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complete IV study drug and did not receive PO switch, it appears that gastrointestinal disorders were a common adverse event associated with doripenem exposure and they were to both subgroups. Anemia and pyrexia were more commonly associated with longer treatment courses of doripenem as was administered in patients who completed i.v. therapy without oral switch. Although, there was insufficient evidence and concomitant confounding factors to establish a causal link between anemia and doripenem exposure, such an association could not be completely excluded in view of the temporal relationships between anemia development and treatment with the drug. The investigators did not systematically record the amount of intra-operative blood loss, and blood transfusions were not routinely recorded by all investigators on the CRFs. Anemia is further investigated as a treatment-emergent adverse event in later sections of this report.

7.1.5.6 Additional analyses and explorations

In terms of demographic trends, exploratory analyses were conducted by the FDA Medical Officer with respect to gender, body mass index (BMI), age, race, baseline creatinine clearance, hepatic impairment, and US versus non-US sites.

Gender

Headache, nausea, vomiting, abdominal pain (upper), and back pain were more common treatment-emergent adverse events among female subjects than in males treated with doripenem in DORI-05 and DORI-06. A similar pattern of female predominance in relation to headache and gastrointestinal disorders was observed in the levofloxacin group in DORI-05. The following table illustrates these gender-related trends in adverse events:

Table 55: FDA Medical Officer Summary of treatment-emergent adverse events (frequency $\geq 3\%$ in doripenem arm) stratified by gender and treatment group for all subjects in the doripenem Phase 3 cUTI Trials, ITT population

Preferred Term	DORI-05				DORI-06	
	Doripenem		Levofloxacin		Doripenem	
	Female	Male	Female	Male	Female	Male
Headache	49 (21.03%)	10 (6.99%)	43 (18.94%)	11 (7.59%)	66 (26.72%)	14 (7.95%)
Vomiting	18 (7.73%)	1 (0.70%)	12 (5.29%)	4 (2.76%)	28 (11.34%)	6 (3.41%)
Abdominal pain upper	15 (6.44%)	2 (1.40%)	11 (4.85%)	2 (1.38%)	10 (4.05%)	3 (1.70%)
Constipation	15 (6.44%)	7 (4.90%)	13 (5.73%)	5 (3.45%)	8 (3.24%)	9 (5.11%)
Nausea	13 (5.58%)	3 (2.10%)	22 (9.69%)	0 (0.00%)	27 (10.93%)	6 (3.41%)
Diarrhea	13 (5.58%)	9 (6.29%)	20 (8.81%)	18 (12.41%)	20 (8.10%)	8 (4.55%)
Back pain	8 (3.43%)	0 (0.00%)	14 (6.17%)	3 (2.07%)	11 (4.45%)	2 (1.14%)
Urinary tract infection	8 (3.43%)	6 (4.20%)	4 (1.76%)	2 (1.38%)	12 (4.86%)	16 (9.09%)
Injection site pain	7 (3.00%)	0 (0.00%)	5 (2.20%)	1 (0.69%)	0 (0.00%)	0 (0.00%)
Dyspepsia	7 (3.00%)	3 (2.10%)	1 (0.44%)	1 (0.69%)	3 (1.21%)	2 (1.14%)
Phlebitis	7 (3.00%)	7 (4.90%)	10 (4.41%)	5 (3.45%)	29 (11.74%)	10 (5.68%)

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Table 56: FDA Medical Officer Summary of treatment-emergent adverse events (frequency $\geq 5\%$ in doripenem arm) stratified by gender and treatment group for all subjects in the doripenem Phase 3 cIAI Trials, ITT population

Preferred Term	Combined Doripenem		Combined Meropenem	
	Female	Male	Female	Male
Nausea	29 (21.01%)	28 (12.44%)	22 (15.71%)	22 (11.64%)
Anaemia	25 (18.12%)	21 (9.33%)	16 (11.43%)	10 (5.29%)
Diarrhoea	22 (15.94%)	29 (12.89%)	24 (17.14%)	28 (14.81%)
Pyrexia	14 (10.14%)	32 (14.22%)	24 (17.14%)	20 (10.58%)
Phlebitis	13 (9.42%)	23 (10.22%)	8 (5.71%)	18 (9.52%)
Hypokalaemia	12 (8.70%)	8 (3.56%)	7 (5.00%)	5 (2.65%)
Vomiting	11 (7.97%)	18 (8.00%)	19 (13.57%)	19 (10.05%)
Pneumonia	11 (7.97%)	9 (4.00%)	5 (3.57%)	2 (1.06%)
Flatulence	10 (7.25%)	9 (4.00%)	7 (5.00%)	4 (2.12%)
Pleural effusion	10 (7.25%)	9 (4.00%)	6 (4.29%)	7 (3.70%)
Headache	10 (7.25%)	11 (4.89%)	16 (11.43%)	8 (4.23%)
Dizziness	9 (6.52%)	6 (2.67%)	7 (5.00%)	8 (4.23%)
Constipation	9 (6.52%)	13 (5.78%)	9 (6.43%)	9 (4.76%)
Urinary tract infection	8 (5.80%)	8 (3.56%)	6 (4.29%)	5 (2.65%)
Insomnia	7 (5.07%)	17 (7.56%)	11 (7.86%)	11 (5.82%)
Abdominal pain	7 (5.07%)	13 (5.78%)	8 (5.71%)	12 (6.35%)
Postoperative wound infection	7 (5.07%)	6 (2.67%)	4 (2.86%)	8 (4.23%)
Wound infection	7 (5.07%)	11 (4.89%)	4 (2.86%)	5 (2.65%)

Gastrointestinal disorders (nausea, diarrhea, flatulence, and constipation), anemia, hypokalemia, headache, pneumonia, pleural effusion, and UTI were more common treatment-emergent adverse events among female subjects than in males treated with doripenem in the combined doripenem cIAI experience. A similar pattern of female predominance with respect to the same adverse events was observed in the combined meropenem experience from DORI-07 and DORI-08.

Body Mass Index (BMI)

The following three tables depict the assessment of body mass index (BMI) stratified by treatment group for the four doripenem phase 3 studies. Assessment of BMI in DORI-05 and DORI-06 revealed the highest incidence of headache as a treatment-emergent adverse event among persons with the smallest BMI (0 – 20 group) and a clear trend of decreasing headache incidence with higher BMI. This observation raises concern that the standard dosage of doripenem in subjects with a small BMI may produce headache as a drug-related intolerance that reflects upon an underlying dose-response relationship. A similar pattern was not observed in the levofloxacin treatment group in DORI-05.

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Table 57: FDA Medical Officer Summary of treatment-emergent adverse events (frequency $\geq 5\%$ in doripenem arm) stratified by body mass index (BMI) and treatment group for all subjects in DORI-05, ITT population

Preferred Term	Doripenem*			Levofloxacin		
	BMI 0 - 20	BMI 21 - 30	BMI 31 - 60	BMI 0 - 20	BMI 21 - 30	BMI 31 - 60
Headache	9 (30.00%)	41 (24.85%)	9 (19.57%)	2 (12.50%)	39 (24.84%)	13 (24.53%)
Diarrhoea	4 (13.33%)	13 (7.88%)	4 (8.70%)	1 (6.25%)	27 (17.20%)	10 (18.87%)
Hypokalaemia	3 (10.00%)	3 (1.82%)	2 (4.35%)	0 (0.00%)	9 (5.73%)	4 (7.55%)
Gamma-glutamyltransferase increased	2 (6.67%)	3 (1.82%)	1 (2.17%)	1 (6.25%)	4 (2.55%)	1 (1.89%)
Nausea	2 (6.67%)	10 (6.06%)	4 (8.70%)	2 (12.50%)	18 (11.46%)	2 (3.77%)
Abdominal pain upper	2 (6.67%)	14 (8.48%)	1 (2.17%)	3 (18.75%)	9 (5.73%)	1 (1.89%)
Oedema peripheral	2 (6.67%)	4 (2.42%)	0 (0.00%)	0 (0.00%)	1 (0.64%)	2 (3.77%)
Constipation	2 (6.67%)	15 (9.09%)	5 (10.87%)	1 (6.25%)	12 (7.64%)	5 (9.43%)

* BMI data was missing for three subjects.

Analysis of treatment-emergent adverse events stratified by BMI for DORI-06 (see table below) revealed a similar pattern in which the highest incidence of headache was observed in patients with the lowest BMI, while the frequency of headaches declined with increasing BMI.

Table 58: FDA Medical Officer Summary of treatment-emergent adverse events (frequency $\geq 5\%$ in doripenem arm) stratified by body mass index (BMI) and treatment group for all subjects in DORI-06, ITT population

Preferred Term	Doripenem*		
	BMI 0 - 20	BMI 21 - 30	BMI 31 - 60
Headache	14 (34.15%)	57 (24.46%)	9 (16.98%)
Diarrhoea	6 (14.63%)	17 (7.30%)	4 (7.55%)
Asymptomatic bacteriuria	6 (14.63%)	17 (7.30%)	6 (11.32%)
Vomiting	6 (14.63%)	20 (8.58%)	8 (15.09%)
Urinary tract infection	5 (12.20%)	20 (8.58%)	2 (3.77%)
Nausea	5 (12.20%)	24 (10.30%)	4 (7.55%)
Phlebitis	5 (12.20%)	28 (12.02%)	6 (11.32%)
Abdominal pain upper	4 (9.76%)	8 (3.43%)	1 (1.89%)
Oedema peripheral	4 (9.76%)	7 (3.00%)	5 (9.43%)
Constipation	4 (9.76%)	10 (4.29%)	2 (3.77%)
Flatulence	3 (7.32%)	4 (1.72%)	3 (5.66%)
Dizziness	3 (7.32%)	15 (6.44%)	1 (1.89%)

* BMI data was missing for six subjects.

The previously described association between headache and BMI among doripenem-treated subjects in the cUTI studies was not observed in an analysis of doripenem-treated subjects in the cIAI studies. Headache was not reported (frequency= 0.0%) as a treatment-emergent adverse event in the combined doripenem cIAI study population. Although the reason for the absence of headaches is unclear, the use of analgesics to relieve postoperative pain is a probably underlying factor. Alternatively, anemia was the most commonly encountered treatment-emergent adverse event in the subgroup of subjects with the smallest BMI, but a clear dose-response relationship was not evident.

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Table 59: FDA Medical Officer Summary of treatment-emergent adverse events (frequency $\geq 5\%$ in doripenem arm) stratified by body mass index (BMI) and treatment group for all subjects in combined DORI-07 and DORI-08 experience, ITT population

Preferred Term	Combined Doripenem*			Combined Meropenem**		
	BMI 0 - 20	BMI 21 - 30	BMI 31 - 60	BMI 0 - 20	BMI 21 - 30	BMI 31 - 60
Anaemia	9 (26.47%)	27 (10.89%)	10 (12.50%)	0 (0.00%)	23 (9.83%)	1 (1.49%)
Nausea	6 (17.65%)	37 (14.92%)	14 (17.50%)	3 (14.29%)	34 (14.53%)	7 (10.45%)
Flatulence	5 (14.71%)	12 (4.84%)	2 (2.50%)	0 (0.00%)	9 (3.85%)	2 (2.99%)
Diarrhoea	4 (11.76%)	38 (15.32%)	9 (11.25%)	4 (19.05%)	38 (16.24%)	9 (13.43%)
Constipation	3 (8.82%)	17 (6.85%)	2 (2.50%)	1 (4.76%)	11 (4.70%)	5 (7.46%)
Abdominal pain	3 (8.82%)	11 (4.44%)	6 (7.50%)	2 (9.52%)	13 (5.56%)	5 (7.46%)
Pyrexia	3 (8.82%)	35 (14.11%)	8 (10.00%)	3 (14.29%)	32 (13.68%)	9 (13.43%)
Rash	2 (5.88%)	11 (4.44%)	3 (3.75%)	0 (0.00%)	5 (2.14%)	0 (0.00%)
Vomiting	2 (5.88%)	20 (8.06%)	7 (8.75%)	5 (23.81%)	26 (11.11%)	6 (8.96%)
Oedema peripheral	2 (5.88%)	14 (5.65%)	5 (6.25%)	1 (4.76%)	9 (3.85%)	4 (5.97%)
Wound dehiscence	2 (5.88%)	2 (0.81%)	5 (6.25%)	1 (4.76%)	3 (1.28%)	2 (2.99%)
Leukocytosis	2 (5.88%)	6 (2.42%)	0 (0.00%)	2 (9.52%)	4 (1.71%)	1 (1.49%)
Hyponatraemia	2 (5.88%)	4 (1.61%)	0 (0.00%)	0 (0.00%)	1 (0.43%)	0 (0.00%)
Hypokalaemia	2 (5.88%)	13 (5.24%)	5 (6.25%)	1 (4.76%)	8 (3.42%)	3 (4.48%)
Hypertension	2 (5.88%)	6 (2.42%)	6 (7.50%)	1 (4.76%)	16 (6.84%)	5 (7.46%)
Abdominal distension	2 (5.88%)	9 (3.63%)	1 (1.25%)	0 (0.00%)	9 (3.85%)	2 (2.99%)
Phlebitis	2 (5.88%)	28 (11.29%)	5 (6.25%)	0 (0.00%)	23 (9.83%)	3 (4.48%)
Abdominal abscess	2 (5.88%)	2 (0.81%)	0 (0.00%)	0 (0.00%)	6 (2.56%)	4 (5.97%)
Confusional state	2 (5.88%)	2 (0.81%)	1 (1.25%)	0 (0.00%)	6 (2.56%)	2 (2.99%)

* BMI data was missing for one subject; **BMI data was missing for seven subjects

In summary, a trend indicative of an increased incidence of headache associated with low BMI was observed in the indication-specific analysis of the cUTI studies. The significance of the trend is uncertain and is confounded by the small patient subgroup having low BMI in the overall study population.

Age

Anemia, nausea, diarrhea, headache, and phlebitis were observed more frequently in doripenem-treated subjects <61 years old in the combined DORI-07/08 experience. However, such trends with respect to anemia and diarrhea were not consistently observed in DORI-05 and DORI-06.

Among doripenem-treated subjects, there were higher rates of asymptomatic bacteriuria in subjects aged >61 years old in DORI-06. Similarly, higher rates of UTI were observed in the doripenem group in DORI-07 and DORI-08, but such trends were not observed in the meropenem treatment experience.

Race

As depicted in Section 7.2.1.2, the safety (ITT) populations in the four doripenem phase 3 studies were predominantly White followed by Hispanic/Latino, Black, and Other in order of frequency. Anemia and pyrexia were reported at a higher rate among Black subjects treated with doripenem in the combined DORI-07/08 experience, but a similar trend with respect to pyrexia was not observed in the DORI-05 and DORI-06. Phlebitis was observed at a higher rate among Hispanic/Latino subjects in DORI-07/08, but a similar trend was not

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observed in the DORI-05 and DORI-06.

Baseline Creatinine Clearance

Doripenem requires dosage adjustment in subjects with moderate to severe renal insufficiency due to its renal route of excretion. As renal function declines with advanced age, some of the treatment-emergent adverse events in patients with a baseline creatinine clearance ≤ 50 mL/min may also be reflective of advanced age.

In the combined DORI-07/08 experience, anemia, pyrexia, gastrointestinal disorders, UTI, and rash were observed more frequently in subjects whose baseline creatinine clearance was ≤ 50 mL/min. These patients were also more likely to have peripheral edema, atrial fibrillation, and respiratory tract-related adverse events (dyspnea, rales, pleural effusion, pneumonia, and bronchospasm). Similar trends were observed in the doripenem-treated subjects in DORI-05 with respect to anemia, pyrexia, and gastrointestinal disorders. Headache was more frequently reported as a treatment-emergent adverse events in doripenem-treated patients with a baseline creatinine clearance > 50 mL/min in all of the phase 3 studies.

Hepatic Impairment

Child-Pugh scores were included for subjects enrolled in the cIAI studies (DORI-07 and DORI-08) but not in the cUTI studies. Thus, safety information with respect to subjects enrolled in DORI-05 and DORI-06 who have hepatic impairment was not collected prospectively.

Baseline hepatic impairment was defined by the sponsor as a Child-Pugh score of ≥ 7 . According to the sponsor's analysis, 32% (152/477) of subjects treated with doripenem 500 mg and 28% (130/469) meropenem-treated subjects had a Child-Pugh total score ≥ 7 . However, the sponsor noted that the validity of the Child-Pugh score in subjects with cIAI may be confounded because ascites, elevated bilirubin and hypoalbuminemia, which are elements of the score, can be features of cIAI. In addition, encephalopathy, another element of the Child-Pugh score, often could not be accurately assessed in post-operative patients receiving pain-relieving medications. Treatment-emergent AEs and study drug-related TEAEs for subjects in both treatment groups with Child-Pugh total score ≥ 7 in the cIAI studies DORI-07 and DORI-08 revealed higher rates of diverse TEAEs for these subjects. In general, these higher rates of TEAEs were observed across both treatment groups. Detailed laboratory analyses by the sponsor did not indicate any sign of any hepatotoxicity of doripenem, only mild reversible transaminase elevations.

The FDA Medical Officer's analysis of adverse events in hepatic impaired subjects in the cIAI studies revealed the following patient demographic distribution:

Table 60: FDA Medical Officer Summary Table of the number of Subjects in the doripenem phase 3 cIAI studies stratified by treatment group and Child-Pugh range, ITT

Child-Pugh Range	Doripenem (combined)	Meropenem (combined)
5-6	325 (68.13%)	339 (72.28%)
7-9	143 (29.98%)	126 (26.87%)
10-13	9 (1.89%)	4 (0.85%)

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The comparative frequencies of select treatment-emergent adverse events among the doripenem- and meropenem-treated subjects in the cIAI studies are provided in the following table:

Table 61: FDA Medical Officer Summary Table of Selected treatment-emergent adverse events in doripenem and meropenem treated subjects in doripenem phase 3 cIAI studies stratified by Child-Pugh range, ITT population

Child-Pugh Range	Combined Doripenem			Combined Meropenem		
	5-6	7-9	10-13	5-6	7-9	10-13
Nausea	35 (10.77%)	21 (14.69%)	1 (11.11%)	28 (8.26%)	15 (11.90%)	1 (25%)
Pyrexia	23 (10.18%)	20 (15.63%)	3 (33.33%)	24 (10.86%)	19 (18.27%)	1 (25%)
Anemia	20 (8.85%)	23 (17.97%)	3 (33.33%)	11 (4.98%)	14 (13.46%)	1 (25%)
Vomiting	16 (7.08%)	12 (9.38%)	1 (11.11%)	23 (10.41%)	15 (14.42%)	0 (0.0%)
Insomnia	15 (6.64%)	7 (5.47%)	2 (22.22%)	16 (7.24%)	6 (5.77%)	0 (0.0%)
Pleural effusion	7 (2.15%)	12 (8.39%)	0 (0.0%)	9 (2.65%)	4 (3.17%)	0 (0.0%)
Hypertension	6 (2.65%)	6 (4.69%)	2 (22.22%)	13 (5.88%)	9 (8.65%)	0 (0.0%)
Peripheral edema	6 (2.65%)	11 (8.59%)	4 (44.44%)	4 (1.81%)	11 (10.58%)	0 (0.0%)
UTI	6 (2.65%)	9 (7.03%)	1 (11.11%)	4 (1.81%)	7 (6.73%)	0 (0.0%)
GGT* increased	5 (2.21%)	7 (5.47%)	2 (22.22%)	5 (2.26%)	5 (3.97%)	0 (0.0%)
Tachycardia	3 (1.33%)	6 (4.69%)	1 (11.11%)	3 (0.88%)	2 (1.92%)	0 (0.0%)
Ascites	3 (0.92%)	4 (2.80%)	0 (0.0%)	1 (0.29%)	2 (1.59%)	1 (25%)
Hypoalbuminemia	3 (0.92%)	2 (1.40%)	0 (0.0%)	0 (0.0%)	4 (3.17%)	0 (0.0%)
Hepatic enzyme increased	3 (0.92%)	0 (0.0%)	1 (11.11%)	3 (0.88%)	5 (3.97%)	0 (0.0%)

*GGT=gamma-glutamyltransferase

As depicted in the table, gastrointestinal disorders, anemia, pyrexia, insomnia, pleural effusion, hypertension, peripheral edema, UTI, GGT increased, and tachycardia were more frequently observed in subjects with underlying hepatic impairment (Child-Pugh total score ≥ 7). Ascites and hypoalbuminemia, which are components of the Child-Pugh score, were also more common in patients with hepatic impairment. Increased hepatic enzymes were observed less frequently in such subjects in the doripenem arm compared to the meropenem arm. Overall, the higher rates of the treatment-emergent adverse events in hepatically-impaired subjects as summarized above were consistent (except for insomnia) in both the doripenem and meropenem treatment groups. No adverse events appeared to be associated preferentially with doripenem administration.

US versus non-US Sites

In the doripenem phase 3 clinical studies, enrollment was predominantly from non-US sites as illustrated in the following table:

Table 62: FDA Medical Officer Summary of demographics by treatment group stratified by US and non-US study sites for the doripenem phase 3 studies, ITT population

Study Sites	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem	Levofloxacin	Doripenem	Doripenem	Meropenem	Doripenem	Meropenem
Non-US	326 (86.7%)	326 (87.63%)	325 (76.83%)	161 (68.51%)	162 (68.64%)	176 (72.7%)	177 (75.97%)
US	50 (13.30%)	46 (12.37%)	98 (23.17%)	74 (31.49%)	74 (31.36%)	66(27.3%)	56 (24.03%)
Total Subjects	376 (100%)	372 (100%)	423 (100%)	235 (100%)	236 (100%)	242 (100%)	233 (100%)

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As subjects were enrolled predominantly from non-US sites, the majority of treatment-emergent adverse events were reported by investigators in sites located outside of the US. Anemia, pyrexia, phlebitis, and gastrointestinal disorders were reported more frequently as treatment-emergent adverse events from non-US sites in the four phase 3 studies. Asymptomatic bacteriuria was reported only from non-US sites in both treatment arms in the cUTI studies. There were few subjects in whom renal failure, renal failure acute, hepatitis cholestatic, and drug hypersensitivity were reported. There were no marked differences in the reporting of such events between US and non-US sites. No cases of erythema multiforme or grand mal convulsions were reported in doripenem-treated subjects in the phase 3 clinical trials.

7.1.6 Less Common Adverse Events

Treatment-emergent adverse events that were reported with an incidence of 1.0% to 2.0% in doripenem- and comparator-treated subjects in the comparative clinical trials DORI-05, DORI-07, and DORI-08 are provided in the two tables below:

Table 63: FDA Medical Officer Table of Treatment-emergent adverse events having incidence of 1.0% to 2.0% in doripenem and levofloxacin-treated subjects, DORI-05, ITT population

Preferred Term	Doripenem (N=376)		Levofloxacin (N=372)	
	n	%	n	%
Abdominal pain	7	1.86	13	3.49
Dyspnoea	7	1.86	6	1.61
Injection site pain	7	1.86	6	1.61
Edema peripheral	7	1.86	3	0.81
Anaemia	6	1.6	4	1.08
Anxiety	6	1.6	8	2.15
Gamma-glutamyltransferase increased	6	1.6	6	1.61
Pyrexia	6	1.6	6	1.61
Vulvovaginitis	6	1.6	1	0.27
Cough	5	1.33	4	1.08
Haematuria	5	1.33	2	0.54
Hypertension	5	1.33	5	1.34
Hypotension	5	1.33	3	0.81
Pain in extremity	5	1.33	5	1.34
Pyelonephritis	5	1.33	0	0.0
Blood alkaline phosphatase increased	4	1.06	6	1.61
Dehydration	4	1.06	1	0.27
Dysmenorrhoea	4	1.06	2	0.54
Flatulence	4	1.06	6	1.61
Hepatic enzyme increased	4	1.06	6	1.61
Nasopharyngitis	4	1.06	0	0.0
Nephrolithiasis	4	1.06	1	0.27
Oral candidiasis	4	1.06	0	0.0
Procedural pain	4	1.06	3	0.81
Vulvovaginal mycotic infection	4	1.06	0	0.0

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Table 64: FDA Medical Officer Table of Treatment-emergent adverse events having incidence of 1.0% to 2.0% in doripenem and meropenem-treated subjects, DORI-07 and DORI-08, ITT population

	Combined Doripenem (N=477)		Combined Meropenem (N=469)	
	n	%	n	%
Blood alkaline phosphatase increased	9	1.89	4	0.85
Hyperglycaemia	9	1.89	11	2.35
Hypotension	9	1.89	5	1.07
Wound dehiscence	9	1.89	6	1.28
Abdominal pain upper	8	1.68	7	1.49
Cough	8	1.68	15	3.20
Decubitus ulcer	8	1.68	2	0.43
Dysuria	8	1.68	4	0.85
Generalised oedema	8	1.68	3	0.64
Leukocytosis	8	1.68	7	1.49
Malnutrition	8	1.68	4	0.85
Oliguria	8	1.68	3	0.64
Ascites	7	1.47	4	0.85
Atrial fibrillation	7	1.47	6	1.28
Back pain	7	1.47	6	1.28
Dehydration	7	1.47	3	0.64
Pharyngolaryngeal pain	7	1.47	5	1.07
Platelet count increased	7	1.47	2	0.43
Post procedural discharge	7	1.47	2	0.43
Tachypnoea	7	1.47	3	0.64
Depression	6	1.26	2	0.43
Hyperhidrosis	6	1.26	10	2.13
Hypomagnesaemia	6	1.26	7	1.49
Hyponatraemia	6	1.26	1	0.21
Ileus	6	1.26	3	0.64
Urinary tract infection fungal	6	1.26	11	2.34
Agitation	5	1.05	6	1.28
Blood pressure increased	5	1.05	5	1.07
Confusional state	5	1.05	8	1.71
Decreased appetite	5	1.05	1	0.21
Hypoalbuminaemia	5	1.05	4	0.85
Incision site haematoma	5	1.05	3	0.64
Injection site reaction	5	1.05	3	0.64
Oral candidiasis	5	1.05	8	1.71
Pain	5	1.05	8	1.71
Pulmonary oedema	5	1.05	2	0.43
Sepsis	5	1.05	7	1.49
Urinary retention	5	1.05	3	0.64
Vulvovaginal mycotic infection	5	1.05	2	0.43
White blood cell count increased	5	1.05	6	1.28

Some of the adverse events listed in each of the two tables above are analyzed by the FDA Medical Officer as part of algorithms involving MedDRA preferred terms that may collectively constitute a marker for study drug toxicity. Please refer to Section 7.1.4 of this report for further details.

