CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210303Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	210303
Priority or Standard	Priority
Submit Date	10/25/2017
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Division/Office	Division of Anti-Infective Products (DAIP)/Office of Antimicrobial Products (OAP)
Reviewer Name	Shrimant Mishra, MD MPH
Review Completion Date	6/13/2018
Established/Proper Name	plazomicin
(Proposed) Trade Name	Zemdri™
Applicant	Achaogen, Inc.
Dosage Form	Solution for Intravenous Injection / 500 mg in a 10-mL single dose vial
Applicant Proposed Dosing Regimen(s)	15mg/kg qd; adjustments based on renal function
Applicant Proposed Indication(s)/Population(s)	Complicated Urinary Tract Infections (cUTI); Bloodstream Infections (BSI)
Recommendation on Regulatory Action	Approval-cUTI Complete Response- BSI
Recommended Indication(s)/Population(s)	Patients with cUTI who have limited or no alternative treatment options

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APPEARS THIS WAY ON ORIGINAL

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Plazomicin (Zemdri™), is a newly developed semi-synthetic aminoglycoside with the proposed indications of treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) and blood stream infection (BSI), both in cases where limited or no treatment alternatives are available.

The Applicant has proposed a dosing regimen in cUTI adjusted according to renal function and serum trough concentrations. For those with normal renal function, the initial dose is 15 mg/kg daily. For BSI, the applicant is again proposing an initial dose of 15 mg/kg daily for those with normal renal function, and this will be adjusted according to a therapeutic drug management (TDM) algorithm that takes into account periodic measured serum concentrations of plazomicin.

The drug is a semi-synthetic new molecular entity (NME) although it is part of the well-recognized aminoglycoside antimicrobial class.

1.2. Conclusions on the Substantial Evidence of Effectiveness

See text below in Benefit-Risk Assessment

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Plazomicin is a semi-synthetic aminoglycoside that brings promise of a new therapy to treat serious infectious diseases. Its clinical development includes a randomized, comparator controlled phase 2 and 3 cUTI trial and a small, randomized, open label phase 3 trial targeting CRE-associated bloodstream and HABP/VABP infections. For both indications, subjects with limited treatment alternatives are targeted. The cUTI data provides compelling evidence of noninferiority to a commonly used comparator (meropenem in the phase 3 trial) on accepted primary endpoints such as composite microbiologic eradication and clinical response at Day 5 and at TOC. Plazomicin's effect seems adequate even with resistant pathogens such as those resistant to one or more aminoglycosides and organisms containing extended spectrum beta-lactamases. The safety database, though small, identifies expected risks of an aminoglycoside, such as nephrotoxicity and ototoxicity, as well as more general adverse effects seen often in drug development trials, such as headaches, nausea, and vomiting. Serum plazomicin trough monitoring should be used to prevent nephrotoxicity; currently a plasma trough level of 3 mcg/ml has been set. (b) (4)

(b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cUTI is generally found in individuals with some functional or physical deficit in the lower or upper urinary tract, predisposing to infection. • Infections are generally from Enterobacteriaciae, though theoretically could be the result of a broad array of pathogens • Treatment courses are generally for 7-10 days. • CRE-associated BSI and HABP/VABP generally are associated with high mortality. • Current therapies, such as colistin can have significant toxicities • Treatment courses can last from 7 to 14 days.	Complicated UTI is a serious bacterial infection most commonly caused by gram-negative bacteria of the family Enterobacteriaceae. BSI and HABP/VABP caused by CRE are serious infections associated with high mortality. Treatment options for CRE infections are limited.
Current Treatment Options	• cUTI Examples: levofloxacin, meropenem, piperacillin-tazobactam, cephalosporins. • CRE - associated infections BSI Examples: ceftazidime/avibactam, meropenem vaborbactam, colistin, tigecycline, aminoglycosides, carbapenems. HABP/VABP Examples: colistin, meropenem, tigecycline, aminoglycosides.	Plazomicin may offer a treatment alternative for infections which have limited treatment options currently.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Note: Includes off label usage	
Benefit	• cUTI Plazomicin had a composite cure rate of 168/191 (88.0%) and 156/191 (81.7%) at Day 5 and TOC, respectively in the mMITT population. For meropenem, the values were 180/197 (91.4%) and 138/197 (70.1%). The noninferiority margin of 15% was met for both time points Day 5 Margin (plazomicin – meropenem): -3.4% (-10.0, 3.1%) TOC Margin: 11.6% (2.7%, 20.3%) BSI (b) (4)	Plazomicin shows noninferiority (using a composite of clinical and microbiological response) to a commonly used therapy for cUTI that persists to the TOC visit. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Major safety findings: Plazomicin does show increased nephrotoxicity relative to a non-nephrotoxic comparator (meropenem). Its nephrotoxicity relative to a potent nephrotoxic agent (such as colistin) may be less, though assessments are limited by a small study population Plazomicin cannot be excluded from having ototoxic effects based on outside assessment of pure tone audiometry and electronystagmography results.	Plazomicin contains risk due to typical aminoglycoside-associate adverse effects.

1.4. Patient Experience Data

Validated (from the Agency perspective) PRO's were not part of this application. However, as part of the Clinical Response in study 009 (cUTI trial), patients were asked about improvement/ worsening in their urinary symptoms. Also, several inventories were used to assess ototoxicity in the same trial. See sections 6.1.1 and 8.5.2 for more details

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
	x	□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

- **Analysis of Condi**

cUTI generally involves a urinary tract infection in the setting of some other physical or functional deficit that predisposes to the development of infection. Such predisposing factors might include an indwelling catheter, renal calculi, vesicoureteral reflux, or diabetes. Subjects generally can be of any age or gender and typically have some combination of urinary symptoms along with urine culture data showing the growth of the offending pathogen. Untreated, the infection may progress to more severe complications such as abscess development, metastatic infection, sepsis, or even death. Pathogens tend to be more varied than in uncomplicated UTI and consist of gram-negative organisms such as *Escherichia coli (E. coli)*, *Klebsiella pneumoniae (KP)*, *Enterobacter* species, *Proteus* species, etc. Many of these organisms are acquired in health care facilities and carry significant resistance mechanisms to currently used antimicrobials. Broad spectrum antimicrobials (either intravenous or oral depending on the clinical status of the patient) such as fluoroquinolones, carbapenems, beta lactam-beta lactamase inhibitors are generally used empirically to start treatment and then adjusted once susceptibilities are known. Treatment is anywhere between 7-10 days.

Acute pyelonephritis is a severe urinary tract infection in which the upper urinary tract has been affected. Patients, which can include young females as well as older adults, generally have some combination of systemic and localized symptoms, including flank pain, and also have corresponding microbiological data on urine culture. As with cUTI, the natural history of AP is unknown (particularly as regards self-resolution), however, bacteremia, sepsis, and death are possible complications. Typical pathogens are gram-negative bacilli, particularly *E. coli*. Therapy typically involves supportive measures such as fluid resuscitation as well as antimicrobial therapy for ~7 days. The choice of therapy is dependent on factors such as patient status and possibility of resistance and includes fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, and extended spectrum cephalosporins. Initial intravenous therapy is recommended for those unable to tolerate oral medications and with unstable medical status.

BSI is a condition associated with another source of infection such as central line or hospital acquired pneumonia/ventilator-associated pneumonia. It is generally a serious condition (occurring often in subjects in the ICU) and can lead to sepsis, metastatic infection, and death. Numerous gram-positive and negative organisms can be the cause, and treatment generally includes 7 to 14 days of broad spectrum therapy which is narrowed based on susceptibilities

and patient condition, if possible. The diagnosis is made through a combination of symptoms/signs, positive blood cultures, and culture data that help to identify a source (such as a urine or sputum culture or blood culture from an indwelling central line).

It should be noted that though these indications are being discussed here broadly, the Applicant plans to pursue a limited use indication, essentially restricting use to patients with limited or no treatment alternatives. In practice, this means primarily targeting subjects with highly resistant organisms or intolerant of available therapies. These highly resistant organisms include Carbapenem Resistant Enterobacteriaceae (CRE) and gram-negative organisms containing Extended Spectrum Beta Lactamases (ESBL); these organisms tend to simultaneously carry resistance to multiple therapeutics. In the case of CRE, though currently more prevalent overseas, such as in locations in Greece, numerous cases in the US have been reported (particularly *Klebsiella pneumoniae* Carbapenemase (KPC) producing organisms), and are rapidly becoming more prevalent domestically. These organisms not only increase the chance for inappropriate initial treatment but also limit treatment to medications with significant toxicity profiles, such as colistin.

2.2. Analysis of Current Treatment Options

As noted above, given the limited use indication of this drug, its comparators primarily include drugs that are expected to still retain an effect on highly-resistant gram-negative organisms, such as ESBL- containing organisms and CREs. Thus, such comparators include the carbapenems, other aminoglycosides such as amikacin and gentamicin, colistin, tigecycline, as well as recently approved combination agents such as ceftazidime/avibactam and meropenem/vaborbactam.

These comparators are only partially able to meet the need of affected subjects. They can be affected by shortages and thus have limited availability. They may be bacteriostatic, such as in the case of tigecycline, or may have uncertain efficacy benefit, such as in the case of colistin treatment for CRE infection. Importantly, as in the case of colistin-induced nephrotoxicity, they may have significant adverse effects that limit use.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Plazomicin is an NME and it is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

This subsection describes significant regulatory interactions between the Applicant and the Agency relating to the design and analysis of Study 007 and 009.

June 4, 2012: A Type B Clinical Development Meeting was held between the Applicant and the Agency. The Agency provided general input on a clinical development plan to study plazomicin for the treatment of CRE infections.

August 12, 2012: Fast Track designation was granted for the treatment of serious and life-threatening infections due to CRE.

December 17, 2012: An End-of-Phase 2 Meeting was held between the Applicant and the Agency. A general agreement was reached on a Phase 3 study design to support approval of plazomicin for patients with bloodstream infections or ventilated nosocomial pneumonia due to CRE. This included agreement on the proposed plazomicin and colistin comparator dosing regimens, and agreement with therapeutic drug management to support plazomicin dosing.

April 5, 2013: A Special Protocol Assessment (SPA) request was submitted for the Phase 3 CRE Study ACHN-490-007 (Study 007).

July 29, 2013: The SPA request for Study ACHN-490-007 was resubmitted based on Agency feedback.

September 12, 2013: The Agency communicated agreement with the Special Protocol Assessment to the Applicant. (b) (4)

September 16, 2014: Study 007 was initiated.

November 4, 2014: A Type B Clinical Development Meeting was held between the Applicant and the Agency. The Applicant proposed to conduct an uncontrolled study in parallel with Study 007, in patients who were ineligible for this randomized trial due to resistance to the colistin comparator or infection at an excluded body site. The Agency provided input on an alternative development pathway based on a single Phase 3 cUTI trial in conjunction with data from the

completed Phase 2 cUTI Study ACHN-490-002 (Study 002), which had completed enrollment in April, 2012.

December 12, 2014: Qualified Infectious Disease Product (QIDP) designation was granted for the indications of hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infections (cIAIs), cUTI, and catheter-related BSI.

February 26, 2015: A Type A Clinical Development Meeting was held between the Applicant and the Agency. The Applicant discussed use of a new primary endpoint for Study 007, based on a composite of all-cause mortality or significant disease-related complications. The applicant and the Agency also discussed (b) (4)

April 28, 2015: Protocol Amendment 1 for Study 007 was submitted to the Agency. This amendment changed the primary efficacy endpoint from all-cause mortality to the composite of all-cause mortality or significant disease-related complications. The definition of significant disease-related complications had been previously proposed by the applicant, and feedback from the Agency had been received. The amendment did not change the planned sample size or planned superiority test at the one-sided $\alpha = 0.05$ statistical significance level for the primary efficacy analysis.

May 15, 2015: The applicant submitted a protocol for the Phase 3 cUTI noninferiority Study ACHN-490-009 (Study 009) to the Agency.

July 15, 2015: Protocol Amendment 2 for Study 007 was submitted to the Agency with a request for comment, adding the nonrandomized, descriptively analyzed Cohort 2 of plazomicin-treated patients. These patients were ineligible for the randomized Cohort 1 due to resistance to the colistin comparator, polymicrobial infection, cUTI as the source of CRE infection, or APACHE II score <15. (b) (4)

January 11, 2016: The Phase 3 cUTI Study 009 was initiated.

March 4, 2016: A Type A Clinical Development Meeting was held between the applicant and the Agency. The applicant discussed enrollment challenges in Study 007. The Applicant stated that "current enrollment projections suggest that the study will be unable to achieve the originally planned enrollment for an adequately powered test of the primary endpoint in a clinically meaningful or operationally feasible timeframe." The Applicant discussed the possibility of changing the primary analysis to a noninferiority analysis, (b) (4)

April 28, 2016: The Applicant proposed to terminate enrollment due to enrollment challenges in Study 007, and proposed a prospective stopping rule such that the end of enrollment would coincide with the completion of the Phase 3 cUTI Study 009.

July 18, 2016: The Applicant revised the prospective stopping rule for Study 007, such that new enrollment would be terminated on August 1, 2016 regardless of enrollment in Study 009.

September 15, 2016: The Phase 3 CRE Study 007 was completed. The last patient had been enrolled on July 22, 2106. The primary analysis population of patients in the randomized cohort with CRE contained 17 patients in the plazomicin group and 20 patients in the colistin group.

September 22, 2016: The Phase 3 cUTI Study 009 was completed.

September 30, 2016: The Applicant submitted a statistical analysis plan for Study 007, which as noted above had completed enrollment. Due to the premature study termination, the hypothesis testing for superiority was removed from the primary efficacy analysis. The Applicant communicated that "While the protocol-specified primary and secondary efficacy endpoints will be analyzed and traditional statistical inference measures such as p-values and/or confidence intervals will be included for descriptive purposes, no formal hypothesis testing is to be performed in this limited sample size."

(b) (4)

March 29, 2017: The Applicant submitted a Breakthrough Therapy Designation Request for plazomicin for the treatment of bloodstream infection in patients with limited or no alternative treatment options. The request was granted by the Agency on May 17, 2017.

April 14, 2017: A pre-NDA meeting was held between the Applicant and the Agency. The Applicant notified the Agency that due to the small number of patients with HABP/VABP in Study 007 that it was considering only using this study to support a BSI indication rather than both BSI and HABP/VABP indications.

October 25, 2017: The Applicant submitted the New Drug Application.

3.3. Foreign Regulatory Actions and Marketing History

[Not Applicable- the drug has no approved foreign marketing application]

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

(b) (4) was Inspected by OSI and no data integrity issues for plazomicin measurements were noted for Study 002 (b) (4) and 009. However, there was concern that a "carryover" effect may overestimate serum concentration measurement and complicate TDM.

Inspection of clinical sites in Poland, Hungary, Estonia, and Greece have concluded; the sites were found to be acceptable. OSI's conclusions are as follows:

*"Studies ACHN-490-007 and ACHN-490-009 were identified for on-site audit at good clinical practice (**GCP**) inspections of four foreign clinical investigator (**CI**) sites and the sponsor site. A Form FDA 483 was issued at Site 6801 (CI Michal Nowicki) in Study ACHN-490-009 for minor GCP deficiencies unlikely to be significant to the study outcome. For all remaining sites, no significant deficiencies were observed and a Form FDA 483 was not issued. For both studies at all inspected sites, study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and case report forms (**CRFs**). The data from the inspected sites appear reliable as reported in the NDA."*

4.2. Product Quality

The CMC assessment is as follows:

"The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, plazomicin injection. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable as documented in the Facility Chapter (dated May 17, 2018). The overall manufacturing inspection recommendation in Panorama is still pending (b) (4) *however, this inspection recommendation does not impact the NDA recommendation. Based on the above assessments, this NDA is currently recommended for Approval by the Office of Pharmaceutical Quality (OPQ).*

(b) (4) is responsible for drug substance manufacturing, packaging, release testing and stability testing, and (b) (4) is responsible for drug product manufacturing, packaging, labeling, release and stability testing. In addition, several other sites are involved in the drug substance testing, and the drug product testing, labeling and secondary packaging. (b) (4)

The drug product is supplied as a 10-mL sterile, aqueous solution for intravenous infusion, containing 500 mg of plazomicin (b) (4) in a single-dose vial with a rubber stopper and a flip top cap. (b) (4) The only excipients in the formulation are sodium hydroxide, NF and Water for Injection, USP, which are both compendial. There are no novel excipients or excipients of human or animal origin in the drug product formulation.

For the most part the analytical methods are compendial. (b) (4) . The HPLC method for assay and impurities is described in reasonable detail and has been validated. The HPLC method was verified by an FDA laboratory and found to be acceptable. Satisfactory batch analysis data are provided for 13 batches including three primary registration stability batches. A risk assessment has been performed for elemental impurities following the recommendations of ICH Q3D.

The drug product (b) (4) plazomicin sulfate in water for injection, with sodium hydroxide used to adjust the pH of the solution to a target of 6.5. Production of plazomicin injection, 500 mg/10 mL, (b) (4)

Stability data has been provided for (b) (4) drug product to support stability out to 36 months (2°-8°C).

Please see the review by Dr. Dorota Matecka, CMC Team Leader, for further details.

4.3. Clinical Microbiology/Nonclinical Pharmacology Toxicology

Clinical Microbiology

Plazomicin is an aminoglycoside antibacterial drug with in vitro activity against certain gram-negative and gram-positive bacteria. Plazomicin contains structural modifications that allow it to maintain activity in the presence of the common aminoglycoside modifying enzymes (AMEs)

that inactivate some currently marketed agents in this class. Mechanism of action studies demonstrated that, as with other aminoglycosides, the antibacterial action of plazomicin is mediated through inhibition of protein synthesis. In surveillance studies, plazomicin was active against Enterobacteriaceae, including isolates encoding common resistance mechanisms conferring resistance to other aminoglycosides, as well as organisms with ESBL and/or carbapenem-resistant phenotypes. The drug is not active against the 16S RNA methyltransferase mechanism of aminoglycoside resistance.

Pharmacokinetic/pharmacodynamic data derived from in vivo animal models and an in vitro chemostat model was used to determine that the ratio of the total-drug plasma area under the concentration-time curve from 0 to 24 hours ($AUC_{0–24h}$) to minimum inhibitory concentration (MIC), [($AUC_{0–24h}$:MIC)], was the PK/PD index most closely associated with plazomicin efficacy.

In Study 009, emergence of decreased plazomicin susceptibility occurred in 7 isolates from 6 plazomicin-treated patients and decreased meropenem susceptibility in one isolate from 1 meropenem-treated patient during the study. Among the 7 isolates that developed decreased susceptibility to plazomicin, all 7 were considered resistant based on the (b) (4) resistance breakpoint of >4 mcg/mL. Of the isolates, 6 contained panresistance to amikacin, tobramycin, and gentamicin while one isolate maintained susceptibility to gentamicin and was intermediate to tobramycin and amikacin Five of the 7 isolates with decreased plazomicin susceptibility were obtained on or before the EOIV visit; the remaining 2 were detected at the TOC and LFU, after demonstrating eradication at the EOIV visit. All patients with a uropathogen(s) that developed decreased susceptibility to plazomicin were clinical cures at the Day 5 and EOIV visits. Two patients were clinical failure at TOC, of which both had *E. cloacae* as the baseline infecting pathogen*:*

-Patient (b) (6) had unresolved frequency that met the programmatic definition for clinical failure and was not treated with nonstudy antibacterial drugs
-Patient (b) (6) was treated with nonstudy antibacterial drugs prior to the TOC visit.

