Table 29. Changes from Baseline to End of IV Therapy in Serum Chemistry Parameters (ITT Analysis Set).

| | Doripenem (N= 376) | | Levofloxacin (N= 372) | |
|---|---|---|---|---|
| **Parameter** | **n** | **Mean (SD)** | **n** | **Mean (SD)** |
| Albumin (g/L) | | | | |
| Baseline | 367 | 39.9 (4.81) | 361 | 40.0 (5.42) |
| Change from Baseline | 327 | -1.9 (3.81) | 322 | -1.9 (4.13) |
| Alkaline Phosphatase (IU/L) | | | | |
| Baseline | 367 | 136 (101.8647) | 361 | 138.848 (99.5032) |
| Change from Baseline | 327 | 4.067 (60.8514) | 323 | 11.548 (59.4293) |
| ALT (SGPT) (IU/L) | | | | |
| Baseline | 367 | 23.507 (18.0136) | 361 | 26.393 (23.2282) |
| Change from Baseline | 327 | 8.645 (24.4514) | 322 | 6.00 (24.7637) |
| AST (SGOT) (IU/L) | | | | |
| Baseline | 367 | 23.902 (18.4126) | 361 | 26.634 (19.7047) |
| Change from Baseline | 327 | 4.055 (19.5402) | 323 | 1.579 (22.0427) |
| Bicarbonate (mmol/L) | | | | |
| Baseline | 272 | 24.0831 (3.52141) | 263 | 24.2091 (3.63327) |
| Change from Baseline | 238 | 1.3315 (3.63133) | 230 | 1.2361 (3.87928) |
| BUN (mmol/L) | | | | |
| Baseline | 365 | 7.4132 (4.32435) | 356 | 7.6229 (4.90296) |
| Change from Baseline | 326 | -1.0549 (3.16407) | 319 | -1.0945 (2.73405) |
| Calcium (mmol/L) | | | | |
| Baseline | 367 | 2.3161 (0.17102) | 360 | 1.2986 (0.18960) |
| Change from Baseline | 327 | -0.0217 (0.15817) | 322 | 0.0101 (0.15565) |
| Chloride (mmol/L) | | | | |
| Baseline | 367 | 102.6022 (4.43222) | 361 | 102.9612 (4.30228) |
| Change from Baseline | 327 | 1.1865 (4.04333) | 323 | 0.5944 (3.62161) |
| Cholesterol (mmol/L) | | | | |
| Baseline | 367 | 4.3849 (1.34196) | 361 | 4.3551 (1.23618) |
| Change from Baseline | 327 | -0.0029 (0.80705) | 323 | 0.0684 (0.83634) |
| CPK, Total (IU/L) | | | | |
| Baseline | 367 | 95.044 (122.0996) | 361 | 114.463 (370.8216) |
| Change from Baseline | 327 | -32.630 (132.6971) | 323 | -53.728 (373.8643) |
| Creatinine (µmol/L) | | | | |
| Baseline | 367 | 89.99 (39.108) | 361 | 89.40 (39.948) |
| Change from Baseline | 327 | -8.91 (29.419) | 323 | -5.19 (20.110) |
| GGT (IU/L) | | | | |
| Baseline | 367 | 39.540 (50.9378) | 361 | 44.349 (56.4319) |
| Change from Baseline | 327 | 9.673 (34.7297) | 323 | 15.950 (56.5920) |
| Indirect Bilirubin (µmol/L) | | | | |
| Baseline | 342 | 7.82 (5.320) | 338 | 8.14 (5.645) |
| Change from Baseline | 280 | -2.76 (5.392) | 278 | -2.90 (5.295) |
| LDH (IU/L) | | | | |
| Baseline | 367 | 278.349 (111.5194) | 358 | 282.12 (113.6838) |
| Change from Baseline | 326 | -8.525 (76.9315) | 320 | -15.084 (72.2424) |
| Magnesium (mmol/L) | | | | |
| Baseline | 367 | 0.8601 (0.13600) | 361 | 0.8588 (0.13545) |
| Change from Baseline | 327 | 0.0108 (0.10966) | 322 | 0.0012 (0.10754) |
| Non-fasting Glucose (mmol/L) | | | | |
| Baseline | 364 | 6.22 (2.468) | 358 | 6.17 (2.771) |
| Change from Baseline | 325 | -0.12 (2.185) | 316 | -0.15 (2.854) |
| Phosphorus (mmol/L) | | | | |
| Baseline | 367 | 1.1242 (0.28517) | 361 | 1.1173 (0.32855) |
| Change from Baseline | 327 | 0.0768 (0.47602) | 322 | 0.0737 (0.32402) |

| | Doripenem (N= 376) | Levofloxacin (N= 372) | | Doripenem (N= 376) |
|---|---|---|---|---|
| **Parameter** | **n** | **Mean (SD)** | **Parameter** | **N** |
| Potassium (mmol/L) | | | | |
| Baseline | 366 | 4.16 (0.699) | 360 | 4.16 (0.715) |
| Change from Baseline | 327 | 0.13 (0.871) | 321 | 0.13 (0.630) |
| Sodium (mmol/L) | | | | |
| Baseline | 367 | 139.8202 (3.6754) | 361 | 140.0748 (3.70097) |
| Change from Baseline | 327 | 0.7523 (3.31868) | 323 | 0.5046 (3.56582) |
| Total Bilirubin (μmol/L) | | | | |
| Baseline | 367 | 11.10 (7.461) | 361 | 11.67 (7.791) |
| Change from Baseline | 326 | -4.20 (7.53) | 323 | -4.22 (7.05) |
| Total Protein (g/L) | | | | |
| Baseline | 367 | 71.4 (6.71) | 361 | 71.1 (6.69) |
| Change from Baseline | 327 | -1.3 (6.69) | 322 | -1.2 (6.41) |
| Uric Acid (mmol/L) | | | | |
| Baseline | 367 | 0.3073 (0.11621) | 361 | 0.3137 (0.12108) |
| Change from Baseline | 327 | -0.0261 (0.07206) | 323 | -0.0204 (0.06025) |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma-glutamyltransferase; LDH = lactic dehydrogenase; N = number of patients in the analysis set; n = number of patients whose laboratory values were not missing for both the corresponding post-baseline visit and the baseline visit; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase.

The baseline serum chemistry parameters were similar between the treatment arms. For all time points (Study Day 3, EOT[IV], TOC, and LFU), mean values and mean changes from baseline in serum chemistry values were similar between treatment arms for all measured parameters. At subsequent time points, observed mean values and mean changes from baseline were similar among patients in both treatment arms. No clinically meaningful differences were seen between treatment arms.

**Clinical Reviewer's Comments:** *The changes in the serum chemistry parameters from baseline between the patients in both treatment arms were consistent with approximately 89.1% of the doripenem patients and 89.4% of the levofloxacin patients experiencing some changes. There did not appear to be any major differences between the two treatment groups in the baseline change in any particular parameter.*

Individual Patient Changes

Overall, 17 patients in the doripenem treatment arm and 24 patients in the levofloxacin treatment arm had laboratory abnormalities reported as adverse events by the investigator. The majority of these events were increases in hepatic enzymes that were considered possibly or probably to study drug therapy. In both treatment arms, most events resolved.

There were 2 patients in each treatment arm who had laboratory abnormalities reported as adverse events of special interest due to study drug intolerability. In the doripenem treatment arm, Patient 403/06039 had an adverse event of hepatic enzyme increased on Study Day 8, which resolved with no action taken; and Patient 403/06059 had an adverse event of hepatic enzyme increased on Study Day 4, which resolved with no action taken. Patient 403/06232 had 4 adverse events considered due to study drug intolerability: gamma-glutamyltransferase elevation on Study Day 4, which was ongoing; alkaline phosphatase increased on Study Day 4,

which resolved with no action taken; and ALT and AST elevations on Study Day 9, which both resolved with no action taken.

Laboratory Parameters of Special Interest

Changes in ALT and AST were considered laboratory parameters of special interest by the Applicant. Shifts from baseline to the worst (maximum) post-baseline value in ALT and AST were measured using pre-defined ranges relative to the upper limit of normal (ULN). The ranges were defined as follows: ≤ ULN, >ULN to 3 X ULN, >3 X ULN to 5 X ULN, and > 5 X ULN.

The following conclusions can be made:

- Most patients in both treatment arms had maximum ALT and AST values that were less than or equal to the ULN.
- The number of patients who demonstrated shifts from baseline in ALT or AST value and the magnitude of the shifts were similar in both treatment arms at each time point assessed.

**Clinical Reviewer's Comments:** *The percentage of doripenem-treated patients who demonstrated a change from baseline in their ALT levels was 89.1% (327/367) compared to 89.2% (322/361) for the levofloxacin-treated patients. Approximately the same number of patients in both treatment arms experienced a shift in their ALT levels from ≤ULN at baseline to >ULN – 3xULN during the study. The Applicant also assessed changes in the ALT level using Hy's High Risk (HHR) classification which is defined as a concurrent increase in ALT to > 3xULN and total bilirubin >1.5 ULN.*

- Seventy-three doripenem-treated patients and 68 levofloxacin-treated patients demonstrated an increase/shift in ALT levels from ≤ULN at baseline to >ULN during the study. Among the patients who demonstrated an increase, most increased from a value ≤ ULN to a range of >ULN - 3xULN (60, doripenem; 61, levofloxacin).
- Sixty doripenem-treated patients and 63 levofloxacin-treated patients demonstrated a post-baseline shift from ≤ULN to >ULN in AST. Among the patients who demonstrated an increase from baseline, most increased from a value ≤ULN to a range of >ULN - 3xULN (56, doripenem; 60, levofloxacin).

**Clinical Reviewer's Comments:** *The numbers in the above statements were verified by a review of the Applicant's dataset Klabs 5 by Dr. Deng.*

- A greater proportion of patients had an ALT or AST value >ULN at EOT(IV) or Day 3 than at TOC or LFU.
- There were 3 patients (Patients 304/04024, 401/06187, and 403/06177) in the doripenem treatment arm and 4 patients (Patients 034/03019, 201/09062, 401/06149, and 403/06219) in the levofloxacin treatment arm who had ALT increases from ≤ULN at baseline to >5xULN. In addition, there was 1 patient (Patient 034/03019) in the

levofloxacin treatment arm who had AST increases from ≤ULN at baseline to >5xULN. None of these patients had a concurrent elevation in total bilirubin that would meet the criteria to fulfill Hy's Rule.

- One of the doripenem-treated patients (Patient 304/04024) had a significant increase in ALT at the TOC assessment after undergoing lipthotripsy for a kidney stone. The findings in her blood chemistry panel likely reflect effects from ongoing lithotripsy and an evolving obstructive biliary condition. Two of the levofloxacin-treated patients had confounding events that could explain the profound increase in ALT. Patient 034/03019 had a gallstone and Patient 201/09062 was diagnosed with hepatitis C. Two of the doripenem-treated patients (Patients 401/06187 and 403/06177) and two of the levofloxacin-treated patients (Patients 401/06149 and 403/06219) had an increase in ALT to >5xULN at the EOT(IV) or TOC assessment, and all had a laboratory findings consistent with pre-existing or evolving biliary obstruction. A relationship to study drug administration could not be definitively ruled out based on the timing at which these observed increases in ALT, AST, ALK, and GGT occurred, however, since these findings were seen only in a similarly small number of patients from both treatment arms, it is likely that these represent background illnesses and unlikely they were related to the administration of IV study drug. Additional details on these patients follow.

Patient 304/04024 was a 58 year-old Caucasian female who was enrolled with cLUTI and randomized to the doripenem treatment. Laboratory parameters of interest are summarized below. The patient had normal transaminase levels while receiving IV study drug but had an elevated ALT to >5xULN at the TOC assessment. AST, ALK, and GGT levels were also elevated at the TOC visit. Serum chemistry elevations at the LFU assessments demonstrated ALT and AST trending towards normal while alkaline phosphatase and GGT levels continuing to rise. Total bilirubin levels were within normal limits at all time points. An evaluation for acute hepatitis was performed between the TOC and LFU visits and was negative to HBV, HAV, HCV, and CMV. Given the resolving ALT and AST, the negative hepatitis work-up and the increasing ALK and GGT at the LFU assessment, it is unlikely that these findings are related to liver injury and more likely reflect effects from ongoing lithotripsy and an evolving obstructive condition.

Patient 304/04024: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 µmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 15 | 17 | 193 | 6.5 | 17 |
| Day 3 | 16 | 14 | 176 | 6.7 | 16 |
| EOT(IV) | 32 | 21 | 194 | 5.6 | 15 |
| TOC | 176* | 148 | 269 | 5.8 | 49 |
| LFU | 127 | 41 | 509 | 5.3 | 205 |

[a] Normal range

**Clinical Reviewer's Comments:** *The patient developed increased levels of ALT, AST, and alkaline phosphatase levels at the TOC visit. The alkaline phosphatase level peaked*

*at the LFU visit, while both the ALT and AST levels decreased. Since the total bilirubin level did not increase, Hy's rule did not apply.*

Patient 401/06187 was a 38 year-old black female who was enrolled with pyelonephritis and was randomized to the doripenem treatment arm. Laboratory parameters of interest are summarized below. This patient had normal serum transaminase levels and elevated ALK at screening and on Day 3 of IV study drug therapy. However, at EOT(IV) visit (Day5), her ALT value increased to >5xULN. At this visit, elevations in AST (to >4xULN) and GGT (to >5xULN) were also noted. ALK remained elevated at all assessments. By the TOC visit, ALT, AST, and GGT values returned to within normal limits without intervention and ALK was trending towards normal. Total bilirubin levels were within normal limits at all time points. Given the timing of these laboratory abnormalities relative to IV study drug therapy, a relationship to doripenem treatment could not be ruled out. However, the concurrent elevations in ALT, AST, and GGT may be related to an obstructive cause rather than an injury to hepatocytes.

Patient 401/06187: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 24 | 26 | 176 | 15.7 | 55 |
| Day 3 | 37 | 36 | 216 | 8.4 | 119 |
| EOT(IV) | 189* | 150 | 202 | 6.2 | 190 |
| TOC | 24 | 16 | 189 | 5.3 | 83 |
| LFU | 12 | 15 | 154 | 4.8 | 28 |

[a] Normal range

**Clinical Reviewer's Comments:** *The Applicant states that the patient had an elevated alkaline phosphatase level at screening and Day 3; however at no time did it rise above the maximum normal range.*

Patient 403/06177 was a 38 year-old black female who was enrolled with pyelonephritis and was randomized to the doripenem treatment arm. Laboratory parameters of interest are summarized below. She had normal serum transaminase levels but elevated ALK and GGT levels at screening. While receiving IV study drug therapy, both ALT and AST levels increased to >5xULN as ALK and GGT levels continued to rise. A renal ultrasound demonstrated increased echogenicity of both kidneys but an evaluation for the potential cause for the serum chemistry findings was not pursued. Transaminase levels, ALK and GGT levels all trended towards normal without intervention after IV study drug was discontinued. Total bilirubin levels were within normal limits at all time points. Based on the timing of these laboratory abnormalities relative to study drug therapy, a relationship to doripenem treatment could not be ruled out. However, the concurrent elevations in ALT, AST, and GGT may also be related to an obstructive cause.

Patient 403/06177: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 16 | 18 | 211 | 3.6 | 73 |
| Day 3 | 149 | 113 | 271 | 5.3 | 200 |
| EOT(IV) | 184* | 158* | 323 | 2.9 | 266 |
| TOC | 40 | 28 | 189 | 2.7 | 172 |
| LFU | 21 | 21 | 143 | 5.8 | 101 |

[a] Normal range

**Clinical Reviewer's Comments:** *Patient #403/06177 had elevated transaminase levels and alkaline phosphatase at the EOT(IV) visit. All of the levels declined by the TOC and LFU visits.*

Patient 034/03019 was a 34 year-old Caucasian female who was enrolled with pyelonephritis and was randomized to the levofloxacin treatment arm. Laboratory parameters of interest are summarized below. The patient had normal transaminase levels while receiving IV study drug therapy. At the TOC visit, elevations in ALT and AST levels to >5xULN were noted along with dramatic increases in ALK and GGT values. All of these abnormalities were trending towards normal at 5 days after the TOC visit. Total bilirubin levels were within normal limits at all time points. This patient had developed abdominal pain and was diagnosed with cholelithiasis between the EOT(IV) and TOC visits. Given the acute onset of symptoms and concurrent diagnosis of gallstones after discontinuation of IV study drug therapy and the rapid resolution of findings after the TOC visit, the elevated transaminases were probably related to the cholelithiasis.

Patient 034/03019: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 21 | 22 | 65 | 3.4 | 14 |
| Day 3 | 34 | 26 | 82 | 3.4 | 17 |
| EOT(IV) | 71 | 77 | 119 | 3.4 | 27 |
| TOC | 376* | 199* | 203 | 6.8 | 127 |
| Repeat 5 days after TOC | 70 | 20 | 149 | 3.4 | 84 |

[a] Normal range

**Clinical Reviewer's Comments:** *The elevated levels in ALT, AST, and GGT appear to be of a short duration for this patient, since the levels dropped sharply at 5 days post TOC visit.*

Patient 201/09062 was a 51 year-old Caucasian female who was enrolled with pyelonephritis and was randomized to the levofloxacin treatment arm. Laboratory parameters of interest are summarized below. She had slowly increasing transaminase

levels while receiving IV study drug therapy, which continued to increase after study drug therapy was discontinued. Both ALT and AST levels were >5xULN at the LFU visit. ALK and GGT levels were within normal limits or were slightly elevated at each visit throughout the study. Total bilirubin levels were within normal limits at all time points. Concurrent with the clinical assessment of an acute infection, the patient was found to be positive for the hepatitis C antibody. Based on these findings, it was probable that the increasing transaminase levels were related to the recently diagnosed hepatitis C and not to IV study drug therapy.

Patient 201/09062: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 30 | 49 | 70 | 15.9 | 61 |
| Day 3 | 48 | 74 | 118 | 16.4 | 90 |
| EOT(IV) | 76 | 129 | 121 | 14.2 | 98 |
| TOC | 105 | 129 | 117 | 12.1 | 79 |
| LFU | 164* | 164* | 114 | 12.0 | 59 |

[a] Normal range

**Clinical Reviewer's Comments:** *This patient had increasing ALT and AST values from baseline that peaked at the LFU visit and most likely is secondary to hepatitis C infection.*

Patient 401/060149 was a 23 year-old Caucasian female who was enrolled with pyelonephritis and was randomized to the levofloxacin treatment arm. Laboratory parameters of interest are summarized below. She had normal serum transaminase levels at screening and on Day 3; however on Day 4, ALT and AST levels both increased to >5xULN. In addition, her GGT level was elevated to >3.5xULN at EOT(IV). By the TOC visit, all three parameters had returned to within normal limits without intervention. Total bilirubin levels were within normal limits or were slightly elevated at all time points assessed. Based on the timing of these elevations in relation to study drug therapy, a relationship to study drug could not be ruled out. However, the concurrent elevations in ALT, AST, and GGT may also be related to an obstructive cause, rather than injury to hepatocytes.

Patient 401/060149: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 20 | 18 | 178 | 22.9 | 53 |
| Day 3 | 59 | 37 | 191 | 6.3 | 77 |
| EOT(IV) | 167* | 120 | 240 | 7.0 | 129 |
| TOC | 24 | 15 | 143 | 14.2 | 41 |
| LFU | 24 | 16 | 119 | 23.4 | 15 |

[a] Normal range

**Clinical Reviewer's Comments:** *Patient # 401/060149 had an elevated bilirubin level at screening, which declined during the study.*

Patient 403/06219 was a 25 year-old black female who was enrolled with pyelonephritis and was randomized to the levofloxacin treatment arm. Laboratory parameters of interest are summarized below. Patient 403/06219 had normal serum transaminase levels but elevated ALK and GGT levels at screening. While receiving IV study drug therapy, both ALT and AST remained within normal limits while ALK and GGT levels decreased slightly but remained above normal limits. At the TOC visit, elevations in ALT and AST levels to >5xULN were noted along with dramatic increases in ALK and GGT values. Total bilirubin levels were within normal levels or were slightly elevated for all time points assessed. Based on the timing of these elevations in relation to study drug therapy, a relationship to study drug could not be ruled out. However, given the pre-existing elevations in ALK and GGT levels and the concurrent rise in ALT, AST, ALK, and GGT levels at the TOC visit, these findings are more likely to be related to a pre-existing obstructive cause.

