded to the review division and sponsor:

- While the data presented do not directly implicate Doripenem as causing hemolytic anemia in this patient population, a number of limitations of the available data (such as: lack of direct Coombs test information on patients in DORI-05 and DORI-06 and for a large number of patients in studies DORI-07 and DORI-08; lack of systematic collection of information about intraoperative and perioperative blood loss; lack of uniform collection of blood transfusion data and missing data for time points beyond early follow-up) make this assessment difficult. Also, from the data that is available it is difficult to directly implicate Doripenem as a cause of anemia and in particular to implicate Doripenem as the cause of hemolytic anemia in patients who converted from a negative direct Coombs test to a positive direct Coombs test. 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.
- Since the possibility of Doripenem causing hemolytic anemia cannot be fully ruled out due to limitations of available data, it is not unreasonable for the review division to recommend that the sponsor undertake an analysis of Doripenem as a possible cause of hemolytic anemia as a phase 4 commitment.

**References:**

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<sup>1</sup> Williams Hematology 6<sup>th</sup> edition.

<sup>2</sup> Calandra, G.B. et al.: the safety profile of Imipenem/Cilastatin: worldwide clinical experience based on 3470 patients. *J. Antimicrobial Chemotherapy*. 1986; 18 (supplement E.): 193-202.

<sup>3</sup> *American Hospital Formulary Service (AHFS) website*: <http://www.ashp.org/mngrp/ahfs/a386013.htm>.

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9/28/2007 04:54:09 PM  
MEDICAL OFFICER

Kathy Robie-Suh  
9/28/2007 05:19:16 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 22-106  
Submission Code 000

Letter Date December 12, 2006  
Stamp Date  
PDUFA Goal Date October 12, 2007

Reviewer Name James Blank, Ph.D.  
Review Completion Date September 20, 2007

Established Name Doripenem  
(Proposed) Trade Name Doribax  
Therapeutic Class Penem  
Applicant Johnson and Johnson

Priority Designation S

Formulation IV infusion  
Dosing Regimen 500 mg q8h  
Indication Complicated Urinary Tract  
Infections  
Intended Population Adults  $\geq$  18 years old

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## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

**The Applicant is seeking approval of the indication, Complicated Urinary Tract Infections, including \_\_\_\_\_ pyelonephritis caused by *Escherichia coli* \_\_\_\_\_ including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, \_\_\_\_\_ *Acinetobacter baumannii* and \_\_\_\_\_**

#### 6.1.1 Methods

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 entitled: "Phase 2, Double-Blind, Dose-Finding Study of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis." It 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 complicated urinary tract infections (cUTI) in adults. One hundred twenty-one subjects were randomized to receive either one of the two doses for 7 -14 days in the treatment of cUTI in adults. One hundred patients were evaluable for microbiological assessment. The cure rate for this group (ME at TOC) was 64.2% (34/53) for the group that received 250 mg compared to 68.1% (32/47) for the group that received 500 mg. Thus, the Applicant selected the higher, 500 mg dose to be used in subsequent comparative and non-comparative studies.

The DORI-03 protocol was submitted on December 2, 2002 and reviewed by Dr. Susan Thompson. (See MO Review of Original IND 64,416 dated January 21, 2004). The Clinical Study Reports for DORI- 03 were submitted on March 15, 2004 and January 10, 2005, and they were reviewed by Dr. Fred Sorbello. (See MO Review for IND 64,416, Document Numbers N-053 (IM) and N-092 (IM) dated December 21, 2006).

Study DORI-05 was entitled: "A Multi-center, Double-blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem and Levofloxacin in Complicated Lower Urinary Tract Infection or Pyelonephritis." The study was a Phase III, multi-center, randomized, double-blind study 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. After  $\geq 9$  doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever ( $<37.8^{\circ}\text{C}$  oral) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved

relative to those before the start of IV study drug therapy; and  $\geq 1$  urine culture had been reported with no growth at 24 hours or growth with a colony count of  $< 10^4$  CFU/mL [colony forming units] and no subsequent cultures with a colony count of  $\geq 10^4$  CFU/mL were observed.

Study DORI-06 was entitled: “A Multicenter, Phase 3 Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis.” This study was a Phase III, multi-center, 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. After  $\geq 9$  doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever ( $< 37.8$  °C oral) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least 1 urine culture had been reported with no growth at 24 hours or growth with a colony count of  $< 10^4$  CFU/mL [colony forming units] and no subsequent cultures with a colony count of  $\geq 10^4$  CFU/mL were observed. Results of this study are summarized in Appendix 10.3.

**Clinical Reviewer’s Comments:** *Since Study DORI-05 is a controlled, comparative study and DORI-06 is an open-label, non-comparative study, the data from the two clinical trials cannot be pooled.*

### 6.1.2 General Discussion of Endpoints

The primary endpoint for both studies was to determine the microbiological response at the test-of-cure (TOC) visit (6 to 9 days after the completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen in the ME and mMITT\_1 populations. Study drug therapy refers to the total number of days that patients were on double-blind intravenous, study drug therapy and oral levofloxacin therapy.

The secondary endpoints of interest for both studies were:

1. Per subject clinical cure at TOC in the CE at TOC analysis set.

The proportion of subjects who were assessed as clinically cured in the CE at TOC analysis set for each treatment arm.

2. Per uropathogen microbiological eradication rate at TOC in the ME at TOC analysis set.

The per uropathogen microbiological outcome for each baseline uropathogen species isolated from subjects in the ME at TOC analysis set and for the subgroup of subjects who had concurrent bacteremia at baseline.

Baseline uropathogen species isolated in at least 10 subjects in the pooled doripenem data from DORI-05 and DORI-06, including levofloxacin-resistant *E. coli*, were included in this analysis.

3. Per uropathogen microbiological eradication rate at TOC in the ME at TOC analysis

set for pathogens isolated in both the urine and blood at baseline.

Only baseline uropathogens isolated in at least 10 subjects in the pooled doripenem data from DORI-05 and DORI-06 were included in this analysis.

4. Per blood pathogen microbiological eradication rate at TOC in the ME at TOC analysis set for pathogens isolated in both the urine and blood at baseline.

Only baseline blood pathogens isolated in at least 10 subjects in the pooled doripenem data from DORI-05 and DORI-06 were included in this analysis.

**Clinical Reviewer Comments:** *The protocols developed by the Applicant for studies DORI-05 and 06 conform to the guideline found in the FDA 1998 Draft Guidance for Industry – Complicated Urinary Tract Infections and Pyelonephritis – Developing Antimicrobial Drugs for Treatment. The document defines complicated UTI as a clinical syndrome in men or women characterized by the development of the systemic and local signs and symptoms of fever, chills, malaise, flank pain, back pain, and CVA pain or tenderness, occurring in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Usually, one or more of the following conditions are present that increase the risk of developing an infection and therefore define complicated UTI:*

- *Presence of catheter*
- *100 mL of residual urine after voiding (neurogenic bladder)*
- *Obstructive uropathy (nephrolithiasis, fibrosis)*
- *Azotemia due to intrinsic renal disease*
- *Urinary retention in men, possibly due to benign prostatic hypertrophy*

*The signs and symptoms of complicated urinary tract infections are similar to those seen in acute pyelonephritis. It is defined as a systemic, ascending urinary tract infection, clinically manifested by fever, chills, flank pain, nausea and/or vomiting, frequently associated with bacteremia due to the same pathogen as isolated in the urine. Symptoms of lower urinary tract infection may or may not be present.*

*The guidelines state that one statistically adequate and well-controlled trial should be conducted establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). In addition, a second comparative or non-comparative trial that establishes statistical equivalence to the success rate of the approved agent in the first complicated UTI trial, or to an effectiveness rate agreed upon with the reviewing division should be conducted. The primary efficacy endpoint in this study is the eradication of the baseline pathogen from the patient at the 5- to 9-day test-of-cure visit. The Applicant has listed this condition as the primary endpoint in the study. A secondary endpoint includes the clinical response at the TOC visit.*

*The Applicant has generally followed the inclusion/exclusion criteria, dosing regimen, and evaluation criteria recommended in the guidance document. In the list of exclusion criteria, additional conditions were added to the protocol.*

### **6.1.3 Study Design**

#### **6.1.3.1 Overview**

This was a phase 3, multicenter, prospective, randomized, double-blind study of doripenem, administered as a 1-hour IV infusion (500 mg q8h), versus levofloxacin, administered as a 1-hour IV infusion (250 mg q24h), in the treatment of cUTI in adults. The study was double-blinded using either placebo levofloxacin q24h for patients receiving active doripenem or placebo doripenem q8h for patients receiving active levofloxacin. Approximately 750 patients were to be enrolled in this study and randomly assigned in a 1:1 ratio to receive either IV doripenem or IV levofloxacin therapy. Urine specimens for culture were collected at screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture. All patients received a minimum of 9 doses (approximately 72 hours) of IV study drug therapy. After receiving a minimum of 9 doses of IV study drug therapy, patients in both treatment arms may have been switched to levofloxacin tablets 250 mg orally once a day. The test of cure visit was to be conducted 6 to 9 days after the final dose of study drug was administered. A late follow-up visit was also to be conducted 28 to 35 days after administration of the final dose of study drug. Microbiological and clinical responses were assessed at both visits.

#### **6.1.3.2 Inclusion and Exclusion Criteria**

##### **Inclusion criteria**

Patients were included in the study if they met all of the following inclusion criteria:

1. Were male or female at least 18 years of age;
2. Demonstrated clinical signs and/or symptoms of cUTI, either of:
  - a. Pyelonephritis as indicated by all 3 of the following:
    - i. Fever (oral temperature greater than or equal to 37.8<sup>0</sup> C);
    - ii. Flank pain or costovertebral angle tenderness;
    - iii. Pyuria (greater than or equal to 10 white blood cells [WBC]/ $\mu$ L in unspun urine or greater than or equal to 10 WBC/high-power field [HPF] in spun urine)
  - b. Complicated lower UTI as indicated by all 3 of the following:
    - i. At least 1 of the following symptoms;
      - Dysuria;
      - Frequency;

- Suprapubic pain;
- Urgency.
- ii. Pyuria (greater than or equal to 10 WBC/ $\mu$ L in unspun urine or greater than or equal to 10 WBC/HPF in spun urine);
- iii. At least 1 of the following complicating factors:
  - Male gender;
  - Current bladder instrumentation or indwelling catheter that was anticipated to be removed during the course of IV study drug therapy administration;
  - Obstructive uropathy that was anticipated to be medically or surgically treated during the course of IV study drug therapy administration;
  - Urogenital surgery within 7 days prior to administration of the first dose of study drug therapy;
  - Functional or anatomical abnormality of the urogenital tract including anatomic malformations or neurogenic bladder with voiding disturbance of at least 100 mL of residual urine.
- 3. Had a study-qualifying pre-treatment baseline urine culture specimen obtained within 48 hours prior to the start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of greater than or equal to  $10^5$  CFU/mL. Patients may have been enrolled in this study and started IV study drug therapy prior to the investigator knowing the results of the baseline urine culture. However, if the final results of the pre-treatment urine culture were negative, then the patient was withdrawn from study drug therapy;
- 4. Required antibacterial therapy for the treatment of the presumed cUTI;
- 5. Had provided written informed consent. If the patient was unable to provide written informed consent, the patient's legally acceptable representative may have provided written consent, as approved by institution-specific guidelines.

### **Exclusion criteria**

Patients were excluded from the study if they met any of the following exclusion criteria:

1. Were women who were pregnant, nursing, or of childbearing potential, and not using a medically accepted, effective method of birth control (e.g., condom, hormonal contraceptive, indwelling intrauterine device, or sexual abstinence);
2. Had a history of moderate or severe hypersensitivity reactions to carbapenems, penicillins, other  $\beta$ -lactam antibiotics, or any quinolone (Mild rash was not a contraindication to enrollment.);
3. Had a complete permanent obstruction of the urinary tract;
4. Had a confirmed fungal UTI with a colony count greater than or equal to  $10^3$  CFU/mL;
5. Had a permanent indwelling bladder catheter or instrumentation including nephrostomy;

6. Had suspected or confirmed perinephric or intrarenal abscess;
7. Had suspected or confirmed prostatitis;
8. Had any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure, respiratory failure, and septic shock;
9. Had an immunocompromising illness including known infection with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hematological malignancy and bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, Imuran and the administration of corticosteroids equivalent to or greater than 40 mg/day of prednisone administered for more than 14 days;
10. Had severe impairment of renal function including a calculated creatinine clearance of less than 10 mL/min; a requirement for peritoneal dialysis, hemodialysis, or hemofiltration; or oliguria (less than 20 mL of urine output/hour over 24 hours);
11. Had 1 or more of the following laboratory abnormalities: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase levels greater than 3 times the upper limit of normal (ULN), absolute neutrophil count of less than 500 cells/ $\mu$ L, platelet count of less than 40,000 cells/ $\mu$ L, or hematocrit of less than 20%;
12. Had known ileal loops or vesico-ureteral reflux;
13. Had a concomitant infection requiring systemic antibiotic or antifungal therapy in addition to IV study drug therapy at the time of randomization; however, possible bacteremia with the presumed same urinary pathogen was acceptable;
14. Received any amount of potentially therapeutic antimicrobial therapy after collection of the pre-treatment baseline urine culture and before administration of the first dose of study drug therapy;
15. Received any amount of potentially therapeutic antibiotic for the treatment of the current UTI within the 96 hours prior to obtaining the study-qualifying pre-treatment baseline urine culture;
16. Had an intractable infection anticipated to require more than 10 days of study drug therapy;
17. Had a current urinary catheter that would not be removed or anticipation of urinary catheter placement that would not be removed during the course of IV study drug therapy administration. Intermittent straight catheterization after the IV study drug therapy administration period was acceptable;
18. Had a known or suspected central nervous system disorder that may have predisposed the patient to seizures or lowered the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or had the presence of other risk factors that may have predisposed the patient to seizures or lowered the seizure threshold (e.g., certain drug therapy, renal dysfunction);
19. Participated in any study of an investigational drug or device with 30 days prior to study entry;
20. Participated in any previous study of doripenem;
21. Had any condition or circumstance that, in the opinion of the investigator, would have compromised the safety of the patient or the quality of study data.

### 6.1.3.3 Study Treatments

Patients were to be randomized to receive either doripenem (500 mg), administered as a 1-hour IV infusion three times/day or levofloxacin (250 mg), administered as a 1-hour IV infusion once a day. In order to maintain the blind, patients on each study arm received an active drug and a placebo as follows:

#### Doripenem arm

Patients randomly assigned to active IV Doripenem (500 mg q8h)<sup>a</sup> received the following:

1 <sup>st</sup> dose	Doripenem Active (500 mg)	Levofloxacin placebo
2 <sup>nd</sup> dose	Doripenem Active (500 mg)	
3 <sup>rd</sup> dose	Doripenem Active (500 mg)	

#### Levofloxacin arm

Patients randomly assigned to Active IV Levofloxacin (250 mg q24h)<sup>a</sup> received the following:

1 <sup>st</sup> dose	Doripenem placebo	Levofloxacin Active (250 mg)
2 <sup>nd</sup> dose	Doripenem placebo	
3 <sup>rd</sup> dose	Doripenem placebo	

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<sup>a</sup> – For the 2-bag dosing occasion, the order of study drug infusion, doripenem or doripenem placebo followed by levofloxacin or levofloxacin placebo or vice versa, was assigned during randomization.

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### 6.1.3.4 Study Procedures

The study procedures are summarized in the following table.

Table 1. Time and Events Schedule

Day	-2 to 0 screening	1	2	3	4-10	EOT (IV) <sup>a</sup>	TOC (6 to 9 days) <sup>b</sup>	LFU (28 to 35 days) <sup>b</sup>
Informed consent	X							
Medical history	X							
Physical examination	X					X	X	
Oral temperature <sup>c</sup>	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X
CBC <sup>d</sup>	X			X		X	X	X
Chemistry panel	X			X		X	X	X
Calculated creatinine clearance <sup>e</sup>	X	X	X	X	X			
Blood sample for culture <sup>f</sup>	X		X	X	X			
Pregnancy test <sup>g</sup>	X						X	X
Urine sample for pyuria	X							
Urinalysis <sup>d</sup>	X			X		X	X	X
Urine for culture <sup>h</sup>	X	X	X	X	X	X	X	X
Randomization	X							
Symptom assessment <sup>i</sup>	X	X	X	X	X	X	X	X
12-lead ECG <sup>j</sup>	X							
Adverse events		X	X	X	X	X	X	X
Clinical response						X	X	X
Doripenem IV or levofloxacin IV or levofloxacin orally		X	X	X	X			
Determination of need for continued therapy				X	X <sup>k</sup>			

CBC = complete blood count; ECG = electrocardiogram; EOT(IV) = end of intravenous study drug therapy; IV = intravenous; LFU = late follow-up; TOC = test-of-cure.

<sup>a</sup> Day of premature withdrawal, day of failure, or last day IV study drug therapy was administered.

<sup>b</sup> Days after administration of the last dose of study drug therapy (IV and oral).

<sup>c</sup> Within 4 hours prior to each infusion while the patient remained on IV study drug therapy.

<sup>d</sup> Safety laboratory tests were performed at screening, on Day 3 and at the EOT(IV) and OC visits. Patients who were withdrawn from study drug therapy early due to non-study-qualifying baseline urine culture and, therefore, were not scheduled to return for the TOC visit had safety laboratory tests performed at the LFU visit.

<sup>e</sup> The most recent serum creatinine value obtained at the local laboratory, the actual body weight, and the Cockcroft=Gault formula were used to calculate the patient's creatinine clearance.

<sup>f</sup> A blood sample for culture was obtained at screening from patients who presented with clinical signs/symptoms of pyelonephritis or bacteremia and from all catheterized patients from whom the baseline urine culture specimen was obtained through the caterer. A blood culture specimen was obtained on Day 2 only when the screening blood culture was positive. Repeat blood cultures were taken approximately every 24 hours until 2 consecutive cultures obtained on separate days were without growth. Blood cultures were performed at anytime signs/symptoms of sepsis were present. Every time blood cultures were indicated, 1 aerobic bottle from each of 2 separate sites, for a total of 2 aerobic bottles per draw, was obtained.

<sup>g</sup> For all women of childbearing potential, a negative urine or serum pregnancy test at screening, prior to enrolling into the study, was required. If a urine pregnancy test was used at the time of screening, blood was obtained at the time of screening for serum  $\beta$ -human chorionic gonadotropin testing also, and negative serum pregnancy test result were confirmed as soon as possible and within 72 hours of study entry. In addition, all women of childbearing potential agreed to continue to use birth control throughout the study and for  $\geq 30$  days after administration of the last dose of study drug therapy (IV and oral). Female patients who were withdrawn from study drug therapy early due to non-study-qualifying baseline urine culture and, therefore, were not scheduled to return for the TOC visit had serum pregnancy testing done at the LFU visit.