In relation to rare adverse events, the FDA Medical Officer has summarized all of the TEAEs with a frequency of 0.1% to <1.0% in the pooled doripenem-treated subjects in the four phase 3 trials the following table stratified by body organ class and preferred term. The incidence rates for the comparator-treated subjects are also provided. Some of the adverse events listed may be clinically important, but the overall doripenem phase 3 clinical program is of insufficient size and statistical power to assess such rare events in

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terms of drug safety. Further post-marketing surveillance will be necessary to evaluate such events.

Table 65: FDA Medical Officer Summary of treatment-emergent adverse events with incidence 0.1% to <1% in the pooled doripenem-treated subjects, phase 3 studies, ITT

Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)	
Blood and lymphatic system disorders	Leukocytosis	9 (0.71%)	2 (0.54%)	7 (1.49%)	
	Thrombocythaemia	4 (0.31%)	0 (0.00%)	6 (1.28%)	
	Eosinophilia	2 (0.16%)	0 (0.00%)	2 (0.43%)	
Cardiac Disorders	Tachycardia	12 (0.94%)	1 (0.27%)	5 (1.07%)	
	Atrial fibrillation	9 (0.71%)	1 (0.27%)	6 (1.28%)	
	Angina pectoris	4 (0.31%)	2 (0.54%)	1 (0.21%)	
	Myocardial ischaemia	3 (0.24%)	0 (0.00%)	1 (0.21%)	
	Supraventricular tachycardia	3 (0.24%)	0 (0.00%)	0 (0.00%)	
	Atrial flutter	2 (0.16%)	0 (0.00%)	0 (0.00%)	
	Bradycardia	2 (0.16%)	0 (0.00%)	3 (0.64%)	
	Cardiac arrest	2 (0.16%)	0 (0.00%)	0 (0.00%)	
	Cyanosis	2 (0.16%)	0 (0.00%)	0 (0.00%)	
	Extrasystoles	2 (0.16%)	0 (0.00%)	1 (0.21%)	
	Myocardial infarction	2 (0.16%)	0 (0.00%)	5 (1.07%)	
	Ear and labyrinth disorders	Ear pain	2 (0.16%)	0 (0.00%)	0 (0.00%)
		Vertigo	2 (0.16%)	0 (0.00%)	0 (0.00%)
Endocrine disorders	Hyperthyroidism	2 (0.16%)	0 (0.00%)	0 (0.00%)	
Eye disorders	Conjunctivitis	5 (0.39%)	1 (0.27%)	0 (0.00%)	
	Vision blurred	3 (0.24%)	0 (0.00%)	0 (0.00%)	
Gastrointestinal disorders	Ascites	7 (0.55%)	0 (0.00%)	4 (0.85%)	
	Ileus	6 (0.47%)	0 (0.00%)	3 (0.64%)	
	Gastritis	5 (0.39%)	1 (0.27%)	2 (0.43%)	
	Abdominal pain lower	4 (0.31%)	1 (0.27%)	6 (1.28%)	
	Dry mouth	4 (0.31%)	0 (0.00%)	2 (0.43%)	
	Dysphagia	4 (0.31%)	0 (0.00%)	3 (0.64%)	
	Enterocutaneous fistula	4 (0.31%)	0 (0.00%)	2 (0.43%)	
	Faecaloma	4 (0.31%)	0 (0.00%)	0 (0.00%)	
	Peritonitis	4 (0.31%)	0 (0.00%)	4 (0.85%)	
	Toothache	4 (0.31%)	2 (0.54%)	1 (0.21%)	
	Abdominal discomfort	3 (0.24%)	0 (0.00%)	3 (0.64%)	
	Colonic atony	3 (0.24%)	0 (0.00%)	1 (0.21%)	
	Impaired gastric emptying	3 (0.24%)	0 (0.00%)	2 (0.43%)	
	Odynophagia	3 (0.24%)	1 (0.27%)	0 (0.00%)	
	Salivary hypersecretion	3 (0.24%)	0 (0.00%)	2 (0.43%)	
	Abdominal haematoma	2 (0.16%)	0 (0.00%)	0 (0.00%)	
	Abdominal tenderness	2 (0.16%)	0 (0.00%)	2 (0.43%)	
Abnormal faeces	2 (0.16%)	0 (0.00%)	0 (0.00%)		

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	Anal fissure	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Bowel sounds abnormal	2 (0.16%)	0 (0.00%)	1 (0.21%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
	Eructation	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Faecal incontinence	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Faeces discoloured	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Gastrointestinal fistula	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Gastrointestinal haemorrhage	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Haematochezia	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Haemorrhoids	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Mouth ulceration	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Pancreatitis	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Small intestinal perforation	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Stomach discomfort	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Tongue blistering	2 (0.16%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions	Chills	12 (0.94%)	6 (1.61%)	6 (1.28%)
	Generalised oedema	9 (0.71%)	0 (0.00%)	3 (0.64%)
	Non-cardiac chest pain	8 (0.63%)	3 (0.81%)	6 (1.28%)
	Pain	8 (0.63%)	1 (0.27%)	8 (1.71%)
	Injection site pain	7 (0.55%)	6 (1.61%)	5 (1.07%)
	Injection site reaction	6 (0.47%)	4 (1.08%)	3 (0.64%)
	Localised oedema	5 (0.39%)	1 (0.27%)	2 (0.43%)
	Catheter related complication	4 (0.31%)	2 (0.54%)	1 (0.21%)
	Hypothermia	4 (0.31%)	0 (0.00%)	3 (0.64%)
	Infusion site pain	4 (0.31%)	6 (1.61%)	0 (0.00%)
	Injection site erythema	4 (0.31%)	2 (0.54%)	1 (0.21%)
	Injection site swelling	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Chest pain	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Malaise	3 (0.24%)	2 (0.54%)	0 (0.00%)
	Prostration	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Impaired healing	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Inflammation	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Injection site irritation	2 (0.16%)	2 (0.54%)	0 (0.00%)
	Irritability	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Multi-organ failure	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Oedema	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Puncture site pain	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Secretion discharge	2 (0.16%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders	Hepatitis	5 (0.39%)	1 (0.27%)	0 (0.00%)
	Cholelithiasis	3 (0.24%)	1 (0.27%)	0 (0.00%)
	Hepatitis toxic	3 (0.24%)	0 (0.00%)	2 (0.43%)
	Hyperbilirubinaemia	3 (0.24%)	0 (0.00%)	2 (0.43%)
	Jaundice	3 (0.24%)	0 (0.00%)	0 (0.00%)

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	Cholecystitis	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Hepatic function abnormal	2 (0.16%)	0 (0.00%)	1 (0.21%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
Immune system disorders	Drug hypersensitivity	4 (0.31%)	0 (0.00%)	1 (0.21%)
	Hypersensitivity	4 (0.31%)	1 (0.27%)	1 (0.21%)
Infections and infestations	Oral candidiasis	10 (0.78%)	0 (0.00%)	8 (1.71%)
	Vulvovaginal mycotic infection	9 (0.71%)	0 (0.00%)	2 (0.43%)
	Vulvovaginitis	9 (0.71%)	1 (0.27%)	0 (0.00%)
	Fungal infection	8 (0.63%)	1 (0.27%)	4 (0.85%)
	Nasopharyngitis	8 (0.63%)	0 (0.00%)	1 (0.21%)
	Upper respiratory tract infection	7 (0.55%)	2 (0.54%)	2 (0.43%)
	Urinary tract infection fungal	7 (0.55%)	0 (0.00%)	11 (2.35%)
	Vaginal infection	7 (0.55%)	2 (0.54%)	1 (0.21%)
	Candidiasis	6 (0.47%)	0 (0.00%)	3 (0.64%)
	Herpes simplex	6 (0.47%)	0 (0.00%)	4 (0.85%)
	Influenza	6 (0.47%)	2 (0.54%)	1 (0.21%)
	Sepsis	6 (0.47%)	0 (0.00%)	7 (1.49%)
	Cellulitis	5 (0.39%)	0 (0.00%)	1 (0.21%)
	Cystitis	5 (0.39%)	2 (0.54%)	0 (0.00%)
	Pyelonephritis	5 (0.39%)	0 (0.00%)	0 (0.00%)
	Vaginal candidiasis	5 (0.39%)	4 (1.08%)	0 (0.00%)
	Abdominal abscess	4 (0.31%)	0 (0.00%)	11 (2.35%)
	Candiduria	4 (0.31%)	0 (0.00%)	1 (0.21%)
	Clostridium difficile colitis	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Infected skin ulcer	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Pelvic abscess	4 (0.31%)	0 (0.00%)	2 (0.43%)
	Septic shock	4 (0.31%)	0 (0.00%)	5 (1.07%)
	Bronchitis acute	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Colostomy infection	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Skin candida	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Staphylococcal infection	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Urosepsis	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Abdominal infection	2 (0.16%)	0 (0.00%)	3 (0.64%)
	Abdominal wall abscess	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Abscess	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Abscess limb	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Bacteraemia	2 (0.16%)	1 (0.27%)	1 (0.21%)
	Erysipelas	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Escherichia urinary tract infection	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Herpes zoster	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Lobar pneumonia	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Postoperative abscess	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Renal abscess	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Sinusitis	2 (0.16%)	0 (0.00%)	0 (0.00%)

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	Tracheobronchitis	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Urinary tract infection bacterial	2 (0.16%)	1 (0.27%)	0 (0.00%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
	Wound abscess	2 (0.16%)	0 (0.00%)	1 (0.21%)
Injury, poisoning and procedural complications	Wound dehiscence	9 (0.71%)	0 (0.00%)	6 (1.28%)
	Post procedural discharge	7 (0.55%)	0 (0.00%)	2 (0.43%)
	Incision site haematoma	5 (0.39%)	0 (0.00%)	3 (0.64%)
	Wound secretion	5 (0.39%)	0 (0.00%)	3 (0.64%)
	Anastomotic leak	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Post procedural haemorrhage	4 (0.31%)	1 (0.27%)	0 (0.00%)
	Seroma	4 (0.31%)	0 (0.00%)	3 (0.64%)
	Post procedural complication	3 (0.24%)	0 (0.00%)	5 (1.07%)
	Post procedural haematoma	3 (0.24%)	0 (0.00%)	2 (0.43%)
	Skin laceration	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Face injury	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Post procedural diarrhoea	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Radius fracture	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Urethral injury	2 (0.16%)	0 (0.00%)	0 (0.00%)
Investigations	Blood pressure increased	9 (0.71%)	0 (0.00%)	5 (1.07%)
	Platelet count increased	8 (0.63%)	1 (0.27%)	2 (0.43%)
	Blood creatinine increased	6 (0.47%)	0 (0.00%)	0 (0.00%)
	Blood potassium decreased	6 (0.47%)	0 (0.00%)	2 (0.43%)
	Alanine aminotransferase increased	5 (0.39%)	7 (1.88%)	4 (0.85%)
	Weight decreased	5 (0.39%)	0 (0.00%)	4 (0.85%)
	White blood cell count increased	5 (0.39%)	1 (0.27%)	6 (1.28%)
	Blood albumin decreased	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Blood lactate dehydrogenase increased	4 (0.31%)	3 (0.81%)	4 (0.85%)
	Body temperature increased	4 (0.31%)	1 (0.27%)	1 (0.21%)
	Aspartate aminotransferase increased	3 (0.24%)	2 (0.54%)	2 (0.43%)
	Blood calcium decreased	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Blood phosphorus decreased	3 (0.24%)	1 (0.27%)	4 (0.85%)
	Breath sounds abnormal	3 (0.24%)	0 (0.00%)	4 (0.85%)
	Neutrophil count increased	3 (0.24%)	0 (0.00%)	2 (0.43%)
	Oxygen saturation decreased	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Urine output decreased	3 (0.24%)	0 (0.00%)	1 (0.21%)
	White blood cells urine positive	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Blood bilirubin increased	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Blood chloride increased	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Blood magnesium decreased	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Blood pressure decreased	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Cardiac murmur	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Haematocrit decreased	2 (0.16%)	0 (0.00%)	1 (0.21%)

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	Neutrophil toxic granulation present	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Platelet count decreased	2 (0.16%)	0 (0.00%)	1 (0.21%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
	Prostatic specific antigen increased	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Protein total decreased	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Urine viscosity abnormal	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Weight increased	2 (0.16%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders	Hypomagnesaemia	11 (0.86%)	3 (0.81%)	7 (1.49%)
	Anorexia	8 (0.63%)	1 (0.27%)	4 (0.85%)
	Decreased appetite	8 (0.63%)	1 (0.27%)	1 (0.21%)
	Malnutrition	8 (0.63%)	0 (0.00%)	4 (0.85%)
	Hypercholesterolaemia	7 (0.55%)	1 (0.27%)	1 (0.21%)
	Hyponatraemia	7 (0.55%)	0 (0.00%)	1 (0.21%)
	Hypoalbuminaemia	6 (0.47%)	0 (0.00%)	4 (0.85%)
	Hyperkalaemia	5 (0.39%)	0 (0.00%)	0 (0.00%)
	Gout	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Hypophosphataemia	4 (0.31%)	1 (0.27%)	5 (1.07%)
	Hyperuricaemia	3 (0.24%)	1 (0.27%)	1 (0.21%)
	Hypocalcaemia	3 (0.24%)	1 (0.27%)	6 (1.28%)
	Hypovolaemia	3 (0.24%)	0 (0.00%)	2 (0.43%)
	Diabetes mellitus	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Fluid overload	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Metabolic acidosis	2 (0.16%)	0 (0.00%)	2 (0.43%)
Musculoskeletal and connective tissue disorders	Arthralgia	8 (0.63%)	1 (0.27%)	3 (0.64%)
	Neck pain	8 (0.63%)	1 (0.27%)	3 (0.64%)
	Bone pain	7 (0.55%)	2 (0.54%)	0 (0.00%)
	Myalgia	5 (0.39%)	1 (0.27%)	0 (0.00%)
	Shoulder pain	5 (0.39%)	2 (0.54%)	2 (0.43%)
	Flank pain	4 (0.31%)	2 (0.54%)	1 (0.21%)
	Muscle contracture	4 (0.31%)	1 (0.27%)	0 (0.00%)
	Groin pain	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Torticollis	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Muscle atrophy	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Musculoskeletal chest pain	2 (0.16%)	0 (0.00%)	3 (0.64%)
	Tendonitis	2 (0.16%)	1 (0.27%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder neoplasm	2 (0.16%)	0 (0.00%)	0 (0.00%)
Nervous system disorders	Paraesthesia	6 (0.47%)	0 (0.00%)	2 (0.43%)
	Tremor	5 (0.39%)	0 (0.00%)	1 (0.21%)
	Dysgeusia	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Syncope	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Somnolence	3 (0.24%)	0 (0.00%)	3 (0.64%)
	Cerebrovascular accident	2 (0.16%)	0 (0.00%)	0 (0.00%)

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	Memory impairment	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Sedation	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Transient ischaemic attack	2 (0.16%)	0 (0.00%)	1 (0.21%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
Psychiatric disorders	Confusional state	9 (0.71%)	0 (0.00%)	8 (1.71%)
	Agitation	7 (0.55%)	0 (0.00%)	6 (1.28%)
	Delirium	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Alcohol withdrawal syndrome	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Nervousness	2 (0.16%)	0 (0.00%)	1 (0.21%)
Renal and urinary disorders	Dysuria	12 (0.94%)	4 (1.08%)	4 (0.85%)
	Nephrolithiasis	9 (0.71%)	1 (0.27%)	1 (0.21%)
	Oliguria	8 (0.63%)	0 (0.00%)	3 (0.64%)
	Renal failure acute	8 (0.63%)	0 (0.00%)	0 (0.00%)
	Pollakiuria	5 (0.39%)	1 (0.27%)	1 (0.21%)
	Renal failure	5 (0.39%)	0 (0.00%)	1 (0.21%)
	Hydronephrosis	4 (0.31%)	1 (0.27%)	0 (0.00%)
	Renal impairment	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Urinary incontinence	4 (0.31%)	0 (0.00%)	2 (0.43%)
	Leukocyturia	3 (0.24%)	1 (0.27%)	0 (0.00%)
	Micturition urgency	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Urethral pain	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Urine odour abnormal	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Haemorrhage urinary tract	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Nocturia	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Pyuria	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Renal colic	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Urethral stenosis	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Urine flow decreased	2 (0.16%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders	Dysmenorrhoea	6 (0.47%)	2 (0.54%)	0 (0.00%)
	Genital pruritus female	6 (0.47%)	0 (0.00%)	3 (0.64%)
	Polymenorrhoea	4 (0.31%)	1 (0.27%)	0 (0.00%)
	Benign prostatic hyperplasia	3 (0.24%)	1 (0.27%)	0 (0.00%)
	Genital discharge	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Balanitis	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Epididymitis	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Metrorrhagia	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Oedema genital	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Penile discharge	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Penile pain	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Penis disorder	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Testicular pain	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Vulvovaginal discomfort	2 (0.16%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	11 (0.86%)	0 (0.00%)	5 (1.07%)

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	Tachypnoea	9 (0.71%)	0 (0.00%)	3 (0.64%)
	Bronchospasm	8 (0.63%)	1 (0.27%)	3 (0.64%)
	Productive cough	6 (0.47%)	0 (0.00%)	2 (0.43%)
Body System	Preferred Term	Pooled Doripenem n (%)	Levofloxacin n (%)	Pooled Meropenem n (%)
	Pulmonary oedema	6 (0.47%)	0 (0.00%)	2 (0.43%)
	Rales	6 (0.47%)	2 (0.54%)	4 (0.85%)
	Hypoxia	5 (0.39%)	2 (0.54%)	1 (0.21%)
	Respiratory failure	5 (0.39%)	1 (0.27%)	6 (1.28%)
	Wheezing	5 (0.39%)	0 (0.00%)	3 (0.64%)
	Acute respiratory distress syndrome	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Hiccups	4 (0.31%)	0 (0.00%)	0 (0.00%)
	Pulmonary embolism	4 (0.31%)	2 (0.54%)	2 (0.43%)
	Hypoventilation	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Pneumothorax	3 (0.24%)	0 (0.00%)	3 (0.64%)
	Pulmonary congestion	3 (0.24%)	0 (0.00%)	4 (0.85%)
	Rhonchi	3 (0.24%)	0 (0.00%)	4 (0.85%)
	Sinus congestion	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Sputum discoloured	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Epistaxis	2 (0.16%)	2 (0.54%)	2 (0.43%)
	Haemoptysis	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Increased upper airway secretion	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Lung infiltration	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Nasal congestion	2 (0.16%)	0 (0.00%)	1 (0.21%)
Skin and subcutaneous tissue disorders	Erythema	5 (0.39%)	1 (0.27%)	7 (1.49%)
	Rash papular	5 (0.39%)	0 (0.00%)	0 (0.00%)
	Dermatitis contact	4 (0.31%)	0 (0.00%)	2 (0.43%)
	Urticaria	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Blister	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Dermatitis	2 (0.16%)	1 (0.27%)	2 (0.43%)
	Dermatitis allergic	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Night sweats	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Pruritus generalised	2 (0.16%)	0 (0.00%)	1 (0.21%)
	Rash macular	2 (0.16%)	0 (0.00%)	2 (0.43%)
	Seborrhoeic dermatitis	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Skin ulcer	2 (0.16%)	0 (0.00%)	0 (0.00%)
Vascular disorders	Haematoma	5 (0.39%)	1 (0.27%)	6 (1.28%)
	Hypertensive crisis	4 (0.31%)	1 (0.27%)	1 (0.21%)
	Deep vein thrombosis	3 (0.24%)	1 (0.27%)	4 (0.85%)
	Hyperaemia	3 (0.24%)	0 (0.00%)	1 (0.21%)
	Orthostatic hypotension	3 (0.24%)	0 (0.00%)	0 (0.00%)
	Hypovolaemic shock	2 (0.16%)	0 (0.00%)	0 (0.00%)
	Thrombophlebitis	2 (0.16%)	1 (0.27%)	0 (0.00%)
	Thrombophlebitis superficial	2 (0.16%)	0 (0.00%)	0 (0.00%)

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7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

According to the sponsor's clinical overview report, routine scheduled clinical laboratory data were collected in the Phase 3 studies and evaluation of these results provided a more thorough profile of anticipated laboratory changes than analysis of laboratory adverse events reported by the investigators. However, both sets of data were analyzed. Laboratory abnormalities were classified using the toxicity grades defined by the Division of Microbiology and Infectious Diseases⁽²⁾ which were slightly modified by the Sponsor to include a normal grade and to remove clinical manifestations. This classification included Grades from 0 (i.e., within normal limits) to 4. For examination of potential hepatic injury, Hy's High Risk (HHR) Classification was used;⁽³⁾ this was defined by an alanine aminotransferase (ALT) > 3 times upper limit of normal (ULN) and a total bilirubin > 1.5 times ULN at the same time point.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

The following tables provide the mean, standard deviation, and median as measures of central tendency with respect to multiple hematologic and chemistry laboratory test parameters. Data related to the change in the parameters from baseline to EOT is presented and the change is stratified by gender. The gender stratification was selected in view of the heterogeneous demographic composition of the cUTI study populations and the DORI-08 study population when assessed by gender. The female subjects in DORI-05 and DORI-06 have a much younger median age compared to the males; Female subjects have an older median age compared to males in DORI-08 (see Section 7.2.1.2).

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Table 66: FDA Medical Officer Summary of measures of central tendency for DORI-05 Serum Hematology Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV (EOT) Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Levofloxacin		
		n	Mean (SD)	Median	n	Mean (SD)	Median
Hematocrit (V/V)	Baseline	352	0.40 (0.05)	0.40	331	0.40 (0.05)	0.40
	Change from Baseline to EOT	305	-0.01 (0.04)	-0.01	284	-0.01 (0.03)	-0.01
	Median Change Baseline to EOT by Gender			F: -0.01 M: -0.01			F: -0.01 M: -0.01
Hemoglobin (g/L)	Baseline	357	130.35 (18.19)	131.00	338	131.29 (17.46)	132.00
	Change from Baseline to EOT	309	-3.55 (11.53)	-3.00	293	-2.99 (10.32)	-3.00
	Median Change Baseline to EOT by Gender			F: -3 M: -3			F: -2.5 M: -4
RBC (x 10 ¹² /L)	Baseline	268	4.34 (0.55)	4.34	244	4.37 (0.55)	4.40
	Change from Baseline to EOT	229	-0.10 (0.37)	-0.09	208	-0.05 (0.32)	-0.10
	Median Change Baseline to EOT by Gender			F: -0.1 M: -0.01			F: -0.08 M: -0.1
WBC (x 10 ⁹ /L)	Baseline	351	10.54 (5.10)	9.10	333	9.96 (4.11)	9.10
	Change from Baseline to EOT	302	-3.07 (4.67)	-1.60	285	-2.38 (3.88)	-1.85
	Change Baseline to EOT by Gender			F: -2.85 M: -0.55			F: -2.82 M: -0.9
Absolute Neutrophils (x 10 ⁹ /L)	Baseline	258	8.11 (4.89)	6.88	235	7.78 (4.26)	7.17
	Change from Baseline to EOT	220	-3.78 (4.68)	-2.55	193	-3.22 (3.91)	-2.73
	Median Change Baseline to EOT by Gender			F: -3.07 M: -0.71			F: -3.45 M: -0.93
Absolute Lymphocytes (x 10 ⁹ /L)	Baseline	258	1.67 (0.73)	1.56	235	1.68 (0.78)	1.61
	Change from Baseline to EOT	220	0.38 (0.68)	0.33	193	0.28 (0.73)	0.19
	Median Change Baseline to EOT by Gender			F: 0.41 M: 0.19			F: 0.22 M: 0.11
Absolute Eosinophils (x 10 ⁹ /L)	Baseline	258	0.12 (0.15)	0.08	235	0.14 (0.18)	0.08
	Change from Baseline to EOT	220	0.11 (0.16)	0.09	193	0.10 (0.17)	0.08
	Median Change Baseline to EOT by Gender			F: 0.09 M: 0.1			F: 0.08 M: 0.07
Platelets (x 10 ⁹ /L)	Baseline	351	246.10 (81.09)	235.00	326	244.50 (80.83)	235.50
	Change from Baseline to EOT	304	42.17 (98.41)	19.0	278	39.14 (79.16)	19.5
	Median Change Baseline to EOT by Gender			F: 23.5 M: 10			F: 29 M: 15

F=female, M=male

There were slight decreases of similar magnitude in hemoglobin, hematocrit, RBC, WBC, and absolute neutrophil counts in both treatment groups in DORI-05. Female subjects had greater median changes in WBC and absolute neutrophil counts compared to males in both treatment arms. Overall, there were no substantial differences between the doripenem and levofloxacin arms of study DORI-05 in the measures of central tendency for select hematologic parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification.