Patient 403/06219: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | ALK Phos (<240 IU/L)[a] | Total bilirubin (6.5-17.1 μmol/L)[a] | GGT (7-32 IU/L)[a] |
|---|---|---|---|---|---|
| Screening | 26 | 15 | 196 | 25.3 | 69 |
| Day 3 | 20 | 15 | 150 | 7.0 | 48 |
| EOT(IV) | 19 | 15 | 132 | 5.3 | 44 |
| TOC | 240* | 103 | 400 | 6.2 | 300 |
| LFU | 15 | 20 | 141 | 14.5 | 20 |

[a] Normal range

**Clinical Reviewer's Comments:** *This patient had an elevated bilirubin level at screening. She later developed elevated levels of transaminases, along with alkaline phosphatase at the TOC visit. All enzyme levels returned to normal at the LFU visit.*

#### 7.1.7.4 Additional analyses and explorations

No additional analysis of laboratory data was performed.

### 7.1.8 Vital Signs

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure, pulse, and respiration rate) were measured at screening, the EOT(IV) visit, and the TOC visit. Oral temperature (or equivalent) was measured within 4 hours prior to administration of each dose of study drug therapy while the patient was receiving IV study drug

therapy. Height and weight were both measured at screening, and weight was measured while the patient was receiving IV study drug therapy at the discretion of the investigator. A full physical examination was performed at screening, and also at the EOT(IV) and TOC visits.

#### 7.1.8.2 Standard analyses and explorations of vital signs data

The Applicant has included a summary table that contains the mean and mean changes in vital signs from baseline to EOT(IV) and to TOC (and for temperature only at the LFU visit). Also, included in another table were the individual vital signs presented by patient. According to the Applicant, the following conclusions can be made regarding the vital signs, physical findings, and other observations related to safety:

- Mean and mean changes in vital sign measurements were similar between the treatment arms for all time points. No clinically meaningful differences were seen between the treatment arms.
- When patients with infections are appropriately treated, mean heart rate, respiratory rate, and temperature decreased from baseline to EOT(IV) and remained relatively stable from EOT(IV) to TOC. Mean and mean changes from baseline were similar between the treatment arms.
- Mean systolic and diastolic blood pressure readings for both patients in both treatment arms were stable throughout the study.
- One patient (Patient 035/01012) in the levofloxacin treatment arm had a vital sign abnormality (elevated diastolic blood pressure) on Day 3 of study drug therapy that resulted in study drug therapy discontinuation. This adverse event later resolved and was considered to be probably related to study drug therapy.

***Clinical Reviewer's Comments:*** *The mean changes in heart rate, respiratory rate, temperature, and systolic and diastolic blood pressure from baseline were comparable for both treatment arms.*

#### 7.1.8.3 Additional analyses and explorations

No additional analysis of vital signs data was performed.

### 7.1.9 Electrocardiograms (ECGs)

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

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

**Clinical Reviewer's Comments:** *The kae.xpt database was searched by the FDA reviewer and there were no reports of QT prolongation in either treatment arm.*

*A report filed by the Interdisciplinary Review Team for QT studies dated April 17, 2007 stated the following: "The upper limit of the two-sided 90% CI for the mean difference between doripenem (for both doses of 500 mg and 1,000 mg) and placebo was under 5 milliseconds at all time points which is below the value of 10 ms, which is identified as the threshold for regulatory concern in the ICH E14 guideline."*

#### 7.1.9.2 Additional analyses and explorations

No additional analysis of electrocardiogram data was performed.

### 7.1.10 Immunogenicity

There were no human immunogenicity data available.

### 7.1.11 Human Carcinogenicity

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

### 7.1.12 Special Safety Studies

See Section 7.2.6 concerning pharmacokinetic studies conducted in healthy subjects and subjects with various levels of renal impairment under IND 64,416.

See the Clinical Pharmacology review by Sarah Robertson, Pharm.D.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no studies conducted to assess the potential for study drug abuse. Generally, antibiotics represent a therapeutic class with a limited history of abuse potential and withdrawal phenomena.

### 7.1.14 Human Reproduction and Pregnancy Data

There were no human reproduction studies conducted.

There were seven pregnancies reported in DORI-05, with five patients who received 500 mg of doripenem and two who received 250 mg of levofloxacin. Three of the doripenem patients had a spontaneous abortion (miscarriage), one had an incomplete abortion, and one had an elective abortion. The two levofloxacin patients had spontaneous abortions (miscarriages).

Two other women were exposed to study drug while pregnant. Conception was determined to have occurred prior to study drug entry for one patient who received doripenem for five days and oral levofloxacin for five days. A second patient, who also was pregnant prior to study entry, received IV levofloxacin for two days and non-study oral levofloxacin for six days. Both of these pregnancies resulted in miscarriages.

### 7.1.15 Assessment of Effect on Growth

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

### 7.1.16 Overdose Experience

For the purposes of this safety analysis, in the Phase 2/3 studies, any dose of doripenem >1g, or a total daily dose >3g was considered a potential "overdose." No subjects received such dosages and thus the effects of doripenem overdose in humans remains unknown.

### 7.1.17 Postmarketing Experience

Doripenem is an injectable carbapenem antibiotic manufactured by Shionogi & Co., Ltd., Osaka, Japan. Peninsula Pharmaceuticals has obtained an exclusive license for the development and commercialization of doripenem in North America, South America, and Europe. Doripenem is approved in Japan for several indications including urinary tract infections at a dose of 250 mg bid/tid.

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

The Applicant has subsequently submitted a 4 month updated safety report that has been reviewed by Dr. Alfred Sorbello, FDA Medical Officer. For the overall safety review of doripenem, which includes the results from studies DORI-03, DORI-05, DORI-06, DORI-07, and DORI-08, please see the safety review by Dr. Alfred Sorbello.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

Within the context of adult patients with complicated urinary tract infections, including pyelonephritis, the extent and duration of exposure needed to assess safety was limited. The

study protocol called for a possible switch from IV doripenem (500 mg q8h) to oral levofloxacin (250 mg q24h) after 9 doses of the doripenem, provided that the patient showed signs of clinical improvement. Those patients who did not improve at that point were allowed to remain on IV doripenem for up to 10 days. Patients who were bacteremic at baseline could be treated for up to 14 days with doripenem.

Therefore, the safety data for those patients who received only 9 doses of IV doripenem followed by oral levofloxacin is very limited.

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

#### 7.2.1.1 Study type and design/patient enumeration

The dosage regimen for doripenem used in Study DORI-05 was 500 mg q8h for 10 days. After ≥ 9 doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h). The study provided adequate patient exposure and safety assessments for the cUTI indication. The safety dataset for this NDA was based on the safety analysis of Study DORI-05, which was a multi-center, randomized, controlled study. The safety analysis included all patients who received at least one dose of study drug. There were 376 patients who received at least one dose of doripenem (500 mg q8h) and 372 patients who received at least one dose of IV levofloxacin (250 mg q24h).

Adverse events were recorded daily during study drug administration, at the EOT(IV), TOC, and LFU visits. Laboratory testing was conducted at study entry, Study Day 3, EOT(IV), TOC, and LFU.

The Applicant conducted a second clinical trial (DORI-06), which also looked at the safety and efficacy of doripenem in treating 423 patients with complicated urinary tract infections. See Appendix 10.1.

#### 7.2.1.2 Demographics

See Table 3 in section 6.1.4.1.

#### 7.2.1.3 Extent of exposure (dose/duration)

See Table 7 in section 6.1.4.6.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

#### 7.2.2.1 Other studies

The Applicant performed a Phase II, dose-finding study (DORI-03) for the purpose of determining the best dosing regimen to be used in later Phase III studies. It was a multi-center, randomized, double-blind, dose finding study of two intravenous (IV) dosing regimens of doripenem (250 mg q8h and 500 mg q8h) for 7 to 14 days in the treatment of complicated urinary tract infections (cUTI) in adults. One hundred twenty-one subjects were randomized to receive either one of the two doses for 7 -14 days in the treatment of cUTI in adults. One hundred patients were evaluable for microbiological assessment. The cure rate for this group (ME at TOC) was 64.2% (34/53) for the group that received 250 mg compared to 68.1% (32/47) for the group that received 500 mg. Thus, the Applicant selected the higher, 500 mg dose to be used in subsequent comparative and non-comparative studies.

The Applicant conducted a second clinical trial (DORI-06), which also looked at the safety and efficacy of doripenem in treating 423 patients with complicated urinary tract infections.7.2

#### 7.2.2.2 Postmarketing experience

Please refer to section 7.1.17 of this review for further information on post-marketing experience with doripenem and to Dr. Sorbello's review for information from the 4-month safety update.

#### 7.2.2.3 Literature

The Applicant included copies of 87 references from the scientific/medical literature. The articles were reviewed for ones concerning the safety of doripenem. Two papers and one abstract written by employees of the company contained information that was taken from earlier Phase I, II, and III studies.

The first paper was a company report written by _____, from Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It concerned a search of the company's database for cases of pregnancy. The search of 1821 patients retrieved 13 cases of pregnancy that occurred in women enrolled in the DORI studies. The indication for 9 of the patients was pyelonephritis. The date of conception for 8 of the 13 women was after exposure to the study drug. Also, 8 cases were reported as miscarriages or spontaneous abortions. No definite conclusions were offered by the author.

The second article was also a company report written by _____. The report described the results of PK and dose escalation studies in DORI-01 & 3, along with numerous ECGs conducted in studies DORI-03 & 4. In DORI-03 65 subjects completed the ECG requirements of 12 ECGs per subject. In DORI-04 24 subjects each received 16 ECGs per person during the study. The DORI-04 results showed no arrhythmias and no statistically differences in the mean PR or QRS intervals.

The abstract (A-21) was presented at the 43rd ICAAC Meeting, September, 2003. It was written by D.A. Thyte, *et al.*, from Peninsula Pharmaceuticals, Inc. The abstract described the results of a Phase I dose escalation study involving 32 Japanese male and female subjects. No serious adverse events were reported; however, transient elevations of AST and ALT exceeding twice the upper limit of normal were seen in some subjects in the highest cohort (1000 mg q8h for 7 days).

### 7.2.3 Adequacy of Overall Clinical Experience

Within the context of adult patients with complicated urinary tract infections, including pyelonephritis, the extent and duration of exposure needed to assess safety was limited. The study protocol called for a possible switch from IV doripenem (500 mg q8h) to oral levofloxacin (250 mg q24h) after 9 doses of the doripenem, provided that the patient showed signs of clinical improvement. Those patients who did not improve at that point were allowed to remain on IV doripenem for up to 10 days. Patients who were bacteremic at baseline could be treated for up to 14 days with doripenem.

Therefore, the safety data for those patients who received IV doripenem without a switch to oral levofloxacin is very limited.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

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

Please see the review by Dr. Wendy Schmidt Ph.D., pharmacology-toxicology reviewer.

### 7.2.5 Adequacy of Routine Clinical Testing

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

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Applicant conducted four pharmacokinetics studies (R1411, R1412, R1414, and R1417) in healthy volunteers. In addition, two Phase I clinical studies in healthy volunteers (DORI-01) and in subjects with renal impairment (DORI-02) were conducted. DORI-01 was a randomized, multiple-dose, dose-escalation study with 4 cohorts containing male and female subjects. Blood and urine samples were collected throughout the study for pharmacokinetic analysis.

DORI-02 was an open-label, controlled study, to evaluate the safety, tolerability, and pharmacokinetics of doripenem administered intravenously to subjects with mild ($CL_{CR}$ 51-79 mL/min), moderate $CL_{CR}$ 31-50 mL/min), and end stage renal impairment requiring hemodialysis. All subjects received a single IV dose of doripenem, 500 mg administered over 30

minutes. Subjects with renal impairment were matched (for age and body weight) in a ratio of 3:1 with control subjects who have normal renal function. Please see Clinical Pharmacology & Biopharmaceutics Review for IND 64,416 by Dr. Charles Bonapace, dated November 6, 2002.

See the Clinical Pharmacology review by Sarah Robertson, Pharm.D.

Also, a dose finding clinical study (DORI-03) involving 100 patients with cUTI was completed.

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

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

### 7.2.8 Assessment of Quality and Completeness of Data

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

### 7.2.9 Additional Submissions, Including Safety Update

A four month safety update was submitted by the Applicant, which included data from an ongoing nosocomial pneumonia studies and updated post-marketing data. Please see Dr. Sorbello's review.

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

Overall, the administration of doripenem (500 mg) by IV infusion over 1 hour q8h was generally safe in patients aged 18 years or older with cUTI or pyelonephritis.

There was one death in the study, an 87-year-old man with an extensive medical history of cardiac disease. His death was due to bradycardia and considered not related to therapy with doripenem.

Serious adverse events were reported in 7% of doripenem-treated patients and in 4% of levofloxacin-treated patients. The most frequently reported SAE in the doripenem-treatment arm was pyelonephritis with 4 cases reported. Infections were the most frequently reported SAEs that occurred within 30 days after receipt of the last dose of study drug. Four percent of the doripenem-treated patients had adverse events in this category compared to 0.5% of the levofloxacin-treated patients.

The most frequently reported adverse event was headache with 16% of the doripenem-treated patients and 15% of the levofloxacin-treated patients reporting this adverse event.

Gastrointestinal disorders were the most commonly reported adverse events with onset during the IV part of therapy. Constipation, diarrhea, vomiting, upper abdominal pain, and nausea were reported by 4% or more of patients overall.

Adverse events of asymptomatic bacteriuria and urinary tract infection were reported more often in doripenem-treated patients than in levofloxacin-treated patients: 4% versus 1% for asymptomatic bacteriuria and 4% versus 2% for urinary tract infection in the doripenem and levofloxacin groups, respectively.

Adverse events of back pain and abdominal pain were reported more often in patients treated with levofloxacin than in patients treated with doripenem: 5% versus 2% for back pain, 4% versus 2% for abdominal pain, respectively.

No seizures were reported in any patient in the doripenem treatment arm and seizure was reported in 1 patient in the levofloxacin treatment arm.

In this study the frequency of liver enzyme elevations was rare and occurred with similar frequency in both treatment arms. No patient in either treatment arm met the definition of the Hy's High Risk classification at any measured time point after the start of study drug therapy.

There were no unexpected clinically significant changes in vital sign measurements .

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was no pooling of data in this study.

### 7.4.2 Explorations for Predictive Factors

Not applicable to this study.

### 7.4.3 Causality Determination

Not applicable to this study.

# 10 APPENDICES

## Review of Individual Study Reports



APPEARS THIS WAY
ON ORIGINAL

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 22-106 |
| Submission Code | 000 |
| | |
| Letter Date | December 12, 2006 |
| Stamp Date | |
| PDUFA Goal Date | October 12, 2007 |
| | |
| Reviewer Name | James Blank, Ph.D. |
| Review Completion Date | September 20, 2007 |
| | |
| Established Name | Doripenem |
| (Proposed) Trade Name | Doribax |
| Therapeutic Class | Penem |
| Applicant | Johnson and Johnson |
| | |
| Priority Designation | S |
| | |
| Formulation | IV infusion |
| Dosing Regimen | 500 mg q8h |
| Indication | Complicated Urinary Tract Infections |
| Intended Population | Adults ≥ 18 years old |

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# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 INDICATION

**Complicated Urinary Tract Infections, Including Pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, , *Acinetobacter baumannii* and**

### 6.1.1 Methods

Study DORI-06 was entitled: "A Multicenter. Phase 3 Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis." This study was a Phase III, multi-center, prospective, open-label, single arm study of doripenem, administered as a 1-hour IV infusion (500 mg q8h) in the treatment of cUTI in adults. After $\geq 9$ doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever (<37.8 °C oral) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least 1 urine culture had been reported with no growth at 24 hours or growth with a colony count of $< 10^4$ CFU/mL [colony forming units] and no subsequent cultures with a colony count of $\geq 10^4$ CFU/mL were observed.

#### 6.1.2 General Discussion of Endpoints

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

The secondary endpoints of interest for this study were:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 6.1.3 Study Design

#### 6.1.3.1 Overview

This was a Phase 3, multicenter, prospective, open-label, single arm study of doripenem, administered as a 1-hour IV infusion (500 mg q8h), in the treatment of cUTI in adults. This study was designed to provide independent confirmation of the response rate for doripenem observed in the double-blind, levofloxacin-controlled study in cUTI (DORI-05). The study was designed to fulfill a requirement for a second non-comparative study to establish statistical equivalence to the success rate of the agent in the first cUTI study (DORI-05). In addition, the levofloxacin treatment arm in DORI-05 was compared with DORI-06 to assess the comparability of demographics and baseline characteristics, inclusion/exclusion criteria, and patient evaluability criteria.

Approximately 450 patients were planned with 423 enrolled in this study. Urine specimens for culture were collected at screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture. All patients received a minimum of 9 doses (approximately 72 hours) of IV study drug therapy. After receiving a minimum of 9 doses of IV study drug therapy, patients may have been switched to levofloxacin tablets 250 mg orally once a day. The total duration of study drug therapy (IV alone or IV and oral therapy combined) was expected to be 10 days ((up to 14 days allowed for patients with concurrent bacteremia at study entry). The test of cure visit was to be conducted 6 to 9 days after the final dose of study drug was administered. A late follow-up visit was also to be conducted 28 to 35 days after administration of the final dose of study drug. Microbiological and clinical responses were assessed at both visits.

### 6.1.3.2 Inclusion and Exclusion Criteria

**Inclusion Criteria**

The inclusion criteria for this study were the same as those in DORI-05. Patients were included in this study if they met all of the following inclusion criteria:

6. Were male or female at least 18 years of age;
7. Demonstrated clinical signs and/or symptoms of cUTI, either of:
c. Pyelonephritis as indicated by all 3 of the following:
    i. Fever (oral temperature greater than or equal to $37.8^0$ C);
    ii. Flank pain or costovertebral angle tenderness;
    iii. Pyuria (greater than or equal to 10 white blood cells [WBC]/μL in unspun urine or greater than or equal to 10 WBC/high-power field [HPF] in spun urine)
d. Complicated lower UTI as indicated by all 3 of the following;
    i At least 1 of the following symptoms;
        - Dysuria;
        - Frequency;
        - Suprapubic pain;
        - Urgency.
    iv. Pyuria (greater than or equal to 10 WBC/μL in unspun urine or greater than or equal to 10 WBC/HPF in spun urine);
    v. At least 1 of the following complicating factors:
        - Male gender;
        - Current bladder instrumentation or indwelling catheter that was anticipated to be removed during the course of IV study drug therapy administration;
        - Obstructive uropathy that was anticipated to be medically or surgically treated during the course of IV study drug therapy administration;
        - Urogenital surgery within 7 days prior to administration of the first dose of study drug therapy;
        - Functional or anatomical abnormality of the urogenital tract including anatomic malformations or neurogenic bladder with voiding disturbance of at least 100 mL of residual urine.
8. Had a study-qualifying pre-treatment baseline urine culture specimen obtained within 48 hours prior to the start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of greater than or equal to $10^5$ CFU/mL. Patients may have been enrolled in this study and started IV study drug therapy prior to the investigator knowing the results of the baseline urine

culture. However, if the final results of the pre-treatment urine culture were negative, then the patient was withdrawn from study drug therapy;
9. Required antibacterial therapy for the treatment of the presumed cUTI;
10. Had provided written informed consent. If the patient was unable to provide written informed consent, the patient's legally acceptable representative may have provided written consent, as approved by institution-specific guidelines.

