

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210303Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY
REVIEW(S)

**Division of Anti-Infective Products
Office of Antimicrobial Products (OND/CDER)
ADDENDUM Review**

Application Number: NDA 210-303 (Plazomicin [ZEMDRI])

Applicant Name: Achaogen

Date Reviewed: 6/22/2018

Dosage Strength: 15 mg/kg Injection as 30-minute infusion, once daily

Dosage Forms: Injection (Intravenous)

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Submission Type: Addendum

Background

Plazomicin is a novel aminoglycoside for the proposed indication of complicated urinary tract infections (cUTI), including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter cloacae*. This review focuses on the proposed susceptibility test interpretive criteria for plazomicin. This review updates the clinical microbiology review (dated May 17, 2018) and clinical pharmacology review (dated May 18, 2018). In addition, addresses the Applicant *Original Response to the Division Breakpoint Question* provided on June 15, 2018 (see communication dated 6/14/2018) as well as *Amended Response to the Division's Breakpoint Question* provided on June 20, 2018.

The following is the recommended plazomicin interpretive criteria as shown in the table:

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥16	14-15	≤13

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The Agency's basis for these interpretive criteria is as follows:

- In the clinical trials, there were only a few patients with cUTI who had a baseline organism with MICs of 2 or 4 mcg/mL. The majority of baseline isolates had MICs of 1 mcg/mL or less. The clinical and microbiologic outcomes in patients with MIC of 2 mcg/mL were 75% (9/12) and 91.7% (11/12) in the plazomicin and meropenem arms, respectively. At an MIC of 2 mcg/mL, 4 organisms were *P. mirabilis* and 75% (3/4) had clinical and microbiologic success. There were 6 isolates from 6 different patients that had MICs of 4 mcg/mL, all isolates were eradicated at Day 5 and TOC visit and all 6 patients were clinical cures. There are no clinical data in patients with concurrent bacteremia from the cUTI trial where the baseline isolate had MICs greater than 1 mcg/mL. The MICs for the baseline organisms in patients with concurrent bacteremia was 0.5 mcg/mL or less. cUTI is a serious infection that could be associated with bacteremia and mortality and it is possible that plazomicin will likely be used in more seriously and potentially critically ill patients in clinical settings as compared to those enrolled in the cUTI trial. Clinical outcomes in the subgroup of patients with bacteremia in the plazomicin arm was similar to that seen in the meropenem arm.
- There was variability in the PK/PD target across different models. In the neutropenic murine thigh infection model, the PK/PD target for 1- \log_{10} CFU reduction was 89 of AUC/MIC, while in the neutropenic murine lung infection model and the in vitro chemostat model it was much lower (6 and 35, respectively). In general, for cUTI, we have used a PK/PD target of 1- \log_{10} CFU reduction in neutropenic murine thigh infection model to evaluate probability of target attainment (PTA). Only 62-73% of simulated cUTI patients with varying renal function achieved the PK/PD target for 1- \log_{10} CFU reduction (i.e., 89 of AUC/MIC) at MIC = 2 mcg/mL compared to >90% at MIC=1 mcg/mL. With the proposed dose, >90% of simulated cUTI patients achieved the PK/PD target for net stasis of CFU from baseline (i.e., 24 of AUC/MIC) at MIC = 2 mcg/mL. The results of PTA analysis using the PK/PD target of 1- \log_{10} CFU reduction support a susceptible breakpoint of 1 mcg/mL. However, a susceptible breakpoint of 2 mcg/mL is considered acceptable based on the clinical and microbiologic data available.
- Overall, from a clinical standpoint, it is difficult to support the Applicant's proposal of a susceptible breakpoint of ^(b)₍₄₎ mcg/mL and the PK/PD target for 1- \log_{10} CFU reduction was attained in only ^(b)₍₄₎ A breakpoint of 2 mcg/mL can be supported based on the clinical and microbiologic outcomes of 12 patients and the overall distribution of isolates (with the wild type distribution ending at an MIC of 4 mcg/mL). The intermediate breakpoint of 4 mcg/mL also provides for a buffer for a 2-fold margin of error with MIC testing.
- By the disk diffusion method, the proposed diameters of ≥ 16 mm as susceptible, 14 – 15 mm as intermediate and ≤ 13 mm as resistant, showed no very major errors, 0.25% major errors and 2.23% minor errors.

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In terms of labeling, the Indication and Usage Section as well as the “first list” in Microbiology Section for the proposed organisms are as follows:

Aerobic Bacteria

Gram-negative Bacteria
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Enterobacter cloacae

The “second list” of organisms will include the following:

Aerobic Bacteria

Gram-negative Bacteria
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia stuartii
Serratia marcescens

The susceptibility test interpretive criteria website will include the following information:

Plazomicin

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥16	14-15	≤13

Signature(s):

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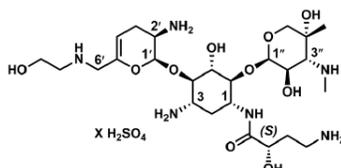
NDA#: 210-303

Reviewer: Simone M. Shurland

(Orig: SDN:001)

Date Company Submitted: 10/25/2017	Date Received by CDER: 10/25/2017	Date Assigned: 10/25/2017
Sponsor Name: Achaogen	Active Ingredient: Plazomicin	Drug Category: Anti-bacterial
Proposed Indications: <ul style="list-style-type: none"> • Complicated urinary tract infections (cUTIs) including pyelonephritis • Bloodstream infections 	Dosage Form: Intravenous	Dose Administration: Injection
	Dose Strength and Frequency: 15 mg/kg as 30-minute infusion, once daily	Dose Duration: 10 - 14 days

DRUG PRODUCT NAME

Proprietary Name:	ZEMDRI™
Non-Proprietary Name:	ACHN-490 sulfate, ACHN-490, A0000008, C001490, 17KJ01
Established Name:	Plazomicin
Chemical Name:	(2''R,3''R,4''R,5''R)-2''-[(1S,2S,3R,4S,6R)-4-amino-6-[(2'''S)-4'''-amino-2'''-hydroxybutanamido)amino]-3-[(2'S,3'R)-3'-amino-6'-((2-hydroxyethylamino)methyl)-3',4'-dihydro-2H-pyran-2'-yloxy]-2-hydroxycyclohexyloxy]-5''-methyl-4''-(methylamino)tetrahydro-2H-pyran-3'',5''-diol sulfate
Molecular Weight:	592.68 Daltons (free base)
Molecular Formula:	C ₂₅ H ₄₈ N ₆ O ₁₀
Structural Formula:	

TYPE OF APPLICATION: Original NDA BLA NDA Supplement (sNDA) Annual Report Emergency Use Authorization (EUA)

TYPE OF ASSESSMENT: 505(b)(1) 505(b)(2) 351(a) 351(k)

REVIEW CLASSIFICATION: Standard Priority Fast Track Designation

Consult (Division) _____ Other (please specify) _____.

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EXECUTIVE SUMMARY

Plazomicin is a novel aminoglycoside for the proposed indication of complicated urinary tract infection (cUIT) including pyelonephritis caused *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*) and *Enterobacter cloacae* as well as treatment of bloodstream infections caused by *K. pneumoniae* and *E. coli*.

Plazomicin shares the mechanism of action of other aminoglycosides by binding to the bacterial 16S ribosomal subunit thereby inhibiting protein synthesis. Plazomicin MIC₉₀ values ranged from 0.5 µg/mL - ≤ 2 µg/mL against *E. coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., *Serratia marcescens*. Plazomicin MIC₉₀ values ranged from 2-8 µg/mL against *P. mirabilis* and indole-positive *Proteus* spp., *Providencia* spp. and *Morganella* spp. The MIC₉₀ values across geographic regions (Asia-Pacific, Europe, Latin America and Canada) were similar to MIC₉₀ values against isolates found in the United States. Plazomicin is resistant to aminoglycoside modifying enzymes (AMEs) commonly found in Enterobacteriaceae; thus, it maintains activity those isolates resistant to traditional aminoglycoside (amikacin, gentamicin and tobramycin) and some MDR Enterobacteriaceae including ESBL-producing and carbapenem-resistant Enterobacteriaceae (CRE). Plazomicin was less active *in vitro* against anaerobes and non-fermentative gram-negative organisms including *A. baumannii* and *S. maltophilia*, with variable activity against *P. aeruginosa*. Similar to other aminoglycosides, plazomicin lacked activity against gram-positive aerobes such as *Enterococcus* spp. (including *E. faecalis* and *E. faecium*) and *Streptococcus* spp. (*S. pneumoniae*, *S. agalactiae*, *S. pyogenes*); however, plazomicin is active against *Staphylococcus* spp. including MRSA, MSSA and coagulase negative staphylococci.

Plazomicin shows concentration-dependent bactericidal activity. Resistance to aminoglycosides is mediated by multiple mechanisms including impaired membrane permeability, efflux mechanisms, ribosomal alterations or expression of AMEs. Plazomicin retains activity against common AMEs that confer resistance to various aminoglycosides including amikacin, gentamicin and tobramycin. The exception is the intrinsic AME chromosomally produced, *aph(2'')-IVa(Id)* and *aac(2')-Ia*, which result in 4-fold and 8-fold increase in plazomicin MICs, respectively. Like other aminoglycosides, bacterial isolates that produce 16S rRNA methyltransferases (RMTases) resulted in high level plazomicin MICs ≥ 128 µg/mL. Though rarely observed in Enterobacteriaceae isolates, overexpression of efflux pumps (e.g., *acrAB-tolC*) or reduced expressions of porins (e.g., *ompF* or *ompK36*) results in moderate plazomicin MIC elevations.