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Table 67: FDA Medical Officer Summary of measures of central tendency for DORI-06 Serum Hematology Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy (EOT) with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Levofloxacin (from DORI-05)		
		N	Mean (SD)	Median	n	Mean (SD)	Median
Hematocrit (V/V)	Baseline	385	0.39 (0.05)	0.39	331	0.40 (0.05)	0.40
	Change from Baseline to EOT	292	-0.006 (0.04)	-0.007	284	-0.01 (0.03)	-0.01
	Median Change Baseline to EOT by Gender			F: -0.01 M: -0.005			F: -0.01 M: -0.01
Hemoglobin (g/L)	Baseline	392	126.05 (16.86)	127.00	338	131.29 (17.46)	132.00
	Change from Baseline to EOT	309	-2.53 (10.55)	-3.0	293	-2.99 (10.32)	-3.00
	Median Change Baseline to EOT by Gender			F: -4 M: -2			F: -2.5 M: -4
RBC (x 10 ¹² /L)	Baseline	384	4.29 (0.58)	4.20	244	4.37 (0.55)	4.40
	Change from Baseline to EOT	307	-0.06 (0.38)	-0.10	208	-0.05 (0.32)	-0.10
	Median Change Baseline to EOT by Gender			F: -0.10 M: -0.10			F: -0.08 M: -0.1
WBC (x 10 ⁹ /L)	Baseline	383	11.21 (4.78)	10.32	333	9.96 (4.11)	9.10
	Change from Baseline to EOT	295	-3.84 (4.80)	-2.70	285	-2.38 (3.88)	-1.85
	Median Change Baseline to EOT by Gender			F: -4.1 M: -1.2			F: -2.82 M: -0.9
Absolute Neutrophils (x 10 ⁹ /L)	Baseline	369	8.23 (4.33)	7.33	235	7.78 (4.26)	7.17
	Change from Baseline to EOT	281	-3.72 (4.48)	-2.70	193	-3.22 (3.91)	-2.73
	Median Change Baseline to EOT by Gender			F: -4.14 M: -1.37			F: -3.45 M: -0.93
Absolute Lymphocytes (x 10 ⁹ /L)	Baseline	369	1.68 (0.75)	1.62	235	1.68 (0.78)	1.61
	Change from Baseline to EOT	281	0.31 (0.69)	0.25	193	0.28 (0.73)	0.19
	Median Change Baseline to EOT by Gender			F: 0.41 M: 0.15			F: 0.22 M: 0.11
Absolute Eosinophils (x 10 ⁹ /L)	Baseline	369	0.17 (0.29)	0.09	235	0.14 (0.18)	0.08
	Change from Baseline to EOT	281	0.14 (0.20)	0.10	193	0.10 (0.17)	0.08
	Median Change Baseline to EOT by Gender			F: 0.1 M: 0.11			F: 0.08 M: 0.07
Platelets (x 10 ⁹ /L)	Baseline	381	256.51 (94.02)	241.00	326	244.50 (80.83)	235.50
	Change from Baseline to EOT	285	36.87 (93.18)	24.0	278	39.14 (79.16)	19.5
	Median Change Baseline to EOT by Gender			F: 39 M: -2			F: 29 M: 15

F=female, M=male

Similar to the findings in DORI-05, slight decreases of similar magnitude in hemoglobin, hematocrit, RBC, WBC, and absolute neutrophil counts were observed in both treatment groups in DORI-06. Female subjects had greater median changes in WBC and absolute neutrophil counts compared to males in both treatment arms. Overall, there were no substantial differences between the doripenem arm of DORI-06 and the levofloxacin arm of DORI-05 in measures of central tendency for select hematologic parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification.

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Table 68: FDA Medical Officer Summary of measures of central tendency for DORI-07 Serum Hematology Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Meropenem		
		n	Mean (SD)	Median	n	Mean (SD)	Median
Hematocrit (V/V)	Baseline	206	0.38 (0.06)	0.39	210	0.38 (0.06)	0.38
	Change from Baseline to EOT	174	-0.01 (0.05)	-0.005	177	-0.01 (0.05)	-0.003
	Median Change Baseline to EOT by Gender			F: -0.0035 M: -0.0065			F: 0 M: -0.01
Hemoglobin (g/L)	Baseline	213	125.44 (20.66)	126.00	216	125.38 (20.03)	126.50
	Change from Baseline to EOT	182	-4.05 (15.39)	-2.50	184	-1.39 (15.30)	-1.0
	Median Change Baseline to EOT by Gender			F: -4 M: -1			F: 1 M: -3
RBC (x 10 ¹² /L)	Baseline	195	4.18 (0.66)	4.20	194	4.25 (0.66)	4.20
	Change from Baseline to EOT	164	-0.11 (0.51)	-0.10	162	-0.01 (0.49)	0.00
	Median Change Baseline to EOT by Gender			F: -0.10 M: -0.10			F: 0 M: -0.1
WBC (x 10 ⁹ /L)	Baseline	211	14.19 (5.79)	13.72	213	12.91 (4.87)	12.80
	Change from Baseline to EOT	179	-5.36 (5.49)	-5.20	181	-4.25 (5.22)	-4.30
	Median Change Baseline to EOT by Gender			F: -5.6 M: -5.0			F: -4.6 M: -4.2
Absolute Neutrophils (x 10 ⁹ /L)	Baseline	180	11.17 (5.10)	10.93	176	10.39 (4.40)	10.0
	Change from Baseline to EOT	149	-5.18 (4.91)	-5.20	144	-4.90 (4.57)	-4.94
	Median Change Baseline to EOT by Gender			F: -5.09 M: -5.32			F: -5.89 M: -4.04
Absolute Lymphocytes (x 10 ⁹ /L)	Baseline	180	1.23 (0.68)	1.08	176	1.21 (0.65)	1.10
	Change from Baseline to EOT	149	0.50 (0.78)	0.50	144	0.54 (0.77)	0.51
	Median Change Baseline to EOT by Gender			F: 0.58 M: 0.44			F: 0.59 M: 0.46
Absolute Eosinophils (x 10 ⁹ /L)	Baseline	180	0.05 (0.12)	0.00	176	0.05 (0.09)	0.00
	Change from Baseline to EOT	149	0.22 (0.22)	0.19	144	0.28 (0.24)	0.24
	Median Change Baseline to EOT by Gender			F: 0.18 M: 0.21			F: 0.2 M: 0.25
Platelets (x 10 ⁹ /L)	Baseline	207	279.29 (140.47)	234.00	211	270.73 (125.28)	239.00
	Change from Baseline to EOT	169	99.93 (127.17)	85.0	178	95.79 (117.02)	83.5
	Median Change Baseline to EOT by Gender			F: 68 M: 86.5			F: 87 M: 81

F=female, M=male

As depicted in the table above, there were no substantial differences in the measures of central tendency for select hematologic parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem and meropenem arms of study DORI-07.

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Table 6: Sponsor Summary Table of Completed Phase 3 Efficacy and Safety Studies (adapted from Table 1, Module 2.5 – Clinical Overview)

Study	Dosage and Design	# Subjects Treated
DORI-05	Multicenter, DB, double-dummy, randomized, comparison study of safety and efficacy of i.v. doripenem and i.v. levofloxacin in subjects with cUTI, including pyelonephritis Doripenem i.v., 500 mg infused over 1 hour q8h or Levofloxacin i.v., 250 mg infused over 1 hour q24h; 10 days (i.v. + oral) (up to 14 days for subjects with concurrent bacteremia at study entry), with option to switch to oral levofloxacin (250 mg q8h) after at least 9 doses of i.v. therapy.	750 Doripenem; n=375 Levofloxacin: n=375
DORI-06	Multicenter, OL, comparison study of safety and efficacy of i.v. doripenem in subjects with cUTI including pyelonephritis Doripenem i.v., 500 mg infused over 1 hour q8h; 10 days (i.v. + oral) (up to 14 days for subjects with concurrent bacteremia at study entry), with option to switch to oral levofloxacin (250 mg q24h) after at least 9 doses of i.v. therapy.	N=450
DORI-07	Multicenter, DB, double-dummy, randomized comparison study of safety and efficacy of i.v. doripenem and i.v. meropenem in subjects with cIAI Doripenem i.v., 500 mg infused over 1 hour q8h or Meropenem, i.v. bolus (3 to 5 min) 1 g q8h; 5 to 14 days (i.v. + oral), with option to switch to oral amoxicillin/clavulanate tablets (875 mg/125 mg) after Day 3	DORI-07: N=471 Doripenem: n=235 Meropenem: n=236 DORI-08: N=475 Doripenem: n=242 Meropenem: n=233

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

^a Subjects enrolled as of clinical cutoff date of 31 August 2006.

According to the sponsor's clinical overview report regarding the pooled Phase 1 studies, in the 164 subjects with normal renal function, 40% of all doripenem-treated subjects experienced at least 1 adverse event (AE) compared with 25% of placebo-treated subjects. Adverse events reported at higher rates in pooled doripenem-treated subjects (i.e., 500 mg and 1,000 mg) than in placebo-treated subjects included diarrhea (6% versus 0%), nausea (6% versus 1%), injection site erythema (5% versus 0%), and injection site swelling (4% versus 1%, respectively).

Although preclinical data showed no potential for cardiotoxicity with doripenem therapy, a definitive Phase 1 QT/QTc study (DORI-NOS-1001) was conducted for completeness. In this study, conducted in 60 subjects, the effect on QT/QTc prolongation of therapeutic (500 mg) and suprathreshold (1000 mg) doses of doripenem infused i.v. over 1 hour were non-inferior to, or no worse than placebo. Furthermore doripenem had no effect on heart rate or other ECG measurements (PR interval, QRS duration, T-wave, or U-wave morphology).

ECGs were not collected systematically in the Phase 3 studies, but were collected at set time points in the Phase 2 DORI-03 study. Given the limitations of interpretation in a

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population with confounding illnesses and medications, as in DORI-03, the results of the thorough Phase 1 QT/QTc study are considered definitive. Like other antibacterials in the carbapenem class, findings in preclinical studies and the definitive DORI-NOS-1001 study demonstrated little to no potential for adverse cardiac electrophysiologic effects.

In the Phase 1 studies in renally impaired subjects, the incidence of AEs did not appear to have any correlation with the degree of renal impairment. In study DORI-NOS-1005, 1 of 6 subjects with end-stage renal disease (ESRD) who were receiving hemodialysis experienced 3 AEs, compared with 2 of 6 healthy subjects who experienced 1 AE each. In study DORI-NOS-1005, after a single dose of doripenem was administered post-dialysis to subjects with ESRD; concentrations of the microbiologically inactive metabolite of doripenem, doripenem-M-1, increased up to a maximum at 18 hours post-dose, and did not decline during the 48 hour sampling period. However, no safety concerns were identified in these subjects.

In the phase 2 study, DORI-03, 70 subjects (57.9 %) experienced at least one treatment-emergent adverse event, four subjects experienced a serious adverse event, and there was one death not attributed to study drug by the investigator. Four subjects were discontinued from the study due to an adverse event. All of the subjects who experienced serious treatment-emergent adverse events or who discontinued from the study due to an adverse event were treated with the 250 mg doripenem regimen. The following table summarizes pertinent information for DORI-03:

Table 7: FDA Medical Officer's Summary of the number of subjects who experienced adverse events, treatment-emergent adverse events, fatalities, and discontinuations in the doripenem Phase 2 clinical trial, DORI-03 (ITT Population)

ITT Population	Doripenem 250 mg (n=65)	Doripenem 500 mg (n=56)	Doripenem Total (n=121)
	n, (%)	n, (%)	n, (%)
≥1 Adverse event	37 (56.9)	34 (60.7)	71 (58.7)
≥1 Treatment-emergent adverse event (TEAE)	36 (55.4)	34 (60.7)	70 (57.9)
Drug-related treatment-emergent adverse event (Investigator designated)	16 (24.6)	23 (41.1)	39 (32.2)
Serious treatment-emergent adverse event	4 (6.15)	0 (0)	4 (3.30)
Deaths	1 (1.54)	0 (0)	1 (0.83)
Discontinuations due to an adverse event	4 (6.15)	0 (0)	4 (3.30)
Discontinuations due to drug-related TEAE (Investigator designated)	2 (3.08)	0 (0)	2 (1.65)
Discontinuations due to a serious TEAE	3 (4.62)	0 (0)	3 (2.48)

Table 8 below summarizes the number of subjects who experienced adverse events and fatalities in the four phase 3 clinical trials stratified by treatment arm. Table 9 summarizes the discontinuations in each study also stratified by treatment arm.

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Table 8: FDA Medical Officer's Summary of the number of subjects in each treatment group who experienced adverse events, treatment-emergent adverse events, and fatalities in the four doripenem Phase 3 clinical trials for cUTI and cIAI, ITT Population

ITT Population	Complicated UTI			Complicated IAI			
	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem n=376	Levofloxacin n=372	Doripenem n=423	Doripenem n=235	Meropenem n=236	Doripenem n=242	Meropenem n=233
≥1 adverse event	245 (65.2)	226 (60.8)	333 (78.7)	198 (84.3)	186 (78.8)	165 (68.2)	143 (61.4)
Treatment-emergent adverse events	240 (63.8)	222 (59.7)	324 (76.6)	195 (83)	184 (78)	162 (66.9)	142 (60.9)
Drug-related adverse event (Investigator designated)	106 (28.2)	93 (25)	124 (29.3)	76 (32.3)	63 (26.7)	37 (15.3)	47 (20.2)
Serious adverse event	33 (8.78)	16 (4.3)	42 (9.9)	31 (13.2)	34 (14.4)	41 (16.9)	44 (18.9)
Deaths	1	0	4*	5	7	8	11

* One patient (452/00201) was enrolled but died of sepsis before receiving study drug

The proportions of subjects who experienced at least one adverse event were comparable within the treatment arms of the four doripenem phase 3 studies. There were more subjects who experienced serious adverse events among the doripenem-treated subjects in the cUTI studies, whereas there were similar frequencies of serious adverse events among patients in the doripenem and comparator arms in the cIAI studies. There were a total of 36 deaths among the pooled doripenem-treated and the pooled meropenem-treated subjects in the four phase 3 clinical trials (18 deaths in each group). There were no deaths involving patients treated with levofloxacin in DORI-05. Further details on patient deaths are provided in Section 7.1.1 of this report.

Table 9: FDA Medical Officer's Summary of Discontinuations of Subjects enrolled in the four doripenem Phase 3 clinical trials, All randomized Population

All Randomized Population	Complicated UTI			Complicated IAI			
	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem N=377 n,(%)	Levofloxacin N=376 n,(%)	Doripenem N=426 n,(%)	Doripenem N=237 n,(%)	Meropenem N=239 n,(%)	Doripenem N=249 n,(%)	Meropenem N=237 n,(%)
Discontinuations due to an adverse event	5 (1.33)*	14 (3.7)	7 (1.65)	12 (5.1)	5 (2.1)	10 (4.1)	8 (3.4)
Discontinuations due to drug-related adverse event (Investigator designated)	1 (0.3)	9 (2.4)	2 (0.5)	5 (2.1)	3 (1.3)	2(0.8)	3 (1.3)
Discontinuations due to a serious adverse event	3 (0.80)	2 (0.5)	6 (1.4)	4 (1.7)	0 (0)	7 (2.89)	5 (2.15)

*An additional subject (#05701016) had pyelonephritis as an adverse event. Study drug was discontinued due to non-compliance, and the patient was lost to followup.

In total in the all randomized population, there were 61 subjects who were discontinued from participation in the four doripenem phase 3 clinical trials due to an adverse event. In DORI-05, fewer subjects in the doripenem arm (1.33%) discontinued due to adverse events compared to those treated with levofloxacin (3.7%). The discontinuation rate due to an adverse event was similar in the doripenem-treated subjects in DORI-05 and DORI-06. In contrast, in the cIAI studies, there were more doripenem-treated subjects (4.5% pooled rate) who discontinued due to an adverse event compared to meropenem-treated subjects (2.7% pooled rate). Section 7.1.3.1 provides further details on the subjects who were discontinued due to an adverse event.

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Table 10: FDA Medical Officer Summary of Study Subjects who were Lost to Follow-up in the doripenem Phase 3 clinical studies, ITT population

ITT Population	Complicated UTI			Complicated IAI			
	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem N=376 n,(%)	Levofloxacin N=372 n,(%)	Doripenem N=423 n,(%)	Doripenem N=235 n,(%)	Meropenem N=236 n,(%)	Doripenem N=242 n,(%)	Meropenem N=233 n,(%)
Lost to Followup	2 (0.53)	1 (0.27)	2 (0.48)	1 (0.43)	2 (0.85)	0 (0.0)	0 (0.0)
Lost to Followup who had a TEAE	1 (0.27)	0 (0.0)	2 (0.48)	1 (0.43)	1 (0.42)	0 (0.0)	0 (0.0)

TEAE=treatment-emergent adverse event

As depicted in Table 10 above, a total of eight study subjects were lost-to-followup in the phase 3 studies (ITT population). Of those eight subjects, five experienced an adverse event. Please refer to Section 7.1.3.2 of this report for further details.

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7.1.1 Deaths

Phase 1 and 2 Studies:

There were no deaths in the doripenem phase 1 studies. In the phase 2 study (DORI-03), there was one death that was not attributed to study drug exposure. The Sponsor's narrative summary is provided below:

Sponsor's narrative (Subject 01P0006) from the Clinical Study Report on DORI-03:

This 81-year-old Caucasian male signed informed consent to participate in the study on 17 July 2003. He was randomized to the 250 mg q8h dose group and received study drug for the treatment of pyelonephritis caused by *Pseudomonas aeruginosa* (MIC of 0.25 µg/mL) from _____ (a total of 35 doses). The subject had mild renal impairment upon entry into the study (estimated creatinine clearance 54 mL/min). His medical history included ongoing cardiac arrhythmia, supraventricular extrasystoles, and arteriosclerosis with circulation disorder diagnosed in 2002. He also had ongoing diabetes mellitus diagnosed in 1997, hyperurecemia, arthritis, and Parkinson's disease. The subject had acute urinary retention just before entering the study and underwent a transurethral resection of the prostate while on study _____, at which time prostate adenoma was found. Ongoing prior medications included glibenclimide for diabetes mellitus, oprimol and metixen for Parkinson's, furosemide for edema, allopurinol for hyperurecemia, magnesium for arteriosclerosis of the brain, and naftidrofuryl for arterial circulation disorder. Prior hydrochlorothiazide for arrhythmia was discontinued on 16 July 2003. In addition, while on study, the subject received metamiole for fever, nordazepam and oxazepam for sleep disorder, vitamin K for low, quick prothrombin time, and heparin for thrombosis prophylaxis.

The subject's surgery on _____ had taken 20 minutes and there was minimal blood loss. Due to a hemoglobin count below the lower limit of normal on 18 July and 20 July, the subject was transfused with erythrocyte concentrate and the post-operative hemoglobin was stable at 10 g/dL, although still slightly below the lower limit of normal (12.6 g/dL). On _____ the subject was 4 days post-operative and his transurethral catheter was removed. He reported he felt well on that afternoon, with no organ dysfunction found on examination except dry skin; fluid intake was increased. The subject ate dinner and was reported to have felt well. At 19:10 on the evening of _____, the subject was found dead in bed without pulse or spontaneous respiration, and with postmortem lividity. Body temperature was not measured. There were no overt signs of anaphylaxis. Suspected causes of death were myocardial infarction or pulmonary embolism. The subject's wife did not permit an autopsy. There were no other AEs reported on study. In the opinion of the investigator, this event was unrelated to study drug. In completing the SAE report, the investigator mistakenly broke the blind for this subject.

Phase 3 Studies:

In the four doripenem phase 3 comparative clinical trials, there were 18 deaths involving doripenem-treated subjects and 18 deaths among comparator-treated subjects. Table 11 below summarizes information derived from the narratives provided by the Sponsor on the deaths among doripenem-treated subjects in the four phase 3 clinical trials. Based on the FDA Medical Officer's review, none of the deaths appeared to be due to an adverse event directly related to doripenem administration.

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Table 11: FDA Medical Officer's Composite List of all Phase 3 Study Deaths among the Doripenem-treated patients (data derived from Sponsor's narrative summaries)

Study	Subject ID #	Age/Sex/Race	Diagnosis	Past Medical History and Significant Concurrent Medical Conditions	Duration of study drug (days)	Life-threatening Adverse Event(s)	Additional Comments
DORI-05	00502002	87/M/W	Asymptomatic cUTI	New left bundle branch block, cardiomegaly, pulmonary edema, CHF, Hypertension, DM II, cUTI, Prostatic hypertrophy	1	Bradycardia	DNR status Day 1: died
DORI-06	35000079	73/M/W	Symptomatic cUTI	COPD, anemia, muscle atrophy, nephrolithiasis, bladder tumor, asymptomatic bacteriuria, prostatic hypertrophy	11	Respiratory failure	Day 17: developed ARF Day 20: tracheostomy Day 26: cardiac arrest Day 27: died
	45000084	81/M/W	cUTI	Acute MI, Chagas cardiomyopathy, pacemaker, CHF,	7	Ventricular arrhythmia	Day 7: developed arrhythmias and died
	45200201	40/F/W	Uncomplicated pyelonephritis		0	Sepsis	Not ITT; did not receive study drug
	45500330	62/M/W	cUTI	Hypertension, intestinal constipation, anemia	6	Bladder neoplasm, Acute Respiratory Failure	Day 4: bladder tumor diagnosed Day 34: renal impairment developed Day 45: lung metastases detected Day 55: died
DORI-07	04602510	61/F/W	cIAI	CHF, hypertension, duodenal ulcer, DM, COPD, hyperlipidemia, tachycardia, elevated white blood cell count	6	Staphylococcal sepsis	Day 6: developed pneumonia Day 10: developed Enterococcal UTI and Staphylococcal bacteremia Day 14: developed pancreatitis, myocardial ischemia, renal insufficiency, staphylococcal sepsis Day 22: died
	04702519	74/M/W	Perforated cecum with probable carcinoma of hepatic flexure	Aortic bi-femoral bypass, atrial fibrillation, coronary artery disease, Greenfield filter*, hypertension, hypotension, COPD, lumbar stenosis, hypoxia, pleural effusion	1	Sepsis	Day 1: developed sepsis and died
	20206503	72/F/W	Perforated duodenal ulcer, multiple intra-abdominal abscesses, damage to bladder wall	Hypertension, peritoneal abscess, subhepatic abscess drainage, sepsis	5	Multi-organ failure	Day 1: life-threatening sepsis Day 5: study drug discontinued due to sepsis Day 10: peritonitis diagnosed Day 12: pneumonia diagnosed Day 16: surgery for peritonitis /closure of jejunal wall Day 30: mechanical

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							ventilation and multi-organ failure; died
	20406002	33/F/W	clAI	Gastric ulcer/tumor, irritable colon	5	Gastric cancer	Day 8: gastric cancer Day 21: anastomotic fistula, gastrectomy, pancreoduodenectomy, splenectomy, right hemicolectomy 3 months later: massive GI hemorrhage; cholestasis, epilepsy, paraneoplastic syndrome, left jugular vein thrombosis, constricted choleduochojejunostomy anastomosis Day 100: acute respiratory arrest and died
	37204503	77/M/H	clAI, peritonitis	Stomach cancer, right sclera hematoma, hematomas of both arms, chronic anemia, decreased total protein	1	Sepsis	Day -5: total gastrectomy Day 1: peritonitis with dehiscence of esophago-jejunal anastomosis; developed septic shock Day 2: died
DORI-08	00502060	80/F/H	clAI	Hypertension of lower extremities, gastritis, status-post perforated sigmoid diverticulitis, hysterectomy, UTI, anxiety	15	ARDS due to MRSA pneumonia	Day -1: sigmoid colectomy and Hartmann's procedure Day 9: tachycardia Day 10: MRSA pneumonia Day 19: tachycardia, hypotension Day 25: acute respiratory distress Day 28: life-support withdrawn, died
	00502515	60/F/H	clAI, peritonitis, perforated sigmoid colon	Hypertension, cholecystectomy, perforated sigmoid colon, bladder retention, osteoporosis, polycystic ovarian disease, neuralgia, probable metastatic cancer	13	ARDS	Day -10: bone metastasis of unknown primary Day 2-3: fluid overload and hypothermia Day 6: ARDS Day 21: tracheostomy Day 26: life-support withdrawn, died
	00502519	85/F/H	clAI	Coronary artery disease, stroke, hypertension, peripheral vascular disease, tachycardia, constipation, reflux disease, necrotic cecum, DM II, anemia, hypercholesterolemia, fever, Meniere's disease, basal cell cancer, COPD	9	Enterococcal sepsis	Day -1: right hemicolectomy with primary anastomosis, right oophorectomy, cholecystectomy Day 6: supraventricular tachycardia, gall bladder edema, pleural effusion Day 9: <i>Enterococcus faecium</i> bacteremia Day 11: Enterococcal sepsis Day 13: life-support withdrawn, died

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05402058	49/F/W	cIAI	Crohn's disease, low back pain, menopause, depression, perforated duodenum and jejunum, fever septicemia, hypotension, ARDS, acute renal failure	8	Multi-organ failure	Day 1: pneumonia diagnosed Day 11: UTI, gastrointestinal hemorrhage, incisional drainage, catheter-related complication Day 27: surgical repair of gastrointestinal bleed Day 34: gastrointestinal bleeding with surgical repair, cardiac arrest, multi-organ failure, ARDS Day 37: gastrointestinal bleeding Day 39: life-support withdrawn, died
05402523	83/F/W	Perforated viscus	Aortic stenosis, atrial fibrillation, coronary artery disease, hypercholesterolemia, hypertension, pernicious anemia, DM, hypothyroidism, nephrotic syndrome, cardiogenic shock, CHF, cardiac arrest x2, cardiac tamponade, MI, intra-aortic balloon pump, ruptured left ventricle, vascular insufficiency, coagulopathy, ARF, ventricular tachycardia	8	Respiratory failure	Prior to study entry: perforated viscus, ischemic bowel, gastrointestinal bleed, unstable angina, postoperative stroke, acute pericarditis, mediastinal hematoma, pericardial effusion, septic shock, atelectasis, staphylococcal pneumonia Day -1: sigmoid resection with end colostomy Day 12: cardiac arrest Day 14: pleural effusions, atelectasis Day 25: died
05402526	86/F/W	cIAI, peritonitis	Hypertension, hypotension, bradycardia, sinus tachycardia, hypermagnesemia, hyperglycemia, acidosis, renal insufficiency	7	Respiratory arrest	Day 1: gastrostomy tube erosion through stomach Day 2: septic shock Days 2-7: anemia, generalized edema, atrial fibrillation, abdominal wound and catheter complications Day 7: life-support withdrawn, died
12606026	69/F/W	Perforated sigmoid colon with peritonitis	Coronary heart disease, peripheral artery disease, hyperlipoproteinemia, COPD	6	Renal insufficiency	Days 2-5: repeat abdominal surgeries Day 6: bacteremia and pneumonia diagnosed Day 8: tracheostomy, mechanical ventilation Day 15: anastomotic leak, repeat laparotomy Day 16: sepsis Day 27: pneumonia, intra-abdominal infection Day 32: repair of anastomotic leak Day 34: pancreatitis Day 40: gall bladder necrosis Day 53: renal insufficiency, died

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	43104023	79/F/W	Peritonitis with perforated appendix	Atrial fibrillation, hypertension, abdominal distension, hypacusia, DM, malnutrition	12	Pneumonia	Day 3: bronchospasm Day 4: septic shock, repeat laparotomy Days 2-4: dyspnea, delirium, atrial fibrillation, oliguria, anemia, decubitus ulcer, generalized edema, infectious hepatitis Day 12: ventilator-associated pneumonia Day 18: wound dehiscence Day 21: second episode of ventilator-associated pneumonia Day 22: atrial fibrillation Day 25: died
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M=Male, F=Female, H=Hispanic, W=White; cUTI=complicated urinary tract infection; cIAI=complicated intra-abdominal infection; DM=Diabetes mellitus; COPD=chronic obstructive pulmonary disease; ARF=acute respiratory failure; CHF=congestive heart failure; MI=myocardial infarction; DNR=do not resuscitate; ARDS=acute respiratory distress syndrome; *filter device to interrupt vena cava to trap blood clots

There was only one death among the doripenem-treated subjects in study DORI-05:

- Subject ID# 00502002 was an elderly male who died on day 1 of the study following an episode of bradycardia, which was not treated. He had been placed on a do-not-resuscitate status prior to the onset of the life-threatening event. He had multiple concurrent medical problems and was under treatment for an asymptomatic cUTI in the study.