Of the 6 plazomicin treated subjects who possessed isolates with decreased susceptibility, in 4 of them 16S RMT mechanisms of resistance were detected (though other resistance mechanisms may have also been present).

Table 1- Patients with Uropathogens that Developed Decreased Susceptibility or Resistance to Study Drug Received by Pathogen - mMITT Population, Study 009

	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)
Patients with Decreased Susceptibility [a]	6 (3.1)	1 (0.5)
Enterobacter cloacae	2 (1.0)	0 (0.0)
Escherichia coli	1 (0.5)	1 (0.5)
Klebsiella pneumoniae	3 (1.6)	0 (0.0)
Proteus mirabilis	1 (0.5)	0 (0.0)
Patients with Resistance [b]	6 (3.1)	1 (0.5)
Enterobacter cloacae	2 (1.0)	0 (0.0)
Escherichia coli	1 (0.5)	1 (0.5)
Klebsiella pneumoniae	3 (1.6)	0 (0.0)
Proteus mirabilis	1 (0.5)	0 (0.0)

MIC=minimum inhibitory concentration; mMITT=microbiological modified intent-to-treat; N=number of patients in the specified population; n=number of patients with a uropathogen in the specified category.
Notes: Percentages are calculated as 100×(n/N). Patients with >1 of the same uropathogen within each type of uropathogen were counted once for that uropathogen.

[a] Decreased susceptibility is defined as a postbaseline MIC >4 µg/mL and a ≥4-fold increase in MIC relative to that of the baseline pathogen.

[b] Development of resistance to plazomicin is defined as postbaseline nonsusceptibility to plazomicin (i.e., MIC >4 mcg/mL) in pathogens susceptible to plazomicin (i.e., MIC ≥4 mcg/mL) at baseline; development of resistance to meropenem will be defined as postbaseline nonsusceptibility to meropenem (i.e., MIC >1 mcg/mL) in pathogens susceptible to meropenem (i.e., MIC ≤1 mcg/mL) at baseline.
Source: Table 42; Study 009 CSR

(b) (4)

(b) (4)

4.4. Clinical Pharmacology

The Clinical Pharmacology issues were broad and required significant internal/external discussion. Some of the central issues involved the following:

1. (b) (4)
2. Serum trough monitoring is used with aminoglycosides to prevent toxicity (particularly nephrotoxicity). The Clinical Pharmacology review team has concluded that a serum plazomicin trough of ≥3 mcg/ml is associated with the development of nephrotoxicity in subjects being treated for cUTI with a baseline creatinine clearance ≤90 ml/min. This value was based on modeling done with serum PK measurements from Study 009 (since trough monitoring was not done in the trial itself). Adjustments made due to trough measurements would involve changes to dosing intervals.

Please see the reviews of Drs. Kunyi Wu and Luning Zhang for further details

Plazomicin has a half-life of 4 to 5 hours in cUTI and BSI patients, and does not accumulate with once-daily dosing in healthy subjects. Plazomicin clearance (CL) was 4.08 L/h and the volume of distribution at steady-state (Vss) was 24.0 L in healthy subjects. The Vss tended to be larger in cUTI/AP patients (31.5 L) and larger still in BSI patients (52.9 L). In patients, CL was typically within 35% of healthy subjects. The mean binding of plazomicin to human plasma proteins is approximately 20%, ranging between 13.9% and 24.2%. Unchanged plazomicin was the only plazomicin-related component detected in any of the pooled clinical plasma samples analyzed by high-resolution mass spectrometry, indicating no significant circulating metabolites of plazomicin in human (this was confirmed by the mass balance study; Study 010). Plazomicin is primarily eliminated by the kidneys. Approximately 90% of administered plazomicin is excreted in urine following a single dose of 15 mg/kg in subjects with normal renal function. The renal clearance of plazomicin was similar to plasma clearance and similar to the glomerular filtration

rate for the unbound fraction, indicating plazomicin is eliminated primarily via glomerular filtration and active renal secretion is not a major elimination pathway.

No dosage adjustment is required in patients with CLcr >60 mL/min based on results from a dedicated renal impairment study and the population PK analysis. Dosage adjustment is required in patients with moderate renal impairment (CLcr >30 to 60 mL/min), as plasma clearance of plazomicin significantly decreases with increasing renal impairment. Dosing in those with severe renal impairment (≤30 ml/min) is based on information obtained from the dedicated renal impairment study (Study 004); very few such subjects were enrolled in the Studies 002 and 009.

No dosage adjustment is required on the basis of age, sex, race, or infection type based on the population PK analysis. Plazomicin does not undergo hepatic metabolism and has low plasma protein binding; therefore, the systemic clearance of plazomicin is not expected to be affected by hepatic impairment.

Plazomicin is considered unlikely to have significant clinical drug interactions. In vitro data show that plazomicin is not a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporters. In addition, as plazomicin is mostly excreted as unchanged drug in urine, metabolism by any of the major drug-metabolizing enzymes is considered to be unlikely. Based on in vitro assessments, plazomicin is unlikely to be an in vivo inhibitor of the following CYP450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Plazomicin is unlikely to be an in vivo inducer of CYP1A2, CYP2B6, or CYP3A4. In addition, plazomicin is unlikely to be an in vivo inhibitor of the following hepatic and renal transporters: P-gp, BCRP, bile salt export pump, multidrug resistance protein 2, organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, or multidrug and toxin extrusion (MATE) 1. Plazomicin selectively inhibited MATE2-K in vitro, and the potential for clinical interactions cannot be completely excluded. However, a clinical DDI study with a MATE substrate (metformin) did not appear to show any clinically relevant drug-drug interaction with plazomicin.

4.5. **Devices and Companion Diagnostic Issues**

(b) (4)

Effectively, this TDM was expected to minimize overdosing (thus minimizing toxicity) and minimize underdosing (thus ensuring therapeutic effect). Currently (b) (4) the applicant is developing the to-be-marketed plazomicin assay with another company, Thermo Fisher. (b) (4)

(b) (4)

(b) (4)

Please note also that the applicant is proposing plazomicin trough monitoring for cUTI (b) (4) in order to minimize the development of nephrotoxicity. No formal trough monitoring was done in study 009, but the applicant submitted post-hoc analyses (based on population modeling using PK data from Study 009) to show the potential merits of setting plazomicin trough cutoffs in reducing nephrotoxicity. Clinical Pharmacology has proposed a plazomicin trough cutoff level of 3 µg/ml for TDM-based dosing interval adjustments (based on their own analyses). (b) (4)

Please see the CDRH review by Dr. Eveline Arnold (Team Lead Dr. James Mullaly) for further details.

4.6. **Consumer Study Reviews**

[Not applicable]

5. Sources of Clinical Data and Review Strategy

5.1. **Table of Clinical Studies**

[Please note the following sponsor Table of Studies which highlight all the studies to date with plazomicin. These include:

- Six phase 1 type studies, including a PK study in healthy volunteers, TQT study, mass balance study, metformin drug interaction study, PK study in subjects with renal impairment, and lung penetration study (Studies 001, 003,004,006,010,011)
- One phase 2 study in cUTI (Study 002)

- Two phase 3 studies; one in cUTI and the other in subjects with CRE-associated BSI and HABP/VABP infections (Studies 007 and 009)

Table 2 - Completed Phase 2 and Phase 3 Clinical Studies of Plazomicin in Patients With Complicated Urinary Tract Infection, Including Acute Pyelonephritis

Study	Phase	No. of Study Centers and Location(s)	Population	Study Objectives	Design Control Type	Study Drug Regimen, Treatment Duration, Route	No. of Patients Enrolled/ Exposed
ACHN-490-002	2	27 sites in United States, India, and Latin America	Adult patients with cUTI/AP	Safety, tolerability, efficacy, PK/PD	Randomized (1:1:1, then 2:1 after dropping 10 mg/kg group), double-blind	Plazomicin 10 mg/kg [a] IV infusion every 24 h for 5 d Plazomicin 15 mg/kg [b] IV infusion every 24 h for 5 d Levofloxacin 750 mg IV every 24 h for 5 d	Total enrolled: 145 Plazomicin 10 mg/kg: 22 Plazomicin 15 mg/kg: 76 Levofloxacin: 47 Total exposed: 140 Plazomicin 10 mg/kg: 22 Plazomicin 15 mg/kg: 74 Levofloxacin: 44
ACHN-490-009 (EPIC)	3	68 sites in Eastern Europe, Western Europe, and North America	Adult patients with cUTI/AP	Efficacy, safety, PK	Randomized (1:1) double-blind, noninferiority study	Plazomicin 15 mg/kg [c] IV infusion every 24 h for 4–7 d followed by option for oral stepdown for a total duration of therapy of 7–10 d Meropenem 1 g IV infusion every 8 h for 4–7 d followed by option for oral stepdown for a total duration of therapy of 7–10 d Oral stepdown: levofloxacin 500 mg once daily or other approved agent for up to 6 d	Total enrolled: 609 Plazomicin: 306 Meropenem: 303 Total exposed: 604 Plazomicin: 303 Meropenem: 301

Abbreviations: AP=acute pyelonephritis; cUTI=complicated urinary tract infection; IV=intravenous; PD=pharmacodynamic(s); PK=pharmacokinetic(s).

[a] Enrollment in the plazomicin 10 mg/kg group was stopped early during the study to permit evaluation of the 15 mg/kg dose in a larger number of patients.

[b] All plazomicin infusions were given over 30 minutes except for 2 patients (Patient (b) (6) [15 mg/kg] and Patient (b) (6) [15 mg/kg]) (Clinical Study Report [CSR] ACHN-490-002, Listing 13.2.5.1).

[c] Dosing adjustments were required based on renal function. All plazomicin infusions were given over 30 minutes (±10 minutes).

Source: Table 1, Applicant Tabular Listing of Clinical Studies

Table 3 - Completed Phase 3 Clinical Study of Plazomicin in Patients With Carbapenem-Resistant Enterobacteriaceae Infection

Study	No. of Study Centers and Location(s)	Study Status	Population	Study Objectives	Design Control Type	Study Drug Regimen, Treatment Duration, Route	No. of Patients Enrolled/ Exposed
ACHN-490-007 (CARE)	22 sites in Europe, South America, Eurasia, and the United States	Terminated early[a]	Cohort 1 Adult patients with BSI or HABP/VABP due to CRE Cohort 2 Adult patients with BSI, HABP/VABP, or cUTI/AP, due to CRE who were not eligible for inclusion in Cohort 1	Efficacy, safety, PK, clinical utility of TDM	Cohort 1 Randomized (1:1), open-label, active-controlled, superiority Cohort 2 Single-group, open-label, descriptive	Cohort 1 Plazomicin[b] 15-mg/kg IV infusion every 24 h for 7–14 d, in combination with either meropenem or tigecycline Colistin 5-mg/kg loading dose followed by 5 mg/kg/d maintenance dose (given either every 8 h or every 12 h) for 7–14 d, in combination with either meropenem or tigecycline Cohort 2 (HABP/VABP, BSI) Plazomicin[b] 15-mg/kg IV infusion every 24 h for 7–14 d in combination with at least 1 additional nonstudy antibiotic with known activity against Enterobacteriaceae Cohort 2 (cUTI/AP) Plazomicin[b] 15-mg/kg IV infusion every 24 h for 4–7 d followed by an optional oral switch for a total of 7–14 d	Cohort 1 Enrolled: 39 Plazomicin: 18 Colistin: 21 Exposed: 39 Plazomicin: 18 Colistin: 21 Cohort 2 Enrolled: 30 Exposed: 30

Abbreviations: AP=acute pyelonephritis; BSI=bloodstream infection; CRE=carbapenem-resistant Enterobacteriaceae; cUTI=complicated urinary tract infection; HABP=hospital-acquired bacterial pneumonia; IV=intravenous; PK=pharmacokinetic; TDM=therapeutic drug management; VABP=ventilator-associated bacterial pneumonia.

[a] Study was terminated early due to slow enrollment and to align with completion of Study ACHN-490-009 for submission in the plazomicin New Drug Application.

[b] Initial dose could vary based on renal function and need for renal replacement therapy. Dose adjustments following the initial dose were based on TDM and changes in clinical status. All plazomicin infusions were given over 30 minutes (±10 minutes).

Source: Table 2, Applicant Tabular Listing of Clinical Studies

Table 4 - Phase 1 Completed Studies (Pre-NDA Submission) of Plazomicin in Heathy Subjects or Otherwise Healthy Subjects with Renal Impairment

Study	No. of Study Centers and Location(s)	Population (Age)	Study Objectives	Design Control Type	Study Drug Regimen, Treatment Duration, Route	No. of Subjects Enrolled/ Exposed
ACHN-490-001 (SAD/MAD Study)	Single center, US	Healthy subjects (18-55 y)	Safety, tolerability, PK following escalating sd and MD; FIH study	Randomized, double-blind, placebo-controlled, parallel-group, single- and multiple-dose escalation study	Plazomicin 10-min IV infusion: Cohort 1a: 1 mg/kg sd[a] (n=5) Cohort 1b: 4 mg/kg sd, then MD[b] for 10 d (n=6) Cohort 2: 7 mg/kg sd, then MD[b] for 10 d (n=7) Cohort 3: 11 mg/kg sd, then MD[b] for 5 d (n=8) Cohort 4: 15 mg/kg sd, then MD[b] for 3 d (n=7)	Overall: 39/37 Active: 30/28 Placebo: 9/9
ACHN-490-003 (Lung Penetration Study)	Multicenter, US	Healthy subjects (18-65 y)	Safety, tolerability, PK following MD, and lung penetration following sd	Randomized, double-blind, placebo-controlled study	Plazomicin 10-min IV infusion: Cohort 1: 15 mg/kg MD for 5 d (n=6) Cohort 2a: 10.7 mg/kg sd (n=9) Cohort 2b: 15 mg/kg sd (n=15)	Overall: 40/40 Active: 30/30 Placebo: 10/10
ACHN-490-004 (Renal Impairment Study)	Multicenter, US	Healthy subjects and otherwise healthy subjects with renal impairment (18-75 y)	Safety, tolerability, PK in renal impairment	Open-label, parallel-group, single-dose study	Plazomicin 30-min IV infusion: Normal renal function (CLcr ≥90): 7.5 mg/kg sd (n=6) Mild renal impairment (CLcr 60-89): 7.5 mg/kg sd (n=6) Moderate renal impairment (CLcr 30-59): 7.5 mg/kg sd (n=6) Severe renal impairment (CLcr 15-29[c]): 7.5 mg/kg sd (n=6)	Overall: 24/24

Study	No. of Study Centers and Location(s)	Population (Age)	Study Objectives	Design Control Type	Study Drug Regimen, Treatment Duration, Route	No. of Subjects Enrolled/ Exposed
ACHN-490-006 (TQT Study)	Single center, US	Healthy subjects (18-75 y)	Safety, PK, and QT/QTc interval effect	Part 1: Randomized, double-blind, placebo-controlled single dose Part 2: Randomized, double-blind, placebo- and positive-controlled crossover	Plazomicin 30-min IV infusion: Part 1: 20 mg/kg sd (n=6) Part 2: ABDC (n=14), BCAD (n=14), CDBA (n=14), DACB (n=14) Treatments in Part 2 (7- to 10-d wash-out periods): A: 15 mg/kg sd + oral placebo; B: 20 mg/kg sd + oral placebo; C: IV placebo + oral placebo; D: IV placebo + 400 mg oral moxifloxacin sd	Part 1: Overall: 8/8 Active: 6/6 Placebo: 2/2 Part 2: Overall: 56/56 (any study drug)

Abbreviations: CLcr=creatinine clearance; IV=intravenous; MAD=multiple ascending dose; MD=multiple dose; PK=pharmacokinetic; QTc=corrected QT; SAD=single ascending dose; sd=single dose; TQT=through QT.

[a] Subjects receiving 1 mg/kg sd (Cohort 1a) were to continue to receive the 4-mg/kg dose level (Cohort 1b) per protocol after ≥7 intervening days.

[b] Multiple dosing started once ≥7 intervening days had elapsed since the single dose.

[c] Otherwise eligible subjects with CLcr <15 mL/min not on dialysis may have been enrolled upon approval from the investigator and sponsor medical monitor per the protocol. One subject with CLcr 10.1 mL/min was enrolled and included in the CLcr 15-29 mL/min (severe renal impairment) renal function group.

Source: Table 3, Applicant Tabular Listing of Clinical Studies

Note: Clinical Study Reports for two studies were submitted after the NDA had been submitted to the Agency - Study 010 (Mass Balance Study) and Study 011 (Metformin Drug Interaction Study). See the table below.

Table 5 - Phase 1 Completed Studies (Post NDA Submission) of Plazomicin in Heathy Subjects

	Site Location	Number of Subjects	Study Design	Dose
Study 010 Mass Balance Study	Celerion, Nebraska, USA	6 subjects enrolled and completed study	Non-randomized mass balance study	Plazomicin 15mg/kg single 30-minute infusion (radiolabeled)
Study 011 Metformin Drug Interaction Study	Celerion, Nebraska, USA	16 subjects enrolled and completed study	Two sequence, two period, crossover study	Metformin 850 mg(Period 1) Metformin 850 mg + Plazomicin 15mg/kg single 30-minute infusion (period 2) Or vice versa

5.2. Review Strategy

For efficacy purposes, review emphasis was placed on the phase 3 studies (Study 007 and 009) and, to a lesser extent, the phase 2 study (Study 002). For safety purposes, Study 009 was given the most review emphasis, with some attention given to all the other clinical development studies, including the phase 1 studies.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 007 (CRE) and Study 009 (cUTI)

6.1.1. Study Design

Overview and Objective

Note: This section combines many elements of the statistical review, sponsor analyses and this reviewer's analyses. Because the applicant is pursuing two indications, each section is generally divided into two sections - first the CRE BSI and HABP/VABP (Study 007) findings are described followed by the cUTI (Study 009) findings.

Study 007

A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE). The primary objective for this study was to demonstrate the superiority of plazomicin over colistin (plus background therapy of either meropenem or tigecycline) in the treatment of BSI, HABP, and VABP due to CRE.

cUTI- Study 009

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.

Trial Design

Study 007

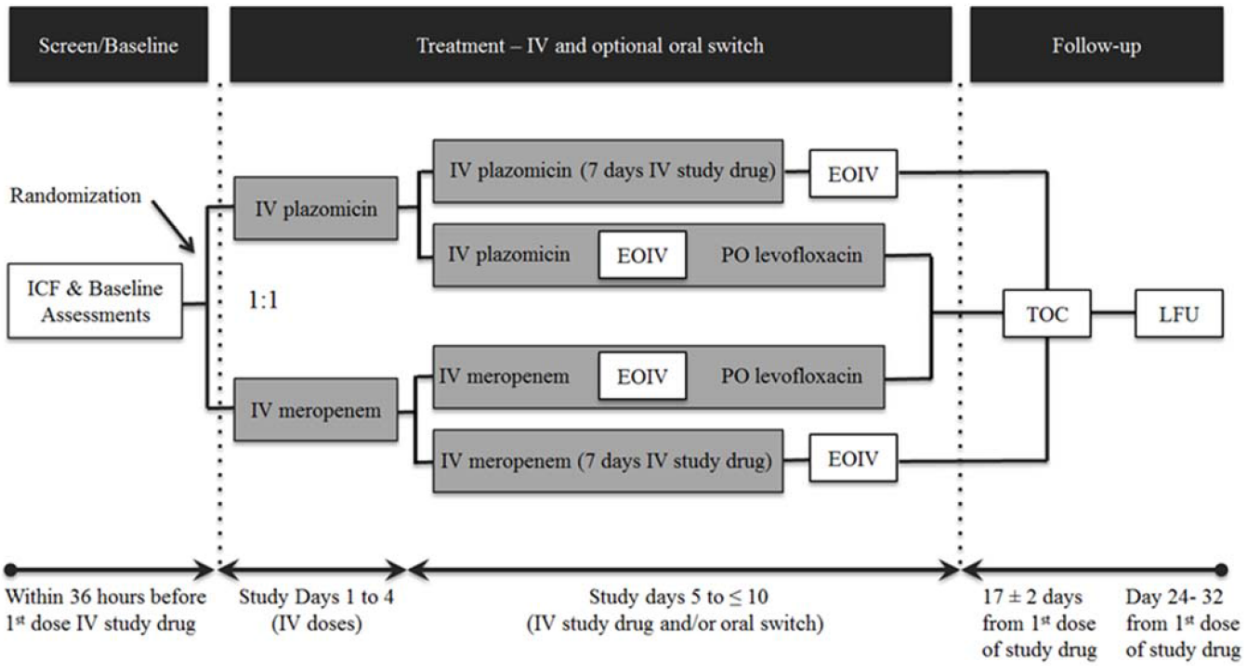
Study ACHN-490-007 was initiated in September 2014 and completed in September 2016.

cUTI- Study 009

This was a randomized, multicenter, multinational, double-blind study evaluating the efficacy and safety of plazomicin compared with meropenem followed by optional oral (PO) therapy in the treatment of cUTI, including AP, in adults.