<sup>h</sup> A urine sample for culture was obtained at baseline and after administration of the third dose of IV study drug therapy each day until 2 consecutive urine cultures were reported with no growth at 24 hours or growth with a colony count  $< 10^4$  CFU/mL. If on the day the patient was eligible to switch from IV to oral study drug therapy, only the most recently obtained urine culture was reported with no growth at 24 hours or a growth with a colony count  $< 10^4$  CFU/mL, then a second urine culture was obtained on the day the patient was switched to oral study drug therapy. If, after switching the patient to oral therapy, the second urine culture grew a uropathogen at  $\geq 10^4$  CFU/mL, the investigator contacted the patient to verify continued clinical improvement while on oral levofloxacin.

<sup>i</sup> Pre-infection symptom assessment was performed at screening. Day 1 symptom assessment was performed prior to infusion of the first dose of IV study drug therapy and then daily until the patient was switched to oral study drug therapy.

<sup>j</sup> A baseline ECG was obtained anytime prior to administration of the first dose of study drug therapy and as medically indicated thereafter. Two copies of each ECG were printed.

<sup>k</sup> While the patient remained on IV study drug therapy, assessments were made and recorded daily whether the patient met the following criteria to switch to oral study drug therapy: 1) no fever ( $<37.8^{\circ}\text{C}$  oral) for at least 24 hours, 2) signs and/or symptoms of cUTI were absent or improved relative to the values prior to dosing on Day 1, and 3) at least 1 urine culture obtained after administration of IV study drug therapy was reported to have no growth at 24 hours or growth with a colony count of  $<10^4$  CFU/mL. Patients remained on IV and/or oral study drug therapy for 10 days unless clinical failure occurred earlier.

### 6.1.3.5 Patient Populations

Intent-to-Treat (ITT): This population consisted of all randomly assigned patients who received any dose or partial dose of study drug therapy whether or not they met all inclusion/exclusion criteria. Safety analyses, but not efficacy analyses, were conducted in this analysis set.

Microbiological Modified Intent-to-Treat 1 (mMITT\_1): This analysis set consists of patients who received any dose or partial dose of study drug and who had a study-qualifying pre-treatment urine culture. Patients who meet both these criteria but who do not meet the protocol definition of cUTI or who have other protocol violations, including the administration of confounding non-study antibiotic, are included in this analysis set.

Microbiological Modified Intent-to-Treat 2 (mMITT\_2): This analysis set consists of patients who received any dose or partial dose of study drug and who had a study-qualifying pre-treatment urine culture and had at least one interpretable culture result from a specimen obtained 1 to 42 days after the end of study drug therapy. Patients who meet both these criteria but who do not meet the protocol definition of cUTI or who have other protocol violations, including the administration of confounding non-study antibiotic, are included in this analysis set.

Microbiologically Evaluable at Test of Cure (ME at TOC): The ME at TOC analysis set consists of all randomized/enrolled patients who met the following conditions:

- Met the protocol definition of cUTI
- Had a bacterial uropathogen isolated from a study-qualifying baseline urine culture
- Had no entry criteria or in-study protocol deviation likely to impact the microbiological outcome
- Were compliant with study drug therapy or were classified as an evaluable microbiological failure after completing at least 3 days of IV study drug therapy
- Had an interpretable urine culture result from a specimen obtained in the appropriate TOC window

Microbiologically Evaluable at Late Follow-Up (ME at LFU): This patient sample consists of individuals with an interpretable urine culture result at the LFU visit (28 to 42 days post-end of therapy) and who did not have any confounding event or receive any systemic antibacterial therapy with potential activity against the baseline uropathogen(s) between the time of the TOC and LFU visits, except resuming oral antimicrobial prophylaxis therapy after the TOC urine culture was obtained.

Clinically Evaluable at Test-of-Cure (CE at TOC): This analysis set was similar to the ME at TOC population except a clinical outcome assessment in the appropriate TOC window was required and an interpretable urine culture result at TOC was not. In order to be CE at TOC, a patient must have been compliant with study drug therapy or classified as an evaluable clinical failure after completing at least 3 days of IV study drug therapy. Patients who were classified as having an asymptomatic cLUTI at study entry because they had an indwelling catheter, a urinary obstruction, or a neurogenic bladder and did not experience symptoms of dysuria, frequency, suprapubic pain, or urgency were excluded from this analysis set.

Clinically Evaluable at Late Follow-up (CE at LFU): This analysis set consisted of patients in the CE at TOC set who were evaluated clinically at the LFU (28 to 42 days after receiving the final dose of study drug therapy). Urine culture results at the LFU visit were not required for inclusion in this analysis set. Exclusion for confounding events or the receipt of concomitant systemic antimicrobial therapy was applied as in the ME at LFU analysis set above.

#### **6.1.3.6 Outcome Criteria**

##### Microbiological Response Definitions

Microbiological outcome by pathogen and response by patient were determined at the EOT(IV), TOC, and LFU visits based on data collected on the CRF for qualifying uropathogens at each of these visits. The collected data consisted of the pathogen names (genus and species) and the count (in CFU/mL). The following definitions were defined by the applicant and taken from page 42 of the CSR:

##### At the EOT(IV) visit:

Eradication	The last interpretable urine culture result from a specimen obtained at the EOT(IV) visit (within 24 hours prior to or after infusion of the last dose of IV study drug therapy) showed the bacterial uropathogen(s) found at entry at greater than or equal to $10^5$ CFU/mL reduced to less than $10^4$ CFU/mL.
Persistence	The last interpretable urine culture result from a specimen obtained at the EOT(IV) visit (within 24 hours prior to or after infusion of the last dose of IV study drug therapy) grew greater than or equal to $10^4$ CFU/mL of the original uropathogen(s).
Indeterminate	No urine culture was obtained at the EOT(IV) visit, or the culture result could not be interpreted for any reason.

##### At the TOC visit:

Eradication	An interpretable urine culture result from a specimen obtained within the 5- to 11-day window after the last dose of study drug therapy showed the
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bacterial uropathogen(s) found at entry at greater than or equal to  $10^5$  CFU/mL were reduced to less than  $10^4$  CFU/mL.

**Persistence** At least 1 interpretable urine culture result from a specimen obtained 1 to 11 days after completion of study drug therapy grew greater than or equal to  $10^4$  CFU/mL of the original uropathogen.

**Indeterminate** No urine culture was obtained during the 5- to 11-day window after the last dose of study drug therapy, or the culture result could not be interpreted for any reason.

At the LFU visit:

**Sustained Eradication** An interpretable urine culture result from a specimen obtained within the 28- to 42-day window after the last dose of study drug therapy showed that the bacterial uropathogen(s) found at entry at greater than or equal to  $10^5$  CFU/mL remained less than  $10^4$  CFU/mL.

**Recurrence** An interpretable urine culture result from a specimen obtained any time after documented eradication at the TOC visit, up to and including the LFU visit, grew greater than or equal to  $10^4$  CFU/mL of the original uropathogen.

**Indeterminate** No urine culture was obtained during the 28- to 42-day window after the last dose of study drug therapy, or the culture result could not be interpreted for any reason.

Emergent Infections

Pathogens arising after baseline were categorized as follows:

**Superinfection** A urine culture grew greater than or equal to  $10^5$  CFU/mL of a uropathogen (including yeast) other than the baseline uropathogen(s) during the course of study drug therapy.

**New infection** A urine culture grew greater than or equal to  $10^5$  CFU/mL of a uropathogen (including yeast) other than the baseline uropathogen(s) after administration of the last dose of study drug therapy.

**Clinical Response Definitions**

Clinical outcome assessments were made at the EOT(IV), TOC, and LFU visits for patients

enrolled with a baseline diagnosis of symptomatic cUTI or pyelonephritis. The following definitions were defined by the applicant and taken from page 45 of the CSR:

At the EOT(IV) visit:

Improvement	Patients had resolution or improvement of signs or symptoms of cUTI since before the first dose of study drug therapy on Day 1.
Clinical Failure	Patients had no apparent response to therapy, persistence of signs and/or symptoms of cUTI infection beyond the pre-infection baseline or reappearance of signs and/or symptoms at or before the EOT(IV) visit, such that use of additional antibacterial therapy was required for the current infection.
Indeterminate	Patients were lost to follow-up such that a determination of clinical response (improvement or failure) could not be made.

At the TOC visit:

Clinical Cure	Patients had resolution or improvement of signs or symptoms of cUTI, or return to pre-infection baseline (if known) at the TOC visit, such that no additional antibacterial therapy was required for the treatment of the current infection.
Clinical Failure	Patients had no apparent response to therapy, persistence of signs and/or symptoms of cUTI infection beyond the pre-infection baseline or reappearance of signs and/or symptoms at or before the TOC visit, such that use of additional antibacterial therapy was required for the current infection.
Indeterminate	Patients were lost to follow-up such that a determination of clinical response (success or failure) could not be made.

At the LFU visit:

Sustained Clinical Cure	All pre-therapy signs and symptoms showed no evidence of resurgence after administration of the last dose of study drug therapy.
Clinical Relapse	Signs and/or symptoms of cUTI that were absent at the TOC visit reappeared at the LFU visit.
Indeterminate	Patients were lost to follow-up such that a determination of clinical response (success or failure) could not be made.

### 6.1.3.7 Statistical Considerations

#### Sample Size Estimation

Per the sponsor, the primary objective of this study was to determine non-inferiority of IV doripenem compared with IV levofloxacin for the treatment of cUTI in adult patients. Doripenem would be considered non-inferior to IV levofloxacin if the lower limit of the 2-sided 95% CI for the difference between treatment arms (doripenem minus levofloxacin) in the per-patient microbiological cure rate at the TOC visit was greater than or equal to -10%. The analysis was conducted in the ME at TOC analysis set. The hypotheses of interest were:

Null hypothesis	$H_0: \pi_1 - \pi_2 < -0.10$ , versus
Alternative hypothesis	$H_0: \pi_1 - \pi_2 \geq -0.10$ ,

Where  $\pi_1$  was the true proportion of patients with cUTI in the doripenem treatment arm who were microbiologically cured (had all baseline pathogens eradicated) at the TOC visit and  $\pi_2$  was the true proportion of patients with cUTI in the levofloxacin treatment arm who were microbiologically cured at the TOC visit.

The original study sample size of 450 patients was based on the assumptions that 70 % of the randomly assigned patients would meet the criteria to be included in the ME at TOC analysis set and that the per patient microbiological cure rate in both study arms would be 93%. These assumptions were based on evaluability rates reported in previous cUTI studies and microbiological cure rates reported for 2 comparative studies (L91-058 and L91-059) of levofloxacin in 250-mg oral tablets, 1 tablet per day for 10 days, for the treatment of cUTI, including acute pyelonephritis, where the majority of patients were considered to have mild to moderate infections. However, interim evaluation of blinded data from the DORI-05 study where patients with cUTI or pyelonephritis required hospitalization for IV antibiotic therapy indicated that approximately 66% of the randomly assigned patients met the criteria to be included in the ME at TOC analysis set and the overall microbiological cure rate was approximately 84%.

Estimation of sample size based on these interim data, the updated assumption of a microbiological cure rate of 84% in both study arms, and a decision to increase the a priori power from 80% to 85% at the (1-sided) 2.5% significance level, indicated that approximately 248 patients per study arm were required to meet the criteria for inclusion in the ME at TOC analysis set in order to demonstrate non-inferiority of IV doripenem to IV levofloxacin. To achieve this, assuming a 66% evaluability rate, a revised sample size of approximately 750 patients was enrolled.

**Clinical Reviewer's Comments:** *In this trial using a non-inferiority design, the ME and mMITT\_1 populations will be considered co-primary.*

### Adjustments to the Original Study Sample Size

Two adjustments to the original study sample size were made in DORI- 05. These were based on updated study estimates of the overall blinded microbiological cure and evaluability rates. In addition, in the second sample size adjustment, the study power was increased from 80% to 85% as a result of the re-evaluation of the development plan that occurred when PPI was acquired by J & JPRD on July 1, 2005.

The study sample size justification in Section 9.7.2.1 was part of Amendment 5 to the study protocol (September 15, 2005) and the corresponding SAP for the study.

An overview of relevant details regarding assumptions for the sample size justification in the original protocol and amendments are provided below.

<b>Protocol Version</b>	<b>Microbiological Cure Rate</b>	<b>Evaluability Rate</b>	<b>Study Power</b>	<b>Total Sample Size</b>	<b>Total Evaluable</b>
Original (9/23/03)	92%	70%	80%	450	320
Amendment 4 (4/18/05)	88%	63%	80%	580	360
Amendment 5 (9/15/05)	84%	66%	85%	750	496

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

Original Population	Patients who were enrolled in the study as part of the initially planned sample size.
Subsequent Population	Patients who were enrolled in the study after the initial sample size was attained.
Final Population	All patients who were enrolled in the study. Final Population = Original Population + Subsequent Populations.

### Statistical and Analytical Plan

The primary efficacy endpoint was the microbiological cure (eradication of all baseline pathogens) rates at the TOC visit (5 to 11 days after administration of the last dose of study drug therapy) in the ME at TOC analysis set. The primary efficacy analysis was to test the hypothesis of non-inferiority of IV doripenem to IV levofloxacin. Non-inferiority was to be concluded if the lower bound of the 2-sided 95% CI for the difference (doripenem minus levofloxacin) in the proportion of patients who were classified as microbiological cures was greater than or equal to

-10%. This 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method).

Analysis of the per-patient microbiological response in the mMITT\_1 analysis set was performed and was considered a co-primary analysis.

A sensitivity analysis was performed for the primary endpoint by adjusting for the effects of the baseline cUTI diagnosis (cUTI or pyelonephritis) on the microbiological response. This analysis was performed using a continuity-adjusted Cochran-Mantel-Haenszed (CMH)-type method weighted by the sample sizes.

Two secondary efficacy endpoints and their corresponding hypotheses were identified as being suitable for formal statistical analyses in support of the primary hypothesis. These endpoints were:

1. Non-inferiority of doripenem with respect to the clinical response at the TOC visit in the CE at TOC analysis set;
2. Superiority of doripenem with respect to the per-pathogen outcome for *E. coli* at the TOC visit in the ME at TOC analysis set.

For these 2 secondary hypotheses, a statistical analysis strategy with control of the type 1 error rate was used. In particular, each hypothesis was tested in the order presented above. If the first hypothesis was not established, the testing of the second hypothesis would not be done. For the first endpoint (clinical response at the TOC visit), the 2-sided 95% CI for the difference (doripenem minus levofloxacin) was calculated. Non-inferiority was to be concluded if the lower limit of this CI was greater than or equal to -10%. If this hypothesis was established, then the superiority of doripenem over levofloxacin in the per-pathogen outcome for *E. coli* was to be tested using the test for proportions (Fisher's exact test). Superiority of doripenem over levofloxacin was to be concluded if the P value for the 1-sided test for proportions was less than 0.025 with higher eradication rates in the doripenem treatment arm as compared with the levofloxacin treatment arm.

#### **6.1.3.8 Protocol Amendments and Changes in the Conduct of the Study**

The following five amendments were made to the original protocol, dated September 23, 2003:

##### Amendment 1 (February 9, 2004)

This amendment changed the duration of study drug therapy to comply with levofloxacin prescribing information and reflected information learned from preparation of the final clinical study report for the PPI-sponsored Phase 2 study in cUTI (DORI- 03), enrollment of the first 2 patients under the original DORI- 05 protocol, and discussions at investigator meetings.

- The days of therapy were changed from "7 to 14 days" to "10 days" in accordance with the levofloxacin prescribing information.

- A second negative urine culture was added at the time of the switch to oral study drug therapy to increase the probability that the patient had received adequate treatment with IV study drug therapy.
- The TOC visit was changed from “5 to 9 days” to “6 to 9 days” after the last dose of study drug therapy to increase the probability that the primary efficacy endpoint data were collected within the 5- to 9-day timeframe.
- A change was made to allow pyuria to be evaluated in both unspun and spun urine.
- Clarification was given that catheterized patients, obstructed patients, and patients with neurogenic bladder who may not have experienced signs/symptoms of dysuria, frequency, suprapubic pain, and urgency were the patients that were referred to within the protocol as “asymptomatic” patients.
- The use of oral antibacterial prophylaxis was allowed after the TOC visit in patients who usually received oral prophylaxis.
- Superficial bladder tumor was deleted as an acceptable complicating factor for cUTI.
- Blood cultures were required to be obtained from catheterized patients at screening.
- Clarification was added that patients with fungus found in the baseline urine culture at greater than or equal to  $10^3$  CFU/mL were not eligible for the study.
- An exclusion criterion was added to exclude immunosuppressive therapy (in addition to the previously stated immunosuppressive conditions).
- Enrollment of patients who were enrolled in a previous trial of doripenem was allowed.
- The requirement to obtain blood for PK analyses was eliminated.
- The number of baseline ECGs was reduced from 3 to 1. The requirement for ECGs after screening was eliminated unless they were medically indicated.
- The schedule for obtaining safety laboratory samples was modified and clarified (screening, Day 3, EOT[IV], TOC, and LFU [if needed]).
- The protocol requirement of documenting patients’ clinical statuses while they were outpatients receiving oral levofloxacin was deleted.
- The window for taking and recording body temperatures 3 times a day was expanded from 1 hour prior to 4 hours prior to administration of each dose of study drug therapy.
- Clarification that patients should have received 72 hours of IV study drug therapy before being considered a clinical failure was added.
- Clarification was added that Day 1 was the 24-hour period starting with the initiation of infusion of the first dose of study drug therapy, and each study day was the 24-hour period thereafter (not calendar days).
- The definition of a study-qualifying urine culture was clarified.
- The dose of levofloxacin was allowed to be increased to 500 mg q24h for patients with confirmed bacteremia.
- The dosage adjustment for doripenem in patients with moderate renal impairment was provided.
- The requirement for hepatitis serologies was eliminated.
- The collection of adverse events of special interests (possible allergic reactions and study drug intolerability) was added.

- The volume in which doripenem was administered was changed from 150 mL to 100 mL because 100-mL bags were more readily available to sites.
- The requirement for aerobic blood cultures was retained, but the requirement for anaerobic blood cultures was eliminated.
- Clarification was added that patients were to be considered compliant with study drug therapy administration if they received at least 8 of the first 9 IV doses and at least 80% of the scheduled doses (IV and oral) overall.