The spontaneous mutation frequency for plazomicin against Enterobacteriaceae with different AMEs and β-lactamases (*E. coli* and *K. pneumoniae*) ranged from 3.0 x 10⁻¹⁰ to

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4.21×10^{-7} when plazomicin was tested at 4x – 8x MIC. No cross resistance was observed between plazomicin and other antibiotics, including β -lactams, carbapenems, fluoroquinolones and colistin.

Plazomicin was active in immunocompetent and neutropenic animal models of infections including septicemia, UTI, lung and thigh infection. Plazomicin activity was comparable or better than comparator antibacterials against Enterobacteriaceae including isolates producing clinically relevant AMEs or characterized β -lactamases with plazomicin MIC values ranging from 0.25 to 4 $\mu\text{g/mL}$.

Pharmacodynamic analyses from *in vitro* and animal models of infection has shown that the best predictor of microbiologic outcome is the ratio of the area under the concentration-time curve from 0 to 24-hours to the MIC for the target organism ($\text{AUC}_{0-24\text{h}}/\text{MIC}$). The targets from the mouse thigh infection model were chosen in target attainment assessment, since it provides the most conservative PK/PD target for a given exposure. A PK/PD target attainment of an AUC/MIC ratio of >24 (stasis) using a 15 mg/kg dose (in patients with normal to moderate renal function) was predicted to achieve $>90\%$ target for MIC values $\leq 4 \mu\text{g/mL}$ against Enterobacteriaceae.

For the cUTI indication, against Enterobacteriaceae based on *surveillance studies* which showed that the upper bound of the wild type population is 4 $\mu\text{g/mL}$; *PK-PD target attainment analyses* and population PK data with Monte Carlo simulations showed that an $\text{AUC}_{0-24}/\text{MIC}$ in the range of 24 – 30 predicts efficacy; and *clinical evidence* showed a high microbiological eradication rate in cUTI infections with MIC values $\leq 4 \mu\text{g/mL}$. ^{(b) (4)}

^{(b) (4)} by the broth microdilution method. For the corresponding zone diameters using the 30- μg plazomicin disk (Mast Group Ltd, Meyersville UK), ^{(b) (4)}

The “first list” of microorganisms includes the following gram-negative bacteria – *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. The “second list” includes the following gram-negative bacteria *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Providencia stuartii* and *Serratia marcescens*.

Susceptibility testing methods have been established for plazomicin. Quality control for plazomicin MIC and zone diameters against standard ATCC strains have been published in CLSI M100-S28 [2018] documents.

Section 8 of this review provides the Agency’s proposed recommendations (with respect to clinical microbiology Section 12.1 and 12.4) of the US Product Labeling.

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1. INTRODUCTION

Plazomicin (Zemdri™) is a novel, semisynthetic compound derived from sisomicin. The proposed indication is for patients 18 years or older for the treatment of

- Complicated urinary tract infections (cUTI) including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*) and *Enterobacter cloacae*
- Bloodstream infections caused by *K. pneumoniae* and *E. coli*
- Limited clinical safety and efficacy in patients who have limited or no alternative treatment options

Urinary tract infections (UTIs) are among the most common bacterial infections and catheter-associated UTIs are the most common nosocomial infections. The majority of cUTI and acute pyelonephritis (AP) are predominantly caused by members of the Enterobacteriaceae family including *Escherichia coli*, *Klebsiella* species, *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp. In addition, non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. account for up to 10% of hospital-acquired infections.

2. NON-CLINICAL MICROBIOLOGY

2.1. Mechanism(s) of action

Like other aminoglycosides, plazomicin bind to the bacterial 16S ribosomal subunit (16S rRNA) of the 30S component of the ribosome. It affects protein synthesis by inhibiting initiation, blocking elongation and promoting misreading of the codon after delivery of the amino-acyl transfer ribonucleic acid (tRNA) leading to error-prone translation after initiation.

Plazomicin shares many basic chemical and structural characteristics to that of traditional aminoglycosides, amikacin, gentamicin, tobramycin and sisomicin. Like sisomicin, plazomicin lacks the 3' and 4' hydroxyl groups present in other aminoglycosides. Plazomicin is distinguished from other aminoglycosides in that it contains an unsaturated hydroxyethyl tail and a hydroxy-amino butyric acid (HABA), which provides no substrate for the activity of AMEs that are associated with resistance to the traditional aminoglycosides (see Section 2.5.1 for further classification of AMEs).

2.2. Spectrum of Activity *In Vitro*

The activity of plazomicin was assessed in 2 major surveillance programs – SENTRY and CANWARD. The SENTRY antimicrobial surveillance program monitored antibiotic susceptibility annually against pathogens collected in 2014, 2015 and 2016 ([ACHN490-MB-031-MIC](#), [ACHN490-MB-034-MIC](#), [ACHN490-MB-050-MIC](#)). These studies included over 7,000 isolates collected from hospitals in North America and over 11,000 isolates from other regions in the world such as Europe, Latin America, Asia and the Western Pacific. The CANWARD surveillance program characterizes antibiotic activity

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against clinical isolates collected from 15 hospital sites residing in major city centers from 8 of the 10 Canadian provinces ([ACHN490-MB-029-MIC](#), [ACHN490-MB-051-MIC](#), [Walkty et al., \[2014\]](#)). Non-duplicate isolates were collected from patients with serious infections including bloodstream, respiratory, urinary tract, intra-abdominal or acute bacterial skin and skin structure infections in hospitalized patients.

The minimum inhibitory concentration (MIC) was determined using standard broth microdilution methods in accordance with CLSI (M07-A10 [2015]) guidelines. Validated frozen-form broth microdilution panels produced at (b) (4) was used in three of these studies and in the one study by the Department of Clinical Microbiology at the Health Sciences Centre (Winnipeg, Canada). Plazomicin concentrations tested ranged from 0.06 – 128 µg/mL. The MIC required to inhibit the growth of 50% of isolates (MIC₅₀) and MIC₉₀ values were calculated for isolate groups by region and year.

Susceptible and resistance breakpoints for comparator antibiotics were based on CLSI M100-S27[2017] and EUCAST [2017] interpretive criteria for studies conducted in 2016, CLSI M100-S26[2016] and EUCAST [2016] in 2015, CLSI M100-S25[2015] and EUCAST[2015] in 2014; where applicable US FDA breakpoints were applied for tigecycline.

2.2.1. Enterobacteriaceae

Plazomicin activity against the Enterobacteriaceae with MIC₉₀ values ranging from 0.5 - 1 µg/mL against *E. coli* (5000 isolates), *K. pneumoniae* (5571 isolates), *E. cloacae* (500 isolates), *K. oxytoca* (1091 isolates), *E. aerogenes* (470 isolates), *C. koseri* (463 isolates). Plazomicin generally displayed MIC₉₀ values ≤ 2 µg/mL against *Serratia marcescens* (490 isolates) and *C. freundii* (430 isolates); whereas the plazomicin MIC₉₀ values were 2 – 8 µg/mL against *P. mirabilis* (526 isolates) and indole-positive Enterobacteriaceae, including *Morganella morganni* (456 isolates), *Providencia* spp. (349 isolates) and *P. vulgaris* (308 isolates) ([ACHN490-MB-029-MIC](#); [ACHN490-MB-031-MIC](#), [ACHN490-MB-034-MIC](#), [ACHN490-MB-050-MIC](#); [ACHN490-MB-051-MIC](#); [Walkty 2014](#))

In global surveillance programs, the plazomicin and other aminoglycosides MIC against Enterobacteriaceae were stable over the three-year period (2014 – 2016). Overall, in the five geographic regions surveyed (United States, Asia-Pacific, Europe, Latin America and Canada), the MIC₉₀ values were comparable across sites. In the U.S., very few isolates had plazomicin MICs > 128 µg/mL and these were found in *K. pneumoniae*, *E. coli* and *K. oxytoca*. In comparison, most of the isolates with plazomicin MICs > 128 µg/mL were found in Europe and Latin America, and were predominantly *E. aerogenes*, *K. pneumoniae*, *E. cloacae*, *Proteus mirabilis*, *Providencia* sp. Less than 10% of the Enterobacteriaceae plazomicin MICs between 8 and 64 µg/mL; these were found in *M.*

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morgannii, *Providencia* spp., *Proteus mirabilis*, and *P. vulgaris* (ACHN490-MB-029-MIC; ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC; ACHN490-MB-051-MIC; Walkty 2014)

In general, aminoglycoside resistance (resistant to amikacin, gentamicin and tobramycin) against Enterobacteriaceae ranged from 10% to 26.3% depending on the aminoglycoside and the organism. More specifically, *K. oxytoca*, *E. aerogenes*, *C. freundii*, *C. koseri*, *P. mirabilis* and *P. vulgaris* group were >90% susceptible to amikacin, gentamicin and tobramycin. Amikacin was the most active of the aminoglycosides against Enterobacteriaceae, >90% were susceptible over the three-year period. Although gentamicin remains active against most Enterobacteriaceae, lower susceptibility (>80%) were reported for *E. coli*, *E. cloacae*, *K. pneumoniae*, *S. marcescens* and *Providencia* spp. Tobramycin susceptibility ranged from 73.7% - 84.5% for *E. coli*, *K. pneumoniae*, *E. cloacae*, *S. marcescens* and *Providencia* spp. Against aminoglycoside non-susceptible Enterobacteriaceae (isolates non-susceptible to amikacin, gentamicin or tobramycin), plazomicin MIC₉₀ values were 2 µg/mL (or within 2-fold) over the three-year period and were similar across regions except in 2015 from Latin America that had MIC₉₀ values of 128 µg/mL. (ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC).