**Exclusion criteria**

The exclusion criteria for this study were the same as those in DORI-05. Patients were excluded from the study if they met any of the following exclusion criteria:

1. Were women who were pregnant, nursing, or of childbearing potential, and not using a medically accepted, effective method of birth control (e.g., condom, hormonal contraceptive, indwelling intrauterine device, or sexual abstinence);
2. Had a history of moderate or severe hypersensitivity reactions to carbapenems, penicillins, other β-lactam antibiotics, or any quinolone (Mild rash was not a contraindication to enrollment.);
3. Had a complete permanent obstruction of the urinary tract;
4. Had a confirmed fungal UTI with a colony count greater than or equal to $10^3$ CFU/mL;
5. Had a permanent indwelling bladder catheter or instrumentation including nephrostomy;
6. Had suspected or confirmed perinephric or intrarenal abscess;
7. Had suspected or confirmed prostatitis;
8. Had any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure, respiratory failure, and septic shock;
9. Had an immunocompromising illness including known infection with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hematological malignancy and bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, Imuran and the administration of corticosteroids equivalent to or greater than 40 mg/day of prednisone administered for more than 14 days;
10. Had severe impairment of renal function including a calculated creatinine clearance of less than 10 mL/min; a requirement for peritoneal dialysis, hemodialysis, or hemofiltration; or oliguria (less than 20 mL of urine output/hour over 24 hours);
11. Had 1 or more of the following laboratory abnormalities: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase levels greater than 3 times the upper limit of normal (ULN), absolute neutrophil count of less than 500 cells/μL, platelet count of less than 40,000 cells/μL, or hematocrit of less than 20%;
12. Had known ileal loops or vesico-ureteral reflux;
13. Had a concomitant infection requiring systemic antibiotic or antifungal therapy in addition to IV study drug therapy at the time of randomization; however, possible bacteremia with the presumed same urinary pathogen was acceptable;
14. Received any amount of potentially therapeutic antimicrobial therapy after collection of the pre-treatment baseline urine culture and before administration of the first dose of study drug therapy;

15. Received any amount of potentially therapeutic antibiotic for the treatment of the current UTI within the 96 hours prior to obtaining the study-qualifying pre-treatment baseline urine culture;
16. Had an intractable infection anticipated to require more than 10 days of study drug therapy;
17. Had a current urinary catheter that would not be removed or anticipation of urinary catheter placement that would not be removed during the course of IV study drug therapy administration. Intermittent straight catheterization after the IV study drug therapy administration period was acceptable;
18. Had a known or suspected central nervous system disorder that may have predisposed the patient to seizures or lowered the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or had the presence of other risk factors that may have predisposed the patient to seizures or lowered the seizure threshold (e.g., certain drug therapy, renal dysfunction);
19. Participated in any study of an investigational drug or device with 30 days prior to study entry;
20. Participated in any previous study of doripenem;
21. Had any condition or circumstance that, in the opinion of the investigator, would have compromised the safety of the patient or the quality of study data.

#### 6.1.3.3 Study Treatments

Patients were to receive doripenem (500 mg), administered as a 1-hour IV infusion three times/day. After receiving a minimum of 9 doses of IV study drug therapy, patients may have been switched to levofloxacin tablets 250 mg orally once a day. The total duration of study drug therapy (IV alone or IV and oral therapy combined) was expected to be 10 days ((up to 14 days allowed for patients with concurrent bacteremia at study entry).

#### 6.1.3.4 Study Procedures

The study procedures are summarized in the following table.

Table 1. Time and Events Schedule

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

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

[a] Day of premature withdrawal, day of failure, or last day IV study drug therapy was administered.

[b] Days after administration of the last dose of study drug therapy (IV and oral).

[c] Within 4 hours prior to each infusion while the patient remained on IV study drug therapy.

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

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

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

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

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

[i] Pre-infection symptom assessment was performed at screening. Day 1 symptom assessment was performed prior to infusion of the first dose of IV study drug therapy and then daily until the patient was switched to oral study drug therapy.
[j] A baseline ECG was obtained anytime prior to administration of the first dose of study drug therapy and as medically indicated thereafter. Two copies of each ECG were printed.
[k] While the patient remained on IV study drug therapy, assessments were made and recorded daily whether the patient met the following criteria to switch to oral study drug therapy: 1) no fever (<37.8 $^{0}$ C oral) for at least 24 hours, 2) signs and/or symptoms of cUTI were absent or improved relative to the values prior to dosing on Day 1, and 3) at least 1 urine culture obtained after administration of IV study drug therapy was reported to have no growth at 24 hours or growth with a colony count of <$10^4$ CFU/mL. [illegible] on IV and/or oral study drug therapy for 10 days unless [illegible]

### 6.1.3.5 Patient Populations

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

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

Two different mMITT analysis sets were evaluated. One analysis set (mMITT_1) consisted of all patients who met the criteria for inclusion in the mMITT analysis set, including those who did not have an interpretable urine culture result available after completing study drug therapy. For the first mMITT analysis, patients who lacked an interpretable urine culture result after completing study drug therapy were considered failures. In the second mMITT population (mMITT_2), patients without interpretable urine culture results after completing study drug therapy were excluded.

Microbiologically Evaluable at Test of Cure (ME at TOC): This analysis set consisted of all enrolled patients who met the following conditions:

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

Microbiologically Evaluable at Late Follow-Up (ME at LFU): This analysis set consisted of patients in the ME at TOC analysis set with an interpretable urine culture result at the LFU visit (28 to 42 days after the final dose of study drug therapy) and who did not have any confounding event or receive any systemic antibacterial therapy with potential activity against the baseline uropathogen(s) between the time of the TOC and LFU visits, except resuming oral antimicrobial prophylaxis therapy after the TOC urine culture was obtained.

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

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

### 6.1.3.6 Outcome Criteria

Microbiological Response Definitions

Microbiological outcome by pathogen and response by patient were determined at the EOT(IV), TOC, and LFU visits based on data collected on the CRF for qualifying uropathogens at each of these visits. The collected data consisted of the pathogen names (genus and species) and the count (in CFU/mL). The following definitions were defined by the applicant and taken from page 40 of the CSR:

At the EOT(IV) visit:

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

At the TOC visit:

| | |
|---|---|
| Eradication | An interpretable urine culture result from a specimen obtained within the 5- to 11-day window after the last dose of study drug therapy showed the |

| | |
|---|---|
| | bacterial uropathogen(s) found at entry at greater than or equal to $10^5$ CFU/mL were reduced to less than $10^4$ CFU/mL. |
| Persistence | At least 1 interpretable urine culture result from a specimen obtained 1 to 11 days after completion of study drug therapy grew greater than or equal to $10^4$ CFU/mL of the original uropathogen. |
| Indeterminate | No urine culture was obtained during the 5- to 11-day window after the last dose of study drug therapy, or the culture result could not be interpreted for any reason. |

At the LFU visit:

| | |
|---|---|
| Sustained Eradication | An interpretable urine culture result from a specimen obtained within the 28- to 42-day window after the last dose of study drug therapy showed that the bacterial uropathogen(s) found at entry at greater than or equal to $10^5$ CFU/mL remained less than $10^4$ CFU/mL. |
| Recurrence | An interpretable urine culture result from a specimen obtained any time after documented eradication at the TOC visit, up to and including the LFU visit, grew greater than or equal to $10^4$ CFU/mL of the original uropathogen. |
| Indeterminate | No urine culture was obtained during the 28- to 42-day window after the last dose of study drug therapy, or the culture result could not be interpreted for any reason. |

Emergent Infections

Pathogens arising after baseline were categorized as follows:

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

Clinical Response Definitions

Clinical outcome assessments were made at the EOT(IV), TOC, and LFU visits for patients enrolled with a baseline diagnosis of symptomatic cUTI or pyeloneprhritis. The following definitions were defined by the applicant and taken from pages 42-43 of the CSR:

At the EOT(IV) visit:

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

At the TOC visit:

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

At the LFU visit:

| | |
|---|---|
| Sustained Clinical Cure | All pre-therapy signs and symptoms showed no evidence of resurgence after administration of the last dose of study drug therapy. |
| Clinical Relapse | Signs and/or symptoms of cUTI that were absent at the TOC visit reappeared at the LFU visit. |

| | |
|---|---|
| Indeterminate | Patients were lost to follow-up such that a determination of clinical response (success or failure) could not be made. |

### 6.1.3.7 Statistical Considerations

Sample Size Estimation

The primary objective of DORI-06 was to establish non-inferiority of doripenem in this study compared with the levofloxacin treatment arm in DORI-05 with respect to the microbiological and clinical response for the treatment of cUTI in adult patients. Doripenem was to be considered non-inferior to levofloxacin if the lower limit of the 2-sided 95% CI for the difference between treatment arms (doripenem minus levofloxacin) in the per-patient microbiological cure rate at the TOC visit was greater than or equal to -10%. The analysis was conducted in the ME at TOC analysis set. The hypotheses of interest were:

| | |
|---|---|
| null hypothesis | $H_0$: $\pi_1 - \pi_2 < -0.10$, versus |
| alternative hypothesis | $H_0$: $\pi_1 - \pi_2 \geq -0.10$, |

Where $\pi_1$ was the true proportion of patients with cUTI in DORI-06 who were microbiologically cured (had all baseline pathogens eradicated) at the TOC visit and $\pi_2$ was the true proportion of patients with cUTI in the levofloxacin treatment arm in DORI-05 who were microbiologically cured at the TOC visit.

Study DORI-06 provides an independent confirmation of the microbiological cure rate for doripenem observed in DORI-05. For this objective, a sample size for DORI-06 was selected that would come close to the number of evaluable patients expected in each treatment arm in DORI-05.

Adjustments to the Original Study Sample Size

There were 2 adjustments to the original study sample size in studies DORI-05 and DORI-06. These were based on updated estimates of the microbiological cure and evaluability rates based on accumulated data in the blinded Study DORI-05. For study DORI-06, the study specific evaluability rate was also considered. In addition, in the second sample size adjustment, the study power was increased from 80% to 85% as a result of the re-evaluation of the development plan that occurred when PPI was acquired by J & JPRD on July 1, 2005.

The study sample size justification in Section 9.7.2.1 was part of Amendment 4 to the DORI-06 study protocol (September 15, 2005) and the corresponding SAP for the study.

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

| Protocol Version | Microbiological Cure Rate | Evaluability Rate | Study Power | Total Sample Size | Total Evaluable |
|---|---|---|---|---|---|
| Original (10/29/03) | 93% | 70% | 80% | 220 | 160 |
| Amendment 3 (4/28/05) | 88% | 63% | 80% | 290 | 180 |
| Amendment 4 (9/15/05) | 84% | 55% | 85% | 450 | 248 |

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

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

Statistical and Analytical Plan

In order to gain approval for the cUTI indication, the regulatory guidelines suggest using 1 statistically adequate and well-controlled trial to establish the safety and similar effectiveness to an approved product for the cUTI indication and a second comparative or non-comparative trial to establish statistical equivalence to the success rate of the approved agent in the first cUTI trial. Therefore, outcomes for patients who received doripenem in DORI-06 were compared with outcomes for patients who received levofloxacin in DORI-05.

DORI-06 was the second of 2 Phase 3 studies to confirm the efficacy and safety of doripenem in patients with cUTI. The first study, DORI-05, was a multicenter, prospective, randomized, double-blind study that compared doripenem (500 mg q8h administered as an IV infusion over 1 hour) to levofloxacin (250 mg q24h administered as an IV infusion over 1 hour) in the treatment of cUTI. Both Phase 3 studies followed identical clinical procedures, had the same inclusion and exclusion criteria, and had a uniform set of evaluability criteria. However, DORI-06 was conducted at different investigational sites and performed by different investigators than DORI-05.

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

The following four amendments were made to the original protocol, dated October 29, 2003.

Amendment 1 (February 13, 2004)

This amendment changed the duration of study drug therapy to comply with levofloxacin prescribing information and reflected information learned from enrolling the first 2 patients under the original DORI- 05 protocol, and discussions at investigator meetings.

- The days of therapy were changed from "7 to 14 days" to "10 days" in accordance with the levofloxacin prescribing information.
- A second negative urine culture was added at the time of the switch to oral study drug therapy to increase the probability that the patient had received adequate treatment with IV study drug therapy.
- The TOC visit was changed from "5 to 9 days" to "6 to 9 days" after the last dose of study drug therapy to increase the probability that the primary efficacy endpoint data were collected within the 5- to 9-day timeframe.
- A change was made to allow pyuria to be evaluated in both unspun and spun urine.
- Clarification was given that catheterized patients, obstructed patients, and patients with neurogenic bladder who may not have experienced signs/symptoms of dysuria, frequency, suprapubic pain, and urgency were the patients that were referred to within the protocol as "asymptomatic" patients.
- The use of oral antibacterial prophylaxis was allowed after the TOC visit in patients who usually received oral prophylaxis.
- Superficial bladder tumor was deleted as an acceptable complicating factor for cUTI.
- Blood cultures were required to be obtained from catheterized patients at screening.
- Clarification was added that patients with fungus found in the baseline urine culture at greater than or equal to $10^3$ CFU/mL were not eligible for the study.
- An exclusion criterion was added to exclude immunosuppressive therapy (in addition to the previously stated immunosuppressive conditions).
- Enrollment of patients who were enrolled in a previous trial of doripenem was allowed.
- The requirement to obtain blood for PK analyses was eliminated.
- The number of baseline ECGs was reduced from 3 to 1. The requirement for ECGs after screening was eliminated unless they were medically indicated.
- The schedule for obtaining safety laboratory samples was modified and clarified (screening, Day 3, EOT[IV], TOC, and LFU [if needed]).
- The protocol requirement of documenting patients' clinical statuses while they were outpatients receiving oral levofloxacin was deleted.
- The window for taking and recording body temperatures 3 times a day was expanded from 1 hour prior to 4 hours prior to administration of each dose of study drug therapy.
- Clarification that patients should have received 72 hours of IV study drug therapy before being considered a clinical failure was added.
- Clarification was added that Day 1 was the 24-hour period starting with the initiation of infusion of the first dose of study drug therapy, and each study day was the 24-hour period thereafter (not calendar days).
- The definition of a study-qualifying urine culture was clarified.

- The dosage adjustment for doripenem in patients with moderate renal impairment was provided.
- The requirement for hepatitis serologies was eliminated.
- The requirement for aerobic blood cultures was retained, but the requirement for anaerobic blood cultures was eliminated.
- Clarification was added that patients were to be considered compliant with study drug therapy administration if they received at least 8 of the first 9 IV doses and at least 80% of the scheduled doses (IV and oral) overall.
- The dose of levofloxacin was allowed to be increased to 500 mg q24h for patients with confirmed bacteremia.

Amendment 2 (August 31, 2004)

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

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

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

Amendment 3 (April 28, 2005)

There were 4 principal reasons for this amendment: 1) to increase sample size; 2) to strengthen and clarify methods to prevent, detect, and report pregnancies; 3) to exclude patients with asymptomatic cLUTI; and 4) to allow European sites to enroll patients into this study.

- The sample size was increased from a planned enrollment of 220 to one of 290 patients to provide a number of ME at TOC patients equivalent to that targeted for enrollment in the corresponding levofloxacin treatment arm in the DORI-05 study. The increase in sample size in the DORI-05 study was based on a review of blinded data from that study that

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

- Language was added to more precisely describe the methods for testing women of childbearing potential for pregnancy at screening and at the Late Follow-up visit. These changes were intended to improve detection of pregnancy at screening and to emphasize the need to inform women that birth control must have been practiced throughout study drug therapy administration and for at least 30 days after the last dose of study drug therapy had been administered.
- Patients with asymptomatic cLUTI were excluded from this study because the increased complexity of these patients' conditions precluded obtaining interpretable urine cultures and the frequent occurrences of confounding infections mandated administration of non-study antibiotics.
- Europe was added as a region where the study could be conducted to increase the rate of patient enrollment.
- The collection of adverse events of special interests (possible allergic reactions and study drug therapy intolerability) was added but never implemented.

Amendment 4 (September 15, 2005)

The purpose of this amendment was to increase the sample size from 290 to approximately 450 patients in order to take into consideration the overall microbiological eradication rates observed from a review of blinded data from DORI-05, the percentage of patients who met the criteria to be included in the ME at TOC analysis set in DORI-06, and to increase the a priori power of the study from 80 to 85% at the 1-sided 2.5% significance level.

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

Changes in Visit Windows

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

**Clinical Reviewer's Comments:** *All of the case report forms submitted by the Applicant for analysis by the Agency were reviewed in accordance with the conditions specified in the*

*protocol, including the five amendments. Thus, the protocol-defined window at TOC of 6 to 9 days after administration of the last dose of study drug was used to determine the patient's response, both clinically and microbiologically.*

## 6.1.4 Efficacy Findings

### 6.1.4.1 Disposition of Patients

A total of 30 centers, with 11 in the United States; 9 in Argentina; 6 in Brazil; 3 in Austria; and 1 in Canada enrolled 426 patients in this study.

Table 2. Disposition of All Randomized Patients in DORI-06.

| | **Doripenem (DORI-06)** | **Levofloxacin (DORI-05)** |
|---|---|---|
| All Patients | 426 | 376 |
| Enrolled but not treated | 3 (0.7%) | 4 (1.1%) |
| Patients who Completed Study[a] | 328 (77.0%) | 280 (74.5%) |
| Treated with IV Therapy Only | 63 (14.8%) | 34 (9.0%) |
| Treated with IV and Oral Therapy | 265 (62.2%) | 246 (65.4%) |
| ME at TOC Treated with IV Therapy Only | 54 (12.7%) | 48 (12.8%) |
| ME at TOC Treated with IV and Oral Therapy | 196 (46.0%) | 217 (57.7%) |
| Patients who did not Complete Study | 98 (23.0%) | 96 (25.5%) |
| Discontinued during screening period | 3 (0.7%) | 4 (1.1%) |
| Discontinued while on study therapy | 73 (17.1%) | 73 (19.4%) |
| On IV Therapy | 64 (15.0%) | 69 (18.4%) |
| On oral therapy | 7 (1.6%) | 3 (0.8%) |
| Discontinued after completing study therapy | 22 (5.2%) | 19 (5.1%) |
| Discontinued from Study Early and Completed LFU Assessment | 73 (17.1%) | 61 (16.2%) |
| Follow-up Visits Completed | | |
| Had TOC and LFU | 320 (75.1%) | 284 (75.5%) |
| Had TOC but Not LFU | 19 (4.5%) | 9 (2.4%) |
| No TOC nor LFU | 14 (3.3%) | 32 (8.5%) |
| No TOC, but Completed LFU | 73 (17.1%) | 51 (13.6%) |

IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable; TOC = test-of-cure.
Notes: Percentages were based on the number of patients randomly assigned to each treatment arm.
[a] Patients were defined as having completed the study if they had received study drug therapy as directed during the 10 days of treatment and had attended the TOC and LFU visits as specified in the protocol.

The data in Table 2 were taken from Applicant's Table 7, found on page 62 of the CSR. Four hundred twenty-three of the 426 patients enrolled in DORI-06 received study drug and comprise the ITT analysis set; 372 of the 376 patients randomly assigned to the levofloxacin treatment arm in DORI-05 received levofloxacin and were included in the ITT analysis set.

Seventy-seven percent of patients in DORI-06 completed the study per protocol and 75% of the patients treated with levofloxacin in DORI-05 completed the study per protocol.

Two hundred fifty (59%) patients in DORI-06 met the criteria for inclusion in the ME at TOC analysis and 265 (70%) of patients in the levofloxacin treatment arm of DORI-05 met the criteria for inclusion in the ME at TOC analysis set. Fifty-four (13%) of the 426 patients were in the ME at TOC analysis set of DORI-06 and received IV therapy only. One hundred ninety-six (46%) of 426 patients were in the ME at TOC analysis set of DORI-06 and received both IV and oral study drug.

The percentages of patients completing both the TOC and LFU visits were comparable for the doripenem-treated (75%) patients in DORI-06 and for the levofloxacin-treated (76%) patients in DORI-05.

The patient disposition was similar between the patients in DORI-06 and the levofloxacin arm of DORI-05, except a larger percentage of patients in DORI-06 completed the study and were treated with IV therapy only (15%, doripenem; 9%, levofloxacin), and a larger percentage of enrolled patients were ME at TOC and treated with both IV and oral therapy in the DORI-05 levofloxacin treatment arm (46% doripenem; 58%, levofloxacin).