In general, the study design was consistent with the guidance on cUTI. Upon meeting inclusion criteria, patients were randomized 1:1 into either receiving IV plazomicin 15 mg/kg daily or meropenem 1 gm every 8 hours (dosing was adjusted daily based on renal function). Subjects had to receive at least four days of IV therapy and no more than 7 days of IV therapy at which point they could be switched to oral levofloxacin 500mg daily for 3 to 6 days. The total treatment duration was 7 to 10 days. If a subject needed more than 7 days of IV therapy, the subject was discontinued from the study and switched to alternative IV therapy. All study doses were to be given as 30 minute infusions of a 50ml solution. A Test- of Cure assessment occurred on Day 17 (Day 1 was first day of study drug), and a Late Follow Up (LFU) visit occurred between Days 24-32.

Figure 2 Study Design Schema and Overview of Study Schedule, Study 009



EOIV=end of intravenous therapy; ICF=informed consent; IV=intravenous; LFU=late follow-up; PO=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-hours (q8h) dosing schedule or 14 doses on an every-12-hour (q12h) dosing schedule (approximately 7 days) of IV study drug and a maximum of 10 days of IV plus oral study drug.

Source: Study 009 Clinical Study Report

The dose for plazomicin chosen for this study was based on efficacy findings in the Phase 2 study, predicted concentrations in the urine (relative to expected pathogen MICs), as well as study 004 which helped assess plazomicin dosing in subjects with renal impairment.

Though meropenem is not approved for treatment of cUTI in the US, the choice of meropenem at 1 gm q 8 hours as the comparator in this study was thought to be acceptable based on its spectrum of activity, particularly with resistant organisms such as ESBLs, its approval for use in this indication in Europe, its common use for this indication in the US, as well as ease of dosing and similarities to plazomicin dosing that facilitated blinding.

Renal function (based on creatinine clearance) was estimated daily and dose/dose interval adjustments made accordingly.

Table 6 Overview of Study Drug Dosing, Study 009

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		

CLcr=creatinine clearance; IV=intravenous; PO=oral; q8h=every 8 hours; q12h=every 12 hours; q24h=every 24 hours. Source: Study 009, Clinical Study Report

Important inclusion criteria included age ≥ 18 years old, IBW≤ 150 kg, pyuria, signs and symptoms of cUTI or AP (included fever, flank pain, lower abdominal pain, CVA tenderness on exam, dysuria, nausea or vomiting), predisposing condition in case of cUTI (such as BPH or presence of indwelling catheter), creatinine clearance > 30 ml/min, and a urine culture taken within 36 hours of starting of study drug.

Important exclusion criteria included GU conditions requiring prolonged treatment (such as abscess or chronic bacterial prostatitis), use of any therapeutic antibacterial agent within 48 hours of starting study drug (exceptions included if prior therapy was directed at gram positives or anaerobes only, organisms resistant to prior therapy, etc.), known fungal or gram positive UTI at time of randomization, known pathogen resistant to meropenem at time of randomization, known nonurinary source of infection, pregnant subjects, and an unwillingness to use appropriate contraceptive measures.

The primary objective of the study was to demonstrate the noninferiority (NI) of plazomicin compared with meropenem based on the difference in the composite microbiological eradication and clinical cure rate in the microbiological Modified Intent-To-Treat (mMITT) population at both the Day 5 and test-of-cure (TOC) visits, using a NI margin of 15%, at a one-sided 0.025 significance level. Though this NI margin is larger than what is proposed in the

Agency guidance on cUTI, it was deemed acceptable given the applicant's intent to pursue a limited use indication.

Premorbid symptoms (present on an ongoing basis prior to the current infection) and current urinary symptoms (present in the past 36 hours as the baseline for the current infection) status were documented at baseline according to assessments based on a patient's provided response (example in the table below).

Table 7 Core Symptoms of cUTI, Study 009

eCRF Field	Absent	Mild	Moderate	Severe
Flank pain	0	1	2	3
Suprapubic pain	0	1	2	3
Dysuria	0	1	2	3
Frequency	0	1	2	3
Urgency	0	1	2	3

eCRF=electronic Case Report Form. Source: Study 009 Clinical Study Report

Efficacy was based on Clinical and Microbiological response at both the Day 5 and TOC visits. Clinical response at the various timepoints was assessed as noted in the following Applicant tables.

Table 8 Clinical Response Categories and Corresponding Criteria at Day 5 and EOIV Visits, Study 009

Category	Criteria
Cure:	Marked improvement defined as complete resolution or return to premorbid levels or reduction in severity of all core baseline symptoms with worsening of none, and no new symptoms develop
Failure:	Patients meeting any of the following criteria will be classified as failure: • Lack of improvement in core baseline symptoms of cUTI or development of new core symptoms of cUTI • AE requiring the discontinuation of study drug and the patient required alternative nonstudy antibiotic therapy for the current cUTI
Indeterminate:	Insufficient data are available to allow an evaluation of clinical outcome for any reason

AE=adverse event; EOIV=end of intravenous therapy. Source: Study 009, Clinical Study Report

Table 9 Clinical Response Categories and Corresponding Criteria at the TOC Visit, Study 009

Category	Criteria
Cure:	Complete resolution or return to premorbid levels of core symptoms of cUTI and no new symptoms develop, and no use of nonstudy antibiotic therapy for the current cUTI
Failure:	Persistence of one or more core symptom of infection or reappearance of or development of new core symptoms that require alternative nonstudy therapy for the current cUTI
Indeterminate:	Insufficient data are available to allow an evaluation of clinical outcome for any reason

TOC=test of cure. Source: Study 009, Clinical Study Report

Programmatic improvement in Clinical Response was designated as follows:

Post Baseline Symptom Response:

Table 10 - Postbaseline Symptom Response Relative to Baseline Status, Study 009

	Postbaseline Symptom Status			
Baseline	**Absent**	**Mild**	**Moderate**	**Severe**
Absent	Resolution	New symptom	New symptom	New symptom
Mild	Resolution	No change	Worsening	Worsening
Moderate	Resolution	Reduction	No change	Worsening
Severe	Resolution	Reduction	Reduction	No change

Source: Study 009, Clinical Study Report

Subjects who discontinued IV therapy due to an AE or use of nonstudy systemic antimicrobial therapy for the cUTI/AP were designated as failures regardless of clinical symptom change. Microbiologic responses were based on both per pathogen and per patient response as defined below.

Table 11 Per-Pathogen Microbiological Outcome Categories at Day 5, EOIV, and TOC, Study 009

Category	Criteria
Eradication:	Urine culture showed that the pathogen found at baseline at $\geq 10^5$ CFU/mL was reduced to $<10^4$ CFU/mL
Presumed eradication (Day 5 and EOIV visit only):	No urine culture was done at the Day 5 or EOIV visit and the last known urine culture, obtained on or after Day 3, showed the baseline pathogen colony count was reduced to $<10^4$ CFU/mL
Persistence:	Urine culture grew $\geq 10^4$ CFU/mL of the original pathogen
Indeterminate:	No urine culture was obtained at corresponding study visit or the culture result could not be interpreted

CFU=colonyforming- units; EOIV=end of intravenous therapy; TOC=test of cure. Source: Study 009, Clinical Study Report

Table 12 Per-Patient Microbiological Outcome Categories at Day 5, EOIV, and TOC, Study 009

Category	Criteria
Eradication:	The outcome of all baseline pathogens was eradication or presumed eradication
Persistence:	The outcome of at least 1 baseline pathogen was persistence
Indeterminate:	The outcome of at least 1 baseline pathogen was indeterminate and there was no outcome of persistence for any baseline pathogen

EOIV=end of intravenous therapy; TOC=test of cure; Source: Study 009, Clinical Study Report

(b) (4)

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cUTI- Study 009

The coprimary efficacy endpoints were the composite microbiological eradication and programmatically derived clinical cure rate in the mMITT population at Day 5 and the TOC visit. To test the null hypothesis, a two-sided 95% CI for the observed difference in composite cure rates (plazomicin treatment group minus meropenem treatment group) for each timepoint was calculated using a continuity corrected Z-statistic for the mMITT population. If the lower limit of the 95% CI for the difference in composite cure rate in the mMITT population was greater than –15% at both Day 5 and the TOC visit, then the null hypothesis was to be rejected and the NI of plazomicin to meropenem would be declared. If the lower limit of the 95% CI for difference in composite cure rate in the mMITT population was less than or equal to ≤15% at either Day 5 or the TOC visit, then the null hypothesis was not to be rejected, and NI of plazomicin to meropenem could not be declared.

Statistical Analysis Plan

(b) (4)

(b) (4)

cUTI – Study 009

The **ITT population** was considered as all randomized patients.

The **MITT population** was considered as all randomized patients who received any amount of study drug.

The **mMITT Population** consisted of all patients in the ITT Population who received any amount of study drug and had at least one qualified baseline pathogen from a study-qualifying baseline urine culture against which meropenem and plazomicin have antibacterial activity, and no pathogens against which either meropenem or plazomicin do not have antibacterial activity. A study-qualifying baseline urine culture specimen must have been obtained within 36 hours before the start of administration of the first dose of study drug and have been collected by an acceptable method (which included midstream clean catch, sample taken after replacement of the indwelling catheter, sterile catheterization, sterile suprapubic aspiration, etc.). A qualified baseline pathogen was a pathogen that grew from a study-qualifying baseline urine culture at ≥ 10^5 CFU/mL and against which meropenem and plazomicin have antibacterial activity. For meropenem, only baseline pathogens with meropenem MIC of ≤1 µg/mL were considered qualifying baseline pathogens. For plazomicin, only baseline pathogens with an MIC of ≤4 µg/mL were considered qualifying, consistent with the tentative susceptibility breakpoint for plazomicin. Any patients with one or more pathogens confirmed from the last blood culture obtained prior to the first dose of study drug were defined as having bacteremia at baseline. All Enterobacteriaceae were considered pathogens, while all *Pseudomonas aeruginosa*, Acinetobacter species, Enterococcus species, fungi, and coagulase-negative staphylococcus species at baseline were not considered pathogens.

The **Clinically Evaluable** population (CE) must have met important key requirements including inclusion criteria, avoidance of prohibited concomitant antimicrobial therapy, and reception at least 3 days of IV therapy in case of cure.

The **Safety Population** included all randomized patients who received any amount of IV study drug.

Protocol Amendments

(b) (4)

cUTI- Study 009

Only one protocol amendment occurred in Dec 2015 to allow for the inclusion of patients with moderate renal impairment, defined as a CLcr of >30 to ≤60 mL/min as estimated by the Cockcroft-Gault equation. This change occurred after data were available from safety/PK Phase 1 study of plazomicin in subjects with renal impairment (Study 004).

6.1.2. Study Results

Compliance with Good Clinical Practices

(b) (4)

cUTI- Study 009

The applicant declared that the study was conducted in accordance with the US Food and Drug Administration (FDA) regulations, the International Council on Harmonisation (ICH) E6 Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), and applicable local, state, and national laws.

Financial Disclosure

(b) (4)

cUTI- Study 009

For study 009, no financial interests were noted for all investigators and subinvestigators. One year follow-up disclosures for all investigators were submitted in May 2018. No new disclosures were noted, though several sub-investigators in site (b) (6) and one sub investigator in site (b) (6) were lost to follow up.

Patient Disposition

(b) (4)

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(b) (4)

cUTI- Study 009

A total of 609 patients were randomized and included in the ITT Population: 306 randomized to plazomicin and 303 randomized to meropenem. In general, patient disposition was comparable between treatment groups. Approximately 97% of patients in both groups completed the LFU visit. The most common reason for withdrawal from the study was patient's withdrawal of consent (1.1%, overall) and loss to follow-up (0.7% overall). Less than 1% of patients (3 in the plazomicin group and 2 in the meropenem group) were randomized but not treated, which was also most frequently due to patient's withdrawal of consent. Almost 75% of subjects in each arm completed IV study drug. The vast majority of those who did not (roughly 20% in each arm), did so because of lack of a study qualifying culture at baseline. 1-2% of subjects discontinued IV study drug due to adverse events. There was very little discontinuation of the oral study drug (around 1% in each arm).

Table 15: Patient Disposition - ITT Population, Study 009

Disposition	Plazomicin (N=306) n (%)	Meropenem (N=303) n (%)	All Patients (N=609) n (%)
Completed study drug treatment [a]	229 (74.8)	227 (74.9)	456 (74.9)
Randomized but not treated	3 (1.0)	2 (0.7)	5 (0.8)
Prematurely discontinued study drug (IV or oral)	74 (24.2)	74 (24.4)	148 (24.3)
Prematurely discontinued IV study drug	70 (22.9)	70 (23.1)	140 (23.0)
Primary reason for prematurely discontinuing IV study drug			
Lack of study-qualifying baseline urine culture	60 (19.6)	61 (20.1)	121 (19.9)
Adverse event	4 (1.3)	6 (2.0)	10 (1.6)
Investigator decision	2 (0.7)	1 (0.3)	3 (0.5)
Withdrawal of consent	1 (0.3)	1 (0.3)	2 (0.3)
Insufficient therapeutic effect	0 (0)	1 (0.3)	1 (0.2)
Pregnancy or nursing	1 (0.3)	0 (0)	1 (0.2)
Significant patient noncompliance	0 (0)	0 (0)	0 (0)
Other	2 (0.7)	0 (0)	2 (0.3)
Death	0 (0)	0 (0)	0 (0)

Disposition	Plazomicin (N=306) n (%)	Meropenem (N=303) n (%)	All Patients (N=609) n (%)
Prematurely Discontinued Oral Study Drug	4 (1.3)	4 (1.3)	8 (1.3)
Primary Reason for Prematurely Discontinuing Oral Study Drug	2 (0.7)	2 (0.7)	4 (0.7)
Adverse Event	1 (0.3)	1 (0.3)	2 (0.3)
Lack of study-qualifying pretreatment baseline urine culture	1 (0.3)	0 (0)	1 (0.2)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Insufficient therapeutic effect	0 (0)	0 (0)	0 (0)
Pregnancy or nursing	0 (0)	0 (0)	0 (0)
Significant patient noncompliance	0 (0)	0 (0)	0 (0)
Withdrawal of Consent	0 (0)	0 (0)	0 (0)
Investigator Decision	0 (0)	0 (0)	0 (0)
Death	0 (0)	1 (0.3)	1 (0.2)
Other			
Completed the LFU Visit [c]	299 (97.7)	294 (97.0)	593 (97.4)
Prematurely Withdrew from the Study	7 (2.3)	9 (3.0)	16 (2.6)
Primary Reason for Premature Withdrawal from the Study			
Withdrawal of Consent	4 (1.3)	3 (1.0)	7 (1.1)
Lost to Follow-up	1 (0.3)	3 (1.0)	4 (0.7)
Significant patient noncompliance	1 (0.3)	1 (0.3)	2 (0.3)
Death	1 (0.3)	0 (0)	1 (0.2)
Investigator Decision	0 (0)	0 (0)	0 (0)
Eligibility Criteria not met	0 (0)	0 (0)	0 (0)
Other	0 (0)	2 (0.7)	2 (0.3)

eCRF=electronic case report form; IV=intravenous; LFU=late follow-up; N=Number of patients in the specified population; n=Number of patients in the specified category. Note: Percentages are calculated as 100×(n/N).
a Defined as patients who did not prematurely discontinue study drug as per the Treatment Completion/Discontinuation eCRF. b Defined as patients who completed the LFU visit as per the Study Completion eCRF.
Source: Study 009, Clinical Study Report

Three and two subjects did not receive study drug in the plazomicin and meropenem arms, respectively, leaving an MITT population of 303 and 301 in those arms. Slightly over 100 subjects from each arm (112 and 104 from plazomicin and meropenem, respectively) were excluded from the mMITT population, almost overwhelmingly due to lack of a qualifying study pathogen (whether due to the pathogen itself or its resistance pattern). The mMITT population thus included 191 and 197 subjects in the plazomicin and meropenem arms, respectively. Relatively few exclusions occurred due to clinical and microbiological evaluability; plazomicin ME-Day 5 and ME-TOC populations were 188 and 179, respectively and meropenem ME – Day 5 and ME-TOC populations of 190 and 177, respectively. Almost all subjects (96%) were enrolled under the amended protocol.

Table 16 Study Populations Overall and by Randomization Stratification Factors, Study 009

Randomized (Intent-to-Treat (ITT) Population)[a], N	Plazomicin n (%)	Meropenem n (%)	All Patients n (%)
	306	303	609
Modified Intent-to-Treat (MITT) Population[b]	303 (99.0)	301 (99.3)	604 (99.2)
Microbiological Modified ITT (mMITT) Population[c]	191 (62.4)	197 (65.0)	388 (63.7)
Clinically Evaluable Day 5 (CE-Day 5) Population	188 (61.4)	190 (62.7)	378 (62.1)
Clinically Evaluable TOC (CE-TOC) Population	180 (58.8)	179 (59.1)	359 (58.9)
Microbiologically Evaluable Day 5 (ME-Day 5) Population	188 (61.4)	190 (62.7)	378 (62.1)
Microbiologically Evaluable TOC (ME-TOC) Population	179 (58.5)	177 (58.4)	356 (58.5)
Safety Population[d]	303 (99.0)	301 (99.3)	604 (99.2)
PK Population[e]	286 (93.5)	0	286 (47.0)

AP=acute pyelonephritis; CE=clinically evaluable; cUTI=complicated urinary tract infection; IV=intravenous; IXRS= interactive voice- or web-based response system; PK=pharmacokinetic; ME=microbiologically evaluable; N=Number of patients randomized; n=Number of patients in the specified category; TOC=test of cure. Note: Percentages are calculated as 100×(n/N). a A patient was considered randomized when a randomization transaction was recorded in the IXRS. b Randomized patients who received any amount of study drug. c Patients in the MITT Population who had ≥1 qualified pathogen from a study-qualifying baseline urine culture. d Randomized patients who received any amount of IV study drug. e Randomized patients who received ≥1 dose of plazomicin and had ≥1 quantifiable plasma concentration(s)available. Source: Study 009, Clinical Study Report

Protocol Violations/Deviations

(b) (4)

cUTI- Study 009

Roughly 40% and 30% of subjects in the plazomicin and meropenem arms (ITT Population), respectively were found to have protocol deviations. In the plazomicin arm, 17% of subjects had “Unblinded Issues” which constituted errors by unblinded personnel regarding dosing and dose preparation. This might be due to errors in weight calculations, creatinine clearance calculations, rounding errors, and errors in study drug reconstitution. Only 6% of subjects in the meropenem arm had similar errors, likely due to the relatively easy and familiar dosing regimen for this drug. 12% and 10% of subjects in the plazomicin and meropenem arms, respectively

had a deviation related to timing of a study visit. The visit in question was usually the TOC visit though when using criteria set out in the SAP for when this visit should occur (had a slightly larger post Day 17 visit window than the protocol) then much fewer subjects were noted to have deviations (7 only). 9% and 6% of subjects in the plazomicin and meropenem arms, respectively had deviations related to continuing in the study despite not having a qualifying baseline urine culture, receiving a prolonged course of study drug (oral or IV or both), or being unblinded to treatment (3 such students in each arm). Other protocol deviations were small in number and essentially equivalent between both arms.

