CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210303Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	210303
Drug Name:	Plazomicin
Indication(s):	Complicated urinary tract infections
Applicant:	Achaogen Inc.
Date(s):	Stamp date: October 25, 2017 PDUFA goal date: June 25, 2018
Review Priority:	Priority review
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1. EXECUTIVE SUMMARY

In this submission, the applicant, Achaogen Inc. is seeking approval of plazomicin sulfate (plazomicin) for the treatment of complicated urinary tract infections (cUTIs) including pyelonephritis and blood stream infections (BSIs), when patients have limited or no alternative treatment options. The submission contains two Phase 3 efficacy studies, one for each of the two indications, cUTI and BSI. The main focus of this review is Study ACHN-490-009, a Phase 3, randomized, double-blind, noninferiority trial for the treatment of cUTI. (b) (4)

In Study ACHN-490-009 male and female subjects ≥ 18 years of age diagnosed with cUTI, including acute pyelonephritis (AP), were randomized to IV plazomicin (15mg/kg/day) or IV meropenem (1.0g every 8 hours) therapy. Dosing of plazomicin could be adjusted based on patient's renal function. After a minimum of 4 days of blinded IV therapy, there was an option to switch patients to open-label oral levofloxacin for an additional 3 to 6 days to complete therapy. The maximum duration of IV therapy was 7 days. Clinical response and microbiological response were assessed at Day 5, End of IV (EOIV, within 24 hours of last dose of IV study drug), Test of Cure (TOC, Day 17 ± 2 days), and Late Follow up (LFU, Day 24 – 32). The co-primary endpoints were composite microbiological eradication and clinical cure rate in the microbiological modified intent-to-treat (mMITT) population at the Day 5 and TOC visits, where the mMITT population was defined as all randomized patients who received any dose of study drug and had at least one qualified baseline pathogen (from a baseline urine culture), against which meropenem and plazomicin had antibacterial activity. To claim this study successful, noninferiority would need to be shown for the primary endpoints at both Day 5 and TOC. The noninferiority margin for this trial was -15% on the risk difference scale.

A total of 609 patients were randomized to the study, and the mMITT population included 388 patients with 191 in the plazomicin group and 197 in the meropenem group. Demographics and baseline characteristics were generally balanced between the two groups. The majority of patients were from Eastern European countries and were predominantly white, with approximately 40% having AP. Of the mMITT population, *Escherichia coli* was the most common baseline uropathogen, which infected almost 70% of the patients. Approximately 25% of the patients had aminoglycoside resistant pathogens, and almost 28% of the patients had pathogens that produce extended-spectrum beta-lactamases. About 80% of the patients switched to oral therapy after at least 4-day IV therapy, and a slightly more than 95% of the patients completed study treatment.

The co-primary composite efficacy endpoints that were assessed at Day 5 and TOC visits are presented in Table 1. The results at both visits support the noninferiority of plazomicin compared to meropenem for the treatment of cUTI including AP. This primary analysis was robust to the handling of indeterminate data. Results were generally consistent for the individual component of the composite endpoints.

Table 1: Composite Response at Day 5 and TOC Visit, mMITT Population

Timepoint	Composite Response	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)
Day 5	Cure	168 (88.0)	180 (91.4)	-3.4 (-10.0, 3.1)
	Failure	20 (10.5)	15 (7.6)	
	Indeterminate	3 (1.6)	2 (1.0)	
TOC	Cure	156 (81.7)	138 (70.1)	11.6 (2.7, 20.3)
	Failure	29 (15.2)	51 (25.9)	
	Indeterminate	6 (3.1)	8 (4.1)	

Source: Reviewer's analysis

In summary, the trial results support the conclusion that plazomicin is noninferior to meropenem for the treatment of cUTI including AP in adults based on the submitted single Phase 3 study. As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin should be reserved for use in patients who have limited or no alternative treatment options.

2. INTRODUCTION

2.1 Overview

The applicant, Achaogen Inc., submitted a New Drug Application seeking authorization to market plazomicin for the treatment of complicated urinary tract infections (cUTIs) and bloodstream infections (BSIs). This review only focuses on cUTI indication. (b) (4) an advisory committee meeting was held to discussed the application of plazomicin indications for cUTI and BSI on May 2, 2018.

In this section, the background of the study drug, the disease, the Phase 3 study under review, and the scope of the application are introduced.

2.1.1 Plazomicin

Plazomicn is a next-generation aminoglycoside antibiotic derived from sisomicin. It is a broad-spectrum drug and has potent activity against Gram-negative and selected Gram-positive bacteria. It is active against resistant *Enterobacteriaceae*, including those that produce extended-spectrum beta-lactamases (ESBL), carbapenemases, and several other enzymes. Plazomicin is not an approved antibacterial therapy currently.

Please refer to the clinical microbiology review for details regarding the mechanism of the bactericidal effect of plazomicin.

2.1.2 Complicated Urinary Tract Infection and Treatment

To be diagnosed as having cUTIs, patients should have a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, plus the presence of a functional or anatomical abnormality of the urinary tract or the presence of catheterization. The accompanying local and systemic signs and symptoms include fever, chills, malaise, flank pain, back pain, and costovertebral angle pain or tenderness. Also, patients with pyelonephritis are considered a subset of patients with cUTIs regardless of underlying abnormalities of the urinary tract. According to FDA guidance document, for an indication of "treatment of cUTIs including pyelonephritis", at least 30% of the clinical trial population should be patients with pyelonephritis.[1]

The treatment for cUTI is normally initiated with intravenous antibacterial therapy followed by oral antibiotics. A successful treatment of cUTI means the bacterial pathogen(s) presented in the urine specimen is eradicated (bacteria growth at a quantification of less than 10^4 CFU/mL) and symptoms are resolved. As antimicrobial resistance increases among urinary tract pathogens, such as ESBL producing *Enterobacteriaceae*, available treatment options for cUTI become limited. Carbapenems are currently considered as the most reliable treatment option for

[1] Food Drug Administration, Center for Drugs Evaluation Research (February 2015). Guidance for Industry: Complicated Urinary Tract Infections: Developing Drugs for Treatment. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf

infections due to ESBL-producing bacteria. With increasing use of carbapenem, resistance to this class of drugs is beginning to emerge.

2.1.3 Study Reviewed

One Phase 3 study, ACHN-490-009 (Study 009), that evaluates the efficacy and safety of plazomicin in the treatment of cUTI, including AP was submitted in this NDA. This review focuses on the statistical evidence from the submitted study. Summary of the study is in the following table (Table 2).

Table 2: Summary of the Study Reviewed

Study	Study Design	Population	Planned Statistical Analysis	Randomized Treatment Groups and Sample Sizes
Study 009	Randomized, multi-center, double-blind, noninferiority study	cUTI patients, including AP, 18 years and older	Noninferiority analysis with a margin of 15%	Plazomicin: 306 Meropenem: 303

2.1.4 Scope of this New Drug Application

The applicant seeks to indicate plazomicin in patients 18 years and older for the treatment of cUTI including pyelonephritis that are caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus* spp. (including *P. mirabilis* and *P. vulgaris*), and *Enterobacter cloacae.* The applicant only seeks to include results from the Phase 3 cUTI noninferiority study 009 in the Clinical Studies section of the product labeling.

2.2 Data Sources

The patient level datasets for Study 009 analyzed in this review can be found at the following link in the Agency's electronic document room:

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In addition to patient level datasets, other materials reviewed included the study protocol, statistical analysis plan, and clinical study report.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data submitted in this NDA were used to reproduce the applicant's major efficacy and safety results without complex manipulation. The protocol amendments and statistical analysis plan

were considered to be sufficient, and the reported analyses were consistent with the planned analyses.

3.2 Evaluation of Efficacy

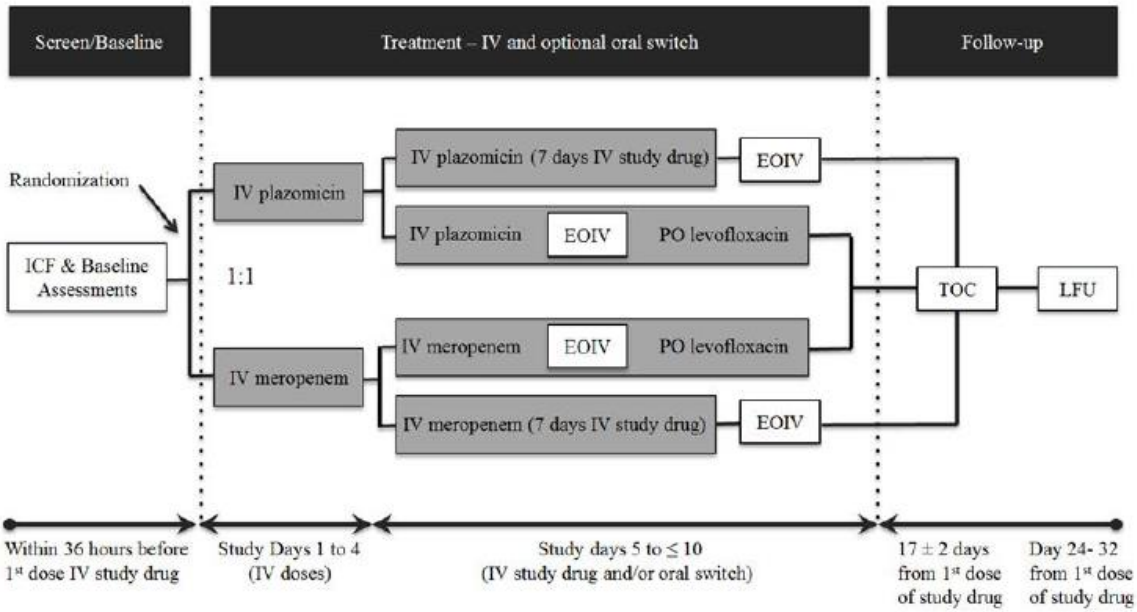
3.2.1 Study Design and Endpoints

Study 009 was titled "A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP), in Adults". It was initiated in January 2016 and completed in September 2016. A total of 68 study sites located in North America and Europe were involved in the study, though a vast majority of subjects were enrolled from Eastern Europe.