#### Amendment 2 (August 31, 2004)

This amendment reflected a change in the dosing regimen for patients with impaired renal function, added Canada as a country where the study could be conducted, and provided clarification to investigator comments and commonly asked questions.

- Clarification was added that actual body weight, not ideal body weight, should have been used when calculating creatinine clearance using the Cockcroft-Gault formula.
- Canada was added to the countries where the study could be conducted.
- Clarification was provided that patients who appeared to be septic, in addition to those that appeared to have pyelonephritis or bacteremia, should have had blood cultures drawn prior to the administration of the first dose of study drug therapy.
- Dosing adjustments and maximum length of treatment for patients with bacteremia were clarified.
- Clarification was added that switching to oral levofloxacin therapy was not mandated and that patients could have remained on IV study drug therapy throughout the entire study drug therapy dosing period.
- The fever-free criterion was modified from 48 hours to 24 hours for a patient to qualify for switching from IV to oral study drug therapy. In the current managed care environment in the US, continuing to hospitalize a patient for more than 24 hours after defervescence was not feasible.
- Clarification was added that the pre-treatment baseline urine culture was to be obtained with 48 hours prior to the start of administration of the first dose of study drug therapy and not within the 48 hours prior to randomization.
- The exclusion criterion concerning immuno-suppression was modified to allow for doses of prednisone equivalent to or greater than 40 mg instead of 10 mg because doripenem and levofloxacin, as bactericidal agents, should have adequately treated patients whose immunity was potentially impaired by a slightly higher dose of prednisone.
- The exclusion criterion for renal impairment was modified to exclude patients with a CrCl of less than 10 mL/min instead of 30 mL/min because PK data for patients with severe renal failure were available and allowed for recommendations for dose adjustment in such patients.
- Clarification was added for when to exclude patients with urinary catheters.
- Clarification was provided that patients who may have received doripenem in a previous Phase 1 or Phase 2 study were excluded from participation in this study because they could not be listed twice in the integrated safety summaries.

- For patients who were discharged from the hospital and refused to return to the investigational site for scheduled evaluations, clarification that data obtained by telephone could not be used in analysis of clinical or microbiological responses was provided.
- Clarification was added that patients who required dialysis or who developed oliguria must have been withdrawn from study drug therapy administration and that women who had been enrolled in the study and from whom a positive pregnancy test was obtained must have been immediately withdrawn from study drug therapy administration and the pregnancy followed to outcome.
- Clarification was added that the need for concomitant antifungal therapy at study entry was an exclusion criterion, but the patients already enrolled in the study could have received antifungal therapy if medically indicated and that a single dose of antibiotic was allowed for surgical prophylaxis only if the non-study antibiotic that was administered had no activity against the baseline uropathogen.
- Clarification that oral antibiotic prophylaxis should have been discontinued prior to obtaining the baseline pre-treatment urine culture was provided.
- Clarification was added that urine cultures obtained at the TOC and LFU visits that were contaminated should have been repeated with 7 days of the respective visits.
- Dosage adjustments for patients with renal impairment were modified based on additional PK data from Phase 1 and Phase 2 clinical trials. Dosage adjustments for patients with renal impairment receiving levofloxacin (IV and/or oral) were consistent with the product label for this drug.
- Guidance was provided on how to manage a patient's oral antibiotic therapy when he/she was responding well to IV study drug therapy and qualified for switch to oral therapy but who had a baseline uropathogen resistant to levofloxacin.
- Follow-up for serious adverse events was modified to a more conservative approach with all serious adverse events, not just those that were study drug related, followed to resolution or stabilization.

#### Amendment 3 (February 10, 2005)

This was an administrative amendment. The purpose of this amendment was to ensure consistency between the definitions of analysis sets and planned efficacy analyses in the protocol with those described in the SAP dated December 22, 2004. The principal change in the protocol-specified analyses was that super-infections or new infections were no longer to be considered causes of microbiological failure but were only listed.

#### Amendment 4 (April 18, 2005)

The purpose of this amendment was to increase sample size; to strengthen and clarify methods to prevent, detect, and report pregnancies; and to exclude patients with asymptomatic cLUTI.

- The sample size was increased from a planned enrollment of 450 to one of 580 patients based on a review of blinded data from this study that indicated that the percentage of

patients who met the criteria to be included in the ME at TOC analysis set and the overall microbiological eradication rate were lower than originally predicted based on data from previous studies.

- Language was added to more precisely describe the methods for testing women of childbearing potential for pregnancy at screening and at the Late Follow-up visit. These changes were intended to improve detection of pregnancy at screening and to emphasize the need to inform women that birth control must have been practiced throughout study drug therapy administration and for at least 30 days after the last dose of study drug therapy had been administered.
- Patients with asymptomatic cLUTI were excluded from this study because the increased complexity of these patients' conditions precluded obtaining interpretable urine cultures and the frequent occurrences of confounding infections mandated administration of non-study antibiotics.

#### Amendment 5 (September 15, 2005)

The purpose of this amendment was to increase the sample size from 580 to approximately 750 patients in order to take into consideration the overall microbiological eradication rates observed from review of blinded data, the percentage of patients who met the criteria to be included in the ME at TOC analysis set, and to increase the a priori power of the study from 80 to 85% at the 1-sided 2.5% significance level.

***Clinical Reviewer's Comments:** The two sample size increases were not defined a priori as part of the protocol reviewed by the Agency. According to the Applicant, the two increases were based on a review of blinded data that showed both the number of evaluable patients and the microbiological eradication rate to be lower than originally predicted. In addition, in the second sample size adjustment, the study power was increased from 80% to 85%. The two increases in sample size were not discussed with the Agency during the conduct of the clinical trial. Sample size re-estimation, if not carefully planned and executed, has the potential to introduce several serious biases. However, since the data were blinded according to the Applicant and a subsequent sensitivity analysis by the Applicant showed similar cure rates among the 3 doripenem populations (see section 6.1.4.9), the increases in sample sizes may be acceptable.*

#### Changes in Visit Windows

For evaluability determinations, the protocol-defined window at TOC of 6 to 9 days after administration of the last dose of study drug was expanded to 5 to 11 days after administration of the last dose.

***Clinical Reviewer's Comments:** All of the case report forms submitted by the Applicant for analysis by the Agency were reviewed in accordance with the conditions specified in the protocol, including the five amendments. Thus, the protocol-defined window at TOC of 6 to 9 days after administration of the last dose of study drug was used to determine the patient's response, both clinically and microbiologically.*

## 6.1.4 Efficacy Findings

### 6.1.4.1 Disposition of Patients

A total of 44 centers, with 18 in the United States; 7 in Germany; 7 in Argentina; 6 in Brazil; 5 in Poland; and 1 in Canada enrolled 753 patients in this study.

Table 2. Disposition of All Randomized Patients in DORI-05.

	<b>Doripenem</b>	<b>Levofloxacin</b>	<b>Total</b>
Randomized Patients	377	376	753
Randomized but not Treated	1 (0.3%)	4 (1.1%)	5 (0.7%)
Patients who Completed Study <sup>a</sup>	317 (84.1%)	280 (74.5%)	597 (79.3%)
Treated with IV Therapy Only	33 (8.8%)	34 (9.0%)	67 (8.9%)
Treated with IV and Oral Therapy	284 (75.3%)	246 (65.4%)	530 (70.4%)
ME at TOC Treated with IV Therapy Only	31 (8.2%)	48 (12.8%)	79 (10.5%)
ME at TOC Treated with IV and Oral Therapy	249 (66.0%)	217 (57.7%)	466 (61.9%)
Patients who did not Complete Study	60 (15.9%)	96 (25.5%)	156 (20.7%)
And Did not Receive Study Therapy	1 (0.3%)	4 (1.1%)	5 (0.7%)
And Did not Complete Study Therapy	48 (12.7%)	73 (19.4%)	121 (16.1%)
Did not Complete IV Therapy	42 (11.1%)	69 (18.4%)	111 (14.7%)
Completed IV but not Oral Therapy	4 (1.1%)	3 (0.8%)	7 (0.9%)
And Completed Study Therapy	11 (2.9%)	19 (5.1%)	30 (4.0%)
Discontinued from Study Early and Completed LFU Assessment	36 (9.5%)	61 (16.2%)	97 (12.9%)
Follow-up Visits Completed			
Had TOC and LFU	313 (83.0%)	284 (75.5%)	597 (79.3%)
Had TOC but Not LFU	8 (2.1%)	9 (2.4%)	17 (2.3%)
Not TOC nor LFU	21 (5.6%)	32 (8.5%)	53 (7.0%)
Not TOC, but Completed LFU	35 (9.3%)	51 (13.6%)	86 (11.4%)

IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable; TOC = test-of-cure.

Notes: Percentages were based on the number of patients randomly assigned to each treatment arm.

<sup>a</sup> Patients were defined as having completed the study if they had received study drug therapy as directed during the 10 days of treatment and had attended the TOC and LFU visits as specified in the protocol.

The data in Table 2 were taken from Applicant's Table 10, found on page 65 of the CSR.

Of the 377 randomized patients in the doripenem arm, 317 (84.1%) completed the study, while 280 (74.5%) of the 376 randomized patients in the levofloxacin arm completed the study. Sixty-seven of the 597 patients completing the study completed IV therapy only, compared to 530 (70.4%) patients who were treated with both IV and oral therapy.

**Clinical Reviewer's Comments:** *Sixty (15.9%) patients in the doripenem treatment arm did not complete the study compared to 96 (25.5%) of the levofloxacin patients. The following reasons*

were noted for differences between the treatment arms (doripenem versus levofloxacin) in the number of patients who discontinued the study early:

- treatment failure (0.5% vs 6.9%);
- adverse event (1.6% vs 2.9%);
- request by patient, investigator, or Applicant (0.5% vs 1.3%);
- need for an additional antibacterial therapy for an infection other than UTI (0.3% vs 1.1%).

Table 3 shows the demographic and baseline characteristics for the Microbiologically Evaluable at the Test-of-Cure population. This table was modified from Applicant's table 13 entitled: "Demographics and Baseline Characteristics (Study DORI-05: Microbiologically Evaluable at TOC Analysis Set), found on pages 73-75 of the CSR.

Table 3. Demographics of the ME at TOC Population.

	Doripenem (N = 280)	Levofloxacin (N = 265)	Total (N = 545)
Sex			
Male	110 (39.3%)	103 (38.9%)	213 (39.1%)
Female	170 (60.7%)	162 (61.1%)	332 (60.9%)
Race <sup>a</sup>			
American Indian or Alaska Native	0	2 (0.8%)	2 (0.4%)
Asian	0	0	0
Black or African Heritage	19 (6.8%)	24 (9.1%)	43 (7.9%)
Caucasian	228 (81.4%)	209 (78.9%)	437 (80.2%)
Native Hawaiian, Other Pacific Islander	0	0	0
Hispanic	30 (10.7%)	27 (10.2%)	57 (10.5%)
Other	3 (1.1%)	3 (1.1%)	6 (1.1%)
Age (years)			
Mean	51.5 (20.76)	51.8 (20.82)	51.6 (20.77)
Median	55.0	55.0	55.0
Min, Max	18, 90	18, 90	18, 90
Age Categories (years)			
<18	0	0	0
18-44	111 (39.6%)	106 (40.0%)	217 (39.8%)
45-74	129 (46.1%)	118 (44.5%)	247 (45.3%)
<65	179 (63.9%)	170 (64.2%)	349 (64.0%)
≥65	101 (36.1%)	95 (35.8%)	196 (36.0%)
<75	240 (85.7%)	224 (84.5%)	464 (85.1%)
≥75	40 (14.3%)	41 (15.5%)	81 (14.9%)
Height (cm)			
Mean (SD)	165.7 (8.97)	165.2 (8.89)	165.5 (8.92)
Median	165	165	165
Min, Max	143, 190	148, 196	143, 196
Weight (kg)			
Mean (SD)	71.58 (16.6)	73.41 (17.2)	72.47 (16.9)
Median	70	71	71
Min, Max	40, 158.8	44, 140	40, 158.8

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	Doripenem (N = 280)	Levofloxacin (N = 265)	Total (N = 545)
Body Mass Index (kg/m <sup>2</sup> ) <sup>b</sup>			
Mean (SD)	25.97 (5.4)	26.85 (5.7)	26.4 (5.6)
Median	25.12	25.95	25.47
Min, Max	13.3, 62.0	16.89, 47.32	13.3, 62.0
Baseline Disease Diagnosis			
cLUTI	145 (51.8%)	131 (49.4%)	276 (50.6%)
Symptomatic	138 (49.3%)	122 (46.0%)	260 (47.7%)
Asymptomatic	7 (2.5%)	9 (3.4%)	16 (2.9%)
Reason for Complication			
Male Gender	91 (32.5%)	85 (32.1%)	176 (32.3%)
Instrumentation/Catheter	41 (14.6%)	55 (20.8%)	96 (17.6%)
Obstructive Uropathy	54 (19.3%)	51 (19.2%)	105 (19.3%)
Urogenital Surgery	32 (11.4%)	29 (10.9%)	61 (11.2%)
Func/Anatomical Abnormality	43 (15.4%)	37 (14.0%)	80 (14.7%)
Anticipated to be Persistent (All males and some females) <sup>c</sup>	124 (44.3%)	116 (43.8%)	240 (44.0%)
Anticipated to be Eliminated (Some females only) <sup>c</sup>	21 (7.5%)	15 (5.7%)	36 (6.6%)
Pyelonephritis	135 (48.2%)	134 (50.6%)	269 (49.4%)
Uncomplicated	114 (40.7%)	107 (40.4%)	221 (40.6%)
Complicated	21 (7.5%)	27 (10.2%)	48 (8.8%)
Reason for Complication			
Male Gender	18 (6.4%)	17 (6.4%)	35 (6.4%)
Instrumentation/Catheter	2 (0.7%)	0	2 (0.4%)
Obstructive Uropathy	3 (1.1%)	6 (2.3%)	9 (1.7%)
Func/Anatomical Abnormality	0	3 (1.1%)	3 (0.6%)
Other	6 (2.1%)	6 (2.3%)	12 (2.2%)
Anticipated to be Persistent (All males and some females) <sup>c</sup>	20 (7.1%)	23 (8.7%)	43 (7.9%)
Anticipated to be Eliminated (Some females only) <sup>c</sup>	1 (0.4%)	4 (1.5%)	5 (0.9%)
Bacteremic at Study Entry	20 (7.1%)	23 (8.7%)	43 (7.9%)
Had a Study-Qualifying Pretreatment Urine Culture	280 (100.0%)	265 (100.0%)	545 (100.0%)
Prior Administration of Doripenem <sup>d</sup>	2 (0.7%)	2 (0.8%)	4 (0.7%)
Baseline Renal Function			
Calculated Creatinine Clearance (mL/min) <sup>e</sup>			
Normal (80 and above)	139 (49.6%)	135 (50.9%)	274 (50.3%)
Mild Failure (50-80)	103 (36.8%)	96 (36.2%)	199 (36.5%)
Moderate Failure (30-50)	33 (11.8%)	30 (11.3%)	63 (11.6%)
Severe Failure (less than 30)	5 (1.8%)	4 (1.5%)	9 (1.7%)
Region			
North America	16 (5.7%)	16 (6.0%)	32 (5.9%)
South America	129 (46.0%)	121 (45.7%)	250 (45.9%)
Europe	135 (48.2%)	128 (48.3%)	263 (48.3%)

cLUTI = complicated lower urinary tract infection; Func = functional; N = number of patients in the analysis set; max = maximum; min = minimum; n = number of patients who meet criteria; SD = standard deviation; TOC = test-of-cure.

Notes: 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.

<sup>a</sup> Mixed race and races not listed were classified as "Other".

<sup>b</sup> Body Mass Index = weight (kg)/height (m<sup>2</sup>).

<sup>c</sup> Patients for whom at least 1 complication, including male gender, was anticipated to persist throughout study drug therapy and patients for whom all complications were anticipated to be eliminated during study drug therapy.

<sup>d</sup> Only applies to patients who were enrolled under the original protocol or protocol Amendment 1.

<sup>e</sup> Calculated using the Cockcroft-Gault formula with the patient's actual body weight.

**Clinical Reviewer’s Comments:** *The demographics of sex, race, and age were similar between the two treatment arms. The vast majority of patients in both groups were outside of the U.S., which had 18 sites that enrolled only 97 patients (12.9%). The baseline diagnosis of cLUTI and pyelonephritis were similar in the number of patients enrolled in both treatment arms.*

#### 6.1.4.2 Urological History

The following table shows the urological history for the ME at TOC population. The data were taken from Applicant’s Table 15.1.4.1-2, found on page 235 of the CSR.

Table 4. Urological History of the ME at TOC Population.

Category	Doripenem IV (N=280)	Levofloxacin IV (N=265)	Total (N=545)
No Clinically Significant History	35 (12.5%)	33 (12.5%)	68 (12.5%)
Clinically Significant History in at Least one Category	245 (87.5%)	232 (87.5%)	477 (87.5%)
Pyelonephritis	101 (36.1%)	103 (38.9%)	204 (37.4%)
Other	104 (37.1%)	91 (34.3%)	195 (35.8%)
Urogenital surgery	68 (24.3%)	61 (23.0%)	129 (23.7%)
Nephrolithiasis	51 (18.2%)	46 (17.4%)	97 (17.8%)
Recurrent UTI	52 (18.6%)	40 (15.1%)	92 (16.9%)
Indwelling catheter/stent/sprint	33 (11.8%)	46 (17.4%)	79 (14.5%)
Prostatic hypertrophy	45 (16.1%)	32 (12.1%)	77 (14.1%)
Complicated UTI	29 (10.4%)	39 (14.7%)	68 (12.5%)
Obstructive uropathy due to fibrosis	31 (11.1%)	34 (12.8%)	65 (11.9%)
Uncomplicated UTI	26 (9.3%)	28 (10.6%)	54 (9.9%)
Cancer of the urinary tract	21 (7.5%)	19 (7.2%)	40 (7.3%)
Residual urine after voiding	17 (6.1%)	7 (2.6%)	24 (4.4%)
Obstructive uropathy due to bladder tumor	3 (1.1%)	3 (1.1%)	6 (1.1%)
Asymptomatic bacteriuria	2 (0.7%)	2 (0.8%)	4 (0.7%)
Congenital urinary tract stricture	3 (1.1%)	1 (0.4%)	4 (0.7%)
Neurogenic bladder	0	2 (0.8%)	2 (0.4%)

Note: Percentages are based on the number of patients in the given patient sample in each treatment group.

For patients in the ME at TOC analysis set, the two treatment arms were balanced with respect to urological history, except slightly more patients in the doripenem than the levofloxacin treatment arm had a history of prostatic hypertrophy (16% - doripenem, 12% - levofloxacin) and residual after voiding (65 versus 3%, respectively). A total of 68 (12.5%) patients overall and 12.5% in each treatment arm had no clinically significant urological history.