Demographic Characteristics

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The majority of subjects in the mMITT population (roughly 60%) in each arm had cUTI (rather than AP) and were generally well balanced between treatment arms. The overwhelming majority of subjects (roughly 98%) in both arms came from Region 2 which primarily consisted of Eastern European countries and former Soviet Republics along with Russia. As concerns gender, while the meropenem arm was evenly split between the sexes, there were more females than males in the plazomicin arm. Virtually all enrolled subjects except 2 subjects were White. The mean age in both arms was around 60 years though the meropenem arm had slightly more subjects (relative to plazomicin) that were ≥65 years old. Interestingly, roughly 40% of subjects in each arm had a TBW/IBW ratio ≥125%; this had consequences in terms of plazomicin dosing and estimation of creatinine clearance. The mean creatinine clearance for both arms was around 75 mL/min. When looking at distribution by creatinine clearance, the two arms were generally evenly matched though the plazomicin arm had slightly more subjects

with clearance > 120 mL/min and the meropenem arm had slightly more subjects with clearance between 30 and 60 mL/min. Most subjects had monomicrobial infections, and slightly more than a quarter of patients in each arm were infected with ESBL pathogens. Importantly, only two subjects took an antimicrobial in the 48 hrs. prior to starting therapy.

Table 22 Reviewer's summary of baseline characteristics, mMITT population, Study 009

Demographic Parameters	**Plazomicin** (N=191) n (%)	**Meropenem** (N=197) n (%)
Sex		
Male	84 (44.0%)	99 (50.2%)
Female	107 (56.0%)	98 (49.8%)
Age		
Mean years (SD)	58.8	60.0
Median (years)		
Min, max (years)	18,88	18, 87
Age Group		
≥ 18 - < 65 years	101 (52.9%)	95 (48.2%)
≥ 65 years	90 (47.1%)	102 (51.8%)
Race		
White	189 (99%)	197 (100%)
Black or African American	1 (0.5%)	0 (0%)
Other	1 (0.5%)	0 (0%)
Multiple		
Ethnicity		
Hispanic or Latino	2 (1.0%)	3 (1.5%)
Not Hispanic or Latino	188 (98.0%)	193 (98.0%)
Not Reported	1 (0.5%)	1 (0.5%)
Region		
Region 1	4 (2.1%)	2 (1%)
Region 2	187 (97.9%)	195 (99%)
Infection Type		
AP	84 (44%)	78 (39.6%)
cUTI	107 (56%)	119 (60.4%)
Indwelling Catheter	25 (13.1%)	26 (13.2%)
Males with history of urinary retention	47.7%	46.2%
TBW:IBW		
<125%	120 (62.8%)	117 (59.4%)
≥125%	71 (37.2%)	80 (40.6%)
Creatinine Clearance (mL/min)		
≤30	0 (0%)	3 (1.5%)

>30-60	61 (31.9%)	71 (36%)
>60-90	70 (36.6%)	75 (38.1%)
>90-120	40 (20.9%)	35 (17.8%)
>120	17 (8.9%)	10 (5.1%)
Missing?	3 (1.6%)	3 (1.5%)
Antibiotic in 48 hrs. Prior to Study Drug	2 (1%)	0 (0%)
ESBL Pathogens	50 (26.2%)	57 (28.9%)
CRE Pathogens	9 (4.7%)	6 (3.0%)
Bacteremia at baseline	25 (13.1%)	23 (11.7%)
AG- Resistance	51 (26.7%)	50 (25.4%)
Switch to Oral therapy		
Yes	154 (80.6%)	151 (76.6%)
Levofloxacin	128 (67.0%)	121 (61.4%)
Levofloxacin resistance	27/128 (21.1%)	32/121 (26.4%)
No	37 (19.4%)	46 (23.4%)
Concomitant systemic antibacterial medication- (14 days prior to randomization until LFU)	11 (5.8)	12 (6.1)
Monomicrobial infection	182 (95.3)	181 (91.9)

Region 1- Mexico, Spain, United States; Region 2- Bulgaria, Czech Republic, Estonia, Georgia, Hungary, Latvia, Poland,Romania, Russia, Serbia, Ukraine. Resistant, based on central laboratory Clinical and Laboratory Standards Institute breakpoints.
Aminoglycoside–R=Not susceptible to any of amikacin, gentamicin, or tobramycin.
Carbapenem-R=Not susceptible to imipenem or doripenem.
ESBL defined as a minimum inhibitory concentration =2 mcg/mL to any of ceftazidime, aztreonam, or ceftriaxone based on central laboratory testing.

Table 23 Most frequent Uropathogens Identified from Baseline Urine Cultures – mMITT Population, Study 009

Baseline Uropathogen	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)
Gram-negative aerobes	189 (99.0)	193 (98.0)
Enterobacteriaceae	189 (99.0)	193 (98.0)
Aminoglycoside-R	51 (27.0)	50 (25.9)
ESBL	50 (26.5)	57 (29.5)
Carbapenem-R	9 (4.8)	6 (3.1)
Escherichia coli	126 (66.0)	137 (69.5)
Aminoglycoside-R	23 (18.3)	26 (19.0)
ESBL	20 (15.9)	28 (20.4)
Carbapenem-R	0 (0)	0 (0)
Klebsiella pneumoniae	33 (17.3)	43 (21.8)
Aminoglycoside-R	18 (54.5)	20 (46.5)
ESBL	20 (60.6)	26 (60.5)
Carbapenem-R	0 (0)	1 (2.3)
Enterobacter cloacae	15 (7.9)	3 (1.5)
Aminoglycoside-R	5 (33.3)	2 (66.7)
ESBL	7 (46.7)	2 (66.7)
Carbapenem-R	0 (0)	0 (0)
Proteus mirabilis	11 (5.8)	7 (3.6)
Aminoglycoside-R	5 (45.5)	3 (42.9)
ESBL	3 (27.3)	1 (14.3)
Carbapenem-R	7 (63.6)	5 (71.4)

Resistant, based on central laboratory Clinical and Laboratory Standards Institute breakpoints. Aminoglycoside–R=Not susceptible to any of amikacin, gentamicin, or tobramycin.
Carbapenem-R=Not susceptible to imipenem or doripenem.
ESBL defined as a minimum inhibitory concentration =2 mcg/mL to any of ceftazidime, aztreonam, or ceftriaxone based on central laboratory testing; Source: Study 009, Clinical Study Report

Prior medical conditions and/or surgical procedures were reported in approximately 90% of patients in the mMITT. Overall, the nature of medical and surgical histories was comparable between treatment groups and consistent with an older population with cUTI. The most common medical conditions (by PT) were hypertension (156/388 [40.2%]) and benign prostatic hyperplasia (BPH; 104/388 [26.8%]). Nineteen [10.0%] and 39 [19.8%] patients in the plazomicin and meropenem groups, respectively, had type 1 or type 2 diabetes mellitus. Baseline clinical signs and symptoms were as expected for a cUTI trial. Interestingly, 20% and 17% of plazomicin and meropenem subjects, respectively had urosepsis at baseline (as determined by SIRS criteria). 13% and 12% of subjects had bacteremia at baseline. Subjects in the meropenem arm had slightly more systemic signs of AP at baseline (such as nausea, vomiting, chills, rigors, and fever) than did plazomicin.

The most common pathogens isolated at baseline were *E. coli* followed by *K. pneumoniae*. Roughly a fifth of the *E. Coli* were ESBLs whereas almost 2/3rds of the *K. pneumoniae* were ESBLs. Among Enterobacteriaceae from the baseline urine cultures in the mMITT population, the plazomicin MIC50 and MIC90 were 0.5 mcg/mL and 1 mcg/mL, respectively (range: 0.06 to 4 mcg/mL). The MIC50/90 for plazomicin against aminoglycoside-resistant and ESBL-producing Enterobacteriaceae were 0.25/2 mcg/mL and 0.25/0.5 mcg/mL.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

cUTI- Study 009

In the mMITT population, the mean duration of IV plus oral study drug therapy was 9.2 and 8.9 calendar days in the plazomicin and meropenem arms, respectively. Only 6 mMITT patients (4 in meropenem and 2 in plazomicin) received >12 calendar days of IV plus oral study drug Overall, 78.6% of patients switched to oral therapy. The proportion of patients who switched to oral therapy and the study day of oral switch was comparable across treatment arms. In general, the switch was made to levofloxacin.

Virtually all subjects (except 2) had not received any antibacterial drugs in the 48 hours prior to start of study drug.

In the mMITT population, the proportion of patients with any prior and/or concomitant systemic antibacterial medication (from 14 days prior to randomization to LFU) was low and was similar between the treatment groups (11 [5.8%] patients in the plazomicin group vs 12

[6.1%] patients in the meropenem group). Quinolones were the most commonly used class of concomitant antibacterial drugs. The proportion of patients with any prior and/or concomitant medication other than systemic antibacterial medication was similar between treatment groups: 244 (80.5%) patients in the plazomicin group vs 240 (79.7%) patients in the meropenem group. In the Safety population, overall, the three most frequent ATC Class Level 3 medications across treatment groups were other analgesics and antipyretics (27.6%; predominantly paracetamol and/or the nonsteroidal anti-inflammatory drug [NSAID] metamizole), IV solution additives (22.5%), and beta blocking agents (22.2%).

Efficacy Results – Primary Endpoint

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cUTI- Study 009

As mentioned above, the coprimary efficacy endpoints were the composite microbiological eradication and programmatically determined clinical cure rate in the mMITT population at both Day 5 and the TOC visit. For noninferiority to be declared, the lower end of the 95% confidence interval for the difference between the composite cure in the two arms would have to be ≥ -15% at BOTH Day 5 and at the TOC.

At Day 5, the difference in composite cure (plazomicin – meropenem) was -3.4% (-10.0, -3.1)]. At TOC, the difference in composite cure was 11.6% (2.7, 20.3). Because the lower end of the 95% confidence interval of the difference in composite cure on both days was ≥ -15%, noninferiority of plazomicin to meropenem in the treatment of cUTI could be declared. Similar findings were noted at EOIV.

When looking at the composite cure rates for the ME population, similar trends were noted for Day 5 and TOC.

Table 30 Composite of Microbiological Eradication and Clinical Cure Rate, and Individual Components at Day 5 and TOC Visits, mMITT Population, Study 009

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

As can be noted from above, at Day 5, the small difference in Composite Cure is reflective of similar Clinical Cure and Microbiological Eradication rates in both arms. At TOC, the large difference in Composite Cure is primarily driven by a large drop off in Microbiologic Eradication in the meropenem arm. The reason behind this drop in microbiological eradication is unclear though not necessarily without precedent. In the cUTI trial for meropenem-vaborbactam, there was a 20% drop in composite cure rates from the EOIV visit to the TOC visit, again driven mostly by microbiologic recurrence (FDA Clinical Review;

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209776Orig1s000MedR.pdf). Still, it's unclear what could account for this precipitous drop in microbiologic eradication. There were slight imbalances between the arms in terms of gender, infection type (cUTI vs. AP), and presence of DM but it is not clear why these would negatively impact meropenem's microbiologic eradication so heavily. The number of subjects who switched to oral therapy was relatively comparable between the arms, however there was a slight imbalance between the arms in terms of subjects receiving levofloxacin despite having a levofloxacin resistant pathogen (roughly 5% more in the meropenem arm). It is also plausible the plazomicin may have some intrinsic benefit with regards to microbiologic eradication (post-antibiotic effect, concentrating in the urine) though the TOC/LFU visits seem somewhat further than expected for such an effect to persist.

Whether this disparity in microbiologic eradication is of relevance clinically is also unclear. At the LFU visit, there were more clinical relapses in the meropenem arm (14/197; 7.1%) compared to the plazomicin arm (3/169; 1.6%), but does not fully reflect the disparity in microbiologic eradication seen in TOC (it should also be noted that at LFU, there were more microbiologic recurrences in the meropenem arm compared to plazomicin).

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

Table 31: Composite of Microbiological Response and Clinical Response at Day 5, EOIV, and TOC Visits, ME Population, Study 009

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: Study 009 Clinical Study Report, .

Table 32 cUTI Composite Cure Rate, mMITT subgroup analysis, Study 009

	Plazomicin Day 5 N=191	Meropenem Day 5 N=197	Difference	Plazomicin TOC N=191	Meropenem TOC N=197	
All	168 (88%)	180 (91.4%)	-3.4%	156 (81.7%)	138 (70.1%)	11.6%
Age (years)						
< 65	93/101 (92.1%)	88/95 (92.6%)	-0.5%	90/101 (89.1%)	68/95 (71.6%)	17.5%
≥ 65	75/90 (83.3%)	92/102 (90.2%)	-6.9%	66/90 (73.3%)	70/102 (68.6%)	4.7%
Sex						
Male	73/84 (86.9%)	87/99 (87.9%)	-1.0%	65/84 (77.4%)	68/99 (68.7%)	8.7%
Female	95/107 (88.8%)	93/98 (94.9%)	-6.1%	91/107 (85.0%)	70/98 (71.4%)	13.6%
ESBL Pathogens	43/50 (86%)	53/57 (93.0%)	-7.0%	36/50 (72%)	37/57 (64.9%)	7.1%
CRE Pathogens	8/9 (88.9%)	6/6 (100%)	-11.1%	6/9 (66.7%)	4/6 (66.7%)	0%
Bacteremia at baseline	19/25 (76%)	21/23 (91.3%)	-15.3%	18/25 (72%)	13/23 (56.5%)	15.5%
AG Non-susceptible	47/51 (92.2%)	47/50 (94%)	-1.8%	35/51 (68.6%)	30/50 (60%)	8.6%
Renal Function (mL/min)						
≤30	0/0	2/3 (66.7%)		0/0	2/3 (66.7%)	
>30-60	51/61 (83.6%)	65/71 (91.5%)	-7.9%	43/61 (70.5%)	47/71 (66.2%)	4.3%
>60-90	61/70 (87.1%)	69/75 (92%)	-4.9%	59/70 (84.3%)	52/75 (69.3%)	15%
>90-120	38/40 (95%)	33/35 (94.3%)	0.7%	37/40 (92.5%)	28/35 (80%)	12.5%
>120	16/17 (94.1%)	9/10 (90%)	4.1%	16/17 (94.1%)	7/10 (70%)	24.1%
Missing?	2	2		1	2	
AP	73/84 (86.9%)	72/78 (92.3%)	-5.4%	72/84 (85.7%)	56/78 (71.8%)	13.9%
cUTI	95/107 (88.8%)	108/119 (90.8%)	-2.0%	84/107 (78.5%)	82/119 (68.9%)	9.6%

cUTI and indwelling foley	22/25 (88%)	25/26 (96.2%)	-8.2%	15/25 (60%)	14/26 (53.8%)	6.2%
Diabetes Mellitus History	12/19 (63.2%)	33/39 (84.6%)	-21.4%	13/19 (68.4%)	27/39 (69.2%)	-0.8%
Oral Therapy						
Yes	138/154 (89.6%)	143/151 (94.7%)	-5.1%	127/154 (82.5%)	110/151 (72.8%)	9.7%
No	30/37 (81.1%)	37/46 (80.4%)	0.7%	29/37 (78.4%)	28/46 (60.9%)	17.5%

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

For the Day 5 outcomes, in general, subpopulation estimates tracked along with the overall findings in that plazomicin performed worse (according to point estimates) than meropenem, particularly in females, subjects ≥ 65 years of age, subjects with ESBL pathogens, subjects with DM, subjects bacteremic at baseline, subjects with mild to moderately impaired renal function, subjects with an indwelling Foley, and subjects who switched to oral therapy. At the TOC visit, plazomicin seemed to perform better than meropenem in almost all subgroups. Interestingly, subjects with DM did not do better (by point estimate) with plazomicin at either visit. Given the small sample size of many of these subgroups (including the DM subgroup), post-randomization factors, etc., these findings should be viewed as purely exploratory.

Of note, of the 51 plazomicin subjects noted to have aminoglycoside-nonsusceptible isolates, almost all had resistance to either tobramycin alone, gentamicin alone, or combined tobramycin/gentamicin resistance. Amikacin "resistance" was only noted in one subject (had isolate that was intermediate to amikacin and resistant to tobramycin and gentamicin).

Microbiological eradication rates at TOC visit by baseline pathogen in the mMITT population are presented in Table 11. As can be noted, eradication rates for the most frequent pathogens (*E. coli* and *K. pneumoniae*) were generally better for plazomicin than for meropenem. For other pathogens, the sample size is too limited to draw any real conclusions. Plazomicin's activity seemed at least comparable to that of meropenem for pathogens containing aminoglycoside resistance or ESBLs (please note that in this study, aminoglycoside resistance was defined as having intermediate or resistant susceptibility to either amikacin, tobramycin, OR gentamicin). Of note, Aminoglycoside resistance meant a baseline uropathogen had resistance to either tobramycin, gentamicin, or amikacin (or some combination thereof). Of the 52 baseline uropathogens, 28 (54%) contained tobramycin and gentamicin resistance (intermediate counted as resistant); 15 (28.8%) tobramycin resistance only, 8 (15.4%) gentamicin resistance only, and 1 (1.9%) pan resistant organism.

Table 33: Microbiological Eradication Rate at TOC by Baseline Pathogen, mMITT Population, Study 009

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

Data Quality and Integrity

(b) (4)

cUTI- Study 009

The statistical reviewer found several subjects (11) who may have been mistakenly coded as Cures at either Day 5 or TOC. However, a sensitivity analysis in which these patients were reclassified as Failures still showed an NI margin ≥ 15% at Day 5 and TOC. However, it should be noted that reclassification did shift margins to the left so that superiority of plazomicin at TOC was eliminated (95% CI crossed zero). See Statistical Review, Tables 15 and 16, for more details.]

Efficacy Results – Secondary and other relevant endpoints

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(b) (4)

cUTI- Study 009

Microbiological eradication for this study was assessed using criterion as bacteria growth at less than 10^4 CFU/mL. As this criterion may change to 10^3 CFU/mL in future guidances, additional analysis was done at the TOC visit (based on the data availability) for microbiological eradication rate at ≤ 10^3 CFU/mL. Compared to the results with criterion 10^4 CFU/mL, the new results favors plazomicin even more.

Table 34: Microbiological Eradication Rate at TOC, Based on Two Different Criteria, mMITT Population, Study 009

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

Dose/Dose Response

(b) (4)

(b) (4)

cUTI- Study 002

As has been noted earlier, though the phase 3 trial only examined one dose of plazomicin (15 mg/kg daily), a phase 2 study was conducted in which several subjects took a 10mg/kg daily plazomicin dose until the protocol was amended and all subjects were switched to the 15mg/kg dose. Thus, there was a dose response comparison, albeit of imbalanced sample size.