Plazomicin displayed MIC₉₀ values of 1 - 2µg/mL against ESBL producing Enterobacteriaceae including *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter* spp (ACHN490-MB-031-MIC, ACHN490-MB-032-MCR, ACHN490-MB-034-MIC, ACHN490-MB-035-MCR, ACHN490-MB-050-MIC, ACHN490-MB-052-MCR).

Most carbapenem-resistant Enterobacteriaceae (CRE) produce carbapenemases belonging to molecular classes A (KPC, SME and IMI types), class D (OXA-48) and less commonly class B (IMP, NDM and VIM) (Livermore et al., [2011]). Several of these mechanisms have strong regional links. The most prevalent carbapenemase genes observed were *bla*_{KPC-2}, *bla*_{KPC-3}, *bla*_{OXA-48} and *bla*_{VIM-1} across regions (ACHN490-MB-031-MIC, ACHN490-MB-032-MCR, ACHN490-MB-034-MIC, ACHN490-MB-035-MCR, ACHN490-MB-050-MIC, ACHN490-MB-052-MCR).

- KPC-producing isolates included most frequently *KPC-2* and *KPC-3* which were predominantly found in *K. pneumoniae*, followed by *E. coli*, *K. oxytoca* and *E. cloacae*. KPC producing isolates were detected in Europe, US, Latin America and Asia-Pacific. *K. pneumoniae* KPCs have spread extensively to the USA, Israel and Greece with much of the problem due to a single producer clone belonging to sequence type (ST) 258. These isolates were least susceptible to tobramycin (MICs ≥ 32 µg/mL) and more or less resistant to amikacin and/or gentamicin. Plazomicin MIC_{50/90} values were 0.25 – 0.5 µg/mL and 1 µg/mL, respectively.
- OXA-producing isolates included mostly OXA-48; other types such as OXA-232,

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OXA-244 and OXA-370 were also detected in 2014 – 2016 surveillance studies. OXA-producing isolates were detected only in Europe and Latin America. Plazomicin MIC_{50/90} values were 0.25 – 0.5 µg/mL and 0.5 - >128 µg/mL, respectively.

- Metallo-β-lactamases were detected in Europe, Asia-Pacific and Latin America; most harbored NDM-1β-lactamase. Organisms with NDM-1 β-lactamase showed plazomicin MICs ranging from 64 to ≥128 µg/mL. These isolates were found in multiple species and had high-level resistance to other aminoglycosides (amikacin, tobramycin and gentamicin).
- Overall, no difference was noted in plazomicin activity against ESBLs, chromosomal or plasmid AmpC cephalosporinases, serine carbapenemases and metallo-β-lactamases producing isolates. Plazomicin MIC₉₀ values were at least 4-fold lower than amikacin, gentamicin and tobramycin.

2.2.2. Gram Negative non-fermenters

Against *P. aeruginosa* (>898 isolates), plazomicin MIC₉₀ values were 8-16 µg/mL generally similar to amikacin and tobramycin and across regions. Against aminoglycoside non-susceptible *P. aeruginosa* isolates, plazomicin MICs ranged from 0.25 - >128 µg/mL across regions and over the 3-year period ([ACHN490-MB-029-MIC](#); [ACHN490-MB-031-MIC](#), [ACHN490-MB-034-MIC](#), [ACHN490-MB-050-MIC](#); [ACHN490-MB-051-MIC](#); Walkty 2014).

Against *Acinetobacter* spp. (>350 isolates) plazomicin MIC₉₀ values were >128 µg/mL. Resistance to amikacin, gentamicin and tobramycin ranged from 21.4% to 34.3% for the US and from 53.3% to 85.7% for isolates from other regions (i.e., Europe, Asia-Pacific and Latin America). Against aminoglycoside non-susceptible isolates, plazomicin MIC_{50/90} values ranged from 8 to > 128 µg/mL and 64 to >128 µg/mL across regions and over the 3-year period ([ACHN490-MB-029-MIC](#); [ACHN490-MB-031-MIC](#), [ACHN490-MB-034-MIC](#), [ACHN490-MB-050-MIC](#); [ACHN490-MB-051-MIC](#); Walkty 2014).

Similar to other aminoglycosides, plazomicin demonstrated poor *in vitro* activity against *Stenotrophomonas maltophilia* isolates (165 isolates) with an MIC₉₀ value >64 µg/mL ([ACHN490-MB-029-MIC](#); [ACHN490-MB-031-MIC](#), [ACHN490-MB-034-MIC](#), [ACHN490-MB-050-MIC](#); [ACHN490-MB-051-MIC](#); Walkty 2014).

2.2.3. Gram positive isolates

Among *Staphylococcus aureus* (2336 isolates) isolates, greater than 90% of isolates inhibited at an MIC value of ≤ 1 µg/mL (range, ≤0.12 – 4 µg/mL). Plazomicin activity was similar for methicillin resistance (MIC_{50/90}, 0.5 -1 µg/mL and 1 µg/mL) and methicillin susceptible (MIC_{50/90}, 0.5 µg/mL and 1 µg/mL). Plazomicin MICs were similar over the 3-year period and across regions. Gentamicin susceptibility ranged from

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75% to 100% across all regions, with the highest gentamicin resistance (25%) reported from Asia-Pacific (ACHN490-MB-029-MIC; ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC; ACHN490-MB-051-MIC; Walkty 2014).

Against coagulase negative staphylococci (389 isolates), plazomicin MIC₉₀ values ranged 0.25 – 0.5 µg/mL. Plazomicin MICs were ≤ 1 µg/mL for all isolates across regions and 8-fold lower than gentamicin. Gentamicin susceptibility ranged from 40% to 70% across regions (ACHN490-MB-029-MIC; ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC; ACHN490-MB-051-MIC; Walkty 2014).

The *in vitro* activity of plazomicin against *Streptococcus pneumoniae* (689 isolates), *Streptococcus pyogenes* (81 isolates) and *Streptococcus agalactiae* (93 isolates) was generally high with MIC₅₀ values ranging from 16 to 64 µg/mL and MIC₉₀ values ranging from 32 to > 64 µg/mL (ACHN490-MB-029-MIC; ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC; ACHN490-MB-051-MIC; Walkty 2014).

Plazomicin *in vitro* activity against *Enterococcus faecium* (70 isolates, 1 laboratory) showed MIC_{50/90} values of 8 µg/mL and 16 µg/mL, respectively. Against *Enterococcus faecalis* (170 isolates, 2 laboratories), the plazomicin MIC_{50/90} values were 64 µg/mL and > 64 µg/mL (range, 2 - >64 µg/mL; ACHN490-MB-029-MIC; ACHN490-MB-031-MIC, ACHN490-MB-034-MIC, ACHN490-MB-050-MIC; ACHN490-MB-051-MIC; Walkty 2014).

2.2.4. Anaerobes

Plazomicin activity against a panel of obligate anaerobes showed MIC_{50/90} values >128 µg/mL. Neither plazomicin nor other aminoglycosides had activity against anaerobes (ACHN490-MB-043-MIC).

2.2.5. Other Bacteria

Plazomicin activity was similar to other aminoglycosides (amikacin, gentamicin and tobramycin) (ACHN490-MB-027-MIC).

Reviewer's Comments:

Plazomicin MIC₉₀ values < 4 µg/mL against Enterobacteriaceae including *Citrobacter spp.*, *E. coli*, *Enterobacter spp.*, *Klebsiella spp.* and *Serratia spp.*, *P. mirabilis* and indole-positive *Proteus spp.*, *Providencia spp.* and *Morganella spp.* Although resistance mechanisms targeting β-lactam antibiotics would not be expected to alter the activity of aminoglycoside antibiotics, the presence of β-lactam and carbapenem-resistant

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phenotypes in Enterobacteriaceae have been associated with concomitant aminoglycoside resistance. The in vitro activity of plazomicin remained unchanged in the presence of ESBL or carbapenemases including KPC-producing, OXA-48-like enzyme and most MBLs.

For the non-fermentative gram-negative bacilli, plazomicin was less active against *A. baumannii* and *S. maltophilia*, showing variable activity against *P. aeruginosa*.

Similar to other aminoglycosides (amikacin, gentamicin and tobramycin), plazomicin lacked activity against *Enterococcus* spp. (including *E. faecalis* and *E. faecium*) and *Streptococci* spp. (*S. pneumoniae*, *S. agalactiae*, *S. pyogenes*). However, plazomicin has activity against MRSA, MSSA and coagulase-negative staphylococci.

The aminoglycoside class also lacks activity against obligate anaerobes because active electron transport is required for aminoglycoside uptake into cells. Plazomicin were ineffective against Gram negative (including *Bacteroides* spp., *Fusobacterium*) and gram-positive anaerobes (*Clostridium* spp. including *C. innocuum*).

2.3. Bactericidal Activity

Aminoglycosides are unique among other protein synthesis inhibitors in that aminoglycosides exhibit concentration-dependent bactericidal activity.

2.3.1. Minimum bactericidal concentrations

Against 30 Enterobacteriaceae isolates (*E. coli* [10], *K. pneumoniae* [6], *K. oxytoca* [2], *E. cloacae* [6], *E. aerogenes* [4], and *C. freundii* [2]) with characterized resistance to the aminoglycoside and β -lactams, plazomicin showed bactericidal activity with MBC/MIC ratios of 1 for 80% of tested isolates with 96.7% of the isolates having an MBC/MIC ratio ≤ 4 . An MBC/MIC of 8 was observed for a single isolate, *E. coli* AECO1154. Overall, plazomicin activity was similar to other aminoglycosides (amikacin and gentamicin) though bactericidal activity were achieved at much higher concentrations than plazomicin (ACHN490-MB-037-MBC, Thwaites et al., [2016]).