### 6.1.4.3 Protocol Violations

Table 5. Protocol Deviation by the ME at TOC Population.

Violation Description	Doripenem IV	Levofloxacin IV	Total
Inclusion or exclusion criteria not met	10/280 (3.6%)	6/265 (2.3%)	16/545 (2.9%)
Clinical assessment not performed at EOT (IV)	7/280 (2.5%)	9/265 (3.4%)	16/545 (2.9%)
TOC urine culture obtained outside the protocol specified 6-9 day post therapy window from patients who were not prior microbiological failures	10/280 (3.6%)	10/265 (3.8%)	20/545 (3.7%)
TOC clinical assessment performed outside of the protocol specified 6-9 days post therapy window on patients who were not prior clinical failures	8/280 (2.9%)	9/265 (3.4%)	17/545 (3.1%)
Patients switched to oral therapy before meeting the final protocol criteria to switch to oral therapy	4/280 (1.4%)	5/265 (1.9%)	9/545 (1.7%)
Non-bacteremic patients received more than 12 days total of IV and oral therapy or bacteremic patients received more than 16 days total of IV and oral therapy	1/280 (0.4%)	0	1/545 (0.2%)
Patients who did not receive 2 days of IV therapy after bladder instrumentation or treatment for an obstruction	6/280 (2.1%)	0	6/545 (1.1%)

Note: Percentages are based on the number of patients who are ME at TOC

Patient 406/05011 received the required number of doses but the timing of the doses was identified as non-compliant.

[1] Missing doses were identified by the check box on the CRF.

[2] Patients randomized to one treatment group who were inadvertently treated throughout the study with the alternative treatment regimen are included in the treatment group for the treatment actually received. Therefore, patients 106/07010 and 405/06194 handled in this manner have been added to the total number of randomized patients for doripenem IV.

Data were taken from Applicant's Table 15.1.1.4-2, found on page 176 of CSR.

### 6.1.4.4 Concomitant Antibacterial Medications

Concomitant antibacterials in the ME at TOC analysis set were allowed per study protocol for treatment of evaluable failures. In addition, patients were allowed to resume the use of concomitant antibiotics for UTI prophylaxis after the TOC visit. The frequency and distribution of concomitant antibacterials were generally similar in both treatment arms in the ME at TOC and CE at TOC analysis sets. In the ITT analysis set, the concomitant antibacterial medications received most commonly were ciprofloxacin and levofloxacin, approximately 5% in both treatment arms.

Approximately 25% of patients in the ITT analysis set and approximately 14% of patients in both the ME at TOC and CE at TOC analysis sets received at least 1 concomitant antibacterial medication.

Overall, the concomitant use of any specific antibacterial medication was low (less than 5% in both treatment arms) and similar in both the ME at TOC and CE at TOC analysis sets. In the ITT analysis set, the concomitant antibacterial medications received most commonly were the

quinolones, ciprofloxacin and levofloxacin, which were used by approximately 5% of the patients in both treatment arms. Concomitant quinolones were prescribed mainly for the treatment of a urinary tract related infection.

#### 6.1.4.5 Reasons for Exclusion from Efficacy Analysis

Table 6 shows the reasons listed by the Applicant for the exclusion from efficacy analysis for the various populations in the study. The data were taken from Table 12, found on page 71 of the CSR and Table 15.1.1.3, found on page 168 of the CSR.

Table 6. Reasons for Exclusion from Efficacy Analysis [1]

	Doripenem IV (N = 377)	Levofloxacin IV (n = 376)	Total (N = 753)
<b>Patients included in the ITT patient sample</b>	<b>376 (99.7%)</b>	<b>372 (98.9%)</b>	<b>748 (99.3%)</b>
MITT_1 Sample			
MITT_1 Evaluable	327 (86.7%)	321 (85.4%)	648 (86.1%)
Not MITT_1 Evaluable	50 (13.3%)	55 (14.6%)	105 (13.9%)
Reasons Not MITT_1 Evaluable [2]			
No Study-Qualifying Baseline Urine Culture	50 (13.3%)	50 (13.3%)	100 (13.3%)
No Study Drug Administered	1 (0.3%)	4 (1.1%)	5 (0.7%)
Other [4]	0	1 (0.3%)	1 (0.1%)
Microbiologically Evaluable at TOC Sample			
ME at TOC Evaluable	280 (74.3%)	265 (70.5%)	545 (72.4%)
Not ME at TOC Evaluable	97 (25.7%)	111 (29.5%)	208 (27.6%)
Reasons Not ME at TOC Evaluable [2]			
No Study-Qualifying Baseline Urine Culture	50 (13.3%)	50 (13.3%)	100 (13.3%)
Clinical Disease Definition Not Met	3 (0.8%)	4 (1.1%)	7 (0.9%)
Significant Inclusion/Exclusion Criteria Violation	3 (0.8%)	10 (2.7%)	13 (1.7%)
Not Compliant with Study Drug Therapy	19 (5.0%)	32 (8.5%)	51 (6.8%)
TOC Window Violation or Missing Interpretable TOC Urine Culture	33 (8.8%)	43 (11.4%)	76 (10.1%)
Prior Antibiotic Violation	0	0	0
Confounding Concomitant Antibiotic	7 (1.9%)	6 (1.6%)	13 (1.7%)
Confounding Event or Procedure	0	0	0
Clinically Evaluable at TOC Sample			
CE at TOC Evaluable	286 (75.9%)	266 (70.7%)	552 (73.3%)
Not CE at TOC Evaluable	91 (24.1%)	110 (29.3%)	201 (26.7%)
Reasons Not CE at TOC Evaluable [2]			
No Study-Qualifying Baseline Urine Culture	50 (13.3%)	50 (13.3%)	100 (13.3%)
Clinical Disease Definition Not Met	3 (0.8%)	4 (1.1%)	7 (0.9%)
Asymptomatic cLUTI at Baseline	15 (4.0%)	15 (4.0%)	30 (4.0%)
Significant Inclusion/Exclusion Criteria Violation	3 (0.8%)	10 (2.7%)	13 (1.7%)
Not Compliant with Study Drug Therapy	19 (5.0%)	32 (8.5%)	51 (6.8%)
TOC Window Violation or Missing TOC Clinical Assessment	65 (17.2%)	82 (21.8%)	147 (19.5%)
Prior Antibiotic Violation	0	0	0
Confounding Concomitant Antibiotic	6 (1.6%)	7 (1.9%)	13 (1.7%)
Confounding Event or Procedure	0	0	0
Other [5]	1 (0.3%)	0	1 (0.3%)

Notes:

[1] Percentages are based on the number of patients randomized to each treatment group.

[2] Reasons for exclusion from a patient sample were assessed in the order presented. More than one reason may have been recorded.

- [3] At LFU, the outcomes of interest are the sustained eradication of baseline pathogens and the sustained clinical cure. Therefore, evaluable microbiological failures at TOC and evaluable clinical failures at TOC are not included in the corresponding summaries at LFU. For completeness in this table, the number of such evaluable failures at TOC is also given.
- [4] Patient 101/07003 was randomized twice to the study and the second patient id is 101/07163. This patient is considered not evaluable for MITT\_1 for the second randomization.
- [5] Patient 205/07047 received a non-study antibiotic prior to TOC confounding the clinical outcome, patient a micro failure at TOC.

#### 6.1.4.6 Drug Exposure

The following table shows the extent of exposure for the patients in both arms of the study. The data were taken from Table 9, found on pages 34-35 of Module 2.7.3 – Summary of Clinical Efficacy, Complicated UTI.

Table 7. Drug Exposure for the Microbiologically Evaluable at TOC Population.

Total Duration, days	Doripenem IV 500 mg 1-h inf q8h (N = 280)	Levofloxacin IV 250 mg 1-h q24h (N = 265)
<b>IV or IV and Oral Therapy</b>		
N	280	265
Category, n (%)		
4 - 7	0	18 (6.8)
8 - 10	216 (77.1)	185 (69.8)
11-14	61 (21.8)	60 (22.6)
> 14	3 (1.1)	2 (0.8)
Mean (SD)	10.3 (0.87)	10.0 (1.51)
Median	10.0	10.0
Range	(9, 15)	(4, 15)
<b>IV Therapy</b>		
N	280	265
Category, n (%)		
<4	11 (3.9)	3 (1.1)
4 - 7	212 (75.7)	217 (81.9)
8 - 10	27 (9.6)	15 (5.7)
11 - 14	30 (10.7)	30 (11.3)
> 14	0	0
Mean (SD)	5.8 (2.40)	5.7 (2.31)
Median	5.0	5.0
Range	(3, 13)	(3, 11)
<b>Duration in Subgroup of Subjects Who Received IV Therapy Only</b>		
N	31	48
Category, n (%)		
≤5	0	10 (20.8)
6 - 7	0	8 (16.7)
>7	31 (100)	30 (62.5)
Mean (SD)	11.1 (0.44)	8.9 (2.86)
Median	11.0	11.0
Range	(10, 13)	(4, 11)

<b>Total Duration, days</b>	<b>Doripenem IV 500 mg 1-h inf q8h (N = 280)</b>	<b>Levofloxacin IV 250 mg 1-h q24h (N = 265)</b>
<b>IV and Oral Therapy in Subjects Who Were Switched to Oral Therapy</b>		
N	249	217
Category, n (%)		
8 - 10	215 (86.3)	185 (85.3)
11 - 14	31 (12.4)	30 (13.8)
> 14	3 (1.2)	2 (0.9)
Mean (SD)	10.2 (0.87)	10.2 (0.82)
Median	10.0	10.0
Range	(9, 15)	(8, 15)
<b>IV Therapy in Subjects Who Were Switched to Oral Therapy</b>		
N	249	217
Category, n (%)		
<4	11 (4.4)	3 (1.4)
4 - 7	212 (85.1)	199 (91.7)
8 - 10	26 (10.4)	15 (6.9)
Mean (SD)	5.2 (1.61)	5.0 (1.40)
Median	5.0	4.0
Range	(3, 10)	(3, 10)
<b>Oral Therapy</b>		
N	249	217
Category, n (%)		
<4	23 (9.2)	15 (6.9)
4 - 7	220 (88.4)	195 (89.9)
8 - 10	4 (1.6)	6 (2.8)
11 - 14	2 (0.8)	1 (0.5)
Mean (SD)	5.9 (1.63)	6.1 (1.49)
Median	6.0	7.0
Range	(1, 11)	(1, 11)
<b>IV and Oral Therapy in the Subgroup of Subjects Who Were Bacteremic at Baseline</b>		
N	20	23
Category, n (%)		
8 - 10	9 (45.0)	11 (47.8)
11 - 14	8 (40.0)	10 (43.5)
> 14	3 (15.0)	2 (8.7)
Mean (SD)	12.1 (2.16)	11.5 (1.88)
Median	11.0	11.0
Range	(10, 15)	(10, 15)

1-h inf q8h = 1 hour infusion every 8 hours; 1-h q24h = 1 hour infusion every 24 hours

#### 6.1.4.7 Efficacy

Primary Endpoints: The co-primary efficacy endpoints in this study are eradication rate for the baseline uropathogens at the Test-of-Cure visit (6 to 9 days after the end of study drug therapy) in the ME at TOC and mMITT\_1 populations. One of the secondary endpoints is the clinical cure rate for the clinically evaluable patients at the TOC visit, (CE at TOC population). The

following table shows the per-patient microbiological cure rates and the per-patient clinical cure rates at the TOC for the Microbiologically Modified Intent-to-Treat\_1 group, the ME at TOC population, and the CE at TOC population. The data were taken from Table 15 and Table 17, respectively, found on pages 81 and 83 of the CSR.

Table 8. The Per-Patient Microbiological and Clinical Cure Rates at the TOC visit for the ME at TOC Population, the mMITT\_1 Population, and the CE at TOC Population.

Analysis Set	Doripenem	Levofloxacin	Difference (2-sided 95% CI)
ME at TOC	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
mMITT_1	259/327 (79.2%)	251/321 (78.2%)	1.0% (-5.6%, 7.6%)
CE at TOC	272/286 (95.1%)	240/266 (90.2%)	4.9% (0.2%, 9.6%)

In the doripenem treatment arm, the microbiological cure rate was 82.1% (230/280), while the cure rate in the levofloxacin arm was 83.4% (221/265). The treatment difference between the microbiological cure rates was -1.3%, with a 2-sided 95% CI of -8.0% to 5.5%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

With regard to the mMITT\_1 analysis set, the microbiological cure rate is slightly higher among the patients who received doripenem compared to those in the levofloxacin arm. The microbiological cure rate was 79.2% (259/327) for doripenem and 78.2% (251/321) for levofloxacin. Again, the treatment difference between the two cure rates showed non-inferiority with a difference of 1% with a 2-sided 95% CI of -5.6% to 7.6%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

**Secondary Endpoints:**

Clinical cure in the CE at TOC population: The clinical cure rates at the TOC visit were greater for the doripenem treatment arm than the levofloxacin arm for patients in the CE at TOC population, 95.1% (272/286) for doripenem and 90.2% (240/266) for levofloxacin. The treatment difference between the two groups was 4.9% with a 2-sided 95% CI of 0.2% to 9.6%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

The data show doripenem to be both microbiologically and clinically effective in the treatment of cUTI including pyelonephritis and non-inferior to IV levofloxacin.

Superiority against *E. coli*:

See Section 6.1.5, Clinical Microbiology.

**Clinical Reviewer’s Comments:** *The Applicant included 40 JMP datasets in the submission that contained information concerning all aspects of the DORI- 05 study. The keval.xpt dataset was searched by the reviewer in order to confirm the results in Table 8. All of the numbers in the table were obtained by selecting for the number of cures, failures, and indeterminate results, along with unevaluable patients, that were associated with the patients in the TRTA [Actual Treatment Group] variable group. The search confirmed the numbers presented in the table.*

#### 6.1.4.8 Per-Patient Microbiological Cure Rates at TOC: Overall and by Subgroups.

The following data were taken from Applicant’s Table 18, found on page 86 of the CSR.

Table 9. Per-Patient Microbiological Cure Rates at TOC: Overall and by Subgroups for the ME at TOC Population.

	Doripenem (N=280)	Levofloxacin (N=265)	Difference
Overall	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
By Subgroup			
cLUTI			
Symptomatic	110/145 (75.9%)	99/131 (75.6%)	0.3%
Asymptomatic	106/138 (76.8%)	94/122 (77.0%)	-0.2%
Persistent Complication (Males and some Females)	4/7 (57.1%)	5/9 (55.6%)	1.6%
Eliminated Complication (Some females only)	92/124 (74.2%)	84/116 (72.4%)	1.8%
Pyelonephritis (All)	18/21 (85.7%)	15/15 (100.0%)	-14.3%
Uncomplicated	120/135 (88.9%)	122/134 (91.0%)	-2.2%
Complicated (All)	103/114 (90.4%)	97/107 (90.7%)	-0.3%
Persistent Complication (Males and some Females)	17/21 (81.0%)	25/27 (92.6%)	-11.6%
Eliminated Complication (Some females only)	17/20 (85.0%)	21/23 (91.3%)	-6.3%
Eliminated Complication (Some females only)	0/1	4/4 (100.0%)	-100.0%
Bacteremic at Baseline	19/20 (95.0%)	22/23 (95.7%)	-0.7%
Sex			
Male	88/110 (80.0%)	82/103 (79.6%)	0.4%
Female	142/170 (83.5%)	139/162 (85.8%)	-2.3%
Race			
American Indian or Alaska Native	0/0	2/2 (100.0%)	
Asian	0/0	0/0	
Black or African Heritage	18/19 (94.7%)	18/24 (75.0%)	19.7%
Caucasian	187/228 (82.0%)	178/209 (85.2%)	-3.1%
Native Hawaiian, Other Pacific Islander	0/0	0/0	
Hispanic or Latino	22/30 (73.3%)	21/27 (77.8%)	-4.4%
Other	3/3 (100.0)	2/3 (66.7%)	33.3%
Age			
<65	153/179 (85.5%)	147/170 (86.5%)	-1.0%
≥65	77/101 (76.2%)	74/95 (77.9%)	-1.7%
<75	202/240 (84.2%)	191/224 (85.3%)	-1.1%
≥75	28/40 (70.0%)	30/41 (73.2%)	-3.2%
Region			
North America	16/16 (100.0%)	15/16 (93.8%)	6.3%
South America	107/129 (82.9%)	101/121 (83.5%)	-0.5%
Europe	107/135 (79.3%)	105/128 (82.0%)	-2.8%

cLUTI = complicated urinary tract infection; N = number of patients in the analysis set; TOC = test-of-cure.

The overall microbiological cure rate was similar between doripenem and levofloxacin patients (82% and 83%, respectively). The difference between the cure rates was -1.3%, with a 2-sided 95% CI of -8.0% to 5.5%. The microbiological cure rates were similar between the doripenem and levofloxacin patients for the subgroups cLUTI (76% for each), pyelonephritis (89% for doripenem and 91% for levofloxacin), and bacteremic patients at baseline (95% for doripenem and 96% for levofloxacin). Patients who had documented bacteremia with the same pathogen isolated in the blood as in the urine were allowed to have the dose of levofloxacin increased to 500 mg q24h. Sixty-five percent (13/20) of the bacteremic patients in the doripenem treatment arm who were ME at TOC had at least 1 dose of oral levofloxacin increased to 500 mg, and 61% (14/23) of the bacteremic patients who were ME at TOC in the levofloxacin treatment arm had at least 1 dose of either IV or oral levofloxacin increased.

The microbiological cure rates by sex, race, and age in the ME at TOC population were similar between treatment arms where a sufficient number of patients ( $\geq 30$ ) were assessed.

#### 6.1.4.9 Sensitivity Analyses on the Primary Endpoint

The microbiological cure rates in the co-primary analysis sets are presented in Table 10 for the patients in the 3 sample-size groups: original population, subsequent population, and final population. The data were taken from Applicant's Table 16, found on page 82 of the CSR.

Table 10. Microbiological Cure Rates in the ME at TOC and the mMITT\_1 Analysis Sets for the Three Sample Size Populations: Original Population, Subsequent Population, and Final Population.