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

Table 3. Demographics and Baseline Characteristics of Patients in Study DORI-06 with Comparison to Levofloxacin Patients in DORI-05 (ME at TOC Population).

| | **Doripenem (N = 250)** | **Levofloxacin (N = 265)** |
|---|---|---|
| Sex | | |
| Male | 112 (44.8%) | 103 (38.9%) |
| Female | 138 (55.2%) | 162 (61.1%) |
| Race | | |
| American Indian or Alaska Native | 1 (0.4%) | 2 (0.8%) |
| Asian | 1 (0.4%) | 0 |
| Black or African Heritage | 45 (18.0%) | 24 (9.1%) |
| Caucasian | 120 (48%) | 209 (78.9%) |
| Native Hawaiian, Other Pacific Islander | 0 | 0 |
| Hispanic | 60 (24%) | 27 (10.2%) |
| Other (also includes more than 1 race) | 23 (9.2%) | 3 (1.1%) |
| Age (years) | | |
| Mean (standard deviation) | 51.8 (19.56) | 51.8 (20.82) |
| Median | 52.0 | 55.0 |
| Min, Max | 18, 97 | 18, 90 |
| Age Categories (years) | | |
| <18 | 0 | 0 |
| 18-44 | 102 (40.8%) | 106 (40.0%) |
| 45-74 | 111 (44.4%) | 118 (44.5%) |
| <65 | 171 (68.4%) | 170 (64.2%) |
| ≥65 | 79 (31.6%) | 95 (35.8%) |
| <75 | 213 (85.2%) | 224 (84.5%) |
| ≥75 | 37 (14.8%) | 41 (15.5%) |

| | Doripenem (N = 250) | Levofloxacin (N = 265) |
|---|---|---|
| Height (cm) | | |
| N | 247 | 265 |
| Mean (SD) | 164.4 (8.75) | 165.2 (8.89) |
| Median | 164 | 165 |
| Min, Max | 145, 198 | 148, 196 |
| Missing | 3 (1.2%) | 0 |
| Weight (kg) | | |
| N | 250 | 265 |
| Mean (SD) | 68.05 (15.582) | 73.41 (17.2) |
| Median | 65 | 71 |
| Min, Max | 38.0,139.0 | 44, 140 |
| Missing | 0 | 0 |
| Body Mass Index (kg/m$^2$) | | |
| N | 247 | 265 |
| Mean (SD) | 25.125 (5.15) | 26.85 (5.7) |
| Median | 24.4 | 25.95 |
| Min, Max | 17.26, 56.75 | 16.89, 47.32 |
| Missing | 3 (1.2%) | 0 |
| Baseline Disease Diagnosis | | |
| cLUTI | 132 (52.8%) | 131 (49.4%) |
| Symptomatic | 128 (51.2%) | 122 (46.0%) |
| Asymptomatic | 4 (1.6%) | 9 (3.4%) |
| Reason for Complication | | |
| Male Gender | 102 (40.8%) | 85 (32.1%) |
| Instrumentation/Catheter | 8 (3.2%) | 55 (20.8%) |
| Obstructive Uropathy | 15 (6.0%) | 51 (19.2%) |
| Urogenital Surgery | 1 (0.4%) | 29 (10.9%) |
| Func/Anatomical Abnormality | 33 (13.2%) | 37 (14.0%) |
| Anticipated to be Persistent (All males and some females) | 122 (48.8%) | 116 (43.8%) |
| Anticipated to be Eliminated (Some females only) | 10 (4.0%) | 15 (5.7%) |
| Pyelonephritis | 118 (47.2%) | 134 (50.6%) |
| Uncomplicated | 99 (39.6%) | 107 (40.4%) |
| Complicated | 19 (7.6%) | 27 (10.2%) |
| Reason for Complication | | |
| Male Gender | 4 (1.6%) | 17 (6.4%) |
| Instrumentation/Catheter | 2 (0.8%) | 0 |
| Obstructive Uropathy | 7 (2.8%) | 6 (2.3%) |
| Func/Anatomical Abnormality | 4 (1.6%) | 3 (1.1%) |
| Other | 5 (2.0%) | 6 (2.3%) |
| Anticipated to be Persistent (All males and some females)[a] | 18 (7.2%) | 23 (8.7%) |
| Anticipated to be Eliminated (Some females only)[a] | 1 (0.4%) | 4 (1.5%) |
| Had a study-qualifying pre-treatment urine culture | 250 (100%) | 265 (100%) |
| Bacteremic at Study Entry | 27 (10.8%) | 23 (8.7%) |
| Prior Administration of Doripenem[b] | 0 | 2 (0.8%) |
| Baseline Renal Function | | |
| Calculated Creatinine Clearance (mL/min)[c] | | |
| Normal (80 and above) | 138 (55.2%) | 135 (50.9%) |
| Mild Failure (50-80) | 67 (26.8%) | 96 (36.2%) |
| Moderate Failure (30-50) | 38 (15.2%) | 30 (11.3%) |
| Severe Failure (less than 30) | 7 (2.8%) | 4 (1.5%) |
| Region | | |
| North America | 53 (21.2%) | 16 (6.0%) |
| South America | 196 (78.4%) | 121 (45.7%) |
| Europe | 1 (0.4%) | 128 (48.3%) |

cLUTI = complicated lower urinary tract infection; Func = functional, N = number of patients in the analysis set; max = maximum; min = minimum; n = number of patients who meet criteria; SD = standard deviation: TOC = test-of-cure.
Notes: Percentages were based on the number of patients in the given analysis set for each treatment arm. Baseline value was defined as the last available value before the start of infusion of the first dose of study drug therapy.
[a] Patients for whom the complication was anticipated to persist throughout study drug therapy and for whom the complication was anticipated to be eliminated during study drug therapy.
[b] Only applied to patients who were enrolled under the original protocol or protocol Amendment 1.
[c] The parenthesis/bracket notation given for the creatinine clearance intervals denoted exclusion/inclusion of the interval endpoint, respectively.

**Clinical Reviewer's Comments:** *The demographics of sex, race, and age for the doripenem patients were similar to those found in the levofloxacin arm of the DORI-05 study. There were more North Americans enrolled in this study, compared to DORI-05. The baseline diagnosis of cLUTI and pyelonephritis were similar among the doripenem patients compared to the levofloxacin patients from the DORI-05 study..*

### 6.1.4.2 Urological History

The following table shows the urological history for the ME at TOC population. The data were taken from Applicant's Table 15.1.4.1-2, found on page 226 of the CSR.

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

| Category | Doripenem (N=250) |
|---|---|
| No Clinically Significant History | 19 (7.6%) |
| Clinically Significant History in at Least one Category | 231 (92.4%) |
| Pyelonephritis | 86 (34.4%) |
| Other | 81 (32.4%) |
| Complicated UTI | 65 (26.0%) |
| Urogenital surgery | 58 (23.2%) |
| Prostatic hypertrophy | 49 (19.6%) |
| Nephrolithiasis | 44 (17.6%) |
| Indwelling catheter/stent/sprint | 40 (16.0%) |
| Recurrent UTI | 40 (16.0%) |
| Uncomplicated UTI | 38 (15.2%) |
| Neurogenic bladder | 27 (10.8%) |
| Cancer of the urinary tract | 21 (8.4%) |
| Obstructive uropathy due to fibrosis | 9 (3.6%) |
| Residual urine after voiding | 7 (2.8%) |
| Asymptomatic bacteriuria | 4 (1.6%) |
| Congenital urinary tract stricture | 2 (0.8%) |
| Obstructive uropathy due to bladder tumor | 1 (0.4%) |

In the ME at TOC analysis set, pyelonephritis was the most common urological history category (34%) followed by the "other" category (32%). The "other" category included, but was not limited to, such conditions as hydronephrosis, prostatic adenoma, and bladder stone.

### 6.1.4.3 Protocol Violations

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

| Violation Description | Doripenem |
|---|---|
| Inclusion or exclusion criteria not met | 7/250 (2.8%) |
| Urine culture not obtained at EOT (IV) and negative urine culture not documented prior to EOT(IV) | 1/250 (0.4%) |
| Clinical assessment not performed at EOT (IV) | 3/250 (1.2%) |
| TOC urine culture obtained outside the protocol specified 6-9 day post therapy window form patients who were not prior microbiological failures | 15/250 (5.6%) |
| TOC clinical assessment performed outside of the protocol specified 6-9 days post therapy window on patients who were not prior clinical failures | 14/250 (5.6%) |
| Patients switched to oral therapy before meeting the final protocol criteria to switch to oral therapy | 13/250 (5.2%) |
| Patients who did not receive 2 days of IV therapy after bladder instrumentation or treatment for an obstruction | 6/250 (2.4%) |

Note: Percentages are based on the number of patients who are ME at TOC.
Data were taken from Applicant's Table 15.1.1.4-2, found on page163-164 of the CSR.

### 6.1.4.4 Concomitant Antibacterial Medications

Concomitant antibacterials in the ME at TOC analysis set were allowed per study protocol for treatment of evaluable failures. In addition, patients were allowed to resume the use of concomitant antibiotics for UTI prophylaxis after the TOC visit.

In the ITT analysis set, 27% received at least 1 concomitant antibacterial medication. Approximately 17% of patients in both the ME at TOC and CE at TOC analysis sets received at least 1 concomitant antibacterial medication.

The most common concomitant antibacterial medications used by patients in the ITT, ME at TOC, and the CE at TOC analysis sets were the quinolones, mostly ciprofloxacin. Quinolones were used by 13% of the patients in the ITT analysis set and approximately 6% of the patients in both the ME and CE at TOC analysis sets. Quinolones were prescribed mainly for the treatment of urinary tract infections.

### 6.1.4.5 Reasons for Exclusion from Efficacy Analysis

Table 6 shows the reasons listed by the Applicant for the exclusion from efficacy analysis for the various populations in the study. The data were taken from Table 9, found on pages 68-69 of the CSR.

Table 6. Reasons for Exclusion from Efficacy Analysis.

| | Doripenem (N = 426)[a] | Levofloxacin (n = 376)[a] |
|---|---|---|
| Patients included in the ITT patient sample | 423 (99.3%) | 372 (98.9%) |
| MITT_1 Sample | | |
| MITT_1 Evaluable | 337 (79.1%) | 321 (85.4%) |
| Not MITT_1 Evaluable | 89 (20.9%) | 55 (14.6%) |
| Reasons Not MITT_1 Evaluable[b] | | |
| No Study-Qualifying Baseline Urine Culture | 89 (20.9%) | 50 (13.3%) |
| No Study Drug Administered | 3 (0.7%) | 4 (1.1%) |
| Other[c] | 0 | 1 (0.3%) |
| MITT_2 Sample | | |
| MITT_2 Evaluable | 327 (76.8%) | 300 (79.8%) |
| Not MITT_2 Evaluable | 99 (23.2%) | 76 (20.2%) |
| Reasons Not MITT_2 Evaluable[b] | | |
| Not MITT_1 | 89 (20.9%) | 55 (14.6%) |
| Missing Interpretable Post Study Therapy Urine Culture | 99 (23.2%) | 75 (19.9%) |
| Microbiologically Evaluable at TOC Sample | | |
| ME at TOC Evaluable | 250 (58.7%) | 265 (70.5%) |
| Not ME at TOC Evaluable | 176 (41.3%) | 111 (29.5%) |
| Reasons Not ME at TOC Evaluable[b] | | |
| No Study-Qualifying Baseline Urine Culture | 89 (20.9%) | 50 (13.3%) |
| Clinical Disease Definition Not Met | 3 (0.7%) | 4 (1.1%) |
| Significant Inclusion/Exclusion Criteria Violation | 8 (1.9%) | 10 (2.7%) |
| Not Compliant with Study Drug Therapy | 31 (7.3%) | 32 (8.5%) |
| TOC Window Violation or Missing Interpretable TOC Urine Culture | 62(14.6%) | 43 (11.4%) |
| Prior Antibiotic Violation | 0 | 0 |
| Confounding Concomitant Antibiotic | 8 (1.9%) | 6 (1.6%) |
| Confounding Event or Procedure | 0 | 0 |
| Microbiologically Evaluable at LFU Sample | | |
| ME at LFU Evaluable | 177 (41.5%) | 207 (55.1%) |
| Not ME at LFU Evaluable | 249 (58.5%) | 169 (44.9%) |
| Reasons Not ME at LFU Evaluable[b] | | |
| Evaluable failure at TOC[d] | 41 (9.6%) | 44 (11.7%) |
| Not ME at TOC | 176 (41.3%) | 111 (29.5%) |
| LFU Window Violation or Missing Interpretable LFU Urine Culture | 50 (11.7%) | 43 (11.4%) |
| Confounding Concomitant Antibiotic After TOC | 28 (6.6%) | 7 (1.9%) |
| Confounding Event or Procedure After TOC | 0 | 0 |
| Clinically Evaluable at TOC Sample | | |
| CE at TOC Evaluable | 257 (60.3%) | 266 (70.7%) |
| Not CE at TOC Evaluable | 169 (39.7%) | 110 (29.3%) |
| Reasons Not CE at TOC Evaluable[b] | | |
| No Study-Qualifying Baseline Urine Culture | 89 (20.9%) | 50 (13.3%) |
| Clinical Disease Definition Not Met | 3 (0.7%) | 4 (1.1%) |
| Asymptomatic cLUTI at Baseline | 18 (4.2%) | 15 (4.0%) |
| Significant Inclusion/Exclusion Criteria Violation | 8 (1.9%) | 10 (2.7%) |
| Not Compliant with Study Drug Therapy | 31 (7.3%) | 32 (8.5%) |
| TOC Window Violation or Missing TOC Clinical Assessment | 125 (29.3%) | 82 (21.8%) |
| Prior Antibiotic Violation | 0 | 0 |
| Confounding Concomitant Antibiotic | 7 (1.6%) | 7 (1.9%) |
| Confounding Event or Procedure | 0 | 0 |
| Clinically Evaluable at LFU Sample | | |
| CE at LFU Evaluable | 202 (47.4%) | 229 (60.9%) |
| Not CE at LFU Evaluable | 224 (52.6%) | 147 (39.1%) |
| Reasons Not CE at LFU Evaluable[b] | | |
| Evaluable failure at TOC | 23 (5.4%) | 30 (8.0%) |
| Not CE at TOC | 169 (39.7%) | 110 (29.3%) |
| LFU Window Violation or Missing LFU Clinical Assessment | 93 (21.8%) | 78 (20.7%) |
| Confounding Concomitant Antibiotic After TOC | 27 (6.3%) | 5 (1.3%) |
| Confounding Event or Procedure After TOC | 0 | 0 |

CE = clinically evaluable; cLUTI = complicated urinary tract infection; ITT = intent-to-treat; IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable; MITT_1 = microbiological intent-to-treat definition 1; MITT_2 = microbiological intent-to-treat definition 2; TOC = test-of-cure; n = number of patients who had a favorable clinical response at that time point in that analysis set.:

[a] Percentages were based on the number of patients randomized to each treatment group.

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

[c] Patient 101/07003 was randomized twice to the study and the second patient id is 101/07163. This patient is considered not evaluable for MITT_1 for the second randomization.

[d] At LFU, the outcomes of interest are the sustained eradication of baseline pathogens and the sustained clinical cure. Therefore, evaluable microbiological failures at TOC and evaluable clinical failures at TOC are not included in the corresponding summaries at LFU. For completeness in this table, the number of such evaluable failures at TOC is also given.

### 6.1.4.6 Drug Exposure

The following table shows the extent of exposure for the patients in DORI-06 and the levofloxacin arm of DORI-05. The data were taken from Table 9, found on pages 34-35 of Module 2.7.3 – Summary of Clinical Efficacy, Complicated UTI.

Table 7. Drug Exposure for the Microbiologically Evaluable at TOC Populations in DORI-06 and the levofloxacin arm of DORI-05.

| **Total Duration, days** | **Doripenem IV 500 mg 1-h inf q8h (N = 250** | **Levofloxacin IV 250 mg 1-h q24h (N = 265)** |
|---|---|---|
| IV or IV and Oral Therapy | | |
| N | 250 | 265 |
| Category, n (%) | | |
| 4 – 7 | 0 | 18 (6.8) |
| 8 – 10 | 156 (62.4) | 185 (69.8) |
| 11-14 | 90 (36.0) | 60 (22.6) |
| > 14 | 4 (1.6) | 2 (0.8) |
| Mean (SD) | 10.5 (0.96) | 10.0 (1.51) |
| Median | 10.0 | 10.0 |
| Range | (9, 16) | (4, 15) |
| IV Therapy | | |
| N | 250 | 265 |
| Category, n (%) | | |
| <4 | 17 (6.8) | 3 (1.1) |
| 4 - 7 | 170 (68.0) | 217 (81.9) |
| 8 - 10 | 14 (5.6) | 15 (5.7) |
| 11 - 14 | 48 (19.2) | 30 (11.3) |
| > 14 | 1 (0.4) | 0 |
| Mean (SD) | 6.0 (2.88) | 5.7 (2.31) |
| Median | 5.0 | 5.0 |
| Range | (3, 15) | (3, 11) |
| Duration in Subgroup of Subjects Who Received IV Therapy Only | | |
| N | 54 | 48 |
| Category, n (%) | | |
| ≤5 | 0 | 10 (20.8) |
| 6 - 7 | 0 | 8 (16.7) |
| >7 | 54 (100) | 30 (62.5) |
| Mean (SD) | 11.1 (0.76) | 8.9 (2.86) |
| Median | 11.0 | 11.0 |
| Range | (10, 15) | (4, 11) |

| Total Duration, days | Doripenem IV 500 mg 1-h inf q8h (N = 250 | Levofloxacin IV 250 mg 1-h q24h (N = 265) |
|---|---|---|
| IV and Oral Therapy in Subjects Who Were Switched to Oral Therapy | | |
| N | 196 | 217 |
| Category, n (%) | | |
| 8 - 10 | 151 (77.0) | 185 (85.3) |
| 11 - 14 | 42 (21.4) | 30 (13.8) |
| > 14 | 3 (1.5) | 2 (0.9) |
| Mean (SD) | 10.3 (0.95) | 10.2 (0.82) |
| Median | 10.0 | 10.0 |
| Range | (9, 16) | (8, 15) |
| IV Therapy in Subjects Who Were Switched to Oral Therapy | | |
| N | 196 | 217 |
| Category, n (%) | | |
| <4 | 17 (8.7) | 3 (1.4) |
| 4 - 7 | 170 (86.7) | 199 (91.7) |
| 8 - 10 | 9 (4.6) | 15 (6.9) |
| Mean (SD) | 4.6 (1.22) | 5.0 (1.40) |
| Median | 4.0 | 4.0 |
| Range | (3, 10) | (3, 10) |
| Oral Therapy | | |
| N | 196 | 217 |
| Category, n (%) | | |
| <4 | 9 (4.6) | 15 (6.9) |
| 4 - 7 | 177 (90.3) | 195 (89.9) |
| 8 – 10 | 8 (4.1) | 6 (2.8) |
| 11 - 14 | 2 (1.0) | 1 (0.5) |
| Mean (SD) | 6.5 (1.37) | 6.1 (1.49) |
| Median | 7.0 | 7.0 |
| Range | (1, 12) | (1, 11) |
| IV and Oral Therapy in the Subgroup of Subjects Who Were Bacteremic at Baseline | | |
| N | | |
| Category, n (%) | 27 | 23 |
| 8 - 10 | | |
| 11 - 14 | 12 (44.4) | 11 (47.8) |
| > 14 | 11 (40.7) | 10 (43.5) |
| Mean (SD) | 4 (14.8) | 2 (8.7) |
| Median | 11.8 (2.14) | 11.5 (1.88) |
| Range | 11.0 | 11.0 |
| | (9, 16) | (10, 15) |

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

### 6.1.4.7 Efficacy

Primary Endpoints: The co-primary efficacy endpoints in this study are eradication rate for the baseline uropathogens at the Test-of-Cure visit (6 to 9 days after the end of study drug therapy) in the ME at TOC and mMITT_1 populations. One of the secondary endpoints is the clinical cure rate for the clinically evaluable patients at the TOC visit, (CE at TOC population). The following table shows the per-patient microbiological cure rates and the per-patient clinical cure rates at the TOC for the Microbiologically Modified Intent-to-Treat_1 group, the ME at TOC population, and the CE at TOC population. The data were taken from Table 12 and Table 14, respectively, found on pages 81 and 83 of the CSR.