2.3.2. Time Kill Studies

Time kill studies were conducted against isolates resistant to aminoglycosides (gentamicin, amikacin, arbekacin) and/or carbapenems (meropenem) with defined resistance mechanisms based on molecular characterization of AMEs (*aac(3')-Ia/Id*, *aac(3')-IIa*, *aac(3)-IV*, *aph(3')-IVa*, *aac(6')-Ib*, *ant(2'')-Ia*,) and β -lactamase phenotypes (CTX-M, TEM, SHV,ACT, KPC-2, OXA). The isolates were tested under standard conditions to determine the activity of plazomicin and comparators at multiple times the MIC on bacterial growth over a 24 hour time- period. The drug was defined as bactericidal if ≥ 3 -log₁₀ decrease in CFU/mL was observed.

- Against 6 *E. coli* clinical isolates (with AMEs [*aac(3')-IIa*, *aac(3)-IV*, *aac(6')-Ib*,

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- aph(3')-IVa*,] and ESBL producing [CTX-M-55, TEM, CTX-M-15]), plazomicin exhibited bactericidal activity in all tested isolates within the first hour post exposure at 8x – 16x the MIC and was maintained up to 24 hours. At 2X – 4X the plazomicin MIC bactericidal activity was observed in all isolates; however, regrowth was observed between 4h and 24h. Results were similar with amikacin and gentamicin at 8X the MIC; regrowth was observed at 24h (Study# [ACHN490-MB-037-MIC](#), [ACHN490-MB-019-TKI](#)).
- In another study performed on 9 *E. coli* clinical isolates, plazomicin was bactericidal (>3 log₁₀ reduction) in 7 of the isolates at 4X the MIC. In the two isolates that exhibited re-growth at 24h, an 8-fold and 16-fold increase in the plazomicin MIC was observed. These increases were not associated with the AMEs present (*aac(3)-IIa* and an integron-associated *aadA5* [*ant(3'')-Ia*]) and was attributed to efflux pump upregulation based on the uniform increase in MICs against all tested aminoglycosides; since the existence of efflux pump was not determined (Landman *et al.*, [2010]).
 - Against 3 *E. aerogenes* and 2 *E. cloacae* (with AMEs [*aac(3')-Ia/Id*, *aac(3')-IIa*, *aac(6')-Ib*, *aph(3')-IVa*, *ant(2'')-Ia*,] and ESBL producing [SHV-12, ACT-7]) isolates, plazomicin was bactericidal at 4X – 32X the MIC within the first 1h post-exposure. At 2X the plazomicin MIC regrowth was observed by 24h; similar to amikacin and gentamicin. Meropenem was bactericidal 4h post-exposure at 2X the MIC, however, re-growth occurred between 6h and 24h (Study# [ACHN490-MB-037-MIC](#), [ACHN490-MB-019-TKI](#)).
 - Against 5 *K. pneumoniae* isolates (with AMEs [*aac(3)-IIa*, *aac(3)-IVa*, *aac(6)-Ib*, *aph(3')-VIa*, *ant(2'')-Ia*] and ESBL producing [*SHV*, *TEM*, *CTX-M-14*, *CTX-M-15*], carbapenemases [KPC-2, KPC-3, OXA-48]), plazomicin was bactericidal at 16X the MIC at 1h post-exposure and was maintained up to 24h. In comparison, at 2X to 8X the plazomicin MIC, there was evidence of re-growth between 4h and 24h. Results for gentamicin and amikacin were similar. Against *K. oxytoca* AKOX1006 (*aac(3)-Ia/d*, *aac(6')-Ib*, *SHV-4*, *TEM-OSBL*, *KPC-2*), plazomicin showed 2.63 – 3.05 log₁₀ kill at 6h at 2X -8X MIC with re-growth at 24h and at 16X MIC re-growth was observed between 4h and 24h (Study# [ACHN490-MB-037-MIC](#), [ACHN490-MB-019-TKI](#)).
 - For *S. aureus* 4621 (*aph(2)-I*, *aac(6')-I*), plazomicin achieved bactericidal activity at 2x - 32x the MIC that was maintained through 24h. The rate of killing within the first 4h and was generally slower than gram-negative isolates tested. Arbekacin was bactericidal at 8x-32x MIC at 24h, at 2x -4x MIC did not achieve bactericidal activity (Study# [ACHN490-MB-019-TKI](#)).

Reviewer's comments:

Plazomicin shows concentration-dependent bactericidal activity. Against Enterobacteriaceae, at 16X plazomicin MIC resulted in ≥ 3 -log₁₀ reduction in

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CFU/mL as early as 1 hour post-exposure and was maintained up to 24 hours. Against *S. aureus*, plazomicin achieved bactericidal activity at 2x – 4x MIC, however, the rate of killing within 4-hours were generally slower compared to Enterobacteriaceae.

2.4. Intracellular antimicrobial concentration assessment

There were no studies that evaluated the activity of plazomicin inside the cell against target microorganisms.

2.5. Development of Resistance and Resistance Mechanisms

Acquired resistance to the aminoglycosides can occur through alteration of the ribosomal target (enzymatic alteration or substitution), alteration to the bacterial membrane (reduced transport or active efflux) and enzymatic alteration of the antimicrobial (aminoglycoside-modifying enzymes). These mechanisms are not mutually exclusive and can co-exist in the same bacterial isolate.

2.5.1. Susceptibility profiles in Characterized AME producing isolates

The main mechanism of resistance is the enzymatic modification and inactivation of aminoglycosides, mediated by aminoglycoside modifying enzymes (AME). AMEs are broadly classified as *acetyltransferases* (AAC) which render aminoglycoside inactive via acetylation, *phosphotransferases* (APH) via phosphorylation, and *nucleotidyltransferases* (ANT) via adenylation ([Armstrong et al., \[2010\]](#); [Cox et al., \[2017\]](#)).

Plazomicin differs from other members of the aminoglycoside class in that it contains structural modifications that allow it to retain activity in the presence of AMEs. Like sisomicin, plazomicin lacks the 3' and 4' hydroxyl groups present in other aminoglycosides and as a result plazomicin is protected from APH(3') and ANT(4') class of AMEs (**Figure 1**). Plazomicin also contains two additional chemical modification conferring additional protection from other AMEs. A hydroxy-amino butyric acid (HABA) at the N1 position protects plazomicin from the AAC(3), ANT(2'') and APH(2'') class AMEs, while addition of an hydroxy ethyl substituent at the 6' amine position protects plazomicin from the AAC(6') class AMEs. These chemical modifications do not compromise plazomicin antibacterial activity but allow for increased activity against isolates harboring these various AMEs.

All these classes of AMEs have been identified in *Enterobacteriaceae*. These may be located on plasmids and transposons and some of these genes have been found on class 1 integrons. AMEs in Enterobacteriaceae associated with gentamicin resistance include *aac(3)-I*, *aac(3)-II*, *aac(3)-IV*, *aac(6')-I* and *ant(2'')-I*, *aph(3)-VI*. AMEs associated with

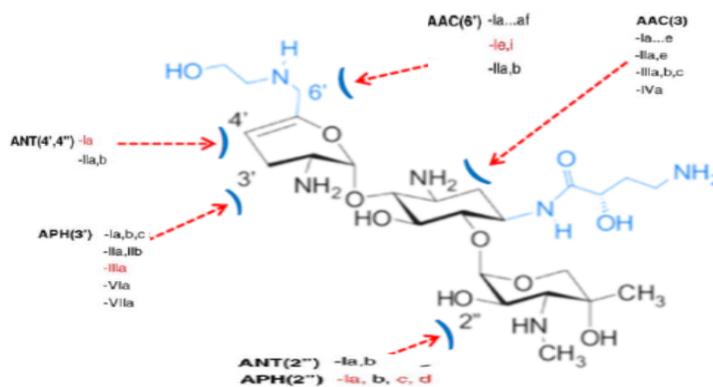
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amikacin resistance include *aac(6')-Ib*, *aac(3)-IV* and *aph(3)-VI* (Armstrong et al., [2010]).

Figure 1 : Major AMEs found in bacteria as illustrated with sisomicin



The chemical structure of plazomicin including sisomicin scaffold in black with the 2 chemical modifications in blue. Concave blue lines indicate region of protection from AMEs, as shown by red dotted arrows and key class members. Arrow point to the functional groups targeted by each AME from gram-negative (black) and gram-positive (red) organisms. AMEs not shown in this figure, for example ACH(3'')-IV/-V are found in aminoglycoside-producing organisms but are not known in clinical isolates. Different genes encoding the same enzyme type are indicated by the alphabetical designation, for example AAC (6')-Ia is encoded by a different gene than AAC(6')-Ib but both have the same spectrum of activity.
Source: Armstrong et al., Curr Opin Microbiol (2010)

Plazomicin activity was evaluated in the presence of a panel of 19 cloned AMEs and 2 16S ribosomal methyltransferases (16S RMTase) in an isogenic strain of *E. coli*. The AMEs were selected based on enzymatic resistance mechanisms and regio-specificity (region of the aminoglycoside that the enzyme modifies). All genes were over-expressed at high levels (*bla* promoter) in *E. coli* BW25113 and a hyper-permeable/efflux deficient derivative of the strain (*E. coli* Δ *bamB* Δ *tolC*). Plazomicin showed activity against various AMEs except *aac(2')-Ia* and *aph(2'')-IVa(Id)* which showed an 8-fold and 4-fold increase in plazomicin MICs compared to vector alone, respectively. Expression of the 16S RMTases, *armA* or *rmtB* showed high plazomicin MICs (>64 μ g/mL and 512 μ g/mL, respectively). *In vitro* enzymatic assays confirmed that the *aac(2')-Ia* and *aph(2'')-IVa(Id)* were able to utilize plazomicin as a substrate with K_m of 280 μ M and 42 μ M, respectively. Although the bifunctional AME *aac(6')-Ie-aph(2'')-Ia* was also able to modify plazomicin ($K_m = 57 \mu$ M) as a substrate in the enzyme assay, susceptibility testing did not reflect this observation (Cox et al., [2017], ACHN490-MG-045-MOA).

