

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # : 22-106

Drug Name: Doripenem for injection (500mg infused over 1 hour q8h)

Indication(s): Complicated Intra-abdominal Infection (cIAI)

Applicant: Johnson and Johnson Pharmaceutical Research & Development, L.L.C.

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TABLE OF CONTENTS

LIST OF TABLES	3
1. EXECUTIVE SUMMARY	4
1.1 INTRODUCTION	4
1.2 CONCLUSIONS AND RECOMMENDATIONS.....	4
1.3 BRIEF OVERVIEW OF CLINICAL STUDIES	10
1.4 NON-INFERIORITY MARGIN JUSTIFICATION	10
1.5 STATISTICAL ISSUES AND FINDINGS	11
2. INTRODUCTION.....	13
2.1 OVERVIEW	13
<i>2.1.1 Class and Indication.....</i>	<i>13</i>
<i>2.1.2 History of Drug Development.....</i>	<i>13</i>
2.2 DATA SOURCES	13
3. STATISTICAL EVALUATION	14
3.1 EVALUATION OF EFFICACY (STUDIES DORI-07 AND DORI-08).....	14
<i>3.1.1 Study Design and Endpoints.....</i>	<i>14</i>
<i>3.1.2 Subject Disposition, Demographic and Baseline Characteristics</i>	<i>18</i>
<i>3.1.3 Statistical Methodologies (Studies DORI-07 and DORI-08).....</i>	<i>26</i>
<i>3.1.4 Efficacy Results</i>	<i>28</i>
<i>3.1.5 Efficacy Conclusions</i>	<i>35</i>
3.2 EVALUATION OF SAFETY	35
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	35
5. SUMMARY AND CONCLUSIONS	45
SIGNATURES/DISTRIBUTION LIST.....	46
APPENDIX 1	47

LIST OF TABLES

Table 1: Summary of the Study Visits of the DORI-7 and DORI-8 studies.....	16
Table 2: Patient Disposition (Study DORI-07).....	18
Table 3: Disposition (Study DORI-08).....	19
Table 4: Reasons for Discontinuation of Study Drug Therapy, All Randomized Subjects (DORI-07)	19
Table 5: Reasons for Discontinuation of Study Drug Therapy, All Randomized Subjects (DORI-08)	20
Table 6: Demographics and Baseline Characteristics in ITT Patients (DORI-07)	20
Table 7: Demographics and Baseline Characteristics in ITT Patients (DORI-08)	24
Table 8: Number (%) of Patients in mMITT Population by Treatment Duration Category (Studies DORI-07 and DORI-08).....	25
Table 9: Sponsor Analysis of Clinical Cure Rates (%) at TOC for Complicated Intra-Abdominal Infections (DORI-07 and DORI-08).....	28
Table 10: FDA Re-Analysis of Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets	29
Table 11: Microbiological Cure Rates (%) at Complicated Intra-Abdominal Infections (DORI-07 and DORI-08).....	30
Table 12: Sponsor Comparison of Additional Clinical Outcomes by Visit and Analysis Set (Study DORI- 07).....	31
Table 13: Sponsor Comparison of Additional Clinical Outcomes by Visit and Analysis Set (Study DORI- 08).....	32
Table 14: Favorable Per-Pathogen Microbiological Outcomes for Selected Baseline Intra-abdominal Pathogens at the TOC Visit ^a (Study DORI-07: Microbiologically Evaluable at TOC Analysis Set).....	32
Table 15: Favorable Per-Pathogen Microbiological Outcomes for Selected Baseline Intra-abdominal Pathogens at the TOC Visit ^a (Study DORI-08: Microbiologically Evaluable at TOC Analysis Set).....	33
Table 16: Per Patient Clinical Cure at mMITT Definition 1 (CR_1): Overall and by Subgroups (DORI-07)	36
Table 17: Per Patient Clinical Cure (%) at mMITT Definition 1 (CR_1): Overall and by Subgroups (DORI- 08).....	37
Table 18: Stratified Analysis of Clinical Cure Rates (%) at TOC for Complicated Intra-Abdominal Infections (DORI-07 and DORI-08).....	37
Table 19: Comparison of Clinical Cure Rates of the ME and mMITT Co-primary Analysis Sets for the Three Sample Size Populations: Original Population, Subsequent Population, Final Population (DORI- 07 and DORI-08).....	38
Table 20: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients Receiving IV Therapy Only	39
Table 21: Clinical Cure Rates (%) at TOC Visit Using Clinical Response Definition CR_2_mMITT	39
Table 22: Clinical Cure Rates (%) in the ME and mMITT Populations Without Surgical Review Panel (SRP) Re-classifications	40
Table 23: Comparison of Clinical Cure Rates (%) in the ME and mMITT Populations in Patients According to Baseline Creatinine Clearance Group.....	41
Table 24: Clinical Cure Rates (%) in the ME Population Using Original TOC Visit Window of 28 to 42 Days and FDA Defined TOC Window of 25 to 45 Days	42
Table 25: Comparison of Influential Sites for All Randomized Patients (DORI-07 and Dori-08 Studies)	42
Table 26: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients With Renal Impairment.....	43
Table 27: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets Excluding Patients Who Were Cured and Received Concomitant Non-Study Antibiotics Taken Between First Dose of Study Drug and TOC Visit	44

1. EXECUTIVE SUMMARY

1.1 Introduction

This NDA submission (NDA 22106) seeks to gain approval for the use of doripenem i.v. therapy in the complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI) indications. In support of these indications, the Sponsor has included safety and pharmacokinetic data from seven completed Phase 1 studies as well as safety and efficacy data from one completed Phase 2 study in cUTI (DORI-03), two completed Phase 3 studies in cUTI (DORI-05 and DORI-06) and two completed Phase 3 studies in (cIAI), (DORI-07 and DORI-08). Safety data regarding deaths and serious adverse events from two ongoing Phase 3 trials for the treatment of nosocomial pneumonia (NP) (DORI-09 and DORI-10) are also included in this submission. The included Phase 3 studies in cUTI and cIAI had been originally analyzed by Peninsula Pharmaceuticals, Inc. (PPI) who was later acquired by the Sponsor, Johnson and Johnson Pharmaceutical Development Inc. (J&JPRD) in July 1st of 2005. At the time of PPI's acquisition, the program was reassessed and, where warranted, changes were made to the clinical development plan overall, as well as to the individual protocols. J&JPRD stated that the changes to the Phase 3 protocols which included increases to the statistical power of the studies were reflected in protocol amendments and implemented in blinded fashion, prior to database lock.

This statistical review focuses primarily on the efficacy findings reported in the two Phase 3 studies in the cIAI indication, DORI-07 and DORI-08. These identical studies aimed to demonstrate the non-inferiority of doripenem therapy to comparator therapy (meropenem). A non-inferiority margin of 15% was determined by the Agency to be acceptable for the DORI-07 and DORI-08 so that at least 50% of the treatment benefit would be preserved while controlling for variability. This determination was based on data submitted by the Sponsor and the Agency's review of the literature and other supportive evidence (Appendix 1). The Sponsor had also proposed a 15% NI margin in designing the DORI-07 and DORI-08 studies.

This statistical review considers evidence based on primary analysis results determined from an FDA re-analysis rather than from the Sponsor's analysis. The FDA analysis had re-evaluated some patient outcomes and/or re-classified patients into an FDA ME and mMITT population. Although both the Sponsor's and FDA re-analyses supported the finding of non-inferiority, the FDA re-analysis showed consistently lower clinical cure rates for patients in the doripenem arm across both studies.

1.2 Conclusions and Recommendations

Based on the review of studies DORI-07 and DORI-08, doripenem injection 500 mg every 8 hours demonstrated non-inferiority to meropenem i.v. using a 15% margin for the treatment of complicated intra-abdominal infections (cIAI) in patients 18 years of age and older. The primary analysis findings of non-inferiority were demonstrated in both the FDA defined ME and mMITT co-primary analysis populations. Microbiological analyses results were supportive of the primary analysis.

Although overall cure rates in the FDA defined ME and mMITT co-primary analysis populations of the DORI-07 and DORI-08 studies provided evidence of non-inferiority, observed cure rates were consistently lower in the doripenem arm than in the meropenem arm. In DORI-07 study, the clinical cure rate at TOC for doripenem was 3.1% worse than meropenem in the ME population and 4.3% worse in the mMITT population. Similarly, in DORI-08, the clinical cure rate at TOC for doripenem was 1.1% worse than meropenem in the ME population and 2.3% worse in the mMITT population. This raises concerns of a potential loss of efficacy with the use of doripenem therapy. There is also a concern that this loss of efficacy would be larger if patients were not allowed a switch from IV to oral medication. In the subset of DORI-07 and DORI-08 study patients receiving only IV therapy, patients in the doripenem arm had clinical cure rates which were approximately 6.3% and 8.1% lower in the ME and mMITT populations, respectively. Interpretations of this analysis, however, may be confounded by differences in the proportions of subjects in each treatment arm who switched to from IV to oral amoxicillin/clavulanate therapy.

Sensitivity and subgroup analyses based on the Sponsor's data were also conducted in the DORI-07 and DORI-08 studies to assess the effects of various factors on overall study findings but did not identify any clear inconsistencies and were therefore considered as generally supportive. Sensitivity analyses examined effects of various factors on primary analysis findings. These factors included influential sites, analysis set definitions, study drug therapy (IV or oral), treatment duration, clinical response definitions, sample size changes, TOC window changes, surgical review panel re-classifications, unplanned study drug treatments. Subgroup analyses also addressed other factors which could have influenced primary analysis results. These factors included the patient's categorization with respect to age, gender, race, geographic region, post-operative infection, APACHE II Score, IVRS Randomization Stratum, treatment duration, renal impairment status, creatinine clearance group. It should be noted that post-hoc subgroup and sensitivity analyses may be severely limited in identifying significant differences between treatments due to a potential lack of power (i.e. inadequate sample size) and a lack of planning (i.e. failure to control for overall type I error rate).

Doripenem also provided some evidence towards microbiological efficacy against major causative pathogens of cIAI at the TOC visit. Eradication rates for these pathogens appeared similar to rates in meropenem arm. However, due to the small number of isolates presented, meaningful statistical inferences could not be drawn.

1.3 Brief Overview of Clinical Studies

Studies DORI-07 and DORI-08

Studies DORI-07 and DORI-08 were identical, Phase 3, prospective, randomized, double-blind, double-dummy multi-center trial comparing the efficacy of intravenous doripenem (500mg q8h administered as a 1-hour infusion) with that of intravenous meropenem (1g q8h administered as an i.v. bolus injection) in treating hospitalized patients with complicated intra-abdominal infections (CIAI). The primary efficacy analysis was to establish non-inferiority of doripenem to

meropenem at the test of cure (TOC) within a NI margin of 15% for the microbiological evaluable (ME) and microbiological modified intent-to-treat (mMITT) co-primary populations.

1.4 Non-inferiority Margin Justification

In a memorandum dated 26 January 2007, the Agency requested additional justification for the use of a 15% non-inferiority margin in the cIAI studies. The Agency stated that “the justification should include the rationale used to estimate the benefit of active drug versus placebo” and that “the non-inferiority margin chosen should preserve at least 50% of this benefit, while controlling for variability.” In addition, the Agency requested a reference for the statement included in study reports for the cIAI studies that “there is a low expectation of cure when treatment is placebo,” to aid in the estimation of the treatment effect of the active comparator, meropenem, in the cIAI studies.

Statistical Reviewer Comments: *Based on data submitted by the Sponsor and the Agency's review of the literature and other supportive evidence, a 15% NI margin was acceptable for the treatment of complicated IAI infections for studies using meropenem as the active comparator. The Agency's justification of a 15% NI margin is included in Appendix 1.*

1.5 Statistical Issues and Findings

Statistical issues identified for Studies DORI-07 and DORI-08 were as follows:

An FDA re-analysis of the primary efficacy results was conducted in which the the Sponsor's primary outcome was re-evaluated and re-classified into FDA defined ME and mMITT populations. FDA and Sponsor analyses of the primary outcome differed according to the following criteria:

- FDA classification of patient deaths as evaluable failures if patient received at least 3 days of study drug.
- FDA Medical Officer re-classifications of patients receiving concomitant non-study anti-bacterial medications. Patients listed in the tables were re-classified in the FDA analysis as either evaluable failures or mMITT indeterminate (i.e. failures).
- FDA exclusion of misrandomized patients from the ME population. Misrandomized patients were included in the mMITT population according to the outcome observed assigned to the planned treatment arm.
- FDA allowable TOC window of 25-45 days (the original protocol window of 28-42 days \pm 3 days). Sponsor analyses were based on an extended TOC window of 21-60 days.

Although both the Sponsor's and FDA re-analyses of the primary outcome supported a finding of non-inferiority, the FDA re-analysis showed consistently lower clinical cure rates for patients in the doripenem arm across both studies. In DORI-07, clinical cure rates were 130/157 (82.8%) versus 128/149 (85.9) in the ME population, a difference (95% CI) of -3.1% (-11.3; 5.2), and 143/194 (73.7%) versus 149/191 (78.0%) in the mMITT population, a difference (95% CI) of -4.3% (-12.8; 4.3). In DORI-08, clinical cure rates were 128/158 (81.0%) versus 119/145

(82.1%) in the ME population, a difference (95% CI) of -1.1% (-9.8; 7.8), and 143/199 (71.9%) versus 138/186 (74.2%) in the mMITT population, a difference (95% CI) of -2.3 (-11.2; 6.6).

Based on previous correspondence with the Sponsor, the primary outcome was analyzed in both the ME and mMITT co-primary populations. An adequate demonstration of non-inferiority would require that non-inferiority be demonstrated in both of these co-primary populations.

In a pooled analysis conducted to look at the subset of patients receiving IV only therapy, lower clinical cure rates were observed in the doripenem arm: 53/74 (71.6%) versus 67/86 (77.9%) in the ME population, a difference (95% CI) of -6.3% (-19.9, 7.1), and 66/123 (53.7) versus 76/123 (61.8) in the mMITT population, a difference (95% CI) of -8.1 (-20.2; 4.2). Interpretations of this analysis, however, may be confounded by differences in the proportions of subjects in each treatment arm who switched to from IV to oral amoxicillin/clavulanate therapy. In addition, estimates from pooled studies may be unreliable due to study differences and lack of randomization.

Study power and sample size were increased without adequate justification, without discussions with the Agency or pre-specification in both the DORI-07 and DORI-08 studies after study initiation but before breaking the study blind. Unplanned sample size increases can potentially increase the overall type I error rate of the study and can make interpretations of results unclear if overall findings relied upon additional data from the unplanned sample size increase. However, sensitivity analyses conducted by the Sponsor indicated that the unplanned sample size increases did not meaningfully affect overall study findings for both DORI-07 and DORI-08.

Efficacy assessment time points were modified after initiations of studies DORI-07 and DORI-08 respectively. In both studies, the Sponsor expanded the protocol-defined visit windows for the EFU (7 to 14 days) and TOC (28 to 42 days) visits to EFU (6 to 20 days) and TOC (21 to 60 days), respectively, after the final dose of study drug therapy (i.v. alone or i.v. plus oral). Based on sensitivity analyses, changes in the EFU and TOC visit windows did not affect overall study results of DORI-07 and DORI-08.

Another finding which should be noted is that the Sponsor's computations of the 95% CIs for binomial proportions assumed a continuity correction which tended to make computed 95% interval estimates conservative in many cases. Continuity corrections are statistically justified in cases with exact formulas (exact at finite N) for the variance but may not be necessary in cases where N is sufficiently large and variance formulas are asymptotic. In this review, 95% CI calculations were based on normal approximation to the difference of 2 binomial proportions without a continuity correction. In cases where normal approximation to the binomial distribution may not be adequate such as when $N(p)(1-p) \leq 5$ in either treatment arm, exact tests were used.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Doripenem is an injectable, sterile, synthetic, broad-spectrum carbapenem (beta-lactam) antibacterial. The bactericidal mode of action of doripenem and other beta-lactams involves binding to penicillin-binding proteins (PBPs) and inhibiting the biosynthesis of the bacterial cell wall in both gram-positive and gram-negative bacteria.

The Sponsor's application presents data to support the use of Doripenem for Infection in the treatment of subjects 18 years of age or older with CIAI caused by *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides caccae*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Streptococcus intermedius*, *Streptococcus constellatus*, and *Peptostreptococcus micros*. The Sponsor's application also presents data to support the use of Doripenem in patients 18 years of age or older with cUTI caused by *Escherichia coli*, including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii*, and

2.1.2 History of Drug Development

Doripenem compound development was originated by Shionogi & Co., Ltd., Osaka, Japan (Shionogi). On 25 July 2005, the Japanese Health Authority approved doripenem 0.25 g i.v. solution (250 mg b.i.d up to a maximum of 1,500 mg daily) for the treatment of moderate to severe bacterial infections. Doripenem was launched in Japan on 16 September 2005 under the trade name Finibax®. In 2003 Peninsula Pharmaceutical, Inc. (PPI) obtained an exclusive license for the development and commercialization of doripenem in North America, South America, and Europe. In accordance with 21 CFR 312 Subpart D, PPI transferred all sponsor obligations for doripenem to Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) in July 2005.

2.2 Data Sources

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (Studies DORI-07 and DORI-08)

3.1.1 Study Design and Endpoints

Objectives: To confirm the hypothesis that treatment with Doripenem i.v. (500 mg infused over 1 hour q8h) is clinically non-inferior to treatment with meropenem i.v. in subjects with cIAI for the co-primary efficacy endpoints (clinical cure rate at the Test-of-Cure [TOC] visit in the microbiologically evaluable [ME] population and clinical cure rate in the mMITT (CR1_mMITT) population. The treatment is 5 to 14 days (i.v. + oral) with option to switch to amoxicillin/clavulanate tablets (875 mg/125 mg) after Day 3.

Design: These are two identical Phase 3, multi-center, randomized, international, double-blind, double-dummy studies in patients 18 years or older with cIAI comparing doripenem (500 mg infused over 1 hour q8h) with meropenem (1 g IV bolus q8h). Subjects in each study were randomized 1:1 to receive either doripenem or meropenem. Across both studies, there were 962 randomized patients, 486 randomized to the doripenem arm and 476 randomized to the meropenem arm. Subjects were stratified at the time of randomization by region (North America, South America, and Europe); primary site of infection (complicated appendicitis with localized peritonitis versus diagnosis of other sites of cIAI); and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≤ 10 versus > 10). Subjects with generalized peritonitis, regardless of the origin were stratified to the “other” group during randomization.

Subjects received a minimum of 3 days IV treatment before being eligible for transition to oral antibiotic therapy with amoxicillin-clavulanic acid at a dose of 875 mg IV every 12 hours. Patients were treated for a minimum of 5 days and a maximum of 14 days with either IV medication or a combination of IV and PO medication. Follow up consisted of an Early Follow-Up Visit (EFU) 6-20 days after the last dose of study drug, and a Late Follow-Up or Test of Cure Visit (TOC) 21-60 days after the last dose of study drug.