This was a multicenter, multinational, double-blind, randomized, comparator-controlled, Phase 2 study of the safety and efficacy of plazomicin compared to levofloxacin (both administered as IV infusions) in patients with cUTI or AP. The coprimary efficacy endpoints were the microbiological eradication (MBE) rates at the test-of-cure (TOC) visit in the modified intent-to-treat (MITT) population and in the microbiologically evaluable (ME) population. The study consisted of a screening period (Day 1), a treatment period (Days 1–5), and a follow-up period (from EOT through Day 40).

The follow-up period consisted of the TOC (or early termination) visit and the long-term follow-up (LTFU) visit. The TOC visit and assessments occurred 7 (±2) days after the last dose of study drug (i.e., on Day 12 ±2). The LTFU visit (the final study visit) occurred 35 (±7) days after the last dose of study drug (i.e., on Day 40 ±7). At both the TOC and LTFU visits, the investigators assessed and recorded clinical outcome.

The study was comparator-controlled, and levofloxacin 750 mg for 5 consecutive days was chosen as the comparator drug for this study. Levofloxacin is approved for treatment of cUTI and AP.

At study entry, patients were to have a bacterial pathogen identified in urine culture at $\geq 10^5$ CFU/mL as well as signs and symptoms of cUTI or AP.

Please note that beyond the small sample size of this study, demographic characteristics, including race, gender distribution, as well as microbiologic susceptibility differed considerably from Study 009.

Table 35 Demographics and Baseline Characteristics (ITT Population), Study 002

	Plazomicin 10 mg/kg (N=22)	Plazomicin 15 mg/kg (N=76)	Levofloxacin 750 mg (N=47)	All Patients (N=145)
Region				
India, n (%)	8 (36.4)	17 (22.4)	17 (36.2)	42 (29.0)
Latin America, n (%)	3 (13.6)	14 (18.4)	8 (17.0)	25 (17.2)
North America, n (%)	11 (50.0)	45 (59.2)	22 (46.8)	78 (53.8)
Type of Infection				
Acute Pyelonephritis, n (%)	12 (54.5)	42 (55.3)	25 (53.2)	79 (54.5)
cUTI, n (%)	10 (45.5)	34 (44.7)	22 (46.8)	66 (45.5)
cUTI with Indwelling Catheter, n (%)	1 (4.5)	6 (7.9)	2 (4.3)	9 (6.2)
cUTI without Indwelling Catheter, n (%)	9 (40.9)	28 (36.8)	20 (42.6)	57 (39.3)
Age (years) n	22	76	47	145
Mean	46.5	40.0	44.8	42.6
SD	18.12	15.02	14.61	15.53
Median	46.0	37.0	43.0	40.0
Min, Max	18, 77	18, 75	23, 82	18, 82
Sex				
Male, n (%)	4 (18.2)	15 (19.7)	10 (21.3)	29 (20.0)
Female, n (%)	18 (81.8)	61 (80.3)	37 (78.7)	116 (80.0)
Race				
White, n (%)	6 (27.3)	13 (17.1)	5 (10.6)	24 (16.6)
Black or African American, n (%)	0 (0.0)	13 (17.1)	9 (19.1)	22 (15.2)
Asian, n (%)	8 (36.4)	17 (22.4)	18 (38.3)	43 (29.7)
American Indian or Alaska Native, n (%)	7 (31.8)	33 (43.4)	14 (29.8)	54 (37.2)
Height (cm) n	22	75	47	144
Mean	160.31	160.60	161.49	160.85
SD	7.782	8.380	9.663	8.688
Median	159.50	160.00	160.00	160.00
Min, Max	150.0, 172.7	142.0, 182.9	141.0, 185.0	141.0, 185.0
Weight (kg) n	22	75	47	144
Mean	68.98	69.19	70.35	69.53
SD	15.721	14.908	14.169	14.704
Median	66.75	66.00	72.30	68.05
Min, Max	44.4, 99.4	42 0, 100.0	40.0, 96.8	40.0, 100.0

Despite these demographic differences, it is still instructive to look at the phase 2 study results in order to see any possible implication of dose on outcomes.

Table 36: Microbiological Response at TOC (MITT and ME Populations), Study 002

Population	By-Patient Microbiological Response	Plazomicin 10 mg/kg	Plazomicin 15 mg/kg	Levofloxacin 750 mg
MITT	N	12	51	29
	Eradication, n (%)	6 (50.0)	31 (60.8)	17 (58.6)
	95% CI	(21.1–78.9)	(46.1–74.2)	(38.9–76.5)
	Non-eradication, n (%)	1 (8.3)	5 (9.8)	4 (13.8)
	Indeterminate, n (%)	5 (41.7)	15 (29.4)	8 (27.6)
	Difference (95% CI) [a]			−2.2 (−272–22.9)
ME	N	7	35	21
	Eradication, n (%)	6 (85.7)	31 (88.6)	17 (81.0)
	95% CI	(42.1–99.6)	(73.3–96.8)	(58.1–94.6)
	Non-eradication, n (%)	1 (14.3)	4 (11.4)	4 (19.0)
	Difference (95% CI) [a]			−7.6 (−31.3–16.0)

Difference is for the difference in microbiological eradication rates between plazomicin 15 mg/kg and levofloxacin and is calculated as levofloxacin – plazomicin 15 mg/kg. The 95% CI for the difference is based on a normal approximation with a continuity correction. Source: Study 002, Clinical Study Report

As can be seen, there did appear to be a trend toward higher eradication in the 15 mg/kg arm, though the number of indeterminates in the MITT analysis set (which the applicant attributed to poor sample collection and tracking), small and imbalanced sample size, etc. make these results difficult to interpret)]

Durability of Response

(b) (4)

cUTI- Study 009

Composite cure was tracked out to the LFU visit. Results did not differ from the TOC visit. Again, note that microbiological eradication drove the positive response at TOC and LFU.

Figure 4 Efficacy Endpoints by Visit, mMITT Population, Study 009

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

Additional Analyses Conducted on the Individual Trial

(b) (4)

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7. Integrated Review of Effectiveness

Integrated Assessment of Effectiveness

The plazomicin clinical development plan was intended to pursue treatment of an unmet need through two distinct tracks. One track involved pursuing a traditional indication (cUTI) using a supportive Phase 2 study and a single Phase 3 study. A larger NI margin (15%) than is usually accepted for an cUTI NI trial was used as plazomicin had the potential to address an unmet medical need. The other track involved pursuing a BSI and HABP/VABP indication (b) (4) A clear understanding of these differing approaches is needed to determine if the standards for efficacy have been met for both indications.

In the case of cUTI, the evidentiary standard was adequately met. An initial small cUTI study (study 002) supported the efficacy of plazomicin compared to a commonly used comparator (levofloxacin) in the treatment of cUTI (descriptive analyses only; no NI margin was prespecified in this study) and provided the basis for Study 009. Study 009 was an, active controlled, double-blind trial conducted using a trial design essentially in line with FDA guidance. An adequate comparator was chosen in meropenem. Noninferiority, as defined by composite cure rates at Day 5 and at TOC, was demonstrated in the mMITT population and supported by similar findings in the ME population. At TOC and LFU, plazomicin trended toward better composite cure rates than meropenem, though this was driven primarily by microbiological eradication findings. It is unclear what the clinical significance of this is, nor is it clear what the underlying reason (chance, confounding by demographics, true plazomicin effect, etc.) is for this finding. Subgroup analyses were generally in line with the mMITT population results; subgroups such as those with bacteremia and those with diabetes mellitus at baseline were difficult to interpret given the very small subgroup sample size. For the most part, the findings are generalizable-subjects had Foley catheters replaced, they were often switched to oral therapy after several days of IV therapy, and they represented an adequate mix of cUTI and AP. Importantly, patients could not have antibacterial therapy 48 hours prior to starting study drug, thus minimizing confounding. Also, almost all patients in the study continued in the study until the LFU visit.

However, it should be noted that there were some factors affecting generalizability. First, the racial makeup of the trial was overwhelmingly White as the trial was conducted primarily in Eastern European countries. Considering the racial diversity in the United States, this is not ideal. However, the Phase 2 study, Study 002, had a more diverse racial makeup and the

efficacy findings there provides at least some assurance that the study medication effect seen in Study 009 is applicable to a broad swath of the US population. The other thing to note is that

the primary efficacy analysis of Study 009 did not evaluate plazomicin activity against potential (though much less common) cUTI pathogens such as *Acinetobacter* and *Pseudomonas*. Due to concerns from prior nonclinical studies about plazomicin's activity against these pathogens, these pathogens were excluded from the mMITT population. Thus, clinical scenarios where such pathogens are expected to be the source of a cUTI may require an alternative therapy to plazomicin. However, plazomicin did appear to show activity against Enterobacteriaceae, the most common cause of cUTI. Importantly, it appeared to show adequate efficacy in Enterobacteriaceae carrying common resistance patterns such as ESBLs and appeared to provide an alternative aminoglycoside option in cases where there was aminoglycoside resistance (particularly tobramycin and gentamicin resistance). Finally, it should be noted that subjects with severe renal impairment were not studied. Considering that it is very likely that patients with severely impaired renal function at baseline are likely to be treated post market, dosing in this population should be appropriately evaluated.

(b) (4)

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(b) (4)

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8. Review of Safety

8.1. Safety Review Approach

[This safety review will focus primarily on the findings from the cUTI studies, Study 002 and Study 009, (b) (4) This emphasis on the cUTI trials is because of their size, design, and ability to obtain to provide less confounded safety information (particularly as regards Study 009 (b) (4) Where relevant, findings from phase 1 studies will also be discussed. Of note, this safety discussion will flow by topic rather than by trial. Thus, deaths in Study 002, Study 009, (b) (4)

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 612 subjects were exposed to plazomicin including 479 subjects who received the therapeutic dose of 15mg/kg. Excluding TDM-adjusted doses, the highest clinical dose evaluated was a single dose of 20 mg/kg in the TQT study. (b) (4) The longest duration evaluated in the absence of TDM was 7 dosing days in Study 009.

Table 39 Adult Plazomicin Exposure by Dose and Duration of Exposure in Completed Phase 1, 2, and 3 Studies

Intravenous Formulation N=612 Cutoff Date: 10 May2018

	Dose					
Duration (d)	**1-7.5 mg/kg (N=37) n (%)**	**10 mg/kg (N=22) n (%)**	**10.7-11 mg/kg (N=17) n (%)**	**15 mg/kg (N=479) n (%)**	**20 mg/kg (N=57) n (%)**	**Total (Any Dose) (N=612) n (%)**
Phase 1 studies in healthy subjects [a]	**37 (100)**		**17 (100)**	**54 (11.3)**	**57 (100)**	**165 (27.0)**
1 (Single dose)	25 (67.6)		11 (64.7)	42 (8.8)	57 (100)	135 (22.1)
2				1 (0.2)		1 (0.2)
3				6 (1.3)		6 (1.0)
5			6 (35.3)	5 (1.0)		11 (1.8)
9	1 (2.7)					1 (0.2)
10	11 (29.7)					11 (1.8)
Phase 2 and Phase 3 studies in patients with cUTI/AP [b]		**22**		**377 (78.7)**		**399 (65.2)**
1 to <4		1 (4.5)		46 (9.6)		47 (7.7)
≥4 to7		21 (95.5)		331 (69.1)		352 (57.5)
(b) (4)						

Abbreviations: AP=acute pyelonephritis; CRE=carbapenem-resistant Enterobacteriaceae; cUTI=complicated urinary tract infection.
[a] Highest dose and longest duration are captured.
[b] Dose may have been adjusted based on renal function. See footnote for SCS Table 7for details on duration of study drug calculation.
(b) (4)

Source: Summary of Clinical Safety

Table 40 Plazomicin Exposure in Healthy Subjects by Dose and Dosing Regimen, Studies 002 and 009

	ACHN-490 Studies						
Dose and Dosing Regimen	001 n	003 n	004 n	006 n	010 n	011 n	Total n
4 mg/kg sd, followed by 4 mg/kg × 10 d	6[a]	–	–	–	–	–	6
7.5 mg/kg sd	–	–	24	–	–	–	24
7 mg/kg sd, followed by 7 mg/kg × 10 d	7	–	–	–	–	–	7
10.7 mg/kg sd	–	9	–	–	–	–	9
11 mg/kg sd, followed by 11 mg/kg × 5 d	8	–	–	–	–	–	8
15 mg/kg sd	–	15	–	4	6	16	41
15 mg/kg sd, followed by 20 mg/kg sd	–	–	–	50	–	–	50
15 mg/kg sd, followed by 15 mg/kg × 3 d	7	–	–	–	–	–	7
15 mg/kg × 5 d	–	6	–	–	–	–	6
20 mg/kg sd	–	–	–	7	–	–	7

Abbreviations: sd=single dose.
Note: The highest dose (mg/kg) and/or duration (doses) are captured in this table.
[a] A subset of subjects (n=5) also received 1 mg/kg sd per protocol.

Source: Summary of Clinical Safety

cUTI Studies- Study 002 and Study 009

In the safety population of the cUTI studies, the median duration of plazomicin therapy was 5 days. 12% of plazomicin subjects received < 4 days of therapy. No subject received > 7 days of therapy. Most durations of therapy were either 4 or 7 days, corresponding with general switches to oral therapy. See the table below.

Table 41 Intravenous Study Drug Exposure—Safety Population, Studies 002 and 009)

Drug Exposure	Phase 2 (ACHN-490-002)			Phase 3 (ACHN-490-009)		Pooled Phases 2 and 3	
	Plazomicin 10 mg/kg (N=22)	Plazomicin 15 mg/kg (N=74)	Levofloxacin 750 mg (N=44)	Plazomicin 15 mg/kg (N=303)	Meropenem 1 g (N=301)	Plazomicin 15 mg/kg (N=377)	All Comparator (N=345)
Duration of IV study drug therapy (d)							
Mean	4.8	4.6	4.9	5.1	5.1	5.0	5.1
SD	0.85	0.88	0.45	1.57	1.61	1.47	1.51
Median	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Min, Max	1, 5	2, 5	2, 5	1, 7	1, 7	1, 7	1, 7
Duration category of IV study drug therapy (d), n (%)							
<4	1 (4.5)	10 (13.5)	1 (2.3)	36 (11.9)	31 (10.3)	46 (12.2)	32 (9.3)
4	0 (0.0)	2 (2.7)	0 (0.0)	108 (35.6)	112 (37.2)	110 (29.2)	112 (32.5)
5	21 (95.5)	62 (83.8)	43 (97.7)	36 (11.9)	31 (10.3)	98 (26.0)	74 (21.4)
6	0 (0.0)	0 (0.0)	0 (0.0)	23 (7.6)	22 (7.3)	23 (6.1)	22 (6.4)
7	0 (0.0)	0 (0.0)	0 (0.0)	100 (33.0)	105 (34.9)	100 (26.5)	105 (30.4)
>7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: IV=intravenous; Max=maximum; Min=minimum.

Notes: N=number of patients in the specified population; n=number of patients in the specified category. Percentages are calculated as 100 × (n/N). For the Phase 2 study, duration of IV study drug is defined as the number of active IV doses received. For the Phase 3 study, duration of IV study drug is defined as the number of IV doses of Dose A received, where the first, second, and third doses in a 24-hour dosing cycle are called Dose A, Dose B, and Dose C, respectively, and the A dose is always expected to represent active therapy for both the plazomicin and meropenem groups.

Source: ISS Table 3.1.

Source: Summary of Clinical Safety

(b) (4)

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(b) (4)

8.2.2. **Relevant characteristics of the safety population:**

cUTI studies- Study 002 and Study 009

In the case of the cUTI trials, there is a slight decrease in equitable distribution in the pooled safety database particularly when it comes to gender, race and age. However, when looking at Study 009 alone, there is better distribution of these factors with the exception of race (which was overwhelmingly white).

Table 43: Demographics and Baseline Characteristics—Safety Population, Studies 002 and 009

		Phase 2 (ACHN-490-002)			Phase 3 (ACHN-490-009)		Pooled Phases 2 and 3	
Patient Characteristic	**Statistic**	**Plazomicin 10 mg/kg (N=22)**	**Plazomicin 15 mg/kg (N=74)**	**Levofloxacin 750 mg (N=44)**	**Plazomicin 15 mg/kg (N=303)**	**Meropenem 1 g (N=301)**	**Plazomicin 15 mg/kg (N=377)**	**All Comparator (N=345)**
Infection type								
cUTI	n (%)	10 (45.5)	33 (44.6)	20 (45.5)	177 (58.4)	179 (59.5)	210 (55.7)	199 (57.7)
AP	n (%)	12 (54.5)	41 (55.4)	24 (54.5)	126 (41.6)	122 (40.5)	167 (44.3)	146 (42.3)
Geographic region								
Asia [a]	n (%)	8 (36.4)	17 (23.0)	17 (38.6)	0 (0.0)	0 (0.0)	17 (4.5)	17 (4.9)
Eastern Europe [a]	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	299 (98.7)	299 (99.3)	299 (79.3)	299 (86.7)
North America, Western Europe, Latin America [a]	n (%)	14 (63.6)	57 (77.0)	27 (61.4)	4 (1.3)	2 (0.7)	61 (16.2)	29 (8.4)
Sex								
Male	n (%)	4 (18.2)	14 (18.9)	10 (22.7)	133 (43.9)	153 (50.8)	147 (39.0)	163 (47.2)
Female	n (%)	18 (81.8)	60 (81.1)	34 (77.3)	170 (56.1)	148 (49.2)	230 (61.0)	182 (52.8)
Race [b]								
White	n (%)	6 (27.3)	12 (16.2)	5 (11.4)	301 (99.3)	300 (99.7)	313 (83.0)	305 (88.4)
Black/African American	n (%)	0 (0.0)	13 (17.6)	7 (15.9)	1 (0.3)	0 (0.0)	14 (3.7)	7 (2.0)
Asian	n (%)	8 (36.4)	17 (23.0)	18 (40.9)	0 (0.0)	0 (0.0)	17 (4.5)	18 (5.2)
American Indian/Alaska Native	n (%)	7 (31.8)	32 (43.2)	13 (29.5)	0 (0.0)	0 (0.0)	32 (8.5)	13 (3.8)
Native Hawaiian/Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other/unspecified	n (%)	1 (4.5)	0 (0.0)	1 (2.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)
Age Category (y) [c]								
18 to <65	n (%)	17 (77.3)	70 (94.6)	39 (88.6)	166 (54.8)	158 (52.5)	236 (62.6)	197 (57.1)
≥65	n (%)	5 (22.7)	4 (5.4)	5 (11.4)	137 (45.2)	143 (47.5)	141 (37.4)	148 (42.9)
≥75	n (%)	1 (4.5)	1 (1.4)	2 (4.5)	58 (19.1)	58 (19.3)	59 (15.6)	60 (17.4)
Age (y) [c]	N	22	74	44	303	301	377	345
	Mean	46.5	40.2	44.4	58.3	58.9	54.7	57.0

Patient Characteristic	Statistic	Phase 2 (ACHN-490-002) Plazomicin 10 mg/kg (N=22)	Phase 2 (ACHN-490-002) Plazomicin 15 mg/kg (N=74)	Phase 2 (ACHN-490-002) Levofloxacin 750 mg (N=44)	Phase 3 (ACHN-490-009) Plazomicin 15 mg/kg (N=303)	Phase 3 (ACHN-490-009) Meropenem 1 g (N=301)	Pooled Phases 2 and 3 Plazomicin 15 mg/kg (N=377)	Pooled Phases 2 and 3 All Comparator (N=345)
Calculated CLcr group (mL/min) [e]								
>120	n (%)	3 (13.6)	8 (10.8)	6 (13.6)	28 (9.2)	19 (6.3)	36 (9.5)	25 (7.2)
>90–120	n (%)	5 (22.7)	26 (35.1)	11 (25.0)	65 (21.5)	62 (20.6)	91 (24.1)	73 (21.2)
>60–90	n (%)	10 (45.5)	23 (31.1)	16 (36.4)	115 (38.0)	111 (36.9)	138 (36.6)	127 (36.8)
>30–60	n (%)	4 (18.2)	15 (20.3)	6 (13.6)	91 (30.0)	103 (34.2)	106 (28.1)	109 (31.6)
≤30	n (%)	0 (0.0)	0 (0.0)	2 (4.5)	1 (0.3)	3 (1.0)	1 (0.3)	5 (1.4)
Missing	n (%)	0 (0.0)	2 (2.7)	3 (6.8)	3 (1.0)	3 (1.0)	5 (1.3)	6 (1.7)

Abbreviations: AP=acute pyelonephritis; BMI=body mass index; CLcr=creatinine clearance; cUTI=complicated urinary tract infection; IBW=ideal body weight; Max=maximum; Min=minimum; TBW=total body weight.