Table 8. The Per-Patient Microbiological and Clinical Cure Rates at the TOC visit for the ME at TOC Population, the MMITT_1 Population, and the CE at TOC Population.

| Analysis Set | Doripenem (DORI-06) | Levofloxacin (DORI-05) | Difference (2-sided 95% CI) |
|---|---|---|---|
| **ME at TOC** | 209/250 (83.6%) | 221/265 (83.4%) | 0.2% (-6.6%, 7.0%) |
| **mMITT_1** | 278/337 (82.5%) | 251/321 (78.2%) | 4.3% (-2.1%, 10.7%) |
| **CE at TOC** | 239/257 (93.0%) | 240/266 (90.2%) | 2.8% (-2.4%, 7.9%) |

In the DORI-06 doripenem treatment arm, the microbiological cure rate was 83.6% (209/250), while the cure rate in the DORI-05 levofloxacin arm was 83.4% (221/265). The treatment difference between the microbiological cure rates was 0.2%, with a 2-sided 95% CI of -6.6% to 7.0%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

With regard to the mMITT analysis set, the microbiological cure rate is higher among the DORI-06 patients who received doripenem compared to those in the DORI-05 levofloxacin arm. The microbiological cure rate was 82.5% (278/337) for doripenem and 78.2% (251/321) for levofloxacin. Again, the treatment difference between the two cure rates showed non-inferiority with a difference of 4.3% with a 2-sided 95% CI of -2.1% to 10.7%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

Secondary Endpoints:
Clinical cure in the CE at TOC population: The clinical cure rates at the TOC visit were greater for the DORI-06 doripenem treatment arm than the DORI-05 levofloxacin arm for patients in the CE at TOC population, 93.0% (239/257) for doripenem and 90.2% (240/266) for levofloxacin. The treatment difference between the two groups was 2.8% with a 2-sided 95% CI of -2.4% to 7.9%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

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

**Clinical Reviewer's Comments:** *The Applicant included 40 JMP datasets in the submission that contained information concerning all aspects of the DORI- 06 study. The keval.xpt dataset was searched by the reviewer in order to confirm the results in Table 8. All of the numbers in the table were obtained by selecting for the number of cures, failures, and indeterminate results,*

*along with unevaluable patients, that were associated with the patients in the TRTA [Actual Treatment Group] variable group. The search confirmed the numbers presented in the table.*

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

The following data were taken from Applicant's Table 15, found on page 87 of the CSR.

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

| | **Doripenem (DORI-06) (N=280)** | **Levofloxacin (DORI-05) (N=265)** | **Difference (2-sided 95% CI)** |
|---|---|---|---|
| Overall | 209/250 (83.6%) | 221/265 (83.4%) | 0.2% (-6.6%, 7.0%) |
| By Subgroup | | | |
| cLUTI (All) | 97/132 (73.5%) | 99/131 (75.6%) | -2.1% |
| Symptomatic | 94/128 (73.4%) | 94/122 (77.0%) | -3.6% |
| Asymptomatic | 3/4 (75.0%) | 5/9 (55.6%) | 19.4% |
| Persistent Complication (Males and some Females) | 88/122 (72.1%) | 84/116 (72.4%) | -0.3% |
| Eliminated Complication (Some females only) | 9/10 (90%) | 15/15 (100.0%) | -10.0% |
| Pyelonephritis (All) | | | |
| Uncomplicated | 112/118 (94.9%) | 122/134 (91.0%) | 3.9% |
| Complicated (All) | 95/99 (96.0%) | 97/107 (90.7%) | 5.3% |
| Persistent Complication (Males and some Females) | 17/19 (89.5%) | 25/27 (92.6%) | -3.1% |
| Eliminated Complication (Some females only) | 16/18 (88.9%) | 21/23 (91.3%) | -2.4% |
| | 1/1 (100.0%) | 4/4 (100.0%) | 0.0% |
| Bacteremic at Baseline | 26/27 (96.3%) | 22/23 (95.7%) | 0.6% |
| Sex | | | |
| Males | 84/112 (75.0%) | 82/103 (79.6%) | -4.6% |
| Females | 125/138 (90.6%) | 139/162 (85.8%) | 4.8% |
| Race | | | |
| American Indian or Alaska Native | 1/1 (100.0%) | 2/2 (100.0%) | 0.0% |
| Asian | 1/1 (100.0%) | 0/0 | |
| Black or African Heritage | 39/45 (86.7%) | 18/24 (75.0%) | 11.7% |
| Caucasian | 99/120 (82.5%) | 178/209 (85.2%) | -2.7%) |
| Native Hawaiian, Other Pacific Islander | 0/0 | 0/0 | |
| Hispanic or Latino | 56/60 (93.3%) | 21/27 (77.8%) | 15.6% |
| Other | 13/23 (56.5%) | 2/3 (66.7%) | -10.1% |
| Age | | | |
| <65 | 149/171 87.1%) | 147/170 (86.5%) | 0.7% |
| ≥65 | 60/79 (75.9%) | 74/95 (77.9%) | -1.9% |
| <75 | 182/213 (85.4%) | 191/224 (85.3%) | 0.2% |
| ≥75 | 27/37 (73.0%) | 30/41 (73.2%) | -0.2% |
| Region | | | |
| North America | 52/53 (98.1%) | 15/16 (93.8%) | 4.3% |
| South America | 156/196 (79.6%) | 101/121 (83.5%) | -3.9% |
| Europe | 1/1 (100.0%) | 105/128 (82.0%) | 18.0% |

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

The overall microbiological cure rate was similar between the DORI-06 doripenem arm and the DORI-05 levofloxacin patients (84% and 83%, respectively). The difference between the cure

rates was 0.2%, with a 2-sided 95% CI of -6.6% to 7.0%. The microbiological cure rates were similar between the doripenem and levofloxacin patients for the subgroups cLUTI (73.5% for doripenem, 75.6% for levofloxacin), pyelonephritis (94.9% for doripenem and 91% for levofloxacin), and bacteremic patients at baseline (96.3% for doripenem and 95.7% for levofloxacin. Patients who had documented bacteremia with the same pathogen isolated in the blood as in the urine were allowed to have the dose of levofloxacin increased to 500 mg q24h. Seventy percent (19/27) of the bacteremic patients in the doripenem treatment arm who were ME at TOC had at least 1 dose of oral levofloxacin increased to 500 mg, and 61% (14/23) of the bacteremic patients who were ME at TOC in the levofloxacin treatment arm had at least 1 dose of either IV or oral levofloxacin increased.

The microbiological cure rates by sex, race, age, and region in the ME at TOC population were similar or better in patients treated with doripenem in DORI-06 compared to patients treated with levofloxacin in DORI-05.

### 6.1.4.9 Sensitivity Analyses on the Primary Endpoint

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

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

| | **Doripenem (DORI-06)** | **Levofloxacin (DORI-05)** | **Difference (2-sided 95% CI)[a]** |
|---|---|---|---|
| **ME at TOC Analysis Set** | | | |
| Original | 102/119 (85.7%) | 122/149 (81.9%) | 3.8% (-5.7%, 13.4%) |
| Subsequent[b] | 107/131 (81.7%) | 99/116 (85.3%) | -3.7% (-13.7%, 6.4%) |
| Final | 209/250 (83.6%) | 221/265 (83.4%) | 0.2% (-6.6%, 7.0%) |
| **mMITT Analysis Set** | | | |
| Original | 141/167 (84.4%) | 142/188 (75.5%) | 8.9% (0.1%, 17.7%) |
| Subsequent[b] | 137/170 (80.6%) | 109/133 (82.0%) | -1.4% (-10.9%, 8.1%) |
| Final | 278/337 (82.5%) | 251/321 (78.2%) | 4.3% (-2.1%, 10.7%) |

Microbiology cure rates in the co-primary analysis sets are presented in Table 10 for the patients in the 3 sample size groups: original population, subsequent population, and final population. In the sensitivity analyses, the 2-sided 95% CIs for the difference between the cure rate (doripenem

minus levofloxacin) from the MEF at TOC and mMITT analysis sets were (-5.7%, 7.4%) and (-1.8%, 10.8%), respectively, where the 2-sided 95%CI was computed using normal approximation to the difference between 2 binomial proportions with adjustment using a continuity-adjusted CMH-type method. The sensitivity analyses indicated that the results of the primary efficacy analyses were robust to disease type. A more detailed description of the statistical methodology used for the sensitivity analyses is described in Appendix 16.1.9, section 7.3.1 of the Statistical Analysis Plan (SAP).

When compared to the original population, cure rates in the subsequent population were higher in the levofloxacin arm and lower in the doripenem arm. Given the higher percentage of patients in the doripenem arm of the subsequent population compared to the levofloxacin arm who had a baseline diagnosis of cLUTI, addition of the subsequent population did not favor the doripenem arm in the final analysis in the ME at TOC and mMITT analysis sets. In general, the differences in microbiological cure rates between the treatment arms for patients within the original population were similar to those of patients in the final population in the ME at TOC and mMITT analysis sets. Consistent with the results from the final population, the results from the original population also demonstrated that doripenem was non-inferior in efficacy to levofloxacin (from DORI-05) in the treatment of cUTI for the pre-defined non-inferiority margin of -0.10.

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

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

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

| **ME at TOC Analysis Set** | |
|---|---|
| Subjects With Concomitant Antibiotics before/on TOC date | 13/16 (81.3%) |
| Subjects with Concomitant Antibiotics taken after TOC date | 17/31 (54.8%) |
| Subjects Without Any Concomitant Antibiotics | 179/203 (88.2%) |
| Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics | 196/234 (83.8%) |
| Overall | 209/250 (83.6%) |

| mMITT_1 Analysis Set | |
|---|---|
| Subjects With Concomitant Antibiotics before/on TOC date | 23/26 (88.5%) |
| Subjects with Concomitant Antibiotics taken after TOC date | 29/50 (58.0%) |
| Subjects Without Any Concomitant Antibiotics | 226/261 (86.6%) |
| Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics | 255/311 (82.0%) |
| Overall | 278/337 (82.5%) |

There were 16 patients who received concomitant antibiotic medications prior to the TOC visit, with 13 of them listed as cures. When these 16 patients are removed from the analysis set, the cure rate (83.8%) is very similar to the overall cure rate with them included (83.6%). Thus, the presence or absence of these patients has no significant effect on the cure rate.

The results for the mMITT_1 analysis set are similar for the 26 patients who received concomitant antibiotics prior to the TOC visit. The overall cure rate decreases by 0.5%, 82.0% versus 82.5%.

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

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

| | **Doripenem** |
|---|---|
| Study Dori-06<br>ME at TOC Analysis Set | |
| Subjects With Concomitant Antibiotics before/on TOC Date Treated As Failure | 196/250 (78.4%) |
| mMITT Analysis Set | |
| Subjects With Concomitant Antibiotics before/on TOC Date Treated As Failure | 255/337 (75.7%) |

When the 13 patients who received concomitant antibiotics prior to the TOC visit are treated as failures, the cure rate for the ME at TOC population decreases from 83.6% (209/250) to 78.4% (196/250). When the change is made to the mMITT analysis set, the cure rate drops from 82.5% (278/337) to 75.7% (255/337).

Table 13. Revised Table Resulting from the FDA Sensitivity Analysis. Patients who received concomitant antibiotics prior to the TOC visit and were considered cures at the TOC visit.

| **Patient Number** | **Baseline pathogen** | **Concomitant medication** | **Condition treated** |
|---|---|---|---|
| 350-0094 | *Escherichia coli* | Metronidazole | Vaginal flux |
| 355-0171 | *Escherichia coli* | Metronidazole | Vaginal trichomoniasis |
| 453-0047 | *Klebsiella pneumoniae* | Levofloxacin | UTI |
| 453-0379 | *Escherichia coli* | Nitrofurantoin | UTI prophylaxis |
| 454-0263 | *Escherichia coli* | Amoxicin<br>Bactrim | Sinusitis<br>UTI |
| 454-0422 | *Pseudomonas aeruginosa* | Nitrofurantoin | Prophylaxis UTI |
| 455-0182 | *Klebsiella oxytoca* | Mysteclin | Candidiasis |
| 455-0299 | *Escherichia coli* | Metronidazole | Worsening of intestinal constipation |
| 455-0411 | *Pseudomonas aeruginosa* | Nitrofurantoin | ITU prophylaxis |
| 633-0096 | *Escherichia coli* | Vancomycin | Bacteremia |
| 633-0108 | *Providencia rettgeri* | Levofloxacin<br>Vancomycin | Fever<br>R/O occult cell bacteremia |
| 633-0210 | *Escherichia coli* | Metronidazole | Empiric treatment coutis (C. difficile) |
| 641-0341 | *Escherichia coli* | Antibiotics | UTI |

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

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

Table 14. Statistical Reviewer's Sensitivity Analysis Results for Study DORI-06 With a TOC Window at 6 to 9 Days After Administration of the Last Dose of Study Drug.

| | **Doripenem** |
|---|---|
| ME at TOC Analysis Set | 229/272 (84.2%) |
| mMITT_1 Analysis Set | 197/236 (83.5%) |

**Clinical Reviewer's Comments:** *The analysis by Dr. Deng shows an increase in the success rate for both the ME at TOC and mMITT_1 populations when the window at the TOC visit is expanded. The cure rate for the ME at TOC analysis set increases from 83.6% (209/250) to 84.2% (229/272), while the cure rate for the mMITT_1 analysis set increases from 82.5% (278/337) to 83.5% (197/236).*

### 6.1.5 Clinical Microbiology

The following table shows the eradication rates for the baseline uropathogens isolated from the doripenem patients in Study DORI-06 compared to the baseline uropathogens isolated from the levofloxacin patients in DORI-05. Confidence intervals are shown for those groups of pathogens containing 30 or more isolates.

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

| | **Doripenem (DORI-06) Patients (N = 250)** | **Levofloxacin DORI-05) Patients (N = 265)** | **Difference (2-sided 95% CI)** |
|---|---|---|---|
| **Baseline Uropathogens** | **(N = 253 F/NI (%)** | **(N = 266) F/NI (%)** | |
| Gram Positive | | | |
| *Staphylococcus aureus* | 5/5 (100.0%) | 0/1 | 100% |
| MSSA | 1/1 (100.0%) | | |
| MRSA | 4/4 (100.0%) | 0/1(0.0) | 100% |
| *Enterococcus faecalis* | 3/5 (60.0%) | 1/3 (33.3%) | 26.7% |
| *Enterococcus faecium* | 0/1 (0.0%) | 0/0 | |
| | | | |
| Gram Negative | | | |
| Enterobacteriaceae | 184/215 (85.6%) | 217/254 (85.4%) | 0.1 (-6.7, 7.0) |
| *Citrobacter freundii* | 0/0 | 3/4 (75%) | |
| *Enterobacter aerogenes* | 0/0 | 2/2 | |
| *Enterobacter cloacae* | 11/21 (52.4%) | 3/7 (42.9%) | 9.5 (-42.4, 61.5) |
| *Enterobacter hormaechei* | 1/1 (100%) | 0/0 | |
| *Escherichia coli* | 145/158 (91.8%) | 184/211 (87.2%) | 4.6 (-2.2, 11.3) |
| Levofloxacin-resistant strains | 15/23 (65.2%) | 6/21 (28.6%) | 36.6 (4.7, 68.6) |
| Levofloxacin-susceptible strains | 122/127 (96.1%) | 173/185 (93.5%) | 2.5 (-3.0, 8.1) |
| ESBL-producing strains | 5/8 (62.5%) | 1/3 (33.3%) | 29.2% |
| Non-ESBL-producing strains | 132/142 (93%) | 178/203 (87.7%) | 5.3 (-1.5, 12.0) |
| | | | |
| *Klebsiella oxytoca* | 3/3 (100%) | 4/4 (100%) | 0 |
| *Klebsiella pneumoniae* | 16/20 (80%) | 5/8 (62.5%) | 17.5 (-29.1, 64.1) |
| ESBL-producing strains | 3/6 (50%) | 0/0 | |
| Non-ESBL-producing strains | 10/11 (90.9%) | 5/7 (71.4%) | 19.5 (-29.7, 68.7) |
| *Morganella morganii* | 1/1 (100%) | 1/1 (100%) | 0.0 |
| *Proteus mirabilis* | 6/7 (85.7%) | 13/15 (86.7%) | -1.0 |
| *Proteus penneri* | 0/0 | 1/1 (100%) | |
| *Providencia alcalifaciens* | 0/1 (0.0%) | 0/0 | |
| *Providencia rettgeri* | 1/1 (100%) | 0/0 | |
| *Serratia marcescens* | 0/2 (0.0%) | 1/1 (100%) | -100% |
| | | | |
| *Non-fermenters* | | | |
| *Acinetobacter baumannii* | 5/7 (71.4%) | 0/1 | 71.4% |
| *Pseudomonas aeruginosa* | 14/18 (77.8%) | 5/7 (71.4%) | 6.3 (-42.2, 54.9) |
| *Pseudomonas species* | 0/1 (0/0%) | 0/0 | |

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

There were 253 organisms isolated at baseline from the 250 patients in the DORI-06 doripenem arm of the study compared to 266 organisms isolated from the DORI-05 levofloxacin arm. Three of the doripenem patients had two pathogens present at the screening visit, while only one of the DORI-05 levofloxacin patients had two pathogens present.

The overall eradication rates for members of the Enterobacteriacae were 85.6% (184/215) for the doripenem group and 85.4% (217/254) for the levofloxacin group for the ME at TOC population. The treatment difference was 0.1% with a 2-sided 95% CI of -6.7% to 7.0%. The most common pathogen isolated among patients in both treatment arms was *E. coli* , with 158 isolates from the DORI-06 doripenem arm and 211 from the DORI-05 levofloxacin arm. The eradication rate was 91.8% in the doripenem group and 87.2% in the levofloxacin group, with a treatment difference of 4.6% and a 2-sided 95% CI of -2.2% to 11.3%. Among the 23 levofloxacin-resistant *E. coli* in the doripenem group, 15 were eradicated for a cure rate of 65.2%. In the levofloxacin group, only 6 of the 21 levofloxacin-resistant *E. coli* were eradicated for a cure rate of 28.6%.

Doripenem was effective in eradicating *Klebsiella pneumoniae* with a cure rate of 80% (16/20), compared to a cure rate of 62.5% (5/8) for levofloxacin. Doripenem and levofloxacin were similar in eradicating *Proteus mirabilis* with a cure rate of 85.7% and 86.7%, respectively.

Among non-fermenters, 5 of 7 isolates of *A. baumannii* and 14 of 18 isolates of *P. aeruginosa* were eradicated.

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

*The data show doripenem to be effective in eradicating Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa with eradication rates of 91.8%, 80%, 85.7%, and 77.8%, respectively. The other organisms are either too few in number or have much lower eradication rates. Both the number of E. coli resistant to levofloxacin and the eradication rates are too small to make any conclusions regarding the effect of doripenem on these strains.*

**FDA Review of Microbiological Datasets.**

As a result of the sensitivity analysis of the microbiological datasets performed by Dr. Yunfan Deng, the table showing the microbiological outcome was revised to include the results of her analysis. In both arms of the study, pathogens from patients who received antibiotics prior to the TOC were now included as failures. The results are shown in the following table.