Visits are described below and summarized in Table 1:

Visit Schedule:

- **Screening Visit occurs on Day –1 to 0 (24 hours prior to randomization)**
 - Diagnosis of cIAI was established.
 - Stratification by region (North America, South America, Europe) by site of infection (complicated localized appendicitis versus other sites of cIAI), and by disease severity (APACHE II ≤ 10 versus > 10).
 - Randomization to study drug therapy

- **Treatment Visit occurs on Day 1 to End of Therapy (Days 1 to 5 through 14)**
 - Doripenem i.v. infusion 500 mg (over 1 hour) q8h or meropenem i.v. bolus 1g (over 3 to 5 min) q8h

- Optional switch to oral therapy with amox/clav therapy after 9 i.v. doses.
- Total study drug therapy (i.v. and oral) was 5 to 14 days.
- Vancomycin therapy was added if *Enterococcus* or MRSA infection was suspected or isolated at baseline.

- **Early Follow-up Visit occurs 7 to 14 days after final dose of study drug therapy**
 - Patient returned to study center for assessment of microbiological and clinical response and safety

- **Test-of-Cure Visit occurs 28 to 42 days after final dose of study drug therapy**
 - Patient returned to study center for assessment of microbiological recurrence or clinical relapse and final safety.

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Table 1: Summary of the Study Visits of the DORI-7 and DORI-8 studies

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

APACHE II = Acute Physiology and Chronic Health Evaluation II; cIAI = complicated intra-abdominal infection; i.v.= intravenous; q8h = every 8 hours; MRSA = methicillin-resistant Staphylococcus aureus.

Source: Figure 1 from DORI-7 Clinical Study Report

Statistical Reviewer Comments: *The Sponsor states that for the purpose of evaluability assessments and data analyses, and before breaking the study blind, the protocol-defined visit windows for the EFU (7 to 14 days) and TOC (28 to 42 days) visits were expanded to 6 to 20 days and 21 to 60 days, respectively, after the final dose of study drug therapy (i.v. alone, or i.v. plus oral) for both the DORI-07 and DORI-08 studies.*

Co-Primary Efficacy Endpoints:

- Clinical cure rates at the TOC visit (21 to 60 days after the final dose of study drug therapy) for the ME at TOC analysis set.
- Clinical cure rate at any time up to 60 days after the last dose of study drug therapy for the mMITT analysis.

Statistical Reviewer Comments: *To meet the primary study objective, the Sponsor must demonstrate non-inferiority in both the ME and mMITT co-primary populations. Selection of either the ME and mMITT populations (individually) as the only analysis in testing for NI can involve potential biases. However, demonstration of NI in both of these populations adequately addresses these concerns and provides more robust results.*

Secondary Efficacy Endpoints:

- Clinical Response Definition 2 in the mMITT Sample (CR_2_mMITT)
- Clinical Response Definition 1 in the cMITT Sample (CR_1_cMITT)
- Clinical cure or improvement rates at the EOT(i.v.) visit in the CE and ME analysis sets
- Clinical cure rates at the EFU visit (6-20 days post-therapy) in the CE and ME analysis sets
- Clinical cure rates at the TOC visit in CE analysis set
- Microbiological endpoints in the ME analysis set evaluated at the TOC visit. This is examined in two ways:
 - Per-patient microbiological cure rates (i.e., eradication or presumed eradication of all baseline pathogens)
 - Per-pathogen microbiological outcomes (i.e., eradication or presumed eradication) at the EFU and TOC visits.
- Microbiological endpoints evaluated in the mMITT analysis set
- Per blood pathogen microbiological outcome in the cMITT sample
- Superinfections
- New Infections

Statistical Reviewer Comments: *The secondary endpoints listed above were included in the Sponsor's final version of the statistical analysis plan (SAP). Secondary analyses as reported by the Sponsor and as described in the study protocol were not conducted for all of these endpoints. It should also be noted that none of the secondary endpoints were prioritized. Therefore, statistical testing of these endpoints would be limited due to a lack of control of the overall type I error rate.*

Populations Analyzed:

All Randomized (or ITT) Subjects: All randomized patients who received any 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.

Clinical Modified Intent-to-Treat (cMITT): All randomized patients who received any amount of study drug therapy and met the minimal disease definition of IAI. The minimal disease definition included all IAI or gynecological infections that required antibiotic therapy, whether complicated (perforating) or not. Identification of a baseline pathogen was not required for this analysis set with the exception of patients enrolled as failing a prior treatment regimen.

Microbiological Modified Intent-to-Treat (mMITT): (Co-primary analysis population) A subset of the cMITT analysis set that consisted of patients in the cMITT analysis set who had a baseline bacterial pathogen identified, regardless of susceptibility to study drug therapies.

Clinically Evaluable (CE): A subset of the cMITT analysis set that consisted of all randomized patients who received an adequate course of study drug therapy, who met the protocol-specified disease definition of cIAI, and for whom sufficient information was available to determine the patient's clinical outcome at the TOC visit. In addition, patients included in this analysis set had no confounding events that interfered with the assessment of that outcome.

Microbiologically Evaluable (ME) : (Co-primary Analysis Population): A subset of the CE analysis set. In addition to meeting the criteria for inclusion in the CE analysis set, patients in the ME analysis set had at least 1 baseline bacterial pathogen, susceptible to both i.v. study drug therapies, isolated from an intra-abdominal culture. Patients whose only reason for exclusion from the ME analysis set was that all baseline pathogens were not susceptible to at least 1 study drug therapy were included in the “expanded” ME analysis set, which was used for evaluating per-pathogen microbiological outcomes by MIC.

Clinically Evaluable at Early Follow-up (CE at EFU): Similar to those for the CE analysis set, however, unlike the CE analysis set, an outcome assessment (other than “indeterminate”) was required at the EFU, but not necessarily at the TOC visit.

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

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 46 centers (23 in the United States; 7 in Argentina; 5 in Brazil; 5 in Germany; 5 in Poland; and 1 in Canada) randomized a total of 476 patients in this study. The table below summarizes the disposition of all randomized patients in this study.

Table 2: Patient Disposition (Study DORI-07)

	Doripenem	Meropenem	Total
Randomized Patients	237	239	476
Randomized and Treated Patients	235 (99.2%)	236 (98.7%)	471 (98.9%)
Patients Who Completed Study	213 (89.9%)	201 (84.1%)	414 (87.0%)
Treated with IV Therapy Only	69 (29.1%)	65 (27.2%)	134 (28.2%)
Treated with IV and Oral Therapy	144 (60.8%)	136 (56.9%)	280 (58.8%)
ME at TOC	163 (68.8%)	156 (65.3%)	319 (67.0%)
ME at TOC Treated With IV Therapy Only	45 (19.0%)	53 (22.2%)	98 (20.6%)
ME at TOC Treated With IV & Oral Therapy	118 (49.8%)	103 (43.1%)	221 (46.4%)
Patients Who Did Not Complete Study	24 (10.1%)	38 (15.9%)	62 (13.0%)
Patients with EFU & TOC Visits Completed	219 (92.4%)	219 (91.6%)	438 (92.0%)

Note: Percentages were based on the number of patients randomly assigned to each treatment arm.
Source: Modified from Sponsor Table 15.1.1.1

Statistical Reviewer Comments: Of the 476 subjects randomized in DORI-07, 471 (99%) subjects were treated with either doripenem or meropenem. 414 (87%) of the randomized

subjects completed the study and 319 (67%) were included in the ME population at TOC. The percentage of patients who completed the study per protocol in both treatment arms were 90% in the doripenem arm and 84% in the meropenem arm.

Table 3: Disposition (Study DORI-08)

	Doripenem (%) ^b	Meropenem (%) ^b	Total (%)
Randomized Patients	249 ^a	237	486
Randomized and Treated Patients	242 (97.2%)	233 (98.3%)	475 (97.7%)
Patients Who Completed Study	208 (83.5%)	204 (86.1%)	412 (84.8%)
Treated with IV Therapy Only	46 (18.5%)	49 (20.7%)	95 (19.5%)
Treated with IV and Oral Therapy	162 (65.1%)	155 (65.4%)	317 (65.2%)
ME at TOC	162 (65.1%)	153 (64.6%)	315 (64.8%)
ME at TOC Treated with IV Therapy Only	32 (12.9%)	33 (13.9%)	65 (13.4%)
ME at TOC Treated with IV and Oral Therapy	130 (52.2%)	120 (50.6%)	250 (51.4%)
Patients Who Did Not Complete Study	41 (16.5%)	33 (13.9%)	74 (15.2%)
Patients with EFU and TOC Visits Completed	213 (85.5%)	208 (87.8%)	421 (86.6%)

a Includes 1 patient (Patient 428/04109) who was randomly assigned to the meropenem treatment arm but received doripenem for all doses of IV study drug therapy. In an additional analysis, this patient was included in the doripenem treatment arm.

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

Source: Partially Modified from Sponsor Table 15.1.1.1

Statistical Reviewer Comments:

Of the 486 subjects randomized in DORI-08, 475 (98%) of subjects were treated with either doripenem or meropenem. 412 (85%) of the randomized subjects completed the study and 315 (65%) were included in the ME population at TOC.

The tables below show the reasons for discontinuation of study drug therapy and premature study discontinuation for all randomized patients. There were no notable differences between treatment groups.

Table 4: Reasons for Discontinuation of Study Drug Therapy, All Randomized Subjects (DORI-07)

	Doripenem N = 237	Meropenem N = 239	Total N=476
Patients Who Completed Study through TOC Visit	213 (89.9%)	201 (84.1%)	414 (87.0%)
Patients Who Did Not Complete the Study	24 (10.1%)	38 (15.9%)	62 (13.0%)
Reason for Discontinuation from Study			
Adverse Event	4 (1.7%)	3 (1.3%)	7 (1.5%)
Treatment Failure	0	2 (0.8%)	2 (0.4%)
Need for Additional Antibacterial Therapy for an Infection Other Than Current IAI	4 (1.7%)	2 (0.8%)	6 (1.3%)
At Request of Patient, Investigator, or Sponsor	1 (0.4%)	3 (1.3%)	4 (0.8%)
Death	4 (1.7%)	7 (2.9%)	11 (2.3%)
Patient Non-compliance	0	1 (0.4%)	1 (0.2%)
Lost to Follow-up	3 (1.3%)	11 (4.6%)	14 (2.9%)

Randomized but Study Drug Not Given	2 (0.8%)	3 (1.3%)	5 (1.1%)
Other	6 (2.5%)	6 (2.5%)	12 (2.5%)

Note: Percentages were based on the number of patients randomly assigned to each treatment arm.
Source: Modified from Sponsor Table 15.1.1.2-1

Statistical Reviewer Comments: *The number of discontinuations were smaller in the doripenem arm than in the meropenem arm, 24 (10.1%) versus 38 (15.9%). The number of patients lost to follow-up was also smaller in the doripenem arm, 3 (1.3%) versus 11 (4.6%). These differences between treatment arms were not statistically significant.*

Table 5: Reasons for Discontinuation of Study Drug Therapy, All Randomized Subjects (DORI-08)

	Doripenem N = 249	Meropenem N = 237	Total N=486
Patients Who Completed Study through TOC Visit	208 (83.5%)	204 (86.1%)	412 (84.8%)
Patients Who Did Not Complete the Study	41 (16.5%)	33 (13.9%)	74 (15.2%)
Reason for Discontinuation from Study			
Adverse Event	8 (3.2%)	8 (3.4%)	16 (3.3%)
Treatment Failure	3 (1.2%)	2 (0.8%)	5 (1.0%)
Need for Additional Antibacterial Therapy for an Infection Other Than Current IAI	2 (0.8%)	1 (0.4%)	3 (0.6%)
At Request of Patient, Investigator, or Sponsor	4 (1.6%)	3 (1.3%)	7 (1.4%)
Death	5 (2.0%)	7 (3.0%)	12 (2.5%)
Patient Non-compliance	4 (1.6%)	0 (0.0%)	4 (0.8%)
Lost to Follow-up	7 (2.8%)	3 (1.3%)	10 (2.1%)
Randomized but Study Drug Not Given	7 (2.8%)	4 (1.7%)	11 (2.3%)
Other	1 (0.4%)	5 (2.1%)	6 (1.2%)

Note: Percentages were based on the number of patients randomly assigned to each treatment arm.
Source: Modified from Sponsor Table 15.1.1.2-1

Statistical Reviewer Comments: *The number of discontinuations and percentage of randomized patients discontinued from their treatment arm were both slightly larger in the doripenem arm than in the meropenem arm, 41 (16.5%) versus 33 (13.9%).*

Demographics and Baseline Characteristics:

Demographic and baseline characteristics are provided in the tables below for the ITT populations of the DORI-07 and DORI-08 studies and were found to be generally similar across both treatment groups.

Table 6: Demographics and Baseline Characteristics in ITT Patients (DORI-07)

	Doripenem IV (N=235)	Meropenem IV (N=236)	Total (N=471)
Sex			
Male	148 (63.0%)	142 (60.2%)	290 (61.6%)
Female	87 (37.0%)	94 (39.8%)	181 (38.4%)
Race			

Black or African Heritage	18 (7.7%)	23 (9.7%)	41 (8.7%)
Caucasian	166 (70.6%)	157 (66.5%)	323 (68.6%)
Hispanic or Latino	49 (20.9%)	53 (22.5%)	102 (21.7%)
Other	2 (0.8%)	3 (1.3%)	5 (0.8%)
Age (years)			
Mean (SD)	47.6 (18.36)	47.2 (17.43)	47.4 (17.88)
Median	47.0	46.0	46.0
Age Categories (years)			
18-44	108 (46.0%)	113 (47.9%)	221 (46.9%)
45-74	107 (45.5%)	105 (44.5%)	212 (45.0%)
>=75	20 (8.5%)	18 (7.6%)	38 (8.1%)
Height (cm)			
Mean (SD)	170.4 (9.52)	169.8 (9.58)	170.1 (9.54)
Median	170.0	170.0	170.0
Weight (kg)			
Mean (SD)	76.92 (17.772)	77.74 (18.638)	77.33 (18.196)
Median	75.00	74.90	75.00
APACHE Score			
<=10	208 (88.5%)	210 (89.0%)	418 (88.7%)
> 10	27 (11.5%)	26 (11.0%)	53 (11.3%)
Post-Operative Infection?			
Yes	36 (15.3%)	22 (9.3%)	58 (12.3%)
No	199 (84.7%)	214 (90.7%)	413 (87.7%)
IVRS Randomization Stratum			
Appendicitis (Apache Combined)	72 (30.6%)	83 (35.2%)	155 (32.9%)
Other (Apache Combined)	163 (69.4%)	153 (64.8%)	316 (67.1%)
Calculated Creatinine Clearance (mL/min)			
Normal [80 and above]	169 (71.9%)	187 (79.2%)	356 (75.6%)
Mild Failure (50-80)	53 (22.6%)	35 (14.8%)	88 (18.7%)
Moderate Failure (30-50]	8 (3.4%)	13 (5.5%)	21 (4.5%)
Severe Failure (at most 30]	5 (2.1%)	1 (0.4%)	6 (1.3%)
Infectious Process			
Generalized Peritonitis	94 (40.0%)	79 (33.5%)	173 (36.7%)
Multiple Abscess	11 (4.7%)	13 (5.5%)	24 (5.1%)
Single Abscess (Includes Visceral Perforation)	73 (31.1%)	67 (28.4%)	140 (29.7%)
Localized Infection (Includes Localized Peritonitis)	56 (23.8%)	76 (32.2%)	132 (28.0%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Bacteremia	7 (3.0%)	15 (6.4%)	22 (4.7%)

Note: Percentages are based on the number of patients in the given patient sample for each treatment group. Baseline value is defined as the last available value before the start of infusion of the first dose of study drug.

Source: Adapted From Sponsor Table 15.1.2.1-1

Statistical Reviewer Comments: Overall, the 2 treatment groups in Study DORI-07 were similar with respect to baseline characteristics. Approximately 62% of all treated subjects were men and 38% were women. A majority of all subjects were white (69%) and were less than 65 years of age with a mean age of 47.4 years and median age of 46.0 years. Approximately 9% of the subjects were black.

Approximately 89% of patients had APACHE scores of 10 or lower. The treatment groups differed in the number of patients with post-operative infections with 15.3% (doripenem) vs.

9.3% (meropenem). There was a greater proportion of renally impaired patients observed in the doripenem arm (28%) than in the meropenem arm (21%).

Table 7: Demographics and Baseline Characteristics in ITT Patients (DORI-08)

	Doripenem IV (N=242)	Meropenem IV (N=233)	Total (N=475)
Sex			
Male	151 (62.4%)	146 (62.7%)	297 (62.5%)
Female	91 (37.6%)	87 (37.3%)	178 (37.5%)
Race			
Black or African Heritage	9 (3.7%)	7 (3.0%)	16 (3.4%)
Caucasian	190 (78.5%)	194 (83.3%)	384 (80.8%)
Hispanic or Latino	36 (14.9%)	29 (12.4%)	65 (13.7%)
Other	7 (2.9%)	3 (1.2%)	10 (1.9%)
Age (years)			
Mean (SD)	46.1 (18.12)	46.4 (17.67)	46.2 (17.88)
Median	45.5	46.0	46.0
Age Categories (years)			
18-44	118 (48.8%)	107 (45.9%)	225 (47.4%)
45-74	110 (45.5%)	112 (48.1%)	222 (46.7%)
>=75	14 (5.8%)	14 (6.0%)	28 (5.9%)
Height (cm)			
Mean (SD)	169.9 (9.28)	170.1 (9.70)	170.0 (9.48)
Median	170.0	170.0	170.0
Weight (kg)			
Mean (SD)	75.91 (18.614)	75.32 (14.953)	75.62 (16.903)
Median	72.00	75.40	74.00
APACHE Score			
<=10	212 (87.6%)	205 (88.0%)	417 (87.8%)
> 10	30 (12.4%)	28 (12.0%)	58 (12.2%)
IVRS Randomization Stratum			
Appendicitis (APACHE Combined)	77 (31.8%)	66 (28.3%)	143 (30.1%)
Other (APACHE Combined)	165 (68.2%)	167 (71.7%)	332 (69.9%)
Calculated Creatinine Clearance (mL/min)			
Normal [80 and above)	178 (73.6%)	165 (70.8%)	343 (72.2%)
Mild Failure (50-80)	39 (16.1%)	44 (18.9%)	83 (17.5%)
Moderate Failure (30-50]	19 (7.9%)	17 (7.3%)	36 (7.6%)
Severe Failure (at most 30]	6 (2.5%)	7 (3.0%)	13 (2.7%)
Infectious Process ^a			
Generalized Peritonitis	106 (43.8%)	110 (47.2%)	216 (45.5%)
Multiple Abscess	7 (2.9%)	5 (2.1%)	12 (2.5%)
Single Abscess (Includes Visceral Perforation)	49 (20.2%)	59 (25.3%)	108 (22.7%)
Localized Infection (Includes Localized Peritonitis)	75 (31.0%)	55 (23.6%)	130 (27.4%)
Other	5 (2.1%)	3 (1.3%)	8 (1.7%)
Bacteremia	10 (4.1%)	16 (6.9%)	26 (5.5%)

Note: Percentages are based on the number of patients in the given patient sample for each treatment group. Baseline value is defined as the last available value before the start of infusion of the first dose of study drug.
 a One patient in meropenem arm had missing value
 Source: Adapted From Sponsor Table 15.1.2.1-1

Statistical Reviewer Comments: *Overall, the 2 treatment groups in Study DORI-08 were similar with respect to baseline characteristics. Approximately 62% of all treated subjects were men and 38% were women. A majority of all subjects were white (81%) and were less than 65 years of age with a mean age of 46.2 years and median age of 46.0 years. Approximately 3% of the subjects were black.*

Approximately 88% of patients had APACHE scores of 10 or lower. There was a lower number of bacteremia cases in the doripenem arm (4%) compared to the meropenem arm (7%). Approximately 26% and 29% of patients in the doripenem and meropenem arms has some degree of renal impairment.