FDA Medical Officer Comment: The patient succumbed to a fatal cardiac arrhythmia (bradycardia), which was not treated in view of the subject's do not resuscitate status.

There were four deaths among the doripenem-treated subjects in study DORI-06. All of the deaths appeared unlikely to be unrelated to doripenem exposure.:

- Subject ID# 35000079 was being treated for a symptomatic cUTI and developed acute respiratory failure on Day 17 (approximately 6 days after completing study drug). The patient had a tracheostomy performed on Day 20. However, he experienced a cardiac arrest on Day 26 and died the following day.
- Subject ID# 45000084 was an elderly male with a history of acute myocardial infarction, Chagas cardiomyopathy, congestive heart failure, and pacemaker. He was treated for a total of seven days with study drug. He developed a ventricular arrhythmia and died on Day 7.
- Subject ID# 45200201 was a female patient who died from sepsis before receiving study drug.
- Subject ID# 45500330 received six days of study drug for a cUTI. He was noted to have a bladder tumor on Day 4 of the study. Renal impairment was observed on Day 34, and lung metastases on Day 45. He died 10 days later.

FDA Medical Officer Comment: Two of the four deaths in DORI-06 occurred post-treatment after the patients had discontinued doripenem. One death occurred before the patient had received doripenem. One death involved a subject with multiple cardiac problems that confounded causality assessment. All of the deaths appeared

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unlikely to be related to doripenem exposure.

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

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

FDA Medical Officer Comment: It was not possible to exclude lack of study drug efficacy as potentially contributing to the patient's demise.

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

FDA Medical Officer Comment: The subject's death appeared to be related to complications from the underlying infection.

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

FDA Medical Officer Comment: It is not possible to exclude lack of study drug efficacy as contributing to the persistent sepsis observed from Days 1 to 5, as the patient was receiving doripenem at that time (concurrent with the septic event).

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

FDA Medical Officer Comment: There was not a clear temporal relationship between the subject's death and exposure to doripenem, as the drug had been discontinued weeks prior to the event.

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

FDA Medical Officer Comment: The subject's death appeared to be related to

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complications of the underlying infection.

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

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

FDA Medical Officer Comment: The patient developed post-operative pneumonia involving a pathogen (MRSA) that is resistant to doripenem. She succumbed to her illness following withdrawal of life support measures.

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

FDA Medical Officer Comment: The patient developed post-operative respiratory complications and succumbed to her illness following withdrawal of life support measures.

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

FDA Medical Officer Comment: The patient developed post-operative bacteremia due to a resistant pathogen and succumbed to sepsis following withdrawal of life support measures.

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

FDA Medical Officer Comment: The patient developed post-operative bleeding requiring multiple surgeries, and she died following withdrawal of life support measures.

- Subject ID# 05402523 was an 83 year old female with multiple medical problems as

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described in the table above. She had a perforated viscus, gastrointestinal bleed, ischemic bowel, postoperative stroke, acute pericarditis, mediastinal hematoma, pericardial effusion, septic shock, and staphylococcal pneumonia prior to entering the study. On Day -1, she had a sigmoid resection with end colostomy. She had a cardiac arrest on Day 12, but developed pleural effusions with atelectasis on Day 14. She died on Day 25.

FDA Medical Officer Comment: The patient developed post-operative complications (cardiac and respiratory) that contributed to her fatal outcome.

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

FDA Medical Officer Comment: The patient developed septic shock and died following withdrawal of life support measures.

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

FDA Medical Officer Comment: It was not possible to exclude lack of study drug efficacy as a contributing factor to the development of postoperative bacteremia and pneumonia.

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

FDA Medical Officer Comment: It was not possible to exclude lack of study drug efficacy in relation to the development of VAP post-operatively.

In examining the timing of the 18 deaths among the doripenem treated patients, one death occurred prior to doripenem administration, four deaths occurred during the time of administration of the drug, and 13 deaths occurred after doripenem administration had been completed such that there was not a clear temporal relationship between doripenem exposure and the fatal event. Many subjects experienced post-operative complications following intra-abdominal surgery. Life support was withdrawn in six of the 18 deaths among the doripenem-treated patients, which was a confounding factor in assessing those

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cases. In five cases, novel infections developed during the patient's course of study drug such that lack of drug efficacy could not be excluded as a contributing factor to infectious complications (pneumonia and bacteremia) subsequently encountered by those subjects. The clinical outcomes of those five subjects were as follows: clinical failure at EOT (subject ID# 12606026), indeterminate at EOT (subject ID# 20206503 and 43104023), indeterminate at TOC (subject ID# 04602510), and clinically improved at EOT (subject ID# 00502519). Subject ID# 00502519 was not clinically evaluable at TOC. There were no subjects whose death could be directly attributed to an adverse drug reaction to doripenem.

7.1.2 Other Serious Adverse Events

In providing an overview of safety, the sponsor commented that no deaths or serious adverse events (SAEs) were reported in healthy or renally impaired subjects in the Phase 1 studies. Even though subjects in the Phase 2 and 3 studies had serious complicated infections, the mortality rate was low (1.5%, doripenem 250 mg; 1.3%, doripenem 500 mg; 0%, levofloxacin; 3.8%, meropenem), and none of the SAEs resulting in death were considered study drug-related. All AEs leading to death were considered related to the underlying infection, or other illnesses that worsened or developed while the subject was enrolled in the study. SAEs were generally more common in the cIAI studies: (15.1%, doripenem; 16.2%, meropenem) with similar incidences in the 2 treatment arms, whereas in cUTI the proportion of subjects with SAEs was 6.2%, 7.8%, and 4.0%, for the doripenem 250 mg, doripenem 500 mg, and levofloxacin treatment arms, respectively. SAEs were frequently related to the underlying infections (e.g., GI events were relatively common in the cIAI studies and urinary complications in the cUTI studies).

In DORI-03, there were four serious treatment-emergent adverse events (in addition to the one death described above). One serious adverse event occurred during screening before the subject (subject 58P0237) was randomized and received study drug. One of the serious adverse events (subject 56P0219) was probably related to study drug. The remaining two subjects had serious adverse events that did not appear to be related to study drug. Relevant information on these subjects is summarized in the following table:

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Table 12: FDA Medical Officer Summary of the subjects who experienced serious treatment-emergent adverse events in DORI-03, ITT Population (Source: Sponsor narratives from the Clinical Study Report DORI-03)

Subject ID #	Age/Sex/Race	Past Medical History and Significant Concurrent Medical Conditions	Duration of doripenem IV (dose)	Adverse Event(s)	Additional Information
18L0021	81/M/W	Chronic heart failure, pulmonary hypertension, mild renal impairment, glaucoma, benign prostatic hypertrophy, COPD, sigmoid colon-urinary bladder fistula excision	1 day (250 mg)	Acute cardio-respiratory failure following the second dose of study drug	The patient required intubation, drainage of pleural effusions, pressors, diuretics, and antibiotics for possible subacute endocarditis. He refused surgical repair of the cardiac valve. His condition improved, and he was transferred to another hospital.
51P0148	71/F/W	Moderate renal impairment, anemia, anxiety, pyelonephritis, fever, allergy to aspirin and dipirone, cholecystectomy, pancreatitis, pancreatic necrotomy.	7 days (250 mg)	Catheter-related infection	The patient developed chills, tachycardia, and fever on the 7 th day of study drug treatment. Blood cultures drawn from the central line grew coagulase-negative <i>Staphylococcus</i> . The patient was treated with vancomycin empirically for three days with improvement.
56P0219	21/F/W	Uncomplicated UTI, allergy to indomethacin	2 days (250 mg)	Allergic reaction, Pleural effusion	The patient experienced laryngeal obstruction without bronchospasm or stridor during the third infusion of study drug. The investigator discontinued the drug and she was withdrawn from study participation. She was treated with hydrocortisone and diphenhydramine for the event, which lasted 2 hours 35 minutes. On the following day, she developed fever, cough, and had dyspnea with thoracic pain. Her chest x-ray and CT scan revealed bilateral pulmonary infiltrates and pleural effusions. She was treated with diphenhydramine, hydrocortisone, iprroprium bromide, and ibuprofen, and she improved. She was treated with ciprofloxacin and gentamicin for the UTI and clarithromycin for the fever. She also received fluconazole for genital mycosis.
58P0237	67/F/H	Hypertension, diabetes mellitus type II, arthritis, mild renal impairment	11 days (250 mg)	Sternal chondritis	The patient experienced thoracic pain that radiated down her left arm while undergoing screening. Cardiac evaluation was negative. Her pain resolved with ibuprofen. After resolution of the pain, she was randomized to study drug and completed study participation. The chondral pain had resolved prior to initiation of study drug.

F=female, M=male, W=white, H=Hispanic

The following series of tables provides the FDA Medical Officer's list of the serious adverse events observed in each treatment arm in the four doripenem phase 3 clinical studies involving cUTI and cIAI.

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Table 13: FDA Medical Officer Summary of the subjects who experienced serious treatment-emergent adverse events in DORI-05, ITT Population

		Doripenem		Levofloxacin	
		(N=376)	%	(N=372)	%
Patients with ≥1 serious treatment-emergent adverse event		28	7.45	15	4.03
System Organ Class	Preferred Term				
Cardiac Disorders		1	0.27	2	0.54
	Atrial fibrillation	0	0	1	0.27
	Bradycardia	1	0.27	0	0
	Cardiac failure	0	0	1	0.27
Eye Disorders		0	0	1	0.27
	Glaucoma	0	0	1	0.27
Gastrointestinal Disorders		1	0.27	1	0.27
	Fecaloma	1	0.27	0	0
	Vomiting	0	0	1	0.27
General Disorders + Administration Site Conditions		1	0.27	0	0
	Hypothermia	1	0.27	0	0
Hepatobiliary		1	0.27	1	0.27
	Cholelithiasis	1	0.27	1	0.27
Infections and Infestations		14	3.72	3	0.81
	Bacteremia	0	0	1	0.27
	Bacterial infection	1	0.27	0	0
	Erysipelas	1	0.27	0	0
	Gastroenteritis viral	1	0.27	0	0
	Orchitis	1	0.27	0	0
	Pneumonia	1	0.27	1	0.27
	Pyelonephritis	4	1.06	0	0
	Respiratory tract infection	1	0.27	0	0
	Sepsis	1	0.27	0	0
	Systemic candida	0	0	1	0.27
	Urinary tract infection	2	0.53	0	0
	Urosepsis	1	0.27	0	0
Injury, poisoning, & procedural complications		1	0.27	1	0.27
	Accidental overdose	0	0	1	0.27
	Hematuria traumatic	1	0.27	0	0
Metabolism and nutrition		2	0.53	2	0.53
	Dehydration	1	0.27	1	0.27
	Diabetes mellitus inadequate control	1	0.27	0	0
	Hyperglycemia	0	0	1	0.27
Neoplasms benign, malignant, and unspecified		3	0.8	0	0
	Bladder neoplasm	1	0.27	0	0
	Colon cancer	1	0.27	0	0
	Colon neoplasm	1	0.27	0	0
Nervous System		2	0.53	1	0.27
	Grand mal convulsion	0	0	1	0.27
	Reversible ischemic neurologic defect	1	0.27	0	0

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Pregnancy, puerperium, perinatal conditions		0	0	1	0.27
	Abortion spontaneous	0	0	1	0.27
Renal and urinary disorders		2	0.53	1	0.27
	Calculus ureteric	0	0	1	0.27
	Hydronephrosis	1	0.27	0	0
	Renal failure acute	1	0.27	0	0
Reproductive System & Breast		1	0.27	0	0
	Benign prostatic hyperplasia	1	0.27	0	0
Respiratory, Thoracic, and Mediastinal Disorders		0	0	3	0.81
	Hypoxia	0	0	1	0.27
	Pulmonary embolism	0	0	2	0.54
Vascular disorders		2	0.53	2	0.54
	Deep vein thrombosis	0	0	1	0.27
	Hypovolemic shock	1	0.27	0	0
	Orthostatic hypotension	1	0.27	0	0
	Peripheral vascular disease	0	0	1	0.27

Among doripenem-treated subjects in DORI-05, the most frequent serious treatment-emergent adverse events involved the system organ class Infections and Infestations (frequency of 3.72%). In that adverse event category, there were seven urinary tract-related serious adverse events, including four cases of pyelonephritis, two urinary tract infections, and one case of urosepsis. In addition, it is noteworthy that there was one doripenem-treated subject with acute renal failure identified as a serious adverse event. In contrast, the serious treatment-emergent adverse events observed among levofloxacin-treated subjects were distributed widely among various system organ classes. Serious adverse events related to the system organ class Infections and Infestations accounted for only 0.81% of all such events in the levofloxacin treatment group. There were no subjects who experienced renal failure as a serious treatment-emergent adverse event in the levofloxacin group. One levofloxacin-treated subject experienced a grand mal convulsion, whereas no doripenem-treated subjects developed seizures.

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Table 14: FDA Medical Officer Summary of the subjects who experienced serious treatment-emergent adverse events in DORI-06, ITT Population

		Doripenem		Levofloxacin (from DORI-05)	
		(N=423)	%	(N=372)	%
Patients with ≥1 Serious Treatment-emergent AEs		39	9.21	15	4.03
System Organ Class	Preferred Term				
Blood + Lymphatic System		1	0.24	0	0
	Anemia	1	0.24	0	0
Cardiac Disorders		5	1.18	2	0.54
	Angina unstable	1	0.24	0	0
	Atrial fibrillation	1	0.24	1	0.27
	Atrial flutter	1	0.24	0	0
	Bradycardia	0	0	0	0
	Cardiac failure	0	0	1	0.27
	Myocarditis	1	0.24	0	0
	Ventricular arrhythmia	1	0.24	0	0
Eye Disorders		0	0	1	0.27
	Glaucoma	0	0	1	0.27
Gastrointestinal Disorders		2	0.47	1	0.27
	Constipation	1	0.24	0	0
	Gastrointestinal hemorrhage	1	0.24	0	0
	Vomiting	0	0	1	0.27
General Disorders + Administration Site Conditions		1	0.24	0	0
	Pyrexia	1	0.24	0	0
Hepatobiliary		0	0	1	0.27
	Cholelithiasis	0	0	1	0.27
Infections and Infestations		12	2.84	3	0.81
	Abscess limb	1	0.24	0	0
	Arthritis infective	1	0.24	0	0
	Bacteremia	0	0	1	0.27
	Lobar pneumonia	1	0.24	0	0
	Pelvic abscess	1	0.24	0	0
	Pneumonia	2	0.47	1	0.27
	Pyelonephritis acute	1	0.24	0	0
	Renal abscess	1	0.24	0	0
	Systemic candida	0	0	1	0.27
	Urinary tract infection	6	1.42	0	0
Injury, poisoning, & procedural complications		1	0.24	1	0.27
	Accidental overdose	0	0	1	0.27
	Pneumonitis chemical	1	0.24	0	0
Metabolism and nutrition		1	0.24	2	0.53
	Dehydration	0	0	1	0.27
	Hyperglycemia	1	0.24	1	0.27
Neoplasms benign, malignant, and unspecified		2	0.47	0	0
	Bladder cancer	1	0.24	0	0
	Bladder neoplasm	1	0.24	0	0

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Nervous System		3	0.71	1	0.27
	Cerebral infarction	1	0.24	0	0
	Cerebrovascular accident	1	0.24	0	0
	Grand mal convulsion	0	0	1	0.27
	Syncope	1	0.24	0	0
Pregnancy, puerperium, perinatal conditions		3	0.71	1	0.27
	Abortion spontaneous	2	0.47	1	0.27
	Ectopic pregnancy	1	0.24	0	0
Renal and urinary disorders		7	1.65	1	0.27
	Calculus ureteric	0	0	1	0.27
	Hematuria	1	0.24	0	0
	Nephrolithiasis	2	0.47	0	0
	Renal failure acute	2	0.47	0	0
	Renal impairment	1	0.24	0	0
	Renal insufficiency	1	0.24	0	0
Reproductive System & Breast		1	0.24	0	0
	Benign prostatic hyperplasia	1	0.24	0	0
Respiratory, Thoracic, and Mediastinal Disorders		3	0.71	3	0.81
	Hypoxia	0	0	1	0.27
	Pleural effusion	1	0.24	0	0
	Pneumonia aspiration	1	0.24	0	0
	Pulmonary embolism	0	0	2	0.54
	Respiratory failure	1	0.24	0	0
Surgical procedures		1	0.24	0	0
	Prostatectomy	1	0.24	0	0
Vascular disorders		4	0.95	2	0.54
	Deep vein thrombosis	2	0.47	1	0.27
	Hypovolemic shock	1	0.24	0	0
	Hypotension	1	0.24	0	0
	Peripheral vascular disease	0	0	1	0.27

Among doripenem-treated subjects in DORI-06, the most frequent serious treatment-emergent adverse events involved the system organ class Infections and Infestations (frequency of 2.84%). In that adverse event category, there were eight urinary tract-related serious adverse events, including six urinary tract infections, one acute pyelonephritis, and one renal abscess. In addition, it is noteworthy that there were seven doripenem-treated subjects who experienced serious treatment-emergent adverse events involving the system organ class Renal and Urinary Disorders, including two patients with acute renal failure, and one patient each with renal impairment and renal insufficiency.

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Table 15: FDA Medical Officer Summary of the subjects who experienced serious treatment-emergent adverse events in DORI-07, ITT Population

		Doripenem		Meropenem	
		(N=235)	%	(N=236)	%
Patients with ≥1 Serious Treatment-emergent Adverse Events		31	13.19	33	13.98
System Organ Class	Preferred Term				
Blood + Lymphatic System		1	0.43	0	0
	Anemia	1	0.43	0	0
Cardiac Disorders		1	0.43	5	2.12
	Angina unstable	0	0	1	0.42
	Atrial fibrillation	0	0	1	0.42
	Atrioventricular block second degree	0	0	1	0.42
	Cardiac failure congestive	0	0	1	0.42
	Myocardial infarction	1	0.43	3	1.27
Gastrointestinal Disorders		11	4.68	9	3.81
	Abdominal adhesions	1	0.43	0	0
	Abdominal pain	1	0.43	0	0
	Ascites	0	0	1	0.42
	Constipation	0	0	1	0.42
	Crohn's disease	1	0.43	0	0
	Diarrhea	1	0.43	0	0
	Duodenal ulcer perforation	0	0	1	0.42
	Gastric mucosal ulcer	1	0.43	0	0
	Gastritis erosive	0	0	1	0.42
	Ileus	1	0.43	0	0
	Intestinal infarction	0	0	1	0.42
	Intestinal ischemia	0	0	1	0.42
	Intestinal obstruction	1	0.43	0	0
	Intestinal perforation	1	0.43	0	0
	Peritonitis	1	0.43	3	1.27
	Small intestinal obstruction	1	0.43	1	0.42
	Small intestinal perforation	2	0.85	0	0
General Disorders + Administration Site Conditions		1	0.43	1	0.42
	Multi-organ failure	1	0.43	1	0.42
Hepatobiliary		1	0.43	1	0.42
	Bile duct obstruction	0	0	1	0.42
	Cholecystitis	1	0.43	0	0
Infections and Infestations		14	5.96	15	6.36
	Abdominal abscess	2	0.85	5	2.12
	Abdominal wall abscess	1	0.43	0	0
	Brain abscess	1	0.43	0	0
	Empyema	0	0	1	0.42
	Enterococcal infection	1	0.43	0	0
	Liver abscess	0	0	1	0.42
	Pelvic abscess	1	0.43	1	0.42
	Pneumonia	1	0.43	1	0.42
	Pneumonia staphylococcal	1	0.43	0	0

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	Postoperative infection	0	0	1	0.42
	Sepsis	3	1.28	5	2.12
	Septic shock	0	0	1	0.42
	Staphylococcal sepsis	1	0.43	0	0
	Tubo-ovarian abscess	1	0.43	0	0
	Urinary tract infection	1	0.43	0	0
	Urosepsis	1	0.43	0	0
	Wound infection	0	0	1	0.42
Injury, poisoning, & procedural complications		3	1.28	5	2.12
	Anastomotic complication	0	0	1	0.42
	Anastomotic leak	1	0.43	0	0
	Barotrauma	1	0.43	0	0
	Post procedural complication	0	0	2	0.85
	Post procedural hemorrhage	0	0	1	0.42
	Seroma	1	0.43	0	0
	Wound dehiscence	0	0	2	0.85
Metabolism and nutrition		1	0.43	0	0
	Malnutrition	1	0.43	0	0
Neoplasms benign, malignant, and unspecified		1	0.43	0	0
	Gastric cancer	1	0.43	0	0
Nervous System		1	0.43	1	0.42
	Cerebrovascular accident	1	0.43	0	0
	Transient ischemic attack	0	0	1	0.42
Psychiatric disorders		0	0	1	0.42
	Acute psychosis	0	0	1	0.42
Renal and urinary disorders		2	0.85	0	0
	Renal failure acute	2	0.85	0	0
Respiratory, Thoracic, and Mediastinal Disorders		5	2.13	4	1.69
	Pleural effusion	1	0.43	3	1.27
	Pneumothorax	0	0	1	0.42
	Pulmonary embolism	2	0.85	0	0
	Respiratory arrest	1	0.43	0	0
	Tachypnea	1	0.43	0	0
Skin and subcutaneous disorders		1	0.43	0	0
	Decubitus ulcer	1	0.43	0	0
Vascular disorders		1	0.43	1	0.42
	Deep vein thrombosis	0	0	1	0.42
	Hypotension	1	0.43	0	0

Among doripenem-treated subjects in DORI-07, the most frequent serious treatment-emergent adverse events involved the system organ classes Gastrointestinal Disorders (4.68%) and Infections and Infestations (5.96%). Eleven subjects experienced serious treatment-emergent adverse events related to Gastrointestinal Disorders, including five subjects with intestinal perforation or obstruction. Among meropenem-treated subjects in the study, there were nine who experienced serious treatment-emergent adverse events related to Gastrointestinal Disorders (3.81%), including three with peritonitis. Of the Infections and Infestations class of serious treatment-emergent adverse events, five

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doripenem treated subjects experienced sepsis and abdominal abscess in contrast to 10 such patients in the meropenem-treatment group. In addition, it is noteworthy that there were two doripenem-treated subjects who experienced serious treatment-emergent adverse events involving the system organ class Renal and Urinary Disorders (both experienced acute renal failure). In contrast, there were no subjects treated with meropenem who experienced renal failure or renal impairment as serious treatment-emergent adverse events.