Notes: N=number of patients in the specified population; n=number of patients in the specified category. Percentages are calculated as 100 × (n/N).

[a] Asia includes India. Eastern Europe includes Bulgaria, Czech Republic, Estonia, Georgia, Hungary, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. North America, Western Europe, Latin America includes Chile, Columbia, Mexico, Spain, and United States.

[b] In Study ACHN-490-002, patients provided their self-reported geographic ancestry from which race was derived. Patients whose geographic ancestry was Americas (e.g., Native North American/Native South American/Canadian First Peoples) were mapped to a race of American Indian/Alaska Native.

[c] Age was calculated from the date of birth and date of informed consent [integer part of (informed consent date – birth date)/365.25] or was as reported per the electronic case report form.

[d] Calculated as baseline weight (kilograms) divided by baseline height (meters squared).

[e] CLcr as estimated by the Cockcroft-Gault formula with the use of baseline serum creatinine (milligrams per deciliter) from the central laboratory and TBW, or 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. (Enrollment in Study ACHN-490-002 included patients with baseline CLcr ≥60 mL/min based on local laboratory determination of serum creatinine and TBW. For consistency across studies, baseline renal function was derived post hoc in a uniform manner for all patients.)

Source: Summary of Clinical Safety

(b) (4)

8.2.3. **Adequacy of the safety database:**

cUTI studies – Study 002 and 009

Typically, a baseline of at least 300 exposed subjects at the expected dose and duration for a proposed indication is expected. In the question of the cUTI indication, there is an acceptable numerical safety database, considering the planned usage for an unmet need. However, it should be noted that this database is not ideal. Typically, a phase 3 development program includes two adequate and well-controlled trials. Moreover, it is expected that adequate racial and geographic diversity is present so that findings can be generalized. From this perspective, the cUTI safety database does not meet those criteria.

(b) (4)

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Generally, the data submission related to safety was adequate. In particular, the applicant did convey information related to aminoglycoside class-associated effects effectively. There was some confusion regarding study drug exposure, particularly in the phase 1 studies, but these concerns were relatively minor and were addressed.

8.3.2. Categorization of Adverse Events

The categorization and assessment of adverse events by the applicant was adequate. MedDRA version 19.0 and CTCAE version 4.0 were used to categorize events. AE monitoring was typical for a phase 3 clinical trial. Importantly, the applicant did try to assess adverse events related to nephrotoxicity and ototoxicity- toxicities of particular interest with aminoglycosides See section 8.5 below).

8.3.3. Routine Clinical Tests

The safety assessments, which included typical laboratory measurements, vital signs measurements, physical examinations, etc. were appropriate and as expected for a phase 3 clinical development program.

8.4. Safety Results

8.4.1. Deaths

cUTI studies – Studies 009 and 002

There were no deaths in the meropenem arm and only one death in the plazomicin arm. This death involved a 63-year-old White woman who was admitted for pyelonephritis. She received one dose of plazomicin and then was discontinued from study drug due to acute kidney injury (switched to piperacillin-tazobactam and then meropenem). At the time of discontinuation, she was found to have metastatic uterine cancer with possible involvement of the lungs and liver. She continued to have worsening renal function (Day 7 creatinine 8.6 mg/dL) and eventually needed hemodialysis. She underwent six sessions of hemodialysis but on Day 17 refused further sessions due to difficulties in tolerating the procedure. On Day 18 she died due to asystole and bradycardia. The cause of death is unlikely study drug related though a relationship cannot be fully excluded; acute kidney injury may have partially been related to study drug, and worsening renal failure could have led to electrolyte disturbances that could have triggered arrhythmias and death.

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(b) (4)

Serious Adverse Events.

cUTI- Studies 009 and 002

The rate of SAEs was low and comparable between study arms. In study 009, five subjects in each arm had Serious Adverse Events (SAEs). In the plazomicin arm, the SAEs were acute kidney injury and metastatic neoplasm (in one subject), acute kidney injury, pneumonia, urosepsis, and calculus urinary. Review of the narratives of each of the five plazomicin cases revealed only possible relatedness of both acute kidney injury cases. In both cases, decreases in creatinine clearance were noted after only one dose of plazomicin. One subject eventually required hemodialysis and passed away, while another had recovery of renal function. Though other nephrotoxic confounders were present, given what is known about the nephrotoxic potential of aminoglycosides, a relationship between plazomicin and these acute kidney injury events is certainly plausible.

Table 45 Incidence of Serious Adverse Events by Preferred Term—Safety Population, Studies 002 and 009

		Phase 2 (ACHN-490-002)		Phase 3 (ACHN-490-009)		Pooled Phases 2 and 3	
Preferred Term	Plazomicin 10 mg/kg (N=22) n (%)	Plazomicin 15 mg/kg (N=74) n (%)	Levofloxacin 750 mg (N=44) n (%)	Plazomicin 15 mg/kg (N=303) n (%)	Meropenem 1 g (N=301) n (%)	Plazomicin 15 mg/kg (N=377) n (%)	All Comparator (N=345) n (%)
Patients with any SAE	0 (0.0)	1 (1.4)	2 (4.5)	5 (1.7)	5 (1.7)	6 (1.6)	7 (2.0)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	0 (0.0)
Abortion spontaneous	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Metastatic neoplasm [a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Clostridium difficile colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Orchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Pyelonephritis acute	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Seizure	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)

Abbreviations: SAE=serious adverse event.

Notes: N=number of patients in the Safety Population; n=number of patients in the specified category. Percentages are calculated as 100 × (n/N). Adverse event verbatim terms were coded with the use of Medical Dictionary for Regulatory Activities version 19.0. Patients reporting a particular adverse event (Preferred Term) more than once are counted only once by Preferred Term and System Organ Class.

[a] This Preferred Term corresponds to a single fatal event in pooled Studies ACHN-490-002 and ACHN-490-009, described in Section 3.1.1.3. A full patient narrative is provided in Study ACHN-490-009 Appendix 16.4.1.

Source: ISS Table 5.2.1.1.

Source: Summary of Clinical Safety

(b) (4)

8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

cUTI Studies- Studies 009 and 002

The rate of discontinuations was low and comparable between study arms. There were 10 subjects total between the plazomicin arms that had an AE leading to discontinuation. The vast majority of events were related to renal injury; in study 009 all the discontinuations were related to renal injury. The applicant noted that the study 009 protocol required discontinuation of IV study drug in patients with two successive creatinine clearance

measurements <30 mL/min during IV treatment. Of the 6 renal discontinuations in the plazomicin arm, four of the subjects started with baseline creatinine clearance between 30-40 mL/min. See the discussion of nephrotoxicity in section 8.5

Table 46: Adverse Events Leading to Premature Discontinuation of Intravenous Study Drug—Safety Population, Studies 002 and 009

	Phase 2 (ACHN-490-002)			Phase 3 (ACHN-490-009)		Pooled Phases 2 and 3	
Preferred Term	Plazomicin 10 mg/kg (N=22) n (%)	Plazomicin 15 mg/kg (N=74) n (%)	Levofloxacin 750 mg (N=44) n (%)	Plazomicin 15 mg/kg (N=303) n (%)	Meropenem 1 g (N=301) n (%)	Plazomicin 15 mg/kg (N=377) n (%)	All Comparator (N=345) n (%)
Patients with any TEAE that led to premature discontinuation of IV study drug	0 (0.0)	4 (5.4)	1 (2.3)	6 (2.0)	6 (2.0)	10 (2.7)	7 (2.0)
Acute kidney injury [a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	0 (0.0)
Dizziness	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Azotaemia [a]	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Blood creatinine increased [a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Chronic kidney disease [a,b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Hypotension	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Metastatic neoplasm [c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Metastatic uterine cancer [c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Renal failure [a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Renal impairment [a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Type 2 diabetes mellitus	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Vertigo	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Creatinine renal clearance decreased [a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Liver function test increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Seizure	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Abbreviations: IV=intravenous; TEAE=treatment-emergent adverse event.

Notes: N=number of patients in the Safety Population; n=number of patients in the specified category. Percentages are calculated as 100 × (n/N). Adverse event verbatim terms were coded with the use of Medical Dictionary for Regulatory Activities version 19.0.

Note: Patients reporting a particular adverse event (Preferred Term) more than once are counted only once by Preferred Term and System Organ Class.

[a] Treatment-emergent adverse events associated with renal function.

[b] Verbatim term was worsening of chronic renal failure; the patient (Patient (b) (6)) had a medical history of chronic kidney disease (verbatim: chronic renal failure).

[c] Both Preferred Terms refer to a single fatal event in pooled Studies ACHN-490-002 and ACHN-490-009; described in Section 3.1.1.3. A full patient narrative is provided in CSR ACHN-490-009, Appendix 16.4.1.

Source: ISS Table 5.1.1.

Source: Summary of Clinical Safety

(b) (4)

8.4.3. Significant Adverse Events

cUTI studies – Studies 009 and 002

In Study 009, nine subjects (3.0%) in the plazomicin arm and 14 subjects (4.7%) in the meropenem arm had Grade ≥ 3 TEAEs. In the plazomicin arm, there was some clustering of such AEs around renal injury, which is not surprising given the nephrotoxic ability of aminoglycosides. In Study 002, two plazomicin subjects had severe events; in one case the patient experienced hypotension and had plazomicin discontinued, however it is unclear whether the hypotensive episode was more related to the plazomicin infusion or placebo infusion (episode happened 30 minutes after placebo infusion).

(b) (4)

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

cUTI trials- Study 009

There was little difference in the frequency of TEAEs between treatment groups in Study 009. A total of 59 (19.5%) and 65 (21.6%) subjects in the plazomicin and meropenem arms, respectively were noted to have TEAEs. In looking at TEAEs that occurred in at least 1% of subjects in either treatment group, frequencies of individual PTs were comparable between both arms and not atypical for a clinical trial. Diarrhea, hypertension, headache, nausea, and vomiting were the most frequent AEs for plazomicin, though they occurred at a level comparable to that of the meropenem arm. It should be noted that TEAEs associated with kidney injury were more concentrated in the plazomicin arm.

Table 47: Treatment-Emergent Adverse Events Reported in at Least 1% of Patients in Either Treatment Group by PT (by Decreasing Frequency in Plazomicin Group) - Safety Population, Study 009

Preferred Term	Plazomicin (N=303) n (%)	Meropenem (N=301) n (%)	All Patients (N=604) n (%)
Patients with any TEAE	59 (19.5)	65 (21.6)	124 (20.5)
Hypertension	7 (2.3)	7 (2.3)	14 (2.3)
Headache	4 (1.3)	9 (3.0)	13 (2.2)
Diarrhoea	7 (2.3)	5 (1.7)	12 (2.0)
Nausea	4 (1.3)	4 (1.3)	8 (1.3)
Vomiting	4 (1.3)	3 (1.0)	7 (1.2)
Anaemia	1 (0.3)	4 (1.3)	5 (0.8)
Dizziness	2 (0.7)	3 (1.0)	5 (0.8)
Hypotension	3 (1.0)	2 (0.7)	5 (0.8)

N=number of patients in the Safety Population; n=number of patients in the specified category; PT=preferred term; TEAE=treatment-emergent adverse event. Source: Study 009, Clinical Study Report

Only 18 (5.9%) and 16 (5.3%) subjects in the plazomicin and meropenem arms, respectively, were noted to have TEAEs thought to be possibly related to study drug. In terms of such TEAEs, in the plazomicin arm they were concentrated within a few categories- typical adverse events (diarrhea, headache, etc.), renal injury (blood creatinine increased, renal failure, etc.) and possible allergic /local reactions (injection site phlebitis and erythema, papular rash, etc.). Related nephrotoxic and ototoxic events appeared to occur with more frequency in the plazomicin arm. Similar findings were noted in Study 002.

Table 48 Incidence of Treatment-Emergent Adverse Events Related to IV Study Drug by PT (By Decreasing Overall Incidence) - Safety Population, Study 009

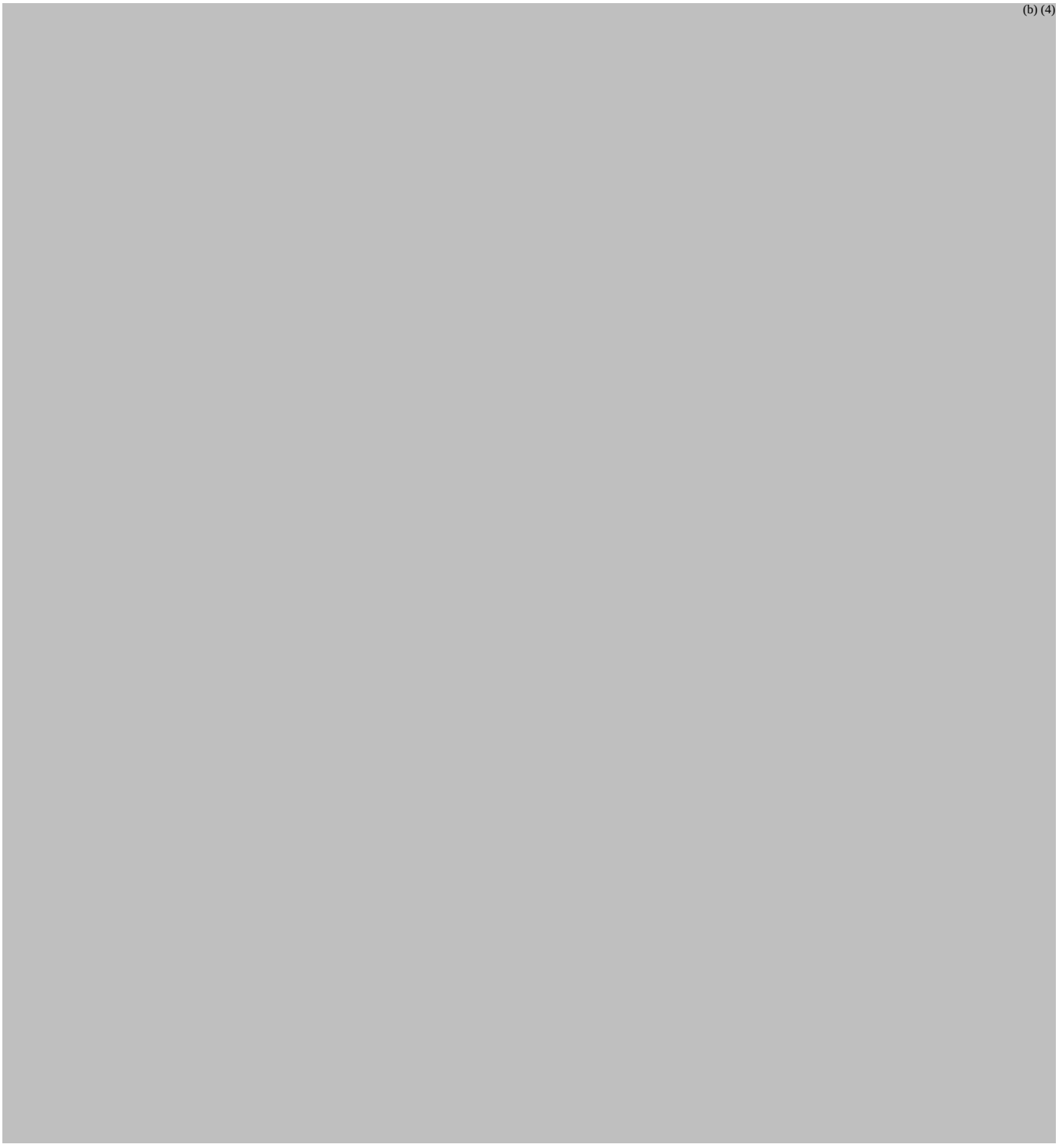
Preferred Term	Plazomicin (N=303) n (%)	Meropenem (N=301) n (%)	All Patients (N=604) n (%)
Patients with at least one TEAE related to IV study drug	18 (5.9)	16 (5.3)	34 (5.6)
Diarrhoea	3 (1.0)	4 (1.3)	7 (1.2)
Headache	2 (0.7)	2 (0.7)	4 (0.7)
Nausea	1 (0.3)	1 (0.3)	2 (0.3)
Vomiting	1 (0.3)	1 (0.3)	2 (0.3)
Blood creatinine increased	2 (0.7)	0 (0)	2 (0.3)
Transaminases increased	0 (0)	2 (0.7)	2 (0.3)
Renal failure	1 (0.3)	1 (0.3)	2 (0.3)
Hypoacusis	1 (0.3)	0 (0)	1 (0.2)
Abdominal pain upper	0 (0)	1 (0.3)	1 (0.2)
Dry mouth	0 (0)	1 (0.3)	1 (0.2)
Stomatitis	1 (0.3)	0 (0)	1 (0.2)
Chest discomfort	0 (0)	1 (0.3)	1 (0.2)
Feeling abnormal	0 (0)	1 (0.3)	1 (0.2)
Infusion site phlebitis	1 (0.3)	0 (0)	1 (0.2)
Injection site erythema	1 (0.3)	0 (0)	1 (0.2)
Pyrexia	0 (0)	1 (0.3)	1 (0.2)
Candiduria	0 (0)	1 (0.3)	1 (0.2)
Vulvovaginal candidiasis	0 (0)	1 (0.3)	1 (0.2)
Creatinine renal clearance decreased	1 (0.3)	0 (0)	1 (0.2)
Hepatic enzyme increased	0 (0)	1 (0.3)	1 (0.2)
Acute kidney injury	1 (0.3)	0 (0)	1 (0.2)
Renal impairment	1 (0.3)	0 (0)	1 (0.2)

Preferred Term	Plazomicin (N=303) n (%)	Meropenem (N=301) n (%)	All Patients (N=604) n (%)
Vulvovaginal pruritus	0 (0)	1 (0.3)	1 (0.2)
Dyspnoea	1 (0.3)	0 (0)	1 (0.2)
Dermatitis allergic	0 (0)	1 (0.3)	1 (0.2)
Rash	0 (0)	1 (0.3)	1 (0.2)
Rash papular	1 (0.3)	0 (0)	1 (0.2)
Hypertension	1 (0.3)	0 (0)	1 (0.2)

IV=intravenous; N=number of patients in the Safety Population; n=number of patients in the specified category; PT=preferred term; TEAE=treatment-emergent adverse event.
Notes: Version 19.0 of Medical Dictionary for Regulatory Activities was used to code adverse events. Percentages are calculated as 100×(n/N). Patients reporting a particular adverse event (PT) more than once are counted only once by PT, and at the strongest reported relationship.
Source: Table 14.3.1.4.