According to the DORI-07 and DORI-08 protocols, patients remained on study drug therapy for a minimum of 5 and a maximum of 14 days (unless a clinical failure occurred earlier) until resolution of signs and symptoms of cIAI.

Table 8: Number (%) of Patients in mMITT Population by Treatment Duration Category (Studies DORI-07 and DORI-08)

Duration Category	Doripenem # (%) ^b	Meropenem # (%) ^b	Total # (%)
<u>Study DORI-07</u>			
> 0 days	195	190	385
< 14 days	157 (80.5)	160 (84.2)	317 (82.3)
≥ 14 days	38 (19.5)	30 (15.8)	68 (17.7)
14	36 (18.5)	24 (12.6)	60 (15.6)
>14, ≤21	2 (1.0)	5 (2.6)	7 (1.8)
>21	0 (0.0)	1 (0.5)	1 (0.3)
<u>Study DORI-08</u>			
> 0 days	200	185	385
< 14 days	175 (87.5)	155 (83.8)	330 (85.7)
≥ 14 days	25 (12.5)	30 (16.2)	55 (14.3)
14	22 (11.0)	28 (15.1)	50 (13.0)
>14, ≤21	2 (1.0)	2 (1.1)	4 (1.0)
>21	1 (0.5)	0 (0.0)	1 (0.3)
<u>Studies DORI-07 and DORI-08</u>			
> 0 days	395	375	780
< 14 days	332 (84.1)	315 (84.0)	647 (82.9)
≥ 14 days	63 (15.9)	60 (16.0)	123 (15.8)
14	58 (14.7)	52 (13.9)	110 (14.1)
>14, ≤21	4 (1.0)	7 (1.9)	11 (1.4)

>21

1 (0.3)

1 (0.3)

2 (0.3)

a Includes 1 patient (Patient 428/04109) who was randomly assigned to the meropenem treatment arm but received doripenem for all doses of IV study drug therapy. In an additional analysis, this patient was included in the doripenem treatment arm.

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

Source: Partially Modified from Sponsor Table 15.1.1.1

Statistical Reviewer Comments: *Overall for Studies DORI-07 and DORI-08, the distributions of study duration categories were largely similar among doripenem and meropenem arms. Treatment durations, however, were shorter in DORI-08 versus DORI-07. In DORI-07, the mean (median) treatment duration was 9.65 (10) for both treatment arms. In DORI-08, the mean (median) was 8.88 (9) for doripenem and 8.90 (9) for meropenem. It was also observed in the DORI-07 study that a smaller number of patients in the doripenem arm had a treatment duration greater than 14 days, 2 (1.0%) versus 6 (3.2%). Similar differences, however, were not observed in the DORI-08 study. It should also be noted that rates of treatment duration of 14 or more days were more variable across the two studies in the doripenem arm, 19.5% (DORI-07) versus 12.5% (DORI-08) in contrast to the meropenem arm with approximately 16% in both studies.*

3.1.3 Statistical Methodologies (Studies DORI-07 and DORI-08)

Primary Efficacy Assessment

The co-primary efficacy endpoints were clinical cure rates at the TOC visit in the ME at TOC analysis set and clinical cure rates at any time point up to 60 days after the last dose of study drug therapy in the mMITT analysis set. The primary efficacy analysis was to test the hypothesis of non-inferiority of i.v. doripenem to i.v. meropenem. According to the Sponsor's submission, non-inferiority was concluded if the lower 2-sided 95% CI for the difference (doripenem minus meropenem), in the proportion of patients who were classified as clinical cures, was greater than or equal to -15%. This CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method). However, based on data submitted by the Sponsor and the Agency's review of the literature and other supportive evidence, a 15% NI margin was considered acceptable for the treatment of complicated IAI infections for studies using meropenem as the active comparator.

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

Secondary Efficacy Analyses

- A sensitivity analysis was conducted for the favorable clinical response in the mMITT analysis set using an alternative clinical outcome assignment for patients in the mMITT analysis set without a clinical assessment in the post-therapy period. In this definition (CR_2_mMITT) the outcome for patients with no clinical assessment in the post-therapy period was based on the last clinical assessment available (usually at EOT[IV]). If this last clinical assessment was indeterminate or an EOT(IV) assessment was not done, the patient was counted as a failure. Otherwise, the CR_2_mMITT analysis was defined according to the CR_1_mMITT outcome.

- Favorable clinical response in the cMITT analysis set (CR_1_cMITT)
- Favorable clinical response at the EOT(IV) (i.e., clinical cure or improvement) was determined in the ME at TOC and the CE at TOC analysis sets, and the favorable clinical response (i.e., clinical cure) at the EFU visit was determined in the ME at EFU and the CE at EFU analysis sets.
- Favorable per-patient microbiological cure rates (i.e., eradication or presumed eradication of all baseline pathogens) and favorable per-pathogen microbiological outcomes (i.e., eradication or presumed eradication) in the ME analysis sets at the EFU and TOC visits.
- Per-blood pathogen microbiological outcome in the cMITT analysis set was based on the last available repeat blood culture result (regardless of the date of the clinical response assessment). If follow-up blood culture results were not available, the outcome for blood pathogens was presumed from the clinical response at the EOT(IV) visit.

Adjustment for Covariates

Sensitivity analyses of the primary and co-primary endpoints were conducted by adjusting for the effects of the site of infection (complicated localized appendicitis versus diagnosis of other sites of IAI) and the severity of illness (APACHE II score less than or equal to 10 or greater than 10) using a continuity-adjusted CMH-type method weighted by the sample sizes.

Handling of dropouts/missing data

Patients who dropped out or had missing or indeterminate outcome data were excluded from the primary analysis based on the ME at TOC analysis set, unless considered to be an early evaluable failure. However, these patients were accounted for in the MITT analyses. For these analyses, 2 different clinical response definitions, denoted CR_1_mMITT and CR_2_mMITT, were used. Under the CR_1_mMITT definition, a more conservative analysis was conducted in which patients who did not have a post-therapy clinical assessment were counted as failures. Under the CR_2_mMITT definition, a less conservative analysis was conducted in which the last clinical outcome was recorded. If all assessments were missing or indeterminate, the outcome was assigned as failure. Patients who failed therapy prior to the TOC visit had this outcome carried forward to the TOC visit. If otherwise evaluable, such patients were included in the primary analysis based on ME patients at TOC.

Sample Size Selection

The original sample size for the primary analysis in each study was based on the selected 15% non-inferiority margin, 80% expected clinical cure rates, 65% subject evaluability for the primary efficacy analysis set, a one-tailed 2.5% significance level, and 80% power. Although two co-primary analysis sets were defined for these studies the sample size estimation was based only on the analysis in the ME at TOC analysis set.

Examination of Subgroups

Subgroups included sex, age (less than 65, 65 years and older, less than 75, 75 years and

older), race, presence of bacteremia at baseline, infectious process, timing of onset of infection (post-operative versus pre-operative), anatomic site of infection, and operative procedure type (laparotomy, percutaneous drainage, open, or other). In addition, summaries by region (North America, South America, or Europe) and within each region, by infection site (complicated localized appendicitis versus other sites of IAI) and APACHE II score (less than or equal to 10, greater than 10) were provided.

Sample Size Adjustments

One adjustment to the original study sample size was done in each study in order to increase study power from 80% to 90% as a result of the re-evaluation of the development plan that occurred when PPI was acquired by J&JPRD on July 1, 2005. This adjustment resulted in an increase the total sample size from 346 (224 evaluable) to 472 (306 evaluable) patients.

Surgical Review Board

A surgical review board (SRB) consisting of 9 surgeons and 2 interventional radiologists assessed the adequacy of the initial surgical or interventional radiology procedure for subjects with intra-abdominal infections classified as clinical failures and for subjects whose deaths met criteria to be classified as clinically indeterminate. The purpose of this review was to attempt to distinguish between true antibiotic failures vs. an inadequate initial procedure which could preclude any chance of antibiotic success.

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

3.1.4 Efficacy Results

The primary analyses of studies DORI-07 and DORI-08 provided evidence of non-inferiority within a 15% non-inferiority margin for both co-primary endpoints, clinical cure rates at TOC in the ME and mMITT populations. Secondary analyses of clinical cure or improvement rate at the EOT(IV) visit, clinical cure rate at the EFU visit and microbiological endpoints at the TOC visit were found to be generally consistent between the two treatments.

Table 9: Sponsor Analysis of Clinical Cure Rates (%) at TOC for Complicated Intra-Abdominal Infections (DORI-07 and DORI-08)

Endpoint/Analysis Set	n/N (%)	n/N (%)	Diff ^a ,(95% CI) (%)
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<u>DORI-07</u>			
Clinical Cure at TOC (ME) ^d	140/163 (85.9)	133/156 (85.3)	0.6 (-7.7; 9.0) ^b , (-7.2; 8.5) ^c
Clinical Cure (mMITT) ^{d,e}	152/195 (77.9)	150/190 (78.9)	-1.0 (-9.7; 7.7) ^b , (-9.2; 7.3) ^c
<u>DORI-08</u>			
Clinical Cure at TOC (ME) ^d	135/162 (83.3)	127/153 (83.0)	0.3 (-8.6; 9.2) ^b , (-8.0; 8.7) ^c
Clinical Cure (mMITT) ^{d,e}	149/200 (74.5)	140/185 (75.7)	-1.2 (-10.3; 8.0) ^b , (-9.8; 7.5) ^c

a Doripenem minus Meropenem (unadjusted difference)

b 2-sided 95% confidence interval (CI) was based on the normal approximation to the difference of 2 binomial proportions with continuity correction.

c Two-sided confidence intervals computed without continuity correction based on the unadjusted difference

d Co-primary endpoints as defined by Sponsor

e CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

Source: Adapted From Sponsor Table 2 of Clinical Overview

Statistical Reviewer Comments: *The Sponsor's co-primary endpoints for Study DORI-07 were clinical cure rates at TOC in the ME population and clinical cure rates in the mMITT population. Differences in these co-primary endpoints were not significant. According to the Sponsor, clinical cure rates in the ME population were 140/163 (85.9%) versus 133/156 (85.3%), a difference (95% CI) of 0.6% (-7.7%; 9.0%). Clinical cure rates in the mMITT population were 152/195 (77.9%) versus 150/190 (78.9%), a difference (95% CI) of -1.0% (-9.7%; 7.7%). The lower limit of the 95% CI was above -15% in both of the co-primary populations. These results provide evidence of non-inferiority within a 15% NI margin. Microbiological cure rates at TOC in the ME population provided further support towards a finding of non-inferiority.*

The primary analysis listed in the above table is based on unadjusted (crude) treatment differences. Analyses based on adjusted differences according to randomization strata are provided in Section 4 of this review. Adjusted analyses were found to be generally consistent with the unadjusted analyses.

The Sponsor's computations of the 95% CIs in the table above assumed a continuity correction which has made 95% interval estimates conservative. Continuity corrections are statistically justified in cases with exact formulas (exact at finite N) for the variance but may not be necessary in cases where N is sufficiently large and variance formulas are asymptotic. Less conservative calculations of the 95% CI without use of a continuity correction are also provided.

Table 10: FDA Re-analysis of Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets

<u>Study</u> Visit/Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI) ^b (%)
<u>DORI-07</u>			
Clinical Cure at TOC (ME) ^c	130/157 (82.8)	128/149 (85.9)	-3.1 (-11.3; 5.2)
Clinical Cure (mMITT) ^c	143/194 (73.7)	149/191 (78.0)	-4.3 (-12.8; 4.3)

DORI-08

Clinical Cure at TOC (ME) ^c	128/158 (81.0)	119/145 (82.1)	-1.1 (-9.8; 7.8)
Clinical Cure (mMITT) ^c	143/199 (71.9)	138/186 (74.2)	-2.3 (-11.2; 6.6)

DORI-07 and DORI-08

Clinical Cure at TOC (ME) ^c	258/315 (81.9)	247/294 (84.0)	-2.1 (-8.1, 3.9)
Clinical Cure (mMITT) ^c	286/393 (72.8)	287/377 (76.1)	-3.4 (-9.5, 2.8)

a Doripenem minus Meropenem.

b Two-sided 95% CI calculated without continuity correction

c Co-primary endpoints as defined by Sponsor

Note that pooled analyses were not included in the primary analysis.

Statistical Reviewer Comments: *The co-primary endpoints for Studies DORI-07 and DORI-08 were re-classified based upon a review by the Medical Officer (MO), Dr. Julie-Ann Crewalk. According to the FDA defined ME population, cure rates were based on the patient's planned rather than actual treatment arm, SRP re-classification without mis-randomized patients and a defined TOC window of 25-45 days (the original protocol window of 28-42 days ± 3 days). Other M.O. patient reclassifications were made for patients receiving concomitant anti-bacterial medications as well as for patients who received 72 hours of study drug. These patients were re-classified as a 'failure' in the FDA ME and mMITT re-analyses.*

For Studies DORI-07 and DORI-08, clinical cure rates at TOC in the FDA-defined ME and mMITT co-primary populations are shown in the above table. Differences in these co-primary endpoints consistently favored meropenem treated patients by 1.1% to 4.3% in both studies. Differences, however, were not statistically significant and did not affect the overall conclusion of non-inferiority within a 15% margin since for both the DORI-07 and DORI-08 studies, the lower limit of the 95% CI was above -15% in both co-primary populations. These results provided evidence of non-inferiority within a 15% NI margin.

In DORI-07, clinical cure rates were 130/157 (82.8) versus 128/149 (85.9) in the ME population, a difference (95% CI) of -3.1 (-11.3; 5.2), and 143/194 (73.7) versus 149/191 (78.0) in the mMITT population, a difference (95% CI) of -4.3 (-12.8; 4.3). In DORI-08, clinical cure rates were 128/158 (81.0) versus 119/145 (82.1) in the ME population, a difference (95% CI) of -1.1 (-9.8; 7.8), and 143/199 (71.9) versus 138/186 (74.2) in the mMITT population, a difference (95% CI) of -2.3 (-11.2; 6.6).

Table 11: Microbiological Cure Rates (%) at Complicated Intra-Abdominal Infections (DORI-07 and DORI-08)

Endpoint/Analysis Set	n/N (%)	n/N (%)	Diff (%) ^a	95% CI ^b
DORI-07				
Microbiological Cure at TOC (ME)	139/163 (85.3)	132/156 (84.6)	0.7	(-7.8; 9.1)
DORI-08				
Microbiological Cure at TOC (ME)	135/162 (83.3)	129/153 (84.3)	-1.0	(-9.7; 7.8)

<u>DORI-07 & DORI-08 (Pooled)</u>				
Microbiological Cure at TOC (ME) ^c	274/325 (84.3)	261/309 (84.5)	-0.2	(-5.8, 5.6)

a Doripenem minus Meropenem.

b 2-sided 95% confidence interval (CI) was based on the normal approximation to the difference of 2 binomial proportions with continuity correction.

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

e Pooled analyses may not provide reliable estimates due to study differences and lack of randomization..

Source: Adapted From Sponsor Table 2 of Clinical Overview

Statistical Reviewer Comments: *Microbiological cure rates were largely similar in the doripenem and meropenem arms across the DORI-07 and DORI-08 studies and ranged from approximately 83%-85%.*

Table 12: Sponsor Comparison of Additional Clinical Outcomes by Visit and Analysis Set (Study DORI-07)

Visit Analysis Set	Doripenem n-Favorable/N (%)	Meropenem n-Favorable/N (%)	Difference (95% CI ^a) % Doripenem – Meropenem
EOT(IV)*			
CE at TOC	179/188 (95.2)	174/186 (93.5)	1.7 (-3.2, 6.7)
ME at TOC	154/163 (94.5)	147/156 (94.2)	0.2 (-5.2, 5.8)
EFU			
CE at EFU	167/188 (88.8)	166/185 (89.7)	-0.9 (-7.4, 5.5)
ME at EFU	145/164 (88.4)	135/152 (88.8)	-0.4 (-7.5, 6.9)
TOC			
CE at TOC	163/188 (86.7)	161/186 (86.6)	0.1 (-6.9, 7.2)
ME at TOC	140/163 (85.9)	133/156 (85.3)	0.6 (-7.2, 8.5)
At Any Time 1 to 60 days After Last Dose of Study Drug Therapy			
mMITT ^b	152/195 (77.9)	150/190 (78.9)	-1.0 (-9.2, 7.3)
cMITT	178/226 (74.1)	183/228 (80.3)	-1.5 (-9.0, 6.0)
At Any Time While on Study Drug and up to 60 Days After Last Dose of IV Study Drug Therapy			
mMITT ^c	153/195 (78.5)	153/190 (80.5)	-2.1 (-10.2, 6.1)

*Favorable clinical outcomes at the EOT(IV) visit included clinical cure and clinical improvement, whereas the favorable clinical outcome at the EFU and TOC visits was clinical cure.

a Two-sided confidence intervals computed without continuity correction.

b CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

c CR_2_mMITT = clinical response definition_2 for the microbiological modified intent-to-treat (mMITT)

Source: Partially Adapted From Sponsor Table 15.2.3.1-2

Statistical Reviewer Comments: *Comparisons in clinical outcomes between doripenem and meropenem were generally consistent across various visit and analysis sets considered. The lower bound of the 95% CI for all comparisons was also greater than -15% in all comparisons providing evidence of non-inferiority within a NI margin of 15%.*

Table 13: Sponsor Comparison of Additional Clinical Outcomes by Visit and Analysis Set (Study DORI-08)

Visit	Doripenem	Meropenem	Difference (95%CI ^a) %
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Analysis Set	n Favorable ^d /N (%)	n Favorable ^d /N (%)	Doripenem – Meropenem
EOT(IV)			
CE at TOC	181/192 (94.3)	178/192 (92.7)	1.6 (-3.6, 6.8)
ME at TOC	151/162 (93.2)	140/153 (91.5)	1.7 (-4.4, 8.0)
EFU			
CE at EFU	163/189 (86.2)	168/186 (90.3)	-4.1 (-10.8, 2.5)
ME at EFU	134/158 (84.8)	133/150 (88.7)	-3.9 (-11.6, 3.9)
TOC			
CE at TOC	161/192 (83.9)	165/192 (85.9)	-2.1 (-9.4, 5.2)
ME at TOC	135/162 (83.3)	127/153 (83.0)	0.3 (-8.0, 8.7)
At Any Time 1 to 60 days After Last Dose of Study Drug Therapy			
mMITT ^b	149/200 (74.5)	140/185 (75.7)	-1.2 (-9.8, 7.5)
cMITT	177/239 (74.1)	177/226 (78.3)	-4.3 (-12.0, 3.5)
At Any Time While on Study Drug and up to 60 Days After Last Dose of IV Study Drug Therapy			
mMITT ^c	153/200 (76.5)	143/185 (77.3)	-0.8 (-9.2, 7.7)

a Two-sided confidence intervals computed without continuity correction.

b CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

c CR_2_mMITT = clinical response definition_2 for the microbiological modified intent-to-treat (mMITT)

d Favorable clinical outcomes at the EOT(IV) visit included clinical cure and clinical improvement, whereas the favorable clinical outcome at the EFU and TOC visits was clinical cure.