Patients with cUTI, including AP, who required hospitalization and intravenous infusion of antibiotic therapy were randomized 1:1 to the plazomicin group or meropenem group. The randomization was stratified by infection type (cUTI or AP) and region. Patients meeting criteria for both cUTI and AP were considered to have cUTI.

The study included a screening period (baseline assessments conducted) of up to 36 hours before randomization, an active treatment period (IV study drug and optional switch to open-label oral antibiotics) of up to 10 days, and a follow-up period up to Day 32 (Figure 1).

Figure 1: Design Schema and Overview of Study Schedule



Abbreviations: EOIV=end-of-IV therapy; ICF=informed consent; IV=intravenous; LFU=late follow-up; PO=per oral; TOC=test-of-cure.

Note: Study Day 1 was the calendar day that first dose of IV study drug is administered. Patients could receive a maximum of 21 doses on an every 8 hour (q8h) dosing schedule or 14 doses on an every 12 hours (q12h) dosing schedule (approximately 7 days) of IV study drug and a maximum of 10 days of IV plus oral study drug.

Source: Study ACHN-490-009 Clinical Study Report, Figure 1.

The study drug was administered as follows:

- Plazomicin was infused intravenously at a dose of 15 mg/kg once daily, followed by matching placebo infused at 8 and 16 hours after the initial infusion. The dosage of plazomicin was adjusted daily based on patients' renal function (Table 3). Please refer to the clinical pharmacology review for more details of the dosing adjustment.
- Meropenem was administered as 1.0g IV every 8 hours.

Table 3: Overview of Study Drug Dosing

Estimated CLcr (mL/min)	Plazomicin IV	Meropenem IV	Levofloxacin PO
>60	15 mg/kg q24h	1.0 g q8h	500 mg q24h
>50 to 60	12 mg/kg q24h	1.0 g q8h	500 mg q24h
>40 to 50	10 mg/kg q24h	1.0 g q12h	250 mg q24h
>30 to 40	8 mg/kg q 24h	1.0 g q12h	250 mg q24h
≤ 30	Discontinue Study Drug		

IV=intravenous; q8h=every 8 hours; q12h=every 12 hours; q24h=every 24 hours.

Source: Protocol version A1, Table 1

For patients with total body weight (TBW) ≥ 125% of the ideal body weight (IBW), plazomicin dosing weight was calculated based on the following equation:

$$\text{Adjusted body weight (kg)} = \text{IBW (kg)} + 0.4 \times [\text{TBW (kg)} - \text{IBW kg})]$$

IBW was determined based on the following equations:

$$\text{For males: IBW (kg)} = 50 + \{2.3 \times [(\text{height in cm}/2.54) - 60]\}$$

$$\text{For females: IBW (kg)} = 45.5 + \{2.3 \times [(\text{height in cm}/2.54) - 60]\}$$

After a minimum of 4 days of blinded IV therapy, there was an option to switch patients to open-label oral levofloxacin for an additional 3 to 6 days to complete the therapy. The maximum days of IV therapy was 7 days. Patients either discontinued therapy or switched to oral therapy afterwards. Patients who required longer than 7 days of IV therapy and could not be switched to oral therapy were removed from study therapy and placed on alternative IV therapy. For the patients who did not tolerate oral levofloxacin, or if the baseline pathogen was not susceptible to it, alternative oral agents that were pre-specified based on local epidemiology and standard of care were administered.

Inclusion criteria for the study required patients diagnosed with cUTI or AP, at least 18 years of age, a total body weight not larger than 150 kg, and with a screening creatinine clearance > 30

mL/min (Cockcroft-Gault formula). All patients were required to have a pretreatment baseline urine culture obtained within 36 hours before the first dose of study drug.

Patients were excluded based on the following criteria:

- Received a potentially therapeutic antibacterial agent within 48 hours prior to start of study therapy;
- Requirement of using any prohibited concomitant therapy;
- Confirmed fungal urinary tract infection;
- Urinary tract infection or colonization with Gram-positive pathogens;
- Pathogen resistant to meropenem;
- Diagnosed as non-cUTI and non-AP infection within 7 days prior to enrollment;
- Receipt of any investigational medication or device within 30 days or prior exposure to plazomicin;
- Documented immunodeficiency or an immunocompromised condition;
- Had rapidly progressing disease or immediately life-threatening illness;
- Known history of otologic surgery or disease; had severe adverse drug reaction to aminoglycosides, carbapenem, or β-lactam antibiotics.
- Baseline AST, ALT, alkaline phosphatase, or total bilirubin level three times the upper limit of normal, platelet count less than 40,000/μL, or hematocrit less than 20%.

Clinical response and microbiological response were assessed at Day 5, EOIV (within 24 hours of last dose of IV study drug), TOC (Day 17 ± 2 days), and LFU (Day 24 – 32) (Table 4). For a patient to have a favorable clinical response, the outcome should be at least one of the following: complete resolution, return to premorbid levels, or reduction in severity of all core baseline symptoms with none of them getting worse and no new symptoms developed. A favorable microbiological response means that the outcome for each baseline pathogen should be eradicated (bacteria colony count reduced to $< 10^4$ CFU/mL). The co-primary endpoints were the composite microbiological eradication and clinical cure rate in the microbiological modified intent-to-treat (mMITT) population at the Day 5 (if a patient had EOIV that occurred before or on Day 5, EOIV assessments were used for the Day 5 endpoint analyses) and TOC visits. The term co-primary for this study means that non-inferiority needs to be shown with the primary endpoint at both Day 5 and TOC to conclude the efficacy. Secondary endpoints included the composite microbiological eradication and clinical cure rate in at the end of IV therapy and late follow-up visits along with clinical response and microbiological response separately at the different time points evaluated using the mMITT population, and the composite microbiological eradication and clinical cure rate in the microbiological evaluable (ME) population at Day 5 and TOC visits.

Table 4: Schedule of Assessment

Study Procedure	Study Visit	Screening [a] Days –1 to 1		Treatment						Follow-up		
	Assessment	Day –1	Day 1 [a]	Days 2–3	Day 4 [b]	Day 5 [b]	Days 6–8 [b]	EOIV [b] ≤24 hours	Days 9–10	TOC [c] Day 17 (±2 days)	LFU [c,d] Day 24–32 Office	LFU [c,d] Day 24–32 Phone
Baseline	Informed consent	X										
	Eligibility verification	X										
	Medical and surgical history [e]	X										
	Randomization		X									
Local Laboratory	Urine microscopy and/or dipstick [f]	X										
	Urine pregnancy test	X										
	Hematology/chemistry [g]	X										
	Serum creatinine and calculated CLcr	X	X [h]	X	X	X [i]	X [i]					
	Urine culture	X		X		X		X		X	X	
	Blood culture [j]	X		X	X	X	X	X		X	X	
Central Laboratory	Hematology/chemistry [k]	X						X		X	X	
	Serum creatinine only			X	X	X [i]	X [i]					
	Serum pregnancy	X						X				
	Blood for PK [l]			X	X							
Clinical	Vital Signs	X	X [m]	X [m]	X [m]	X [m]	X [i,m]	X [m]		X	X	
	Complete physical exam	X										
	Targeted physical exam							X		X	X	
	Height and weight	X										
	Prior and/or concomitant medications [n]	X	X	X	X	X	X	X	X	X	X	X
	Assessment of hearing, tinnitus and dizziness [o]	X						X			X	X
	Urinary symptom status [p]	X	X	X	X	X	X [i]	X		X	X	X
	Assessment of clinical response							X		X	X	X
	Adverse events [q]		X	X	X	X	X	X	X	X	X	X
	IV study drug [r]		X	X	X	X [i]	X [i]					
	Oral step down [s]					X	X		X			

EOIV=end-of-IV therapy visit; LFU=late follow-up visit; TOC=test of cure visit.

[a] Study Day 1 is the calendar day that first dose of IV study drug is administered. On Day 1, all study procedures except adverse event collection are to be performed prior to study drug administration. Note that screening procedures may occur on Day 1 provided they are completed within the 36 hour screening window prior to administration of first dose of study drug.

[b] EOIV assessments will be completed within 24 hours of last dose of IV study drug and before first dose of oral step-down therapy (if administered). EOIV may occur anywhere between Study Day 4 and Study Day 8. On the last day of IV therapy, EOIV assessments will replace the assessments for that corresponding study day. If EOIV occurs prior to or on Day 5 for any individual patient, EOIV assessments will be used for the Day 5 endpoint analyses.

[c] For TOC and LFU, study days indicated are timed from administration of the first dose of study drug.

[d] Permissible to conduct LFU visit by telephone for subset of patients (Section 6.4.2).

[e] Record inactive conditions diagnosed within previous 5 years and all active conditions.

[f] To test for pyuria.

[g] At baseline, perform local laboratory tests (WBC, absolute neutrophil count, % bands or immature neutrophils, platelets, hematocrit, AST, ALT, alkaline phosphatase, total bilirubin, serum creatinine and calculated creatinine clearance) to verify that the patient meets all study inclusion and does not meet any exclusion criteria before randomization.

[h] Does not need to be repeated if Baseline and Day 1 occur on same calendar day.