Source: Study 009, Clinical Study Report

(b) (4)



8.4.5. **Laboratory Findings**

Hematology

cUTI- Study 009

In study 009, there were 2 AEs coded to anemia in the plazomicin arm. None of these AEs were considered related to the study drug. As regards changes in typical hematology parameters in study 009, increases in at least 2 Grades (by CTCAE criteria) were few and comparable between treatment arms; missing data between the two arms was also similar. When looking at median changes from baseline to the EOIV, TOC, and LFU visits in WBC, neutrophils, hemoglobin (hgb), and platelets, changes were clinically insignificant and comparable between arms and generally did not have extremes that tended in one direction or another.

Table 50 Patients with at Least a Two-Grade Increase from Baseline in CTCAE Grade by Hematology Central Laboratory Parameter - Safety Population, Study 009

Laboratory Parameter	Plazomicin (N=303) n/N1 (%)	Meropenem (N=301) n/N1 (%)
White blood cell		
Increased values	0/291 (0.0)	0/290 (0.0)
Decreased values	2/291 (0.7)	5/290 (1.7)
Absolute neutrophil count		
Decreased values	4/290 (1.4)	7/289 (2.4)
Hemoglobin		
Decreased values	3/291 (1.0)	4/290 (1.4)
Platelet count		
Decreased values	0/281 (0.0)	1/276 (0.4)

CTCAE=Common Terminology Criteria for Adverse Events (version 4.0); N=number of patients in the Safety Population; N1=number of patients with a baseline and postbaseline value specified for the specified laboratory parameter; n=number of patients in the specified category.
Notes: Percentages are calculated as 100×(n/N1). Baseline is defined as the last laboratory measurement from the central laboratory prior to the first dose of study drug administered.
Source: Table 14.3.4.4.1.

Source: Study 009, Clinical Study Report

(b) (4)

Serum Chemistry/Liver Function

cUTI- Study 009

In Study 009, there were 4 AEs coded to LFT elevations and 1 AE coded to hypokalemia in the plazomicin arm. All were considered not related to study drug. As regards blood chemistry, subjects with at least two grade increases were generally few and similar between both treatment arms though such increases in potassium and serum creatinine occurred slightly more in the plazomicin arm. In the case of potassium, there were 16 (5.8%) such subjects in the plazomicin arm versus 9 (3.2%) in the meropenem arm. However, 6.1mmol/L was the highest potassium level recorded in these 16 plazomicin subjects, and the highest change recorded in these subjects was an increase of 1.9 mmol/L from baseline. In the plazomicin arm, median changes in blood chemistry parameters from baseline to EOIV, TOC, and LFU visits were clinically insignificant and comparable in both arms.

Table 51 Patients with at Least a Two-Grade Increase from Baseline in CTCAE Grade by Chemistry Central Laboratory Parameter - Safety Population, Study 009

Laboratory Parameter	Plazomicin (N=303) n/N1 (%)	Meropenem (N=301) n/N1 (%)
Sodium		
Increased values	0/299 (0.0)	4/297 (1.3)
Decreased values	4/299 (1.3)	2/297 (0.7)
Potassium		
Increased values	16/276 (5.8)	9/283 (3.2)
Decreased values	1/276 (0.4)	2/283 (0.7)
Calcium		
Increased values	3/299 (1.0)	0/297 (0.0)
Decreased values	5/299 (1.7)	8/297 (2.7)
Magnesium		
Increased values	0/299 (0.0)	0/297 (0.0)
Decreased values	0/299 (0.0)	0/297 (0.0)
Creatinine		
Increased values	7/300 (2.3)	2/297 (0.7)
Albumin		
Deceased values	1/299 (0.3)	3/297 (1.0)
Total bilirubin		
Increased values	1/299 (0.3)	2/297 (0.7)
Alkaline phosphatase		
Increased values	2/297 (0.7)	1/295 (0.3)
Alanine transaminase (SGPT)		
Increased values	1/299 (0.3)	1/297 (0.3)
Aspartate transaminase (SGOT)		
Increased values	1/275 (0.4)	1/283 (0.4)

CTCAE=Common Terminology Criteria for Adverse Events (version 4.0); N=Number of patients in the Safety Population; N1=Number of patients with a baseline and postbaseline value specified for the specified laboratory parameter; n=Number of patients in the specified category; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvate transaminase. Notes: Percentages are calculated as 100×(n/N1). Baseline is defined as the last laboratory measurement from the central laboratory prior to the first dose of study drug administered. Source: Study 009, Clinical Study Report

In Study 009, LFT elevations were minimal in both arms. At the EOIV visit, one plazomicin subject had an ALT > 3X ULN and at the TOC visit, one plazomicin subject had AST > 5 X ULN. For the first subject, ALT increased from 17 to 167 at the EOIV visit but then decreased back to normal in the ensuing visits; the event was considered as not related to study drug and was nonserious; the patient was on some slightly hepatotoxic concomitant medications as well

(calcium channel blocker, nsaid, etc.). In the second case, AST increased from 11 to 314 at the TOC visit, however this was 13 days after stopping plazomicin. This patient only got a single dose of plazomicin because of deterioration of renal function; the patient had AST of 14 at the EOIV visit. No patients in the plazomicin group met Hy's Law.

(b) (4)

Vital Signs

cUTI- Study 009

[In study 009, vital signs (including respiratory rate, heart rate, systolic/diastolic blood pressure, and temperature) were measured roughly 15 minutes prior to and after study drug infusion and during follow up (TOC/LFU) visits (if they occurred in person). There were no clinically significant mean changes from baseline to EOIV, TOC, and LFU visits in vital signs for both arms; mean changes were comparable between arms. In terms of potentially clinically significant (prespecified) postbaseline values, there was a slight trend toward increased incidences of low SBP and DBP in the plazomicin arm, however this trend was not necessarily seen in conjunction with the EOIV, TOC or LFU visits. Also, a trend for decreased temperature was also seen in the plazomicin arm overall postbaseline and at the EOIV, TOC, and LFU visits. Three plazomicin subjects actually low SBPs that were PCS that were associated with the plazomicin infusion. In one subject the drop was 20mm Hg only and occurred with placebo infusions as well. In another case, the incident occurred on Day 1 only, was associated with a 20 mm Hg drop, and also occurred with placebo infusion. In a third case, this hypotension occurred in conjunction with suspected urosepsis and stent placement for hydronephrosis and was not seen at the EOIV therapy visit. It is notable that only 4 AEs related to hypotension were seen in the plazomicin arm and none were temporally related to plazomicin infusion or thought to be related to study drug. All other vital signs saw comparable incidences of PCS postbaseline values.

(b) (4)

(b) (4)

Study 003

It should be noted that in the phase 1 study- Study 003 (Lung penetration study), 5 subjects who received a 15 mg/kg dose had episodes of hypotension soon after the plazomicin infusion was finished. Though these episodes required normal saline in some cases, they generally resolved within a few minutes to hours. Of importance, is that all of these subjects received a 10 minute plazomicin infusion. Subsequent to this study, all studies used a 30-minute infusion time, and no events of decreased blood pressure temporally associated with plazomicin infusions were subsequently observed in the subsequent completed Phase 1 studies.

8.4.6. **Electrocardiograms (ECGs)**

[In Study 004, ECGs were performed pre-dose and 10-20 minutes after study drug infusion. In general, ECGs remained stable over the course of drug infusion. In study 002, ECGs were performed pre-and post Day 1 dose and as needed at STFU. No clinically significant ECG changes were noted (b) (4) No ECGs were performed in Study 009.]

8.4.7. **QT**

[The applicant conducted a TQT study in which 15mg/kg and 20mg/kg doses of plazomicin were compared to a positive control (moxifloxacin) as well as placebo in 56 healthy subjects. This study was evaluated by the Agency's Interdisciplinay Review Team for QT studies. This committee concluded that the study was adequate and that at the doses tested plazomicin did not prolong the QTc interval to any clinically relevant extent.]

8.4.8. **Immunogenicity**

[Not Applicable]

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Nephrotoxicity

[Aminoglycosides as a class have long been associated with nephrotoxicity, particularly with increased duration of dose/larger dose amounts. The applicant attempted to quantify the risk/degree of nephrotoxicity with a combination of assessments, including recording of nephrotoxic adverse events and following/categorizing changes in serum creatinine levels.

cUTI Study 009

In study 009, there were slightly more TEAEs associated with nephrotoxicity that occurred in the plazomicin arm relative to the meropenem arm (11 cases (3.6%) in the plazomicin arm and 4 cases (1.3%) in the meropenem arm). In the plazomicin arm 7/11 (63.6%) cases involved were mild to moderate in severity and 6/11 (54.5%) cases required discontinuation of IV plazomicin (primarily due to protocol mandates as explained earlier). Interestingly, in the plazomicin arm all such TEAEs occurred in patients with Creatinine Clearance < 90 ml/min.). There were two subjects who had a nephrotoxic serious adverse event, only one of whom's renal function recovered after discontinuation of plazomicin IV. Of the 11 plazomicin associated- nephrotoxic cases, only 2 were considered as not recovered by end of study.

The applicant also evaluated increases (at any time postbaseline) in serum creatinine ≥ 0.5mg/dl. These changes happened with more frequency in the plazomicin arm (7.0%; 21/300) than the meropenem arm (4.0%12/297); a slightly increased trend was also noted for the plazomicin arm when evaluating increases ≥ 1.0mg/dl, 2.0mg/dl, 3.0mg/dl, or 4.0 mg/dl. In general, though, increases were mild. Only 1.7% (5/300) and 1.0% (3/297) of patients had increases of ≥1.0 mg/dL in the plazomicin and meropenem groups, respectively. As expected, not all increases occurred while on IV therapy; increases could manifest post study drug administration as well.

Table 52 Patients With Any Serum Creatinine Increase of 0.5 mg/dL or Greater Above Baseline—Safety Population, Studies 002, (b) (4) and 009

	Study 002 cUTI		Study 009 cUTI		(b) (4)
Serum Creatinine Increase mg/dL	Plazomicin N=74, N1=72 n/N1 (%)	Levofloxacin N=44, N1=41 n/N1 (%)	Plazomicin N=303; N1=300 n/N1 (%)	Meropenem N=301; N1=297 n/N1 (%)	
≥0.5	4 (5.6%)	1 (2.4%)	21 (7.0%)	12 (4.0%)	
≥1.0	0	0	5 (1.7%)	3 (1.0%)	
≥2.0	0	0	2 (0.7%)	0	
≥3.5	0	0	1 (0.3%)	0	
≥4.0	0	0	1 (0.3%)	0	

N1=number of patients with a baseline value and a value at the specified time point for serum creatinine from the central laboratory
Source: Adapted from Summary of Clinical Safety

The applicant also evaluated changes in serum creatinine relative to RIFLE criteria. In general, post-baseline changes were increased in the "Risk" category but comparable relative to meropenem for all other categories

Table 53 RIFLE Classification of Renal Injury, Safety Population, Studies 002, (b) (4) and 009

	Study 002 cUTI		Study 009 cUTI		(b) (4)
RIFLE Classification Worst Postbaseline	Plazomicin N=74, N1=72 n/N1 (%)	Levofloxacin N=44, N1=41 n/N1 (%)	Plazomicin N=303; N1=300 n/N1 (%)	Meropenem N=301; N1=297 n/N1 (%)	
Risk	8 (11.1%)	2 (4.9%)	16 (5.3%)	9 (3.0%)	
Injury	0	1(2.4%)	3 (1.0%)	3 (1.0%)	
Failure	0	0	2 (0.7%)	2 (0.7%)	
Loss of Function	0	0	0	0	
ESRD	0	0	0	0	

N1=number of patients with a baseline value and a value at the specified time point for serum creatinine from the central laboratory
Source: Adapted from Summary of Clinical Safety

The applicant noted that most cases of creatinine increase recovered (recovery being defined as a visit creatinine value < 0.5 mg/dl above baseline value). The table below shows that recovery from creatinine increases that occurred while on IV therapy was common.

Table 54 Renal Recovery for Patients With Any Serum Creatinine Increase of 0.5 mg/dL or Greater Above Baseline While on Intravenous Study Drug—Safety Population, Studies 002 and 009)

	Phase 2 (ACHN-490-002)			Phase 3 (ACHN-490-009)		Pooled Phases 2 and 3	
	Plazomicin 10 mg/kg (N=22)	Plazomicin 15 mg/kg (N=74)	Levofloxacin 750 mg (N=44)	Plazomicin 15 mg/kg (N=303)	Meropenem 1 g (N=301)	Plazomicin 15 mg/kg (N=377)	All Comparator (N=345)
Serum creatinine increase ≥0.5 mg/dL above baseline with onset during IV therapy, N2/N1 (%)	0/22 (0.0)	3/72 (4.2)	0/41 (0.0)	11/300 (3.7)	9/297 (3.0)	14/372 (3.8)	9/338 (2.7)
Full recovery at EOIV visit, n/N2	0/0	2/3	0/0	6/11	4/9	8/14	4/9
Full recovery at last follow-up visit, n/N2	0/0	2/3	0/0	9/11	9/9	11/14	9/9

Abbreviations: EOIV=end of intravenous therapy; IV=intravenous.

Notes: N=number of patients in the specified population; N1=number of patients with a baseline and postbaseline value for serum creatinine from the central laboratory; N2=number of patients with serum creatinine increase ≥0.5 mg/dL above baseline with onset during IV therapy; n=number of patients in the specified category. A patient is considered to have full recovery at the EOIV visit or last follow-up visit if the serum creatinine value at the scheduled EOIV visit or last postbaseline serum creatinine value, respectively, is <0.5 mg/dL above their baseline value.

Source: Summary of Clinical Safety

Importantly, the applicant noted that increases in serum creatinine were directly associated with decreasing renal function and increased duration of therapy. The following table shows incidences of serum creatinine increases in Study 009 in relation to baseline renal function.

Table 55 Patients with any >= 0.5 mg/dL Increase from Baseline in Serum Creatinine by Baseline CLcr Category - Safety Population, Study 009

Protocol: ACHN-490-009

Table 14.3.4.7.2

Patients with any >= 0.5 mg/dL Increase from Baseline in Serum Creatinine by Baseline CLcr Category - Safety Population

	Plazomicin			Meropenem		
	<=60 mL/min (N=92) n/N1 (%)	>60-90 mL/min (N=115) n/N1 (%)	>90 mL/min (N=93) n/N1 (%)	<=60 mL/min (N=106) n/N1 (%)	>60-90 mL/min (N=111) n/N1 (%)	>90 mL/min (N=81) n/N1 (%)
Patients with any Increase from Baseline in Serum Creatinine of:						
>= 0.5 mg/dL	14/92 (15.2)	6/115 (5.2)	1/93 (1.1)	4/106 (3.8)	5/111 (4.5)	3/80 (3.8)
>= 1.0 mg/dL	3/92 (3.3)	2/115 (1.7)	0/93 (0)	2/106 (1.9)	0/111 (0)	1/80 (1.3)
>= 1.5 mg/dL	2/92 (2.2)	1/115 (0.9)	0/93 (0)	1/106 (0.9)	0/111 (0)	0/80 (0)
>= 2.0 mg/dL	1/92 (1.1)	1/115 (0.9)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)
>= 3.0 mg/dL	1/92 (1.1)	0/115 (0)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)
>= 4.0 mg/dL	1/92 (1.1)	0/115 (0)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)
Patients with any Increase from Baseline in Serum Creatinine while on IV Study Drug of [1]:						
>= 0.5 mg/dL	5/92 (5.4)	5/115 (4.3)	1/93 (1.1)	4/106 (3.8)	4/111 (3.6)	1/80 (1.3)
>= 1.0 mg/dL	1/92 (1.1)	1/115 (0.9)	0/93 (0)	1/106 (0.9)	0/111 (0)	0/80 (0)
>= 1.5 mg/dL	0/92 (0)	1/115 (0.9)	0/93 (0)	1/106 (0.9)	0/111 (0)	0/80 (0)
>= 2.0 mg/dL	0/92 (0)	1/115 (0.9)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)
>= 3.0 mg/dL	0/92 (0)	0/115 (0)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)
>= 4.0 mg/dL	0/92 (0)	0/115 (0)	0/93 (0)	0/106 (0)	0/111 (0)	0/80 (0)

Source: Study 009, Clinical Study Report

(b) (4)

8.5.2. **Ototoxicity**

Aminoglycosides have been associated with permanent ototoxicity, manifested as both audiometric losses as well as vestibulotoxicity. In the applicant's clinical development plan, ototoxicity was evaluated in the phase 1 trials and cUTI trials. (b) (4)

cUTI- Study 009

In Study 009, ototoxicity could not practically be assessed through typical measurements such as audiometric tests or Romberg testing because of the hospitalized status of most of the

subjects. Thus, the applicant attempted to gauge ototoxicity through the use of several inventories, including the Hearing Handicap Inventory Assessment (HHIA), the Tinnitus Handicap Inventory (THI), and Dizziness Handicap Inventory.

Per the applicant, hearing was assessed using the HHIA at baseline, EOIV and LFU. Patients were asked if they had a history of hearing problems or if they currently had a problem with hearing. If "yes", the HHIA was administered to determine how much the hearing problem impacted the patient's daily activities. The HHIA consists of 25 questions, which are answered as yes, sometimes, or no. A total score is derived as follows: Total HHIA score = (number of 'Yes' responses ×4) + (number of 'Sometimes' responses ×2). Patients indicating "no" in response to the initial screening question were assigned a score of 0 for that visit. Patients who answered "yes" to the initial screening question, but did not answer all 25 questions, were considered to have missing data and were excluded from the analysis for that visit. The total score was also categorized into perceived hearing handicap categories as follows:

Figure 5: HHIA Categorization, Study 009

Score	Description
0–16	No handicap
18–42	Mild to moderate handicap
≥44	Significant handicap

Source: Study 009, Clinical Study Report

Tinnitus was assessed using the THI at baseline, EOIV, and LFU. Patients were asked if they had a history of hearing any noises such as ringing or buzzing in their ears or currently had noises such as ringing or buzzing in their ears. If "yes", the THI was administered to determine how much the tinnitus impacted the patient's daily activities. The THI consists of 25 questions which are answered as yes, sometimes, or no. A total score is derived as follows: Total THI score = (number of 'Yes' responses ×4) + (number of 'Sometimes' responses ×2). Patients indicating "no" in response to the initial screening question were assigned a score of 0 for that visit. Patients who answered "yes" to the initial screening question, but did not answer all 25 questions were considered to have missing data and were excluded from the analysis for that visit. The total score was also categorized into perceived tinnitus handicap categories as follows:

Figure 6: THI Categorization, Study 009

Score	Description
0–16	Slight or no handicap (Only heard in quiet environments)
18–36	Mild handicap (Easily masked by environmental sounds and easily forgotten with activities)
38–56	Moderate handicap (Noticed in presence of background noise, although daily activities can still be performed)
58–76	Severe handicap (Almost always heard, leads to disturbed sleep patterns and can interfere with daily activities)
78–100	Catastrophic handicap (Always heard, disturbed sleep patterns, difficulty with any activities)

Source: Study 009, Clinical Study Report

Dizziness was assessed using the DHI at baseline, EOIV and LFU. Patients were asked if they had a history of dizziness or problems with their balance or were currently experiencing dizziness or problems with their balance. If "yes", the DHI was administered to determine how much the dizziness impacted the patient's daily activities. The DHI consists of 25 questions which are answered as yes, sometimes, or no. A total score is derived as follows:
Total DHI score = (number of 'Yes' responses ×4) + (number of 'Sometimes' responses ×2)
Patients indicating "no" in response to the initial screening question were assigned a score of 0 for that visit. Patients who answered "yes" to the initial screening question, but did not answer all 25 questions, were considered to have missing data and were excluded from the analysis for that visit. The total score was also categorized into perceived dizziness handicap categories as follows:

Figure 7: DHI Categorization, Study 009

Score	Description
0–14	No handicap
16–34	Mild handicap
36–52	Moderate handicap
≥54	Severe handicap

Source: Study 009, Clinical Study Report

The HHIA criteria for referral to an audiologist required a 12-point increase from baseline accompanied by an associated shift in handicap category. The THI criteria for referral to an ENT required a 20-point increase from baseline accompanied by an associated shift in handicap category. The DHI criteria for referral to an ENT required an 18-point increase from baseline accompanied by an associated shift in handicap category.