Source: Partially Adapted From Sponsor Table 15.2.3.1-2

Statistical Reviewer Comments: *Comparisons in clinical outcomes between doripenem and meropenem were generally consistent across various visit and analysis sets considered. The lower bound of the 95% CI for all comparisons was also greater than -15% in all comparisons providing evidence of non-inferiority within a margin of 15%.*

Table 14: Favorable Per-Pathogen Microbiological Outcomes for Selected Baseline Intra-abdominal Pathogens at the TOC Visit^a (Study DORI-07: Microbiologically Evaluable at TOC Analysis Set)

	<u>Doripenem</u>	<u>Meropenem</u>	
Gram Stain Status			
Higher Level Group			
Baseline IA Pathogen ^b	F/NQ(%) ^{c,d}	F/NQ(%) ^{c,e}	Difference(%) (95% CI) ^f
Gram-positive Aerobes			
Viridans Group Streptococci	50/54 (92.6)	35/41 (85.4)	7.2 (-7.8, 22.3)
<i>Streptococcus intermedius</i>	15/16 (93.8)	8/10 (80.0)	13.7 (-14.6, 48.9)
Other Gram-positive Aerobes	27/33 (81.8)	32/38 (84.2)	-2.4 (-22.8, 18.0)
<i>Enterococcus faecalis</i>	9/12 (75.0)	8/9 (88.9)	-13.9 (-49.0, 26.2)
Gram-positive Anaerobes	27/33 (81.8)	30/37 (81.1)	0.7 (-20.4, 21.8)
Gram-negative Aerobes			
Enterobacteriaceae	140/157 (89.2)	122/141 (86.5)	2.6 (-5.5, 10.8)
<i>Escherichia coli</i>	91/104 (87.5)	84/100 (84.0)	3.5 (-7.1, 14.1)
Levofloxacin-resistant Strains	2/4 (50.0)	2/3 (66.7)	-16.7 (-79.4, 59.3)

Non-levofloxacin-resistant Strains	86/96 (89.6)	79/93 (84.9)	4.6 (-5.9, 15.2)
ESBL-producing Strains	2/3 (66.7)	2/2 (100)	-33.3 (-90.6, 60.4)
Non-ESBL-producing Strains	86/97 (88.7)	79/94 (84.0)	4.6 (-6.2, 15.4)
Non-fermenters	22/23 (95.7)	17/24 (70.8)	24.8 (2.7, 47.3)
<i>Pseudomonas aeruginosa</i>	18/19 (94.7)	15/19 (78.9)	15.8 (-8.0, 40.7)

Gram-negative Anaerobes

<i>Bacteroides fragilis</i> Group	67/75 (89.3)	75/89 (84.3)	5.1 (-6.5, 16.6)
<i>Bacteroides caccae</i>	11/12 (91.7)	8/8 (100.0)	-8.3 (-38.6, 28.3)
<i>Bacteroides fragilis</i>	23/27 (85.2)	16/22 (72.7)	12.5 (-11.2, 37.0)
<i>Bacteroides thetaiotaomicron</i>	14/16 (87.5)	19/20 (95.0)	-7.5 (-33.2, 14.9)
<i>Bacteroides uniformis</i>	10/11 (90.9)	8/11 (72.7)	18.2 (-18.8, 52.9)
Other Gram-negative Anaerobes	21/27 (77.8)	28/30 (93.3)	-15.6 (-36.0, 3.5)

CI= confidence interval; ESBL = extended spectrum β -lactamase; F = number of qualifying IA baseline pathogens with a favorable microbiological outcome among ME at TOC patients; IA = intra-abdominal; IV = intravenous; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; NQ = number of qualifying IA baseline pathogens in the ME at TOC analysis set; S = susceptible; TOC = test-of-cure.

a A microbiological outcome of eradication or presumed eradication was considered favorable.

b For patients with more than 1 pathogen at baseline, the outcome for each pathogen was determined independently.

c For each patient, a baseline IA pathogen was uniquely represented using the most resistant strain. Qualifying pathogens were susceptible to the IV study drug therapy administered, and the patient did not receive confounding antibacterial therapy. Baseline isolates for which susceptibility testing was missing were assumed susceptible to the IV study drug therapy received except for *E. faecium*, methicillin-resistant *S. aureus*, and *Stenotrophomonas maltophilia*, which were considered resistant to both IV study drug therapies. Percentages were given with respect to the NQ for the given genus and species in the respective treatment arm.

d For doripenem, pathogens were considered S if the MIC level was ≤ 4 μ g/mL.

e For meropenem, the MIC defining pathogens as S was obtained according to the Clinical and Laboratory Standards Institute (2004) recommendations.

f The unadjusted difference in percent favorable (doripenem minus meropenem) was presented. The 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions. These analyses were done for isolates with an NQ count of at least 10 in the doripenem arm. Exact two-sided 95% CI calculated for isolates with an NQ count less than 10 in the doripenem arm.

Source: Adapted From Sponsor Study Report Table 17

Statistical Reviewer Comments: *Treatment comparisons in rates of favorable per pathogen microbiological outcomes were generally similar between doripenem i.v. and meropenem i.v. arms. Doripenem compared favorable to meropenem for "Non-fermenters" with a treatment difference (95% CI) of 24.8% (2.7, 47.3). Although the 95% CI excludes 0, this result may not be meaningful since it was not pre-specified but rather obtained through post-hoc testing involving a large number of comparisons and a high false positive rate.*

Table 15: Favorable Per-Pathogen Microbiological Outcomes for Selected Baseline Intra-abdominal Pathogens at the TOC Visit^a (Study DORI-08: Microbiologically Evaluable at TOC Analysis Set)

	<u>Doripenem</u>	<u>Meropenem</u>	
Gram Stain Status			
Higher Level Group			
Baseline IA Pathogen ^b	F/NQ ^{c,d}	F/NQ ^{c,e}	Difference (95% CI) ^f
Gram-positive Aerobes			
Viridans Group Streptococci	43/55(78.2)	36/49 (73.5)	4.7 (-13.7, 23.1)
<i>Streptococcus intermedius</i>	15/20 (75.0)	13/19 (68.4)	6.6 (-22.7, 35.3)
Other Gram-positive Aerobes	22/26 (84.6)	17/29 (58.6)	26.0 (1.1, 48.5)

Gram-positive Anaerobes	34/40 (85.0)	32/45 (71.1)	13.9 (-5.7, 33.5)
Gram-negative Aerobes			
Enterobacteriaceae	131/158 (82.9)	112/133 (84.2)	-1.3 (-10.5, 7.9)
<i>Escherichia coli</i>	98/112 (87.5)	84/99 (84.8)	2.7 (-7.6, 13.0)
Levofloxacin-resistant Strains	8/9 (88.9)	5/5 (100.0)	-11.1 (-48.7, 40.1)
Non-levofloxacin-resistant Strains	86/98 (87.8)	79/92 (85.9)	1.9 (-8.8, 12.6)
ESBL-producing Strains	3/3 (100.0)	2/2 (100.0)	0.0 (-72.1, 84.2)
Non-ESBL-producing Strains	91/104 (87.5)	82/94 (87.2)	0.3 (-10.0, 10.5)
<i>Klebsiella pneumoniae</i>	11/17 (64.7)	10/11 (90.9)	-26.2 (-55.1, 10.4)
Non-fermenters	22/28 (78.6)	11/15 (73.3)	5.2 (-21.0, 35.0)
<i>Pseudomonas aeruginosa</i>	16/21 (76.2)	9/13 (69.2)	7.0 (-23.9, 40.1)
Gram-negative Anaerobes			
<i>Bacteroides fragilis</i> Group	85/98 (86.7)	77/92 (83.7)	3.0 (-8.1, 14.2)
<i>Bacteroides caccae</i>	12/13 (92.3)	10/11 (90.9)	1.4 (-23.9, 40.1)
<i>Bacteroides fragilis</i>	33/40 (82.5)	38/46 (82.6)	-0.1 (-18.5, 18.3)
<i>Bacteroides thetaiotaomicron</i>	16/18 (88.9)	13/16 (81.3)	7.6 (-19.1, 35.6)
<i>Bacteroides uniformis</i>	9/11 (81.8)	7/7 (100.0)	-18.2 (-52.3, 23.8)
Other Gram-negative Anaerobes	23/31 (74.2)	21/27 (77.8)	-3.6 (-29.0, 21.9)

CI=confidence interval; ESBL = extended spectrum β -lactamase; F = number of qualifying IA baseline pathogens with a favorable microbiological outcome among ME at TOC patients; IA = intra-abdominal; IV = intravenous; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; NQ = number of qualifying IA baseline pathogens in the ME at TOC analysis set; S = susceptible; TOC = test-of-cure.

- A microbiological outcome of eradication or presumed eradication was considered favorable.
- For patients with more than 1 pathogen at baseline, the outcome for each pathogen was determined independently.
- For each patient, a baseline IA pathogen was uniquely represented using the most resistant strain. Qualifying pathogens were susceptible to the IV study drug therapy administered, and the patient did not receive confounding antibacterial therapy. Baseline isolates for which susceptibility testing was missing were assumed susceptible to the IV study drug therapy received except for *E. faecium*, methicillin-resistant *S. aureus*, and *Stenotrophomonas maltophilia*, which were considered resistant to both IV study drug therapies. Percentages were given with respect to the NQ for the given genus and species in the respective treatment arm.
- For doripenem, pathogens were considered S if the MIC level was ≤ 4 $\mu\text{g/mL}$.
- For meropenem, the MIC defining pathogens as S was obtained according to the Clinical and Laboratory Standards Institute (2004) recommendations.
- The unadjusted difference in percent favorable (doripenem minus meropenem) was presented. The 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions. These analyses were done for isolates with an NQ count of at least 10 in the doripenem arm. Exact two-sided 95% CI calculated for isolates with an NQ count less than 10 in the doripenem arm.

Source: Partially Adapted From Sponsor Study Report Table 17

Statistical Reviewer Comments: *Treatment comparisons in rates of favorable per pathogen microbiological outcomes were generally similar between doripenem i.v. and meropenem i.v. treated patients. Although estimates of favorable per-pathogen rates in the doripenem arm were 26.2% lower for the pathogen Klebsiella pneumoniae, this difference was not found to be statistically significant. Doripenem compared favorable to meropenem for "Other Gram-positive Aerobes" with a treatment difference (95% CI) of 26.0% (1.1, 48.5). Although the 95% CI excludes 0, this result may not be meaningful since it was not pre-specified but rather obtained through post-hoc testing involving a large number of comparisons and a high false positive rate.*

3.1.5 Efficacy Conclusions

Studies DORI-07 and DORI-08

In the DORI-07 and DORI-08 studies, clinical cure rates at TOC in the FDA-defined ME and mMITT co-primary populations consistently favored Meropenem treated patients by a margin of 1.1% to 4.3%. These differences were not statistically significant and did not affect the overall conclusion of non-inferiority. However, there are concerns regarding some potential loss of efficacy in patients treated with doripenem. There is also a concern that this loss of efficacy would be larger if patients were not allowed a switch from IV to oral medication. In the subset of DORI-07 and DORI-08 study patients receiving only IV therapy, patients in the doripenem arm had clinical cure rates which were approximately 6.3% and 8.1% lower in the ME and mMITT populations, respectively. Interpretations of this analysis, however, may be confounded by differences in the proportions of subjects in each treatment arm who switched to from IV to oral amoxicillin/clavulanate therapy.

Secondary analyses of clinical cure or improvement rate at the EOT(IV) visit, clinical cure rate at the EFU visit and microbiological endpoints at the TOC visit were found to be generally consistent between the two treatments. Note that secondary analyses of Study DORI-07 were not powered to demonstrate non-inferiority. Sensitivity and subgroup analyses were also generally consistent with primary analysis findings and considered supportive. Doripenem also provided some evidence towards microbiological efficacy against major causative pathogens of cIAI at the TOC visit. Eradication rates for these pathogens appeared similar to rates in meropenem arm. However, due to the small number of isolates presented, statistical inferences are limited.

3.2 Evaluation of Safety

Please refer to the safety review provided by the medical officer, Dr. Julie-Ann Crewalk.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Sensitivity and subgroup analyses were also conducted to assess the effects of various factors on overall study results but did not identify any clear inconsistencies with treatment comparisons in the primary analyses and were therefore considered as supportive of overall study findings. Sensitivity analyses examined effects of various factors on the Sponsor's primary analysis findings. These factors included influential sites, analysis set definitions, study drug therapy (IV or oral), treatment duration, clinical response definitions, sample size changes, TOC window changes, surgical review panel re-classifications, unplanned study drug treatments. Subgroup analyses also addressed other factors which could have influenced the Sponsor's primary analysis results. These factors included the patient's categorization with respect to age, gender, race, geographic region, post-operative infection, APACHE II Score, IVRS Randomization Stratum, treatment duration, renal impairment status and creatinine clearance group. It should be noted that post-hoc subgroup and sensitivity analyses may be severely limited in identifying significant differences between treatments due to a potential lack of power (i.e. inadequate sample size) and a lack of planning (i.e. failure to control for overall type I error rate).

Statistical Reviewer Comments: *Sensitivity analyses presented in Section 4 of this review were performed for comparisons with the Sponsor's primary analysis results.*

Table 16: Per Patient Clinical Cure at mMITT Definition 1 (CR_1): Overall and by Subgroups (DORI-07)

Clinical Cure (%)	Doripenem	Meropenem	% Difference (95% CI)
Overall:	152/195(77.9%)	150/190(78.9%)	-1.0 (-9.2, 7.3)
By Subgroups:			
APACHE Score			
<=10	141/172 (82.0)	137/169 (81.1)	0.9 (-7.4, 9.2)
>10	11/23 (47.8)	13/21 (61.9)	-14.1 (-43.0, 16.2)
Post-Operative Infection?			
No	135/166 (81.3)	138/171 (80.7)	0.6 (-9.0, 7.8)
Yes	17/29 (58.6)	12/19 (63.2)	-4.5 (-32.2, 24.4)
Sex			
Females	52/72 (72.2)	61/76 (80.3)	-8.0 (-21.8, 5.7)
Males	100/123 (81.3)	89/114 (78.1)	3.2 (-7.0, 13.6)
Race			
Black or African Heritage	11/15 (73.3)	13/15 (86.7)	-13.3 (-43.4, 18.8)
Caucasian	102/136 (75.0)	100/128 (78.1)	-3.1 (-13.3, 7.2)
Hispanic or Latino	37/42 (88.1)	35/44 (79.5)	8.5 (-7.6, 24.6)
Age			
Age < 65	124/156 (79.5)	127/154 (82.5)	-3.0 (-11.8, 5.8)
Age >= 65	28/39 (71.8)	23/36 (63.9)	7.9 (-13.1, 28.6)
Age < 75	142/180 (78.9)	141/176 (80.1)	-1.2 (-7.2, 9.6)
Age >= 75	10/15 (66.7)	9/14 (64.3)	2.4 (-33.1, 37.4)
Region			
Europe	38/48 (79.2)	39/48 (81.3)	-2.1 (-18.3, 14.2)
North America	37/61 (60.7)	48/67 (71.6)	-11.0 (-27.0, 5.4)
South America	77/86 (89.5)	63/75 (84.0)	5.5 (-5.0, 16.8)

a Two-sided 95% CI computed using without continuity correction. Exact test used for comparisons of smaller groups where $N(n/N)(1-n/N) < 5$ in at least one group.

Source: Partially Adapted From Sponsor Study Report Table 15.2.2.1-3

Statistical Reviewer Comments: *Clinical cure rates both overall and in subgroups were generally consistent with a finding of non-inferiority of doripenem i.v. therapy to meropenem i.v. therapy. Clinical cure rate estimates were substantially lower in the doripenem arm in North American patients, female patients, black patients and patients with APACHE Scores > 10. However, differences based on these estimates were not found to be significantly different from 0.*

Table 17: Per Patient Clinical Cure (%) at mMITT Definition 1 (CR_1): Overall and by Subgroups (DORI-08)

	Doripenem	Meropenem	% Difference (95% CI) ^a
Clinical Cure			
Overall:	149 (74.5%)	140 (75.7%)	-1.2 (-9.8, 7.5)
By Subgroups:			
APACHE Score			
<=10	133/171(77.8)	130/163(79.8)	-2.0 (-10.8, 6.9)
>10	16/29 (55.2)	10/22 (45.5)	9.7 (-18.7, 37.2)
IVRS Randomization Stratum			
Appendicitis	57/65 (87.7)	38/49 (77.6)	10.1 (-3.7, 25.2)
Other	92/135 (68.1)	102/136 (75.0)	-6.9 (-17.5, 3.9)
Post-Operative Infection?			
No	140/185 (75.7)	132/168 (78.6)	-2.9 (-11.6, 6.0)
Yes	9/15 (60.0)	8/17 (47.1)	12.9 (-22.6, 46.5)
Sex			
Females	50/73 (68.5)	46/68 (67.6)	0.8 (-16.2, 14.4)
Males	99/127 (78.0)	94/117 (80.3)	-2.4 (-18.4, 2.5)
Race			
Black or African Heritage	4/6 (66.7)	2/2 (100.0)	-33.3 (-78.9, 53.4)
Caucasian	121/154 (78.6)	119/156 (76.3)	2.3 (-7.1, 11.6)
Hispanic or Latino	22/33 (66.7)	18/24 (75.0)	-8.3 (-31.8, 16.9)
Age			
Age < 65	126/164 (76.8)	116/150 (77.3)	-0.5 (-9.8, 8.9)
Age ≥ 65	23/36 (63.9)	24/35 (68.6)	-4.7 (-26.1, 17.2)
Age < 75	142/187 (75.9)	131/174 (75.3)	0.6 (-8.2, 9.6)
Age ≥ 75	7/13 (53.8)	9/11 (81.8)	-28.0 (-63.1, 11.9)
Region			
Europe	32/38 (84.2)	30/38 (79.0)	5.3 (-12.7, 23.2)
North America	40/68 (58.8)	36/59 (61.0)	-2.2 (-18.9, 14.8)
South America	77/94 (81.9)	74/88 (84.1)	-2.2 (-13.2, 9.0)

^a Two-sided 95% CI computed without continuity correction. Exact test used for comparisons of smaller groups where $N(n/N)(1-n/N) < 5$ in at least one group.