[i] For patients continuing IV therapy beyond the minimum of approximately 4 days (eg, 12 doses for patients on a q8h dosing schedule; 8 doses for patients on a q12h dosing schedule).

[j] When clinically indicated; see Sections 4.3.3, 6.2, and 6.3.2 through 6.4.2.

[k] Hematology and chemistry evaluations, including serum creatinine (see Appendix 2 for details).

[l] Collected on Day 3 (±1 day) at the following time points relative to Dose A (always active study drug for both treatment groups) of study drug infusion: just prior to infusion and 90 minutes (±15 minutes), 4 hours (±1 hour), and 10 hours (±1 hour) after initiation of study drug infusion. Samples should be drawn from the arm opposite the infusion or away from infusion site if the opposite arm is not available.

[m] To be performed 15 minutes (±10 minutes) prior to start of each study drug infusion and 15 minutes (±10 minutes) after the end of each study drug infusion.

[n] All prescription and over-the-counter medications and herbal, nutritional and dietary supplements that the patient took or received within 7 days before the first dose of study drug and any anti-bacterial agents that the patient took or received within 14 days before the first dose of study drug and through the LFU visit will be documented in the appropriate eCRF. Record new concomitant medications starting after EOIV at the TOC visit.

[o] See Appendix 4–Appendix 6.

[p] Record core systems (dysuria, urinary frequency, urinary urgency, suprapubic pain, flank pain) at all time points and additional symptoms/signs (nausea, vomiting, chills, rigors, warmth, CVA tenderness) at baseline only (see Appendix 3).

[q] AE collection period begins with first dose of study drug and ends at LFU. Record AEs occurring between EOIV and TOC at the TOC visit.

[r] Blinded plazomicin up to 15 mg/kg followed by matching placebo infusions *or* blinded meropenem 1.0 gram q8h administered as 30-minute (±10 minutes) 50 mL IV infusions for approximately 4 to 7 days (dosing may be adjusted, including adjustment in dosing schedule, based on renal function).

[s] Open-label levofloxacin 250 or 500 mg PO daily, depending on renal function, for a maximum of 6 doses, depending on duration of blinded IV study drug. First dose of oral therapy to be given within 8 to 12 hours of last dose of IV study drug. Refer to section 4.8.3 for patients requiring extended therapy beyond 10 days. Record number of doses completed at TOC visit.

Source: Study ACHN-490-009 Protocol, Appendix 1.

3.2.1 Statistical Methodologies

The primary analysis population was the mMITT population. Compared to the modified intent-to-treat (MITT) population, which included all randomized patients who received any dose of study drug, the mMITT population was defined as having at least one qualified baseline pathogen (from a baseline urine culture), against which meropenem and plazomicin had antibacterial activity. The ME population included patients in the mMITT population who complied with all key protocol requirements and had interpretable data for all efficacy assessments.

Clinical response at Day 5, EOIV, and TOC was defined as cure, failure, or indeterminate. Clinical repose at LFU was defined as sustained cure, relapse, or indeterminate. All patients had Day 5 and EOIV assessments. Day 5 clinical response was determined programmatically, and clinical response assessments at all other visits were determined both programmatically and by the site investigator. If the patient's clinical response was determined by the investigator as failure on or after EOIV, no subsequent assessments of clinical response were performed.

Microbiologic response at Day 5, EOIV, and TOC was determined for each pathogen isolated at baseline. The categories of the outcome were eradication, presumed eradication (Day 5 and EOIV only), persistence, and indeterminate. Per-pathogen microbiological response at LFU was

determined in patients with a favorable microbiological response at TOC. The outcome categories were sustained eradication, presumed sustained eradication, recurrence, and indeterminate.

Missing values in clinical and microbiological response were defined as indeterminate. Patients who required longer than 7 days of IV therapy and switched to alternative IV therapy were considered clinical failures at the EOIV visit. Patients who discontinued IV study drug on or prior to Day 5 or EOIV due to an adverse event and received a non-study systemic antibiotics for cUTI or AP were considered as failures at Day 5 or EOIV. Patients who received a non-study systemic antibiotics for cUTI or AP on or before TOC (excluding approved oral step-down therapies and system antibiotics with a narrow spectrum of activity limited to gram-positive or anaerobic organisms) were considered as failures at TOC.

The composite of microbiological eradication and clinical cure were defined in the table below (Table 5):

Table 5: Definition for the Composite Microbiological Eradication and Clinical Cure Rate

Microbiological Response	Programmatically Derived Clinical Response	Composite Response
Eradication	Cure	Cure
Eradication	Failure	Failure
Eradication	Indeterminate	Indeterminate
Persistence	Cure	Failure
Persistence	Failure	Failure
Persistence	Indeterminate	Failure
Indeterminate	Cure	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

Source: Study ACHN-490-009 SAP v2.0, Table 12.

The statistical analysis plan proposed using a continuity corrected Z-statistic to calculate a two-sided 95% confidence interval (CI) for the observed difference for the composite cure rate (plazomicin – meropenem). Noninferiority of plazomicin to meropenem was to be claimed if the lower limit of the 95% CI for the difference in the composite cure rate was greater than -15% at both Day 5 and TOC visit.

The planned sample size for the study was 394 patients in the mMITT population. This was expected to provide at least 85% power using a non-inferiority margin of -15% at one-sided α level of 0.025, assuming a response rate for the co-primary endpoints in both treatment groups being 64% at Day 5 and 73.2% at TOC. This noninferiority margin of -15% is wider than the -

10% margin recommended in the FDA guidance document on antibacterial drugs for cUTI (historical data show that the effect of antibacterials for the cUTI were 20% for EOIV and 30% for end of therapy[2]). It was agreed on by the Agency to support a limited use indication.

Additional analyses for the primary endpoint were also proposed. Two-sided 95% CIs for the observed differences in the composite cure rate at Day 5 and TOC visit were to be calculated for each geographic region stratum and infection type (cUTI and AP) using a continuity corrected Z-statistic. Additional subgroup analyses were to be conducted descriptively.

3.2.2 Patient Disposition, Demographic, and Baseline Characteristics

There was a total of 609 patients randomized to this Phase 3 cUTI study (306 in the plazomicin group and 303 in the meropenem group). Five patients did not receive study drug thus were not included in the MITT population. The mMITT population had 388 patients (191 in the plazomicin group and 197 in the meropenem group). The ME population had 188 and 190 patients in the plazomicin group and meropenem group, respectively, at Day 5. At TOC, ME population had 179 patients in the plazomicin group and 177 in the meropenem group. For the patients in the mMITT population, only a small proportion of patients did not complete study drug or prematurely discontinued study. The following table contains the subject disposition for the mMITT population (Table 6).

Table 6: Disposition Table, mMITT Population

	Plazomicin (N=191)	**Meropenem (N=197)**
Completed Study	189 (99%)	194 (98.5%)
Prematurely Discontinued Study	2 (1%)	3 (1.5%)
Lost to Follow-up	1 (0.5%)	1 (0.5%)
Withdrawal of Consent	1 (0.5%)	2 (1%)
Completed Study Treatment	183 (95.8%)	187 (94.9%)
Prematurely Discontinued Study Drug (IV or Oral)	8 (4.2%)	10 (5.1%)
Prematurely Discontinued IV Study Drug		
Adverse Event	1 (0.5%)	5 (2.5%)
Lack of Study Qualifying Pre-treatment Baseline Urine Culture	1 (0.5%)	1 (0.5%)
Withdrawal of Consent		1 (0.5%)
CLCR<30mL/min	1 (0.5%)	
Investigator Decision	2 (1%)	
Prematurely Discontinued Oral Study Drug		
Adverse Event	2 (1%)	2 (1%)
Pathogen Resistant to Levofloxacin		1 (0.5%)
Lost to Follow-up	1 (0.5%)	

[2] Food Drug Administration, Center for Drugs Evaluation Research (February 2015). Guidance for Industry: Complicated Urinary Tract Infections: Developing Drugs for Treatment. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf

Source: Statistical reviewer

More patients in the mMITT population were in the cUTI stratum (58.2%) compared to the patients who had AP (41.8%). The majority of the patients were from Eastern European countries (98.5%), they were predominately white (99.5%), they had a mean age of 59.4 years, and there was a roughly equal representation of males (47.2%) and females (52.8%). The baseline factors were generally balanced between the plazomicin and meropenem groups. Details of the patient demographics and baseline disease characteristics for mMITT population and MITT population are shown in Tables 7 and 8.