	Doripenem	Levofloxacin	Difference (2-sided 95% CI) <sup>a</sup>
<b>ME at TOC Analysis Set</b>			
Original	133/163 (81.6%)	122/149 (81.9%)	-0.3% (-9.5%, 8.9%)
Subsequent <sup>b</sup>	97/117 (82.9%)	99/116 (85.3%)	-2.4% (-12.7%, 7.8%)
Final	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
<b>mMITT_1 Analysis Set</b>			
Original	152/192 (79.2%)	142/188 (75.5%)	3.6% (-5.3%, 12.6%)
Subsequent <sup>b</sup>	107/135 (79.3%)	109/133 (82.0%)	-2.7% (-12.9%, 7.5%)
Final	259/327 (79.2%)	251/321 (78.2%)	1.0% (-5.6%, 7.6%)

CI = confidence interval; ME = microbiologically evaluable; mMITT\_1 = microbiologically modified intent-to-treat, definition 1; TOC = test-of-cure

<sup>a</sup> 2-sided 95% CI for difference in cure rates using the normal approximation to the difference between 2 binomial distributions with continuity correction

<sup>b</sup> Subsequent Population is equivalent to Beyond the Original Sample Size Population in source tables.

Cure rates in the doripenem arm were comparable between the original and subsequent populations for each treatment arm and analysis set. In the levofloxacin arm, cure rates were higher in the subsequent population, which favored the comparator in the final analysis. Furthermore, the microbiological cure rates were similar between the treatment arms for patients in the subsequent population in the ME at TOC and mMITT\_1 analysis sets. With the original set, the results are robust and consistent with the later populations.

**FDA Sensitivity Analyses of the Applicant’s Microbiological Datasets.**

A sensitivity analysis based on receipt of concomitant antibiotics was performed by Dr. Yunfan Deng, FDA statistician. The results are shown in the following tables.

Table 11. Sensitivity Analysis for Concomitant Antibiotics II -- Per-Patient Microbiological Cure Rates at the TOC Visit (Microbiologically Evaluable (ME) at TOC and Microbiologically Modified Intent-to-Treat Definition 1 (mMITT\_1) Analysis Set)

	Doripenem	Levofloxacin	Difference (95% CI)
<b>Study Dori-05 ME at TOC Analysis Set</b>			
Subjects With Concomitant Antibiotics before/on TOC date	8/12 (66.7.1%)	7/11 (63.6%)	3.0%
Subjects with Concomitant Antibiotics taken after TOC date	20/31 (64.5%)	8/29 (27.6%)	36.9%
Subjects Without Any Concomitant Antibiotics	202/237 (85.2%)	206/225 (91.6%)	-6.3% (-12.5%, -0.01%)
Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics	222/268 (82.8%)	214/254 (84.3%)	-1.4% (-8.2%, 5.3%)
Overall	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)

	Doripenem	Levofloxacin	Difference (95% CI)
<b>mMITT 1 Analysis Set</b>			
Subjects With Concomitant Antibiotics before/on TOC date	17/22 (77.3%)	15/22 (68.2%)	9.1%
Subjects with Concomitant Antibiotics taken after TOC date	26/42 (61.9%)	14/44 (31.8%)	30.1%
Subjects Without Any Concomitant Antibiotics	216/263 (82.1%)	222/255 (87.1%)	-4.9% (-11.5%, 1.7%)
Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics	242/305 (79.3%)	236/299 (78.9%)	0.4% (-6.4%, 7.2%)
Overall	259/327 (79.2%)	252/321 (78.2%)	1.0% (-5.6%, 7.6%)

There were 12 patients in the doripenem arm and 11 patients in the levofloxacin arm who received concomitant antibiotics prior to the TOC visit. The cure rate for the doripenem patients in this group was 66.7% (8/12) compared to a cure rate of 63.6% (7/11) for the levofloxacin group. When these patients are excluded from analysis, the cure rates for the doripenem patients and the levofloxacin patients are 222/268 (82.8%) and 214/254 (84.3%), respectively. The difference between the two treatment arms is -1.4% with a 95% CI around the difference of (-8.2%, 5.3%). Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

Another sensitivity analysis was performed with the same group of patients treated as microbiological failures at the TOC visit. The results are shown in the following table.

Table 12. Sensitivity Analysis for Concomitant Antibiotics III -- Per-Patient Microbiological Cure Rates at the TOC Visit (Microbiologically Evaluable (ME) at TOC and Microbiologically Modified Intent-to-Treat Definition 1 (mMITT\_1 Analysis Set) Where Subjects with Concomitant Antibiotics before/on TOC Date Treated as Failure

	Doripenem	Levofloxacin	Difference (95% CI)
<b>Study Dori-05</b>			
<b>ME at TOC Analysis Set</b>			
Subjects With Concomitant Antibiotics before/on TOC Date Treated As Failure	222/280 (79.2%)	214/265 (80.8%)	-1.5% (-8.6%, 5.6%)
<b>mMITT_1 Analysis Set</b>			
Subjects With Concomitant Antibiotics before/on TOC Date Treated As Failure	242/327 (74.0%)	236/321 (73.5%)	0.5% (-6.6%, 7.6%)

The cure rate for the doripenem arm with the 12 patients who received concomitant antibiotics prior to the TOC visit treated as microbiological failures was 79.2% compared to 80.8% for the levofloxacin group. The difference between the two treatment groups was -1.5% with a 95% CI around the difference of (-8.6%, 5.6%). Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

Similar results were obtained for the mMITT\_1 analysis set where the cure rates for the doripenem and levofloxacin treatment arms were 74.0% and 73.5, respectively. The treatment difference was 0.5% with a 95% CI around the difference of (-6.6 %, 7.6%). Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

Table 13. Patients who received concomitant antibiotics prior to the TOC visit and were considered cures in both treatment arms.

Patient Number	Baseline pathogen	Concomitant medication	Condition treated
<b>Doripenem Treatment arm</b>			
013 - 3007	<i>Proteus mirabilis</i>	Polysporin ointment (polymyxin B) (bacitracin)	laceration
034 - 3023	<i>Escherichia coli</i>	Vancomycin Metronidazole	pneumonia
101 - 7063	<i>Klebsiella oxytoca</i>	Corticosteroids Combination with antibiotics	Prophylaxis against urethra stenosis
201 - 7123	<i>Klebsiella pneumoniae</i>	Gentamicin	Postoperative prophylaxis
301 - 6020	<i>Escherichia coli</i>	Linfol (norfloxacin)	Vulvovaginitis
401-6126	<i>Escherichia coli</i>	Amoxicillin	Odynophagia/cough/fever
401 - 6173	<i>Escherichia coli</i>	Nitrofurantoin	Dysuria and suprapubic pain
401 - 6182	<i>Escherichia coli</i>	Secnidazole	Vaginitis
<b>Levofloxacin Treatment arm</b>			
101 - 7020	<i>Escherichia coli</i>	Corticosteroids Combination with antibiotics	Inflammation of urethra
101 - 7061	<i>Escherichia coli</i>	Corticosteroids Combination with antibiotics	Prophylaxis against urethra stenosis
101 - 7187	<i>Escherichia coli</i>	Doxycycline	Not reported
103 - 9033	<i>Enterococcus Faecalis</i>	Clindamycin	Preoperative treatment during extra-corporeal shock wave lithotripsy
104 - 17081	<i>Escherichia coli</i>	Not reported	Not reported
304 - 6002	<i>Escherichia coli</i>	Corticosteroids Combination with Antibiotics Linfol (norfloxacin)	Vulvovaginitis
401 - 6197	<i>Escherichia coli</i>	Tinidazole	Vaginosis

**Clinical Reviewer's Comment:** *Some of the concomitant antibiotics received by the patients in the above table do have coverage against their baseline pathogen. For example, amoxicillin, nitrofurantoin, and norfloxacin in most instances, will eradicate strains of E. coli and other members of the Enterobacteriaceae. Unfortunately, no susceptibility tests were conducted with the antibiotics they received.*

One of the changes made by the Applicant in analyzing the microbiological data was to expand the protocol-defined window at the TOC visit from 6 to 9 days after administration of the last dose of study drug to 5 to 11 days after administration of the last dose of study drug. The data presented in Table 8 was based on the expanded window at the TOC visit, 5 to 11 days after administration of the last dose of study drug. A sensitivity analysis was performed by Dr.

Yunfan Deng, FDA statistician, using the protocol-defined window of 6 to 9 days after administration of the last dose of study drug. The results are shown in the following table.

Table 14. Statistical Reviewer’s Sensitivity Analysis Results for Study DORI-05 With a TOC Window at 6 to 9 Days After Administration of the Last Dose of Study Drug.

	Doripenem	Levofloxacin	Difference (95% CI)
ME at TOC Analysis Set	223/271 (82.3%)	213/256 (83.2%)	-1.0% (-7.8%, 5.9%)
mMITT_1 Analysis Set	240/293 (81.9%)	232/286 (81.1%)	0.8% (-5.9%, 7.5%)

**Clinical Reviewer’s Comments:** *The analysis by Dr. Deng shows the changes in the two treatment arms to be very similar. In both populations, results are consistent with those seen with the expanded visit windows as evidenced by the lower bound of the 95% CI exceeding -10% and the 95% CI including the value 0.*

*In the doripenem-treatment arm, the success rate for the ME at TOC population improves slightly from a cure rate of 82.1% (230/280) to a cure rate of 82.3% (223/271). In the levofloxacin-treatment arm, the success rate for this population decreases slightly from 83.4% (221/265) to 83.2% (213/256).*

*In the mMITT\_1 population, both treatment arms show an improvement in the success rate. The cure rate for patients treated with doripenem increases from 79.2% (259/327) to 81.9% (240/293), while the cure rate for patients treated with levofloxacin increased from 78.2% (251/321) to 81.1% (232/286). Therefore, the re-analysis showed no major differences between the two treatment arms as a result of expanding the TOC visit window.*

### 6.1.5 Clinical Microbiology

The following table shows the eradication rates for the baseline uropathogens isolated from both treatment groups in the study. Confidence intervals are shown for those groups of pathogens containing 30 or more isolates.

Table 15 The Per-Pathogen Microbiological Outcome (Eradication) for Baseline Pathogens at the TOC Visit for the ME at the TOC Population.

	<b>Doripenem Patients (N = 280)</b>	<b>Levofloxacin Patients (N = 265)</b>	<b>Difference (2-sided 95% CI)</b>
<b>Baseline Uropathogens</b>	(N = 283) F/N1 (%)	(N = 266) F/N1 (%)	
<b>Gram Positive</b>			
<i>Staphylococcus aureus</i>	1/1 (100%)	0/1	100%
MRSA	1/1 (100%)	0/1	100%
<i>Enterococcus faecalis</i>	5/7 (71.4%)	1/3 (33.3%)	38.1%
<i>Enterococcus hirae</i>	1/1 (100%)	0/0	
<b>Gram Negative</b>			
Enterobacteriaceae	217/260 (83.4%)	217/254 (85.4%)	-2.0% (-8.6%, 4.7%)
<i>Citrobacter freundii</i>	4/4 (100%)	3/4 (75%)	25%
<i>Enterobacter aerogenes</i>	1/1 (100%)	2/2 (100%)	
<i>Enterobacter cloacae</i>	7/7 (100%)	3/7 (42.9%)	57.1%
<i>Escherichia coli</i>	168/199 (84.4%)	184/211 (87.2%)	-2.8% (-10.0%, 4.5%)
Levofloxacin-resistant strains	11/20 (55.0%)	6/21 (28.6%)	26.4%
Levofloxacin-susceptible strains	150/172 (87.2%)	173/185 (93.5%)	-6.3% (-13.0%, 0.4%)
ESBL-producing strains	2/3 (66.7%)	1/3 (33.3%)	33.3%
Non-ESBL-producing strains	159/189 (84.1%)	178/203 (87.7%)	-3.6% (-11.0%, 3.9%)
<i>Klebsiella oxytoca</i>	5/5 (100%)	4/4 (100%)	0
<i>Klebsiella pneumoniae</i>	10/12 (83.3%)	5/8 (62.5%)	20.8%
<i>Morganella morganii</i>	0/0	1/1 (100%)	
<i>Proteus mirabilis</i>	16/23 (69.6%)	13/15 (86.7%)	-17.1%
<i>Proteus penneri</i>	0/0	1/1 (100%)	
<i>Serratia marcescens</i>	3/4 (75%)	1/1 (100%)	-25%
<b>Non-fermenters</b>			
<i>Acinetobacter baumannii</i>	3/3 (100%)	0/1	100%
<i>Pseudomonas aeruginosa</i>	5/9 (55.6%)	5/7 (71.4%)	-15.9%
<b>Other Species</b>			
<i>Chromobacterium violaceum</i>	1/1 (100%)	0	100%
<i>Pasteurella multocida</i>	0/1 (0%)	0	0

CI = confidence interval; ESBL = extended spectrum  $\beta$ -lactamase; F = the number of pathogens eradicated; MRSA = methicillin-resistant *Staphylococcus aureus*; N = number of patients; NI = number of patients with a baseline pathogen and a follow-up culture at the TOC visit; TOC = test-of-cure. CIs are presented for groups of pathogens containing 30 or more isolates.

There were 283 organisms isolated at baseline from the 280 patients in the doripenem arm of the study and 266 organisms isolated from the 265 patients in the levofloxacin arm. Three of the doripenem patients had two pathogens present at the screening visit, while only one levofloxacin patient had two pathogens present.

The overall eradication rates for members of the Enterobacteriaceae were 83.4% (217/260) for the doripenem group and 85.4% (217/254) for the levofloxacin group for the ME at TOC population. The treatment difference was -2.0% with a 2-sided 95% CI of -8.6% to 4.7%. The most common pathogen isolated among patients in both treatment arms was *E. coli*, with 199 isolates from the doripenem arm and 211 from the levofloxacin arm. The eradication rate was 84.4% in the doripenem group and 87.2% in the levofloxacin group, with a treatment difference of -2.8% and a 2-sided 95% CI of -10.0% to 4.5%. Among the 20 levofloxacin-resistant *E. coli* in the doripenem group, 11 were eradicated for a cure rate of 55%. In the levofloxacin group, only 6 of the 21 levofloxacin-resistant *E. coli* were eradicated for a cure rate of 28.6%.

Doripenem was effective in eradicating *Klebsiella pneumoniae* with a cure rate of 83.35% (10/12), compared to a cure rate of 62.5% (5/8) for levofloxacin. Levofloxacin was more effective in eradicating *Proteus mirabilis* with a cure rate of 86.7% compared to 69.6% for doripenem.

Among non-fermenters, three isolates of *A. baumannii* were all eradicated, while only 5 of 9 isolates of *P. aeruginosa* were eradicated among patients who received doripenem.

**Clinical Reviewer's Comments:** *The KBPATHG.xpt dataset was searched by the reviewer in order to confirm the results in Table 15. All of the numbers in the table were obtained by selecting for the number of eradications, failures, and indeterminate results listed for the variable group BPTOCO [Baseline Pathogen Outcome at TOC], along with unevaluable patients, that were associated with the patients in the TRTA [Actual Treatment Group]. The search confirmed the numbers presented in the table.*

*The data show doripenem to be effective in eradicating E. coli and K. pneumoniae, with eradication rates of 84.4% and 83.3%, respectively. The other organisms are either too few in number or have much lower eradication rates. Both the number of E. coli resistant to levofloxacin and the eradication rates are too small to make any conclusions regarding the effect of doripenem on these strains.*

#### **FDA Review of Microbiological Datasets.**

As a result of the sensitivity analysis based on concomitant antibiotics received prior to the TOC visit performed by Dr. Yunfan Deng, the table showing the microbiological outcome was revised to include the results of her analysis. In both arms of the study, pathogens from patients who received antibiotics prior to the TOC were now included as failures. This affected 12 patients in the doripenem arm and 11 in the levofloxacin arm. The results are shown in the following table.

Table 16. The Per-Pathogen Microbiological Outcome (Eradication) for Baseline Pathogens at the TOC Visit for the ME at the TOC Population (Re-classifying patients who received concomitant antibiotics as failures)

	Doripenem Patients (N = 280)	Levofloxacin Patients (N = 265)	Difference (2-sided 95% CI)
<b>Baseline Uropathogens</b>	(N = 283)	(N = 266)	
Gram Positive	F/NI (%)	F/NI (%)	
<i>Staphylococcus aureus</i>	1/1 (100%)	0/1	100%
MRSA	1/1 (100%)	0/1	100%
<i>Enterococcus faecalis</i>	5/7 (71.4%)	0/3	71.4%
<i>Enterococcus hirae</i>	1/1 (100%)	0/0	
Gram Negative			
Enterobacteriaceae	209/260 (80.4%)	211/254 (83.1%)	-2.7% (-9.4%, 4.0%)
<i>Citrobacter freundii</i>	4/4 (100%)	3/4 (75%)	25%
<i>Enterobacter aerogenes</i>	1/1 (100%)	2/2 (100%)	
<i>Enterobacter cloacae</i>	7/7 (100%)	3/7 (42.9%)	57.1%
<i>Escherichia coli</i>	163/199 (81.9%)	178/211 (84.3%)	-2.4% (-9.7%, 4.8%)
Levofloxacin-resistant strains	11/20 (55.0%)	5/21 (23.8%)	31.2%
Levofloxacin-susceptible strains	145/172 (84.3%)	168/185 (90.8%)	-6.5% (-13.4%, 0.3%)
ESBL-producing strains	2/3 (66.7%)	1/3 (33.3%)	33.3%
Non-ESBL-producing strains	154/189 (81.4%)	172/203 (84.7%)	-3.3% (-10.7%, 4.2%)
<i>Klebsiella oxytoca</i>	4/5 (80%)	4/4 (100%)	-20%
<i>Klebsiella pneumoniae</i>	9/12 (75%)	5/8 (62.5%)	12.5%
<i>Morganella morganii</i>	0/0	1/1 (100%)	
<i>Proteus mirabilis</i>	15/23 (65.2%)	13/15 (86.7%)	-21.5%
<i>Proteus penneri</i>	0/0	1/1 (100%)	
<i>Serratia marcescens</i>	3/4 (75%)	1/1 (100%)	-25%
Non-fermenters			
<i>Acinetobacter baumannii</i>	3/3 (100%)	0/1	100%
<i>Pseudomonas aeruginosa</i>	5/9 (55.6%)	5/7 (71.4%)	-15.9%
Other Species			
<i>Chromobacterium violaceum</i>	1/1 (100%)	0	100%
<i>Pasteurella multocida</i>	0/1 (0%)	0	0

**Clinical Reviewer's Comments:** The inclusion of Dr. Deng's data resulted in lower eradication rates for 8 pathogens in the doripenem arm and 7 in the levofloxacin arm. *E. coli*

*was the principal pathogen most affected in both treatment arms. The eradication rate for this organism dropped in the doripenem arm from 84.4% to 81.9%, while the cure rate for E. coli from the levofloxacin arm changed from 87.2% to 84.3%.*

#### **6.1.5.1 Baseline Uropathogen Susceptibility**

The susceptibility characteristics for the uropathogens isolated at baseline from the ME at TOC population are shown in Table 17. The data were extracted from Applicant's Table 15.1.2.2-3, found on pages 223-224 of the CSR.