Source: Partially Adapted From Sponsor Study Report Table 15.2.2.1-3

Statistical Reviewer Comments: *Clinical cure rates both overall and in subgroups were generally consistent with a finding of non-inferiority of doripenem i.v. therapy to meropenem i.v. therapy. Clinical cure rate estimates were substantially lower in the doripenem arm in older patients (i.e. age ≥ 65 or age ≥ 75), black or Hispanic patients and patients with IVRS Randomization Stratum of "Other." However, differences based on these estimates were not found to be significantly different from 0.*

Table 18: Stratified Analysis of Clinical Cure Rates (%) at TOC for Complicated Intra-Abdominal Infections (DORI-07 and DORI-08)

Endpoint/Analysis Set	n/N (%)	n/N (%)	Weighted Diff ^a , (95% CI) ^b
DORI-07			
Clinical Cure at TOC (ME) ^d	140/163 (85.9)	133/156 (85.3)	0.7 (-7.6, 8.9)

Clinical Cure (mMITT) ^{d,e}	152/195 (77.9)	150/190 (78.9)	-0.7 (-9.2, 7.9)
<u>DORI-08</u>			
Clinical Cure at TOC (ME) ^d	135/162 (83.3)	127/153 (83.0)	0.5 (-8.4; 9.3) ^b ,
Clinical Cure (mMITT) ^{d,e}	149/200 (74.5)	140/185 (75.7)	-0.8 (-9.7; 8.1) ^b ,

a For the overall cure rate, the weighted difference between percentages is the weighted sum of the difference between the percent cure in the Doripenem IV treatment arm and the percent cure in the Meropenem IV treatment arm in each baseline stratum, which is the combination of infection site (appendix versus other intra-abdominal site) and APACHE score (<=10, >10) for a total of four randomization strata. Weights are obtained via the Cochran-Mantel-Haenszel (CMH) approach using the number of patients in each baseline stratum.

b The 95% CI is calculated using the normal approximation to the binomial distribution with adjustment using the CMH method with continuity correction.

c Two-sided confidence intervals computed without continuity correction.

d Co-primary endpoints as defined by Sponsor

e CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

Source: Sponsor Tables 15.2.21-1, 15.2.21-3

Table 19: Comparison of Clinical Cure Rates of the ME and mMITT Co-primary Analysis Sets for the Three Sample Size Populations: Original Population, Subsequent Population, Final Population (DORI-07 and DORI-08)

Study Analysis Set/Visit Sample	Doripenem (%)	Meropenem (%)	Difference (95% CI) ^a
<u>DORI-07</u>			
ME at TOC Analysis Set			
Original	101/117 (86.3)	96/113 (85.0)	1.4 (-8.6, 11.3)
Subsequent	39/46 (84.8)	37/43 (86.0)	-1.3 (-18.2, 15.6)
Final	140/163 (85.9)	133/156 (85.3)	0.6 (-7.7, 9.0)
mMITT Analysis Set			
Original	108/141 (76.6)	110/139 (79.1)	-2.5 (-13.0, 7.9)
Subsequent	44/54 (81.5)	40/51 (78.4)	3.1 (-14.2, 20.3)
Final	152/195 (77.9)	150/190 (78.9)	-1.0 (-9.7, 7.7)
<u>DORI-08</u>			
ME at TOC Analysis Set			
Original	94/113 (83.2)	91/114 (79.8)	3.4 (-7.6, 14.3)
Subsequent	41/49 (83.7)	36/39 (92.3)	-8.6 (-24.2, 7.0)
Final	135/162 (83.3)	127/153 (83.0)	0.3 (-8.6, 9.2)
mMITT Analysis Set			
Original	103/140 (73.6)	101/137 (73.7)	-0.2 (-11.2, 10.9)
Subsequent	46/60 (76.7)	39/48 (81.3)	-4.6 (-21.8, 12.7)
Final	149/200 (74.5)	140/185 (75.7)	-1.2 (-10.3, 8.0)

a The 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions.

Source: Sponsor Tables 15.2.2.1-1, 15.2.2.1-1b, 15.2.2.1-1c, 15.2.2.1-3, 15.2.2.1-3b, and 15.2.2.1-3c

Statistical Reviewer Comments: *Clinical cure rates of co-primary analysis sets for three sample size populations: “Original”, “Subsequent” and “Final” were largely consistent with an overall finding of non-inferiority. Note that the lower bounds of the “Original” and “Final” populations in both the ME and mMITT populations were within an acceptable non-inferiority margin of 15%.*

Table 20: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients Receiving IV Therapy Only

Analysis Set/Treatment Study	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI ^b)
Clinical Cure at TOC (ME) ^{c,d}			
DORI-07	34/45 (75.6)	43/53 (81.1)	-5.6 (-22.4; 10.7)
DORI-08	19/29 (65.5)	24/33 (72.7)	-7.2 (-29.8; 15.6)
DORI-07& 08 ^e	53/74 (71.6)	67/86 (77.9)	-6.3 (-19.9; 7.1)
Clinical Cure (mMITT) ^{c,d}			
DORI-07	41/68 (60.3)	45/68 (66.2)	-5.9 (-21.8; 10.3)
DORI-08	25/55 (45.5)	31/55 (56.4)	-10.9 (-28.8; 7.7)
DORI-07&08 ^e	66/123 (53.7)	76/123 (61.8)	-8.1 (-20.2; 4.2)

a Doripenem minus Meropenem.

b Two-sided 95% CI computed without continuity correction

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

e Pooled analyses may not provide reliable estimates due to study differences and lack of randomization.

Source: FDA Table

Statistical Reviewer Comments: *Clinical cure rates for patients in DORI-07 and DORI-08 receiving only IV therapy were higher in the meropenem arm than in the doripenem arm, although differences were not significant. In the ME population, comparisons of pooled cure rates were 53/74 (71.6%) versus 67/86 (77.9%), a difference (95% CI) of -6.3% (-19.9, 7.1). In the mMITT (CR1_mMITT) population, pooled comparisons were 66/123 (53.7) versus 76/123 (61.8), a difference (95% CI) of -8.1(-20.2; 4.2). Interpretations of this analysis, however, may be limited since comparisons of clinical cure rates may have been confounded by differences in the proportions of ME subjects in each study arm who switched to oral amoxicillin/clavulanate therapy.*

Table 21: Clinical Cure Rates (%) at TOC Visit Using Clinical Response Definition CR_2_mMITT

Analysis Set/Treatment Study	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI ^b) (%)
Clinical Cure (CR_2_mMITT) ^c			
DORI-07	153/195 (78.5)	153/190 (80.5)	-2.0 (-10.2; 6.1)

DORI-08	153/200 (76.5)	143/185 (77.3)	-0.8 (-9.2; 7.7)
DORI-07 & DORI-08	306/395 (77.5)	296/375 (78.9)	-1.5 (-7.3, 4.4)

a Doripenem minus Meropenem.

b Two-sided 95% CI without continuity correction computed

c CR_2_mMITT = clinical response definition_2 for the microbiological modified intent-to-treat (mMITT)

Source: FDA Table

Statistical Reviewer Comments: *Differences in the clinical response definition were consistent among treatments and did not appear to have influenced overall study findings of non-inferiority.*

An independent expert SRP, under blinded conditions, assessed the adequacy of surgical interventions in all patients who were clinical failures and evaluated whether second procedures in patients assessed as cures actually represented failures. In Study DORI-07, approximately 11% of all randomized patients met the criteria of review by the SRP. Following their blinded review, the panel changed the clinical response from clinical cure to failure in only 1 patient (in the meropenem treatment arm) and assessed 4 patients (2 in each treatment arm) as non-evaluable because of inadequate initial infection source control. In Study DORI-08, the SRP panel reviewed the outcomes in approximately 12% of all randomized patients. Following their blinded review, the panel assessed 2 patients (1 in each treatment arm), previously classified as evaluable, to be non-evaluable because of inadequate initial infection source control. This panel changed the clinical response in 9 patients (5, doripenem; 4, meropenem) from clinical cure to failure.

Table 22: Clinical Cure Rates (%) in the ME and mMITT Populations Without Surgical Review Panel (SRP) Re-classifications

<u>Study</u> Visit/Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI ^b) (%)
<u>DORI-07</u>			
Clinical Cure at TOC (ME) ^{c,e}	141/165 (85.5)	134/158 (84.8)	0.6 (-7.2; 8.6)
Clinical Cure (mMITT) ^{c,d,e}	152/195 (77.9)	151/190 (79.5)	-1.5 (-9.7; 6.7)
<u>DORI-08</u>			
Clinical Cure at TOC (ME) ^{c,e}	139/163 (85.3)	131/154 (85.1)	0.2 (-7.7; 8.2)
Clinical Cure (mMITT) ^{c,d,e}	153/200 (76.5)	144/185 (77.8)	-1.3 (-9.7; 7.1)
<u>DORI-07 & DORI-08</u>			
Clinical Cure at TOC (ME) ^f	280/328 (85.4)	265/312 (84.9)	0.4 (-5.1, 6.0)
Clinical Cure (mMITT) ^f	305/395 (77.2)	295/375 (78.7)	-1.5 (-7.3, 4.4)

a Doripenem minus Meropenem.

b Two-sided 95% CI calculated without continuity correction

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

e Comparisons assume actual treatment received and re-evaluation for mis-randomization

f Pooled analyses may not provide reliable estimates due to study differences and lack of randomization.

Statistical Reviewer Comments: *Differences in the clinical response definition were consistent among treatments and did not appear to have influenced overall study findings of non-inferiority. SRP re-classification affected results of DORI-08 more than DORI-07.*

The effect of using planned rather than actual treatment randomization was also examined. There were two patients, one in DORI-07 and one in DORI-08, who were considered as evaluable cures in the doripenem arm. However, using planned randomization without mis-randomizations these two patients would not be included in the ME population.

Table 23: Comparison of Clinical Cure Rates (%) in the ME and mMITT Populations in Patients According to Baseline Creatinine Clearance Group

<u>Study</u> Visit/Analysis Set Clearance	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a , 95%CI ^b (%)
<u>Study DORI-07</u>			
Clinical Cure at TOC (ME) ^c			
≥ 80	104/122 (85.2)	109/124 (87.9)	-2.7 (-11.5; 6.0)
≥ 50, < 80	33/34 (97.1)	18/23 (78.3)	18.8 (1.8; 40.2)
> 30, ≤ 50	2/4 (50.0)	5/8 (62.5)	-12.5 (-66.7; 45.7)
≤ 30	1/3 (33.3)	1/1 (100)	-66.7 (-99.2; 59.1)
Clinical Cure (mMITT) ^{c,d}			
≥ 80	111/139 (79.9)	123/149 (82.6)	-2.7 (-11.9; 6.4)
≥ 50, < 80	37/47 (78.7)	20/31 (64.5)	14.2 (-6.3; 35.5)
> 30, ≤ 50	2/5 (40.0)	6/9 (66.7)	-26.7 (-72.3; 29.6)
≤ 30	1/4 (25.0)	1/1 (100)	-75.0 (-99.4; 46.1)
<u>Study DORI-08</u>			
Clinical Cure at TOC (ME) ^c			
≥ 80	102/123 (82.9)	94/109 (86.2)	-3.3 (-12.7; 6.3)
≥ 50, < 80	20/24 (83.3)	24/29 (82.8)	0.6 (-22.2; 21.8)
> 30, ≤ 50	10/11 (90.9)	6/9 (66.7)	24.2 (-14.2; 62.6)
≤ 30	3/4 (75.0)	2/5 (40.0)	35.0 (-36.0; 84.4)
Clinical Cure (mMITT) ^{c,d}			
≥ 80	114/146 (78.1)	101/126 (80.2)	-2.1 (-11.7; 7.8)
≥ 50, < 80	21/31 (67.7)	29/39 (74.4)	-6.6 (-28.0; 14.4)
> 30, ≤ 50	10/17 (58.8)	7/14 (50.0)	8.8 (-27.1; 43.4)
≤ 30	3/5 (60.0)	2/5 (40.0)	20.0 (-47.5; 75.7)

a Doripenem minus Meropenem.

b Two-sided 95% confidence intervals computed without continuity correction

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

Source: FDA Table

Statistical Reviewer Comments: *There were no consistent trends in clinical cure rates versus baseline creatinine clearance scores. However, for patients with scores of 50 or more but less than 80, cure rates were observed to be significantly higher in the Doripenem arm in DORI-07,*

33/34 (97.1) versus 18/23 (78.3) , a difference (95% CI) of 18.8 (1.8; 40.2). Although the 95% CI excludes 0, this result may not be meaningful since it was not pre-specified but rather obtained through post-hoc testing involving a large number of comparisons and a high false positive rate. In addition, findings for the same category were not supported in the DORI-08 study in which cure rates were observed to be lower in the doripenem arm.

Table 24: Clinical Cure Rates (%) in the ME Population Using Original TOC Visit Window of 28 to 42 Days and FDA Defined TOC Window of 25 to 45 Days

TOC Window/Treatment Study	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95%CI ^b) (%)
Clinical Cure (ME)			
Sponsor's Original Protocol TOC Window of 28-42 Days			
DORI-07	124/146 (84.9)	122/137 (89.1)	-4.1 (-12.1; 3.9)
DORI-08	120/142 (84.5)	113/136 (83.1)	1.4 (-7.3; 10.3)
DORI-07 & DORI-08 ^c	244/288 (84.7)	235/273 (86.1)	-1.4 (-7.2, 4.6)
FDA Defined TOC Window of 25-45days (28-42 Days ± 3 days)			
DORI-07	131/153 (85.6)	128/147 (87.1)	-1.5 (-9.4; 6.5)
DORI-08	129/153 (84.3)	119/142 (83.8)	0.5 (-7.9; 9.1)
DORI-07 & DORI-08 ^c	260/306 (85.0)	247/289 (85.5)	-0.5 (-6.2, 5.3)

a Doripenem minus Meropenem.

b Two-sided 95% confidence intervals computed without continuity correction

c Pooled analyses may not provide reliable estimates due to study differences and lack of randomization.

Source: FDA Table

Statistical Reviewer Comments: *In DORI-07, defining a TOC window of 28-42 days or 25-45 days versus a TOC window of 21-60 days (Table 9) reduced the estimated treatment benefit of doripenem therapy from 0.6% to -4.1% and from 0.6% to -1.5%, respectively. Similar reductions in the estimated treatment benefit, however, were not observed in DORI-08. Note that the definition used in defining the TOC window did not influence overall study findings of non-inferiority within 15%.*

The table below compares the top enrolling for randomized patients in Study DORI-07 and Study DORI-08 to evaluate the impact of one or a few sites on overall study results. Top enrolling sites listed enrolled 5% or more patients in their respective study.

Table 25: Comparison of Influential Sites for All Randomized Patients (DORI-07 and Dori-08 Studies)

DORI Study / Site#	Country	#Subjects (%)	Cure Rate (mMITT)	Cure Rate (ME)
07/372	Argentina	47 (9.9)	36/41 (87.8)	34/38 (89.5%)
07/402	Brazil	40 (8.4)	26/32 (81.3)	25/28 (89.3)

07/204	Poland	29 (6.1)	19/21 (90.5)	18/20 (90.0)
07101	Germany	25 (5.3)	13/18 (72.2)	10/11 (90.9)
07/374	Argentina	25 (5.3)	18/18 (100.0)	18/18 (100.0)
08/428	Brazil	80 (16.5)	64/68 (94.1)	61/63 (96.8)
08/382	Argentina	35 (7.2)	27/31 (87.1)	27/29 (93.1)
08/385	Argentina	32 (7.2)	22/28 (78.6)	21/27 (77.8)
08/430	Brazil	25 (5.2)	15/18 (83.3)	15/16 (93.8)

* Top enrolling sites listed enrolled 5% or more patients in the respective study.

Source: FDA Table

Statistical Review Comments: *Seven of the top nine enrolling sites came for South America (3 from Brazil and 4 from Argentina). The Brazilian site 08/428 enrolled the largest number of subjects across either study. Sites 08/428 and 07/374 had substantially higher cure rates and evaluability rates than observed in other study sites. Differences in cure rates between treatments were similar to differences observed among all other study sites.*

Table 26: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets for Patients With Renal Impairment

Analysis Set/Treatment Study	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI ^b)
<u>DORI-07</u>			
Clinical Cure at TOC (ME) ^c	3/7 (42.9)	5/9 (55.6)	-12.7 (-58.7; 37.8)
Clinical Cure (mMITT) ^{c,d}	3/10 (30.0)	6/10 (60.0)	-30.0 (-69.2; 18.4)
<u>DORI-08</u>			
Clinical Cure at TOC (ME) ^c	9/10 (90.0)	6/11 (54.5)	35.5 (-5.4; 69.5)
Clinical Cure (mMITT) ^{c,d}	9/17 (52.9)	7/16 (43.8)	9.2 (-26.0; 43.1)
<u>DORI-07& 08</u>			
Clinical Cure at TOC (ME) ^c	12/17 (70.6)	11/20 (55.0)	15.6 (-16.8; 46.7)
Clinical Cure (mMITT) ^c	12/27 (44.4)	13/26 (50.0)	-5.6 (-31.1; 20.7)

a Doripenem minus Meropenem.

b 2-sided 95% confidence interval (CI) computed using exact test

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

e Pooled analyses may not provide reliable estimates due to study differences and lack of randomization.

Source: FDA Table

Statistical Reviewer Comments: *Lower cure rates for doripenem therapy versus meropenem therapy were observed in DORI-07 while higher cure rates were observed in DORI-08. Overall, clinical cure rates in patients with renal impairment appeared generally similar between the treatments. However, meaningful statistical inferences cannot be made due to the small number of subjects with renal impairment in each study.*

Table 27: Comparisons of Clinical Cure Rates (%) in the ME and mMITT Co-primary Analysis Sets Excluding Patients Who Were Cured and Received Concomitant Non-Study Antibiotics Taken Between First Dose of Study Drug and TOC Visit

<u>Study</u> Visit/Analysis Set	Doripenem n/N (%)	Meropenem n/N (%)	Diff ^a (95% CI ^b) (%)
<u>DORI-07</u>			
Clinical Cure at TOC (ME) ^{c,e}	132/155 (85.2)	126/149 (84.6)	0.6 (-7.6; 8.8)
Clinical Cure (mMITT) ^{c,d,e}	134/177 (75.7)	137/177 (77.4)	-1.7 (-10.5; 7.2)
<u>DORI-08</u>			
Clinical Cure at TOC (ME) ^{c,e}	128/155 (82.6)	121/147 (82.3)	0.3 (-8.4; 9.0)
Clinical Cure (mMITT) ^{c,d,e}	136/187 (72.7)	124/169 (73.4)	-0.7 (-9.8; 8.6)

a Doripenem minus Meropenem.

b Two-sided 95% CI calculated without continuity correction

c Co-primary endpoints as defined by Sponsor

d CR_1_mMITT = clinical response definition_1 for the microbiological modified intent-to-treat (mMITT)

e Comparisons assume actual treatment received and re-evaluation for mis-randomization

f Pooled analyses may not provide reliable estimates due to study differences and lack of randomization.