Table 16. Revised Table Resulting from the FDA Sensitivity Analysis. The Per-Pathogen Microbiological Outcome (Eradication) for Baseline Pathogens at the TOC Visit for the ME at the TOC Population.

| | **Doripenem (DORI-06) Patients (N = 250)** | **Levofloxacin DORI-05) Patients (N = 265)** | **Difference (2-sided 95% CI)** |
|---|---|---|---|
| **Baseline Uropathogens** | **(N = 253 F/NI (%)** | **(N = 266) F/NI (%)** | |
| Gram Positive | | | |
| *Staphylococcus aureus* | 5/5 (100.0%) | 0/1 | 100% |
| MSSA | 1/1 (100.0%) | | |
| MRSA | 4/4 (100.0%) | 0/1(0.0) | 100% |
| *Enterococcus faecalis* | 3/5 (60.0%) | 0/3 | 60% |
| *Enterococcus faecium* | 0/1 (0.0%) | 0/0 | |
| | | | |
| Gram Negative | | | |
| Enterobacteriaceae | 173/215 (80.5%) | 211/254 83.1%) | -2.6 (-9.6%, 4.4%) |
| *Citrobacter freundii* | 0/0 | 3/4 (75%) | |
| *Enterobacter aerogenes* | 0/0 | 2/2 | 9.5 (-42.4, 61.5) |
| *Enterobacter cloacae* | 11/21 (52.4%) | 3/7 (42.9%) | |
| *Enterobacter hormaechei* | 1/1 (100%) | 0/0 | |
| *Escherichia coli* | 137/158 (86.7%) | 178/211 (84.3%) | 2.4 (-4.9, 9.6) |
| Levofloxacin-resistant strains | 14/23 (60.9%) | 5/21 (23.8%) | 37.1 (10.0, 64.1) |
| Levofloxacin-susceptible strains | 115/127 (90.6%) | 168/185 (90.8%) | -0.2 (-6.8, 6.3) |
| ESBL-producing strains | 4/8 (50.0%) | 1/3 (33.3%) | 16.7 |
| Non-ESBL-producing strains | 125/142 (88%) | 172/203 (84.7%) | 3.3 (-4.0, 10.6) |
| | | | |
| *Klebsiella oxytoca* | 2/3 (66.7%) | 4/4 (100%) | 33.3 |
| *Klebsiella pneumoniae* | 15/20 (75%) | 5/8 (62.5%) | 12.5 |
| ESBL-producing strains | 2/6 (33.3%) | 0/0 | 33.3 |
| Non-ESBL-producing strains | 10/11 (90.9%) | 5/7 (71.4%) | 19.5 (-29.7, 68.7) |
| *Morganella morganii* | 1/1 (100%) | 1/1 (100%) | 0.0 |
| *Proteus mirabilis* | 6/7 (85.7%) | 13/15 (86.7%) | -1.0 |
| *Proteus penneri* | 0/0 | 1/1 (100%) | |
| *Providencia alcalifaciens* | 0/1 (0.0%) | 0/0 | |
| *Providencia rettgeri* | 0/1 (0.0%) | 0/0 | |
| *Serratia marcescens* | 0/2 (0.0%) | 1/1 (100%) | -100% |
| | | | |
| *Non-fermenters* | | | |
| *Acinetobacter baumannii* | 5/7 (71.4%) | 0/1 | 71.4% |
| *Pseudomonas aeruginosa* | 12/18 (66.7%) | 5/7 (71.4%) | -4.7 |
| *Pseudomonas species* | 0/1 (0/0%) | 0/0 | |
| *Proteus penneri* | 0/0 | 1/1 (100%) | |
| *Providencia alcalifaciens* | 0/1 (0.0%) | 0/0 | |
| *Providencia rettgeri* | 0/1 (0.0%) | 0/0 | |

**Clinical Reviewer's Comments:** *The inclusion of Dr. Deng's data resulted in lower eradication rates for 5 species.. E. coli was the principal pathogen most affected in both treatment arms. The eradication rate for this organism dropped in the doripenem arm from 91.8% to 86.7%, while the cure rate for E. coli from the levofloxacin arm changed from 87.2% to 84.3%.*

### 6.1.5.1 Baseline Uropathogen Susceptibility

Table 17 shows the susceptibility characteristics for the uropathogens isolated at baseline from the ME at TOC population in DORI-06 are compared to the uropathogens isolated from the levofloxacin arm in DORI-05. The data were extracted from Applicant's Table 15.1.2.2-3, found on pages 215-216 of the CSR.

Among the 250 doripenem patients in Study DORI-06, there were three who had two different pathogens each at the screening visit for a total of 253 isolates. Only one levofloxacin patient in DORI-05 had two different pathogens for a total of 266 isolates.

In the doripenem group, there were three gram positive organisms resistant to doripenem, one strain of *Enterococcus faecium* and two isolates of *Staphylococcus aureus*. Among the gram negative organisms, there were two strains of *Pseudomonas aeruginosa* (12.5%) resistant to doripenem. There were 34 pathogens among the levofloxacin patients that were resistant to levofloxacin. One was a *Staphylococcus aureus,* while the others were all Gram negative organisms. Twenty-three strains of *E. coli* were resistant to levofloxacin in the DORI-06 doripenem group and 21 similar strains were present in the levofloxacin arm.

Among the ME at TOC populations, there were 27 in the DORI-06 doripenem arm and 23 in the levofloxacin arm from DORI-05 who were bacteremic at baseline. *E. coli* was the most common pathogen isolated from bacteremic patients with 22 found in the DORI-06 doripenem arm and 20 in the DORI-05 levofloxacin arm. None of them was resistant to either doripenem or levofloxacin.

Table 17. Baseline Uropathogen Susceptibility Characteristics.

| Baseline Uropathogen | Doripenem IV Patients (N = 250) | | | | Levofloxacin IV Patients (N = 265) | | | |
|---|---|---|---|---|---|---|---|---|
| | NI [1] | NT [1] | Susceptible or Intermediate | Resistant [2] | NI [1] | NT [1] | Susceptible or Intermediate | Resistant [3] |
| Gram Positive | 11 | 11 | 8 | 3 | 4 | 4 | 3 | 1 |
| Enterococcus faecalis | 5 | 5 | 5 (100%) | 0 | 3 | 3 | 3 (100%) | 0 |
| Enterococcus faecium | 1 | 1 | 0 | 1(100%) | 0 | 0 | 0 | 0 |
| Staphylococcus aureus | 5 | 5 | 3 (60%) | 2 (40%) | 1 | 1 | 0 | 1 (100%) |
| Gram Negative | 242 | 226 | 224 | 2 | 262 | 255 | 222 | 33 |
| Acinetobacter baumannii | 7 | 7 | 7 (100%) | 0 | 1 | 1 | 1 (100%) | 0 |
| Citrobacter freundii | 0 | 0 | 0 | 0 | 4 | 3 | 2 (66.7%) | 1 (33.3%) |
| Enterobacter aerogenes | 0 | 0 | 0 | 0 | 2 | 2 | 2 (100%) | 0 |
| Enterobacter cloacae | 21 | 21 | 21 (100%) | 0 | 7 | 7 | 3 (42.9%) | 4 (57.1%) |
| Enterobacter hormaechei | 1 | 1 | 1 (100%) | 0 | 0 | 0 | 0 | 0 |
| Escherichia coli | 158 | 150 | 150 (100%) | 0 | 211 | 206 | 185 (89.8%) | 21 (10.2%) |
| Levofloxacin-resistant strains [4] | 23 | 23 | 23 (100%) | 0 | 21 | 21 | 0 | 21 (100%) |
| Klebsiella oxytoca | 3 | 3 | 3 (100%) | 0 | 4 | 4 | 4 (100%) | 0 |
| Klebsiella pneumoniae | 21 | 17 | 17 (100%) | 0 | 8 | 7 | 6 (85.7) | 1 (14.3%) |
| Morganella morganii | 1 | 1 | 1 (100%) | 0 | 1 | 1 | 1 (100%) | 0 |
| Proteus mirabilis | 7 | 7 | 7 (100%) | 0 | 15 | 15 | 13 (86.7%) | 2 (13.3%) |
| Proteus penneri | 0 | 0 | 0 | 0 | 1 | 1 | 1 (100%) | 0 |
| Providencia alcalifaciens | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Providencia rettgeri | 1 | 1 | 1 (100%) | 0 | 0 | 0 | 0 | 0 |
| Pseudomonas aeruginosa | 18 | 16 | 14 (87.5%) | 2 (12.5%) | 7 | 7 | 3 (42.9%) | 4 (57.1%) |
| Pseudomonas species | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Serratia marcescens | 2 | 2 | 2 (100%) | 0 | 1 | 1 | 1 (100%) | 0 |

Notes:
[1] NI is the number of pathogens isolated. NT is the number of pathogens in which an interpretation of susceptibility results was available. Within each patient, a pathogen is uniquely represented using the most resistant strain. Percentages are given with respect to the NT for the given genus and species in the respective study arm.
[2] For doripenem IV, pathogens are considered susceptible (S), intermediate (I) or resistant (R) if the MIC level is ≤ 4 μg/mL, = 8 μg/mL or ≥ 16 μg/mL, respectively.

[3] For levofloxacin IV, susceptible, intermediate or resistant is defined according to the CLSI recommendations.
[4] Escherichia coli; Drug tested = levofloxacin; Test Method = MIC Micro Broth Dilution testing; Result Value = ≥ 8, Result unit = mg/mL.

Table 18. Baseline Blood Pathogen Susceptibility for pathogens isolated in both urine and blood for the ME at TOC population.

| **Baseline Uropathogen** | **Doripenem IV (N = 20)** | | | | **Levofloxacin IV (N = 23)** | | | |
|---|---|---|---|---|---|---|---|---|
| | NI [1] | NT [1] | Susceptible or Intermediate | Resistant [2] | NI [1] | NT [1] | Susceptible or Intermediate | Resistant [3] |
| Gram Negative | 27 | 25 | 25 | 0 | 23 | 19 | 19 | 0 |
| Enterobacter cloacae | 1 | 1 | 1(100%) | 0 | 0 | 0 | 0 | 0 |
| Escherichia coli | 22 | 20 | 20 (100%) | 0 | 20 | 16 | 16 (100%) | 0 |
| Levofloxacin-resistant strains [4] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Klebsiella oxytoca | 2 | 2 | 2 (100%) | 0 | 0 | 0 | 0 | 0 |
| Klebsiella pneumoniae | 1 | 1 | 1 (100%) | 0 | 2 | 2 | 2 (100%) | 0 |
| Proteus mirabilis | 0 | 0 | 0 | 0 | 1 | 1 | 1 (100%) | 0 |
| Providencia rettgeri | 1 | 1 | 1 (100%) | 0 | 0 | 0 | 0 | 0 |

Notes: Data were taken from Applicant's Table 15.1.2.3-1, page 220 of CSR.
[1] NI is the number of pathogens isolated. NT is the number of pathogens in which an interpretation of susceptibility results was available. Within each patient, a pathogen is uniquely represented using the most resistant strain. Percentages are given with respect to the NT for the given genus and species in the respective study arm.
[2] For doripenem IV, pathogens are considered susceptible (S), intermediate (I) or resistant (R) if the MIC level is ≤ 4 μg/mL, = 8 μg/mL or ≥ 16 μg/mL, respectively.
[3] For levofloxacin IV, susceptible, intermediate or resistant is defined according to the CLSI recommendations.
[4] Escherichia coli; Drug tested = levofloxacin; Test Method = MIC Micro Broth Dilution testing; Result Value = ≥ 8, Result unit = mg/mL.

Table 19 Per Patient Microbiological and Clinical Outcome at LFU for the DORI-06 patients.

| Outcome at LFU | Doripenem IV |
|---|---|
| Sustained Eradication [1 | 154/177 (87.0%) |
| Sustained Clinical Cure [2] | 180/202 (89.1%) |

[1] For sustained eradication, percentages are based on the total number of patients in the treatment arm that are ME at LFU and had eradication of baseline uropathogens at TOC.
[2 For the sustained clinical cure, percentages are based on the number of patients in the treatment arm that are CE at LFU and were classified as clinically cured at TOC.

The data in Table 19 were taken from Table 15.2.3.1-2, found on page 464 of the CSR.

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

**FDA Review of Random Sampling of Case Report Forms from Study DORI- 06.**

The Division requested that the Applicant submit a 10 % random sample of the doripenem case report forms (CRFs) from study DORI-06. The CRFs were reviewed for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of the protocol, and accuracy in reporting of results. The results were then compared to those of the Applicant. Forty-three CRFs were examined.

During the review, there was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer for 41 of the 43 CRFs. However, there were some discrepancies present for two of the CRFs. These discrepancies are summarized in the following list:

| Patient Number | Comments |
|---|---|
| 453-0340 Doripenem | The Applicant has this patient listed as a clinical cure and a microbiological failure at the Test-of-Cure visit after receiving 10 days of IV doripenem therapy. However, the patient had positive urine cultures with the baseline uropathogen (*Enterobacter cloacae* at $\geq 10^5$ CFU/mL) at the TOC and LFU visits, along with signs/symptoms of dysuria and frequency. He was given ciprofloxacin prior to the TOC visit and should be considered both a clinical and microbiological failure. |
| 453-0377 Doripenem | This patient is listed as a microbiological and clinical cure at the TOC visit and a relapse at the LFU visit by the Applicant. The patient received 6 doses of IV doripenem (250 mg q12h) followed by 6 doses of levofloxacin (250 mg q24h). He received the wrong dose of doripenem due to an incorrect creatinine clearance value and he received less than 8 doses of doripenem as required by the protocol. He had clinical signs/'symptoms at the EOT, TOC, and LFU visits. He should be considered unevaluable for efficacy assessment. |

### 6.1.6 Efficacy Conclusions

DORI-06 was an international, multi-center, Phase 3, prospective, open-label study involving 423 patients with complicated urinary tract infections or pyelonephritis enrolled by 30 centers. The study was designed to provide independent confirmation of the response rate for doripenem observed in the double-blind, levofloxacin-controlled study in cUTI (DORI-05). Thus, the levofloxacin treatment arm in DORI-05 was compared with the doripenem treatmenta arm in DORI-06 to assess the comparability of efficacy, demographics and baseline characteristics, inclusion/exclusion criteria, and patient evaluability criteria. Doripenem was to be considered non-inferior to levofloxacin if the lower limit of the 95% CI for the difference between treatment arms (doripenem minus levofloxacin) in the per-patient microbiological cure rate at the TOC visit was greater than or equal to -10%

In the DORI-06 doripenem-treatment arm, the microbiological cure rate was 83.6% (209/250), while the cure rate in the DORI-05 levofloxacin-treatment arm was 83.4% (221/265). The treatment difference between the microbiological cure rates was 0.2%, with a 2-sided 95% CI of -6.6% to 7.0%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

The microbiological cure rate in the mMITT_1 analysis set was higher among the DORI-06 patients compared to those in the DORI-05 levofloxacin-treatment arm. The microbiological cure rate was 82.5% (278/337) for doripenem and 78.2% (251/321) for levofloxacin. The treatment difference between the two cure rates showed non-inferiority with a difference of 4.3% and a 2-sided 95% CI of -2.1% to 10.7%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

The clinical cure rates at the TOC visit were greater for the DORI-06 doripenem-treatment arm than the DORI-05 levofloxacin arm for patients in the CE at TOC population, 93.0% (239/257) for doripenem and 90.2% (240/266) for levofloxacin. The treatment difference between the two groups was 2.8% and a 2-sided 95% CI of -2.4% to 7.9%. Non-inferiority was demonstrated as the lower bound of the 95% CI around the difference in the cure rates was greater than the pre-specified non-inferiority margin of -10% and the CI interval includes the value 0.

Doripenem was microbiologically effective against the major causative pathogens of cUTI as shown by the high eradication rates of major causative pathogens including *E. coli (91.8%), K. pneumoniae (80%), P. mirabilis (85.7%),* and *P. aeruginosa (77.8%).*

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

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

The safety analysis set in Study DORI-06 includes all patients in the Intent-to-Treat (ITT) population who received at least one dose of study drug. Of the 426 enrolled patients, there were 423 who received study drug therapy.

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

Adverse events included any side effect, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death (whether or not it was considered study drug related) that occurred during a patient's study participation. Adverse events were to be reported by the patient or the investigator from the time of the first study related procedure through the last study visit (28 to 42 days after the final dose of study drug).

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

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

### 7.1.1 Deaths

There were four deaths among the doripenem treated patients in this study. All of the deaths appeared to be unrelated to the therapy with doripenem.

One patient died before starting study drug therapy and three died after receiving at least one dose of doripenem. All treatment emergent adverse events leading to death were single events; respiratory failure, ventricular arrhythmia, and bladder neoplasm. No relationship between the number of days of study drug therapy and dates of death was observed.

Patient 452/00201 died of sepsis before receiving any study drug therapy.

Patient 350/00079 was a 73-year-old man with a history of anemia, general muscular atrophy, anxiety, and chronic pulmonary disease. He developed acute respiratory failure approximately 6 days after completing study drug therapy (Day 17). On Day 26 he experienced a cardiac arrest and expired the following day.

Patient 450/00084 was treated for 7 days with study drug. He developed a ventricular arrhythmia and died on Day 7.

Patient 455/00330 expired due to a bladder tumor that eventually metastasized on Day 45. He died 10 days later.

**Clinical Reviewer's Comment:** *Please see Dr. Sorbello's review for more details concerning these patients.*

### 7.1.2 Other Serious Adverse Events

The following table shows the serious adverse events that occurred for the ITT analysis set. The data were taken from Applicant's Table 28, found on page 108 of the CSR.

Table 20. Serious Adverse Events Among The ITT Population.

| **System Organ Class**<br>**Preferred Term** | **Doripenem**<br>**(N=423)** |
|---|---|
| Number of Patients with at least 1 treatment-emergent serious adverse event | 39 (9.2%) |
| Blood and lymphatic system disorders | 1 (0.2%) |
| Anemia | 1 (0.2%) |
| Cardiac disorders | 5 (1.2%) |
| Angina unstable | 1 (0.2%) |
| Atrial fibrillation | 1 (0.2%) |
| Atrial flutter | 1 (0.2%) |
| Myocarditis | 1 (0.2%) |
| Ventricular arrhythmia | 1 (0.2%) |
| Gastrointestinal disorders | 2 (0.5%) |
| Constipation | 1 (0.2%) |
| Gastrointestinal hemorrhage | 1 (0.2%) |
| General disorders and administration site Conditions | 1 (0.2%) |
| Pyrexia | 1 (0.2%) |
| Infections and infestations | 12 (2.8%) |
| Abscess limb | 1 (0.2%) |
| Arthritis infective | 1 (0.2%) |
| Lobar pneumonia | 1 (0.2%) |
| Pelvic abscess | 1 (0.2%) |
| Pneumonia | 2 (0.5%) |
| Pyelonephritis acute | 1 (0.2%) |
| Renal abscess | 1 (0.2%) |
| Urinary tract infection | 6 (1.4%) |
| System Organ Class<br>Preferred Term | Doripenem<br>(N=423) |
| Injury, poisoning and procedural complications | 1 (0.2%) |
| Pneumonitis chemical | 1 (0.2%) |
| System Organ Class<br>Preferred Term | Doripenem<br>(N=423) |
| Metabolism and nutrition disorders | 1 (0.2%) |
| Hyperglycemia | 1 (0.2%) |

| System Organ Class<br>Preferred Term | Doripenem<br>(N=423) |
|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.5%) |
| Bladder cancer | 1 (0.2%) |
| Bladder neoplasm | 1 (0.2%) |
| Nervous system disorders | 3 (0.7%) |
| Cerebral infarction | 1 (0.2%) |
| Cerebrovascular accident | 1 (0.2%) |
| Syncope | 1 (0.2%) |
| Renal and urinary disorders | 7 (1.7%) |
| Hematuria | 1 (0.2%) |
| Nephrolithiasis | 2 (0.5%) |
| Renal failure acute | 2 (0.5%) |
| Renal impairment | 1 (0.2%) |
| Renal insufficiency | 1 (0.2%) |
| Reproductive system and breast disorders | 1 (0.2%) |
| Benign prostatic hyperplasia | 1 (0.2%) |
| Respiratory, thoracic and mediastinal disorders | 3 (0.7%) |
| Pleural effusion | 1 (0.2%) |
| Pneumonia aspiration | 1 (0.2%) |
| Respiratory failure | 1 (0.2%) |
| Surgical and medical procedures | 1 (0.2%) |
| Prostatectomy | 1 (0.2%) |
| Vascular disorders | 4 (0.9%) |
| Deep vein thrombosis | 2 (0.5%) |
| Hypotension | 1 (0.2%) |
| Hypovolemic shock | 1 (0.2%) |

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

There were 39 (9%) patients in DORI-06 that reported at least one serious adverse event. Three events were judged possible related to study drug therapy: atrial flutter (Patient #450/00303) and atrial fibrillation and renal impairment (Patient # 630/00035).