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Table 16: FDA Medical Officer Summary of the subjects who experienced serious treatment-emergent adverse events in DORI-08, ITT Population

		Doripenem		Meropenem	
		(N=242)	%	(N=233)	%
Patients with ≥1 Serious Treatment-emergent Adverse Events		41	16.94	43	18.45
System Organ Class	Preferred Term				
Blood + Lymphatic System		3	1.24	0	0
	Anemia	2	0.83	0	0
	Disseminated intravascular coagulation	1	0.41	0	0
Cardiac Disorders		4	1.65	3	1.29
	Atrial fibrillation	0	0	1	0.43
	Atrial flutter	1	0.41	0	0
	Cardiac arrest	2	0.83	0	0
	Cardiac failure	0	0	1	0.43
	Myocardial infarction	1	0.41	1	0.43
Gastrointestinal Disorders		11	4.54	16	6.87
	Abdominal compartment syndrome	0	0	1	0.43
	Abdominal hernia	1	0.41	0	0
	Abdominal strangulated hernia	0	0	1	0.43
	Abdominal wall disorder	0	0	1	0.43
	Ascites	2	0.83	1	0.43
	Colitis	0	0	1	0.43
	Dyspepsia	1	0.41	0	0
	Dysphagia	1	0.41	0	0
	Enterocutaneous fistula	1	0.41	2	0.86
	Femoral hernia	0	0	1	0.43
	Gastric ulcer perforation	0	0	1	0.43
	Gastritis	0	0	1	0.43
	Gastrointestinal fistula	1	0.41	0	0
	Gastrointestinal hemorrhage	1	0.41	0	0
	Intestinal fistula	0	0	1	0.43
	Intestinal ischemia	0	0	1	0.43
	Intestinal obstruction	0	0	1	0.43
	Lower gastrointestinal hemorrhage	0	0	1	0.43
	Peptic ulcer	0	0	1	0.43
Peritonitis	3	1.24	0	0	
Vomiting	0	0	1	0.43	
General Disorders + Administration Site Conditions		1	0.41	1	0.43
	Multi-organ failure	1	0.41	1	0.43
Hepatobiliary		0	0	2	0.86
	Hepatic failure	0	0	1	0.43
	Cholecystitis	0	0	1	0.43
Infections and Infestations		20	8.26	22	9.44
	Abdominal abscess	2	0.83	4	1.72
	Abdominal infection	1	0.41	2	0.86
	Abdominal wall abscess	1	0.41	0	0
	Abscess	1	0.41	2	0.86

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	Abscess intestinal	1	0.41	0	0
	Bacteremia	1	0.41	1	0.43
	Enterococcal sepsis	1	0.41	0	0
	Hematoma infection	1	0.41	0	0
	Liver abscess	1	0.41	0	0
	Necrotizing fasciitis	0	0	1	0.43
	Pelvic abscess	1	0.41	1	0.43
	Peritoneal abscess	0	0	2	0.86
	Pleural infection	1	0.41	1	0.43
	Pneumonia	6	2.47	3	1.29
	Postoperative abscess	1	0.41	0	0
	Postoperative infection	0	0	1	0.43
	Sepsis	0	0	1	0.43
	Septic shock	2	0.83	0	0
	Subdiaphragmatic abscess	0	0	1	0.43
	Urinary tract infection	1	0.41	0	0
	Wound infection	0	0	1	0.43
	Injury, poisoning, & procedural complications	10	4.13	3	1.29
	Anastomotic complication	0	0	1	0.43
	Anastomotic leak	2	0.83	0	0
	Anastomotic stenosis	1	0.41	0	0
	Femoral neck fracture	1	0.41	0	0
	Post procedural complication	1	0.41	0	0
	Post procedural discharge	1	0.41	0	0
	Postoperative ileus	0	0	1	0.43
	Procedural complication	0	0	1	0.43
	Radius fracture	1	0.41	0	0
	Wound dehiscence	3	1.24	0	0
	Metabolism and nutrition	0	0	2	0.86
	Anorexia	0	0	1	0.43
	Dehydration	0	0	1	0.43
	Nervous System	1	0.41	0	0
	Syncope	1	0.41	0	0
	Renal and urinary disorders	2	0.83	0	0
	Renal impairment	1	0.41	0	0
	Renal insufficiency	1	0.41	0	0
	Respiratory, Thoracic, and Mediastinal Disorders	5	2.07	5	2.15
	Acute respiratory distress syndrome	2	0.83	0	0
	Pneumothorax	1	0.41	1	0.43
	Pulmonary embolism	0	0	2	0.86
	Respiratory arrest	1	0.41	0	0
	Respiratory failure	1	0.41	2	0.86
	Surgical procedures	2	0.83	0	0
	Colostomy	1	0.41	0	0
	Fracture treatment	1	0.41	0	0
	Vascular disorders	0	0	1	0.43
	Deep vein thrombosis	0	0	1	0.43

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	iliac artery thrombosis	0	0	1	0.43
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Among doripenem- and meropenem-treated subjects in DORI-08, the most frequent serious treatment-emergent adverse events involved the system organ classes Gastrointestinal Disorders (4.54% and 6.87%, respectively) and Infections and Infestations (8.26% and 9.44%, respectively). The serious treatment-emergent adverse events were distributed among a wide group of disorders within the system organ classes Gastrointestinal Disorders for both drugs. In relation to Infections and Infestations, there were twice as many pneumonias in the doripenem group compared to the meropenem group. In addition, it is noteworthy that there were two doripenem-treated subjects who experienced serious treatment-emergent adverse events involving the system organ class Renal and Urinary Disorders (one each experienced renal impairment and renal insufficiency). In contrast, there were no subjects treated with meropenem who experienced renal insufficiency or renal impairment as serious treatment-emergent adverse events in this study.

The pooled clinical experience in terms of serious TEAEs occurring in 2 or more patients in the doripenem Phase 3 comparator controlled studies is depicted in the following table:

Table 17: FDA Medical Officer Summary of serious treatment-emergent adverse events, comparative doripenem phase 3 studies (DORI-05, DORI-07, DORI-08), ITT population

	Doripenem			Comparators		
	DORI-05	DORI-07 + -08	Total	Levofloxacin	Combined Meropenem*	Total
All patients (ITT)	376	477	853	372	469	841
Pneumonia	1	8	9 (1.05)	0	4	4 (0.48)
Acute renal failure/ impairment/insufficiency	1	4	5 (0.59)	0	0	0 (0.0)
Abdominal abscess	0	4	4 (0.47)	0	9	9 (1.07)
Peritonitis	0	4	4 (0.47)	0	3	3 (0.36)
Pyelonephritis	4	0	4 (0.47)	0	0	0 (0.0)
Sepsis	1	3	4 (0.47)	0	6	6 (0.71)
Anastomotic leak	0	3	3 (0.35)	0	0	0 (0.0)
Anemia	0	3	3 (0.35)	0	0	0 (0.0)
Urinary tract infection	2	1	3 (0.35)	0	0	0 (0.0)
Wound dehiscence	0	3	3 (0.35)	0	2	2 (0.24)
ARDS	0	2	2 (0.23)	0	0	0 (0.0)
Ascites	0	2	2 (0.23)	0	2	2 (0.24)
Cardiac arrest	0	2	2 (0.23)	0	0	0 (0.0)
Pulmonary embolism	0	2	2 (0.23)	2	2	4 (0.48)
Septic shock	0	2	2 (0.23)	0	1	1 (0.12)
Small intestine perforation	0	2	2 (0.23)	0	0	0 (0.0)
Spontaneous abortion	0	0	0 (0.0)	1	0	1 (0.12)

* from DORI-07 and -08

In order to further explore the serious treatment-emergent adverse events observed in the doripenem phase 3 studies, the FDA Medical Officer assessed the incidence of such events having a frequency of $\geq 1\%$ in each treatment group by clinical indication. The patient characteristics within specific subgroups were summarized in the following tables:

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Table 18: FDA Medical Officer Summary of the incidence (n, %) of serious treatment-emergent adverse events having a frequency of ≥ 1 % in either treatment group in the doripenem Phase 3 cUTI Studies, ITT Population

Serious adverse event	DORI-05 Doripenem n=376	DORI-05 Levofloxacin n=372	DORI-06 Doripenem n=423
Pyelonephritis	4 (1.06)	0 (0)	1 (0.24)
Urinary tract infection	2 (0.53)	0 (0)	6 (1.42)

As depicted in the table above, the only serious treatment-emergent adverse events having a frequency of ≥ 1 % in either treatment group were UTI-related events (pyelonephritis and UTI). Those cases occurred only among doripenem-treated subjects; no cases were observed among the levofloxacin-treated subjects. Selected features of the eight patients with UTI as a serious treatment-emergent adverse event are summarized in the table below:

Table 19: FDA Medical Officer Summary of the eight doripenem-treated subjects with Urinary Tract Infection (UTI) as a serious treatment-emergent adverse event in the Phase 3 cUTI Studies, ITT Population

Study	Subject ID#	Age/Sex/Race	Baseline Pathogen	Clinical Outcome at TOC	Microbiologic Outcome at TOC (baseline pathogen)	Pathogen isolated at Relapse
DORI-05	30404024	58/F/W	<i>Proteus mirabilis</i>	Cure	Failure	<i>Proteus mirabilis</i>
DORI-05	30406007	50/M/W	<i>Pseudomonas aeruginosa</i>	Cure	Failure	<i>Pseudomonas aeruginosa</i>
DORI-06	35900350	78/F/W	<i>Proteus mirabilis</i>	Cure	Failure	<i>Proteus mirabilis</i>
DORI-06	45000030	69/M/W	<i>Klebsiella pneumoniae</i>	Cure	Failure	<i>Klebsiella pneumoniae</i>
DORI-06	45300109	21/F/B	<i>Escherichia coli</i>	Cure	Eradicated	<i>Klebsiella pneumoniae</i>
DORI-06	45300140	45/M/W	<i>Serratia marcescens</i>	Cure	Failure	<i>Enterobacter sakazakii</i>
DORI-06	45300288	65/M/B	<i>Proteus mirabilis</i>	*	Indeterminate	<i>Klebsiella pneumoniae</i>
DORI-06	45300424	53/M/B	<i>Klebsiella pneumoniae</i>	Failure	Failure	<i>Klebsiella pneumoniae</i>

*discontinued from study on Day 9 due to pneumonia;
 M=male, F=female, W=White, B=Black, TOC=test of cure

Of the eight doripenem-treated subjects who experienced UTI as a serious adverse event in the cUTI clinical studies, six were considered to be cured clinically, one was a clinical failure, and one was discontinued from the study prior to TOC due to pneumonia. However, in terms of the microbiologic outcome (primary endpoint) with respect to the baseline pathogen, six were assessed as failures, one was indeterminate, and one had eradication of the baseline pathogen. In three instances, a different bacterial pathogen was isolated at the time of relapse compared to the baseline pathogen.

Selected features of the five patients with pyelonephritis as a serious treatment-emergent adverse event are summarized in the table below:

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Table 20: FDA Medical Officer Summary of the five doripenem-treated subjects with Pylonephritis as a serious treatment-emergent adverse event in the Phase 3 cUTI Studies, ITT Population

Study	Subject ID#	Age/Sex/Race	Baseline Pathogen	Clinical Outcome at TOC	Microbiologic Outcome at TOC (baseline pathogen)
DORI-05	00703060	58/F/W	<i>Citrobacter koseri</i>	Failure	Indeterminate
DORI-05	05701014	52/M/H	<i>E. coli</i>	Cure	Eradicated
DORI-05	05701016	35/M/B	<i>E. coli</i>	Not reported	Indeterminate
DORI-05	20509065	49/F/W	<i>K. pneumoniae</i>	Cure	Eradicated
DORI-06	60800032	23/F/H	<i>E. coli</i>	Cure	Indeterminate

M=male, F=female, W=White, B=Black, H=Hispanic, TOC=test of cure

Of the five doripenem-treated subjects who experienced pyelonephritis as a serious adverse event in the cUTI studies, three were assessed as clinical cures with one failure and one outcome that was not reported. In terms of microbiological outcome, three had indeterminate outcomes at TOC and two had eradication of the baseline pathogen.

In summary, UTI-related serious adverse events (pyelonephritis and UTI) were the only such events reported with an incidence of $\geq 1\%$ in the doripenem phase 3 cUTI studies. A total of 13 cases involved doripenem-treated patients compared to no cases involving levofloxacin-treated patients. Of the 13 cases, six were microbiologic failures, four were microbiologically indeterminate, and three were microbiological eradications of the baseline pathogen (one relapse involved a different pathogen than isolated at baseline). Thus, the UTI-related adverse events appeared to reflect on a lack of drug efficacy rather than indicating a potential safety signal.

Table 21: FDA Medical Officer Summary of Incidence (n, %) of serious treatment-emergent adverse events having a frequency of $\geq 1\%$ in either treatment group in the Phase 3 cIAI Studies, ITT Population

Serious adverse event	DORI-07 Doripenem n=235	DORI-07 Meropenem n=236	DORI-08 Doripenem n=242	DORI-08 Meropenem n=233
Abdominal abscess	2 (0.85)	5 (2.12)	2 (0.83)	4 (1.72)
Myocardial infarction	1 (0.43)	3 (1.27)	1 (0.41)	1 (0.43)
Peritonitis	1 (0.43)	3 (1.27)	3 (1.24)	0 (0)
Pleural effusion	1 (0.43)	3 (1.27)	0 (0)	0 (0)
Pneumonia	2 (0.85)	1 (0.42)	6 (2.47)	3 (1.29)
Sepsis	3 (1.28)	5 (2.12)	0 (0)	1 (0.43)
Wound dehiscence	0 (0)	2 (0.85)	3 (1.24)	0 (0)

Of the seven serious adverse events with frequencies $\geq 1\%$ in either treatment group in the cIAI studies, pneumonia was the only event that occurred with a greater incidence in the doripenem arm consistently compared to the meropenem arm. There were more patients with pneumonia as a serious adverse event among the doripenem-treated subjects (total=8) in the cIAI studies compared to subjects treated with meropenem (total=4). In relation to the other serious adverse events cited in the table, the incidence of abdominal abscess and sepsis was consistently higher in the meropenem group compared to the doripenem group.

The following table summarizes select characteristics of the eight doripenem-treated

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subjects with pneumonia as a serious adverse event in the cIAI trials and provides additional information on the four doripenem-treated subjects from the cUTI studies who had pneumonia as a serious treatment-emergent adverse event.

Table 22: FDA Medical Officer Summary of all doripenem-treated subjects with Pneumonia as a serious treatment-emergent adverse event in the Phase 3 cUTI and cIAI Studies, ITT Population

Study	Subject ID#	Age/Sex /Race	Medical History	Study Drug Duration	Brief synopsis of clinical course during study*
DORI-05	20407137	84/M/W	Heart failure, cholelithiasis, Coxarthrosis	IV=8, PO=3, Total=10	Developed pneumonia on Day 30
DORI-06	45000305	22/F/W	None reported	IV=2, PO=0, Total=2	Misdiagnosed as pyelonephritis on Day-1, but actually had CAP; Discontinued from study on Day 2; developed respiratory failure and required mechanical ventilation and tracheostomy; treated for VAP
	45300288	65/M/B	Traumatic spinal cord injury (horse riding)	IV=4, PO=6, Total=9	Diagnosed with NP on Day 9 and discontinued from study. NP resolved, but later recurred on Day 39
	63300176	85/F/B	Hypertension, gastroesophageal reflux, breast cancer, stroke, right hemiplegia, aspiration pneumonia, dementia	IV=4, PO=0, Total=4	Discontinued from study due to lack of qualifying culture; diagnosed with aspiration pneumonia on Day 3
DORI-07	01301505	71/M/W	Renal and respiratory insufficiency, COPD, prostatic hypertrophy, Abnormal liver function, status-post appendectomy with wound dehiscence and respiratory failure	IV=14, PO=0, Total=14	<i>S. aureus</i> isolated from baseline blood culture; Developed <i>S. aureus</i> pneumonia on Day 23; tracheostomy on Day 26
	02102023	75/F/W	Hypertension, myocardial infarct, COPD, cervical cancer, UTIs, recurrent pneumonia; had laparoscopic chole for stones and chronic cholecystitis complicated by small bowel injury and respiratory failure	IV=6, PO=0, Total=6	Had multiple re-explorations of abdomen with repairs, bile leak, intra-abdominal candidiasis; discontinued from study due to multiple unplanned surgeries; had <i>S. aureus</i> isolated from BAL RLL on Day 31
DORI-08	00502503	32/M/AM IND	Diabetes mellitus, obesity, small Bowel resection, paraplegia from Spinal fracture, alcoholism	IV=8, PO=0, Total=8	Had MVA with spinal fracture on Day -3; required mechanical ventilation and surgery for necrotic bowel; Day 8 developed pneumonia and study drug discontinued; Day 19 had surgery for spine fracture; Day 22 pneumonia had resolved
	02902033	52/F/AM IND	Angina, peptic ulcer, pancreatitis, Gastrointestinal bleed,	IV=15, PO=0, Total=15	Developed respiratory failure and septic shock Day 1-2; Developed pneumonia on Day 13 (resolved by Day 22)
	12606026	69/F/W	Perforated sigmoid colon	IV=6, PO=0, Total=6	Days 2-5 had multiple laprotomies; Day 6 diagnosed with bacteremia and pneumonia, and was discontinued from the study; Day 8 had tracheotomy and mechanical ventilation; Day 32 had surgery for anastomotic leak; Day 32 developed renal insufficiency from sepsis; Day 34 developed pancreatitis;

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					Day 40 developed gallbladder necrosis; Day 53 died
	12706003	43/M/W	Hypertension, trigeminal neuralgia, Neurovascular decompression	IV=3, PO=0, Total=3	Developed pneumonia on Day 3 and was discontinued from study; pneumonia resolved by Day 13
	23016029	54/M/W	Perforated stomach tumor	IV=8, PO=0, Total=8	Diagnosed with HAP on Day 15; HAP resolved by Day 21
	43104023	79/F/H	Perforated appendix	IV=12, PO=0, Total=12	Day 2 septic shock necessitated repeat laparotomy; Diagnosed with VAP on Day 12 and was discontinued from study; Wound dehiscence on Day 18; Another episode of VAP on Day 21; died on Day 25

*based on review of Sponsor's narratives of serious adverse events; M=male, F=female, W=White, B=Black, H=Hispanic, AM IND=American Indian; VAP=ventilator-associated pneumonia; BAL=bronchoalveolar lavage; RLL=right lower lobe; HAP=hospital-acquired pneumonia

Among the 12 cases of pneumonia summarized in the table above, it is noteworthy that five subjects were discontinued from study participation due to the new onset of pneumonia (subject ID# 00502503, 02902033, 12606026, 12706003, 43104023) while receiving doripenem. The clinical outcomes for the five subjects were clinical failure at EOT (subject ID# 00502503, 02902033, and 12606026) and indeterminate at EOT (subject ID# 12706003 and 43104023). There was insufficient microbiologic data to determine whether the pneumonias observed were due to resistant superinfecting pathogens.

Nine doripenem-treated subjects experienced renal failure, renal impairment, and renal insufficiency as serious treatment-emergent adverse events in the doripenem Phase 3 cUTI and cIAI Studies. Please refer to Section 7.1.7.5 of this report for further analysis of the cases.

There were two subjects who experienced serious treatment-emergent adverse events that were assessed as related to doripenem treatment by the investigators in the phase 3 clinical studies. Both of the subjects had been enrolled in DORI-06: Subject ID# 63000035 and 45000303. The Sponsor's narratives are provided below:

Subject 63000035 (Doripenem 500 mg IV infusion q8h):

This 71-year-old Caucasian woman had a history of hypertension, diabetes mellitus, and renal failure. Her urological history included recurrent urinary tract infections. Concomitant medications included metformin, nifedipine, insulin, paracetamol, glipizide, gabapentin, multivitamins, acetylsalicylic acid, zolpidem tartrate, carvedilol, pantoprazole, heparin-fraction sodium salt, digoxin, potassium chloride, and metoprolol tartrate. Antibacterial medications included gentamicin, imipenem with cilastatin, metronidazole, cefepime, and meropenem. The subject was scheduled to receive doripenem 500 mg as a 60-minute IV infusion q8h for the treatment of uncomplicated pyelonephritis. The subject received treatment with IV study drug therapy for 2 days (Days 1 through 2) after which IV study drug therapy was permanently discontinued due to the events of atrial fibrillation and renal impairment. Study drug therapy was adjusted for renal impairment on Days 1 and 2. Calculated creatinine clearance was 30.3 mL/min on Day 1 and 23.0 mL/min on Day 2.

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Twelve 12 days later, when the subject met the criteria set in the protocol for the switch to oral therapy, the subject received oral levofloxacin (250 mg once daily) for 7 days (Days 14 through 20). The subject received study drug therapy for a total of 9 days (Days 1, 2, and 14 through 20). The baseline pathogen isolated from blood and urine was *Klebsiella pneumoniae*. On Day 2, the subject had a temperature of 102.8° F, chills, weakness, abdominal and back pain, dysuria, urinary frequency, nausea, and loss of appetite. Intravenous hydration was started for dehydration secondary to presumed sepsis and volume depletion. Her fever subsided over the next few days. On Day 3, the subject showed signs and symptoms of renal impairment (unspecified), became diaphoretic, hypotensive, and had respiratory distress. Her arterial blood gas, while on 2 liters of oxygen, showed a markedly decreased PO₂ of 54 mmHg. A 2-D echocardiogram, thyroid function tests, and a renal ultrasound were unremarkable. An electrocardiogram showed atrial fibrillation with rapid ventricular rate. Treatment with IV imipenem with cilastatin and gentamicin was started. On Day 4, the subject's heart rate was controlled after starting digoxin therapy. On Day 9, the subject was noted to have increased hepatic enzymes (laboratory test results not reported). The investigator assessed the increased hepatic enzyme moderate in severity, resolved on Day 13, and probably related to treatment with study drug therapy. According to the study records, treatment with study drug therapy was permanently discontinued; however, the subject was not taking any study drug medication at the time of the event. The renal impairment resolved on Day 14 and the subject was discharged from the hospital that same day with instructions to take a 7-day course of oral study drug levofloxacin. The atrial fibrillation was not considered resolved until Day 157 as determined at a follow-up visit. The investigator assessed the event of renal impairment severe in severity, serious due to prolongation of hospitalization, probably related to sepsis and dehydration, and possibly related to treatment with study drug therapy. The investigator assessed the event of atrial fibrillation severe in severity, serious due to prolongation of hospitalization, and possibly related to treatment with study drug therapy.

FDA Medical Officer Comments: The subject was treated with multiple antibiotics from Day 3 to Day 14, including gentamicin, imipenem/cilastatin, metronidazole, and cefepime. There was a temporal association between the adverse events atrial fibrillation and renal impairment with doripenem administration. However, the patient had multiple issues confounding causality assessment, including underlying renal failure and diabetes mellitus, sepsis, dehydration, gram-negative bacteremia, and exposure to potentially nephrotoxic drugs (gentamicin).

Subject 45000303 (Doripenem 500 mg IV infusion q8h):

This 69-year-old Caucasian woman had a history of diarrhea, gastritis, myalgia, chills, and intermittent dyspnea. No urological history was reported. Concomitant medications included omeprazole, clonazepam, and metamizole sodium. Antibacterial medications included ceftriaxone. The subject received doripenem 500 mg as a 60-minute IV infusion q8h for the treatment of uncomplicated pyelonephritis for a total of 3 days (Days 1 through 3). The baseline pathogen isolated from urine and blood was *Escherichia coli*. On Day 2, the subject experienced dyspnea and tachycardia (heart rate 120 beats per minute). On physical examination, the subject was noted to have facial and eyelid edema; cardiac auscultation revealed an arrhythmia suggesting atrial flutter. An electrocardiogram

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(ECG) 2 disclosed atrial flutter, and a transesophageal echocardiogram showed mild pulmonary hypertension. Diltiazem was administered, study drug therapy was permanently discontinued after Day 3 due to the atrial flutter. The subject responded well to cardioversion on Day 3 with an ECG returning to her baseline pattern. The investigator considered the atrial flutter resolved on Day 3 and assessed the event as severe, serious because of its life-threatening status, and possibly related to treatment with study drug therapy. A thoracic computed tomography follow-up scan on Day 4 revealed pulmonary embolism and pleural effusion, which the investigator considered resultant from the atrial flutter and unrelated to treatment with study drug therapy. The case description documents a temporal relationship between the onset of atrial flutter and the study drug administration although it was considered that the subject had a baseline disease (pelvic thrombi or cancer) that served as a source for the documented pulmonary embolism leading to pulmonary hypertension and increased atrial pressure, triggering the reported atrial flutter.

FDA Medical Officer Comments: Except for her advanced age, the underlying medical disorder predisposing the patient to develop atrial flutter and pulmonary embolism is uncertain. There were no diagnostic imaging studies described in the report to provide objective evidence of pelvic thrombi or cancer as predisposing factors for pulmonary embolism. In view of the temporal relationship with doripenem administration, it is not possible to definitively rule-out an association with the drug.