Table 7: Patient Demographics and Baseline Disease Characteristics for Study 009, mMITT Population

	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	All Patients (N=388) n (%)
Infection Type per eCRF			
cUTI	107 (56.0)	119 (60.4)	226 (58.2)
cUTI with Indwelling Catheter	25 (13.1)	26 (13.2)	51 (13.1)
cUTI without Indwelling Catheter	82 (42.9)	93 (47.2)	175 (45.1)
AP	84 (44.0)	78 (39.6)	162 (41.8)
Region and Country			
Region 1	4 (2.1)	2 (1.0)	6 (1.5)
Mexico	1 (0.5)	1 (0.5)	2 (0.5)
Spain	1 (0.5)	0 (0)	1 (0.3)
United States	2 (1.0)	1 (0.5)	3 (0.8)
Region 2	187 (97.9)	195 (99.0)	382 (98.5)
Bulgaria	20 (10.5)	30 (15.2)	50 (12.9)
Czech Republic	1 (0.5)	0 (0)	1 (0.3)
Estonia	9 (4.7)	18 (9.1)	27 (7.0)
Georgia	31 (16.2)	24 (12.2)	55 (14.2)
Hungary	12 (6.3)	10 (5.1)	22 (5.7)
Latvia	23 (12.0)	15 (7.6)	38 (9.8)
Poland	15 (7.9)	25 (12.7)	40 (10.3)
Romania	29 (15.2)	22 (11.2)	51 (13.1)

	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	All Patients (N=388) n (%)
Russia	24 (12.6)	21 (10.7)	45 (11.6)
Serbia	8 (4.2)	8 (4.1)	16 (4.1)
Ukraine	15 (7.9)	22 (11.2)	37 (9.5)
Sex			
Male	84 (44.0)	99 (50.3)	183 (47.2)
Female	107 (56.0)	98 (49.7)	205 (52.8)
Race			
White	189 (99.0)	197 (100)	386 (99.5)
Black or African American	1 (0.5)	0 (0)	1 (0.3)
Asian	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian/Other Pacific Islander	0 (0)	0 (0)	0 (0)
Other	1 (0.5)	0 (0)	1 (0.3)
Not Reported	0 (0)	0 (0)	0 (0)
Age (years)[a]	191	197	388
Mean	58.8	60.0	59.4
SD	17.99	17.94	17.95
Median	63.0	65.0	64.0
Min, Max	18, 88	18, 87	18, 88
Age Group (years)			
<65	101 (52.9)	95 (48.2)	196 (50.5)
≥65	90 (47.1)	102 (51.8)	192 (49.5)
Height (cm)	191	197	388
Mean	168.1	168.8	168.5
SD	8.84	7.90	8.37
Median	167.0	168.0	168.0
Min, Max	142, 190	149, 187	142, 190
Weight (kg)	191	197	388
Mean	75.73	77.27	76.51
SD	16.083	16.250	16.165
Median	75.00	76.00	75.40
Min, Max	43.2, 135.0	39.0, 131.0	39.0, 135.0
TBW/IBW Ratio			
≥ 125%	71 (37.2)	80 (40.6)	151 (38.9)
< 125%	120 (62.8)	117 (59.4)	237 (61.1)
BMI (kg/m^2)[b]	191	197	388
Mean	26.73	27.05	26.89
SD	5.142	5.081	5.107
Median	26.20	26.70	26.35
Min, Max	16.5, 51.4	15.6, 43.8	15.6, 51.4
Calculated Creatinine Clearance (mL/min) (CLcr)[c]	188	194	382
Mean	77.44	72.44	74.90
SD	30.609	28.704	29.723

	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	All Patients (N=388) n (%)
Median	71.95	68.55	70.25
Min, Max	30.7, 194.0	28.3, 190.4	28.3, 194.0
Calculated Creatinine Clearance Group [c]			
> 120 mL/min	17 (8.9)	10 (5.1)	27 (7.0)
> 90 to 120 mL/min	40 (20.9)	35 (17.8)	75 (19.3)
> 60 to 90 mL/min	70 (36.6)	75 (38.1)	145 (37.4)
> 30 to 60 mL/min	61 (31.9)	71 (36.0)	132 (34.0)
≤ 30 mL/min	0 (0)	3 (1.5) [d]	3 (0.8)
Missing	3 (1.6)	3 (1.5)	6 (1.5)
Receipt of any antibiotic within 48 hours prior to start of study drug	2 (1.0)	0 (0)	2 (0.5)
For treatment of current cUTI or AP	2 (1.0)	0 (0)	2 (0.5)
Failure of prior antibiotic therapy with documented cUTI/ AP causing pathogen susceptible to study drug	2 (1.0)	0 (0)	2 (0.5)
Developed cUTI/ AP on potentially therapeutic antibiotic and has gram-negative bacilli	0 (0)	0 (0)	0 (0)
Receiving UTI prophylaxis, all other eligibility criteria met	0 (0)	0 (0)	0 (0)
Developed cUTI/AP after receipt of antibacterial drugs limited to gram-positive and/or anaerobic pathogens	0 (0)	0 (0)	0 (0)

Abbreviations: AP=acute pyelonephritis; BMI=body mass index; CLcr=creatinine clearance; cUTI=complicated urinary tract infection; eCRF=electronic case report form; IBW=ideal body weight; mMITT=microbiological modified intent-to-treat; N=number of patients randomized; n=number of patients in the specified category; SD=standard deviation; TBW=total body weight.

Note: Percentages are calculated as 100 x (n/N).

[a] Age per eCRF and as reported by the patient.

[b] BMI calculated as baseline weight (kg) divided by baseline height $(m)^2$.

[c] CLcr as estimated by the Cockcroft-Gault formula using baseline serum creatinine (mg/dL) from the central laboratory and total body weight (TBW), or ideal body weight (IBW), for patients whose TBW was >125% of IBW. Baseline serum creatinine was defined as the last central laboratory measurement prior to the first dose of study drug administered.

[d] The three patients shown here with CLcr ≤ 30 mL/min (derived per central laboratory serum creatinine values) had CLcr >30 mL/min based on local laboratory serum creatinine values (Patients (b) (6) [30.6 mL/min], (b) (6) [31.7 mL/min], and (b) (6) [30.6 mL/min]; see Listing 16.2.5.1).

Source: ACHN-490-009 Clinical Study Report, Table 14.1.4.3.1

Table 8: Patient Demographics and Baseline Disease Characteristics, MITT Population

	Statistic	MITT		
		Total (N=604)	Plazomicin (N=303)	Meropenem (N=301)
Age (Year)				
	Mean	58.6	58.3	58.9
	SD	17.95	18.28	17.63
	Median	63	62	64
	Min, Max	18.0, 90.0	18.0, 90.0	18.0, 89.0
Age Group	n (%)			
<65		324 (53.6)	166 (54.8)	158 (52.5)
>=65		280 (46.4)	137 (45.2)	143 (47.5)
Sex	n (%)			
Male		286 (47.4)	133 (43.9)	153 (50.8)
Female		318 (52.6)	170 (56.1)	148 (49.2)
Race	n (%)			
White		601 (99.5)	301 (99.3)	300 (99.3)
Other		3 (0.5)	2 (0.7)	1 (0.3)

Ethnicity	n (%)			
Hispanic or Latino		6 (1.0)	2 (0.7)	4 (1.3)
Not Hispanic or Latino		593 (98.2)	298 (98.3)	295 (98.0)
Region	n (%)			
Region 1		6 (1.0)	4 (1.3)	2 (0.7)
Region 2		598 (99.0)	299 (98.7)	299 (99.3)
Weight (kg)				
	Mean	76.8	76	77.6
	SD	16.2	16.14	16.25
	Median	76	75	77
	Min, Max	39.0, 135.0	40.5, 135.0	39.0, 131.0
BMI (kg/m2)				
	Mean	26.9	26.8	27
	SD	5.07	5.15	4.99
	Median	26.4	26.4	26.4
	Min, Max	14.5, 51.4	15.4, 51.4	14.5, 43.8
TBW/IBW Ratio Group	n (%)			
<125%		367 (60.8)	189 (62.4)	178 (59.1)
>=125%		237 (39.2)	114 (37.6)	123 (40.9)
Infection Type	n (%)			
cUTI		356 (58.9)	177 (58.4)	179 (59.5)
AP		248 (41.1)	126 (41.6)	122 (40.5)
Baseline Creatinine Clearance	n (%)			
>120 mL/min		47 (7.8)	28 (9.2)	19 (6.3)
>90 to 120 mL/min		127 (21.0)	65 (21.5)	62 (20.6)
>60 to 90 mL/min		226 (37.4)	115 (38.0)	111 (36.9)
>30 to 60 mL/min		194 (32.1)	91 (30.0)	103 (34.2)
<=30 mL/min		4 (0.7)	1 (0.3)	3 (1.0)
Missing		6 (1.0)	3 (1.0)	3 (1.0)
Catheter	n (%)			
Without Indwelling Catheter		513 (84.9)	262 (86.5)	251 (83.4)
With Indwelling Catheter		91 (15.1)	41 (13.5)	50 (16.6)
Medical History	n (%)			
No Diabetes		522 (86.4)	269 (88.8)	253 (84.1)
Diabetes		82 (13.6)	34 (11.2)	48 (15.9)
IV/Oral	n (%)			
IV Only		226 (37.4)	109 (36.0)	117 (38.9)
IV and oral		378 (62.6)	194 (64.0)	184 (61.1)
Duration of IV				
	Mean	5	5	5
	SD	1.65	1.65	1.66
	Median	5	4	5
	Min, Max	1.0, 7.0	1.0, 7.0	1.0, 7.0
Duration of IV and Oral				
	Mean	7.8	7.9	7.7
	SD	2.8	2.78	2.83
	Median	9	9	8
	Min, Max	1.0, 15.0	1.0, 15.0	1.0, 14.0

Source: Reviewer's analysis

3.2.3 Study Drug Administration

According to the dosing scheme specified in the protocol, the dose for plazomicin was adjusted for each patient daily based on CLCR and body weight (or adjusted body weight). The reviewer found that more than 25% of the doses (414 doses/a total of 1545 doses of plazomicin) administered to the patients were either at least 10mg higher or 10mg lower than the dose calculated using the algorithm provided in the protocol (the difference between the administered dose and the calculated daily dose ranges from -490mg to +500mg). This involved 151 out of 303 patients who received plazomicin. For this calculation, CLCR values from central lab were used.