Among the 280 Doripenem patients, there were three who had two different pathogens each at the screening visit. Only one levofloxacin patient had two different pathogens. There was an isolate of *Enterococcus faecalis* that was resistant to doripenem among those isolates in the doripenem arm. There were 34 pathogens among the levofloxacin patients that were resistant to levofloxacin. One was an *Enterococcus faecalis*, while the others were all Gram negative organisms. Twenty strains of *E. coli* were resistant to levofloxacin in the doripenem arm and 21 similar strains were present in the levofloxacin arm.

Among the ME at TOC population, there were 20 in the doripenem arm and 23 in the levofloxacin arm who were bacteremic at baseline. *E. coli* was the most common pathogen isolated from bacteremic patients with 17 found in the doripenem arm and 20 in the levofloxacin arm. None of them was resistant to either doripenem or levofloxacin.

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Table 17. Baseline Uropathogen Susceptibility Characteristics.

Baseline Uropathogen	Doripenem IV Patients (N = 280)				Levofloxacin IV Patients (N = 265)			
	NI [1]	NT [1]	Susceptible or Intermediate	Resistant [2]	NI [1]	NT [1]	Susceptible or Intermediate	Resistant [3]
Gram Positive	9	9	8	1	4	4	3	1
Enterococcus faecalis	7	7	6 (85.7%)	1 (14.3%)	3	3	3 (100%)	0
Enterococcus hirae	1	1	1 (100%)	0	0	0	0	0
Staphylococcus aureus	1	1	1 (100%)	0	1	1	0	1 (100%)
Gram Negative	274	262	262	0	262	255	222	33
Acinetobacter baumannii	3	3	3 (100%)	0	1	1	1 (100%)	0
Chromobacterium violaceum	1	0	0	0	0	0	0	0
Citrobacter freundii	4	4	4 (100%)	0	4	3	2 (66.7%)	1 (33.3%)
Citrobacter koseri (diversus)	1	1	1 (100%)	0	0	0	0	0
Enterobacter aerogenes	1	1	1 (100%)	0	2	2	2 (100%)	0
Enterobacter cloacae	7	7	7 (100%)	0	7	7	3 (42.9%)	4 (57.1%)
Escherichia coli	199	192	192 (100%)	0	211	206	185 (89.8%)	21 (10.2%)
Levofloxacin-resistant strains [4]	20	20	20 (100%)	0	21	21	0	21 (100%)
Klebsiella oxytoca	5	5	5 (100%)	0	4	4	4 (100%)	0
Klebsiella pneumoniae	12	10	10 (100%)	0	8	7	6 (85.7)	1 (14.3%)
Morganella morganii	1	1	1 (100%)	0	1	1	1 (100%)	0
Pasteurella multocida	1	0	0	0	0	0	0	0
Proteus mirabilis	23	23	23 (100%)	0	15	15	13 (86.7%)	2 (13.3%)
Proteus penneri	0	0	0	0	1	1	1 (100%)	0
Providencia rettgeri	1	1	1 (100%)	0	0	0	0	0
Providencia stuartii	1	1	1 (100%)	0	0	0	0	0
Pseudomonas aeruginosa	9	8	8 (100%)	0	7	7	3 (42.9%)	4 (57.1%)
Salmonella species	1	1	1 (100%)	0	0	0	0	0
Serratia marcescens	4	4	4 (100%)	0	1	1	1 (100%)	0

Notes:

[1] NI is the number of pathogens isolated. NT is the number of pathogens in which an interpretation of susceptibility results was available. Within each patient, a pathogen is uniquely represented using the most resistant strain. Percentages are given with respect to the NT for the given genus and species in the respective study arm.

- [2] For doripenem IV, pathogens are considered susceptible (S), intermediate (I) or resistant K<sup>®</sup> if the MIC level is  $\leq 4$   $\mu\text{g/mL}$ , = 8  $\mu\text{g/mL}$  or  $\geq 16$   $\mu\text{g/mL}$ , respectively.  
 [3] For levofloxacin IV, susceptible, intermediate or resistant is defined according to the CLSI recommendations.  
 [4] Escherichia coli; Drug tested = levofloxacin; Test Method = MIC Micro Broth Dilution testing; Result Value =  $\geq 8$ , Result unit = mg/mL.

Table 18. Baseline Blood Pathogen Susceptibility

Baseline Uropathogen	Doripenem IV (N = 20)				Levofloxacin IV (N = 23)			
	NI [1]	NT [1]	Susceptible or Intermediate	Resistant [2]	NI [1]	NT [1]	Susceptible or Intermediate	Resistant [3]
Gram Negative	20	19	19	0	23	19	19	0
Acinetobacter baumannii	1	0	0	0	0	0	0	0
Escherichia coli	16	16	16 (100%)	0	20	16	16 (100%)	0
Levofloxacin-resistant strains [4]	0	0	0	0	0	0	0	0
Klebsiella pneumoniae	2	2	2 (100%)	0	2	2	2 (100%)	0
Proteus mirabilis	0	0	0	0	1	1	1 (100%)	0
Pseudomonas aeruginosa	1	1	1 (100%)	0	0	0	0	0

Notes: Data were taken from Applicant's Table 15.1.2.3-1, page 229 of CSR.

- [1] NI is the number of pathogens isolated. NT is the number of pathogens in which an interpretation of susceptibility results was available. Within each patient, a pathogen is uniquely represented using the most resistant strain. Percentages are given with respect to the NT for the given genus and species in the respective study arm.  
 [2] For doripenem IV, pathogens are considered susceptible (S), intermediate (I) or resistant K<sup>®</sup> if the MIC level is  $\leq 4$   $\mu\text{g/mL}$ , = 8  $\mu\text{g/mL}$  or  $\geq 16$   $\mu\text{g/mL}$ , respectively.  
 [3] For levofloxacin IV, susceptible, intermediate or resistant is defined according to the CLSI recommendations.  
 [4] Escherichia coli; Drug tested = levofloxacin; Test Method = MIC Micro Broth Dilution testing; Result Value =  $\geq 8$ , Result unit = mg/mL.

Table 19. Per Patient Microbiological and Clinical Outcome at LFU.

Outcome at LFU	Doripenem IV	Levofloxacin IV	Difference in % Doripenem – Levofloxacin [1]
Sustained Eradication [2]	185/209 (88.5%)	186/207 (89.9%)	-1.4%
Sustained Clinical Cure [3]	228/251 (90.8%)	218/229 (95.2%)	- 4.4%

[1] Difference in percentages = percentages of Doripenem IV – percentages of levofloxacin IV.

[2] For sustained eradication, percentages are based on the total number of patients in each treatment arm that are ME at LFU and had eradication of baseline uropathogens at TOC.

[3] For the sustained clinical cure, percentages are based on the number of patients in each treatment arm that are CE at LFU and were classified as clinically cured at TOC.

The data in Table 18 were taken from Applicant's Table 15.2.3.1-2, found on page 521 of the CSR.

**Clinical Reviewer's Comments:** *The KEVAL.xpt dataset was searched by the reviewer in order to confirm the results in Table 19. All of the numbers in the table were obtained by selecting for the number of evaluable patients at the final visit, along with the number of eradications, cures, failures, and relapses that were associated with the patients in the TRTA [Actual Treatment Group]. The search confirmed the numbers presented in the table.*

*The data in Table 19 were reviewed by Scott Komo, Dr.P.H., FDA Statistician. He found that the difference in the Sustained Eradication rates was -1.34%, instead of -1.4%. He also determined the 95% CIs for both cure rates, since the Applicant had not done so. He found the 95% CI around the difference of -1.34% for the Sustained Eradication rate was (-7.3%, 4.6%). For the Sustained Clinical Cure rate difference of -4.4%, he found a 95% CI of (-8.9%, 0.2%).*

**FDA Review of Random Sampling of Case Report Forms from Study DORI- 05.**

The Division requested that the Applicant submit a 10 % random sample of the doripenem and levofloxacin case report forms (CRFs) from study DORI-05. The CRFs were reviewed for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of the protocol, and accuracy in reporting of results. The results were then compared to those of the Applicant. Seventy-six CRFs were examined, 38 from each treatment arm.

During the review, there was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer for 71 of the 76 CRFs. As no systematic errors were identified, no additional CRFs were reviewed and the Applicant's data were used for the review. However, there were some discrepancies present for five of the CRFs. These discrepancies are summarized in the following list:

Patient Number	Comments
101-7007 Doripenem	The Applicant has this patient listed as evaluable at the TOC and LFU visits. However, the patient did not come in for a TOC visit or submit a TOC urine according to comments in the CRF. The patient should not be considered evaluable for efficacy analysis.
109-9040 Doripenem	This patient is listed as a microbiological and clinical cure at the TOC by the Applicant. The patient has serious/severe symptoms of frequency and urgency at the EOT (IV), TOC, and the LFU visits. She had a new infection at the LFU visit caused by a Streptococcus species $\geq 10^5$ CFU/mL. Her baseline pathogen, <i>E. coli</i> , was eradicated at the TOC and the LFU visits. She should be listed as a microbiological cure and a clinical failure.
202-7095 Doripenem	The Applicant considered this patient to be a clinical cure and a microbiological cure at the TOC visit, followed by a relapse at the LFU visit. She had mild to moderate symptoms of dysuria, frequency, suprapubic pain, and urgency at the EOT (IV), TOC, and LFU visits. Her baseline pathogen, <i>E. coli</i> , was absent at the TOC visit, however, she had a <i>Candida albicans</i> infection ( $10^4$ CFU/mL) and an Enterococcus species infection ( $10^3$ CFU/mL) present. The <i>E. coli</i> returned at the LFU visit ( $10^6$ CFU/mL). She should be considered as both a clinical and microbiological failure.
203-7225 Levofloxacin	Patient 7225 is listed as a microbiological and clinical failure at the TOC visit, but not evaluable at the LFU visit. He had a <i>Proteus mirabilis</i> count of $10^6$ CFU/mL at the TOC visit and $10^4$ CFU/mL at the LFU visit. He had mild symptoms of frequency at the TOC visit and serious symptoms at the LFU visit. He should be a clinical and microbiological failure at the LFU visit also.
205-9029 Levofloxacin	The TOC visit for this patient was one day past the 6-9 day window. The Applicant had widened the TOC window before doing the final analysis, which included this patient. The patient should not be considered evaluable for efficacy analysis.

### 6.1.6 Efficacy Conclusions

DORI-05 was an international, multi-center, Phase 3 study involving 753 patients with complicated urinary tract infections or pyelonephritis enrolled at 44 centers. The objective of the trial was to compare the efficacy and safety of doripenem 500 mg q8h given as an IV infusion over 1 hour with that of levofloxacin 250 mg q24h, also given as an IV infusion over 1 hour, in the treatment of cUTI or pyelonephritis. There were 377 patients in the doripenem arm and 376 in the levofloxacin arm. Based on the data provided by the Applicant, the following conclusions can be stated.

Patients were well balanced across both treatment groups with regard to demographics with the possible exception of a higher proportion of elderly males in both study arms.

Doripenem was both microbiologically and clinically effective in the treatment of cUTI including pyelonephritis. Treatment with doripenem 500 mg q8h for up to 10 days was shown to

be non-inferior to treatment with IV levofloxacin 250 mg q24h as determined by the microbiologic response rates at the TOC visit in the ME and mMITT\_1 populations.

The microbiological cure rate for the ME at TOC population was 82.1% for the doripenem arm compared to 83.4% 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 group at the TOC visit was 79.2% for the doripenem patients and 78.2% 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 Test-of-Cure visit. The clinical cure rate for patients in the doripenem arm (CE at TOC) was 95.1% compared to 90.2% 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. Cure rates in the two treatment arms were also comparable across most subgroups based on demographic characteristics and underlying diseases (cUTI/pyelonephritis).

An important limitation of the study is that most patients switched to oral therapy, hence the number of patients treated with intravenous doripenem alone was limited. As patients had to meet certain pre-specified criteria suggestive of clinical improvement prior to switching to oral therapy and the anti-infective spectrum of levofloxacin is fairly similar to that of doripenem, it can be assumed that cure rates would not be very different if patients were treated with IV doripenem alone for the entire length of therapy.

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.

## 7 Integrated Review of Safety

### 7.1 Methods and Findings

- The safety analysis set in Study DORI-05 includes all patients in the Intent-to-Treat (ITT) population who received at least one dose of study drug. Of the 753 randomized patients, there were 748 who received study drug therapy ( 376 doripenem and 372 levofloxacin).

- 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, intercurrent 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 (28 to 42 days after the final dose of study drug).
- 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.

**Clinical Reviewer's Comment:** *For the overall safety review of doripenem, which includes the results from studies DORI-03, DORI-05, DORI-06, DORI-07, and DORI-08, please see the safety review by Dr. Alfred Sorbello, FDA Medical Officer.*

#### 7.1.1 Deaths

There was one death in the study, an 87-year-old male patient (005-02002) with an extensive pre-existing cardiac disease. His medical history included atrial fibrillation, congestive heart failure, hypertension, tachycardia, new left bundle branch block, and type 2 diabetes. He died during study drug therapy approximately 2 hours after receiving the first dose of doripenem and 1 hour after receiving the first dose of levofloxacin placebo. The death was attributed to bradycardia and was considered unlikely by the Applicant to be related to study drug therapy.

**Clinical Reviewer's Comment:** *Since the patient was placed on a do-not-resuscitate status prior to the onset of the life-threatening event, no attempt was made to resuscitate him. As the event occurred after one dose, it was probably not drug-related.*

#### 7.1.2 Other Serious Adverse Events

The following table shows the SAEs that occurred for the ITT analysis set. The data were taken from Applicant's Table 29, found on page 107 of the CSR.

Table 20. Serious Adverse Events Among The ITT Population.

System Organ Class Preferred Term	Doripenem (N=376)	Levofloxacin (N=372)	Total (n=748)
Number of Patients with at least 1 treatment-emergent serious adverse event	28 (7.4%)	15 (4.0%)	43 (5.7%)
Cardiac disorders	1 (0.3%)	2 (0.5%)	3 (0.4%)
Atrial fibrillation	0	1 (0.3%)	1 (0.1%)
Bradycardia	1 (0.3%)	0	1 (0.1%)
Cardiac failure	0	1 (0.3%)	1 (0.1%)
Eye disorders	0	1 (0.3%)	1 (0.1%)
Glaucoma	0	1 (0.3%)	1 (0.1%)
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Fecaloma	1 (0.3%)	0	1 (0.1%)
Vomiting	0	1 (0.3%)	1 (0.1%)
General disorders and administration site Conditions	1 (0.3%)	0	1 (0.1%)
Hypothermia	1 (0.3%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cholelithiasis	1 (0.3%)	1 (0.3%)	2 (0.3%)
System Organ Class Preferred Term	Doripenem (N=376)	Levofloxacin (N=372)	Total (n=748)
Infections and infestations	14 (3.7%)	2 (0.5%)	16 (2.1%)
Bacteremia	0	1 (0.3%)	1 (0.1%)
Bacterial infection	1 (0.3%)	0	1 (0.1%)
Erysipelas	1 (0.3%)	0	1 (0.1%)
Gastroenteritis viral	1 (0.3%)	0	1 (0.1%)
Orchitis	1 (0.3%)	0	1 (0.1%)
Pneumonia	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pyelonephritis	4 (1.1%)	0	4 (0.5%)
Respiratory tract infection	1 (0.3%)	0	1 (0.1%)
Sepsis	1 (0.3%)	0	1 (0.1%)
Systemic Candida	0	1 (0.3%)	1 (0.1%)
Urinary tract infection	2 (0.5%)	0	2 (0.3%)
Urosepsis	1 (0.3%)	0	1 (0.1%)
Injury, poisoning and procedural complications	1 (0.3%)	1 (0.3%)	2 (0.3%)
Accidental overdose	0	1 (0.3%)	1 (0.1%)
Hematuria traumatic	1 (0.3%)	0	1 (0.1%)
Metabolism and nutrition disorders	2 (0.5%)	2 (0.5%)	4 (0.5%)
Dehydration	1 (0.3%)	1 (0.3%)	2 (0.3%)
Diabetes mellitus inadequate control	1 (0.3%)	0	1 (0.1%)
Hyperglycemia	0	1 (0.3%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.8%)	1 (0.3%)	4 (0.5%)
Bladder cancer	0	1 (0.3%)	1 (0.1%)
Bladder neoplasm	1 (0.3%)	0	1 (0.1%)
Colon cancer	1 (0.3%)	0	1 (0.1%)
Colon neoplasm	1 (0.3%)	0	1 (0.1%)
Nervous system disorders	2 (0.5%)	1 (0.3%)	3 (0.4%)
Grand mal convulsion	0	1 (0.3%)	1 (0.1%)
Reversible ischemic neurological deficit	1 (0.3%)	0	1 (0.1%)
Transient ischemic attack	1 (0.3%)	0	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	0	1 (0.3%)	1 (0.1%)
Abortion spontaneous	0	1 (0.3%)	1 (0.1%)
Renal and urinary disorders	2 (0.5%)	1 (0.3%)	3 (0.4%)
Calculus ureteric	0	1 (0.3%)	1 (0.1%)
Hydronephrosis	1 (0.3%)	0	1 (0.3%)
Renal failure acute	1 (0.3%)	0	1 (0.3%)

System Organ Class Preferred Term	Doripenem (N=376)	Levofloxacin (N=372)	Total (n=748)
Reproductive system and breast disorders	1 (0.3%)	0	1 (0.1%)
Benign prostatic hyperplasia	1 (0.3%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	3 (0.8%)	3 (0.4%)
Hypoxia	0	1 (0.3%)	1 (0.1%)
Pulmonary embolism	0	2 (0.5%)	2 (0.3%)
Vascular disorders	2 (0.5%)	2 (0.5%)	4 (0.5%)
Deep vein thrombosis	0	1 (0.3%)	1 (0.1%)
Hypovolemic shock	1 (0.3%)	0	1 (0.1%)
Orthostatic hypotension	1 (0.3%)	0	1 (0.1%)
Peripheral vascular disorder	0	1 (0.3%)	1 (0.1%)

SNS=number of patients in the intent-to-treat analysis set.

Note: Treatment-emergent adverse events are defined as adverse events that were observed during study therapy and for 30 days after study drug therapy.

A total of 28 patients in the doripenem treatment arm and 15 patients in the levofloxacin treatment arm experienced a treatment emergent serious adverse event. There were no study drug related serious adverse events reported in either treatment arm.