7.1.3 Dropouts and Other Significant Adverse Events

As reported by the Sponsor, in the pooled Phase 1 safety analysis set, one subject in each of the doripenem 500 mg and placebo arms discontinued study drug therapy prematurely and was withdrawn from the study due to adverse events. The doripenem-treated subject experienced diarrhea, abdominal cramps, and a swollen throat sensation, all of which were considered study drug-related. In the Phase 2 and 3 studies, the rate of study drug therapy discontinuations due to adverse events was low and comparable across the treatment arms (2.7%, doripenem 500 mg; 3.8%, levofloxacin; 2.8%, meropenem). No specific AE observed in doripenem-treated subjects led to discontinuation from study drug therapy for more than 0.5% of subjects. The most frequently reported AEs leading to discontinuation in doripenem-treated subjects were infectious complications including pneumonia (0.5%) and sepsis (0.2%), mainly occurring in the cIAI studies. Such complications are not unexpected in post-operative subjects with severe intra-abdominal infections.

The FDA Medical Officer reviewed the dropouts due to adverse events in the four Phase 3 studies, including narratives provided by the Sponsor. Please refer to sections 7.1.3.1 and 7.1.3.2 for further details.

7.1.3.1 Overall profile of dropouts

The following series of tables provides a summary of the key characteristics of the subjects who were discontinued due to an adverse event in the doripenem phase 3 studies and includes both treatment groups in the three comparative studies.

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Table 23: Sponsor Table of Adverse Events leading to Treatment Discontinuation, DORI-05, ITT

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
Doripenem							
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	Hypovolaemic shock	7	Resolved with sequelae	3	Unrelated	8
405/06194	53/F	Sepsis	2	Resolved	24	Unrelated	9
Levofloxacin							
007/03030	75/F	Encephalopathy	4	Resolved	7	Unrelated	4
007/03037	37/F	Vomiting	5	Resolved	4	Unlikely	4
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	3	Resolved	2	Probably	3
		Blood pressure diastolic increased	3	Resolved	1	Probably	3
101/07019	74/M	Diarrhoea	2	Resolved	4	Possibly	3
101/07062	66/M	Pyrexia	7	Resolved	2	Unrelated	8
101/07213	73/M	Diarrhoea	2	Ongoing		Possibly	5
101/07214	90/M	Diarrhoea	5	Resolved	5	Possibly	6
104/07151	39/M	Pruritus	2	Resolved	5	Possibly	3
		Rash pustular	2	Resolved	5	Possibly	3
104/09027	26/F	Phlebitis	1	Resolved	1	Possibly	1
201/07231	66/M	Diarrhoea	4	Resolved	5	Probably	5
201/09062*	51/F	Hepatitis	8	Ongoing		Unrelated	8
204/09070*	77/F	Diarrhoea	4	Resolved	5	Probably	6

M=male, F=female

* Patients microbiologically evaluable at test-of-cure

Note: Patient 057/01016 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 was discontinued from 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.

Among the five doripenem-treated subjects who had adverse events leading to discontinuation, only one case was considered to be potentially related to study drug involving a 72 year old female who developed vasculitis on Day 5. In the levofloxacin arm, diarrhea was the most frequent adverse event to cause discontinuation from the study.

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Table 24: Sponsor Table of Adverse Events leading to Treatment Discontinuation, DORI-06, ITT

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
Doripenem							
357/ 00366 ^a	81/Female	Renal insufficiency	11	resolved	17	unrelated	11
450/ 00303	69/Female	Atrial flutter	2	resolved	2	possibly related	3
453/ 00288	65/Male	Pneumonia	9	resolved	9	unrelated	9
455/ 00183	26/Female	Pleural effusion	8	resolved	9	unlikely to be related	8
630/ 00035	71/Female	Atrial fibrillation	3	resolved	155	possibly related	20
		Renal impairment	3	resolved	12	possibly related	20
		Hepatic enzyme increased	9	resolved	5	probably related	20
640/ 00308	23/Female	Pneumonitis chemical	3	resolved	3	unrelated	3
640/ 00322	55/Male	Prostatitis	7	ongoing		unrelated	8

^a Patient ME at TOC

Note: Patient 641/ 00293, a 30-year-old female had a nonserious adverse event of pruritus that started on Day 1 and resolved on Day 3. She continued receiving IV therapy uninterrupted until Day 4 and then began 7 days of oral therapy. She completed the study through the LFU visit. The event of pruritus was captured as an adverse event leading to discontinuation on the AE CRF but was not captured as an event leading to study drug therapy discontinuation or study termination on the Study Therapy Discontinuation CRF or on the Study Termination Summary CRF.

In DORI-06, two elderly subjects developed atrial arrhythmias, two subjects developed pneumonia, and two subjects developed renal impairment as adverse events leading to discontinuation. Although there was a temporal association with doripenem treatment, there were multiple factors that confounded causality assessment including co-morbid illnesses and concomitant medications.

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Table 25: Sponsor Table of Adverse Events leading to Treatment Discontinuation, DORI-07, ITT

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 (Days) ^a
Doripenem							
008/02043	44/F	Vomiting	7	Resolved	3	Possibly	8
016/11018	67/F	Pyrexia	2	Resolved	4	Unlikely	3
		White Blood Cell Count Increased	3	Resolved	3	Unlikely	3
018/01006	35/M	Nausea	6	Resolved	4	Possibly	6
027/02000	53/M	Anastomotic Leak	11	Resolved with sequelae	8	Unrelated	10
046/02510	61/F	Pneumonia	6	Resolved	4	Unrelated	6
047/01043	21/M	Injection Site Reaction	4	Resolved	1	Unrelated	11
047/02056	48/F	Rash	3	Resolved	29	Possibly	3
047/02519	74/M	Sepsis	1	Fatal	1	Unrelated	1
047/02520	38/F	Vaginal Mycosis	8	Resolved	6	Possibly	10
202/06503	72/F	Sepsis	1	Resolved	30	Unrelated	5
372/04075	42/M	Cholecystitis	5	Resolved	3	Unrelated	7
402/04101	55/F	Dyspepsia	5	Resolved	3	Probably	15
Meropenem							
009/01010	55/M	Stomatitis	9	Resolved	6	Probably	15
009/02502	53/M	Small Intestinal Perforation	5	Resolved with sequelae	7	Unrelated	11
		Small Intestinal Obstruction	5	Resolved with sequelae	7	Unrelated	11
		Abdominal Abscess	5	Resolved with sequelae	7	Unrelated	11
035/01026	33/F	Vomiting	2	Resolved	5	Possibly	4
		Diarrhoea	2	Resolved	5	Possibly	4
		Nausea	2	Resolved	5	Possibly	4
203/06047	52/M	Hypertension	4	Resolved	1	Unrelated	3
402/04100	42/F	Dyspepsia	6	Resolved	7	Probably	12

F = female; M = male.

Note: The day of the last dose of study drug therapy was the same as the total days of study drug therapy.

a Total days on study drug therapy included IV only or IV and oral study drug therapy.

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Table 26: Sponsor Table of Adverse Events leading to Treatment Discontinuation, DORI-08, ITT

Site number/ Patient number	Age/Sex	Preferred Term	Relationship to Study Drug Therapy	Total Days of Study Drug Therapy (days)
Doripenem				
005/02503	32/M	Pneumonia	Unrelated	8
014/01010	29/M	Anaemia	Unlikely to be Related	7
015/12034	55/F	Dizziness	Possibly Related	2
		Nausea	Possibly Related	2
037/02505	61/M	Abdominal abscess	Unrelated	8
054/02526	86/F	Respiratory arrest	Unrelated	7
060/25209	60/F	Haematocrit decreased	Unrelated	2
126/06026	69/F	Bacteraemia	Unrelated	6
		Pneumonia	Unrelated	6
127/06003	43/M	Pneumonia	Unrelated	3
382/04063	71/M	Abdominal pain	Possibly Related	4
431/04023	79/F	Pneumonia	Unrelated	12
Meropenem				
003/02508	53/F	Hepatic failure	Unrelated	2
014/01015	50/F	Femoral hernia	Unrelated	8
015/01036	31/M	Dizziness	Possibly Related	1
		Asthenia	Possibly Related	1
		Tinnitus	Possibly Related	1
		Tinnitus	Possibly Related	1
		Deafness	Possibly Related	1
029/01006	31/M	Abdominal pain	Unlikely to be Related	2
		Confusional state	Unrelated	2
		Dysphoria	Unrelated	2
		Gastrointestinal discomfort	Possibly Related	2
		Anxiety	Unrelated	2
127/05000	41/F	Hypersensitivity	Probably Related	1
232/06020	31/F	Pneumonia	Unrelated	5
428/04050	25/M	Peritoneal abscess	Unrelated	5
428/04112	30/F	Septic shock	Unrelated	2

The adverse events leading to study subject discontinuation in DORI-07 and DORI-08 appeared to involve post-operative infectious complications (pneumonia, sepsis, and bacteremia) primarily. There was one case of hepatic failure involving a meropenem-treated subject.

In the pooled Phase 3 studies, there were six doripenem-treated, five meropenem-treated, and one levofloxacin-treated subjects who had adverse events leading to interruption of study drug administration. Adverse events in four doripenem-treated subjects that were considered to be related to study drug by investigators included nausea, chills, facial swelling, and puncture site pain. The relevant data are summarized in the table below:

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Table 27: FDA Medical Officer Table of Adverse Events leading to Study Drug Interruption, pooled doripenem Phase 3 studies, ITT

Study	Subject #	Study Drug	Relationship to Study Drug	Preferred Term
DORI-05	40106072	Levofloxacin	Not related	Pain in puncture site
	40106074	Doripenem	Not related	Venous puncture pain
	40106097	Doripenem	Related	Puncture site pain
DORI-06	62700121	Doripenem	Related	Facial swelling after 10 min of infusion
DORI-07	00802043	Doripenem	Related	Nausea
	04701043	Doripenem	Related	Chills
	02202071	Meropenem	Not related	Atrial fibrillation, CHF
	02502018	Meropenem	Not related	Arm pain, gastric reflux
	4201017	Meropenem	Not related	Phlebitis
	04702066	Meropenem	Not related	IV infiltrate
	10106007	Meropenem	Not related	Sepsis because of mesenteric ischemia
DORI-08	00502019	Doripenem	Not related	Oral intolerance (to food, medication, dairy)

There were eight subjects who were lost to follow-up in the pooled Phase 3 studies. Five of the subjects experienced an adverse event as depicted in the following table. The only event that was potentially related to study drug involved a doripenem treated patient who developed candiduria.

Table 28: FDA Medical Officer Composite List of the pooled Phase 3 subjects who were Lost to Follow-up and experienced an Adverse Event

Study	Subject ID #	Age/Sex/Race	Study Drug	Diagnosis	Duration of study drug (days)	Adverse Event(s)
DORI-05	03103018	27/F/H	Doripenem	Uncomplicated pyelonephritis	6	Candiduria
DORI-06	60800013	19/F/W	Doripenem	Uncomplicated pyelonephritis	6	Nausea, vomiting Hypokalemia Insomnia
	60800249	41/F/W	Doripenem	Uncomplicated pyelonephritis	4	Groin pain Headache Insomnia
DORI-07	01801504	38/M/W	Doripenem	Complicated appendicitis	8	Peripheral edema, Pyrexia Neutrophil count increased, White blood cell count increased
DORI-08	10205034	26/M/W	Meropenem	cIAI		Pain

M=Male, F=Female, H=Hispanic, W=White, B=Black;
cIAI=complicated intra-abdominal infection

7.1.3.2 Adverse events associated with dropouts

The most frequently reported adverse events that accounted for discontinuations among doripenem-treated subjects in the pooled phase 3 studies were pneumonia and sepsis, which were observed in the cIAI studies, predominantly. Diarrhea was the most common adverse event leading to discontinuation among levofloxacin-treated subjects. No single adverse event caused the majority of discontinuations in the meropenem-treated subjects.

- The most frequent adverse events accounting for interruptions of study drug treatment

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in the pooled phase 3 studies involved puncture site reactions or phlebitis. Most of those AEs were assessed as not related to study drug according to investigators.

Among subjects who were lost to follow-up, only one patient had an adverse event that was possibly related to study drug (candiduria in subject # 03103018).

7.1.3.3 Other significant adverse events

Please refer to Section 7.1.3. for details.

7.1.4 Other Search Strategies

The FDA Medical Officer constructed algorithms involving combinations of clinical findings using MedDRA preferred terms that may (in composite) constitute a marker for potential toxicities. The four potential toxicities assessed in this manner were oral and vaginal fungal infection-related adverse events, UTI-related adverse events, cutaneous adverse events (rash), and phlebitis and other infusion-related adverse events. The following tables provide more detailed adverse event information for each of the doripenem phase 3 studies.

Oral and vaginal fungal infection-related adverse events:

Table 29: FDA Medical Officer Summary of the number of subjects with oral and vaginal fungal infection-related treatment-emergent adverse events (ITT Population) using MedDRA 9.0 Dictionary Terms:

Preferred Term	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem n (%)	Levofloxacin n (%)	Doripenem n (%)	Doripenem n (%)	Meropenem n (%)	Doripenem n (%)	Meropenem n (%)
genital candidiasis	0 (0)	0 (0)	1 (0.24)	0 (0)	0 (0)	0 (0)	0 (0)
oral candidiasis	4 (1.06)	0 (0)	1 (0.24)	5 (2.13)	6 (2.54)	0 (0)	2 (0.86)
vaginal candidiasis	2 (0.53)	4 (1.08)	3 (0.71)	0 (0)	0 (0)	0 (0)	0 (0)
genital fungal infection	0 (0)	0 (0)	1 (0.24)	0 (0)	0 (0)	0 (0)	0 (0)
oral fungal infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.41)	0 (0)
Vulvovaginal mycotic infection	4 (1.06)	0 (0.0)	0 (0.0)	4 (1.70)	1 (0.42)	1 (0.41)	1 (0.43)
TOTAL # (%) of subjects with TEAE	10 (2.66)	4 (1.08)	6 (1.42)	9 (3.83)	7 (2.97)	2 (0.83)	3 (1.29)
# (%) of subjects with drug-related TEAE	10 (2.66)	1 (0.27)	2 (0.47)	8 (3.40)	7 (2.97)	1 (0.41)	1 (0.43)

As is evident from the table above, oral and vaginal fungal infection-related treatment-emergent adverse events occurred in both treatment arms in the comparative Phase 3 studies. There were a total of 41 subjects (27 doripenem-treated, 4 levofloxacin-treated, and 10 meropenem-treated) who experienced oral and vaginal fungal infection-related treatment-emergent adverse events in the doripenem phase 3 clinical studies. Of the 41 subjects, 30 experienced drug-related adverse events as assessed by the study investigators, including 21 doripenem-treated, 1 levofloxacin-treated, and 8 meropenem-treated patients. All of the drug-related TEAEs were mild to moderate in severity and none were assessed as

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 serious.

UTI-related adverse events:

Table 30: FDA Medical Officer Summary of the number of subjects with UTI-related treatment-emergent adverse events using MedDRA 9.0 Dictionary Terms, ITT Population:

Preferred Term	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem n (%)	Levofloxacin n (%)	Doripenem n (%)	Doripenem n (%)	Meropenem n (%)	Doripenem n (%)	Meropenem n (%)
asymptomatic bacteriuria	14 (3.72)	4 (1.08)	30 (7.09)	0 (0)	0 (0)	0 (0)	0 (0)
bacteriuria	0 (0)	0 (0)	1 (0.24)	0 (0)	0 (0)	0 (0)	0 (0)
cystitis	3 (0.8)	2 (0.54)	2 (0.47)	0 (0)	0 (0)	0 (0)	0 (0)
cystitis escherichia	0 (0)	1 (0.27)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
escherichia UTI	2 (0.53)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
bacteria urine	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.85)	0 (0)	0 (0)
pyelonephritis	5 (1.33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
pyelonephritis acute	0 (0)	0 (0)	1 (0.24)	0 (0)	0 (0)	0 (0)	0 (0)
urinary tract infection	14 (3.72)	6 (1.61)	28 (6.62)	13 (5.53)	6 (2.54)	3 (1.24)	5 (2.15)
urinary tract infection bacterial	0 (0)	1 (0.27)	2 (0.47)	0 (0)	0 (0)	0 (0)	0 (0)
urosepsis	2 (0.53)	0 (0)	0 (0)	1 (0.43)	1 (0.42)	0 (0)	0 (0)
TOTAL # (%) of subjects with TEAE	40 (10.64)	14 (3.76)	64 (15.13)	14 (5.96)	9 (3.81)	3 (1.24)	5 (2.14)

There were a total of 149 subjects (121 doripenem-treated, 14 levofloxacin-treated, and 14 meropenem-treated) who experienced UTI-related treatment-emergent adverse events in the doripenem phase 3 clinical studies. As is evident from the table above, UTI-related treatment-emergent adverse events were much more frequent in the doripenem-treated subjects in the cUTI trials. In DORI-05, the frequency of asymptomatic bacteriuria and UTI in the doripenem-treated subjects was more than twice that observed in the levofloxacin group. In DORI-07, UTI-related adverse events were more frequent in the doripenem group, whereas they were more common in the meropenem-treated subjects in DORI-08. Asymptomatic bacteriuria was not reported as a treatment-emergent adverse event in any subject in either treatment arm of studies DORI-07 and DORI-08. The possible reasons for the lack of such adverse events in the cIAI trials are uncertain.

Rash and cutaneous adverse events:

Table 31: FDA Medical Officer Summary of the number of subjects with rash-related treatment-emergent adverse events using MedDRA 9.0 Dictionary Terms, ITT Population:

Preferred Term	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem n (%)	Levofloxacin n (%)	Doripenem n (%)	Doripenem n (%)	Meropenem n (%)	Doripenem n (%)	Meropenem n (%)
Rash	0 (0)	1 (0.27)	9 (2.12)	8 (3.40)	1 (0.42)	8 (3.30)	4 (1.72)
Rash macular	1 (0.27)	0 (0)	0 (0)	0 (0)	1 (0.42)	1 (0.41)	1 (0.43)
Rash papular	0 (0)	0 (0)	3 (0.71)	1 (0.43)	0 (0)	1 (0.41)	0 (0)
Rash generalized	0 (0)	0 (0)	0 (0)	1 (0.43)	0 (0)	0 (0)	0 (0)
Rash maculo-papular	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.42)	0 (0)	0 (0)
Rash pruritic	0 (0)	1 (0.27)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rash erythematous	0 (0)	0 (0)	1 (0.24)	0 (0)	1 (0.42)	0 (0)	0 (0)
Dermatitis allergic	0 (0)	0 (0)	0 (0)	2 (0.85)	0 (0)	0 (0)	1 (0.43)
Dermatitis bullous	0 (0)	0 (0)	0 (0)	1 (0.43)	0 (0)	0 (0)	0 (0)
Urticaria	1 (0.27)	0 (0)	1 (0.24)	1 (0.43)	0 (0)	0 (0)	0 (0)
Urticaria localized	1 (0.27)	2 (0.54)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Erythema multiforme	0 (0)	1 (0.27)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TOTAL # (%) of subjects with TEAE	3 (0.80)	5 (1.34)	13 (3.07)*	14 (5.96)	4 (1.69)	10 (4.13)	6 (2.58)

*One subject had multiple events

There were a total of 55 subjects (40 doripenem-treated, 5 levofloxacin-treated, and 10 meropenem-treated) who experienced 58 rash-related treatment-emergent adverse events in the doripenem phase 3 clinical studies. Of the 55 subjects, 22 experienced drug-related rash as assessed by the study investigators, including 18 doripenem-treated, 3 levofloxacin-treated, and one meropenem-treated subject. All of the drug-related rashes were mild to moderate in severity, and none was assessed as serious. As is evident from the table above, there were few rash-related adverse events in either treatment group in DORI-05; in contrast, 3.07% of the doripenem-treated subjects in DORI-06 experienced a rash-related adverse event. In studies DORI-07 and DORI-08, rash-related treatment-emergent adverse events were observed more frequently in doripenem-treated subjects compared to those treated with meropenem. Study drug was withdrawn from two subjects related to rash: One levofloxacin-treated patient in DORI-05 (Subject #01303002) who developed erythema multiforme, and one doripenem-treated patient in DORI-07 (Subject #04702056) who developed a diffuse rash.

The following table summarizes the study day of onset of cutaneous TEAEs in doripenem and comparator treated subjects in the pooled Phase 3 studies. As depicted in the table below, the median study day of onset for rash in doripenem-treated subjects was Study Day 6-7, which was intermediate to the onset of rash in the comparator-treated subjects.

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Table 32: FDA Medical Officer Summary of the Study Day of Onset of 58 Cutaneous treatment-emergent adverse events in 55 subjects, doripenem phase 3 studies, ITT population

Study Day of Onset	Combined Doripenem	Levofloxacin	Combined Meropenem
	n=43	n=5	n=10
Mean ±SD	10 ± 7.9	10.6 ± 12	9.2 ± 10.8
Median	6.5	8	5.5
Range	1-29	1-31	2-38

Phlebitis and infusion-site related adverse events:

Phlebitis was reported as a TEAE more commonly in the pooled doripenem treatment groups (6.97%) compared to the lower incidences reported in the levofloxacin (4.03%) and pooled meropenem (5.54%) groups in the doripenem phase 3 studies. Phlebitis was also reported as a drug-related adverse event more frequently in the pooled doripenem treatment groups (4.15%) compared to the lower incidences reported in the levofloxacin (2.96%) and pooled meropenem (2.10%) groups in the doripenem phase 3 studies. The following table summarizes various infusion- and injection site-related MedDRA preferred terms that could collectively indicate a signal for potential study drug toxicity.

Table 33: FDA Medical Officer Summary of the number of subjects with phlebitis and other infusion-related treatment-emergent adverse events (ITT Population) using MedDRA 9.0 Dictionary Terms:

Preferred term	DORI-03		DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem 250 mg	Doripenem 500 mg	Doripenem	Levofloxacin	Doripenem	Doripenem	Meropenem	Doripenem	Meropenem
Injection site pain	0 (0.0)	0 (0.0)	7 (1.86)	6 (1.61)	0 (0.0)	0 (0.0)	2 (0.85)	0 (0.0)	3 (1.29)
Injection site reaction	0 (0.0)	0 (0.0)	1 (0.27)	4 (1.08)	0 (0.0)	4 (1.70)	2 (0.85)	1 (0.41)	1 (0.43)
Injection site swelling	0 (0.0)	0 (0.0)	2 (0.53)	0 (0.0)	1 (0.24)	1 (0.43)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.54)	1 (0.24)	3 (1.28)	1 (0.42)	0 (0.0)	0 (0.0)
Infusion site pain	0 (0.0)	1 (1.79)	3 (0.80)	6 (1.61)	1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site induration	0 (0.0)	0 (0.0)	1 (0.27)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site edema	0 (0.0)	0 (0.0)	1 (0.27)	1 (0.27)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.86)
Injection site phlebitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.42)	1 (0.41)	0 (0.0)
Infusion site phlebitis	2 (3.08)	0 (0.0)	1 (0.27)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL # of subjects with TEAE	2 (3.08)	1 (1.79)	16 (4.26)	19 (5.11)	3 (0.71)	9 (3.83)	6 (2.54)	2 (0.83)	6 (2.58)

In general, injection site and infusion site-related TEAEs as depicted above were reported more frequently in the comparator treatment groups (levofloxacin, 5.11% and combined meropenem, 2.56%) in contrast to the pooled doripenem groups (2.35%) in the phase 3 clinical studies. Similar infusion and injection site events were rarely reported in the phase 2 doripenem study in either treatment arm.

7.1.5 Common Adverse Events

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7.1.5.1 Eliciting adverse events data in the development program

The Sponsor's approach to eliciting and assessing adverse events is summarized from the Integrated Summary of Safety Report as follows: Adverse events (AEs) experienced by the subjects were assessed at each visit throughout the studies. Adverse events were defined as any adverse experiences including side-effects, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death that occurred (or worsened) during a subject's participation in a clinical study. An AE did not necessarily have a causal relationship with the treatment, and was therefore any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product. This included any event that was new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. The investigator assessed the relationship of the AEs to the study drug therapy as unrelated, unlikely to be related, possibly related, or probably related. Adverse events with possible, probable, or missing relationship were considered to be related to study drug therapy.

Phase 1 Studies

For the integrated analysis of Phase 1 studies, only AEs that occurred (or worsened in severity) from start of the first infusion of treatment with i.v. study drug therapy until the post-study follow-up visit were included. For crossover designs, a treatment-emergent adverse event (TEAE) that began or worsened in severity from initiation of the first dose in a given treatment period to the start of administration of the first dose in the next period, or up to and including post-study follow-up contact, was attributed to the treatment administered in the given period. Adverse events persisting from previous periods were not attributed to the current treatment unless the severity worsened.

Phase 2 and 3 Studies

In all Phase 2 and 3 studies included in the Sponsor's Summary of Clinical Safety, only TEAEs occurring during the "study drug therapy and follow-up" analysis phase (i.e., from the start of administration of the first dose of i.v. study drug therapy to 30 days after administration of the last dose of study drug therapy [i.v. or oral]) were included in the Sponsor's summary tables. Adverse events that occurred during the "i.v. study drug therapy" analysis phase of the studies were summarized separately by treatment group. Adverse events with onset before the start of the first infusion of i.v. study drug therapy or more than 30 days after the administration of the last dose of study drug therapy (i.v. and oral) were excluded from the summary tables, but captured in the listings of AEs. If it was not possible to determine whether an AE was treatment-emergent due to missing or partial onset date and/or time, the AE was regarded as treatment-emergent unless any partial date or relevant data, such as AE end date and time, definitely indicated that the event occurred prior to the start of infusion of the first dose of i.v. study drug therapy.