All treatment emergent serious adverse events were reported by less than 1% of all patients in the ITT analysis set, except urinary tract infection, which was reported by 6 (1.4%) patients.

The most commonly reported serious adverse event was urinary tract infection, reported by 6 (1.4%) patients followed by deep vein thrombosis, nephrolithiasis, pneumonia, and acute renal failure, each reported by 2 (0.5%) patients.

Twelve patients reported serious adverse events that had an onset during IV study drug administration. These included atrial flutter, ventricular arrhythmia, constipation, pelvic abscess, renal abscess, chemical pneumonitis, cerebrovascular accident, renal insufficiency, benign prostatic hyperplasia, aspiration pneumonia, prostatectomy, and deep vein thrombosis. Each event occurred only once.

### 7.1.3 Dropouts and Other Significant Adverse Events

FDA Review of Case Report Forms of Discontinued Patients from Study DORI-06.

In its submission, the Applicant was required to include CRFs for patients who discontinued the study due to death, serious adverse events, or adverse events causing discontinuation. A total of 46 CRFs were submitted from Study DORI-06.

The CRFs were reviewed, along with individual patient narratives describing each patient's medical history. Of interest was any type of pattern of adverse events possibly associated with either study drug. The adverse events of most interest were renal failure, recurrent UTIs, and pyelonephritis. Among the 46 discontinued doripenem patients there were 9 with the following adverse events: pyelonephritis (1), recurrent UTIs (6), and renal failure (2).

During the review, there was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer for 42 of the 46 CRFs. There were discrepancies present for 4 of the CRFs involving the same issue, i.e., were these events related to study drug therapy.

**Clinical Reviewer's Comments:** *Four patients [#359/0350; #450/0030; #453/0140 and #453/0424] had UTIs or pyelonephritis due to a uropathogen ($\geq 10^5$ CFU/mL) at the screening visits. Two of the patients had Klebsiella pneumoniae, one had Proteus mirabilis, and the fourth had Enterobacter saskazaki as baseline pathogens. All were treated with doripenem and completed the study. All of them received additional antibiotics during the study. Each of them had positive urine cultures ($\geq 10^5$ CFU/mL) due to their baseline pathogen at the TOC visit and were listed as microbiological failures. Two were listed as evaluable clinical cures at TOC, one was listed as a clinical failure, and the fourth patient was listed as not evaluable for efficacy assessment (asymptomatic patient). The Applicant has the four patients listed as being discontinued due to serious adverse events, recurrent UTIs and pyelonephritis. Since the patients had those conditions at study drug entry, they should not be considered as adverse events possibly associated with doripenem therapy. If there was an adverse event that occurred it should be "lack of efficacy" because the baseline pathogen was never truly eradicated.*

### 7.1.3.1 Overall profile of dropouts

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

| Site number/ Patient number | Age/Sex | Preferred Term | Day of Adverse Event Onset | Outcome | Duration (Days) | Relationship to Study Drug Therapy | Total Days of Study Drug Therapy |
|---|---|---|---|---|---|---|---|
| Doripenem | | | | | | | |
| 357/00366[a] | 81/F | Renal insufficiency | 11 | resolved | 17 | unrelated | 11 |
| 450/00303 | 69/F | Atrial flutter | 2 | resolved | 2 | possibly related | 3 |
| 453/00288 | 65/M | Pneumonia | 9 | resolved | 9 | unrelated | 9 |
| 455/00183 | 26/F | Pleural effusion | 8 | resolved | 9 | Unlikely to be related | 8 |
| 630/00035 | 71/F | Atrial fibrillation<br>Renal impairment<br>Hepatic enzyme increased | 3<br>3<br>9 | Resolved<br>Resolved<br>resolved | 155<br>12<br>5 | possibly related<br>possibly related<br>probably related | 20<br>20<br>20 |
| 640/00308 | 23/F | Pneumonitis chemical | 3 | Resolved | 3 | Unrelated | 3 |
| 640/00322 | 55/M | Prostatitis | 7 | ongoing | | Unrelated | 8 |

[a] Patients ME at TOC

Patient 641/00293, a 30 year-old female had a nonserious adverse event of pruritus that started on Day 1 and resolved on Day 32. 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.
Data were taken from Applicant's Table 25, found on page 103 of the CSR.

### 7.1.3.2 Adverse events associated with dropouts

Eight patients were discontinued from study drug therapy because of a treatment emergent adverse event. Two patients discontinued because of adverse events considered related to study drug therapy. No patients discontinued from study drug therapy due to the same treatment emergent adverse event.

### 7.1.3.3 Other significant adverse events

Headache was the only adverse event reported by more than 10% of patients; this occurred in 19% of the DORI-06 patients. Phlebitis was reported in 39 (9.2%) patients.

In addition to headache and phlebitis, the next most frequently reported treatment emergent adverse events were within the gastrointestinal (GI) and infections and infestations system organ classes. Vomiting, nausea and diarrhea occurred in 8%, 8% and 6% of the patients, respectively, and asymptomatic bacteriuria and urinary tract infection each were reported as adverse events in 7% of the patients. Insomnia occurred in 6% of patients.

No seizures were reported during the study.

### 7.1.4 Other Search Strategies

Not applicable to this study.

### 7.1.5 Common Adverse Events

All safety results were reported in the ITT analysis set. At each level of patient summarization, a patient was counted only once if the patient reported 1 or more events. Patients were included in the treatment arm according to the study drug therapy received, not the study drug therapy to which they were randomly assigned. The following table shows an overview of the treatment-emergent adverse events, serious adverse events, adverse events leading to study drug therapy discontinuation, and adverse events leading to death that occurred in both treatment arms. The data were taken from Applicant's Table 22, found on page 98 of the CSR.

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

| **Category**[a] | **Doripenem (N=423)** |
|---|---|
| Number (%) of patients with at least 1 adverse event[b] | 324 (76.6%) |
| Number (%) of patients with at least 1 related adverse event | 124 (29.3%) |
| Patients with at least 1 treatment-emergent serious adverse event | 39 (9.2%) |
| Treatment-emergent serious adverse events related to study drug (including possibly or probably related) | 2 (0.5%) |
| Study drug therapy discontinuations due to adverse events[c] | |
| Number (%) patients who discontinued IV therapy due to Nonfatal Adverse Events | 4 (0.9%) |
| Number (%) patients who discontinued IV therapy due to Death | 1 (0.2%) |
| Number (%) patients who discontinued oral therapy due to Nonfatal Adverse Events | 3 (0.7%) |
| Number (%) patients who discontinued oral therapy due to Death | 0 |
| Number (%) patients with treatment emergent adverse events leading to death | 3[c] |

N=number of patients in the analysis set.
[a] Patients could have been included in more than 1 category.
[b] All adverse events summarized were treatment-emergent adverse events.
[c] One patient was enrolled in the study but died before receiving study drug. This patient was included in the "All Enrolled Patients" analysis set but was excluded from the ITT analysis set.

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

The protocol for Study DORI-06 called for a change in therapy from an intravenous dose of doripenem to an oral dose of levofloxacin provided that the following conditions occurred: After ≥ 9 doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever (<37.8 °C oral) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least 1 urine culture had been reported with no growth at 24 hours or growth with a colony count of < $10^4$ CFU/mL and no subsequent cultures with a colony count of ≥ $10^4$ CFU/mL were observed. Therefore, it is important to review what adverse events occurred during the IV part of therapy and what adverse event occurred during the oral part.

Table 23 shows the adverse events related to study drug that emerged during IV study drug therapy. The data were taken from Applicant's Table 15.3.1.2-4, found on pages 517-520 of the CSR.

Overall, 108 (25.5%) of 423 patients experienced a study drug-related adverse event with onset during IV study drug therapy. Diarrhea and headache were the most common treatment-emergent adverse events related to study drug that occurred during IV study drug therapy. Diarrhea occurred in 2.4% and headache occurred in 7.6% of the study patients, respectively.

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

| **System Organ Class**<br>**Preferred Term** | **Doripenem IV**<br>**(N = 423)** |
|---|---|
| Number of patients with at least one related adverse event | 108 (25.5%) |
| Cardiac disorders | 2 (0.5%) |
| Arrhythmia | 1 (0.2%) |
| Atrial flutter | 1 (0.2%) |
| Gastrointestinal disorders | 30 (7.1%) |
| Abdominal distension | 2 (0.5%) |
| Abdominal pain | 2 (0.5%) |
| Abdominal pain upper | 1 (0.2%) |
| Constipation | 1 (0.2%) |
| Diarrhea | 10 (2.4%) |
| Dry mouth | 1 (0.2%) |
| Dyspepsia | 1 (0.2%) |
| Frequent bowel movements | 1 (0.2%) |
| Gastritis | 1 (0.2%) |
| Nausea | 6 (1.4%) |
| Palatal disorder | 1 (0.2%) |
| Tongue ulceration | 1 (0.2%) |
| Vomiting | 9 (2.1%) |
| General disorders and administration site conditions | 2 (0.5%) |
| Infusion site burning | 1 (0.2%) |
| Venipuncture site pain | 1 (0.2%) |
| Hepatobiliary disorders | 4 (0.9%) |
| Hepatitis cholestatic | 1 (0.2%) |
| Hepatitis toxic | 2 (0.5%) |
| Liver disorder | 1 (0.2%) |
| Immune system disorders | 1 (0.2%) |
| Hypersensitivity | 1 (0.2%) |
| Infections and infestations | 3 (0.7%) |
| Genital infection fungal | 1 (0.2%) |
| Vaginitis | 2 (0.5%) |
| Investigations | 5 (1.2%)0 |
| Blood creatine phosphokinase increased | 1 (0.2%) |
| Blood creatinine increased | 2 (0.5%) |
| Blood lactate dehydrogenase increased | 1 (0.2%) |
| Blood uric acid increased | 1 (0.2%) |
| Gamma-glutamyltransferase increased | 1 (0.2%) |
| Hepatic enzyme increased | 2 (0.5%) |

| System Organ Class<br>Preferred Term | Doripenem IV<br>(N = 423) |
|---|---|
| Metabolism and nutrition disorders | 5 (1.2%) |
| Decreased appetite | 1 (0.2%) |
| Hypercholesterolemia | 1 (0.2%) |
| Hypoglycemia | 2 (0.5%) |
| Hypokalemia | 1 (0.2%) |
| Nervous system disorders | 40 (9.5%) |
| Dizziness | 5 (1.2%) |
| Dysgeusia | 3 (0.7%) |
| Headache | 32 (7.6%) |
| Tremor | 1 (0.2%) |
| Psychiatric disorders | 2 (0.5%) |
| Anxiety | 1 (0.2%) |
| Insomnia | 1 (0.2%) |
| Renal and urinary disorders | 1 (0.2%) |
| Renal failure acute | 1 (0.2%) |
| Reproductive system and breast disorders | 1 (0.2%) |
| Genital pruritus female | 1 (0.2%) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.2%) |
| Dyspnoea | 1 (0.2%) |
| Throat irritation | 1 (0.2%) |
| Skin and subcutaneous tissue disorders | 14 (3.3%) |
| Hyperhidrosis | 3 (3.3%) |
| Pruritus | 5 (1.2%) |
| Pruritus generalised | 1 (0.2%) |
| Rash | 2 (0.5%) |
| Rash popular | 3 (0.7%) |
| Swelling face | 1 (0.2%) |
| Vascular disorders | 33 (7.8%) |
| Flushing | 1 (0.2%) |
| Hematoma | 1 (0.2%) |
| Hypertension | 1 (0.2%) |
| Phlebitis | 32 (7.6%) |

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

Table 24 shows the serious adverse events that occurred during the IV phase of the study. The data were taken from Applicant's Table 15.3.1.4-3, found on pages 548 – 549 of the CSR.

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

| System Organ Class<br>Preferred Term | Doripenem IV<br>(N =423) |
|---|---|
| Number of patients with at least one treatment emergent serious adverse event | 12 (2.8%) |
| Cardiac disorders | 2 (0.5%) |
| Atrial flutter | 1 (0.2%) |
| Ventricular arrhythmia | 1 (0.2%) |
| Gastrointestinal disorders | 1 (0.2%) |
| Constipation | 1 (0.2%) |
| Infections and infestations | 2 (0.5%) |
| Pelvic abscess | 1 (0.2%) |
| Renal abscess | 1 (0.2%) |
| Injury, poisoning and procedural complications | 1 (0.2%) |
| Pneumonitis chemical | 1 (0.2%) |
| Nervous system disorders | 1 (0.2%) |
| Cerebrovascular accident | 1 (0.2%) |
| Renal and urinary disorders | 1 (0.2%) |
| Renal insufficiency | 1 (0.2%) |
| Reproductive system and breast disorders | 1 (0.2%) |
| Benign prostatic hyperplasia | 1 (0.2%) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.2%) |
| Pneumonia aspiration | 1 (0.2%) |
| Surgical and medical procedures | 1 (0.2%) |
| Prostatectomy | 1 (0.2%) |
| Vascular disorders | 1 (0.2%) |
| Deep vein thrombosis | 1 (0.2%) |

Note: At each level of patient summarization, a patient is counted once if the patient reported one or more events. Treatment emergent adverse events are defined as adverse events with onset dates on or after the date of start of infusion of the first dose of study medication and within 30 days after administration of the last dose of study medication. Adverse event terms are coded using MedDRA version 7.0.

### 7.1.6 Less Common adverse Events

A total of 324 (77%) patients in DORI-06 experienced a treatment emergent adverse event during the study. Eighty patients (19%) reported headache, 34 (8.0%) reported vomiting, and 33 (&.8%) developed diarrhea while taking the study drug.

Rates of asymptomatic bacteriuria (7%) and urinary tract infection (7%) were recorded as treatment emergent adverse events, but are more comprehensively accounted for as efficacy outcomes. Rates of asymptomatic bacteriuria reflect the number of patients who were symptomatically cured but continued to have bacteria in their urine, 93% clinical cure rate in the CE at TOC analysis set and 84% microbiological cure rate in the ME at TOC analysis set.

Table 25. Treatment Emergent Adverse Events Occurring in at Least 2% of Patients by System Organ Class and Preferred Term (ITT Analysis Set).

| **System Organ Class**<br>**Preferred Term** | **Doripenem**<br>**(N=423)**<br>**N (%)** |
|---|---|
| Number of patients with at least one treatment emergent adverse event | 324 (76.6) |
| Blood and lymphatic system disorders | 17 (4.0) |
| Anemia | 17 (4.0) |
| Gastrointestinal disorders | 114 (27.0) |
| Vomiting | 34 (8.0) |
| Nausea | 33 (7.8) |
| Diarrhea | 27 (6.4) |
| Constipation | 17 (4.0) |
| Abdominal pain | 13 (3.1) |
| Abdominal pain upper | 13 (3.1) |
| Flatulence | 10 (2.4) |
| General disorders and administration site conditions | 50 (11.8) |
| Pyrexia | 21 (5.0) |
| Odema peripheral | 16 (3.8) |
| Suprapubic pain | 11 (2.6) |
| Infections and infestations | 102 (24.1) |
| Asymptomatic bacteruria | 30 (7.1) |
| Urinary tract infection | 28 (6.6) |
| Metabolism and nutrition disorders | 40 (9.5) |
| Hypokalemia | 11 (2.6) |
| Hypoglycemia | 9 (2.1) |
| Musculoskeletal and connective tissue disorders | 32 (7.6) |
| Back pain | 13 (3.1) |
| Pain in extremity | 9 (2.1) |
| Nervous system disorders | 103 (24.3) |
| Headache | 80 (18.9) |
| Dizziness | 19 (4.5) |
| Psychiatric disorders | 38 (9.0) |
| Insomnia | 24 (5.7) |
| Respiratory, thoracic and mediastinal disorders | 39 (9.2) |
| Dyspnea | 11 (2.6) |
| Cough | 9 (2.1) |
| Skin and subcutaneous tissue disorders | 41 (9.7) |
| Pruritus | 9 (2.1) |
| Rash | 9 (2.1) |
| Vascular disorders | 68 (16.1) |
| Phlebitis | 39 (9.2) |
| Hypotension | 11 (2.6) |
| Hypertension | 10 (2.4) |

Note: At each level of patient summarization, a patient is counted once if the patient reported one or more events. Treatment emergent adverse events are defined as adverse events with onset dates on or after the date of the start of infusion of the first dose of the study medication and within 30 days after the administration of the last dose of the study medication. AE terms are coded using MedDRA version 7.0.
Data were taken from Applicant's Table 23, found on pages 99-100 of the CSR.

### 7.1.6.1 Additional analyses and explorations

Adverse events of special interest in this study included adverse events that were possible allergic reactions and indications of study drug therapy intolerability. All adverse events that, in the opinion of the investigator, represented either possible allergic reactions to IV study drug

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

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

### 7.1.7 Laboratory Findings

Clinical Laboratory Tests

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

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

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

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

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

Laboratory Test Abnormalities Reported as Adverse Events

Investigators were asked to report as adverse events only laboratory abnormalities that had clinical manifestations or required medical intervention. Where possible, syndromes, rather than individual laboratory values, were to have been reported. For example, jaundice associated with

elevated hepatic transaminases was reported as "hepatitis," and decreased hemoglobin and hematocrit requiring iron supplementation was recorded as "anemia." These adverse events were listed and identified using adverse events assigned to MedDRA system organ class (SOC) of "Investigations."

Pregnancy Tests

All women of childbearing potential were required to continue to use birth control throughout the study and for at least 30 days after administration of the last dose of study drug therapy (IV and oral). In addition, all women of childbearing potential had a negative urine or serum pregnancy test confirmed at screening, prior to enrolling into the study. If a urine pregnancy test was used at the time of screening, blood was obtained at the time of screening for serum β-human chorionic gonadotropin testing also, and negative serum pregnancy test results were confirmed as soon as possible and within 72 hours of study entry. Serum pregnancy testing was also performed on all women of childbearing potential at the TOC visit. For women who withdrew from study drug therapy administration early, serum pregnancy testing was performed when these patients returned for the LFU visit. All positive pregnancy test results were reported to the Applicant's Medical Monitor within 24 h ours of the site's knowledge of the positive results, and all pregnancies were followed to outcome.

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

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

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

### 7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 *Analyses focused on measures of central tendency*

Hematology

Mean and mean changes from baseline to the end of IV therapy in hematology parameters are summarized in the following table. The data were taken from Applicant's table 29, found on pages 113-114of the CSR.