The applicant later explained that local lab values of CLCR were used for the dosing calculation during the study. By using local lab values, 193 doses/a total of 1545 plazomicin doses administered to the patients (12%) were either at least 10mg higher or 10mg lower than the dose that was supposed to be administered based on the protocol. The number of patient involved was 66 (out of 303 in plazomicin group). When considering the total dose administered over the duration of the treatment, 55 out of the previously mentioned 66 patients had a total dose administered that was either more than 50 mg greater or 50 mg less than the total doses they were supposed to receive. 39 of them belong to the mMITT population. Some of those dosing discrepancies are likely due to using the wrong body weight in the dosing calculation (using actual body weight instead of adjusted body weight in patients whose TBW $\geq$ 125% IBW). Other discrepancies cannot be explained by using the wrong body weights. Considering the dosing issue, analyses for exposure-response relationship were conducted by clinical pharmacology team. Please refer to the clinical pharmacology review for details.

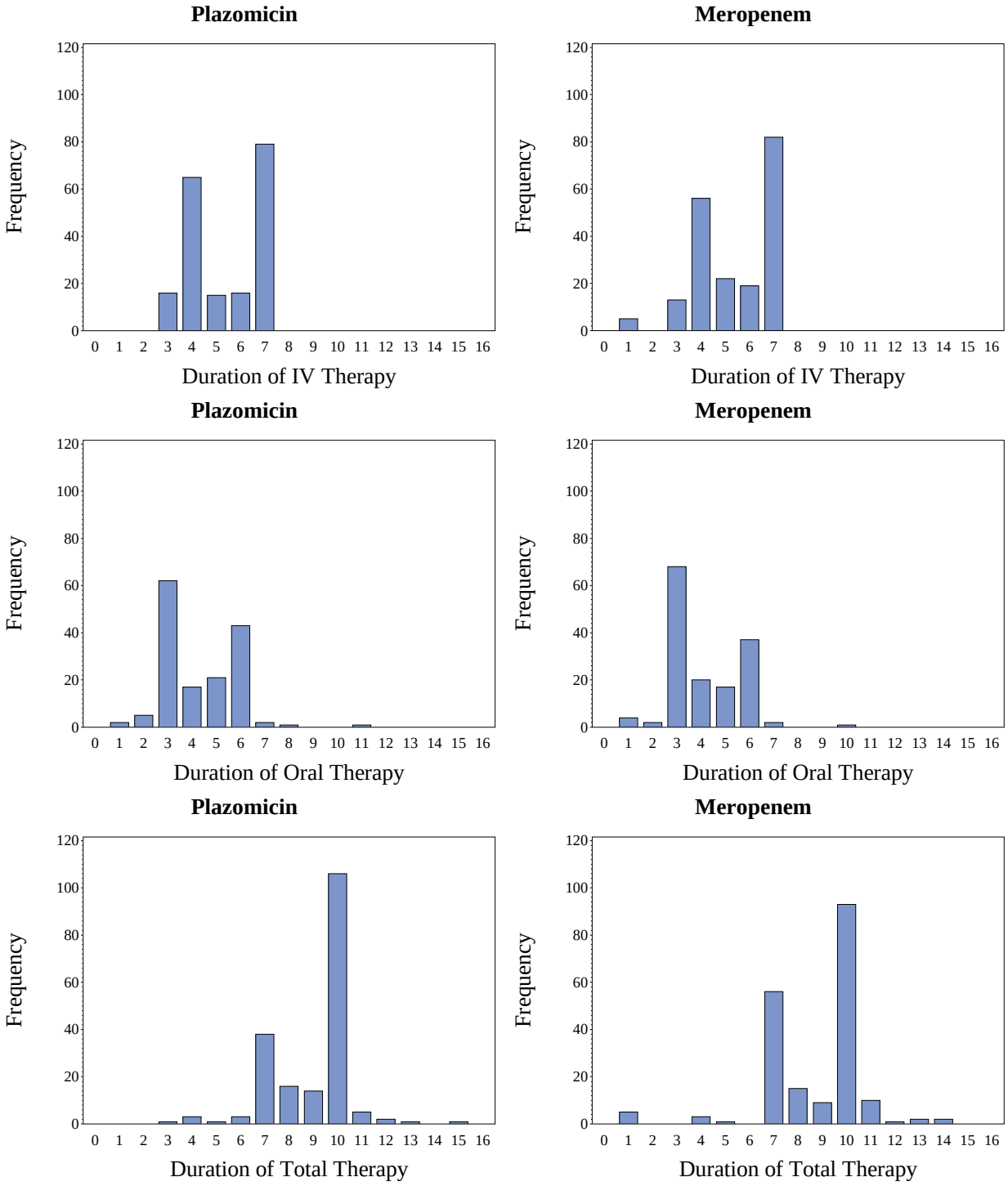
After a minimum of 4 days and a maximum of 7 days of IV therapy, patients could be switched to an optional open-label oral levofloxacin treatment for an additional 3 to 6 days to complete therapy. The numbers of patients who switched to oral therapy in the two treatment arms seem balanced (Table 9). In addition, the duration of IV therapy and overall therapy are comparable for the two treatment arms (Figure 2).

Table 9: Proportion of Subjects Administered IV Drug Only or Oral Drug Following IV, mMITT Population

mMITT population	Plazomicin (N=191)	Meropenem (N=197)
IV only	37 (19.4%)	46 (23.4%)
IV then oral		
Oral Levofloxacin	128 (67%)	121 (61.4%)
Other Approved Oral	26 (13.6%)	30 (15.2%)

Source: Reviewer's analysis

Figure 2: Duration of Treatment, mMITT Population



Source: Reviewer's analysis

3.2.4 Efficacy Results

3.2.4.1 Primary and Key Secondary Efficacy Analyses

There were co-primary endpoints, the composite cure of microbiological and clinical cure assessed at Day 5 and the same endpoint assessed at TOC. The composite cure rate of microbiological response and clinical response at Day 5 was 168/191 (88.0%) in the plazomicin group compared to 180/197 (91.4%) in the meropenem group, with a response rate difference (plazomicin - meropenem) of -3.4 and a 95% CI of (-10.0, 3.1). At TOC, the response rates were 156/191 (81.7%) and 138/197 (70.1%) for the plazomicin group and meropenem group, respectively. The difference of the response rate was 11.6 with a 95% CI of (2.7, 20.3). Compared to the prespecified NI margin of -15%, both lower limits of the 95% CIs at Day 5 and TOC were larger than the NI margin (Table 10).

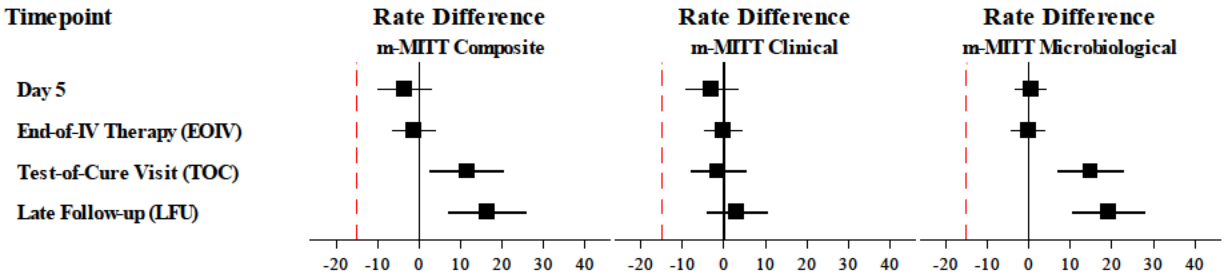
Table 10: Composite of Microbiological Eradication and Clinical Cure Rate, and Individual Components at Day 5 and TOC Visits, mMITT Population

Timepoint	Response	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)
Day 5	Composite			
	Cure	168 (88.0)	180 (91.4)	-3.4 (-10.0, 3.1)
	Failure	20 (10.5)	15 (7.6)	
	Indeterminate	3 (1.6)	2 (1.0)	
	Clinical			
	Cure	171 (89.5)	182 (92.4)	-2.9 (-9.1, 3.3)
	Failure	17 (8.9)	13 (6.6)	
	Indeterminate	3 (1.6)	2 (1.0)	
	Microbiological			
	Eradication	188 (98.4)	193 (98.0)	0.5 (-3.1, 4.1)
	Persistence	3 (1.6)	2 (1.0)	
	Indeterminate	0	2 (1.0)	
TOC	Composite			
	Cure	156 (81.7)	138 (70.1)	11.6 (2.7, 20.3)
	Failure	29 (15.2)	51 (25.9)	
	Indeterminate	6 (3.1)	8 (4.1)	
	Clinical			
	Cure	170 (89.0)	178 (90.4)	-1.4 (-7.9, 5.2)
	Failure	17 (8.9)	12 (6.1)	
	Indeterminate	4 (2.1)	7 (3.6)	
	Microbiological			
	Eradication	171 (89.5)	147 (74.6)	14.9 (7.0, 22.7)
	Persistence	14 (7.3)	41 (20.8)	
	Indeterminate	6 (3.1)	9 (4.6)	

Notes: Difference = difference in proportion (plazomicin – meropenem). Confidence interval is calculated using the Newcombe method with continuity correction. Missing outcomes are categorized as indeterminate.
Source: Statistical reviewer

The lower limits of the 95% CI for the visits EOIV and LFU were also larger than the NI margin. In addition, such results were observed for the two individual components of the composite endpoints at each visit. Note that the improved effect seen at TOC and LFU is driven by the microbiological results. No similar improvement is seen with the clinical endpoint. The forest plots below present the results for the composite response, as well as a breakdown by clinical and microbiological response at Day 5, EOIV, TOC, and LFU (Figure 3).

Figure 3: Efficacy Endpoints by Visit, mMITT Population



Note: Red vertical lines respresent the NI margin of -15%.
Source: Statistical reviewer

Microbiological eradication rates at TOC visit by baseline pathogen in the mMITT population are presented in Table 11.