All SAEs that occurred during or after the start of administration of the first dose of i.v. study drug therapy and within 30 days after administration of the last dose of study drug therapy were considered treatment-emergent.

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All TEAEs from the controlled Phase 3 studies (except DORI-06) that, in the opinion of the investigator, represented possible allergic reactions (PAR) to treatment with study drug therapy were summarized by treatment group for each of the three study groups. These AEs were identified by the appropriately marked checkbox on the Adverse Event Case Report Form (CRF) pages. This information was not collected for the DORI-06 study, since it was a single-arm study and the perspective of comparative data was not available. Summaries were provided for the “study drug therapy and follow-up” phase within each study group. Descriptive terms were reported whenever possible.

All TEAEs from the controlled Phase 3 studies (except DORI-06) that, in the opinion of the investigator, represented study drug intolerability (SDI) were summarized by treatment group for each of the three study groups. These AEs were identified by the appropriately marked checkbox on the Adverse Event CRF pages. This information was not collected for the DORI-06 study, since it was a single-arm study and the perspective of comparative data was not available. In general, these events are temporally related to study drug infusion. Summaries are provided for the “study drug therapy and follow-up” phase within each study group.

During the ongoing safety review of the Phase 3 studies, it was observed that the incidence of phlebitis reported as an AE varied, sometimes markedly, by site. Therefore, guidelines regarding proper i.v. catheter care were issued to investigational sites and a new CRF worksheet was introduced on 17 May 2005 to collect additional information on AEs reported as phlebitis. The incidence of phlebitis, as well as study drug-related phlebitis, before and after the introduction of the phlebitis worksheet was summarized in the four-month safety update (refer to Section 7.2.9).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA 6.0 was used for adverse event coding in DORI-03, and MedDRA 7.0 was used for coding in the four Phase 3 clinical trials. For data analysis, the adverse events were recoded by the Sponsor using MedDRA 9.0 for DORI-03 and the four phase 3 studies.

7.1.5.3 Incidence of common adverse events

The sponsor commented on the following issues in providing an overview of adverse events. The profile of AEs in the different studies generally reflected the different complications anticipated in each indication e.g., urinary tract complications were reported more frequently in the cUTI studies, whereas GI AEs were reported more frequently in the cIAI studies. Overall, in the pooled Phase 2 and 3 safety analysis set, headache was the most commonly reported AE. However, the incidence of headache was higher in subjects in the cUTI safety analysis set (9.2%, doripenem 250 mg; 17.2%, doripenem 500 mg; 14.5%, levofloxacin) compared with the cIAI safety analysis set (4.4%, doripenem; 5.1%, meropenem). The reasons for the lower incidence of headache in subjects with cIAI compared with subjects with cUTI are unclear, although the presence of post surgical pain and administration of pain relieving medications in the cIAI studies were likely important factors. Most episodes of headache were mild or moderate in severity in the 3 treatment

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arms. No subjects discontinued study drug therapy prematurely due to headache. However, because of the frequency with which headache was reported in the cUTI studies, this was included as an adverse drug reaction (ADR). An ADR is defined by the Sponsor as an undesirable effect, reasonably associated with the use of doripenem that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

Diarrhea was reported in 7.9%, 10.2%, and 11.1% of subjects in the doripenem, levofloxacin, and meropenem treatment arms, respectively. Across all treatment arms, most episodes of diarrhea were mild or moderate in severity. These rates of diarrhea are typical of a broad-spectrum antibacterial agent. One doripenem-treated subject and 4 levofloxacin-treated subjects reported severe diarrhea, which resulted in study drug discontinuation for the levofloxacin-treated subjects. Nausea was reported in 6% to 9% of subjects across the 3 treatment arms. Most episodes of nausea were mild or moderate in severity, and generally resolved within 1 to 2 days. Two doripenem-treated subjects experienced severe nausea and discontinued study drug therapy prematurely, in addition to 1 meropenem-treated subject with moderate nausea. Both diarrhea and nausea were included as ADRs by the Sponsor.

Phlebitis was reported in 6.9%, 4.0%, and 5.5% of subjects in the doripenem, levofloxacin, and meropenem arms, respectively. All reports of phlebitis, except one, were mild or moderate in severity and did not result in premature discontinuation of study drug therapy, with the exception of 1 levofloxacin-treated subject. Although phlebitis was not a predefined AE of interest, during the conduct of the Phase 3 studies (DORI-05, -06, -07, -08), the incidence of phlebitis reported as an AE varied, sometimes markedly, by site. Therefore, sites were educated regarding the care of i.v. catheters and a CRF worksheet was included to collect additional information on phlebitis. In addition, the occurrence of phlebitis before and after site education was analyzed. Prior to site education, high-incidence sites (i.e., those with phlebitis rates > 25%) reported phlebitis rates of 39.0% during i.v. study drug administration. Following site education, the incidence of phlebitis during i.v. study drug administration at these sites decreased to 24.6%. At standard-incidence sites (i.e., those with phlebitis rates ≤ 25%), the rate of phlebitis remained relatively stable. High-incidence sites were identified in Argentina (8 sites) and Brazil (2 sites). Since approximately 75% of subjects were already enrolled in the studies before the site education, the impact on the reduction in the incidence rate of phlebitis was considered minor. After the site education, the overall rate of phlebitis during i.v. study drug administration decreased from 6.2% to 4.4%. Phlebitis was included as an ADR by the Sponsor.

Anemia was reported at similar rates in the doripenem and meropenem arms (5.3% and 5.5%, respectively) and was more common in the cIAI studies than in the cUTI studies. According to the Sponsor, this was not surprising as most cases occurred shortly after surgery and were likely caused by operative blood loss. Reports of anemia were evaluated by the Sponsor as not being plausibly related to doripenem use and clinical laboratory evaluations did not reveal any different trends among the treatment arms. Thus, anemia was not included as an ADR by the Sponsor. The FDA Medical Officer has conducted an in-depth review of cases involving anemia (refer to Sections 7.1.5.5 and 7.1.7.5).

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No seizures were reported in any doripenem-treated or meropenem-treated subjects in the Phase 1, 2 and 3 studies. One levofloxacin-treated subject (in DORI-05) experienced a generalized seizure. Seizures and other CNS events have been reported for subjects treated with approved carbapenems, especially imipenem, and the labels for carbapenems contain a precautionary statement regarding seizures. CNS complications associated with imipenem use are important safety concerns, especially in high-risk subjects such as those encountered in the intensive care units. Preclinical data suggest a reduced risk for seizures associated with doripenem compared with other carbapenems, based upon its low affinity for displacing ³H-muscimol from GABA receptors in mouse brain synaptic membrane in vitro studies.⁽¹⁰⁾ In addition, in vivo, doripenem did not induce seizures or affect seizure-related neurological activity in mice, rat, or dog models. Furthermore, doripenem did not affect the anticonvulsive effects of sodium valproate in a rat seizure model.⁽¹⁰⁾ These data suggest that doripenem has a very low potential for inducing seizures.

Urinary tract related infections were commonly reported as adverse events in DORI-06. Asymptomatic bacteriuria and urinary tract infection were each reported in 30 (7%) patients, and pyelonephritis was reported in 1 additional patient. Furthermore, urinary tract infection was reported as a serious adverse event in 6 (1%) patients while pyelonephritis was reported as a serious adverse event in 1 additional patient. According to the Sponsor's report, since DORI-06 was a single-arm, open-label study design, it is possible that reporting of adverse events may have been unintentionally biased. Therefore, given cUTI is the indication under evaluation in this study, the Sponsor's approach to rates of these particular events was that they are more comprehensively described as outcome measures than as adverse events. Rates of asymptomatic bacteriuria reflect the number of patients who were cured of symptoms but continued to have bacteria in their urine. Microbiological cure rates were similar and clinical cure rates were slightly higher for patients receiving doripenem in this study compared to those receiving IV levofloxacin in DORI-05. In summary, reports of UTI outcomes as adverse events were not believed to indicate any safety concern by the Sponsor. The FDA Medical Officer has additional comments regarding cases of UTI-related adverse events in Section 7.1.4 of this report.

Although ADRs were determined by the Sponsor, the investigators' assessment of study drug relationship was one of the factors considered in this determination. In the pooled Phase 2 and 3 safety analysis set, the overall incidence of study drug-related AEs (i.e., events considered by the investigator as probably or possibly related to study drug therapy), was comparable across the 3 treatment arms (24% to 28%). Specific study drug-related AEs were uncommon, with none reported in more than 4.2% of doripenem-treated subjects. Study drug-related AEs with a higher incidence in doripenem-treated subjects versus levofloxacin-treated subjects and meropenem-treated subjects (other than the marginally higher rate for vomiting), included headache (4.2% versus 2.7% and 0.9%), phlebitis (4.1% versus 3.0% and 2.1%), and nausea (3.4% versus 1.6% and 1.9%), respectively, reflecting the order of frequency of AEs reported overall.

The most commonly reported study drug-related AEs that were considered by the Sponsor to be ADRs (i.e., headache, phlebitis, nausea and diarrhea). Indication-specific differences were reported by the Sponsor for study drug-related AEs. In the cUTI studies, the study

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drug-related AEs of headache (5.8%), phlebitis (4.9%), and nausea (2.3%) were reported more frequently in doripenem 500 mg-treated subjects versus levofloxacin-treated subjects (2.7%, 3.0%, and 1.6%, respectively), with study drug-related diarrhea reported at a lower rate in doripenem 500 mg-treated subjects (3.5% versus 6.2%). In the cIAI safety analysis set, study drug-related nausea was reported at a higher rate in doripenem-treated subjects versus meropenem-treated subjects (5.2% versus 1.9%, respectively). The higher rate of nausea in doripenem-treated subjects was reported mainly in subjects in DORI-07; most episodes of nausea were mild or moderate in severity. One doripenem-treated subject discontinued study drug therapy prematurely due to severe study drug-related nausea. Of note, similar incidences were observed for the study drug-related AEs of diarrhea, headache, and phlebitis, in both doripenem and meropenem treatment arms.

The FDA Medical Officer's overview of the treatment-emergent adverse events most commonly encountered among patients enrolled in the doripenem phase 3 clinical studies is summarized in the series of tables in Section 7.1.5.4 of this report. Overall, the treatment-emergent adverse events observed in 5% or greater frequency in doripenem- and meropenem-treated subjects included headache, gastrointestinal disorders (nausea, vomiting, diarrhea), phlebitis, pyrexia, and anemia. Among levofloxacin-treated subjects in the cUTI studies, headache and gastrointestinal disorders (nausea and diarrhea) were observed in 5% or greater frequency.

7.1.5.4 Common adverse event tables**Phase 1 Studies**

There were eight Phase 1 studies conducted by the Sponsor. Four studies (DORI-01, DORI-04, DORI-NOS-1001, and DORI-NOS-1004) involved two doripenem doses (500 mg and 1,000 mg). Three Phase 1 studies included a placebo arm (DORI-01, DORI-04, and DORI-NOS-10010). The adverse event data for the doripenem phase 1 studies stratified by treatment group are summarized below:

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Table 34: FDA Medical Officer Summary Table of the number of subjects who experienced Adverse Events for doripenem Phase 1 studies

Study	Parameter	Dori-500 mg	Dori-1000 mg	Placebo
DORI-01	n	12	12	8
	≥1 TEAE	9	7	6
	≥1 drug related TEAE	8	6	4
DORI-02	n	8	NA	NA
	≥1 TEAE	5	NA	NA
	≥1 drug related TEAE	3	NA	NA
DORI-04	n	6	12	6
	≥1 TEAE	6	10	5
	≥1 drug related TEAE	6	6	1
NOS-1001	N	58	59	58
	≥1 TEAE	6	15	7
	≥1 drug related TEAE	4	12	6
NOS-1004	N	24	24	NA
	≥1 TEAE	5	3	NA
	≥1 drug related TEAE	1	0	NA
NOS-1005	N	6	NA	NA
	≥1 TEAE	2	NA	NA
	≥1 drug related TEAE	2	NA	NA
NOS-1006	N	24	NA	NA
	≥1 TEAE	3	NA	NA
	≥1 drug related TEAE	2	NA	NA
NOS-1007	n	8	NA	NA
	≥1 TEAE	3	NA	NA
	≥1 drug related TEAE	2	NA	NA

n=number of subjects; TEAE=treatment-emergent adverse events; NA = not applicable

When assessed by treatment regimen, headache was the most frequently reported TEAE in all of the groups with an incidence of 8.7% in the Dori-500 mg group, 6.54% in the Dori-1000 mg group, and 9.72% in the placebo group. Nausea and diarrhea were reported with frequencies of >5% in the Dori-500 mg group, whereas infusion site pain, injection site erythema, and injection site swelling were the next most frequently reported TEAEs in the Dori-1000 mg group (incidence of 4.62%, 3.74%, and 3.74%, respectively). In the placebo group, constipation and vomiting were both reported at a frequency of 4.16% followed by infusion site erythema, pharyngolaryngeal pain, and abdominal discomfort (all at a frequency of 2.78%). There were no serious adverse events reported for any of the phase 1 doripenem studies. Study drug was withdrawn from two subjects in study DORI-01: Subject #00000008 in the placebo group experienced vomiting and an upper respiratory infection that were not considered to be related to the drug, and Subject #00000012 in the doripenem 500 mg group experienced abdominal pain, diarrhea, and pharyngeal edema that were all considered to be related or possibly related to the drug. There were no subjects in the other phase 1 studies who experienced adverse events that necessitated study drug withdrawal. The following table provides pooled treatment-emergent adverse event data for the phase 1 clinical studies:

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Table 35: FDA Medical Officer Summary Table of the treatment-emergent adverse events in the pooled doripenem phase 1 studies*

Preferred Term	Doripenem 500-mg n=138	Doripenem 1000-mg n=107	Placebo n=72
	n (%)	n (%)	n (%)
Abdominal discomfort	0	0	2 (2.78)
Abdominal pain	3 (2.17)	1 (0.93)	1 (1.39)
Anorexia	1 (0.72)	1 (0.93)	0
Anxiety	0	1 (0.93)	0
Arthralgia	0	1 (0.93)	0
Asthenopia	1 (0.72)	0	0
Back pain	0	1 (0.93)	0
Catheter site bruise	0	0	1 (1.39)
Chest discomfort	1 (0.72)	0	0
Chest pain	0	0	1 (1.39)
Constipation	0	3 (2.8)	3
Cough	0	0	1 (1.39)
Decreased appetite	0	1 (0.93)	0
Dermatitis contact	1 (0.72)	0	0
Diarrhoea	8 (5.8)	2 (1.87)	0
Dizziness	4 (2.9)	1 (0.93)	1 (1.39)
Dizziness postural	3 (2.17)	0	1 (1.39)
Dry throat	1 (0.72)	0	1 (1.39)
Dysgeusia	3 (2.17)	2 (1.87)	1 (1.39)
Dysmenorrhoea	1 (0.72)	0	0
Dyspepsia	3 (2.17)	1 (0.93)	1 (1.39)
Dyspnoea	1 (0.72)	0	0
Ear pain	0	0	1 (1.39)
Erythema	1 (0.72)	1 (0.93)	0
Eye pain	0	1 (0.93)	0
Fatigue	0	1 (0.93)	0
Feeling hot	1(0.72)	0	1 (1.39)
Feeling hot and cold	1 (0.72)	0	0
Flatulence	1 (0.72)	0	0
Flushing	1 (0.72)	0	0
Fungal infection	1 (0.72)	0	0
Generalised erythema	0	1 (0.93)	0
Genital pruritus female	1 (0.72)	0	0
Headache	12 (8.7)	7 (6.54)	7 (9.72)
Herpes simplex	0	1 (0.93)	0
Influenza like illness	0	2 (1.87)	0
Infusion site erythema	1 (0.72)	2 (1.87)	2 (2.78)
Infusion site inflammation	1 (0.72)	0	0
Infusion site pain	2 (1.45)	5 (4.62)	2 (2.78)
Infusion site pruritus	0	0	1 (1.39)
Injection site erythema	5 (3.62)	4 (3.74)	0
Injection site pain	2 (1.45)	0	1 (1.39)
Injection site swelling	2 (1.45)	4 (3.74)	1 (1.39)
Lethargy	5 (3.62)	0	0
Limb discomfort	1 (0.72)	0	0
Musculoskeletal chest pain	1 (0.72)	0	0
Musculoskeletal pain	0	1 (0.93)	1 (1.39)
Myalgia	1 (0.72)	0	0
Nausea	8 (5.8)	2 (1.87)	1 (1.39)
Neck pain	0	0	1 (1.39)
Pain in extremity	2 (1.45)	0	1 (1.39)
Pharyngeal oedema	2 (1.45)	0	0
Pharyngolaryngeal pain	1 (0.72)	1 (0.93)	2 (2.78)
Pruritus	0	1 (0.93)	0
Pruritus generalised	0	1 (0.93)	0
Rash generalised	0	1 (0.93)	0
Rhinorrhoea	2 (1.45)	0	0
Skin irritation	0	1 (0.93)	0

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	Doripenem 500-mg n=138	Doripenem 1000-mg n=107	Placebo n=72
Somnolence	2 (1.45)	3 (2.8)	0
Stomach discomfort	0	0	1 (1.39)
Swelling face	0	1 (0.93)	0
Testicular pain	0	1 (0.93)	0
Thirst	0	0	1 (1.39)
Toothache	0	0	1 (1.39)
Transaminases increased	1 (0.72)	1 (0.93)	0
Upper respiratory tract infection	0	0	1 (1.39)
Urticaria	0	1 (0.93)	0
Vision blurred	1 (0.72)	0	0
Vomiting	3 (2.17)	1 (0.93)	3 (4.16)

*DORI-01, -02, -04, -NOS-1001, -NOS-1004, -NOS-1005, -NOS-1006

When assessed by treatment regimen, headache was the most frequently reported TEAE in all treatment groups with an incidence of 8.7% in the pooled Dori-500 mg group, 6.54% in the pooled Dori-1000 mg group, and 9.72% in the pooled placebo group. Nausea and diarrhea were reported with frequencies of >5% in the Dori-500 mg group. In contrast, in the Dori-1000 mg group, infusion site pain, injection site erythema, and injection site swelling were frequently reported TEAEs having an incidence of 4.62%, 3.74%, and 3.74%, respectively. In the placebo group, constipation and vomiting were both reported at a frequency of 4.16% followed by infusion site erythema, pharyngolaryngeal pain, and abdominal discomfort (all at a frequency of 2.78%). There were no serious adverse events reported for any of the phase 1 doripenem studies. Study drug was withdrawn from two subjects in study DORI-01: Subject #00000008 in the placebo group experienced vomiting and an upper respiratory infection that were not considered to be related to the drug, and Subject #00000012 in the doripenem 500 mg group experienced abdominal pain, diarrhea, and pharyngeal edema that were all considered to be related or possibly related to the drug. There were no subjects in the other phase 1 studies who experienced adverse events that necessitated study drug withdrawal.

Phase 2 Study

In DORI-03, the doripenem phase 2 study, the most common treatment-emergent adverse events were eosinophil count increased and headache (11.6% incidence each) as depicted in the following table. Other treatment-emergent adverse events noted with an incidence of ≥5% in the combined 250 mg and 500 mg doripenem dosing experience included alanine aminotransferase increased (8.3%), aspartate aminotransferase increased (7.4%), phlebitis (5.8%), and gastrointestinal disorders (dyspepsia, diarrhea, and constipation at 5% each). There were differences in the incidence of some treatment-emergent adverse events between the two dosing regimens. As depicted in the following table, the most frequently observed treatment-emergent adverse event in subjects in the 500 mg dosing group was eosinophil count increased (17.9%) compared to 6.2% in the 250 mg dosing group. Of note, there were two additional subjects in the 250 mg group who had eosinophilia as a treatment-emergent adverse event. This issue will be further reviewed in Section 7.1.7.5 of this report.

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Table 36: FDA Medical Officer Summary of the treatment-emergent adverse events with an incidence of $\geq 5\%$ in either doripenem dosing arm in phase 2 study DORI-03, ITT population

Adverse Event	Doripenem 250 mg	Doripenem 500 mg*	Doripenem
	n=65	n=56	total n=121
Eosinophil count increased	4 (6.2)	10 (17.9)	14 (11.6)
Headache	6 (9.2)	8 (14.3)	14 (11.6)
Alanine aminotransferase increased	3 (4.6)	7 (12.5)	10 (8.3)
Aspartate aminotransferase increased	3 (4.6)	6 (10.7)	9 (7.4)
Dyspepsia	1 (1.5)	5 (8.9)	6 (5.0)
Blood cholesterol increased	0 (0)	4 (7.1)	4 (3.3)
Nasopharyngitis	0 (0)	4 (7.1)	4 (3.3)
Diarrhea	2 (3.1)	4 (7.1)	6 (5.0)
Hematuria	2 (3.1)	4 (7.1)	6 (5.0)
Phlebitis	4 (6.2)	3 (5.4)	7 (5.8)
Blood alkaline phosphatase increased	0 (0)	3 (5.4)	3 (2.5)
Platelet count increased	0 (0)	3 (5.4)	3 (2.5)
Leukopenia	2 (3.1)	3 (5.4)	5 (4.1)
Constipation	3 (4.6)	3 (5.4)	6 (5.0)
Anxiety	4 (6.2)	1 (1.8)	5 (4.1)

*data sorted by doripenem 500 mg dose experience

Phase 3 Studies

The common adverse events associated with doripenem exposure in the phase 3 clinical studies are summarized in the following table:

Table 37: FDA Medical Officer Summary of pooled treatment-emergent adverse events having an incidence (% of patients) of $\geq 5\%$ among subjects in the phase 3 cUTI studies (ITT Population):

Adverse Events	Combined Doripenem (DORI-05, -06) (n=799)	Levofloxacin (DORI-05) (n=372)
Headache	17.40	14.52
Phlebitis	6.63	4.03
Vomiting	6.63	4.30
Nausea	6.13	5.91
Diarrhea	6.01	9.95
Asymptomatic bacteriuria	5.51	1.08
Urinary tract infection	5.26	1.61

Among subjects in the cUTI studies, headache, gastrointestinal disorders, and phlebitis were the most frequently observed adverse events in both treatment groups. Diarrhea was more frequent in levofloxacin-treated subjects, whereas asymptomatic bacteriuria and UTI were observed more frequently among doripenem-treated subjects in those studies. As discussed above in Section 7.1.2, UTI and pyelonephritis were identified as serious adverse events more frequently among doripenem-treated subjects in the cUTI studies.

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Asymptomatic Bacteriuria

There were 44 doripenem-treated subjects in DORI-05 and DORI-06 compared to 4 levofloxacin-treated subjects in DORI-05 who had asymptomatic bacteriuria as a treatment-emergent adverse event. Of the 44 subjects, 12 (27%) were aged 65-74 years old, 21 (48%) were aged 45 to 64 years, and 11 (25%) were aged 18 to 44 years old. Ten of the 44 subjects (22.7%) had indwelling urinary catheters or had urinary catheters as part of bladder instrumentation or for the treatment of obstruction, and seven of the 10 subjects were ≥ 70 years old. Eleven of the 44 subjects (25%) had been treated with doripenem IV without a PO switch agent. When assessed in terms of medical history, no subjects were reported as having neurogenic bladder as a co-morbid condition. Eight doripenem-treated subjects (one in DORI-05 and seven in DORI-06) had either paraplegia, tetraplegia, hemiparesis, or paraparesis that may predispose to urinary retention and increase the risk for asymptomatic bacteriuria. Based on the data above, it is apparent that advanced age, the presence of indwelling urinary catheters, and medical history of significant neurologic deficits, three recognized risk factors for asymptomatic bacteriuria, underpinned some but not the preponderance of cases in which asymptomatic bacteriuria was observed.

Adverse Events with Incidence of $\geq 5\%$

Table 38: FDA Medical Officer Summary of pooled treatment-emergent adverse events having an Incidence (% of patients) of $\geq 5\%$ among all subjects in the phase 3 cIAI studies (ITT Population):

Adverse Events	Combined Doripenem (DORI-07, -08) (n=477)	Combined Meropenem (n=469)
Nausea	11.95	9.38
Diarrhea	10.27	9.81
Anemia	9.64	5.54
Pyrexia	9.63	9.38
Phlebitis	7.55	5.54
Insomnia	5.03	4.69
Headache	4.40	5.12

Among subjects in the cIAI studies, gastrointestinal disorders, pyrexia, phlebitis, insomnia, and headache were the most frequently observed adverse events in both treatment groups. However, anemia was observed at a substantially higher frequency among doripenem-treated subjects than in meropenem-treated subjects (9.64% versus 5.54%) in those studies.

The following table provides composite data regarding treatment-emergent adverse events in the four doripenem phase 3 studies.