Overall, plazomicin activity against molecularly characterized AMEs in Enterobacteriaceae based on global surveillance 2014 – 2016 studies showed that:

- The most common AMEs have not changed in recent years; *aac(6')-I*, and *aac(3)-II* either alone or in combination remain the key resistance determinants among

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- the Enterobacteriaceae. These genes confer resistance to various commonly used aminoglycosides including gentamicin, tobramycin and amikacin.
- The *aac(6')-Ib* were most commonly found in *K. pneumoniae*, *E. coli*, *E. cloacae*, *K. oxytoca*, *E. aerogenes* and *P. mirabilis*. Plazomicin MIC_{50/90} values were 0.25 – 0.5 µg/mL and 1 µg/mL, respectively (range, ≤ 0.06 – 4 µg/mL).
 - Isolates carrying *aac(3)-IIa/d* were most commonly found in *K. pneumoniae*, *E. coli*, *E. cloacae*, *P. mirabilis*, *E. aerogenes*, *K. oxytoca* and *P. vulgaris* which showed plazomicin MIC_{50/90} values of 0.25 µg/mL and 1 µg/mL (range, ≤ 0.06 – 4 µg/mL). Isolates carrying *aac(3)-IVa-like* found in *E. coli*, *P. mirabilis*, *K. pneumoniae* and *P. vulgaris* showed plazomicin MIC_{50/90} values of 0.5 µg/mL and 2 µg/mL (range, 0.12 – 2 µg/mL). Other *aac* genes detected and found less frequently in Enterobacteriaceae isolates included *aac(3)-Ia-like*, *aac(3)-IIa-like*, *aac(3)-IIc-like*, *aac(3)-VIa like*, *aac(6')-33*, *aac(6')-Iaf-like*, *aac(6')-Iic*, and *aac(6')-Iic-like*; plazomicin MIC values < 4 µg/mL.
 - Similar to isogenic studies, plazomicin was inactive in the presence of *aac(2')-IIa*, an intrinsic chromosomally located gene found in *Providencia stuartii*; no other studies have reported the presence of this enzyme in other Enterobacteriaceae species ([ACHN490-MB-052-MCR](#), [Macinga et al., \[1999\]](#)).
- The most prevalent ANTs was *ant(2'')-Ia*, predominantly found in *E. coli* and *P. mirabilis* and in few *E. aerogenes*, *E. cloacae*, *K. pneumoniae*, *K. oxytoca* and *P. vulgaris* isolates. Plazomicin MIC_{50/90} values were 1 µg/mL and 4 µg/mL (range, 0.12 – 4 µg/mL) alone or in combination with other AME genes.
 - APHs were less frequently detected in Enterobacteriaceae and those that modify clinically used aminoglycosides (i.e., amikacin, gentamicin, tobramycin) were *aph(3')-VIa-like*, *aph(3')-IIa* and *aph(2')-IVa*. These AMEs were found in *E. coli*, *K. pneumoniae* and *E. cloacae* and were detected mostly in Europe and Latin America. None of the studies reported *aph(2')-IVa* among Enterobacteriaceae isolate in the global surveillance 2014 – 2016 studies. Plazomicin MIC_{50/90} values were 0.25 µg/mL and 1 µg/mL (range, 0.12 – 2 µg/mL). Various other APH genes were detected that encode resistance to other aminoglycosides that are not broadly used clinically, plazomicin showed activity against these APH (data not shown).
 - Overall, plazomicin showed activity against Enterobacteriaceae isolates carrying AMEs; these isolates were non-susceptible to gentamicin (81.2%) and tobramycin (87%). Amikacin remains active against most of these AME (91.8%); however, amikacin was 8 to 16-fold less active (MIC₉₀ 8 - >32 µg/mL) than plazomicin

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(MIC₉₀ 1 - 4 µg/mL) (ACHN490-MB-032-MCR, ACHN490-MB-035-MCR, ACHN490-MB-052-MCR).

- The staphylococci have a limited repertoire of AMEs; only three are known *ant(4')-Ia*, *aph(3')-IIa* and *aac(6')-Ie,i* and are widespread particularly in MRSA (Armstrong et al., [2010], Tenover et al., [2011]). Against 500 MRSA isolates collected from hospitals in the US, the plazomicin MIC₉₀ was 2 µg/mL. Plazomicin activity was not altered by any of the AMEs found in staphylococci, either alone or in combinations of up to three enzymes (data not shown).

2.5.2. Alteration of target sites - 16S RMTases

Resistance mediated by the 16S RMTases appears to be rare in Enterobacteriaceae (Livermore et al., [2011]). Based on the 2014 – 2016 global surveillance studies, 0.92% of the overall isolates tested carried these genes (ACHN490-MB-032-MCR, ACHN490-MB-035-MCR, ACHN490-MB-052-MCR). The most common 16S RMTases were *armA*, *rmtB* and *rmtC* methylases. These were commonly found in *K. pneumoniae*, *E. coli* and less frequently in *C. koseri*, *E. cloacae*, *K. oxytoca*, *E. aerogenes*, *E. cloacae*, *P. mirabilis* and *P. stuartii*. Other variants included *rmtA*, *rmtB1*, *rmtB2*, *rmtF1*, *rmtD*, *rmtD1*, *rmtD2*, *rmtE*, *rmtF*, *rmtF1*, *rmtG* and *rmtH*. Most of which were detected in Europe, followed by Latin America and Asia-Pacific; very few were detected in North America. Isolates that produce 16S rRNA methyltransferases resulted in high level plazomicin MICs ≥ 128 µg/mL and showed elevated MICs for other aminoglycosides including amikacin, gentamicin and tobramycin.

The 16S rRNA methyltransferases ribosome-modifying enzyme has been primarily reported among strains in which production of New Delhi metallo-β-lactamase-1 (NDM-1) is the mechanism of carbapenem resistance (Almaghrabi 2014). Plazomicin is not active against many New Delhi metallo-β-lactamase-1 (NDM-1) positive organisms because both resistance mechanisms appear to coexist together. Most *K. pneumoniae* appear to carry the *rmtB* methylase and NDM-1 metallo-β-lactamase.

It is important to note carbapenem-resistant *K. pneumoniae* strains in the US are classified as sequence type 258 (ST258) clones by multilocus sequence typing (MLST) and produce KPC-2 or KPC-3 rather than NDM-1. To date, other than the known association of this mechanism with NDM-1, 16S rRNA methyltransferases are not found with other metallo-β-lactamases.

2.5.3. Decreased Outer Membrane Permeability and Active Efflux

In Enterobacteriaceae, aminoglycoside resistance is rarely attributed to mutations that result in reduced permeability via porin loss or upregulation of efflux. Modification of the outer membrane due to reduce expression of porins involved in aminoglycoside resistance include the *ompC* and *ompF* found in *E. coli* and *C. freundii*; *ompK35*,

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ompK36 and *ompK37* porins found in *K. pneumoniae*, *K. oxytoca* and *E. aerogenes*. In the global surveillance studies, few *E. coli* isolates (2 in 2015, 9 in 2014) exhibited reduction in the expression of *ompF*; these isolates had plazomicin MICs of 4 - 16 µg/mL. Among *K. pneumoniae* tested, three displayed reduction in *ompK36* with plazomicin MICs of 64 µg/mL ([ACHN490-MB-032-MCR](#), [ACHN490-MB-035-MCR](#), [ACHN490-MB-052-MCR](#)).

Efflux pumps associated with aminoglycoside resistance in Enterobacteriaceae include the *acrAB-tolC*. In surveillance studies (2014 – 2016) showed that 2 *K. oxytoca* had elevated expression of *acrAB-tolC* in combination with reduction in *ompK36*; plazomicin MIC values against these isolates were 64 µg/mL ([ACHN490-MB-032-MCR](#), [ACHN490-MB-035-MCR](#), [ACHN490-MB-052-MCR](#)).

2.5.4. Spontaneous mutation frequency

The spontaneous mutation frequency for plazomicin was determined against 10 Enterobacteriaceae isolates with a variety of AMEs and β-lactamases. Overgrowth of bacteria was observed at 2X – 4X the plazomicin MIC for all isolates tested. At 4X – 8X the MIC, spontaneous mutation frequencies ranged from 3.0×10^{-10} to 3.03×10^{-7} . At higher plazomicin concentrations (16x – 32x the MIC), no isolates were recovered for 9 of 11 parent strains tested, resulting in spontaneous mutation frequency values of $<10^{-10}$ to $<10^{-12}$. Similar mutation frequencies were observed for the comparator aminoglycosides at 4X – 8X MIC ranging from 9.62×10^{-11} to 3.47×10^{-7} ([Study# ACHN490-MB-40-SMF](#)).

Spontaneous mutants showed increases in plazomicin MICs ranging from 4- to 64-fold change (MIC, 0.5 - 64 µg/mL). These recovered isolates were also associated with a ≥ 4-fold increase in amikacin, gentamicin and/or tobramycin MICs indicating that mutations also affected the activity of other aminoglycosides. Increase in the MICs of plazomicin and comparators against these mutants were generally stable up to 5 passages on drug-free media ([ACHN490-MB-040-SMF](#)).