Table 11: Microbiological Eradication Rate at TOC by Baseline Pathogen, mMITT Population

Pathogen	Plazomicin n/N (%)	Meropenem n/N (%)
All *Enterobacteriaceae*	177/198 (89.4)	157/208 (75.5)
Aminoglycoside-non-susceptible	41/52 (78.9)	35/51 (68.6)
Carbapenem-non-susceptible	7/9 (77.8)	5/6 (83.3)
ESBL-producing	42/51 (82.4)	45/60 (75.0)
Escherichia coli	120/128 (93.8)	106/142 (74.7)
Aminoglycoside-non-susceptible	20/23 (87.0)	16/26 (61.5)
Carbapenem-non-susceptible	---	---
ESBL-producing	18/20 (90.0)	19/28 (67.9)
Klebsiella pneumoniae	27/33 (81.8)	32/43 (74.4)
Aminoglycoside-non-susceptible	14/18 (77.8)	15/20 (75)
Carbapenem-non-susceptible	---	1/1 (100)
ESBL-producing	15/20 (75)	20/26 (76.9)
Proteus mirabilis	9/11 (81.8)	4/7 (57.1)
Proteus vulgaris	1/1 (100)	0/1 (0)

Enterobacter cloacae	13/16 (81.3)	3/3 (100)

Note: Aminoglycoside-non-susceptible: not susceptible to amikacin, gentamicin, or tobramycin. Carbapenem-non-susceptible: not susceptible to imipenem or doripenem (while susceptible to meropenem).
Source: Statistical reviewer

The composite cure rates and their 95% CIs at each visit in the ME population were similar to the mMITT population (Table 12).

Table 12: Composite of Microbiological Response and Clinical Response at Day 5, EOIV, and TOC Visits, ME Population

Timepoint (Population)	Composite Response	Plazomicin (%)	Meropenem (%)	Difference (95% CI)
Day 5 (ME-Day 5)	N	188	190	
	Composite Cure	168 (89.4)	179 (94.2)	–4.8 (–11.0, 1.2)
	Composite Failure	20 (10.6)	11 (5.8)	
EOIV (ME-TOC)	N	179	177	
	Composite Cure	169 (94.4)	172 (97.2)	–2.8 (–7.8, 2.1)
	Composite Failure	10 (5.6)	5 (2.8)	
TOC (ME-TOC)	N	179	177	
	Composite Cure	152 (84.9)	133 (75.1)	9.8 (1.1, 18.4)
	Composite Failure	27 (15.1)	44 (24.9)	

Abbreviations: EOIV=end-of-IV (therapy); ME=microbiologically evaluable; N=number of patients in the ITT Population; n=number of patients in the specified category; TOC=test-of-cure.
Notes: Difference=difference in composite cure rate (plazomicin minus meropenem). Confidence interval is calculated using the Newcombe method with continuity correction.

Source: ACHN-490-009 Clinical Study Report, Tables 14.2.14.1.

3.2.4.2 Sensitivity Analyses

The primary analyses above essentially treated missing data as failures in the analysis. We conducted additional analyses using a very conservative approach. This approach treats indeterminate outcomes as failures in the plazomicin group and successes in the meropenem group. Results of these analyses also concluded the non-inferiority of plazomicin to meropenem, allowing us to conclude the non-inferiority of the primary analysis are not sensitive to the method for handling missing data (Table 13).

Table 13: Sensitivity Analysis for the Composite Response, mMITT Population

Composite Response mMITT	Plazomicin (N=191) n(%)	Meropenem (N=197) n(%)	Difference (95% CI)
Day 5	168 (88)	182 (92.4)	-4.4 (-10.9, 1.9)
End-of-IV Therapy (EOIV)	179 (93.7)	188 (95.4)	-1.7 (-7, 3.4)
Test-of-Cure Visit (TOC)	156 (81.7)	146 (74.1)	7.6 (-1.1, 16)
Late Follow-up (LFU)	147 (77)	128 (65)	12 (2.6, 21.1)

Source: Statistical reviewer

In addition, this reviewer found some inconsistent responses for the composite endpoint between early visits and late visits for some of the patients. For example, two patients who completed IV therapy at Day 5 had composite responses at Day 5 as "Cure", and "Failure" at EOIV. As stated in SAP, Day 5 clinical response was determined programmatically, and EOIV clinical response was determined both programmatically and by site investigator. Therefore, it is reasonable to believe that those two composite responses at Day 5 should be considered "Failure". Also, some patients were "Failure" at EOIV, but were "Cure" at TOC visit. For this situation, the treatment responses at later visits were likely due to oral antibiotics taken after the IV therapy. To evaluate the treatment effect of IV therapy without the impact of oral therapy, those "Cures" happening at later visits were re-coded as "Failure" for the purpose of sensitivity analyses. A total of 11 patients had responses re-coded as previously indicated (Table 14).

Table 14: List of Subjects with Inconsistent Composite Responses by Visit, mMITT Population

USUBJID	Last IV Study Day	First PO Study Day	TOC Visit Day	Day_5	EOIV	TOC	LFU	Comment
ACHN-490-009-(b) (6)	Day 5	Day 5	17	Failure	Failure	Cure	Failure	TOC cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 6	Day 6	15	Failure	Failure	Cure	Cure	TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 6	Day 7	18	Cure	Failure	Cure	Cure	Day 5 cure is questionable. TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 5	Day 5	17	Failure	Failure	Cure	Cure	TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 5	Day 5	18	Failure	Failure	Cure	Cure	TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 7	Day 7	18	Failure	Failure	Cure	Cure	TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 5	Day 5	19	Failure	Failure	Cure	Cure	TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 5	Day 6	19	Cure	Failure	Cure	Cure	Day 5 cure is questionable. TOC and LFU cure might be due to oral antibiotics
ACHN-490-009-(b) (6)	Day 4			Failure	Failure	Indeterminate	Indeterminate	TOC and LFU should be failure
ACHN-490-009-(b) (6)	Day 8		20	Failure	Failure	Cure	Cure	TOC and LFU cure are questionable
ACHN-490-009-(b) (6)	Day 5		15	Cure	Failure	Failure	Failure	Day 5 cure is questionable.

Source: Statistical reviewer

Efficacy was re-evaluated after considering the above mentioned questionable responses as failures (Table 15), as well as treating indeterminate outcomes as failures in the plazomicin group and successes in the meropenem group (Table 16). Compared to the applicant's efficacy results, the risk differences and 95% CI shift to the left at all visits, with the lower limit of the 95% CI lower than 0 at TOC visit (Table 15), and at both TOC visit and LFU visit (Table 16). All lower limits of the 95% CI are still higher than the pre-specified NI margin of -15%.

Table 15: Composite Cure Rate, with Questionable Responses Considered as Failure, by Visits, mMITT Population

Composite Response mMITT	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)
Day 5	166 (86.9%)	179 (90.9%)	-4 (-10.7, 2.7)
End-of-IV Therapy (EOIV)	179 (93.7%)	187 (94.9%)	-1.2 (-6.5, 4)
Test-of-Cure Visit (TOC)	149 (78%)	136 (69%)	9 (-0.2, 17.9)
Late Follow-up (LFU)	140 (73.3%)	118 (59.9%)	13.4 (3.6, 22.8)

Source: Statistical reviewer

Table 16: Composite Cure Rate, with Questionable Responses Considered as Failure, and Indeterminate Outcomes Treated Conservatively, by Visits, mMITT Population

Composite Response mMITT	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)
Day 5	166 (86.9%)	181 (91.9%)	-5 (-11.6, 1.6)
End-of-IV Therapy (EOIV)	179 (93.7%)	188 (95.4%)	-1.7 (-7, 3.4)
Test-of-Cure Visit (TOC)	149 (78%)	144 (73.1%)	4.9 (-4, 13.7)
Late Follow-up (LFU)	140 (73.3%)	127 (64.5%)	8.8 (-0.8, 18.2)

Source: Statistical reviewer

Microbiological eradication for this study was assessed using a cutoff for bacteria growth of less than 10^4 CFU/mL. As this cutoff may change to less than 10^3 CFU/mL in the future, an additional analysis of microbiological eradication at TOC visit (based on the data availability) using this new cutoff was conducted. The result were comparable to the results obtained with the criterion of 10^4 CFU/mL.

Table 17: Microbiological Eradication Rate at TOC, Based on Two Different Criteria, mMITT Population

Microbiological Eradication Criterion	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)

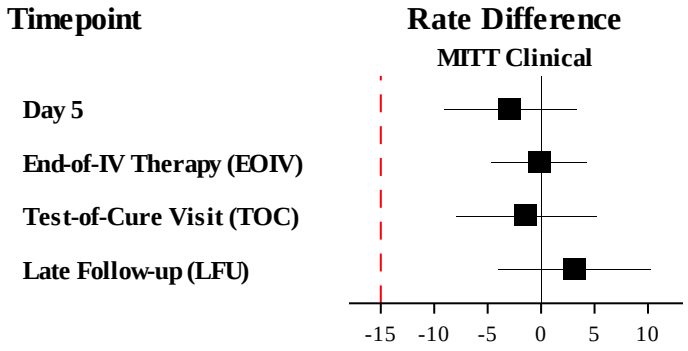
10^4 CFU/mL	171 (89.5)	147 (74.6)	14.9 (7.0, 22.7)
10^3 CFU/mL	167 (87.4)	142 (72.1)	15.4 (7.5, 23.2)

Source: Statistical reviewer

3.2.4.3 Results in the MITT Population

The primary analysis was designed to be conducted on the m-MITT population because subjects with microbiologically confirmed infection are likely to provide better sensitivity in detecting treatment difference between the two antibiotic drugs. However, the microbiological results are generally unknown at the time the treatment is initiated in practice. Therefore, assessing the treatment effect using the MITT population maybe more relevant to point of care decision making. Figure 4 shows the treatment effect in terms of clinical response. For this analysis, microbiological response rate would not be of interest because some patients did not have microbiologically identified baseline infection.