The most frequently reported serious adverse event that occurred within 30 days after receipt of the last dose of study drug was pyelonephritis, which was reported in 4 (1%) of patients in the doripenem treatment arm and in no patients in the levofloxacin treatment arm. The onset of pyelonephritis occurred on Day 4 in 1 patient who was hospitalized and subsequently lost to follow-up. This patient presented with cLUTI and pyelonephritis. At Day 21 or later, the remaining 3 patients were also hospitalized due to the event. These 3 cases were recurrent or relapsed pyelonephritis that resolved with alternative antibacterial treatment. All of these events were considered unrelated or unlikely to be related to study drug therapy.

Overall, 11 (1.5%) patients experienced treatment-emergent serious adverse events during IV study therapy. More patients in the doripenem treatment arm experienced treatment-emergent serious adverse events compared with the levofloxacin treatment arm (doripenem, less than 3%; levofloxacin, less than 1%).

**Clinical Reviewer's Comments:** *The number of patients who developed a serious adverse event was higher in the doripenem treatment arm compared to the number in the levofloxacin treatment arm, 28 (7.4%) compared to 15 (4.0%). The types of adverse events were similar between the two arms with the exception of infections and infestations. The doripenem arm had 14 patients (3.7%) who developed a serious infection, e.g., pyelonephritis, while the levofloxacin arm had only 2 patients (0.3%) who developed infections, pneumonia and candidiasis.*

### 7.1.3 Dropouts and Other Significant Adverse Events

#### FDA Review of Case Report Forms of Discontinued Patients from Study DORI-05.

The Applicant submitted the CRFs for patients who discontinued the study due to death, serious adverse events, or adverse events causing discontinuation. A total of 62 CRFs were submitted, with 35 from the doripenem treatment arm and 27 from the levofloxacin treatment arm.

The CRFs were reviewed, along with individual patient narratives describing each patient's medical history. Of interest was any type of pattern of adverse events possibly associated with either study drug. The adverse events of most interest were renal failure, recurrent UTIs, and pyelonephritis. Among the 35 discontinued doripenem patients there were 9 with the following adverse events: pyelonephritis (4), recurrent UTIs (3), bacterial infection (1), and sepsis (1).

During the review, there was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer for 59 of the 62 CRFs. There were discrepancies present for 3 of the CRFs involving the same issue, i.e., were these events related to study drug therapy.

**Clinical Reviewer's Comments:** *Three patients [#303-6011; #304-4024; and #304-6007] had UTIs or pyelonephritis due to a uropathogen ( $\geq 10^5$  CFU/mL) at the screening visits. Two of the patients had Pseudomonas aeruginosa and the third had Proteus mirabilis as baseline pathogens. All were treated with doripenem and completed the study. All of them received additional antibiotics during the study. Each of them had positive urine cultures ( $\geq 10^5$  CFU/mL) due to his/her baseline pathogen at the TOC visit and were listed as microbiological failures. Two were listed as evaluable clinical cures at TOC. The Applicant has the three patients listed as being discontinued due to serious adverse events, recurrent UTIs and pyelonephritis. Since the patients had those conditions at study drug entry, they should not be considered as adverse events possibly associated with doripenem therapy. If there was an adverse event that occurred it should be "lack of efficacy" because the baseline pathogen was never truly eradicated.*

#### 7.1.3.1 Overall profile of dropouts

Table 21. Adverse Events Leading to Treatment Discontinuation (ITT Analysis Set).

Site number/ Patient number	Age/Sex	Preferred Term	Day of Adverse Event Onset	Outcome	Duration (Days)	Relationship to Study Drug Therapy	Total Days of Study Drug Therapy
<b>Doripenem</b>							
204/09037	72/F	Vasculitis	5	Resolved	21	Possibly	6
303/06241	25/F	Bacterial infection	4	Resolved	11	Unrelated	5
306/04035	41/F	Hypovolemic shock	7	Resolved with sequelae	3	Unrelated	8
404/06194	53/F	Sepsis	2	Resolved	24	Unrelated	9
<b>Levofloxacin</b>							
007/03030	75/F	Encephalopathy	4	Resolved	7	Unrelated	4
007/03037	37/F	Vomiting	5	Resolved	4	Unlikely	4

Site number/ Patient number	Age/Sex	Preferred Term	Day of Adverse Event Onset	Outcome	Duration (Days)	Relationship to Study Drug Therapy	Total Days of Study Drug Therapy
013/03002	52/F	Erythema multiforme	8	Resolved	9	Probably	8
031/01000*	60/M	Pulmonary embolism	3	Resolved	304 ??	Unlikely	10
035/01012	47/M	Arthralgia Blood pressure diastolic increased	3 3	Resolved Resolved	2 1	Probably Probably	3 3
101/07019	74/M	Diarrhea	2	Resolved	4	Possible	3
101/07062	66/M	Pyrexia	7	Resolved	2	Unrelated	8
101/07213	73/M	Diarrhea	2	Ongoing		Possibly	5
101/07214	90/M	Diarrhea	5	Resolved	5	Possibly	6
104/07151	39/M	Pruritus Rash pustular	2 2	Resolved Resolved	5 5	Possibly Possibly	3 3
104/09027	26/F	Phlebitis	1	Resolved	1	Possibly	1
201/07231	66/M	Diarrhea	4	Resolved	5	Probably	5
201/09062*	51/F	Hepatitis	8	Ongoing		Unrelated	8
204/09070*	77/F	Diarrhea	4	Resolved	5	Probably	6

F=female; M=male

\* Patients microbiologically evaluable at test-of-cure

Note: Patient 057/01016 is included in Section 15.1 Listing 4 as discontinuing study drug therapy due to an adverse event of pyelonephritis. However, the patient discontinued IV therapy on Day 4 due to non-compliance and received no IV or oral study drug therapy after that. The adverse event started the same day of the discontinuation, but at a later time. The patient was lost to follow-up. Patient 205/07066 is included in Section 15, Listing 4 as discontinuing the study due to an adverse event of acute bronchitis. The patient completed both IV and oral study drug therapy. The adverse event started about 18 days after completion of oral therapy and resolved 11 days later. The patient completed the test-of-cure visit, but not the late follow-up visit and did not complete the study. For both patients, the event was considered unrelated to study drug therapy.

Data were taken from Applicant's Table 27, found on pages 102-103 of the CSR.

Treatment-emergent adverse events led to discontinuation of study drug therapy in <1% of patients in the doripenem treatment and 3% of patients in the levofloxacin treatment arm and 1% of patients in both arms on oral therapy.

### 7.1.3.2 Adverse events associated with dropouts

Four patients in the doripenem treatment arm and 14 patients in the levofloxacin treatment arm were discontinued from study drug therapy due to an adverse event. One of the 4 patients in the doripenem treatment arm discontinued due to an adverse event considered related to study drug therapy compared with 9 of the 14 patients in the levofloxacin treatment arm.

A variety of adverse events led to study drug therapy discontinuation in the doripenem treatment arm. One patient discontinued doripenem therapy due to vasculitis, which was considered related to study drug therapy. Diarrhea was the most common adverse event that led to discontinuation of levofloxacin therapy and occurred in 5 of the 14 patients; all cases were considered possible or probably related to study drug therapy.

### 7.1.3.3 Other significant adverse events

One patient in the levofloxacin treatment arm experienced a seizure (grand mal convulsion) on Study Day 5, which was determined by the investigator to be unrelated to study drug therapy. No seizures were reported in the doripenem treatment arm.

### 7.1.4 Other Search Strategies

Not applicable to this study.

### 7.1.5 Common Adverse Events

All safety results were reported in the ITT analysis set. At each level of patient summarization, a patient was counted only once if the patient reported 1 or more events. Patients were included in the treatment arm according to the study drug therapy received, not the study drug therapy to which they were randomly assigned. The following table shows an overview of the treatment-emergent adverse events, serious adverse events, adverse events leading to study drug therapy discontinuation, and adverse events leading to death that occurred in both treatment arms. The data were taken from Applicant's table 24, found on page 97 of the CSR.

Table 22. Overview of Adverse Events in the ITT Analysis Set.

Category <sup>a</sup>	Doripenem (N=376)	Levofloxacin (N=372)
Number (%) of patients with at least 1 adverse event <sup>b</sup>	240 (63.8%)	222 (59.7%)
Number (%) of patients with at least 1 related adverse event	106 (28.2%)	93 (25.0%)
Patients with at least 1 treatment-emergent serious adverse event	28 (7.4%)	15 (4.0%)
Treatment-emergent serious adverse events related to study drug (including possibly or probably related)	0	0
Study drug therapy discontinuations due to adverse events <sup>c</sup>		
Number (%) patients who discontinued IV therapy	2 (0.5%)	11 (2.9%)
Number (%) patients who discontinued oral therapy	2 (0.5%)	3 (0.8%)
Number (%) patients with adverse events leading to death	1 (0.3%)	0

N=number of patients in the analysis set.

<sup>a</sup> Patients could have been included in more than 1 category.

<sup>b</sup> All adverse events summarized were treatment-emergent adverse events.

<sup>c</sup> All patients randomized to doripenem (N=377) or levofloxacin (N=376).

#### 7.1.5.1 Eliciting adverse events data in the development program

The protocol for Study DORI-05 called for a change in therapy from an intravenous dose of doripenem to an oral dose of levofloxacin provided that the following conditions occurred: After  $\geq 9$  doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever ( $<37.8$  °C oral) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least 1 urine culture had been reported with no growth at 24 hours or growth

with a colony count of  $< 10^4$  CFU/mL and no subsequent cultures with a colony count of  $\geq 10^4$  CFU/mL were observed. Therefore, it is important to review what adverse events occurred during the IV part of therapy and what adverse event occurred during the oral part.

Table 23 shows the adverse events related to study drug that emerged during IV study drug therapy. The data were taken from Applicant's Table 15.3.1.2-4, found on pages 584-588 of the CSR.

Overall, 168 (23%) of 748 patients experienced a study drug-related adverse event with onset during IV study drug therapy, with a similar incidence between the 2 treatment arms (23%, doripenem; 22%, levofloxacin), whereas 199 (27%) of 748 intent-to-treat patients experienced a study related adverse event during IV or oral study drug therapy (28%, doripenem; 25% levofloxacin).

Diarrhea and headache were the most common treatment-emergent adverse events related to study drug that occurred during IV study drug therapy. Diarrhea occurred in 3% and 5% of patients in the doripenem and levofloxacin treatment arms, respectively, and headache occurred in 5% and 3% of patients in the doripenem and levofloxacin treatment arms, respectively.

Table 23 Treatment emergent adverse events related to study drug during IV study drug therapy (ITT population).

System Organ Class Preferred Term	Doripenem IV (N = 376)	Levofloxacin IV (N = 372)	Total (N = 748)
Number of patients with at least one related adverse event	88 (23.4%)	80 (21.5%)	168 (22.5%)
Blood and lymphatic system disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Eosinophilia	1 (0.3%)	0	1 (0.1%)
Leukopenia	0	1 (0.3%)	1 (0.1%)
Ear and labyrinth disorders	1 (0.3%)	0	1 (0.1%)
Vertigo	1 (0.3%)	0	1 (0.1%)
Gastrointestinal disorders	28 (7.4%)	35 (9.4%)	63 (8.4%)
Abdominal pain	0	1 (0.3%)	1 (0.1%)
Abdominal pain upper	1 (0.3%)	8 (2.2%)	9 (1.2%)
Constipation	2 (0.5%)	2 (0.5%)	4 (0.5%)
Diarrhea	10 (2.7%)	19 (5.1%)	29 (3.9%)
Dyspepsia	2 (0.5%)	0	2 (0.3%)
Flatulence	1 (0.3%)	2 (0.5%)	3 (0.4%)
Loose stools	1 (0.3%)	0	1 (0.1%)
Nausea	11 (2.9%)	5 (1.3%)	16 (2.1%)
Vomiting	5 (1.3%)	3 (0.8%)	8 (1.1%)

<b>System Organ Class Preferred Term</b>	<b>Doripenem IV (N = 376)</b>	<b>Levofloxacin IV (N = 372)</b>	<b>Total (N = 748)</b>
General disorders and administration site conditions	11 (2.9%)	13 (3.5%)	24 (3.2%)
Asthenia	1 (0.3%)	0	1 (0.1%)
Extravasation	1 (0.3%)	0	1 (0.1%)
Generalized edema	1 (0.3%)	0	1 (0.1%)
Infusion related reaction	0	3 (0.8%)	3 (0.4%)
Infusion site burning	0	1 (0.3%)	1 (0.1%)
Infusion site inflammation	1 (0.3%)	3 (0.8%)	4 (0.5%)
Infusion site pain	1 (0.3%)	0	1 (0.1%)
Infusion site phlebitis	0	1 (0.3%)	1 (0.1%)
Infusion site rash	0	2 (0.5%)	2 (0.3%)
Injection site burning	0	2 (0.5%)	2 (0.3%)
Injection site erythema	1 (0.3%)	0	1 (0.1%)
Injection site induration	4 (1.1%)	0	4 (0.5%)
Injection site pain	0	2 (0.5%)	2 (0.3%)
Injection site reaction			
Hepatobiliary disorders	1 (0.3%)	0	1 (0.1%)
Hepatitis	1 (0.3%)	0	1 (0.1%)
Immune system disorders	1 (0.3%)	0	1 (0.1%)
Hypersensitivity	1 (0.3%)	0	1 (0.1%)
Infections and infestations	10 (2.7%)	2 (0.5%)	12 (1.6%)
Candiduria	1 (0.3%)	0	1 (0.1%)
Fungal infections	1 (0.3%)	0	1 (0.1%)
Oral candidiasis	2 (0.5%)	0	2 (0.3%)
Rash pustular	0	1 (0.3%)	1 (0.1%)
Vaginal mycosis	3 (0.8%)	0	3 (0.4%)
Vulvovaginitis	3 (0.8%)	1 (0.3%)	4 (0.5%)
Investigations	10 (2.7%)	17 (4.6%)	27 (3.6%)
Alanine aminotransferase increased	2 (0.5%)	6 (1.6%)	8 (1.1%)
Aspartate aminotransferase increased	2 (0.5%)	2 (0.5%)	4 (0.5%)
Blood alkaline phosphatase increased	3 (0.8%)	5 (1.3%)	8 (1.1%)
Blood creatine phosphokinase increased	0	1 (0.3%)	1 (0.1%)
Blood glucose increased	0	1 (0.3%)	1 (0.1%)
Blood lactate dehydrogenase increased	0	2 (0.5%)	2 (0.3%)
Blood pressure diastolic increased	0	1 (0.3%)	1 (0.1%)
Gamma-glutamyltransferase increased	6 (1.6%)	4 (1.1%)	10 (1.3%)
Glucose urine present	0	1 (0.3%)	1 (0.1%)
Hepatic enzyme increased	2 (0.5%)	4 (1.1%)	6 (0.8%)
Urinary sediment present	1 (0.3%)	0	1 (0.1%)
Metabolism and nutrition disorders	1 (0.3%)	0	1 (0.1%)
Hypokalemia	1 (0.3%)	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	0	2 (0.5%)	2 (0.3%)
Arthralgia	0	1 (0.3%)	1 (0.1%)
Back pain	0	1 (0.3%)	1 (0.1%)
Nervous system disorders	18 (4.8%)	10 (2.7%)	28 (3.7%)
Dizziness	1 (0.3%)	0	1 (0.1%)
Headache	17 (4.5%)	10 (2.7%)	27 (3.6%)
Paraesthesia oral	1 (0.3%)	0	1 (0.1%)
Psychiatric disorders	1 (0.3%)	0	1 (0.1%)
Irritability	1 (0.3%)	0	1 (0.1%)

System Organ Class Preferred Term	Doripenem IV (N = 376)	Levofloxacin IV (N = 372)	Total (N = 748)
Reproductive system and breast disorders	3 (0.8%)	1 (0.3%)	4 (0.5%)
Metrorrhagia	0	1 (0.3%)	1 (0.1%)
Polymenorrhoea	3 (0.8%)	1 (0.3%)	4 (0.5%)
Skin and subcutaneous tissue disorders	2 (0.5%)	5 (1.3%)	7 (0.9%)
Hyperhidrosis	0	1 (0.3%)	1 (0.1%)
Pruritus	1 (0.3%)	2 (0.5%)	3 (0.4%)
Rash pruritic	0	1 (0.3%)	1 (0.1%)
Urticaria localized	1 (0.3%)	1 (0.3%)	2 (0.3%)
Vascular disorders	11 (2.9%)	10 (2.7%)	21 (2.8%)
Hypertension	2 (0.5%)	0	2 (0.3%)
Phlebitis	9 (2.4%)	10 (2.7%)	19 (2.5%)
Vasculitis	1 (0.3%)	0	1 (0.1%)

Note: At each level of patient summarization, a patient is counted once for the most related event if the patient reported one or more occurrences of the same event. If the relationship of an AE is missing, the AE is included as drug related. Treatment emergent adverse events related to study drug are defined as adverse events with a relationship to study drug of either "possible" or "probably" related or the relationship is missing, with onset dates on or after the date of start of infusion of the first dose of study medication and within 30 days after the administration of the last dose of study medication. Adverse event terms are coded using MedDRA version 7.0.

Table 24 shows the serious adverse events that occurred during the IV phase of the study. The data were taken from Applicant's Table 15.3.1.4-3, found on pages 621-622 of the CSR.

Table 24 Treatment emergent serious adverse events during IV study drug therapy (ITT population).

System Organ Class Preferred Term	Doripenem IV (N = 376)	Levofloxacin IV (N = 372)	Total (N = 748)
Number of patients with at least one treatment emergent serious adverse event	9 (2.4%)	2 (0.5%)	11 (1.5%)
Cardiac disorders	1 (0.3%)	0	1 (0.1%)
Bradycardia	1 (0.3%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.3%)	0	1 (0.1%)
Cholelithiasis	1 (0.3%)	0	1 (0.1%)
Infections and infestations	3 (0.8%)	0	3 (0.4%)
Bacterial infection	1 (0.3%)	0	1 (0.1%)
Pyelonephritis	1 (0.3%)	0	1 (0.1%)
Sepsis	1 (0.3%)	0	1 (0.1%)
Injury, poisoning and procedural complications	1 (0.3%)	0	1 (0.1%)
Hematuria traumatic	1 (0.3%)	0	1 (0.1%)
Renal and urinary disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Calculus ureteric	0	1 (0.3%)	1 (0.1%)
Renal failure acute	1 (0.3%)	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.3%)	0	1 (0.1%)
Benign prostatic hyperplasia	1 (0.3%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3%)	1 (0.1%)
Pulmonary embolism	0	1 (0.3%)	1 (0.1%)
Vascular disorders	1 (0.3%)	0	1 (0.1%)
Hypovolemic shock	1 (0.3%)	0	1 (0.1%)

Note: At each level of patient summarization, a patient is counted once for the most related event if the patient reported one or more occurrences of the same event. If the relationship of an AE is missing, the AE is included as drug related. Treatment emergent adverse events related to study drug are defined as adverse events with a relationship to study drug of either "possible" or "probably" related or the relationship is missing, with onset dates on or after the date of start of infusion of the first dose of study medication and within 30 days after the administration of the last dose of study medication. Adverse event terms are coded using MedDRA version 7.0.