Select mutants were evaluated by whole genome sequencing to determine the presence of genetic mutations (AME or OMP genes):

- None of the recovered mutants acquired any additional AME gene compared with the parent strain; however, two mutants lost an existing AME during the selection process. One mutant from *E. coli* AECO1156 (8X plazomicin MIC) lost *aac(3)-IIa* and one mutant from *K. pneumoniae* AKPN078 lost *aadA2*.
- Three AMEs mutated during the selection process. A different mutant from *E. coli* AECO1156 (8X plazomicin MIC) had a point mutation in the AME gene *aph(6)-Ia* compared with the parent strain sequence. Three mutants recovered from *K. oxytoca* AKOX1007 (selection on 2X, 4X and 8X plazomicin MIC) had the *aac(6')-Ib* gene with either a single amino acid substitution (D164Y on 4X

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plazomicin MIC) or double amino acid substitution (D164Y and W97R selected on 2X and 8X plazomicin MIC). One mutant from *E. coli* AECO1143 (selection on 16X tobramycin MIC) had a 4-amino acid insertion at the beginning of the AME gene *aadA1* which resulted in a transformation to another AME gene *ant(3'')-Ia*. It is important to note that *aadA1* and *ant(3'')-Ia* are considered to be the same gene, and thus it is unlikely that this mutation would confer any functional change. The plazomicin MICs against these mutants ranged from 8 – 64 µg/mL.

- Among the major outer membrane proteins hypothesized to be involved with aminoglycoside resistance, mutants from *E. coli* AECO001 showed coding region changes within *ompC* genes. Two mutants were selected on 8X plazomicin MIC and one mutant was selected on 4X gentamicin MIC. All mutants had 1 amino acid substitution (L229W) in *ompC*. The plazomicin MICs against these mutants were 8 µg/mL. No other sequence changes in *ompC*, *ompF*, *ompK35*, *ompK36* or *ompK37* genes were detected in mutants compared with the parent strains.

2.5.5. Resistance Selection in serial passage studies

Serial passage studies against 10 Enterobacteriaceae isolates expressing a variety of AMEs showed that plazomicin MICs increased after 10 passages; similar to comparator aminoglycosides. After 10 passages, plazomicin MICs were 8- to 64-fold higher than the parent MIC. Of the 10 isolates tested, 3 had plazomicin MICs ≤ 4 µg/mL, 3 isolates had plazomicin MICs of 8 µg/mL, and five isolates had plazomicin MICs of 16 – 64 µg/mL after passaging 10 times. For comparator aminoglycosides, the MICs were 20 to 64-fold greater than parental strain with MICs ranging from 1 to 512 µg/mL. The elevated MICs for plazomicin and comparators were confirmed to be stable after passage in drug free media ([ACHN490-MB-039-SPA](#)).

2.5.6. Cross Resistance

Enterobacteriaceae that express ESBLs and carbapenemases are typically MDR because β-lactam resistant mechanisms often travel on the same plasmid with mechanisms of resistance to other classes, including AMEs and 16S RMTases. Plazomicin activity was assessed in vitro against isolates with molecularly characterized β-lactam resistance mechanisms. These studies showed that:

- In the global surveillance studies conducted in 2014 - 2016, the most common ESBL phenotype was *bla*_{CTX-M} variant alone or in combination with β-lactamases. Overall plazomicin had MIC₉₀ values of 1 µg/mL against groups of isolates carrying only ESBL genes, CTX-M, SHV-ESBLs, transferable AmpC and narrow-spectrum β-lactamases ([ACHN490-MB-062-MCR](#)).
- Carbapenemases were most predominantly found in *K. pneumoniae* isolates and the most prevalent carbapenemase detected was the *bla*_{KPC} variant (48 – 60%). Other carbapenemases included *bla*_{OXA-48} (8.6% - 21.2%) and *bla*_{NDM-1} (8.6% -

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- 16.7%) and less frequently *bla*_{VIM}, *bla*_{SME-4}, *bla*_{OXA-23-like}, and *bla*_{IMP}. Other organisms such as *E. coli*, *C. freundii*, *E. cloacae* complex and *K. oxytoca* were occasionally found to encode a carbapenemase, but this was rare. In isolates encoding *bla*_{KPC}, the plazomicin MIC₉₀ value were 1 µg/mL. CRE isolates with plazomicin MICs ≥ 128 µg/mL were as a result of the 16S RMTase gene ([ACHN490-MB-032-MCR](#), [ACHN490-MB-035-MCR](#), [ACHN490-MB-052-MCR](#), [Zhang et al., \[2017\]](#)).
- Against CRE isolates that possessed common AMEs (e.g., *aac(6′)-Ib*, *aph(3′)-Ia*, *aac(3)-IV* and *ant(2′′)*), plazomicin MICs ranged from 0.25 to 1 µg/mL. Plazomicin activity remained unchanged when more than one AME was present in an isolate (i.e. up to 3 AMEs present). In comparison, isolates AAC(6′)-Ib combined with another AME resulted in higher gentamicin and tobramycin MICs ([Almaghrabi et al., \[2014\]](#), [Haidar et al., \[2016\]](#)).
 - Mutants from spontaneous mutation frequency and serial passage studies rarely developed cross-resistance to β-lactam antibiotics and carbapenems. Plazomicin mutants from *E. aerogenes* AEAE1025 and the *K. oxytoca* AKOX1007 isolates showed plazomicin MICs > 4 µg/mL also had consistently increased MICs; however, the parent strains were also ceftazidime-resistant, making the significance of the increased MICs of the recovered isolates unclear ([ACHN490-MB-040-SMF](#), [ACHN490-MB-039-SPA](#)).

Fluoroquinolone resistance is usually via chromosomal mutations to the target sites, bacterial DNA gyrase and topoisomerase IV. Resistance can also be conferred via plasmid-acquired mechanisms (*qnr*) that usually carries the AME variant, *aac(6′)-Ib-cr*, which can also inactivate the activity of fluoroquinolones. In addition, alterations of the membrane permeability and upregulation of efflux pumps are also contributing factors to fluoroquinolone resistance.

- Plazomicin activity is not affected by the presence of the AME, *aac(6′)-Ib-cr*. Surveillance studies have shown that plazomicin MIC₉₀ values against these isolates were ≤1 µg/mL. In comparison, amikacin, gentamicin and tobramycin showed MIC₉₀ values > 16 µg/mL. The levofloxacin MIC₉₀ values against isolates carrying *aac(6′)-Ib-cr* were > 4 µg/mL.
- Mutants from spontaneous mutation frequency studies rarely developed cross-resistance to levofloxacin. Plazomicin mutants from *C. freundii* AFCE1028 and *E. cloacae* AECL1060 with plazomicin MICs > 4 µg/mL also showed a 4- to 8-fold increased levofloxacin MICs. There was no obvious pattern to the increases, since these increases were observed for isolates selected on other aminoglycosides. ([ACHN490-MB-052-MCR](#), [ACHN490-MB-040-SMF](#), [ACHN490-MB-039-SPA](#)).

Providencia spp., *M. morgannii*, *S. marcescens* or *Proteus* spp are intrinsically resistant

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to colistin. Acquired colistin resistance in Enterobacteriaceae have been reported particularly in *K. pneumoniae*. The primary mechanism of resistance to colistin involves reducing the negative charge on the outer membrane via alteration of the phosphate groups of lipid A. This resistance has been associated with chromosomal alterations of the two component regulatory system PhoPQ and PmrAB as well as inactivation of the *mgrAB* gene. In addition, a plasmid-encoded mechanism of resistance, *mcr(-1 or -2)* has also been described.

- Against colistin-resistant Enterobacteriaceae, plazomicin MIC₉₀ values ranged from 2 – 4 µg/mL. Isolates with plazomicin MICs \geq 128 µg/mL were due to the presence of 16S RMTase gene, with the exception of one *P. stuartii* isolate from Europe that encoded *aac(2')-Ia* gene.
- In spontaneous mutation frequency studies, mutants rarely developed cross-resistance to colistin. Plazomicin mutants from four parent strains (*K. oxytoca* AKOX1007, *K. pneumoniae* AKPN1158, *K. pneumoniae* AKPN1152 and *C. freundii* ACFR1028) with plazomicin MICs $>$ 4 µg/mL also showed \geq 4-fold increase in colistin MICs. There was no observed correlation between increase in plazomicin and colistin MICs.

Reviewer's comments:

Resistance to aminoglycosides is mediated by multiple mechanisms including impaired membrane permeability, efflux mechanisms, ribosomal alterations or expression of AMEs. Production of AMEs is the most prevalent mechanism of resistance in Enterobacteriaceae and confer resistance to various commonly used aminoglycosides including amikacin, gentamicin and tobramycin. The exception is the intrinsic chromosomally produced AME, *aac(2')-Ia* found in *P. stuartii* isolates; no other studies have reported the presence of this gene in other members of the Enterobacteriaceae. Like other aminoglycosides, bacterial isolates that produce 16S rRNA methyltransferases shows reduced activity in plazomicin.

Though rarely observed in isolates, reduced permeability via porins *ompC* and *ompF* in *E. coli* and *ompK36* in *K. pneumoniae* showed reduced susceptibility to plazomicin. Overexpression of the efflux pump *acrAB-tolC* have also resulted in reduced susceptibility to plazomicin.