Figure 4: Clinical Response by Visit, MITT Population



Note: Red vertical line respresents the NI margin of -15%.
Source: Statistical reviewer

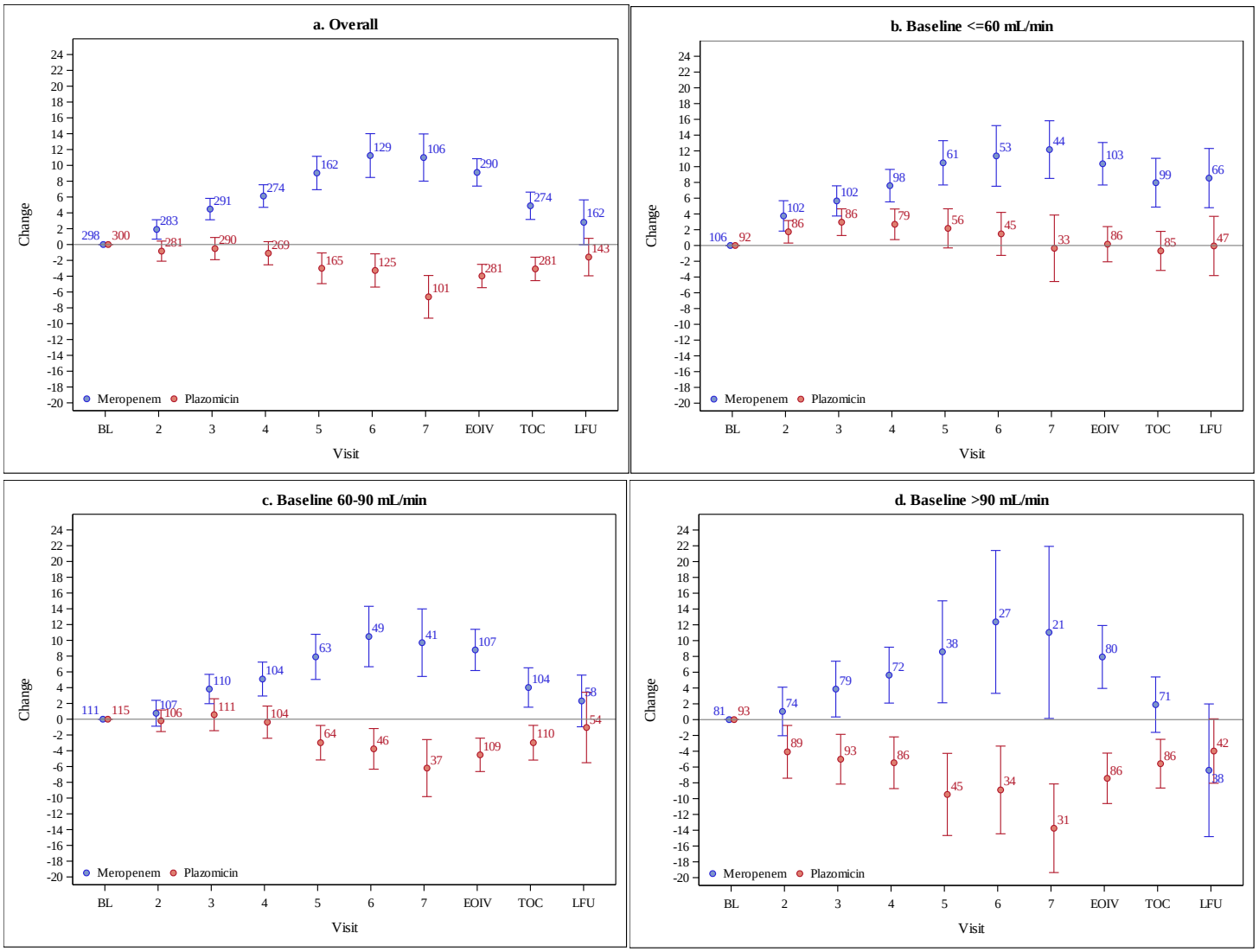
3.3 Evaluation of Safety

3.3.1 Nephrotoxicity

Aminoglycosides have long been known to be associated with nephrotoxicity. Decreases in mean creatinine clearance (CRCL) change were observed after taking plazomicin for about 5 days in the overall MITT population. In general, these deacreases disappeared by the LFU visit (Figure 5). Note that in this study, the duration of IV threrapy spans 4 to 7 days; therefore, the EOIV visit does not occur at the same study day for all patients, and could in fact occur any time from day 4 to 7. The number of patients who had CRCL measurements at each visit are shown in the figure. Panels b-d of the figure show CRCL change from baseline by baseline CRCL levels. It appears that the patients with higher baseline CRCL had larger decreases compared to the patients with

lower baseline CRCL (Figure 5b-d). The observed different responses by baseline CRCL category may be confounded by lower doses of plazomicin received by patients with lower CRCL due to dose adjustments.

Figure 5: Creatinine Clearance, Change from Baseline and 95% CI, MITT Population



Note: Numbers represent the sample sizes of the CRCL measurements at visit
Source: Reviewer's analysis

To compare CRCL decrease by baseline CRCL levels between the two treatment groups, a shift table is presented (Table 17). Since only about half of the patients had CRCL measurements at LFU visit, the last on-study CRCL was used to represent the renal function after taking study drugs. There are 300 patients in the plazomicin arm and 298 patients in the meropenem arm who had both baseline and at least one after baseline CRCL measurements. Compared to 5.7% in the

meropenem arm, the proportion of patient who had CRCL level decreased by at least one level is 13.7% in the plazomicin arm (highlighted cells).

Table 18: Creatinine Clearance Shift Table

Baseline CRCL	Last on-Study CRCL		
	<=60 mL/min	>60-90 mL/min	>90 mL/min
Plazomicin arm (N=300)			
<=60 mL/min	75 (25%)	17 (5.7%)	0
>60-90 mL/min	27 (9%)	76 (25.3%)	12 (4%)
>90 mL/min	0	14 (4.7%)	79 (26.3%)
Meropenem arm (N=298)			
<=60 mL/min	68 (22.8%)	32 (10.7%)	6 (2%)
>60-90 mL/min	10 (3.4%)	77 (25.8%)	24 (8.1%)
>90 mL/min	1 (0.3%)	6 (2%)	74 (24.8%)

Source: Reviewer's analysis

Serum creatinine increase highly correlates with nephrotoxicity. There are 3% of the patients in the plazomicin arm had last on-study serum creatinine increase ≥ 0.5 mg/dL, versus 1% in the meropenem arm (Table 18).

Table 19: Last on-Study Serum Creatinine Increase ≥ 0.5 mg/dL, by Baseline CRCL

Baseline CRCL	Last on Study Serum Creatinine Increase ≥ 0.5 mg/dL	
	Plazomicin (N=300)	Meropenem (N=298)
<=60 mL/min	8 (2.7%)	0
>60-90 mL/min	1 (0.3%)	1 (0.3%)
>90 mL/min	0	2 (0.7%)

Source: Reviewer's analysis

Please refer to clinical pharmacology review and clinical review for more details of nephrotoxicity and other safety issues.

4. FINDING IN SPECIAL SUBGROUP POPULATIONS

This section summarizes the subgroup results for Study 009. The composite endpoints at Day 5 and TOC were of main interest for this analysis. All subgroups were assessed within the mMITT population.

4.1 Gender, Race, Age, and Geographic Region

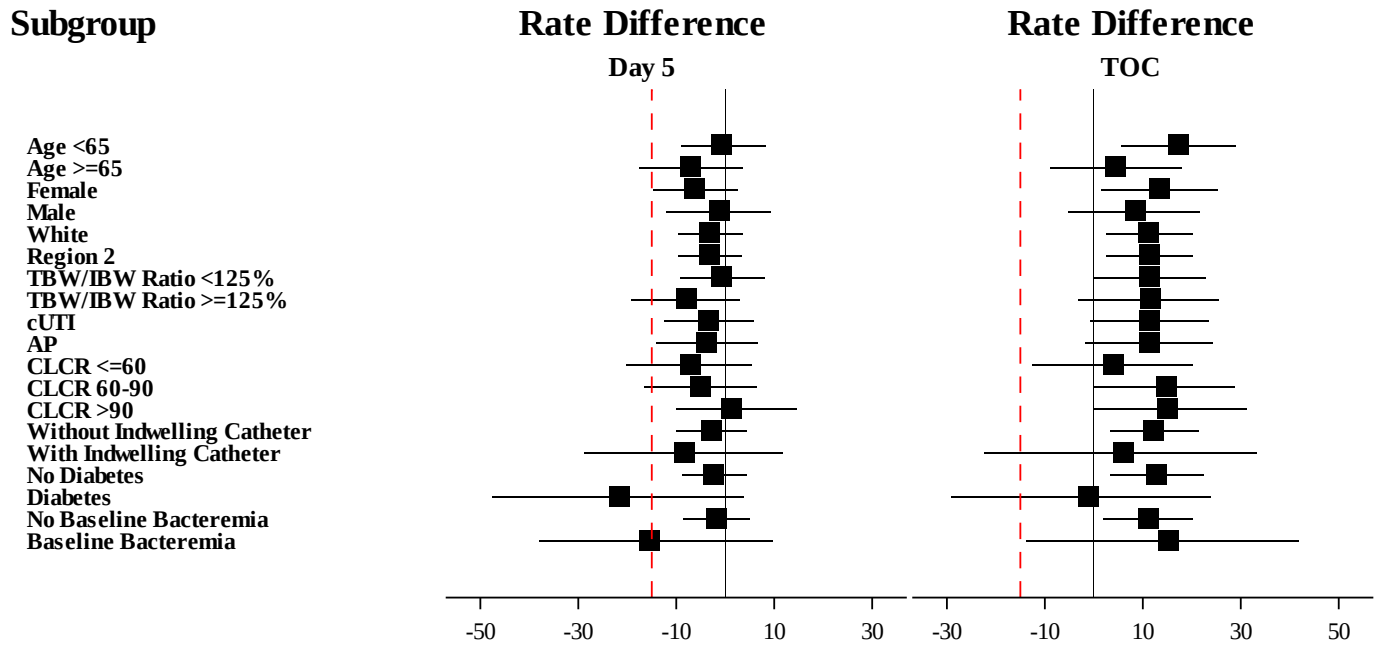
Results of the composite response rate difference at Day 5 and TOC for the demographic subgroups are displayed in Figure 6. In general, the trends are consistent with what have been