Statistical Reviewer Comments: *Treatment differences were similar before and after excluding patients receiving concomitant non-study antibacterial medications between first dose and the TOC visit.*

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5. SUMMARY AND CONCLUSIONS

Based on the review of studies DORI-07 and DORI-08, doripenem injection 500 mg every 8 hours demonstrated non-inferiority to meropenem i.v. using a 15% margin for for the treatment of complicated intra-abdominal infections (cIAI) in patients 18 years of age and older. The primary analysis findings of non-inferiority were demonstrated in both the FDA defined ME and mMITT co-primary analysis populations. Microbiological analyses results were supportive of the primary analysis.

Although overall cure rates in the FDA defined ME and mMITT co-primary analysis populations of the DORI-07 and DORI-08 studies provided evidence of non-inferiority, observed cure rates were consistently lower in the doripenem arm than in the meropenem arm. In DORI-07 study, the clinical cure rate at TOC for doripenem was 3.1% worse than meropenem in the ME population and 4.3% worse in the mMITT population. Similarly, in DORI-08, the clinical cure rate at TOC for doripenem was 1.1% worse than meropenem in the ME population and 2.3% worse in the mMITT population. This raises concerns of a potential loss of efficacy with the use of doripenem therapy. There is also a concern that this loss of efficacy would be larger if patients were not allowed a switch from IV to oral medication. In the subset of DORI-07 and DORI-08 study patients receiving only IV therapy, patients in the doripenem arm had clinical cure rates which were approximately 6.3% and 8.1% lower in the ME and mMITT populations, respectively. Interpretations of this analysis, however, may be confounded by differences in the proportions of subjects in each treatment arm who switched to from IV to oral amoxicillin/clavulanate therapy.

Sensitivity and subgroup analyses based on the Sponsor's data were also conducted in the DORI-07 and DORI-08 studies to assess the effects of various factors on overall study findings but did not identify any clear inconsistencies and were therefore considered as generally supportive. Sensitivity analyses examined effects of various factors on primary analysis findings. These factors included influential sites, analysis set definitions, study drug therapy (IV or oral), treatment duration, clinical response definitions, sample size changes, TOC window changes, surgical review panel re-classifications, unplanned study drug treatments. Subgroup analyses also addressed other factors which could have influenced primary analysis results. These factors included the patient's categorization with respect to age, gender, race, geographic region, post-operative infection, APACHE II Score, IVRS Randomization Stratum, treatment duration, renal impairment status, creatinine clearance group. It should be noted that post-hoc subgroup and sensitivity analyses may be severely limited in identifying significant differences between treatments due to a potential lack of power (i.e. inadequate sample size) and a lack of planning (i.e. failure to control for overall type I error rate).

Doripenem also provided some evidence towards microbiological efficacy against major causative pathogens of cIAI at the TOC visit. Eradication rates for these pathogens appeared similar to rates in meropenem arm. However, due to the small number of isolates presented, meaningful statistical inferences could not be drawn.

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Appendix 1

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

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

Overview of Sponsor's Approach

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

1. A literature search was performed using several databases (PubMed, Embase, Medline, Biosis) to assess the spontaneous resolution rate with surgery alone (placebo cure rate) for cIAI based on the following:
 - Clinical trials involving antibiotics for this indication with a placebo control.
 - Clinical trials involving antibiotics for surgical prophylaxis.
 - Clinical trials involving antibiotics for this indication reporting results of delayed treatment or inappropriate treatment.

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

2. The cure rate of meropenem, the comparator in both Studies DORI-07 and DORI-08, and corresponding variability of this estimate was estimated from seven published studies of meropenem for the treatment of cIAI in a meta-analysis using a random-effects model, i.e. DerSimonian-Laird method. The pooled estimate of the cure rate and corresponding two-sided 95% confidence interval for meropenem was 96.749 (94.963-98.535)
3. Literature was reviewed for studies of delayed/inappropriate therapy in intra-abdominal infections. The aim was to examine the effect of a delay in receipt or nonreceipt of effective therapy on clinical outcomes. Results of these studies were not included in the calculation of the putative placebo rate.
4. The lower bound of the 95% confidence interval for the active comparator cure rate and the point estimate of the putative placebo cure rate were then used to calculate the largest difference between meropenem and placebo that would still preserve 50% of the benefit of meropenem. The most conservative estimated value for Δ_{50} obtained from the two-sided 95% CI is 16.5%.

Agency's Approach

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

Estimation of placebo rates:

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

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

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

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

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

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

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Table 1: Complication rates from placebo-controlled prophylaxis trials

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

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

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Table 2: Summary of placebo-controlled prophylaxis trials

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

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

Group A: Received ampicillin, gentamicin, and clindamycin

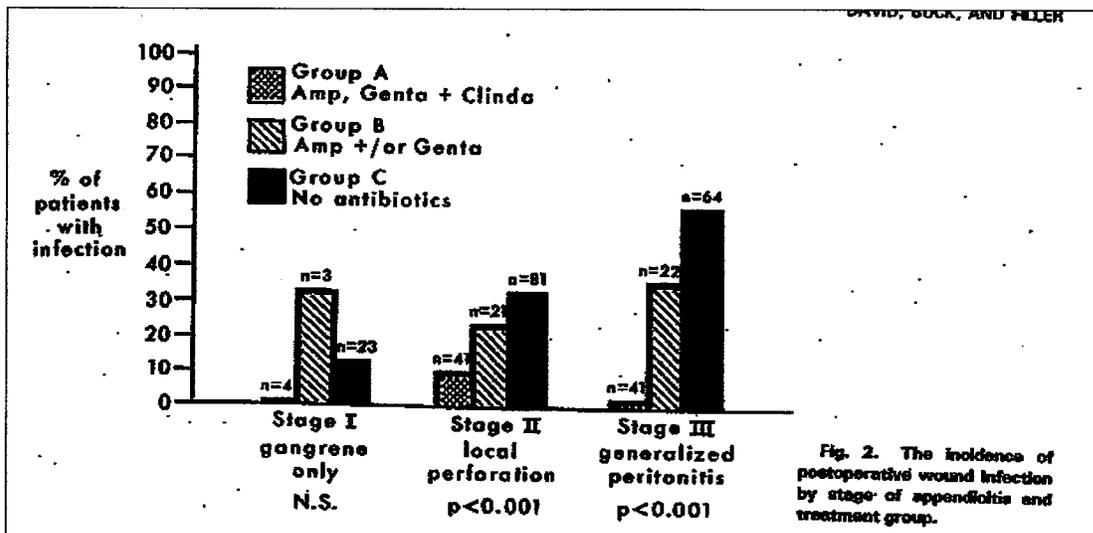
Group B: Received ampicillin and/or gentamicin

Group C: Received no antibiotics

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

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

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



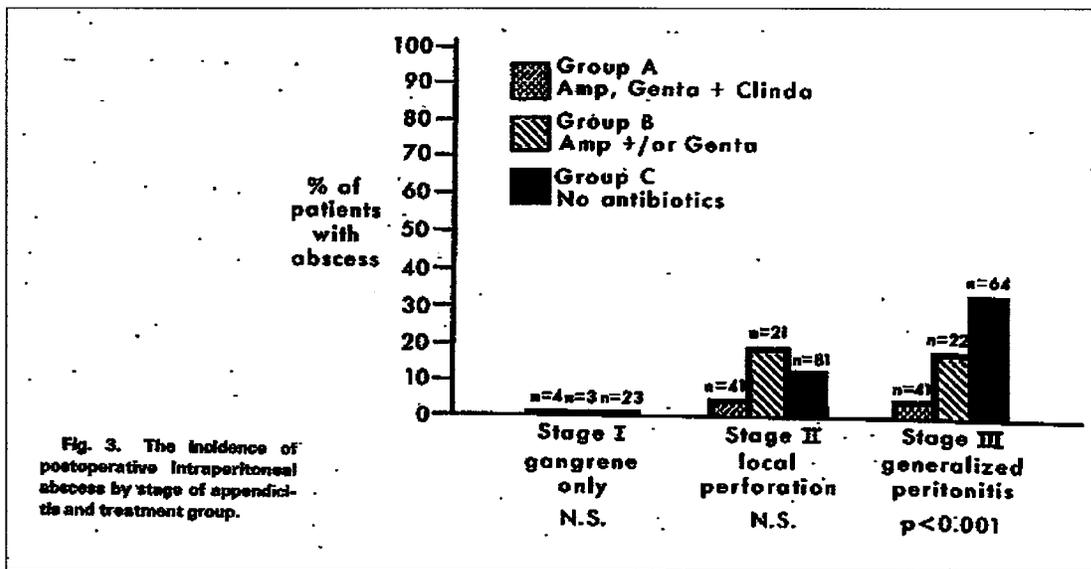


Fig. 3. The incidence of postoperative Intra-abdominal abscess by stage of appendicitis and treatment group.

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

Delayed treatment/inappropriate treatment

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

1. Bare et al. 2006- Patients with community acquired cIAI were studied. Appropriateness of therapy defined based on literature (no specific criteria listed). Out of 376 cases, 51 received inappropriate therapy. This was associated with need for a second-line antibiotic.⁸
2. Krobot et al. 2004- 425 patients with community-acquired cIAI (38 % perforated appendicitis, 27% colon, 22% gastro-duodenal) were studied. In patients with documented pathogen on blood culture/intraabdominal swab, inappropriate therapy was defined as one or more bacteria isolated at baseline that were resistant regardless of whether regimen was subsequently changed. For those with no culture or negative culture appropriate therapy included coverage for beta-lactamase positive gram negative bacteria, *S. aureus*, and *B. fragilis*. 54 patients received inappropriate treatment. Clinical success was higher in the appropriate therapy group, 79% (74-84) vs. 53 (41-69).⁹
3. Sturkenboom et al. 2005- This was a population based retrospective cohort study of 175 cases of IAI. Inappropriate was defined as regimen that did not cover facultative and aerobic gram negative bacteria plus anaerobes. ~ 50% had perforated appendicitis, 147 (84%) had received appropriate therapy and 28 received inappropriate therapy. Risk of clinical failure was 3.4 fold (1.3-9.1) with inappropriate therapy.¹⁰
4. Manes et al. 2006. This was a randomized controlled trial of early vs. delayed treatment in patients with pancreatitis. 108 patients were started on meropenem 500 mg tid within 1.07 +/- 0.6 days compared to 4.56 +/- 1.2 days. Pancreatic infection occurred in four patients in group A and nine in group B. Extra-pancreatic infection, need for surgery and length of hospitalization was higher in group B.¹¹

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

I. Estimating placebo cure rate

- A. Using 4 antibiotic prophylaxis trials provided by the Sponsor and an additional trial identified by the Agency, we computed the placebo complication rate using a fixed-effects model for gangrenous/perforated appendicitis and nonappendiceal disease separately. The complication rate for gangrenous/perforated appendicitis was 45.6% with a 95% confidence interval (CI) of (37.3%, 54.2%). For nonappendiceal disease, the complication rate was 46.2% with a 95% CI of (36.2%, 56.4%).
- B. An overall complication rate of 44% was computed as a weighted average, with weights based on the proportion of patients seen in the Sponsor's phase III studies (60% appendiceal disease; 40% nonappendiceal disease). The weighted complication rate was 45.8% with a 95% CI of (39.5%, 52.2%).
- C. The placebo cure rate was assumed to be 1 – complication rate (from Step I (B)). The weighted placebo cure rate was 54.2% with a 95% CI of (47.8%, 60.5%)

II. Estimating active comparator cure rate

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

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

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

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

Estimating the non-inferiority margin

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

- Weighted placebo complication rate of 45.8% with a 95% CI of (39.5 %, 52.2%)
- Assuming the response rate was the complement of the complication rate, the weighted placebo cure rate was estimated to be 54.2% with a 95% CI of (47.8%, 60.5%)
- Active comparator (meropenem) cure rate of 80.9% with a 95% CI of (75.4%, 85.3%).
- The putative placebo clinical cure rate, obtained from placebo cure rate for prophylaxis of cIAI was at best about 60.5% (using the upper bound of the 95% CI for the estimated placebo prophylaxis cure rate). The conservative estimate of the clinical cure rate for meropenem was 75.4% (using the lower bound of the 95% CI for the estimated meropenem cure rate). This estimate was similar to the observed meropenem clinical cure rates based on the current submission (NDA22-106), which were 78.0% and 74.2% in the microbiological ITT population for Studies DORI-07 and DORI-08 respectively. Therefore, the conservative estimate of the active

control (meropenem) over the placebo is 14.9% (75.4%-60.5%) which provides an estimate of 14.9% for M1. Considering that the M1 was computed based on the placebo rate for prophylaxis rather than for treatment of cIAI, it is likely that M1 is larger than 14.9%.

- A limitation of this estimation is that no fraction of M1 was preserved. However, it is felt that the estimated placebo cure rate for treatment of cIAI will be much lower than that estimated based on the placebo cure rate for prophylaxis. Firstly, patients in these studies do not have cIAI and are only at risk of infection. Secondly, some of these studies assessed prevention of wound infection rather than prevention of IAI. Placebo cure rates for prevention of wound infection are likely to be higher than that seen for prevention of IAI. Thirdly, the preponderance of evidence was from studies in patients with appendicitis and thus does not represent all types of cIAI.
- Additionally we used conservative estimates for the placebo cure rate, using the upper bound of the 95% CI, and for the comparator cure rates, using the lower bound of 95% CI in the ITT population. Also, as a conservative approach among patients with appendicitis, only data from patients with gangrenous/perforated appendicitis was used as they tend to be sicker and more likely to have poorer outcomes. This was combined with data from patients undergoing colo-rectal surgeries.

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

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

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REFERENCES

1. Gottrup F. Prophylactic metronidazole in prevention of infection after appendicectomy: report of a double-blind trial. *Acta Chir Scand* 1980;146:133-136
2. Donovan IA, Ellis D, Gatehouse D, et al. One-dose antibiotic prophylaxis against wound infection after appendicectomy: a randomized trial of clindamycin, cefazolin sodium and a placebo. *Br J Surg.* 1979 Mar;66(3):193-6
3. Hojer H, Wetterfos J. Systemic prophylaxis with doxycycline in surgery of the colon and rectum. *Ann Surg* 1978;187(4):362-368.
4. Bauer T, Vennits BO, Holm B et al. Antibiotic prophylaxis in acute nonperforated appendicitis. *Ann Surg.* 1989;209(3):307-11.
5. Gomez-Alonso A, Lozano F, Perez A et al. Systemic prophylaxis with gentamicin-metronidazole in appendicectomy and colorectal surgery: A prospective controlled clinical study.
6. David IB, Buck JR, Filler RM, et al. Rational use of antibiotics for perforated appendicitis in childhood. *Journal of Pediatric Surgery* 1982. 17 (5) 494-500.
7. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Cochrane Database Syst Rev.* 2005;(3):CD001439.
8. Bare M, Castells X, Garcia A, Riu M, Comas M, Egea MJ. Importance of appropriateness of empiric antibiotic therapy on clinical outcomes in intra-abdominal infections. *Int J Technol Assess Health Care.* 2006;22(2):242-8.
9. Krobot K, Yin D, Zhang Q et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery *Eur J Clin Microbiol Infect Dis.* 2004;23(9):682-7.
10. Sturkenboom MC, Goettsch WG, Picelli G, et al. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. *Br J Clin Pharmacol.* 2005;60(4):438-43.
11. Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. *Am J Gastroenterol.* 2006;101(6):1348-53.
12. Brismar B, Malmborg AS, Tunevall G et al. Meropenem versus imipenem/cilastatin in the treatment of intra-abdominal infections. *J Antimicrob Chemother.* 1995;35(1):139-48.

13. Condon RE, Walker AP, Sirinek KR, et al. Meropenem versus tobramycin plus clindamycin for treatment of intraabdominal infections: results of a prospective, randomized, double-blind clinical trial. *Clin Infect Dis.* 1995;21(3):544-50.
14. Zanetti G, Harbarth SJ, Trampuz A, et al. Meropenem (1.5 g/day) is as effective as imipenem/cilastatin (2 g/day) for the treatment of moderately severe intra-abdominal infections. *Int J Antimicrob Agents.* 1999;11(2):107-13.

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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22106 / N_000

Drug Name: Doripenem for Injection

Indication(s): Complicated Lower Urinary Tract Infection or Pyelonephritis

Applicant: Peninsula Pharmaceuticals, Inc.

Date(s): Submitted: 12/12/06

PDUFA Date: 10/12/2007

Review Priority: Standard

Biometrics Division: DBIV

Statistical Reviewer: Yunfan Deng, Ph.D.

Concurring Reviewer: Thamban Valappil, Ph.D.

Medical Division: Division of Anti-Infective and Ophthalmologic Drug Products
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Keywords: NDA, non-inferiority

Table of Contents

FOOD AND DRUG ADMINISTRATION	1
STATISTICAL REVIEW AND EVALUATION	1
1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS.....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES.....	4
1.3 STATISTICAL ISSUES AND FINDINGS.....	4
2. INTRODUCTION	7
2.1 OVERVIEW	7
2.2 DATA SOURCES.....	7
3. STATISTICAL EVALUATION	7
3.1 EVALUATION OF EFFICACY	7
3.1.1 Study Design and Endpoints.....	7
3.1.2 Patient Disposition, Demographic and Baseline Characteristics	9
3.1.3 Statistical Methodologies.....	11
3.1.4 Results and Conclusions	13
3.2 EVALUATION OF SAFETY	15
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	15
4.1 GENDER, RACE AND AGE	15
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	16
4.2.1 Different types of cUTI	16
4.2.2 Different test of cure (TOC) evaluation window	18
4.2.3 Different treatment regimen.....	19
4.2.4 Subjects with concomitant antibiotics	19
5. SUMMARY AND CONCLUSIONS	22
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	22
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	22
APPENDIX (NOT FOR PUBLIC DISTRIBUTION).....	23
SIGNATURES/DISTRIBUTION LIST.....	27

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review focused on the efficacy of intravenous (IV) Doripenem in complicated lower urinary tract infection (cLUTI) or pyelonephritis. For this submission, the sponsor submitted two pivotal studies: study DORI-05 and study DORI-06. Study DORI-05 is a phase 3, multicenter, prospective, randomized, double-blind active controlled non-inferiority study of Doripenem IV infusions (500 mg every 8 hours [q8h]) versus Levofloxacin IV infusion (250 mg every 24 hours [q24h]) in the treatment of cUTI in adults using a 10% margin. Study DORI-06 is a phase 3, multicenter, prospective, open-label study of Doripenem infusions (500 mg every 8 hours [q8h]) in the treatment of complicated urinary tract infection (cUTI) in adults.