Single and multiple in vitro passage studies indicate there is a potential for development of plazomicin resistance against Enterobacteriaceae, similar to other aminoglycosides. The spontaneous mutation frequency at 4x – 8X the plazomicin MIC ranged from 3.0×10^{-10} to 3.03×10^{-7} . The recovered spontaneous mutants showed increases in plazomicin MIC ranging from 4- to 64-fold change. Similarly, in serial passage studies (after 10 passages), the

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plazomicin MICs were 8- to 64-fold higher than parent MIC. The elevated MICs for plazomicin were stable after passage in drug free media, as well as showed elevated MICs to other aminoglycosides (amikacin, gentamicin and tobramycin). Molecular studies showed that no additional AMEs recovered from mutants; however, additional mutations in existing AMEs and reduced expression of outer membrane porins (*ompC*) were associated with higher plazomicin MICs. The plazomicin MIC values of these passage selected isolates were rarely encountered in global surveillance and clinical studies.

No cross resistance was observed between plazomicin and other antibiotics, including β -lactams, carbapenems, fluoroquinolones and colistin.

2.6. Antimicrobial interactions and fixed combination studies

Synergistic activity was evaluated for plazomicin and comparators using the checkerboard technique. Synergy was evaluated according to the respective fraction inhibitory concentration (FIC) for each isolate/combination by calculating the mean FIC determined as (MIC plazomicin in combination/MIC plazomicin alone + MIC of comparator combined/MIC comparator). A FIC index (FICI) < 0.5 was considered synergistic, FIC between 0.5 to 1 were additive, FICI values between 1 and 4 were indifferent, FICI values > 4 were antagonistic.

- Against 8 carbapenem-resistant *K. pneumoniae* isolates, no antagonism was observed for plazomicin in combination with meropenem, ceftazidime, piperacillin-tazobactam, tigecycline, rifampin and phosphomycin. There were two exceptions, synergy was observed of plazomicin in combination with meropenem against the Kp-MMX 4689 and with ceftazidime against Kp-MMX4688 ([ACHN490-MB-030-SYN](#)).
- Against 8 *K. pneumoniae* isolates, most isolates were additive/indifferent except one isolate which showed synergy with ceftazidime. No antagonism was observed with piperacillin-tazobactam, levofloxacin, tigecycline, colistin, daptomycin, linezolid, clindamycin and vancomycin ([ACHN490-MB-038-SYN](#)).
- Against 10 *E. coli* isolates, most isolates showed additive/indifferent combination against 6 isolates. Four isolates showed synergy, one isolate with piperacillin-tazobactam, 1 isolate with daptomycin and 2 isolates with clindamycin. No antagonism was observed with plazomicin combination ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, tigecycline, colistin, daptomycin, linezolid, clindamycin or vancomycin. The synergy observed for plazomicin in combination with piperacillin-tazobactam was confirmed in time kill synergy analyses ([ACHN490-MB-038-SYN](#)).
- Against 2 *C. freundii* isolates, one isolate showed synergistic effects with piperacillin-tazobactam which was confirmed in time kill synergy analyses. Both

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- isolates showed no antagonism in combinations with ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, tigecycline, colistin, daptomycin, linezolid, clindamycin and vancomycin ([ACHN490-MB-038-SYN](#)).
- Against 4 *E. aerogenes*, one isolate showed synergy with clindamycin; no antagonism was reported with ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, tigecycline, colistin, daptomycin, linezolid, clindamycin and vancomycin ([ACHN490-MB-038-SYN](#)).
 - Against 6 *E. cloacae*, no antagonism was observed in combination with ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, tigecycline, colistin, daptomycin, linezolid, clindamycin and vancomycin ([ACHN490-MB-038-SYN](#)).

Synergy time-kill assays were performed over 24 hours using plazomicin with one of the other agents at 0.5X or 0.25X MIC. Synergy was defined as a 2 log₁₀ or greater reduction in CFU/mL compared with the most active drug (and at least 2 log₁₀ reduction in CFU/mL count compared with initial inoculation); antagonism was 2 log₁₀ or greater increase in CFU/mL count and indifference as a 0- 2 log₁₀ reduction or increase in CFU/mL count.

- Against 47 *S. aureus* clinical isolates with a broad range of resistance phenotypes, including hospital-acquired MRSA, Panton-Valentine leukocidin positive (PVL) community-acquired MRSA, PVL negative community-acquired MRSA, heteroresistant vancomycin -intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA), synergy was observed for plazomicin and daptomycin in 91% of isolates, for plazomicin and ceftobiprole in 36% of isolates and for plazomicin and linezolid in 13% of isolates. At 24 hours, antagonism was only observed for plazomicin and linezolid in 4% of isolates ([Lin et al., \[2010\]](#)).
- Against 2 *P. aeruginosa* strain, for the *P. aeruginosa* APAE1149 strain, synergy was observed with plazomicin in combination with doripenem, ceftobriopole or piperacillin-tazobactam. Against *P. aeruginosa* APAE1091 strain, synergy was observed with ceftobriopole and piperacillin-tazobactam and indifference with doripenem ([ACHN490-MB-009-SYN](#)).
- Against 25 *P. aeruginosa* clinical isolates synergy was observed with plazomicin and cefepime in 80% of isolates, for plazomicin and doripenem in 80% of isolates, for plazomicin and imipenem in 68% of isolates and for plazomicin and piperacillin-tazobactam in 92% of isolates. No antagonism was observed for the combinations evaluated in the study ([Pankuch et al., \[2011\]](#)).

Reviewer's comments:

Against Enterobacteriaceae, no antagonism was observed for plazomicin in combination with meropenem, ceftazidime, piperacillin-tazobactam, levofloxacin,

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tigecycline, colistin, phosphomycin, daptomycin, linezolid, clindamycin rifampin and vancomycin; few isolates showed synergy with meropenem, ceftazidime and piperacillin-tazobactam.

Against *S. aureus*, synergy was observed with plazomicin and daptomycin, ceftobipole and linezolid.

Against *P. aeruginosa*, synergy was observed with plazomicin in combination with cefepime, doripenem, imipenem and piperacillin-tazobactam.

2.7. Post Antibiotic Effect

Against MDR Enterobacteriaceae, plazomicin PAE varied by isolate and showed concentration dependent activity which increased with increasing concentrations across isolates tested ([Study# ACHN490-MB-041-PAE](#)):

- Against 3 *E. coli* isolates, the PAE ranged from 0.2 to 1.4 hours when tested at 2x MIC, 0.4 to 2.5 hours at 4x MIC and 1.7 to 3.4 hours at 8x MIC.
- Against 4 *Klebsiella* spp. isolates, the PAE ranged from 0.4 to 1.8 hours at 2x MIC, 1.0 to 2.3 at 4x MIC and 1.3 to 2.7 hours at 8x MIC.
- Against 3 *Enterobacter* spp. isolates, the PAEs ranged from 0.5 to 2.6 at 2x MIC, 1.2 to >4.5 hours at 4x MIC and 2.5 to >4.5 hours at 8x MIC.
- Prolonged PAE was observed with plazomicin and comparator aminoglycosides, the PAE observed with meropenem and ceftazidime was typically <1 hour.

In another study, against Enterobacteriaceae isolates with known AMEs, the post-antibiotic effect for plazomicin ranged from 0.1 to 0.9 hours, with most isolates (6/7) exhibiting PAE \geq 0.5 hours. For *S. aureus*, plazomicin PAE was 0.1h at MIC and 0.6 at 2X MIC. Plazomicin PAE was similar to other aminoglycosides which ranged from 0.2 to 1.8 hours, with most of the isolates (5/7) exhibiting PAE \geq 0.5 hours. In comparison, the PAE for ceftazidime ranged from 0 to 0.5 hours, with most isolates (6/7) exhibiting no PAE (0 hours) ([ACHN490-MB-010-PAE](#)).

Reviewer's comments:

Against Enterobacteriaceae including those with known AMEs, plazomicin PAE ranged from 0.2 to >4.5 hours; however, was prolonged at 8X the MIC relative to 2X the MIC. Against *S. aureus*, plazomicin PAE ranged from 0.1 to 0.6 hours at 1X – 2X MIC.

3. SUSCEPTIBILITY TESTING METHODS

3.1. Broth Microdilution method

MIC testing were performed using frozen microdilution panels manufactured by TREK Diagnostics (Cleveland, OH).

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3.1.1. Effect of various testing conditions

Using the broth microdilution method, the MIC for plazomicin and comparator were measured under standard and non-standard conditions. Under standard conditions, isolates were tested in Mueller Hinton broth (pH 7.2 – 7.4) supplemented with 20 – 25 mg/L of Ca²⁺ and 10-12.5 mg/L of Mg²⁺ (CA-MHB). Panels were inoculated with 5 x 10⁵ CFU/mL, incubated at 35°C in ambient air and read after 16 – 20 hours of incubation. Non-standard conditions were modified for inoculum, broth pH, in the presence of human serum and horse blood, altered ion concentration and atmospheric conditions. The MIC values (modal or median) were compared between each standard and modified test condition and MIC shifts of >2-fold were considered significant.