Table 26 Changes from Baseline to End of IV Therapy in Hematology Parameters (ITT Analysis Set).

| | Doripenem (N= 423) | |
|---|---|---|
| **Parameter** | **n** | **Mean (SD)** |
| Basophils (%) | | |
| Baseline | 377 | 0.209 (0.3021) |
| Change from Baseline | 284 | 0.060 (0.3004) |
| Basophils, ABS (x $10^9$/L) | | |
| Baseline | 369 | 0.019 (0.0311) |
| Change from Baseline | 282 | 0.001 (0.0329) |
| Eosinophils (%) | | |
| Baseline | 377 | 1.867 (2.9599) |
| Change from Baseline | 284 | 2.154 (2.4957) |
| Eosinophils ABS (x $10^9$/L) | | |
| Baseline | 369 | 0.167 (0.2853) |
| Change from Baseline | 282 | 0.138 (0.2016) |
| Hematocrit (V/V) | | |
| Baseline | 385 | 0.3852 (0.05027) |
| Change from Baseline | 294 | -0.0055 (0.03559) |
| Hemoglobin (g/L) | | |
| Baseline | 392 | 126.0 (16.86) |
| Change from Baseline | 311 | -2.6 (10.52) |
| Lymphocytes (%) | | |
| Baseline | 377 | 17.654 (9.8537) |
| Change from Baseline | 284 | 11.045 (11.6367) |
| Lymphocytes ABS (x $10^9$/L) | | |
| Baseline | 369 | 1.684 (0.7522) |
| Change from Baseline | 282 | 0.310 (0.6960) |
| MCH (pg/cell) | | |
| Baseline | 392 | 29.47 (2.345) |
| Change from Baseline | 311 | -0.18 (1.193) |
| MCHC (ghb/L) | | |
| Baseline | 385 | 327.5 (18.27) |
| Change from Baseline | 294 | -1.4 (17.12) |
| MCV (fL) | | |
| Baseline | 385 | 89045 ( ) |
| Change from Baseline | 294 | -0.01 (2.978 |
| Monocytes (%) | | |
| Baseline | 377 | 7.134 (2.7571) |
| Change from Baseline | 24 | 0.735 (3.2504) |
| Monocytes, ABS (x $10^9$/L) | | |
| Baseline | 369 | 0.778 (0.4343) |
| Change from Baseline | 282 | -0.217 (0.4115) |
| Neutrophils (%) | | |
| Baseline | 370 | 71.479 (11.4612) |
| Change from Baseline | 283 | -12.647 (14.0770) |
| Neutrophils + Bands (%) | | |
| Baseline | 370 | 72.894 (12.0580) |
| Change from Baseline | 283 | -13.933 (13.8104) |
| Neutrophils, ABS (x $10^9$/L) | | |
| Baseline | 369 | 8.227 (4.3332) |
| Change from Baseline | 282 | -3.743 (4.4910) |
| Platelet Count (x $10^9$/L) | | |
| Baseline | 381 | 256.5 (94.02) |
| Change from Baseline | 286 | 37.2 (93.20) |
| RBC (x $10^{12}$/L) | | |
| Baseline | 384 | 4.289 (0.5808) |
| Change from Baseline | 309 | -0.064 (0.3764) |
| WBC (x $10^9$/L) | | |
| Baseline | 383 | 11.205 (4.7833) |
| Change from Baseline | 296 | -3.856 (4.8081) |

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

There were no unusual mean changes in hematology parameters from baseline to Study Day 3 and to the end of IV therapy, TOC, and LFU visits.

There were decreases seen in mean WBC counts from baseline, which was due to patients recovering from an infection,

Decreases from baseline were seen in hemoglobin and hemacrit among hospitalized patients who had phlebotomy and surgical procedures,

Small and clinically insignificant increases from baseline in mean platelet count were seen.

**Clinical Reviewer's Comments:** *Approximately 76% of doripenem patients experienced some change in the hematology parameters from baseline. This rate was lower than that seen in the DORI-05 study.*

Serum Chemistry

Mean and mean changes from baseline to the end of IV therapy in serum chemistry parameters are summarized in the following table. The data were taken from Applicant's Table 30, found on pages 115-116 of the CSR.

Table 27. Changes from Baseline to End of IV Therapy in Serum Chemistry Parameters (ITT Analysis Set).

| | Doripenem (N=423) | |
|---|---|---|
| **Parameter** | **n** | **Mean (SD)** |
| Albumin (g/L) | | |
| Baseline | 399 | 39.1 (5.36) |
| Change from Baseline | 321 | -1.9 (3.82) |
| Alkaline Phosphatase (IU/L) | | |
| Baseline | 398 | 178.807 (105.5121) |
| Change from Baseline | 321 | 28.380 (98.8287) |
| ALT (SGPT) (IU/L) | | |
| Baseline | 398 | 23.997 (19.9289) |
| Change from Baseline | 320 | 13.366 (37.0948) |
| AST (SGOT) (IU/L) | | |
| Baseline | 398 | 23.178 (14.5088) |
| Change from Baseline | 320 | 8.213 (43.1849) |
| Bicarbonate (mmol/L) | | |
| Baseline | 378 | 24.4061 (3.56036) |
| Change from Baseline | 295 | 0.9424 (3.35107) |
| BUN (mmol/L) | | |
| Baseline | 374 | 9.2334 (6.51660) |
| Change from Baseline | 299 | -1.6379 (3.96161) |

| | Doripenem (N= 423) | |
|---|---|---|
| **Parameter** | **n** | **Mean (SD)** |
| Calcium (mmol/L) | | |
| Baseline | 398 | 2.2653 (0.16669) |
| Change from Baseline | 321 | 0.16266) |
| Chloride (mmol/L) | | |
| Baseline | 398 | 102.7337 (4.80023) |
| Change from Baseline | 321 | 1.4081 (4.40438) |
| Cholesterol (mmol/L) | | |
| Baseline | 399 | 4.1230 (1.16211) |
| Change from Baseline | 321 | 0.0800 (0.82602) |
| CPK, Total (IU/L) | | |
| Baseline | 399 | 113.066 (238.9485) |
| Change from Baseline | 321 | -29.991 (232.9995) |
| Creatinine (μmol/L) | | |
| Baseline | 399 | 88.44 (41.202) |
| Change from Baseline | 321 | -12.64 (32.445) |
| GGT (IU/L) | | |
| Baseline | 399 | 49.185 (69.8516) |
| Change from Baseline | 321 | 18.037 (61.6201) |
| Indirect Bilirubin (μmol/L) | | |
| Baseline | 392 | 7.44 (6.065) |
| Change from Baseline | 309 | -2.48 (5.676) |
| LDH (IU/L) | | |
| Baseline | 398 | 286.804 (112.3728) |
| Change from Baseline | 318 | 10.673 (85.4257) |
| Magnesium (mmol/L) | | |
| Baseline | 399 | 0.8632 (0.13805) |
| Change from Baseline | 322 | 0.0177 (0.11278) |
| Non-fasting Glucose (mmol/L) | | |
| Baseline | 397 | 6.60 (2.879) |
| Change from Baseline | 318 | -0.51 (2.214) |
| Phosphorus (mmol/L) | | |
| Baseline | 399 | 1.0923 (0.24510) |
| Change from Baseline | 321 | 0.0794 (0.29298) |
| Potassium (mmol/L) | | |
| Baseline | 397 | 4.10 (0.552) |
| Change from Baseline | 318 | 0.16 (0.567) |
| Sodium (mmol/L) | | |
| Baseline | 398 | 138.7324 (4.12639) |
| Change from Baseline | 321 | 1.3053 (3.54704) |
| Total Bilirubin (μmol/L) | | |
| Baseline | 398 | 10.76 (8.09) |
| Change from Baseline | 321 | -3.66 (7.655) |
| Total Protein (g/L) | | |
| Baseline | 399 | 70.9 (7.66) |
| Change from Baseline | 322 | -1.3 (7.26) |
| Uric Acid (mmol/L) | | |
| Baseline | 399 | 0.2917 (0.10974) |
| Change from Baseline | 322 | -0.0285 (0.06624) |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma-glutamyltransferase; LDH = lactic dehydrogenase; N = number of patients in the analysis set; n = number of patients whose laboratory values were not missing for both the corresponding post-baseline visit and the baseline visit; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase.

No unusual mean changes in serum chemistry parameters from baseline to Study Day 3 and to the end of IV therapy, TOC, and LFU visits were observed.

**Clinical Reviewer's Comments:** *Approximately 80% of doripenem patients experienced some change in the serum chemistry parameters from baseline. This rate was lower than that seen in the DORI-05 study.*

Individual Patient Changes

- Overall, 20 patients had laboratory abnormalities reported as adverse events by the investigator. Elevations in liver function test results (e.g., AST, ALT, gamma glutamyl transferase, alkaline phosphatase, and LDH) were the most frequently reported clinical laboratory abnormalities that were judged to be adverse events.

- One clinical laboratory adverse event resulted in study drug therapy discontinuation. Patient 630/00035 discontinued study drug therapy on Study Day 9 because of elevated liver function test results (Grade 1 alkaline phosphatase). The event was considered resolved and judged by the investigator to be probably related to study drug therapy.

Hematology

- No patients had a maximum or last post-baseline Grade 4 hematology parameter except for Patient 453/00150 who had a Grade 3 WBC count (24.65 x $10^9$ /L) at the LFU visit.

- Among patients who had an increase in grade at some point during the study, most had an increase of 1 grade only.

Serum Chemistry

Most patients had Grade 0 serum chemistry parameters at baseline and throughout the study. There were only a few patients who had an increase in a serum chemistry value of Grade 1, 2, 3, or 4 during IV study drug therapy that demonstrated a further increase of at least post-baseline visit. For each affected parameter, a maximum of 1 patient met this criterion. Additionally, most of the increases were of 1 grade only. There were several patients who had a decrease in grade of a serum chemistry parameter.

There was 1 patient who had a maximum post-baseline shift in potassium level from Grade 0 at baseline to Grade 4. Patient 359/00350 was a 78-year-old Caucasian female with pyelonephritis who received doripenem IV for 10 days. Follow-up urine cultures were sterile and the patient did clinically well. At the TOC visit, the patient was clinically cured, however she had asymptomatic bacteriuria with *P. mirabilis*. Potassium levels were 5.4 mmol/L (normal 3.5-5.5) at baseline, 4.9 while receiving IV study drug, 5.1 at EOT(IV) and 7.1 at the TOC visit. It is doubtful that the hyperkalemia at the TOC visit was related to IV study drug given the patient's potassium level was within normal limits while receiving IV study drug therapy. It is probable that this finding is secondary to hemolysis of the sample since this was an isolated event that occurred after the patient was removed from study drug therapy.

Reversibility for serum chemistry values varied by parameter. Zero to 11 patients who had an increase in a specific chemistry parameter of at least 1 grade while receiving IV therapy, had that chemistry parameter reversed post therapy.

Only 2 patients had an increase in ALT of at least 1 grade while receiving IV therapy that did not reverse after therapy. One patient had a maximum ALT grade of 1 while receiving therapy as well as at post-baseline and a second patient had a maximum ALT grade of 2 while receiving therapy as well as at post-baseline.

Two patients had a shift in ALT from Grade 0 at baseline to Grade 4 post-baseline and 1 patient had a shift in AST from Grade 0 at baseline to Grade 4 post-baseline. See the following section for narratives of these two patients.

- Patient 350/00106 had a baseline post-baseline shift in ALT and AST values from Grade 0 at baseline to Grade 4 at some point during the study. ALT and AST values increased from <ULN at baseline to >5xULN at some point during the study. This patient had a confounding medical history that could have contributed to the observed liver findings; a history of gallstones and acute myocarditis associated with recent mycoplasm and/or viral infection.

- Patient 355/00169 had a maximum post-baseline shift in ALT value from Grade 0 at baseline to Grade 4 at some point during the study. The ALT level increased from <ULN at baseline to >5xULN at some point during the study. This subject received concomitant medications that may have contributed to the observed increases in serum transaminase levels; however, the role of doripenem in contributing to these findings cannot be ruled out.

Laboratory Parameters of Special Interest

Changes in ALT and AST were considered laboratory parameters of special interest by the Applicant. Shifts from baseline to the worst (maximum) post-baseline value in ALT and AST were measured using pre-defined ranges relative to the upper limit of normal (ULN). The ranges were defined as follows: ≤ ULN, >ULN to 3 X ULN, >3 X ULN to 5 X ULN, and > 5 X ULN.

Shifts in ALT were also assessed using Hy's High Risk K(HHR) classification defined as concurrent increase in ALT to >3xULN and total bilirubin >1.5 ULN.

Sixty-six percent of DORI-06 patients remained within normal ALT values between baseline and the EOT(IV) or Day 3 visits.

Similar finding are seen between baseline and EOT(IV) or Day 3 visits in AST values; approximately 76% of patients had AST values that remained within normal limits.

Among the 104 patients who demonstrated a post-baseline increase in ALT, 86 (83%) demonstrated an increase from a value ≤ULN to <ULN-3xULN.

Among the 72 patients who demonstrated a post-baseline increase in AST, 60 (83%) demonstrated an increase from a value ≤ULN to <ULN-3xULN.

At the TOC and LFU visits, 76% and 86% of patients remained within normal ALT and AST limits, respectively. No patient had a worst (maximum) ALT or AST value more than 5xULN.

Two patients had an increase in ALT from ≤ULN to >5xULN and one patient had an increase in AST from ≤ULN to >5xULN.

Patient 355/00169 was a 26-year-old Hispanic female who was enrolled with pyelonephritis. Laboratory parameters of interest are summarized below. She had a prior history of hypokalemia and no prior urologic history. Concomitant medications included: acetaminophen, dipirone, metoclopramide and rantidine. *Escherichia coli* was isolated from her baseline urine culture at $>10^5$ CFU/mL. This patient received doripenem for 5 days followed by oral levofloxacin 500 mg daily for an additional 10 days. Follow-up urine cultures were sterile after she received 2 days of IV study drug therapy. She was clinically well and had a normal physical examination at the end of IV therapy and at the TOC visit. However, her liver transaminases increased while receiving IV study drug therapy and returned to within normal (ALT) or were returning to within normal (AST) levels without intervention by the TOC visit. Concomitant medications may have contributed to the observed increases in transaminase levels; however, the role of doripenem in contributing to these observed findings cannot be ruled out.

Patient 355/00169: Laboratory Values of Interest

| Visit | ALT (<31 IU/L)[a] | AST (<32 IU/L)[a] | Total bilirubin (<17.1 μmol/L)[a] |
|---|---|---|---|
| Baseline | 21 | 20 | 13.5 |
| On IV therapy | 419 | 368 | 7.2 |
| EOT(IV) | 257 | 82 | 6.2 |
| TOC | 25 | 22 | 6.0 |

[a] Normal range

Patient 350/00106 had elevations in ALT and AST values from <ULN at baseline to >5xULN maximum post-baseline shift and met the criteria to fulfill Hy's rule while participating in this study. A brief narrative of this patient is included in the discussion of Hy's High Risk Classification.

Hy's High Risk classification was conservatively defined as an ALT value greater than 3xULN in combination with a total bilirubin greater than 1.5xULN at a given time point.

Two patients met the criteria to fulfill Hy's rule while participating in this study. Both patients had confounding medical histories that could have contributed to the observed liver findings: acute myocarditis associated with recent mycoplasma and/or viral infection in a patient with a

history of gallstones (Patient 350/00106), and congestive hepatitis in a patient with Chagas disease receiving concomitant amiodarone (Patient 450/00084).

- Patient 350/00106 was a 37-year-old Caucasian male who was enrolled in DORI-06 with a diagnosis of cLUTI. His past medical history was significant for gallbladder stones, choledochal syndrome and chest pain. Medications at the time of study entry were ranitidine and metoclopramide. Screening laboratory values for serum chemistries were remarkable for ALT and AST at the ULN, and GGT>ULN. The patient received a total of six 500-mg doses of doripenem over 2 days and was discontinued on Day 3 due to the lack of a qualifying pretreatment urine culture. No oral study drug therapy was administered. The patient was assessed as clinically improved at EOT(IV); the physical examination at EOT was significant for mild hypogastric pain only. Safety labs obtained at EOT(IV) on Day 3 met the criteria to fulfill Hy's rule; ALT and AST >10xULN with concurrent elevation in total bilirubin to approximately 1.5xULN. However GGT was also elevated to >5xULN and ALP>2xULN. Repeat labs performed on Day 8 demonstrated decreasing ALT and AST to levels to >5xULN, a persistently elevated total bilirubin to approximately 1.5xULN and increasing GGT to>5xULN and ALP to >4xULN. On Day 10, the patient was diagnosed with a deep vein thrombosis via ultrasound after developing significant dyspnea and left lower limb edema. A chest radiograph performed the same day showed cardiac enlargement. An ECHO was performed, and the patient was diagnosed with acute myocarditis. The myocarditis was considered to be caused by Mycoplasma pneumoniae (IgM 1/1024; positive >1/16) and/or a coxsackie A virus (IgM positive). Serology for hepatitis B, HIV, and Coxsackie B were negative. The patient was managed medically. LFU assessment occurred on Day 31 at which time the ALT, AST, and total bilirubin levels had returned to WNL and GGT remained >5xULN and ALP decreased to >2xULN. This patient's physical findings and laboratory values are consistent with acute myocarditis and hepatitis due to mycoplasma and/or viral infections and concurrent development of obstructive jaundice in a patient with a history of biliary obstruction.

- Patient 450/00084 was an 91-year-old Caucasian male who was enrolled in DORI-06 with a diagnosis of cLUTI. His past medical history was significant for ongoing Chagas myocardiopathy, congestive heart failure, ventricular thrombus, regurgitant systolic murmur, cardiac pacemaker, tachypnea, pulmonary edema, hepatomegaly, chronic severe renal impairment. Lower extremity edema, hypothyroidism and body petechiae, Recent past medical history was significant for sustained ventricular tachycardia leading to cardiogenic shock which was treated with electrocardioversion, amiodarone and life support measures including assisted ventilation and isotropic agents within the 2 weeks prior to study enrollment. Medications at the time of study entry were amiodarone, furosemide, omeprozole, dobutamine, mirtazapine, levothyroxine, warfarin, domperidone and metoclopramide. Screening laboratory values for serum chemistry were remarkable for hypoalbuminemia, elevated ALT and AST to >2xULN, total bilirubin at the ULN, elevated GGT to >2xULN, and ALP>ULN. The patient's calculated creatinine clearance at study entry was 14.5mL/min. He initially received 500-mg doses of doripenem q8h for a total of 5 doses. On Day 2, the dose of doripenem was adjusted for the patient's renal

function and he received a total of 9 doses of 250 mg q12h to complete a total of 6 days of therapy. The last dose of doripenem was administered on Day 7. Safety labs obtained on Day 3 met the criteria to fulfill Hy's rule: ALT>4xULN, AST>6xULN, total bilirubin 1.8xULN, GGT>3xULN and ALP approximately 1.5xULN. Follow-up serum chemistries were not obtained. On Day 7, the patient experienced ventricular tachycardia which was treated with electrocardioversion, intubation and assisted ventilation, and intropic support. However, the patient developed intermittent arrhythmias and cardiac arrest and died the same day. The investigator confirmed that the event of cardiogenic shock was probably related to Chagas cardiomyopathy and assessed the cardiac arrhythmia as related to the Chagas disease. This patient's physical findings and laboratory values are consistent with liver congestion due to the patient's right-sided heart failure.

#### 7.1.7.4 Additional analyses and explorations

No additional analysis of laboratory data was performed.

### 7.1.8 Vital Signs

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure, pulse, and respiration rate) were measured at screening, the EOT(IV) visit, and the TOC visit. Oral temperature (or equivalent) was measured within 4 hours prior to administration of each dose of study drug therapy while the patient was receiving IV study drug therapy. Height and weight were both measured at screening, and weight was measured while the patient was receiving IV study drug therapy at the discretion of the investigator. A full physical examination was performed at screening, and also at the EOT(IV) and TOC visits.

#### 7.1.8.2 Standard analyses and explorations of vital signs data

The Applicant has included a summary table that contains the mean and mean changes in vital signs from baseline to EOT(IV) and to TOC (and for temperature only at the LFU visit). Also, included in another table were the individual vital signs presented by patient. According to the Applicant, the following conclusions can be made regarding the vital signs, physical findings, and other observations related to safety:

- No unusual mean values or mean changes from baseline in vital signs were observed for any time point.

- Mean heart rate and mean temperature decreased from baseline to EOT(IV) and remained relatively stable from EOT(IV) to TOC, as expected when patients recover from infections.

- Mean heart rate and mean systolic and diastolic blood pressure readings were stable throughout the study.

#### 7.1.8.3 Additional analyses and explorations

No additional analysis of vital signs data was performed.

### 7.1.9 Electrocardiograms (ECGs)

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

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

**Clinical Reviewer's Comments:** *The kae.xpt database was searched by the FDA reviewer and there were no reports of QT prolongation in either treatment arm.*

*A report filed by the Interdisciplinary Review Team for QT studies dated April 17, 2007 stated the following: "The upper limit of the two-sided 90% CI for the mean difference between doripenem (for both doses of 500 mg and 1,000 mg) and placebo was under 5 milliseconds at all time points which is below the value of 10 ms, which is identified as the threshold for regulatory concern in the ICH E14 guideline."*

#### 7.1.9.2 Additional analyses and explorations

No additional analysis of electrocardiogram data was performed.

### 7.1.10 Immunogenicity

There were no human immunogenicity data available.

### 7.1.11 Human Carcinogenicity

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

### 7.1.12 Special Safety Studies

See Section 7.2.6 concerning pharmacokinetic studies conducted in healthy subjects and subjects with various levels of renal impairment under IND 64,416.

See the Clinical Pharmacology review by Sarah Robertson, Pharm.D.