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Table 39: FDA Medical Officer Table of pooled treatment-emergent adverse events occurring in $\geq 5\%$ frequency for all subjects in studies DORI-05, -06, -07, and -08

Preferred Term	Combined Doripenem (DORI-05, -06, -07 and -08)					Levofloxacin (N=372) n (%)	Combined Meropenem (N=469) n (%)
	Doripenem DORI-05 (N=376) n (%)	Doripenem DORI-06 (N=423) n (%)	Doripenem DORI-07 (N=235) n (%)	Doripenem DORI-08 (N=242) n (%)	Total Combined Doripenem (N=1276) n (%)		
Headache	59 (16)	80 (18.9)	13 (5.5)	8 (3.3)	160 (12.54)	54 (14.52)	24 (5.12)
Nausea	16 (4)	33 (7.8)	34 (14.5)	23 (9.5)	106 (8.31)	22 (5.91)	44 (9.38)
Diarrhea	21 (5.6)	27 (6.4)	31 (13.2)	18 (7.4)	97 (7.6)	37 (9.95)	52 (9.81)
Phlebitis	14 (3.7)	39 (9.2)	25 (10.6)	11 (4.5)	89 (6.97)	15 (4.03)	26 (5.54)
Vomiting	19 (5.1)	34 (8)	13 (5.5)	16 (6.6)	82 (6.43)	16 (4.3)	38 (8.10)
Pyrexia	6 (1.6)	21 (5)	32 (13.6)	14 (5.8)	73 (5.72)	6 (1.61)	44 (9.38)
Anemia	6 (1.6)	17(4)	29 (12.3)	17 (7)	69 (5.41)	4 (1.08)	26 (5.54)

As evidenced from the preceding three tables, the most common treatment-emergent adverse events (frequency $\geq 5\%$) common to all patients in both treatment groups in the phase 3 studies involving both clinical indications (cUTI and cIAI) were nausea, diarrhea, and headache. Among patients in the cUTI studies, vomiting, asymptomatic bacteriuria, and UTI were also observed with a frequency of $\geq 5\%$. Among patients in the cIAI studies, anemia, pyrexia, and insomnia were observed with a frequency of $\geq 5\%$. The possible reasons for the indication-specific differences in the treatment-emergent adverse event profiles include inherent demographic differences between the patient populations studied for the two clinical indications, differences in the pathophysiology of cUTI compared to cIAI, and differences in disease severity and associated morbidities associated with cUTI and cIAI. The greater number of deaths among all patients in the cIAI compared to the cUTI studies that were related to septic complications provides indirect evidence of the greater severity of illness in the cIAI study population.

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Adverse Events with Incidence of $\geq 2\%$

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

As depicted in the table above, the most frequent treatment-emergent adverse events observed in doripenem-treated subjects in DORI-05 included headache and gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and upper abdominal pain). Treatment-emergent adverse events that occurred more frequently in doripenem-treated subjects compared to levofloxacin-treated subjects included dyspepsia and asymptomatic bacteriuria, both at a frequency that was more than twice that observed in the levofloxacin group. In the single-arm DORI-06 study, the most frequent treatment-emergent adverse events observed (in addition to gastrointestinal disorders) include anemia, asymptomatic bacteriuria, peripheral edema, insomnia, phlebitis, pyrexia, and UTI. Anemia, peripheral edema, phlebitis, and pyrexia occurred at twice the frequency in the doripenem-treated subjects in DORI-06 compared to similarly treated subjects in DORI-05. The possible reasons for the differences in the treatment-emergent adverse event profiles include inherent demographic differences between the patient populations studied in DORI-05 and DORI-06 and/or differences in disease severity. Another consideration is that DORI-06 is an open-label study that may be subject to investigator bias in assessment of adverse events.

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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

As depicted in the table above, the most frequent treatment-emergent adverse events observed in doripenem-treated subjects in DORI-07 included anemia, phlebitis, pyrexia, and gastrointestinal disorders (nausea and diarrhea). Other frequently observed adverse events included headache, peripheral edema, flatulence, insomnia, and vomiting; hypokalemia and UTI occurred twice as frequently among doripenem-treated subjects in this study compared to meropenem-treated subjects. The most frequent treatment-emergent adverse events observed in doripenem-treated subjects in DORI-08 included anemia, pyrexia, and gastrointestinal disorders (nausea, vomiting, and diarrhea). Anemia occurred as a treatment-emergent adverse event twice as frequently in the doripenem group compared to the meropenem group. In studies DORI-07 and DORI-08, phlebitis, anemia, and flatulence were consistently more common among doripenem-treated subjects than in the comparator treatment groups. An assessment of anemia as a treatment-emergent adverse event is provided in Sections 7.1.5.5 and 7.1.7.5 in this report.

7.1.5.5 Identifying common and drug-related adverse events

Phase 1 Studies

In the pooled doripenem phase 1 studies, 26 subjects treated with doripenem 500 mg, 24 subjects treated with doripenem 1,000 mg, and 11 treated with placebo experienced drug-related TEAEs. The following table summarizes the pooled treatment-emergent adverse events that were assessed as being related or possibly related to study drug by investigators

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for the doripenem phase 1 studies stratified by treatment group:

Table 42: FDA Medical Officer Table of the Incidence (n, %) of drug-related treatment-emergent adverse events for the pooled doripenem phase 1 studies*

Preferred Term	Doripenem 500-mg N=138	Doripenem 1000-mg N=107	Placebo N=72
Diarrhea	8 (5.80)	2 (1.87)	0
Headache	7 (5.07)	4 (3.74)	3 (4.17)
Injection site erythema	5 (3.62)	4 (3.74)	0
Lethargy	5 (3.62)	0	0
Nausea	5 (3.62)	2 (1.87)	1 (1.39)
Abdominal pain	3 (2.17)	1 (0.93)	1 (1.39)
Dizziness postural	3 (2.17)	0	1 (1.39)
Dysgeusia	3 (2.17)	1 (0.93)	1 (1.39)
Dizziness	2 (1.45)	0	0
Dyspepsia	2 (1.45)	0	1 (1.39)
Infusion site pain	2 (1.45)	4 (3.74)	2 (2.78)
Injection site pain	2 (1.45)	0	1 (1.39)
Injection site swelling	2 (1.45)	4 (3.74)	1 (1.39)
Pharyngeal edema	2 (1.45)	0	0
Somnolence	2 (1.45)	2 (1.87)	0
Anorexia	1 (0.72)	1 (0.93)	0
Asthenopia	1 (0.72)	0	0
Feeling hot	1 (0.72)	0	1 (1.39)
Feeling hot and cold	1 (0.72)	0	0
Flatulence	1 (0.72)	0	0
Flushing	1 (0.72)	0	0
Genital pruritus female	1 (0.72)	0	0
Infusion site erythema	1 (0.72)	2 (1.87)	2 (2.78)
Transaminases increased	1 (0.72)	1 (0.93)	0
Vomiting	1 (0.72)	1 (0.93)	1 (1.39)
Abdominal discomfort	0	0	2 (2.78)
Anxiety	0	1 (0.93)	0
Back pain	0	1 (0.93)	0
Chest pain	0	0	1 (1.39)
Constipation	0	1 (0.93)	0
Decreased appetite	0	1 (0.93)	0
Fatigue	0	1 (0.93)	0
Infusion site pruritus	0	0	1 (1.39)
Pharyngolaryngeal pain	0	0	1 (1.39)
Pruritus	0	1 (0.93)	0
Stomach discomfort	0	0	1 (1.39)
Thirst	0	0	1 (1.39)

*DORI-01, -02, -04, -NOS-1001, -NOS-1004, -NOS-1005, -NOS-1006

Headache, diarrhea, and injections site disorders were the most frequently reported drug-related TEAEs in the three treatment groups in the pooled doripenem phase 1 studies. Gastrointestinal disorders appeared to be more frequent as drug-related TEAEs in the doripenem 500 mg group, whereas infusion site related TEAEs were more frequently reported as drug-related events in the higher dose doripenem 1,000 mg group. Compared to both of the doripenem-treated subject groups, the placebo group had the lowest incidence of gastrointestinal and infusion site related disorders.

Phase 2 Study

The drug-related TEAEs reported in the doripenem phase 2 study (DORI-03) are provided in the following table:

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Table 43: FDA Medical Officer Table of the Incidence (n, %) of drug-related treatment-emergent adverse events for the phase 2 study, DORI-03, ITT population

Preferred Term	Dori 250 mg q8h n=37	Dori 500 mg q8h n=34
Eosinophil count increased	4 (10.81%)	9 (26.47%)
Alanine aminotransferase increased	3 (8.11%)	7 (20.59%)
Aspartate aminotransferase increased	3 (8.11%)	6 (17.65%)
Leukopenia	2 (5.41%)	3 (8.82%)
Gamma-glutamyltransferase increased	2 (5.41%)	2 (5.88%)
Red blood cell count decreased	1 (2.70%)	2 (5.88%)
Monocyte count decreased	0 (0.00%)	2 (5.88%)
Neutropenia	0 (0.00%)	2 (5.88%)
Platelet count increased	0 (0.00%)	2 (5.88%)
White blood cell count decreased	0 (0.00%)	2 (5.88%)
Blood alkaline phosphatase increased	0 (0.00%)	2 (5.88%)
Monocyte count increased	0 (0.00%)	2 (5.88%)
Prothrombin time prolonged	2 (5.41%)	1 (2.94%)
Haemoglobin decreased	1 (2.70%)	1 (2.94%)
Headache	1 (2.70%)	1 (2.94%)
Anisocytosis	1 (2.70%)	1 (2.94%)
Haematocrit decreased	1 (2.70%)	1 (2.94%)
Nausea	1 (2.70%)	1 (2.94%)
Diarrhoea	1 (2.70%)	1 (2.94%)
Vision blurred	0 (0.00%)	1 (2.94%)
Phlebitis	0 (0.00%)	1 (2.94%)
Neutrophil count increased	0 (0.00%)	1 (2.94%)
Neutrophil count decreased	0 (0.00%)	1 (2.94%)
Monocytosis	0 (0.00%)	1 (2.94%)
Blood cholesterol increased	0 (0.00%)	1 (2.94%)
Fungal skin infection	0 (0.00%)	1 (2.94%)
Infusion site pain	0 (0.00%)	1 (2.94%)
Macrocytosis	0 (0.00%)	1 (2.94%)
Mean cell volume increased	0 (0.00%)	1 (2.94%)
Platelet count decreased	2 (5.41%)	0 (0.00%)
Cough	1 (2.70%)	0 (0.00%)
Dyspepsia	1 (2.70%)	0 (0.00%)
Balanoposthitis	1 (2.70%)	0 (0.00%)
Pruritus	1 (2.70%)	0 (0.00%)
Eosinophilia	1 (2.70%)	0 (0.00%)
Hypochromasia	1 (2.70%)	0 (0.00%)
Hypersensitivity	1 (2.70%)	0 (0.00%)
Dermatitis	1 (2.70%)	0 (0.00%)

As depicted in the table above, the most frequent drug-related TEAEs in DORI-03 stratified by dose revealed that increased eosinophil count and increased ALT and AST

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were reported with the greatest incidence in the low (250 mg) and the high dose (500 mg) treatment groups.

Phase 3 Studies

The treatment-emergent adverse events that were assessed as being related or possibly related to study drug by investigators are summarized for the comparative clinical trials in the doripenem phase 3 program: DORI-05 for cUTI and DORI-07/DORI-08 for cIAI. The following two tables summarize the drug-related adverse events reported in DORI-05, DORI-07, and DORI-08 with an incidence of $\geq 1\%$ among doripenem-treated subjects:

Table 44: FDA Medical Officer Summary of Treatment-emergent adverse events with incidence $\geq 1\%$ that were assessed as being related or possibly related to study drug by investigators, DORI-05, ITT population

Preferred Term	Doripenem N=376		Levofloxacin N=372	
	n	%	n	%
Headache	17	4.52	10	2.69
Diarrhea	16	4.30	23	6.18
Nausea	11	2.93	6	1.61
Phlebitis	9	2.39	11	2.96
Gamma-glutamyltransferase increased	6	1.60	6	1.61
Vomiting	5	1.33	4	1.08
Vulvovaginitis	5	1.33	1	0.27
Injection site pain	4	1.06	0	0.0
Oral candidiasis	4	1.06	0	0.0
Vulvovaginal mycotic infection	4	1.06	0	0.0

Table 45: FDA Medical Officer Summary of Treatment-emergent adverse events with incidence $\geq 1\%$ that were assessed as being related or possibly related to study drug by investigators, DORI-07 and DORI-08, ITT population

Preferred Term	Combined Doripenem N=477		Combined Meropenem N=469	
	n	%	n	%
Nausea	25	5.24	9	1.92
Diarrhea	21	4.40	21	4.48
Phlebitis	12	2.52	10	2.13
Rash	9	1.89	0	0.0
Vomiting	9	1.89	8	1.71
Headache	6	1.26	4	0.85
Gamma-glutamyltransferase increased	6	1.26	7	1.49
Anaemia	5	1.04	2	0.43
Pyrexia	5	1.04	8	1.71
Dizziness	5	1.04	2	0.43
Blood alkaline phosphatase increased	5	1.04	3	0.64
Oral candidiasis	4	0.84	7	1.49

Overall, headache, phlebitis, nausea, and diarrhea were the most frequently reported drug-related TEAEs among doripenem-treated subjects as depicted in the tables above. The most frequent drug-related laboratory TEAE was GGT increased. Indication-specific, doripenem-related TEAEs included vulvovaginal fungal infections in the cUTI studies and rash, anemia, and dizziness in the cIAI studies.

Exploratory Analysis of Subjects who completed IV study drug without PO switch

In an attempt to identify potential doripenem-related adverse events, the FDA Medical Officer conducted exploratory analyses of all subjects in the phase 3 cUTI and cIAI studies who were exposed to i.v. study drug but who were not treated with an oral (PO) switch agent. The following table summarizes the overall experience in the pooled doripenem and comparator treatment groups across the four phase 3 clinical studies:

Table 46: FDA Medical Officer’s compilation of the treatment-emergent adverse events (≥5% frequency) for all subjects who completed IV study drug without PO switch, Phase 3 Clinical Studies, ITT Population

Preferred Term	Combined Doripenem* (N=244) (n,%)	Levofloxacin DORI-05 (N=42) (n,%)	Combined Meropenem** (N=128) (n,%)
Anemia	31 (12.7)	0 (0)	10 (7.8)
Pyrexia	27 (11.1)	1 (2.4)	13 (10.2)
Urinary tract infection	25 (10.2)	0 (0)	6 (4.7)
Nausea	23 (9.4)	1 (2.4)	15 (11.7)
Edema peripheral	19 (7.8)	0 (0)	5 (3.9)
Insomnia	17 (7.0)	2 (4.8)	4 (3.1)
Diarrhea	16 (6.6)	6 (14.3)	17 (13.3)
Constipation	14 (5.7)	0 (0)	6 (4.7)
Headache	14 (5.7)	2 (4.8)	4 (3.1)
Wound Infection	13 (5.3)	0 (0)	4 (3.1)

*all doripenem phase 3 clinical studies; **DORI-07 and DORI-08 only

There are several trends evident from the table above. Although gastrointestinal events occur commonly in the doripenem and meropenem treatment groups, anemia, UTI, peripheral edema, insomnia, headache, and wound infection were reported more frequently as treatment-emergent adverse events among the doripenem-treated patients even though both drugs are carbapenem antibiotics. The frequency of treatment-emergent adverse events in the levofloxacin-treated patients who completed IV study drug without PO switch was quite low, except for a high incidence of diarrhea. However, this finding may reflect the small sample size of levofloxacin-treated subjects.

In order to explore the doripenem experience in this subgroup further, the analysis focused upon the 244 subjects out of the pooled phase 3 study populations who completed IV doripenem treatment without PO switch and 133 subjects out of the pooled phase 3 study populations who did not complete IV therapy and did not receive PO switch agent. Thirty-six doripenem-treated subjects (9.6%) in DORI-05, 72 doripenem-treated subjects (17.0%) in DORI-06, 78 doripenem-treated subjects (33.2%) in DORI-07, and 58 doripenem-treated subjects (24%) in DORI-08 were exposed to doripenem but not treated with the PO switch agent. The treatment-emergent adverse events observed in each of those groups are summarized in the following table:

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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)

Anemia, pyrexia, and UTI were the most frequently reported treatment emergent adverse events (frequency $\geq 10\%$) among all of the doripenem-treated subjects in the pooled doripenem phase 3 studies who completed doripenem therapy without receiving the PO switch agent. It is evident from the table that the incidence of treatment-emergent adverse events was higher overall among subjects in DORI-06 and DORI-07. The explanation for the underpinning differences between those groups and the doripenem-treated subjects in DORI-05 and DORI-08 is uncertain, although the loss of the effect of random patient allocation in conducting this subgroup analysis may be a contributing factor.

Table 48: FDA Medical Officer’s summary of the proportion of treatment emergent adverse events observed in the 244 subjects who completed IV Doripenem therapy without PO switch in relation to the total number of such adverse events experienced by all subjects exposed to Doripenem, pooled Phase 3 Clinical Studies, ITT Population

Preferred Term	n/N* (%)
Anemia	31/69 (44.9)
Pyrexia	27/73 (37)
Urinary tract infection	25/58 (43.1)
Nausea	23/106 (21.7)
Edema peripheral	19/44 (43.2)
Insomnia	17/62 (27.4)
Diarrhea	16/97 (16.5)
Constipation	14/61 (23)
Headache	14/160 (8.75)
Wound Infection	13/19 (68.4)

*n/N=number of subjects who completed IV doripenem without PO switch who experienced the AE/total number of subjects exposed to doripenem in all of the phase 3 clinical studies who experienced the AE

As depicted in the table above, the adverse events of anemia, pyrexia, peripheral edema, and UTI observed in subjects exposed to doripenem but not the PO switch agent accounted for between one-third and one-half of all such events noted among doripenem-exposed subjects. Wound infections in patients in this subgroup accounted for 68% of all subjects in which wound infections were considered as treatment-emergent adverse events; this finding raised concern about potential lack of drug efficacy. Further investigation revealed that all 13 of the wound infection treatment-emergent adverse events in this subpopulation of subjects exposed to doripenem but not the PO switch agent involved patients in DORI-

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07 only. The clinical outcomes of those 13 patients are summarized in the next table. Wound infections resolved in nine subjects (four required a drainage procedure), whereas four wound infections did not resolve.

Table 49: FDA Medical Officer Summary of clinical outcome for 13 subjects with wound infections who were treated with i.v. doripenem but not the PO switch agent

Subject ID#	Adverse event	Outcome	Drainage Procedure
01502052	Wound infection	Not resolved	
04102020	Wound infection	Resolved	
04102037	Wound infection	Not resolved	
10106040	Wound infection	Resolved	
20005025	Wound infection	Resolved	X
20006019	Wound infection	Resolved	X
20106049	Wound infection	Resolved	
20106050	Wound infection	Resolved	
20206044	Wound infection	Not resolved	X
20306041	Wound infection	Not resolved	X
20405033	Wound infection	Resolved	
20405048	Wound infection	Resolved	
40204513	Wound infection	Resolved	

When the data are assessed further by treatment group within each study individually in the following table, treatment-emergent adverse events were observed more frequently in subjects in DORI-06 compared to either treatment group in DORI-05 (except for diarrhea).

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)

As is evident from the table above, anemia, UTI, peripheral edema, constipation, and asymptomatic bacteriuria were treatment-emergent adverse events reported in doripenem-treated subjects who completed IV study drug without exposure to PO switch agent in both DORI-05 and DORI-06, but not in any of the levofloxacin-treated subjects without exposure to PO switch agent in DORI-05. In contrast, diarrhea was reported more frequently in levofloxacin-treated subjects without exposure to PO switch agent compared to doripenem-treated subjects in those studies.

Subjects treated with intravenously administered study drug alone without a PO switch included 28.3% (135/477) in the combined doripenem experience in studies DORI-07 and DORI-08, and such subjects constituted 27.3% (128/469) of the combined meropenem

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experience in those studies as illustrated in the following table.

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)
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)

As is evident from the table above, anemia, UTI, peripheral edema, wound infection, and insomnia were treatment-emergent adverse events that were observed approximately twice as frequently among doripenem-treated subjects who completed IV study drug without exposure to PO switch agent compared to similar meropenem-treated subjects without exposure to PO switch agent in DORI-07 and DORI-08. In contrast, vomiting and hypertension were observed twice as frequently in meropenem-treated subjects without exposure to PO switch agent compared to doripenem-treated subjects in those studies.

In summary, based on the data regarding the patients who received only i.v. study drug without treatment with the PO switch drug presented in the series of tables above in this section, it appears that anemia, UTI, and peripheral edema are more frequently associated with doripenem exposure compared to the incidence of those events in patients treated with the comparator agents (levofloxacin and meropenem).

Exploratory Analysis of Subjects who did not complete IV study drug and did not receive a PO switch agent

In order to further explore potential adverse events related to doripenem, the subgroup of subjects who did not complete IV study drug and did not receive PO switch agent were assessed, including 133 doripenem-treated subjects, 66 levofloxacin-treated, and 34 meropenem-treated subjects across the four doripenem phase 3 studies in cUTI and cIAI. The following table summarizes the primary reasons (excluding "Other") that subjects who did not complete IV study drug were discontinued from the respective clinical study.

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Table 52: FDA Medical Officer's summary of the primary reasons (excluding "Other") for study discontinuation for subjects who did not complete IV study drug and did not receive PO switch, Phase 3 cUTI and cIAI Studies, ITT Population

Reason Discontinued	Study	Doripenem	Levofloxacin	Meropenem
Treatment Failure (n=26)	DORI-05	2	19	NA
	DORI-06	2	NA	NA
	DORI-07	0	NA	0
	DORI-08	1	NA	2
Adverse Event (n=30)	DORI-05	2	10	NA
	DORI-06	3	NA	NA
	DORI-07	3	NA	1
	DORI-08	5	NA	6
Negative Clinical Response (n=25)	DORI-05	2	17	NA
	DORI-06	1	NA	NA
	DORI-07	1	NA	2
	DORI-08	0	NA	2
Death (n=16)	DORI-05	1	0	NA
	DORI-06	1	NA	NA
	DORI-07	2	NA	6
	DORI-08	2	NA	4
Negative Pretreatment Culture (n=103)	DORI-05	27	23	NA
	DORI-06	53	NA	NA
	DORI-07	0	NA	0
	DORI-08	0	NA	0

NA=not applicable

As depicted above with respect to the patient subgroup who did not complete IV study drug and did not receive PO switch, besides the Other group, negative pre-treatment culture was the most frequent reason for discontinuation for doripenem-treated patients in the cUTI studies (DORI-05 and DORI-06), whereas there were greater numbers of subjects discontinued from the levofloxacin arm with treatment failure and negative clinical response. Adverse events and deaths were the most frequent reasons for discontinuation for doripenem- and meropenem-treated patients in the cIAI studies (DORI-07 and DORI-08).

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Table 69: FDA Medical Officer Summary of measures of central tendency for DORI-08 Serum Hematology Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Meropenem		
		n	Mean (SD)	Median	n	Mean (SD)	Median
Hematocrit (V/V)	Baseline	197	0.39 (0.06)	0.39	201	0.39 (0.06)	0.39
	Change from Baseline to EOT	172	-0.02 (0.04)	-0.02	172	-0.01 (0.05)	-0.01
	Median Change Baseline to EOT by Gender			F: -0.01 M: -0.02			F: -0.01 M: -0.01
Hemoglobin (g/L)	Baseline	205	127.25 (21.15)	131.00	206	126.76 (20.20)	129.50
	Change from Baseline to EOT	180	-5.15 (13.58)	-4.5	177	-3.95 (14.01)	-3.0
	Median Change Baseline to EOT by Gender			F: -3.67 M: -5.75			F: -2 M: -3
RBC (x 10 ¹² /L)	Baseline	183	4.23 (0.71)	4.30	181	4.25 (0.63)	4.31
	Change from Baseline to EOT	153	-0.14 (0.41)	-0.10	147	-0.10 (0.46)	-0.05
	Median Change Baseline to EOT by Gender			F: -0.1 M: -0.2			F: -0.1 M: 0
WBC (x 10 ⁹ /L)	Baseline	202	13.3 (4.89)	12.85	203	12.99 (5.25)	12.54
	Change from Baseline to EOT	175	-4.55 (4.84)	-4.70	174	-4.25 (5.09)	-4.32
	Median Change Baseline to EOT by Gender			F: -4.7 M: -4.7			F: -3.1 M: -4.90
Absolute Neutrophils (x 10 ⁹ /L)	Baseline	173	10.62 (4.40)	10.44	166	10.31 (4.36)	9.49
	Change from Baseline to EOT	140	-4.91 (4.32)	-4.73	130	-4.79 (4.30)	-5.11
	Median Change Baseline to EOT by Gender			F: -5.19 M: -4.23			F: -4.1 M: -5.16
Absolute Lymphocytes (x 10 ⁹ /L)	Baseline	173	1.20 (0.69)	1.06	166	1.24 (0.79)	1.09
	Change from Baseline to EOT	140	0.52 (0.82)	0.50	130	0.44 (0.76)	0.47
	Median Change Baseline to EOT by Gender			F: 0.41 M: 0.56			F: 0.51 M: 0.39
Absolute Eosinophils (x 10 ⁹ /L)	Baseline	173	0.05 (0.09)	0.00	166	0.05 (0.08)	0.01
	Change from Baseline to EOT	140	0.23 (0.21)	0.20	130	0.23 (0.24)	0.19
	Median Change Baseline to EOT by Gender			F: 0.2 M: 0.19			F: 0.19 M: 0.19
Platelets (x 10 ⁹ /L)	Baseline	197	250.62 (99.27)	231.00	197	268.88 (129.01)	240.00
	Change from Baseline to EOT	172	85.40 (107.14)	69.00	170	89.96 (130.53)	66.0
	Median Change Baseline to EOT by Gender			F: 79 M: 63.5			F: 70 M: 64

F=female, M=male

In DORI-08, there were no substantial differences in the measures of central tendency for select hematologic parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem and meropenem arms. It is also noteworthy that although anemia was identified more frequently as a TEAE in doripenem-treated subjects compared to meropenem-treated subjects in DORI-07 and DORI-08, there were no marked differences between the treatment arms in hemoglobin and hematocrit when assessed in terms of measures of central tendency.