#### 7.1.5.4 Common adverse event tables

A total of 64% of patients in the doripenem treatment arm and 60% of patients in the levofloxacin treatment arm experienced a treatment emergent adverse event and 28% and 25% of patients in the 2 treatment arms, respectively, experienced a drug-related adverse event.

Diarrhea and headache were the most common treatment-emergent adverse events related to study drug that occurred during IV study drug therapy. Diarrhea occurred in 3% and 5% of patients in the doripenem and levofloxacin treatment arms, respectively, and headache occurred in 5% and 3% of patients in the doripenem and levofloxacin treatment arms, respectively.

Table 25. Treatment Emergent Adverse Events Occurring with at Least 3% Frequency in Either Treatment Arm by System Organ Class.

System Organ Class Preferred Term	Doripenem (N=376)	Levofloxacin (N=372)	Total (N=748)
Number of patients with at least one treatment emergent adverse event	240 (63.8%)	222 (59.7%)	462 (61.8%)
Gastrointestinal disorders	94 (25.0%)	101 (27.2%)	195 (26.1%)
Constipation	22 (5.9%)	18 (4.8%)	40 (5.3%)
Diarrhea	21 (5.6%)	37 (9.9%)	58 (7.8%)
Vomiting	19 (5.1%)	16 (4.3%)	35 (4.7%)
Abdominal pain upper	17 (4.5%)	13 (3.5%)	30 (4.0%)
Nausea	16 (4.3%)	22 (5.9%)	38 (5.1%)
Abdominal pain	7 (1.9%)	13 (3.5%)	20 (2.7%)
Infections and infestations	80 (21.3%)	36 (9.7%)	116 (15.5%)
Asymptomatic bacteruria	14 (3.7%)	4 (1.1%)	18 (2.4%)
Urinary tract infection	14 (3.7%)	6 (1.6%)	20 (2.7%)
Metabolism and nutrition disorders	22 (5.9%)	23 (6.2%)	45 (6.0%)
Hypokalemia	8 (2.1%)	13 (3.5%)	21 (2.8%)
Musculoskeletal and connective tissue disorders	25 (6.6%)	34 (9.1%)	59 (7.9%)
Back pain	8 (2.1%)	17 (4.6%)	25 (3.3%)
Nervous system disorders	70 (18.6%)	67 (18.0%)	137 (18.3%)
Headache	59 (15.7%)	54 (14.5%)	113 (15.1%)
Psychiatric disorders	27 (7.2%)	21 (5.6%)	48 (6.4%)
Insomnia	14 (3.7%)	11 (3.0%)	25 (3.3%)
Vascular disorders	30 (8.0%)	29 (7.8%)	59 (7.9%)
Phlebitis	14 (3.7%)	15 (4.0%)	29 (3.9%)

Note: At each level of patient summarization, a patient is counted once if the patient reported one or more events. Treatment emergent adverse events are defined as adverse events with onset dates on or after the date of the start of infusion of the first dose of the study medication and within 30 days after the administration of the last dose of the study medication. AE terms are coded using MedDRA version 7.0. Data were taken from Applicant's Table 15.3.1.1-4, found on page 560 of the CSR.

- The only adverse event reported in more than 10% of patients in either treatment arm was headache, which occurred in approximately 15% of patients in both treatment arms.
- The difference between treatment arms in the incidence of specific treatment-emergent adverse events was <5% for all adverse events although 4% more levofloxacin-treated patients reported diarrhea compared with doripenem-treated patients (10%, levofloxacin; 6%, doripenem).
- With the exception of headache, the most frequently reported treatment-emergent adverse events were within the gastrointestinal (GI) system organ class. Constipation, diarrhea, vomiting, upper abdominal pain, and nausea were reported by 4% or more of patients overall.
- Adverse events of asymptomatic bacteriuria and urinary tract infection were reported more often in doripenem-treated patients than in levofloxacin-treated patients: 4% versus 1% for asymptomatic bacteriuria and 4% versus 2% for urinary tract infection in the doripenem and levofloxacin groups, respectively. The rates of asymptomatic bacteriuria seen in both treatment arms are consistent with rates observed in clinical practice.
- Adverse events of back pain and abdominal pain were reported more often in patients treated with levofloxacin than in patients treated with doripenem: 5% versus 2% for back pain, 4% versus 2% for abdominal pain, respectively.
- No seizures were reported in any patient in the doripenem treatment arm and seizure was reported in 1 patient in the levofloxacin treatment arm.

#### 7.1.6 Less common and drug-related adverse events

Table 26. Treatment Emergent Adverse Events Occurring with at Least 3% Frequency in Either Treatment Arm by Preferred Term (ITT analysis set).

Preferred Term	Doripenem IV (N=376)	Levofloxacin IV (N=372)	Total (N=748)
Number of patients with at least one treatment emergent adverse event	240 (63.8%)	222 (59.7%)	462 (61.8%)
Headache	59 (15.7%)	54 (14.5%)	113 (15.1%)
Constipation	22 (5.9%)	18 (4.8%)	40 (5.3%)
Diarrhea	21 (5.6%)	37 (9.9%)	58 (7.8%)
Vomiting	19 (5.1%)	16 (4.3%)	35 (4.7%)
Abdominal pain upper	17 (4.5%)	13 (3.5%)	30 (4.0%)
Nausea	16 (4.3%)	22 (5.9%)	38 (5.1%)
Asymptomatic bacteriuria	14 (3.7%)	4 (1.1%)	18 (2.4%)
Urinary tract infection	14 (3.7%)	6 (1.6%)	20 (2.7%)
Insomnia	14 (3.7%)	11 (3.0%)	25 (3.3%)
Phlebitis	14 (3.7%)	15 (4.0%)	29 (3.9%)
Hypokalemia	8 (2.1%)	13 (3.5%)	21 (2.8%)
Back pain	8 (2.1%)	17 (4.6%)	25 (3.3%)
Abdominal pain	7 (1.9%)	13 (3.5%)	20 (2.7%)

Note: At each level of patient summarization, a patient is counted once if the patient reported one or more events. Treatment emergent adverse events are defined as adverse events with onset dates on or after the date of the start of infusion of the first dose of the study medication and within 30 days after the administration of the last dose of the study medication. AE terms are coded using MedDRA version 7.0. Data were taken from Applicant's Table 15.3.1.1-5, found on page 561 of the CSR.

Table 27. Treatment Emergent Adverse Events Related to Study Drug Occurring with at Least 2% Frequency in Either Treatment Arm (ITT Analysis Set).

System Organ Class Preferred Term	Doripenem IV (N=376)	Levofloxacin IV (N=372)	Total (N=748)
Number of patients with at least one treatment emergent adverse event	106 (28.2%)	93 (25.0%)	199 (26.6%)
Gastrointestinal disorders	37 (9.8%)	39 (10.5%)	76 (10.2%)
Abdominal pain upper	2 (0.5%)	8 (2.2%)	10 (1.3%)
Diarrhea	15 (4.0%)	22 (5.9%)	37 (4.9%)
Nausea	11 (2.9%)	6 (1.6%)	17 (2.3%)
Nervous system disorders	18 (4.8%)	10 (2.7%)	28 (3.7%)
Headache	17 (4.5%)	10 (2.7%)	27 (3.6%)
Vascular disorders			
Phlebitis	9 (2.4%)	11 (3.0%)	20 (2.7%)

N=number of patients in the intent-to-treat population.  
 Data were taken from Applicant's Table 26, found on page 100 of the CSR.

Treatment-emergent adverse events related to study drug therapy occurring with at least 2% frequency in either treatment arm by system organ class (Table 26) are shown above. Overall, 27% of patients had at least 1 treatment-emergent adverse event that was related to study drug therapy. There were 17 cases of headache (5%) in the doripenem arm compared to 10 cases (3%) in the levofloxacin treatment arm. The other adverse events were as follows: (diarrhea 15 [4%], doripenem, 22 [6%], levofloxacin), (nausea 11 [3%], doripenem, 6 [2%], levofloxacin), (phlebitis 9 [2%], doripenem, 11 [3%], levofloxacin), and (upper abdominal pain 2 [ $<$ 1%], doripenem, 8 [2%], levofloxacin). The incidence of these events was similar in the doripenem and levofloxacin treatment arms.

#### 7.1.6.1 Additional analyses and explorations

Adverse events of special interest in this study included adverse events that were possible allergic reactions and indications of study drug therapy intolerance. All adverse events that, in the opinion of the investigator, represented either possible allergic reactions to IV study drug therapy or IV study drug therapy intolerance were marked as such on the adverse event CRF. In general, these events were temporally related to the study drug therapy infusion. For example, if a patient experienced an urticarial rash, "urticarial rash" was recorded as the adverse event and not "rash." Examples of possible systemic reactions representing study drug therapy intolerance included fever, flushing, or nausea temporally related to the infusion of study drug therapy. Examples of local intolerance included erythema, pain, induration, swelling, or phlebitis at the infusion site that was not related to mechanical malfunction of the infusion apparatus.

Additional information that was collected included the site of phlebitis, a description of phlebitis, action taken, the number of days study drug was infused through the catheter before the onset of phlebitis, and other medication and fluids that were infused through the catheter.

**Clinical Reviewer's Comments:** *There were 9 (2%) doripenem patients and 6 (2%) levofloxacin patients who developed a possible allergic reaction to a study drug. The most*

*frequently reported specific adverse events associated with a possible allergic reaction were: hypersensitivity [3 (0.8%), doripenem; 1 (0.3%), levofloxacin] and pruritus [2 (0.5%), doripenem; 1 (0.3%), levofloxacin]. Thus, the two treatment arms were evenly balanced regarding adverse events of special interest.*

### **7.1.7 Laboratory Findings**

#### Clinical Laboratory Tests

The following clinical laboratory tests were performed on all patients at screening, on Study Day 3, and at the EOT(IV) and TOC visits:

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, ALT, AST, creatine kinase, lactate dehydrogenase, total and indirect bilirubin, total cholesterol, glucose (non-fasting), total protein, albumin, creatinine, urea nitrogen, and uric acid.

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

Laboratory tests with abnormal results from the TOC visit were repeated at the LFU visit. Patients who were withdrawn from study drug therapy administration early due to a non-study-qualifying baseline urine culture and were, therefore, not scheduled to return for the TOC visit provided blood and urine specimens for clinical laboratory testing when they returned for the LFU visit. All blood and urine specimens obtained for clinical laboratory testing were shipped to the regional laboratory for processing.

#### Laboratory Test Abnormalities Reported as Adverse Events

Investigators were asked to report as adverse events only laboratory abnormalities that had clinical manifestations or required medical intervention. Where possible, syndromes, rather than individual laboratory values, were to have been reported. For example, jaundice associated with elevated hepatic transaminases was reported as "hepatitis," and decreased hemoglobin and hematocrit requiring iron supplementation was recorded as "anemia." These adverse events were listed and identified using adverse events assigned to MedDRA system organ class (SOC) of "Investigations."

#### Pregnancy Tests

All women of childbearing potential were required to continue to use birth control throughout the study and for at least 30 days after administration of the last dose of study drug therapy (IV and

oral). In addition, all women of childbearing potential had a negative urine or serum pregnancy test confirmed at screening, prior to enrolling into the study. If a urine pregnancy test was used at the time of screening, blood was obtained at the time of screening for serum  $\beta$ -human chorionic gonadotropin testing also, and negative serum pregnancy test results were confirmed as soon as possible and within 72 hours of study entry. Serum pregnancy testing was also performed on all women of childbearing potential at the TOC visit. For women who withdrew from study drug therapy administration early, serum pregnancy testing was performed when these patients returned for the LFU visit. All positive pregnancy test results were reported to the Applicant's Medical Monitor within 24 hours of the site's knowledge of the positive results, and all pregnancies were followed to outcome.

#### **7.1.7.1 Overview of laboratory testing in the development program**

Safety laboratory tests were performed at screening, on Day 3 and at the EOT(IV) and TOC visits. Patients who were withdrawn from study drug therapy early due to non-study-qualifying baseline urine culture and, therefore, were not scheduled to return for the TOC visit had safety laboratory tests performed at the LFU visit.

The most recent serum creatinine value obtained at the local laboratory, the actual body weight, and the Cockcroft-Gault formula were used to calculate the patient's creatinine clearance.

#### **7.1.7.2 Standard analyses and explorations of laboratory data**

##### *7.1.7.3.1 Analyses focused on measures of central tendency*

#### **Hematology**

Mean and mean changes from baseline to the end of IV therapy in hematology parameters are summarized in the following table. The data were taken from Applicant's table 30, found on pages 112-113 of the CSR.

Table 28. Changes from Baseline to End of IV Therapy in Hematology Parameters (ITT Analysis Set).

Parameter	Doripenem (N= 376)		Levofloxacin (N= 372)	
	n	Mean (SD)	n	Mean (SD)
<b>Basophils (%)</b>				
Baseline	347	0.315 (0.4305)	329	0.363 (0.4778)
Change from Baseline	300	0.192 (0.5283)	281	0.096 (0.4841)
<b>Basophils, ABS (x 10<sup>9</sup>/L)</b>				
Baseline	258	0.021 (0.0253)	235	0.021 (0.0267)
Change from Baseline	220	0.007 (0.0243)	193	0.003 (0.0253)
<b>Eosinophils (%)</b>				
Baseline	347	1.607 (1.7628)	329	1.815 (1.9923)
Change from Baseline	300	1.622 (2.1131)	281	1.351 (2.2551)
<b>Eosinophils ABS (x 10<sup>9</sup>/L)</b>				
Baseline	258	0.123 (0.1458)	235	0.136 (0.1796)
Change from Baseline	220	0.106 (0.1613)	193	0.100 (0.1685)
<b>Hematocrit (V/V)</b>				
Baseline	352	0.3985 (0.05195)	332	0.4047 (0.05114)
Change from Baseline	305	-0.0105 (0.03741)	284	-0.0112 (0.03632)
<b>Hemoglobin (g/L)</b>				
Baseline	357	130.8 (18.19)	339	131.3 (17.43)
Change from Baseline	309	-3.5 (11.53)	293	-3.0 (10.32)
<b>Lymphocytes (%)</b>				
Baseline	347	19.547 (10.6102)	329	19.948 (10.4843)
Change from Baseline	300	8.945 (11.5151)	281	6.963 (11.2228)
<b>Lymphocytes ABS (x 10<sup>9</sup>/L)</b>				
Baseline	258	1.667 (0.7285)	235	1.675 (0.7811)
Change from Baseline	220	0.379 (0.6764)	193	0.280 (0.7293)
<b>MCH (pg/cell)</b>				
Baseline	357	29.85 (2.573)	337	29.94 (2.411)
Change from Baseline	309	- 0.12 (0.786)	292	-0.15 (0.832)
<b>MCHC (g/bb/L)</b>				
Baseline	352	326.8 (16.34)	332	325.5 (15.07)
Change from Baseline	305	1.0 (13.93)	284	2.0 (13.44)
<b>MCV (fL)</b>				
Baseline	352	91.34 (7.172)	332	91.91 (6.928)
Change from Baseline	305	-0.70 (3.847)	284	-0.94 (3.277)
<b>Monocytes (%)</b>				
Baseline	347	7.566 (3.6706)	329	7.317 (3.6973)
Change from Baseline	300	0.811 (3.7310)	281	0.643 (3.6498)
<b>Monocytes, ABS (x 10<sup>9</sup>/L)</b>				
Baseline	258	0.884 (0.5657)	235	0.816 (0.4761)
Change from Baseline	220	-0.212 (0.5387)	193	-0.168 (0.4626)
<b>Neutrophils (%)</b>				
Baseline	323	69.384 (12.5751)	310	69.362 (12.9116)
Change from Baseline	275	-11.343 (13.4089)	253	-9.691 (13.2469)
<b>Neutrophils + Bands (%)</b>				
Baseline	323	70.124 (12.8911)	310	69.904 (13.1275)
Change from Baseline	275	-11.590 (13.5010)	253	-9.960 (13.3044)
<b>Neutrophils, ABS (x 10<sup>9</sup>/L)</b>				
Baseline	258	8.114 (4.8945)	235	7.782 (4.2602)
Change from Baseline	220	-3.777 (4.6757)	193	-3.222 (3.9080)
<b>Platelet Count (x 10<sup>9</sup>/L)</b>				
Baseline	351	246.1 (81.09)	327	244.5 (80.71)
Change from Baseline	304	42.2 (98.41)	278	39.1 (79.16)
<b>RBC (x 10<sup>12</sup>/L)</b>				
Baseline	268	4.345 (0.5451)	244	4.366 (0.5457)
Change from Baseline	229	-0.096 (0.3702)	208	-0.054 (0.3154)
<b>WBC (x 10<sup>9</sup>/L)</b>				
Baseline	351	10.539 (5.1062)	334	9.961 (4.1066)
Change from Baseline	302	-3.071 (4.6745)	285	-2.380 (3.8837)

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; N = number of patients in the analysis set; n = number of patients whose laboratory values were not missing for both the corresponding post-baseline visit and the baseline visit; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

- The baseline hematology parameters were similar between the treatment arms. For all time points (Study Day 3, EOT[IV], TOC and LFU), mean values and mean changes from baseline in hematology parameters were similar among patients in both treatment arms for all measured parameters. No clinically meaningful differences were seen between treatment arms.
- In patients recovering from an infection, decreases from baseline were seen in mean WBC and mean segmented WBC counts.
- In hospitalized patients who may undergo phlebotomy and surgical procedures, decreases from baseline were seen in hemoglobin and hematocrit.
- Small and clinically insignificant increases from baseline in mean platelet count were seen in both study arms.

**Clinical Reviewer's Comments:** *The changes in the hematology parameters from baseline between the patients in both treatment arms were consistent with approximately 86.5% of doripenem patients and 84% of the levofloxacin patients experiencing some change. There did not appear to be any major difference between the two treatment groups in the baseline change in any particular parameter.*

#### Serum Chemistry

Mean and mean changes from baseline to the end of IV therapy in serum chemistry parameters are summarized in the following table. The data were taken from Applicant's table 31, found on pages 114-115 of the CSR.

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