For study DORI-05, Doripenem was considered non-inferior to Levofloxacin if the 95% (two-sided) CI for the difference in response rates between two treatment groups contained zero and the lower limit of the CI was greater than -10%. In supporting the proposed non-inferiority margin of 10%, the Sponsor's justification for choosing this margin was based on placebo cure rate for uncomplicated UTI for female subjects and cure rate of Levofloxacin (the comparator in study DORI-05) for cUTI and corresponding variability of this estimate. The 10% non-inferiority margin may be acceptable considering lack of historical placebo-controlled studies available for cUTI and based on the limited information available on the Levofloxacin treatment effect for the treatment of cUTI (see Appendix).

Two sample size re-estimations were carried out for both studies DORI-05 and DORI-06 without pre-specification and without any discussion with the agency. According to the Sponsor, 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 original estimates. In addition, in the second sample size adjustments, the study power was increased from 80% to 85%. Sample size re-estimation, if not carefully planned, discussed with the agency and executed, have the potential to introduce several serious biases. According to the Sponsor, the data were blinded for the sample size increases and a subsequent sensitivity analysis by the Sponsor showed similar cure rates among the three Doripenem populations (the original planned population, the subsequent added population, and the final overall population, see Table 4 and Table 5).

For non-inferiority study DORI-05, the test of cure (TOC) visit per-patient microbiological cure rate of Doripenem vs. Levofloxacin in the microbiologically evaluable (ME) population was 82.1% vs. 83.4%, a -1.3% treatment difference with 95% confidence interval of (-8.0%, 5.5%); and in the microbiologically modified intent-to-treat (mMITT) population was 79.2% vs. 78.2%, a 1.0% treatment difference with 95% CI of (-5.6%, 7.6%). For the open-label study DORI-06, the TOC visit microbiological cure rate of Doripenem was 83.6% in the ME population; and in the mMITT population was 82.5%.

From study DORI-05 results, Doripenem has demonstrated non-inferiority to Levofloxacin based on the proposed 10% non-inferiority margin. The efficacy results for study DORI-06 seemed to be consistent with the results observed in study DORI-05.

1.2 Brief Overview of Clinical Studies

This submission contains two efficacy/safety studies.

Study DORI-05 is a phase 3, multicenter, prospective, randomized, double-blind study of Doripenem IV infusions (500 mg every 8 hours [q8h]) versus Levofloxacin IV infusions (250 mg every 24 hours [q24h]) in the treatment of cUTI in adults. After 9 or more doses of IV study drug therapy, patients could have been switched to oral Levofloxacin therapy if specific criteria were met. The duration of study drug therapy (IV alone or IV plus oral) was 10 days (up to 14 days allowed for patients who were bacteremic at baseline). The co-primary efficacy endpoints were the per-patient microbiological cure rate at the TOC visit in the ME at TOC analysis set and in the microbiological modified intent-to-treat (mMITT) analysis set. 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.

Study DORI-06 is a phase 3, multicenter, prospective, open-label study of Doripenem infusions (500 mg every 8 hours [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). After receiving a minimum of 9 doses of IV study drug therapy, if specific criteria were met, patients could be switched to oral Levofloxacin tablets, 250 mg q24h. 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 co-primary efficacy endpoints were the per-patient microbiological cure rate at the TOC visit in the ME at TOC analysis set and in the microbiological modified intent-to-treat (mMITT) analysis set. 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. In addition, analysis of the per-patient microbiological cure rate in the microbiological modified intent-to-treat (mMITT) analysis set was performed and was considered a co-primary analysis.

1.3 Statistical Issues and Findings

There are two main statistical issues for this submission: the choice of non-inferiority margin for the study DORI-05; the increase of sample size in the middle of the trial for both studies DORI-05 and DORI-06 without pre-specification or discussion with the Agency.

Choice of Non-inferiority Margin of 10%

Regarding when a non-inferiority trial design would be appropriate and what the non-inferiority margin should be, based on the ICH E10 guideline stated as follows:

“The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug.”

“The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. If a difference between active control and the new drug favors the control by as much as or more than this margin, the new drug might have no effect at all. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence.”

“The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.”

In supporting the proposed non-inferiority margin of 10%, the Sponsor's justification for choosing this margin was based on placebo cure rate for uncomplicated UTI for female subjects and cure rate of Levofloxacin (the comparator in study DORI-05) and corresponding variability of this estimate. The 10% non-inferiority margin may be acceptable considering lack of historical placebo-controlled studies available for cUTI and based on the limited information available on the Levofloxacin treatment effect for the treatment of cUTI (see Appendix).

Unplanned Sample Size Increase

According to the sponsor:

"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 01 July 2005."

The overview of relevant details regarding assumptions for the sample size justification in the original protocol and amendments for both studies DORI-05 and DORI-06 are provided below.

Table 1 Overview of Sample Size Re-estimation for Study DORI-05 and Study DORI-06

Sample Size Re-estimation for DORI-05					
Protocol Version	Microbiological Cure Rate	Evaluability Rate	Study Power	Total Sample Size	Total Evaluable
Original (9/23/03)	92%	70%	80%	450	320
Unplanned Increase 1 (4/18/05)	88%	63%	80%	580	360

Unplanned Increase 2 (9/15/05)	84%	66%	85%	750	496
Sample Size Re-estimation for DORI-06					
Protocol Version	Microbiological Cure Rate	Evaluability Rate	Study Power ¹	Total Sample Size	Total Evaluable
Original (10/29/03)	93%	70%	80%	220	160
Unplanned Increase 1 (4/28/05)	88%	63%	80%	290	180
Unplanned Increase 2 (9/15/05)	84%	55%	85%	450	248

The two sample size increases for both study DORI-05 and DORI-06 were carried out without pre-specification and without any discussion with the agency. According to the Sponsor, 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 original estimates. In addition, in the second sample size adjustments, the study power was increased from 80% to 85%. Sample size re-estimation, if not carefully planned and executed, have the potential to introduce several serious biases. According to the Sponsor, the data were blinded and a subsequent sensitivity analysis by the Sponsor showed similar cure rates among the three Doripenem populations (original planned population, subsequent added population, and the final overall population, see Table 4 and Table 5).

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2. INTRODUCTION

2.1 Overview

Doripenem is an injectable, synthetic, broad-spectrum carbapenem (β -lactam) antibacterial agent. Doripenem binds to penicillin-binding proteins and inhibits cell wall synthesis in both gram-positive and gram-negative bacteria.

This submission contains two efficacy/safety studies. Study DORI-05 is a phase 3, multicenter, prospective, randomized, double-blind study of Doripenem IV infusions (500 mg every 8 hours [q8h]) versus Levofloxacin IV infusions (250 mg every 24 hours [q24h]) in the treatment of cUTI in adults. Study DORI-06 is a phase 3, multicenter, prospective, open-label study of Doripenem infusions (500 mg every 8 hours [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).

2.2 Data Sources

The Sponsor's study reports for studies DORI-05 and DORI-06 are available on the EDR at \\CDSESUB1\EVSPROD\NDA022106\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The primary objective of both studies DORI-05 and DORI-06 was to determine the microbiological response at the test-of-cure (TOC) visit (5 to 11 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 double-blind intravenous (IV) study drug therapy and oral Levofloxacin therapy.

Secondary objectives of both studies were to:

- Determine the clinical response at the TOC visit in patients with cUTI following a 10-day treatment regimen.
- Evaluate the safety of Doripenem in patients with cUTI.

3.1.1 Study Design and Endpoints

DORI-05 was a phase 3, multicenter, prospective, randomized, double-blind study of Doripenem IV infusions (500 mg every 8 hours [q8h]) versus Levofloxacin IV infusions (250 mg every 24 hours [q24h]) in the treatment of cUTI in adults. Approximately 750 patients were to be enrolled in this study and randomly assigned in a 1:1 ratio to receive IV Doripenem or IV Levofloxacin therapy. Patients were to be recruited from approximately 60 centers in North America, South America, and Europe. Randomization was stratified by region (North America, South America,

or Europe) and within each region by baseline diagnosis (symptomatic cUTI, asymptomatic cUTI, or pyelonephritis). In addition, within the combinations of region and baseline diagnosis, patients were to be randomly assigned to a treatment arm by order study drug therapy was infused (i.e., Doripenem or Doripenem placebo followed by Levofloxacin or Levofloxacin placebo or vice versa) for a total of four possible assignments. The study was double-blinded using either placebo Levofloxacin q24h for patients receiving active Doripenem or placebo Doripenem q8h for patients receiving active Levofloxacin. All active drug and placebo doses were administered as 1-hour IV infusions.

DORI-06 was a Phase 3, multicenter, prospective, open-label study of Doripenem infusions (500 mg every 8 hours [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 sample size for DORI-06 was estimated to achieve approximately the same number of microbiologically evaluable patients as in the Levofloxacin arm in study DORI-05. Based on this goal, the target enrollment for study DORI-06 was estimated to be 450 patients. This DORI-06 study was conducted by different investigators and at different sites than those in the DORI-05 study. The patients in DORI-06 were recruited from North America, South America, and Europe. After receiving a minimum of 9 doses of IV study drug therapy, if specific criteria were met, patients could be switched to oral Levofloxacin tablets, 250 mg q24h. 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).

For both studies DORI-05 and study DORI-6, The co-primary efficacy endpoints were the per-patient microbiological cure rate at the TOC visit in the ME at TOC analysis set and in the microbiological modified intent-to-treat (mMITT) analysis set. 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.

Microbiologically evaluable at test-of-cure (ME at TOC): This analysis set consisted of all randomly assigned patients who:

- 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.

The mMITT analysis set consisted of all enrolled patients who received any dose or partial dose of study drug therapy and who had a study-qualifying pre-treatment urine culture. Patients who met both these criteria but who did not meet the protocol definition of cUTI or who had other protocol violations (including the administration of confounding non-study antibiotic) were also included in the mMITT analyses. For the mMITT analysis, patients who lacked an interpretable urine culture result after completing study drug therapy were considered failures.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 44 centers (18 in the United States; 7 in Germany; 7 in Argentina; 6 in Brazil; 5 in Poland; and 1 in Canada) randomized 753 patients in DORI-05 study. The following table summarizes the disposition of all randomized patients in this study.

- Three hundred seventy-six of the 377 patients randomly assigned to the Doripenem treatment arm received study drug and comprise the intent-to-treat (ITT) analysis set; 372 of the 376 patients randomly assigned to the Levofloxacin treatment arm received study drug and were included in the ITT analysis set.
- A high percentage of patients completed the study per protocol in both treatment arms (84%, Doripenem; 75%, Levofloxacin). Of these:
 - 67 (9%) of 753 patients received only IV study drug therapy and completed the study; the percentages were similar between the 2 treatment arms.
 - 530 (70%) of 753 patients were treated with both IV and oral study drug therapy and completed the study; 75% of patients in the Doripenem treatment arm and 65% of patients in the Levofloxacin treatment arm received both IV and oral study drug therapy and completed the study.
- Five hundred forty-five (72%) of 753 patients met the criteria for inclusion in the ME at TOC analysis set. The percentages of patients meeting the criteria for inclusion in the ME at TOC analysis set were comparable for the Doripenem (74%) and Levofloxacin (70%) treatment arms. Of these,
 - 79 (11%) of 753 patients were in the ME at TOC analysis set and received IV therapy only.
 - 466 (62%) of 753 patients were in the ME at TOC analysis set and received IV and oral therapy (66%, Doripenem; 58%, Levofloxacin).
- A total of 597 (79%) of 753 patients completed the TOC and late follow-up (LFU) visits. The percentages of patients completing both the TOC and LFU visits were comparable for the Doripenem (83%) and Levofloxacin (76%) treatment arms.
- The patient disposition was similar in the 2 treatment arms, except more patients in the Levofloxacin treatment arm did not complete IV only or IV and oral study therapy (19%, Levofloxacin; 13%, Doripenem).
- Of the 21% of patients who did not complete the study, 15% discontinued while receiving IV therapy (11%, Doripenem; 18%, Levofloxacin).

Table 2 Disposition (Study DORI-05: All Randomized Patients)

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

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

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

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.

From sponsor's Table 10 of CSR, p 65

A total of 30 centers (11 in the United States, 9 in Argentina, 6 in Brazil, 3 in Austria, and 1 in Canada) enrolled 426 patients for DORI-06 study. The investigators and centers participating in this study were different from those involved in DORI-05.

- Four hundred twenty-three of the 426 patients enrolled in DORI-06 received study drug and comprise the ITT analysis set.
- Seventy-seven percent of patients in DORI-06 completed the study per protocol. Of these,
 - 63 (15%) patients who received Doripenem in DORI-06 and completed the study received IV study drug only, and 265 (62%) received both IV and oral study drug.
- Two hundred fifty (59%) patients in DORI-06 met the criteria for inclusion in the ME at TOC analysis.
 - 54 (13%) of 426 patients were in the ME at TOC analysis set of DORI-06 and received IV therapy only
 - 196 (46%) of 426 patients were in the ME at TOC analysis set of DORI-06 and received both IV and oral study drug.

Table 3 Disposition of DORI-06 Patients with Comparisons to DORI-05 Levofloxacin Patients (All Patients)

	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 visit	73 (17.1%)	61 (16.2%)
Follow-up Visits Completed		
Had TOC and LFU	320 (75.1%)	284 (75.5%)
Had TOC but no LFU	19 (4.5%)	9 (2.4%)
No TOC or 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.

Patients were defined as having completed the study if they had received study drug therapy as directed and had attended the TOC and LFU visits as specified in the protocol.

Note: Percentages were based on the number of patients enrolled in each treatment.

From sponsor's Table 7 of CSR, p 62

Statistical Reviewer's comments:

Note that these are cross study comparisons and it lacks the original randomization.

3.1.3 Statistical Methodologies

3.1.3.1 Study DORI-05

The co-primary efficacy endpoints were the microbiological cure rates at the TOC visit (5 to 11 days after administration of the last dose of study drug therapy) in the ME at TOC analysis set and in the mMITT analysis set.

The primary efficacy analysis was to test the hypothesis of non-inferiority of IV Doripenem to IV Levofloxacin. Non-inferiority was to be concluded if the lower bound of the 2-sided 95% CI for the difference (Doripenem minus Levofloxacin) in the proportion of patients who were

classified as microbiological cures was greater than or equal to -10%. This 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method).

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

Determination of Sample Size

The primary objective of this study was to determine non-inferiority of IV Doripenem compared with IV Levofloxacin for the treatment of cUTI in adult patients. Doripenem would be considered non-inferior to IV Levofloxacin if the lower limit of the 2-sided 95% CI for the difference between treatment arms (Doripenem minus Levofloxacin) in the per-patient microbiological cure rate at the TOC visit was greater than or equal to -10%.

The analysis was conducted in the ME at TOC analysis set. The hypotheses of interest were:

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

Alternative hypothesis $H_1: \pi_1 - \pi_2 \geq -0.10$,

Where π_1 was the true proportion of patients with cUTI in the Doripenem treatment arm who were microbiologically cured (had all baseline pathogens eradicated) at the TOC visit and π_2 was the true proportion of patients with cUTI in the Levofloxacin treatment arm who were microbiologically cured at the TOC visit.

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

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

3.1.3.2 Study DORI-06

Analysis of Primary Efficacy Endpoint

The co-primary efficacy endpoints were the microbiological cure rates at the TOC visit (5 to 11 days after administration of the last dose of study drug therapy) in the ME at TOC analysis set and the mMITT analysis set.

The primary efficacy analysis was to test the hypothesis of non-inferiority of Doripenem treatment in this study to Levofloxacin treatment in DORI-05. Non-inferiority was to be concluded if the lower bound of the 2-sided 95% CI for the difference (Doripenem minus Levofloxacin) in the percentage of patients who were classified as microbiological cures was greater than or equal to -10%. This 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method).

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

Statistical Reviewer's Comments:

Two sample size increases for both study DORI-05 and DORI-06 were carried out without pre-specification and without any discussion with the agency. According to the Sponsor, 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 original estimates. In addition, in the second sample size adjustments, the study power was increased from 80% to 85%. Sample size re-estimation, if not carefully planned and executed, have the potential to introduce several serious biases.

Cross study comparison between the Doripenem treatment in the open-label DORI-06 and the Levofloxacin treatment in DORI-05 is not valid due to the lack of randomization protection.

3.1.4 Results and Conclusions

The sponsor's efficacy results of microbiological cure rates in the ME at TOC and the mMITT analysis sets for the three different sample size populations: original planned population, subsequent added population, and final overall population.

Table 4 Efficacy Analysis Results for Study DORI-05

	Doripenem	Levofloxacin	Difference (95% CI)
Study DORI-05			
ME at TOC Analysis Set			
Original Planned Population	133/163 (81.6%)	122/149 (81.9%)	-0.3% (-9.5%, 8.9%)
Subsequent Added Population	97/117 (82.9%)	99/116 (85.3%)	-2.4% (-12.7%, 7.8%)
Final Overall Population	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
mMITT Analysis Set			
Original Planned Population	152/192 (79.2%)	142/188 (75.5%)	3.6% (-5.3%, 12.6%)
Subsequent Added Population	107/135 (79.3%)	109/133 (82.0%)	-2.7% (-12.9%, 7.5%)
Final Overall Population	259/327 (79.2%)	252/321 (78.2%)	1.0% (-5.6%, 7.6%)

From sponsor's Table 16 of CSR, p 82

Table 5 Efficacy Analysis Results for Study DORI-06

	Doripenem
Study DORI-06	
ME at TOC Analysis Set	
Original Planned Population	102/119 (85.7%)
Subsequent Added Population	107/131 (81.7%)
Final Overall Population	209/250 (83.6%)
mMITT Analysis Set	
Original Planned Population	141/167 (84.4%)
Subsequent Added Population	137/170 (80.6%)
Final Overall Population	278/337 (82.5%)

From sponsor's Table 13 of CSR, p 82

Statistical Reviewer's Comments:

From study DORI-05 results, Doripenem has demonstrated evidence of non-inferiority to Levofloxacin based on the proposed 10% non-inferiority margin for the original planned

population and final overall population. The efficacy results for study DORI-06 seemed to be consistent with the results observed in study DORI-05.