observed for the overall population. Since this study was conducted mainly in Eastern European countries (region 2) and in white subjects, subgroups for the other region or race would not characterize efficacy with any precision, and therefore, subgroups for region 1 and non-white were not included in the analyses. Also, because region 2 included several countries, subgroup analyses for those countries were conducted to compare the results across countries (Figure 7). There was no plot for Estonia at Day 5, because both plazomicin and meropenem group had 100% cure rate at Day 5. Thus, the confidence interval could not be calculated. Considering the small sample sizes for each country, wide confidence intervals are observed. The numeric values of the point estimates for Bulgaria, Romania, and Serbia are in the direction that slightly favor meropenem, while all other countries have trends that favor plazomicin at TOC.

4.2 Other Special Subgroup Populations

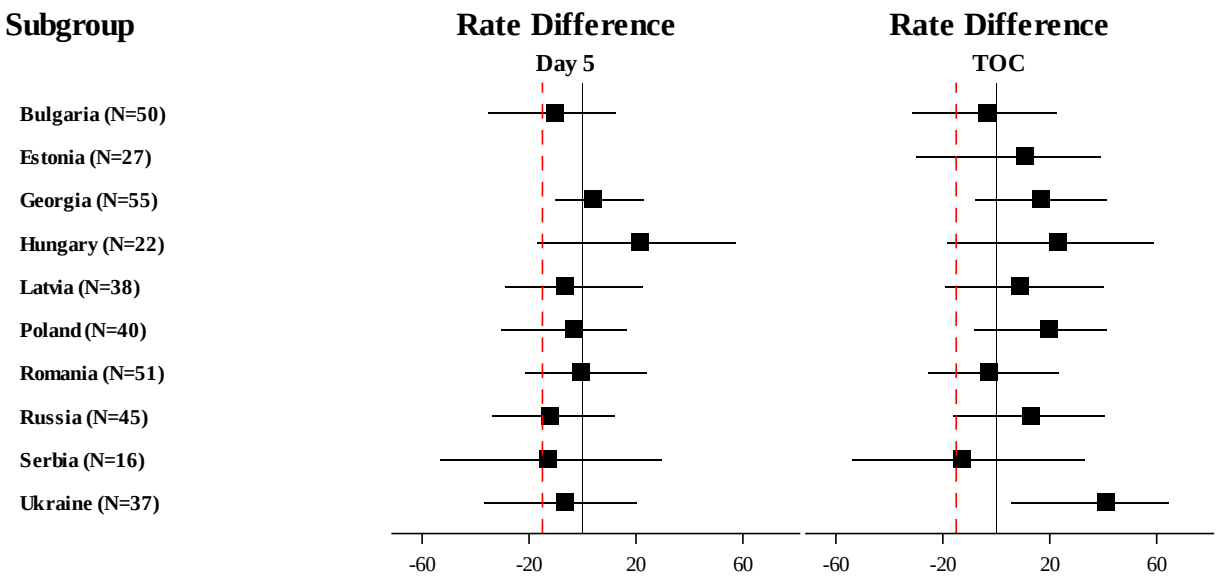
Some important subgroups based on the baseline characteristics were also analyzed (Figure 6). Compared to Day 5, all subgroups had results moving towards the direction that favors plazomicin at TOC. Because of the small sample sizes for some of the subgroups, wide confidence intervals are observed, for example, patients with indwelling catheters, baseline bacteremia, or diabetes. In general, the results are consistent across the subgroups.

Figure 6: Subgroup Analyses for the Composite Response at Day 5 and TOC, mMITT Population



Note: Red vertical lines respresent the NI margin of -15%.
Source: Statistical reviewer

Figure 7: Composite Response at Day 5 and TOC, by Country, mMITT Population



Note: Red vertical lines respresent the NI margin of -15%.
Source: Statistical reviewer

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This review focused on a single Phase 3 trial for the treatment of cUTI including AP. The main statistical issues impacting the interpretability of this study are as follows:

- In this submission, a single Phase 3 trial was submitted for the cUTI indication. As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin should be reserved for use in patients who have limited or no alternative treatment options.
- The primary efficacy endpoint was assessed on Day 5 and TOC visits (co-primary). If a patient had less than 5 days of IV therapy, response at the EOIV vist was used as the Day 5 result. Therefore, the Day 5 response was a mixture of response of IV therapy for 5 days or shorter time period. The TOC visit happened after both IV and oral therapies had been completed, and thus it incorperated clinical and microbiological outcomes that possibily related to the oral therapy, which may have complicated noninferiority assessments for IV plazomicin.
- Microbiological response is an objective measure. Clinical response, while more subjective, may be more clinically relevant since it is based on patients' feeling and function.

- This study was mainly conducted in East European countries (region 2, with 98.5% of the ranomized mMITT population), with patients enrolled were predominantly white (99%). The results may not be representative for the patients from other regions or other races.

5.2 Collective Evidence

In addition to the submitted Phase 3 study, the applicant also completed a Phase 2 study (Study 002) for the treatment of cUTI. Study 002 was a randomized, double-blind, active controlled study to assess the safety, efficacy, and pharmacokinetics of plazomicin compared to levofloxacin when administered intravenously for 5 days. This study was conducted in India, Latin America, and North America.

A total of 145 patients were randomized to the plazomicin 10 mg/kg group (N=22), the plazomicin 15 mg/kg group (N=76), and the levofloxacin group (N=47). Due to slow enrollment, the plazomicin 10 mg/kg group was removed from the protocol to maximize the enrollment to the higher plazomicin group. The race distribution in this study were more balanced compared to Study 009, with 24 (16.6%) white, 22 (15.2%) black or African American, 43 (29.7%) Asian, and 54 (37.2%) American Indian or Alaska Native. A lot more patients in the plazomicin 15 mg/kg group discontinued study drug prematurely (12/76, 15.8%), compared to the levofloxacin group (1/47, 2.1%). The co-primary endpoints for the study were the microbiological eradication rates evaluated in the MITT population and ME population. For the MITT population, 31/51 (60.8%) of the patients in the plazomicin 15 mg/kg group had microbiological eradication, while 17/29 (58.6%) patients in the levofloxacin group had eradication. The difference of the eradication rates was 2.2 (95% CI: -22.9 to 27.2). For the ME population, the microbiological eradication rates were 31/35 (88.6%) and 17/21 (81%) for plazomicin 15 mg/kg group and levofloxacin group, respectively. The rate difference was 7.6 with 95% CI as -16.0 to 31.3. This study was not designed for the hypothesis testing and had relatively small sample size. In addition, subjects were not excluded if they had levofloxacin resistance, which makes the study hard to interpret. In brief, Study 002 did not show any concerning trends regarding the efficacy; no conclusion can be made for this study because of the small sample size.

The results of Study 009 provided statistical evidence for the efficacy of plazomicin for the treatment of cUTI including AP for the following reasons:

- The composite cure rates at Day 5 in the mMITT population were 168/191 (88%) for plazomicin and 180/197 (91.4%) for meropenem, and 156/191 (81.7%) for plazomicin and 138/197 (70.1%) for meropenem at TOC visit. Lower limits of the 95% CIs for the rate differences for both visits were above the pre-specified -15% NI margin.
- The efficacy findings were robust to the handling of indeterminate data, and to the handling of the data for the cures that were likely due to oral therapy.
- The results for plazomicin compared to meropenem were consistent in terms of the composite endpoints and the components of the composite such as clinical cure and microbiological eradication, and at EOIV and LFU visits.

- Results from the subgroup analyses were consistent.

Collectively, Study 009 provided efficacy evidence for plazomicin with some support from Study 002.

5.3 Conclusions and Recommendations

In summary, Study 009 results support the conclusion that a plazomicin regimen is non-inferior to a meropenem regimen for the treatment of cUTI including AP in adults, based on a single Phase 3 study with a pre-specified noninferiority margin of -15%. Note that this study was mainly conducted in East European countries with almost 100% white patients. The results may not be representative for patients from other regions or other races

5.4 Labeling Recommendations

The applicant is seeking approval for the treatment of cUTI including AP in adults based on the results from Study 009.

The indication proposed by the applicant in the labeling is as follows:

"is indicated (b) (6) in patients 18 years or older for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli* (b) (6) *Klebsiella pneumoniae*, (b) (6) *P. mirabilis* (b) (6) and *Enterobacter cloacae*."

(b) (6)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HENGRUI N SUN
05/16/2018

KAREN M HIGGINS
05/16/2018
I concur.

TSAE YUN D LIN
05/16/2018
I concur.