For the HHIA, only one plazomicin subject had a shift in handicap category. However, the shift was mild (a two-point change to move from no handicap at baseline to mild handicap at EOIV), and then reverted to baseline by the LFU visit. Only one subject in the meropenem arm had a handicap change.

A single patient in the plazomicin group experienced a one-category handicap increase in THI at the LFU visit. The subject had pre-existing tinnitus in both ears and experienced a one-category shift in THI at the LFU visit (from 22 [mild handicap] at screening and EOIV to a score of 40 [moderate handicap] at the LFU visit). This change did not meet the criteria for referral to an audiologist and was not reported as a TEAE. She received four doses of plazomicin.

One female subject experienced a one handicap category increase in DHI. The DHI score at EOIV was 20 (Mild Handicap), increased from the baseline score of 0 (No Handicap). Although the change at EOIV met protocol-specified criteria for otolaryngology referral, the DHI score returned to 0 at the LFU visit, and the patient was not referred. The subject had a TEAE of dizziness on Study Day 3 but recovered on the same calendar day following treatment with intramuscular dexamethasone. The dizziness was considered moderate and unrelated to blinded IV study drug. The patient's scores for the HHIA and THI were 0 at all three visits.

There was one plazomicin subject who reported a TEAE of hypoacusis. This involved an 83 y/o male who received four doses of plazomicin. At screening and at the end-of-intravenous-therapy, the subject did not report any prior or current problems with dizziness or balance,

ringing or buzzing in ears, or hearing. The patient's Dizziness Handicap Inventory, Tinnitus Handicap Inventory, and Hearing Handicap Inventory for Adult (HHIA) scores were each 0 for these visits. Three days following the test-of-cure visit, an AE of Grade 1 hypoacusis (verbatim: decrease of hearing; continuous course) was reported. At the late follow-up visit (Study Day 28), the patient reported hearing problems affecting both ears, and the HHIA score was 8 on a scale of 0 to 100. This HHIA score is categorized as "No handicap"; thus, this score change did not meet the protocol-specified criteria for an audiologist referral. At an unscheduled visit 3 months later, the AE of Grade 1 hypoacusis was reported as fully recovered/resolved. A relationship with study drug cannot be ruled out but given the short course of aminoglycoside treatment and full recovery, it's unlikely an association exists.

Phase 1 Studies

In the phase 1 studies, five subjects had reports of transient tinnitus following a single dose of plazomicin (one of the five subjects also reported transient nystagmus). Another subject had an abnormal vestibular function test.

In the phase 2 and 3 cUTI trials, there were three reports of adverse events associated with cochlear or vestibular function. These were reports of hypoacusis, tinnitus, and vertigo. These events were somewhat atypical for aminoglycoside-related ototoxicity in that the hypoacusis and vertigo events resolved and the tinnitus event was unilateral.

Pure tone audiometry (PTA) was performed in phase 1 and phase 2 studies. These procedures varied by study in terms of the frequencies measured, duration of follow up, etc. The applicant conducted an independent expert analysis of the PTA data. Their findings are reported as below.

"*The criteria applied to individual Phase 1 and 2 studies for interpretation of potentially clinically meaningful changes in audiometry findings differed, rendering an overall assessment of this data challenging. As such, an external expert assessment of all Phase 1 and 2 audiometry data was conducted in order to apply widely accepted, uniform criteria for meaningful change in hearing thresholds as defined by the American Speech-Language-Hearing Association (ASHA; 1994) and to confirm the findings from individual Phase 1 and 2 studies.*

Based on this expert review, of the 203 plazomicin-exposed and 56 comparator-exposed adults (levofloxacin, moxifloxacin, and/or placebo only) with PTA data across 4 Phase 1 studies and 1 Phase 2 study, 182/203 (89.7%) and 49/56 (87.5%), respectively, had evaluable data. Four of the 182 plazomicin-exposed individuals (2.2%) and 1 of the 49 comparator-exposed individuals (2.0%) were assessed as having findings for which study drug-related ototoxicity could not be definitively excluded. Overall, the expert review concluded that there were no widespread signs of study drug-related ototoxicity as determined by PTA across Phase 1 and 2 studies. Given the known ototoxic potential of aminoglycosides, the small number of individuals with longer-term

follow-up (e.g., at 6 months following treatment) as recommended by ASHA, and findings in a small number of individuals for which ototoxicity could not be definitively excluded, ototoxicity remains an identified risk for plazomicin."

Also in the phase 1 studies, a mix of electronystagmography, modified Romberg testing, and Dynamic Visual Acuity testing was performed; modified Romberg testing was also performed in the phase 2 study. Electronystamography (ENG) data was submitted by the applicant to outside experts for evaluation and their findings are summarized as follows:

"Expert review was limited to ENG data obtained in the SAD/MAD and lung penetration studies (Studies ACHN-490-001 and ACHN-490-003 respectively), as this testing was felt to be the most objective method used. Overall, no standard behavioral assessment scale for vestibular function has been universally accepted and approved for use in clinical trials as these tests in general are fairly unreliable and only detect vestibular toxicity if the damage is very severe. Further, results of this type of testing should be interpreted in the context of clinical findings. There were 31 plazomicin-dosed subjects and 11 placebo-dosed subjects for whom ENG data were reviewed. Of these, 4/31 plazomicin subjects (12.9%) and 1/11 placebo subjects (9.1%) had a change in vestibular function as evidenced by abnormal findings on caloric symmetry. It is unclear whether these were unilateral or bilateral changes, based on the available data. Per expert review, if vestibulotoxicity had been present, the subjects should have experienced imbalance or oscillopsia. No AEs of that nature were reported by these subjects; therefore, it was concluded that, in spite of the limitations in the ENG available, no clear sign of vestibulotoxicity can be inferred based on this testing."

The Agency does not have in-house expertise to evaluate this PTA and ENG data, however given the outside expert conclusions (essentially not ruling out ototoxicity), this is not needed given that class warnings related to ototoxicity are likely to be placed in labelling.

8.6. Safety Analyses by Demographic Subgroups

[Given the large size of Study 009 and much smaller sizes of Studies 002 (b) (4) demographic analyses were analyzed primarily for Study 009. Also, subgroup comparisons are made primarily within the plazomicin arm. TEAEs, including related TEAEs, occurred with more frequency in the elderly (≥ 65 years old) population relative to the similar age group in the comparator arm and relative to the 18 to <65-year-old age group in the plazomicin arm. Some of this disparity can be related to TEAEs related to renal function, but not all. See the table below (Note: most elderly subjects were in Study 009).

Table 56 Overall Summary of Treatment-Emergent Adverse Events, by Age Group, for the Pooled Complicated Urinary Tract Infection Studies—Safety Population, Studies 002 and 009

	Phase 2 (ACHN-490-002)				Phase 3 (ACHN-490-009)				Pooled Phases 2 and 3			
	Age 18 to <65 y		Age ≥65 y		Age 18 to <65 y		Age ≥65 y		Age 18 to <65 y		Age ≥65 y	
TEAE or Serum Creatinine Increase by Age Group	PLZ 15 mg/kg (N=70; N1=68) n (%)	LVX 750 mg (N=39; N1=36) n (%)	PLZ 15 mg/kg (N=4; N1=4) n (%)	LVX 750 mg (N=5; N1=5) n (%)	PLZ 15 mg/kg (N=166; N1=165) n (%)	MEM 1.0 g (N=158; N1=155) n (%)	PLZ 15 mg/kg (N=137; N1=135) n (%)	MEM 1.0 g (N=143; N1=142) n (%)	PLZ 15 mg/kg (N=236; N1=233) n (%)	All Comp (N=197; N1=191) n (%)	PLZ 15 mg/kg (N=141; N1=139) n (%)	All Comp (N=148; N1=147) n (%)
TEAE	25 (35.7)	19 (48.7)	1 (25.0)	2 (40.0)	22 (13.3)	38 (24.1)	37 (27.0)	27 (18.9)	47 (19.9)	57 (28.9)	38 (27.0)	29 (19.6)
IV study drug-related TEAE	14 (20.0)	10 (25.6)	1 (25.0)	2 (40.0)	6 (3.6)	8 (5.1)	12 (8.8)	8 (5.6)	20 (8.5)	18 (9.1)	13 (9.2)	10 (6.8)
Severe/Grade ≥3 [a] TEAE	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	6 (3.8)	6 (4.4)	8 (5.6)	5 (2.1)	6 (3.0)	6 (4.3)	8 (5.4)
TEAE associated with renal function	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	9 (6.6)	4 (2.8)	4 (1.7)	0 (0.0)	9 (6.4)	4 (2.7)
Serum creatinine increase ≥0.5 mg/dL above baseline [b]	4 (5.9)	1 (2.8)	0 (0.0)	0 (0.0)	5 (3.0)	5 (3.2)	16 (11.9)	7 (4.9)	9 (3.9)	6 (3.1)	16 (11.5)	7 (4.8)
TEAE that led to discontinuation of IV study drug	4 (5.7)	1 (2.6)	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.3)	4 (2.9)	4 (2.8)	6 (2.5)	3 (1.5)	4 (2.8)	4 (2.7)
SAE	1 (1.4)	2 (5.1)	0 (0.0)	0 (0.0)	4 (2.4)	2 (1.3)	1 (0.7)	3 (2.1)	5 (2.1)	4 (2.0)	1 (0.7)	3 (2.0)
IV study drug-related SAE	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	1 (0.5)	0 (0.0)	1 (0.7)
SAE that led to discontinuation of IV study drug	0 (0.0)	1 (2.6)	0 (0.0)	0 (00)	2 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	1 (0.5)	0 (0.0)	1 (0.7)
Fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Note: N=number of patients in the Safety Population; N1=number of patients with a baseline and postbaseline value for serum creatinine from the central laboratory; n=number of patients in the specified category. Percentages are calculated as 100 × (n/N) for AEs. Patients reporting a particular adverse event (Preferred Term) more than once are counted only once by Preferred Term. a Common Terminology Criteria for Adverse Event. b Percentages are calculated as 100 × (n/N1) for serum creatinine increase ≥ 0.5 mg/dL above baseline. Source: Summary of Clinical Safety

When looking at sex, TEAEs were comparable in incidence between the males and females in the plazomicin arm. Race could not be appropriately evaluated given that the vast majority of the subject population was white. In terms of disparities by baseline BMI, none were noted in the plazomicin arm between those with baseline BMI 18.5 - <30 kg/m^2 and those with BMI ≥30 kg/$m^{2,}$ and disparities between cUTI and AP were minimal in the plazomicin arm as well. Unsurprisingly, the incidence of TEAE increased in the plazomicin arm with increasing renal impairment. A similar trend was noted in the meropenem arm though to a lesser degree.]

8.7. Specific Safety Studies/Clinical Trials

[Not Applicable]

8.8. Additional Safety Explorations

The phase 1 studies were briefly reviewed; notable findings are discussed below.

I both the drug interaction study with metformin (Study 011) as well as the lung penetration study (Study 003), dizziness was noted. In the metformin DDI study, three subjects had an onset of dizziness 9, 18, and 41 minutes, respectively, following start of concurrent dosing with plazomicin and metformin and had fasting blood glucose values of 91, 78, and 88 mg/dL measured within 20 minutes of onset of dizziness. These values were considered by the PI to be normal for fasting blood glucose via finger stick (greater than or equal to 70 mg/dL). Though hypoglycemia and/or hypotension may have contributed to the symptoms, a relationship to plazomicin cannot be excluded. In the 003 study, dizziness, somnolence and oral hypoaesthesia AEs were noted.

8.8.1. Human Carcinogenicity or Tumor Development

[Not Applicable given the short duration of usage of aminoglycosides. Also, aminoglycosides as a class have not been associated with malignancy.]

8.8.2. Human Reproduction and Pregnancy

[Per the protocol of study 009, pregnant subjects were not to be enrolled in the study. One 41-year-old female subject with pyelonephritis was randomized to the plazomicin arm; she had a negative urine pregnancy test at baseline but then was found to have a positive serum pregnancy test on Day 3. Plazomicin was discontinued on Day 3, and the patient underwent a therapeutic abortion on Day 10 (was an unwanted pregnancy).]

8.8.3. Pediatrics and Assessment of Effects on Growth

[Numerous deliberations between the applicant, division, and PeRC have been held in order to formulate a pediatric clinical development program, and an agreed iPSP is in place. Currently the applicant has applied for deferrals for the full pediatric population on the basis of having an adult formulation ready for an unmet need. (b) (4)

See the table below outlining the planned studies (Note: discussions have continued with PeRC and slight alterations to the timings, etc. of the study are being recommended).

Table 57: Planned Pediatric Studies

Source: iPSP

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

[Not Applicable. The highest dose studied was 20mg/kg in the TQT study; in general, the safety findings were similar to what was noted for lower doses.]

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

[Not Applicable- no postmarket experience]

8.9.2. Expectations on Safety in the Postmarket Setting

[Much will depend on the final approval decision for the drug. If, for example, only the cUTI indication is approved and not the BSI indication, it can be assumed that the drug will be used off-label for the BSI indication. The safety database we have for such patients is limited, and it is certainly plausible that given the level of morbidity in such patients, adverse effects such as nephrotoxicity may become more prominent.]

8.9.3. **Additional Safety Issues From Other Disciplines**

[See Section 4 – Clinical Pharmacology]

8.10. **Integrated Assessment of Safety**

[Plazomicin hails from the aminoglycoside class of antibiotics. This class has been extensively used for decades, and, thus, there is at least a general sense of some of the safety issues that may be anticipated with plazomicin.

Plazomicin's safety findings are in line with what was expected. In Study 009, diarrhea, headache, nausea, and vomiting were the most common adverse events and were present at rates similar to the comparator. These adverse events are typical of drug development trials and though they are certainly a source of discomfort for patients, they are also not particularly worrisome in a setting where a drug is expected to provide some basic benefit. Other "general" adverse events noted with plazomicin included dizziness and hypoaesthesia, particularly in the earlier phase 1 trials. It should be noted that early in clinical development, a possible link between hypotension and a rapid 10 minute plazomicin infusions was noted. Thus, the plazomicin infusion time was increased to 30 minutes, and subsequently the infusion was generally tolerated well.

Plazomicin does not appear to have any clinically significant QTc prolonging effects, and its effects on clinical laboratory parameters are expected (namely its effects on renal function parameters). It does not appear to have any significant hepatotoxic effects.

Plazomicin does appear to have a slight nephrotoxic effect. It appeared to be associated with creatinine increases/nephrotoxic adverse events at a rate higher than meropenem in Study 009, though most of the serum increases were mild and reversible. (b) (4) Regardless, nothing was noted in the safety profile that suggested either bolstering or lessening the nephrotoxicity 'Warnings' labelling language typically associated with aminoglycosides. As has been discussed earlier, the Clinical Pharmacology review team has set a serum plazomicin trough cutoff of 3 mcg/ml for nephrotoxicity monitoring and subsequent dosing interval adjustments.

Plazomicin also cannot be ruled out of having ototoxic effects. The use of hearing inventories in study 009 did not highlight any real plazomicin-associated ototoxic effects, however outside analysis of PTA and ENG testing from the phase 1 studies could not definitively exclude ototoxic effects. Thus, typical class labelling language related to ototoxicity should likely remain.

Plazomicin was noted to have a disproportionate incidence of TEAEs in the elderly relative to the younger population and this should be noted in labelling

Overall, nothing unexpected was noted in the safety profile of plazomicin and would not preclude approval of the drug, assuming the drug was associated also with significant clinical benefit.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was held on May 2, in which both the applicant and Agency presented the Study 009 and 007 findings in detail to a committee of experts composed of pediatric and adult Infectious Diseases physicians, statisticians, pharmacologists, and patient/industry representatives. Multiple public speakers also presented their viewpoints.

The committee was asked to consider two questions:

1. Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options? If yes, please provide any recommendations regarding labeling. If no, what additional studies/analyses are needed?

The committee voted 15-0 in favor of plazomicin on this question. In general, members felt that substantial evidence was presented (NI margin met), particularly in the setting of an unmet need. However, there was concern by many members that the issues regarding plazomicin trough measurements for the prevention of nephrotoxicity had not been fully explored/resolved and would need to be explicitly explained in labelling. Some members advocated for trough monitoring in all subjects to simplify use and one member suggested usage of the drug be restricted to Infectious Diseases physicians. There were also recommendations to consider a PMR in order to address the trough issue. Members also pointed out that labelling should mention that safety data (such as ototoxicity data) was limited and highlight limitations of the trial, including the homogenous racial makeup. Members pointed out that pediatric data and data in immunosuppressed individuals was necessary.

2. Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options? If yes, please provide any recommendations regarding labeling. If no, what additional studies/analyses are needed?

The committee voted 11-4 against plazomicin on this question. (b) (4)

(b) (4)

.

10.Labeling Recommendations

10.1. Prescription Drug Labeling

1. (b) (4)
2. TDM/trough monitoring will need to be clearly and explicitly explained if used. Specifically, clarity will be needed on which populations such monitoring should be used for, dosing interval adjustments made as a result of monitoring, etc. Every effort should be made to make it as simple as possible given the drug's possible use in a variety of settings.
3. Class safety labeling with regards to nephrotoxicity and ototoxicity should likely remain unchanged for plazomicin though relevant trial results should be reported.
4. Given the disparities in TEAEs seen in the elderly, this should be noted in labeling.
5. Limited use language should be included
6. In-vitro data relevant to activity against common resistance phenotypes should be included where possible.

10.2. Nonprescription Drug Labeling

[Not Applicable]

11.Risk Evaluation and Mitigation Strategies (REMS)

[No REMS are recommended]

12.Postmarketing Requirements and Commitments

The following post marketing studies are suggested:

1. Conduct an open-label multiple dose pharmacokinetic and safety study of plazomicin in hospitalized children ages birth to 18 years with infections and receiving standard of care antibacterial drugs.

2. Conduct a randomized active-controlled pharmacokinetic and safety trial of plazomicin in children ages birth to 18 years with complicated urinary tract infection including acute pyelonephritis.

3. Conduct US surveillance studies for five years from the date of marketing plazomicin to determine if resistance to plazomicin has developed in those organisms specific to the indication in the label.

4. Conduct a clinical study in subjects with end stage renal disease (ESRD) receiving hemodialysis to evaluate the pharmacokinetics of plazomicin.

5. Establish an FDA cleared or approved in-vitro diagnostic device for therapeutic drug monitoring of plazomicin that is recommended for patients with baseline creatinine clearance < 90 mL/min for the treatment of complicated urinary tract infections (cUTI).

Please see final approval letter (if approved) with further details.

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/s/

SHRIMANT MISHRA
06/25/2018