3.2 Evaluation of Safety

Please see the medical officer Dr. Alfred Sorbello's review for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 6 Efficacy Analysis Results for Study DORI-05 By Gender, Race, and Age

Study DORI-05					
ME at TOC Analysis Set					
	Doripenem		Levofloxacin		Observed Differences
	(N=280)		(N=265)		
	n/m	%	n/m	%	
Gender					
Female	142/170	83.5	139/162	85.8	-2.3
Male	88/110	80.0	82/103	79.6	0.4
Age					
< 65 years	153/179	85.5	147/170	86.5	-1.0
≥ 65 years	110/151	72.8	78/145	53.8	19.1
< 75 years	202/240	84.2	191/224	85.3	-1.1
≥ 75 years	28/40	70.0	30/41	73.2	-3.2
Race					
Hispanic	22/30	73.3	21/27	77.8	-4.5
Black	18/19	94.7	18/24	75.0	19.7
White	187/228	82.0	178/209	85.2	-3.2
Other	3/3	100.0	4/5	80.0	20.0
N = Number of Microbiologically Evaluable patients in each treatment group n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment. From sponsor's Table 18 of CSR, p 86					

Table 7 Efficacy Analysis Results for Study DORI-06 By Gender, Race, and Age

Study DORI-06		
ME at TOC Analysis Set		
	Doripenem	
	(N=280)	
	n/m	%
Gender		
Female	125/138	90.6
Male	84/112	75.0
Age		
< 65 years	149/171	87.1
≥ 65 years	60/79	75.9
< 75 years	182/213	85.4
≥ 75 years	27/37	73.0
Race		
Hispanic	56/60	93.3
Black	39/45	86.7
White	99/120	82.5
Other	15/25	60.0
N = Number of Microbiologically Evaluable patients in each treatment group n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment. From sponsor's Table 15 of CSR, p 87		

Statistical Reviewer's Comments:

In these subgroups, the difference in cure rates between the treatment groups were similar to the difference seen for the overall cure rates at the TOC visit.

4.2 Other Special/Subgroup Populations

4.2.1 Different types of cUTI

Per-patient microbiological cure rates in subgroups of symptomatic and asymptomatic cLUTI, pyelonephritis (including complicated pyelonephritis), and patients who had concurrent bacteremia at baseline are listed in the following tables.

Table 8 Efficacy Analysis Results for Study DORI-05 in Subgroups of Symptomatic and Asymptomatic cLUTI, Pyelonephritis (including complicated pyelonephritis), and Patients Who Had Concurrent Bacteremia

Study DORI-05					
ME at TOC Analysis Set					
	Doripenem		Levofloxacin		Observed Differences
	(N=280)		(N=265)		
	n/m	%	n/m	%	%
By Subgroup					
cLUTI (All)	110/145	75.9	99/131	75.6	0.3
Symptomatic	106/138	76.8	94/122	77.0	-0.2
Asymptomatic	4/7	57.1	5/9	55.6	1.6
Pyelonephritis (All)	120/135	88.9	122/134	91.0	-2.2
Uncomplicated	103/114	90.4	97/107	90.7	-0.3
Complicated	17/21	81.0	25/27	92.6	-11.6
Bacteremic at Baseline	19/20	95.0	22/23	95.7	-0.7

N = Number of Microbiologically Evaluable patients in each treatment group
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
From sponsor's Table 18 of CSR, p 86

Table 9 Efficacy Analysis Results for Study DORI-06 in Subgroups of Symptomatic and Asymptomatic cLUTI, Pyelonephritis (including complicated pyelonephritis), and Patients Who Had Concurrent Bacteremia

Study DORI-06		
ME at TOC Analysis Set		
	Doripenem	
	(N=250)	
	n/m	%
By Subgroup		
cLUTI (All)	97/132	73.5
Symptomatic	94/128	73.4
Asymptomatic	3/4	75.0
Pyelonephritis (All)	112/118	94.9
Uncomplicated	95/99	96.0
Complicated	17/19	89.5
Bacteremic at Baseline	26/27	96.3

N = Number of Microbiologically Evaluable patients in each treatment group
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
From sponsor's Table 15 of CSR, p 87

Statistical Reviewer's Comments:

For these subgroups, when the numbers of subjects within a subgroup were sufficient, the difference in cure rates between the treatment groups were similar to the difference seen for the overall cure rate at the test of cure visit.

4.2.2 Different test of cure (TOC) evaluation window

According to the Sponsor, 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. Additional sensitivity analysis using the original designed TOC window (6 to 9 days after administration of the last dose of study drug) was performed by the statistical reviewer. The results are listed in the following table.

Table 10 Statistical Reviewer's Sensitivity Analysis Results for Study DORI-05 and DORI-06 With TOC Window at 6 to 9 Days after Administration of the Last Dose of Study Drug

	Doripenem	Levofloxacin	Difference (95% CI)
Study DORI-05			
ME at TOC Analysis Set	223/271 (82.3%)	213/256 (83.2%)	-1.0% (-7.8%, 5.9%)
mMITT Analysis Set	240/293 (81.9%)	232/286 (81.1%)	0.8% (-5.9%, 7.5%)
Doripenem			
Study DORI-06			
ME at TOC Analysis Set	229/272 (84.2%)		
mMITT Analysis Set	197/236 (83.5%)		

Statistical Reviewer's Comments:

Overall, the results based on TOC window at 6-9 days after administration of the last dose of study drug were consistent with the primary analysis results.

4.2.3 Different treatment regimen

For both study DORI-05 and DORI-6, after receiving a minimum of 9 doses of IV study drug therapy, patients in both treatment arms may have been switched to Levofloxacin tablets 250 mg orally (PO) q24h if they met specific criteria. Therefore, in order to access the treatment effect of IV Doripenem vs. IV Levofloxacin, additional sensitivity analysis based on patients who were treated with IV therapy only was performed by the statistical reviewer. The results are listed in the following table.

Table 11 Statistical Reviewer's Sensitivity Analysis Results for Study DORI-05 and DORI-06 With IV Treatment only

	Doripenem	Levofloxacin	Difference
Study DORI-05			
ME at TOC Analysis Set	18/31 (58.1%)	18/48 (37.5%)	20.6%
mMITT Analysis Set	24/46 (52.2%)	31/73 (42.5%)	9.7%
Doripenem			
Study DORI-06			
ME at TOC Analysis Set	38/54 (70.4%)		
mMITT Analysis Set	47/71 (66.2%)		

Statistical Reviewer's Comments:

In study DORI-05, there were more IV treated only patients in the Levofloxacin arm than in Doripenem arm. The outcomes were consistent with the overall outcomes at the test of cure visit; however, the number of patients in this subset is relatively small.

4.2.4 Subjects with concomitant antibiotics

Additional sensitivity analysis excluding patients who received concomitant antibiotics was also performed by the statistical reviewer. The results are listed in the following tables.

Table 12 Statistical Reviewer's Sensitivity Analysis Results for Study DORI-05 Based on Concomitant Antibiotics

	Doripenem	Levofloxacin	Difference (95% CI)
Study DORI-05			
ME at TOC Analysis Set			
Subjects With Concomitant Antibiotics before/on TOC date	8/12 (66.7.1%)	7/11 (63.6%)	3.0%
Subjects with Concomitant Antibiotics taken after TOC date	20/31 (64.5%)	8/29 (27.6%)	36.9%
Subjects Without Any Concomitant Antibiotics	202/237 (85.2%)	206/225 (91.6%)	-6.3% (-12.5%, -0.01%)
Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics	222/268 (82.8%)	214/254 (84.3%)	-1.4% (-8.2%, 5.3%)
Overall	230/280 (82.1%)	221/265 (83.4%)	-1.3% (-8.0%, 5.5%)
mMITT Analysis Set			
Subjects With Concomitant Antibiotics before/on TOC date	17/22 (77.3%)	15/22 (68.2%)	9.1%
Subjects with Concomitant Antibiotics taken after TOC date	26/42 (61.9%)	14/44 (31.8%)	30.1%
Subjects Without Any Concomitant Antibiotics	216/263 (82.1%)	222/255 (87.1%)	-4.9% (-11.5%, 1.7%)
Combined Outcomes of Subjects with Concomitant Antibiotics taken after TOC date and Subjects Without Any Concomitant Antibiotics	242/305 (79.3%)	236/299 (78.9%)	0.4% (-6.4%, 7.2%)
Overall	259/327 (79.2%)	252/321 (78.2%)	1.0% (-5.6%, 7.6%)

Table 13 Statistical Reviewer's Sensitivity Analysis Results for Study DORI-06 Based on Concomitant Antibiotics

Study DORI-06 ME at TOC Analysis Set	
	Doripenem
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 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%)

Statistical Reviewer's Comments:

From these sensitivity results, the outcomes were similar to the overall outcomes at the test of cure visit.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objective of both studies DORI-05 and DORI-06 was to determine the microbiological response at the test-of-cure visit (5 to 11 days after the completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen. For this submission, the sponsor submitted two pivotal studies: study DORI-05 and study DORI-06. Study DORI-05 is a phase 3, multicenter, prospective, randomized, double-blind active controlled non-inferiority study of Doripenem IV infusions (500 mg every 8 hours [q8h]) versus Levofloxacin IV infusion (250 mg every 24 hours [q24h]) in the treatment of cUTI in adults using a 10% margin. Study DORI-06 is a phase 3, multicenter, prospective, open-label study of Doripenem infusions (500 mg every 8 hours [q8h]) in the treatment of complicated urinary tract infection (cUTI) in adults.

In supporting the proposed non-inferiority margin of 10%, the Sponsor's justification for choosing this margin was based on placebo cure rate for uncomplicated UTI for female subjects and cure rate of Levofloxacin (the comparator in study DORI-05) and corresponding variability of this estimate. The 10% non-inferiority margin may be acceptable considering lack of historical placebo-controlled studies available for cUTI and based on the limited information available on the Levofloxacin treatment effect for the treatment of cUTI.

Two sample size increases for both study DORI-05 and DORI-06 were carried out without pre-specification and without any discussion with the agency. According to the Sponsor, 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 original estimates. In addition, in the second sample size adjustments, the study power was increased from 80% to 85%. Sample size re-estimation, if not carefully planned and executed, have the potential to introduce several serious biases. However, according to the Sponsor, the data were blinded and a subsequent sensitivity analysis by the Sponsor showed similar cure rates among the three Doripenem populations (see Table 4 and Table 5).

For non-inferiority study DORI-05, the test of cure (TOC) visit per-patient microbiological cure rate of Doripenem vs. Levofloxacin in the microbiologically evaluable (ME) population was 82.1% vs. 83.4%, a -1.3% treatment difference with 95% confidence interval of (-8.0%, 5.5%); and in the microbiologically modified intent-to-treat (mMITT) population was 79.2% vs. 78.2%, a 1.0% treatment difference with 95% CI of (-5.6%, 7.6%). For the open-label study DORI-06, the TOC visit microbiological cure rate of Doripenem was 83.6% in the ME population; and in the mMITT population was 82.5%.

5.2 Conclusions and Recommendations

Based on the review of the data for study DORI-05, Doripenem has demonstrated non-inferiority to Levofloxacin based on the proposed 10% non-inferiority margin. The efficacy results for study DORI-06 seemed to be consistent with the results observed in study DORI-05.

Appendix (not for public disclosure)

Justification for the Non-Inferiority Margin Used in Study DORI-05 Comparing Doripenem to Levofloxacin in the Treatment of Complicated Urinary Tract Infection (cUTI)

In assessing the Sponsor's proposed non-inferiority margin of 10%, the statistical reviewer conducted an analysis of the supportive studies cited to assess the placebo rate, the supportive studies used to assess the comparator response rate, and the response rates reported in other supportive studies for the urinary tract infection (UTI) indication for both the placebo and the active control available within the Agency.

Placebo Response Rate for Uncomplicated Urinary Tract Infection (uUTI)

There were no placebo-controlled cUTI studies identified from the Sponsor's search of the English language medical literature. The absence of placebo-controlled clinical trials may be due to concerns physicians may have about the low placebo response rate for cUTI and the feasibility of doing such a study because of ethical reasons. There were two placebo-controlled studies identified by the Sponsor in the literature in women who had uUTI. However, there were differences in terms of the duration of study drug, the endpoints assessed, and the diagnostic criteria for significant bacteriuria. Moreover, there were no placebo-controlled trials identified in men with UTI without significant co-morbid conditions.

The estimates of the placebo response rates provided by the Sponsor were only based on studies for uncomplicated UTI (uUTI). According to the Sponsor, no studies reporting placebo response rates in cUTI were found in the English language medical literature. The placebo bacteriological response rate for subjects with uncomplicated UTI was 44% (95/217) and 20% (5/25) respectively in the two identified placebo-controlled studies (Ferry et al, and Christiaens et al). The results for the two studies were summarized in the following table.

Table 1 Historical Placebo Data from Published uUTI Studies Identified by the Sponsor

Author	Type of UTI	Placebo	95% CI
Ferry et al	uUTI	95/217 (44%)	(37.3%, 50%)
Christianes et al	Acute uUTI	5/25 (20%)	(8.6%, 40.0%)

Additional information of placebo response rate for uncomplicated UTI was identified by the statistical reviewer from NDA20634 related cUTI non-inferiority margin justification document. The rate is 44% (8/18) in this published document by Dubi, et al. The result for the study was listed in the following table.

Table 2 Historical Placebo Data from Published uUTI Studies Identified by the Statistical Reviewer

Author	Type of UTI	Placebo	95% CI
Dubi et al	uUTI	8/18 (44%)	(22%, 67%)

The data from the applicable historical studies in Tables 1 and 2 were pooled together to obtain a weighted estimate of the placebo cure rate and its corresponding two-sided 95% confidence interval (CI). The weighted non-iterative method for random effects model described by DerSimonian and Laird was used to obtain the estimate and its 95% CI; and the weighted estimate is 37% with 95% CI of (24%, 53%).

Outcomes with Inadequate or Inappropriate Therapy for Complicated Urinary Tract Infection (cUTI) / Acute Pyelonephritis (AP)

Upon review of NDA20634 related cUTI non-inferiority margin justification document by the statistical reviewer, three studies were identified in which the active agent was inadequate to resistant pathogens for the treatment of cUTI and acute pyelonephritis (AP). In one study, the microbiological eradication rate for all pathogens reported with trimethoprim-sulfamethoxale (TMP-SMX) was low due to inclusion of TMP-SMX-resistant pathogens. In two other studies, eradication rates for those pathogens susceptible or resistant to treatment were reported. Eradication rates for resistant pathogens may be considered as the surrogate outcomes for cUTI placebo effect. It should be noted that the sample size is not large for all the studies identified. The results for the three studies were summarized in the following table.

Table 3 Historical Inadequate Therapy Data from Published cUTI Studies Identified by the Statistical Reviewer from NDA20634 Related Document

Author	Type of UTI	Inadequate Therapy (Placebo Effect)	95% CI
Allais et al	cUTI/AP	12/23 (52%)	(27%, 69%)
Fang et al	cUTI/AP	4/28 (15%)	(4%, 34%)
Talan	AP	7/14 (50%)	(23%, 77%)

The data from the historical studies in Tables 3 were pooled together to obtain a weighted estimate of the inadequate therapy response rate and its corresponding two-sided 95% confidence interval (CI). The weighted non-iterative method for random effects model described by DerSimonian and Laird was used to obtain the estimate and its 95% CI. The weighted estimate is 37.1% with 95% CI of (16%, 64.7%).

Active Comparator's Response Rate for Complicated UTI (cUTI)

In order to assess the active comparator Levofloxacin efficacy rates, the Sponsor used historical studies from published medical literature that involved men and women ≥ 18 years old that had cUTI. One study (by Ping and colleagues) was a randomized, double-blind study. However, the microbiological eradication rate was evaluated on Day 5 in this study while antibiotic therapy was still ongoing, which could falsely elevate the response rates. The second study (by Klimberg and colleagues) was an open-label study and, thus, more susceptible to introduce bias into the study. Therefore, it is possible that the cure rates of Levofloxacin were all overestimated in these two studies identified by the Sponsor. Bearing the possibility of over-estimation in mind, the outcomes of the two trials are provided in the following table.

Table 4 Historical Levofloxacin Data from Published cUTI Studies Identified by the Sponsor

Author	Type of UTI	Levofloxacin Microbiological Eradication Rate	95% CI
Klimberg, et al	cUTI	163/171 (95.3%)	(90.1%, 98.0%)
Christinanes et al	cUTI	18/20 (90%)	(68.3%, 98.8%)

By reviewing the FDA NDA database, the statistical reviewer found out two additional studies using Levofloxacin in the treatment of cUTI. One study was double-blinded and the other one open-label. Both studies involved men and women with complicated UTI. The efficacy result for the open-label study was not available. In the double-blinded study, the microbiological eradication rate for Levofloxacin was 84.2% (154/183). The outcome of this study was summarized in the following table.

Table 5 Historical Levofloxacin Data in FDA NDA Database Identified by the Statistical Reviewer

Study	Type of UTI	Levofloxacin Microbiological Eradication Rate	95% CI
L91-058	cUTI and AP	154/183 (84.2%)	(78%, 89.1%)

The data from the applicable studies in Tables 4 and 5 were pooled together to obtain a weighted estimate of the placebo cure rate and its corresponding two-sided 95% CI. The weighted non-iterative method for random effects model described by DerSimonian and Laird was used to obtain the estimate and its 95% CI. The weighted estimate is 90.7% with 95% CI of (78.1%, 96.4%).

Estimated Noninferiority Margin for Complicated UTI (cUTI) Using Levofloxacin as the Active Comparator

Summarizing the response rate for placebo, inadequate therapy, and the active comparator, we have:

- The weighted estimate of placebo response rate for uncomplicated UTI is 37% with 95% CI of (24%, 53%).
- The weighted estimate of the inadequate therapy response rate for complicated UTI is 37.1% with 95% CI of (16%, 64.7%).
- The weighted estimate of the active comparator Levofloxacin response rate for complicated UTI is 90.7% with 95% CI of (78.1%, 96.4%)

The putative placebo cure rate, obtained from placebo response rate for uUTI and outcomes with inadequate or inappropriate therapy for cUTI, was at best about 65% (using the upper bound of the 95% CI for the estimated cUTI inadequate therapy response rate). Note that the 65% is based on inadequate therapy, and it may over-estimate the placebo rate. The conservative estimated value for cure rate of Levofloxacin was 78% (using the lower bound of the 95% CI for the

estimated Levofloxacin response rate). The observed microbiological eradication rate of Levofloxacin based on the current submission (NDA22106) was 78.2% in the mITT population. Therefore, the conservative estimate of the active control Levofloxacin over the placebo is about 13%, which provides an estimate of 13% for M1. This estimate was most likely underestimated and probably be much larger than 13% given that the placebo cure rate for cUTI as high as 65% is probably hard to achieve. Assuming that $M1 \geq 13\%$, it can be concluded that a 10% non-inferiority margin would still preserve an unknown fraction of the treatment effect over placebo for cUTI indication. Therefore, a 10% non-inferiority margin is justifiable given all the information summarized above, even with the caveats stated.

It should be noted that the acceptability of a 10% non-inferiority margin using Levofloxacin as the active control for cUTI is based on the limited information currently available. These estimates and conclusions could change based on the availability of more information on the placebo and control effect.

**APPEARS THIS WAY
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