- **Cation concentration** - Variation of the cation concentration of the media had minimal effect on plazomicin MICs (\leq 2-fold change) against Enterobacteriaceae, *S. aureus* and *A. baumannii* isolates. However, *P. aeruginosa* isolates were most affected by cation concentrations, with \geq 4-fold changes in plazomicin MICs when trace amounts of cations were used. The presence of calcium and magnesium in the media is associated with decreased uptake of aminoglycosides by *P. aeruginosa*. This antagonistic effect is reliant on the functional MexXY-OprM efflux pump in *P. aeruginosa* ([ACHN490-MB-005-MIV](#), [ACHN490-MB-006-MIV](#), [ACHN490-MB-036-MIC](#), [Duncan 2017](#)).
- **Inoculum effect** – Varying the inoculum, a low inoculum (5 x 10⁴ CFU/mL) or a high inoculum (5 x 10⁶ CFU/mL) had minimal effects on the plazomicin MIC against *P. aeruginosa* and *A. baumannii*. Against Enterobacteriaceae, plazomicin MICs remained within 2-fold for most isolates tested except of 2 isolates which increased 4-fold with a high inoculum. Similarly, against 1 *S. aureus* isolate increased 4-fold when a high inoculum count was used in the broth microdilution assay ([ACHN490-MB-005-MIC](#), [ACHN490-MB-036-MIC](#), [Duncan 2017](#), [Serio 2015](#)).
- **pH effect** - For Enterobacteriaceae, *P. aeruginosa* and *S. aureus* tested at pH5 or pH6 showed significantly high plazomicin MICs than the MIC values obtained under standard conditions; in some cases, MIC values increased >8-fold. For *S. aureus* at pH8 the MIC values were similar to standard conditions except for 1 strain where the plazomicin MIC value was 4-fold lower. Changes in media pH is well documented phenomenon in testing aminoglycosides. As such pH changes are expected and the media needs to be initially adjusted to CLSI recommended pH 7.2 – 7.4. Cation-adjusted MHB is recommended for testing aminoglycosides, since it is buffered and shifts in pH under normal storage conditions does not affect testing ([ACHN490-MB-005-MIC](#), [ACHN490-MB-036-MIC](#), [Duncan 2017](#); [Serio 2015](#)).
- **Incubation Conditions** – Under anaerobic conditions, plazomicin MICs decreased by \geq 4-fold against Enterobacteriaceae and *S. aureus*, with minimal

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- effect against *P. aeruginosa* isolates. Decreased activity of aminoglycosides under anaerobic conditions is a well-documented phenomenon. For *S. aureus* isolates, in 5% CO₂ incubation caused \geq 4-fold increase in plazomicin MICs. There was no effect on the plazomicin MIC under 5% CO₂ incubations against Enterobacteriaceae and *P. aeruginosa* (ACHN490-MB-036-MIC, Duncan 2017).
- **Serum** – Addition of serum (10%) or 3.75% lysed horse blood had no effect (within 2-fold) on plazomicin MICs against Enterobacteriaceae, *P. aeruginosa* and *S. aureus* isolates. The presence of 50% human increased plazomicin MIC values 4-fold in 2 isolates (1 *P. aeruginosa* and 1 *S. aureus*) (ACHN490-MB-036-MIV, Duncan 2017).
 - **White blood cell lysate** - No effect on plazomicin MICs (within 2-fold) were observed in the presence of intact or lysed human leukocytes, indicating that plazomicin activity is not likely to be affected by white blood cells (ACHN490-MB-007-MIV; Serio 2015).
 - **Lung surfactant** - Pulmonary surfactant, a primary component of the epithelial lining fluid has the potential to interfere with the activity of antibiotics used to treat lung infections. Using bovine-derived lung surfactant (Survana®) at 5% and 10% had no effect on plazomicin MICs (ACHN490-MB-008-MIV, Feeney 2011).

3.1.2. Quality Control Parameters

Prior to the conduct of the phase2/3 clinical studies, plazomicin quality control limits were determined in a tier 2, multi-center study which tested 4 standard QC strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853). The MICs were determined in accordance with CLSI M23-A3 (2008) guidelines. **Table 1** shows the plazomicin quality control for MIC testing.

Table 1: Quality Control ranges of plazomicin broth microdilution tests

QC Organism	QC range* (µg/mL)	% results in proposed range
<i>S. aureus</i> ATCC 29213	(b) (4)	96.9
<i>Enterococcus faecalis</i> ATCC 29212		95.6 (100)
<i>Escherichia coli</i> ATCC 25922		99.4
<i>Pseudomonas aeruginosa</i> ATCC 27853		98.4

Panels contained three lots of cation-adjusted Mueller-Hinton broth (Oxoid Lot#597351, Hampshire, United Kingdom; BD Lot#7143673, Franklin Lakes, NJ and Difco Lot#7263432 and Lot#6319361 Detroit, MI)

*Range Finder results, if different, are in parentheses

Source: ACHN490-MB-014-QCS

In the phase 3 studies, pre-made frozen broth microdilution MIC plates for gram-negative and gram-positive organisms were provided by Thermofisher (Remel). Eight different panels were used containing two-fold serial plazomicin dilutions at a concentration ranging from 0.12 to 256 µg/mL (**Table 2**).

- For *E. coli* ATCC25922, there were 51 distinct MIC tests performed and all were within QC range ((b) (4) µg/mL) except one isolate ((Lot# 16365) which

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- showed an MIC value of (b) (4) µg/mL. All relevant clinical isolates were re-tested as well as the QC isolate which was within range.
- For *Enterococcus faecalis* ATCC 29212, there were 31 distinct results using two different plate lots. All plazomicin MICs were within range (b) (4) µg/mL) except 2 results (Lot#16212) which showed an MIC of (b) (4) µg/mL, respectively. Because no *Enterococcus* species were tested during the study, the MICs were not repeated.
 - For *P. aeruginosa* ATCC 27853, there were 51 distinct MIC tests performed using five different plate lots. All plazomicin MICs were within range (b) (4) µg/mL) except one isolate (Lot# 16014) which showed an MIC value of (b) (4) µg/mL. No clinical isolates were tested on that day, the isolate did not need to be re-tested.
 - For *S. aureus* ATCC 29213, there were 31 distinct tests performed using 2 different plate lots. All plazomicin MICs were within plazomicin QC ranges (b) (4) µg/mL.

Table 2: Plazomicin QC MIC results from the phase 3 clinical trails

QC Strain (Lot#)	No. Tested	MIC (µg/mL)		
		Number of occurrences at MIC of:	Mode	Median
(b) (4)				
<i>Enterococcus faecalis</i> ATCC 29212				
Lot# 16212	28		32	32
Lot# 16263	3		64	64
<i>Escherichia coli</i> ATCC 25922				
Lot# 16015	9		0.5	0.5
Lot# 16153	17		0.5	0.5
Lot# 16204	7		0.5	0.5
Lot# 16344	12		0.25	0.25
Lot# 16365	4		0.25	0.25
Lot# 17035	2			
<i>Pseudomonas aeruginosa</i> ATCC 27853				
Lot# 16015	9		2	2
Lot# 16153	17		2	2
Lot# 16204	7		2	2
Lot# 16344	12		2	1.5
Lot# 16365	4		1	1
Lot# 17035	2		2	2
<i>Staphylococcus aureus</i> ATCC 29213				
Lot# 16212	28		1	1
Lot# 16263	3		0.25	0.25

Shading indicates the proposed QC range
Source: [ACHN490-MB-049-QCS](#)

Reviewer's comments:

Plazomicin behaves similarly to amikacin and gentamicin with regards to conditions for testing

- For **Enterobacteriaceae**, plazomicin MICs were not affected by cation concentration and addition of supplements (including serum). Minimal effects on the plazomicin MICs were observed with changes to the inoculum density. Similar to other aminoglycosides, changes in pH and incubation conditions

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- (anaerobic and 5% CO₂) affects the activity of plazomicin against these organisms.
- For *A. baumannii*, plazomicin MICs were not affected by cation concentration and inoculum density. Similar to other aminoglycosides, changes in pH affects the activity of plazomicin against these organisms. No information was provided for incubation conditions or addition of serum on plazomicin activity.
 - For *P. aeruginosa*, the impact of the cation concentration on plazomicin activity was primarily limited to these isolates. Plazomicin MICs were not affected by inoculum density or incubation conditions. Minimal effects on the plazomicin MICs were observed with changes to the inoculum density and addition of supplements (including serum). Similar to other aminoglycosides, changes in pH affects the activity of plazomicin against these organisms.
 - For *S. aureus*, plazomicin MICs were not affected by cation concentration. Minimal effects on the plazomicin MIC were seen with changes to the inoculum density and addition of supplements (including serum) in the media. Similar to other aminoglycosides, changes in pH and incubation conditions affects the activity of plazomicin against these organisms.

The presence of lung surfactant (5% or 10%) or white blood cells (intact or lysed) had no effect on plazomicin MICs against the gram-positive and gram-negative isolates tested.

Based on these results, plazomicin broth microdilution assays should be conducted in accordance with CLSI recommended methodology (M07-A10 [2015]). The following QC MIC ranges is acceptable and recommended for:

(b) (4)

The Thermofisher (Remel) pre-made frozen panels is acceptable for testing plazomicin MIC by the broth microdilution method.

3.2. Agar Dilution method

Plazomicin MICs generated by broth dilution method were compared to those generated by the agar dilution method. Isolates tested included 487 Enterobacteriaceae (90%), 27 *P. aeruginosa* (5%), and 27 *S. aureus* (5%) collected in 2015 globally (Africa, Asia, Europe, Latin America, Middle East, North America, and South Pacific) from multiple sources (intra-abdominal, skin and soft tissue, respiratory, urinary tract, blood, and other infections). The range of plazomicin concentrations tested by both methods were 0.5 – 64 µg/mL for *P. aeruginosa* and 0.06 – 8 µg/mL against Enterobacteriaceae and *S. aureus*. Good correlation was observed for plazomicin between the agar dilution compared with the broth microdilution method; showing 80.9% of the MICs for Enterobacteriaceae, 100% of MICs for *P. aeruginosa*, and 96.3% of MICs of *S. aureus* within ± 1- 2 doubling

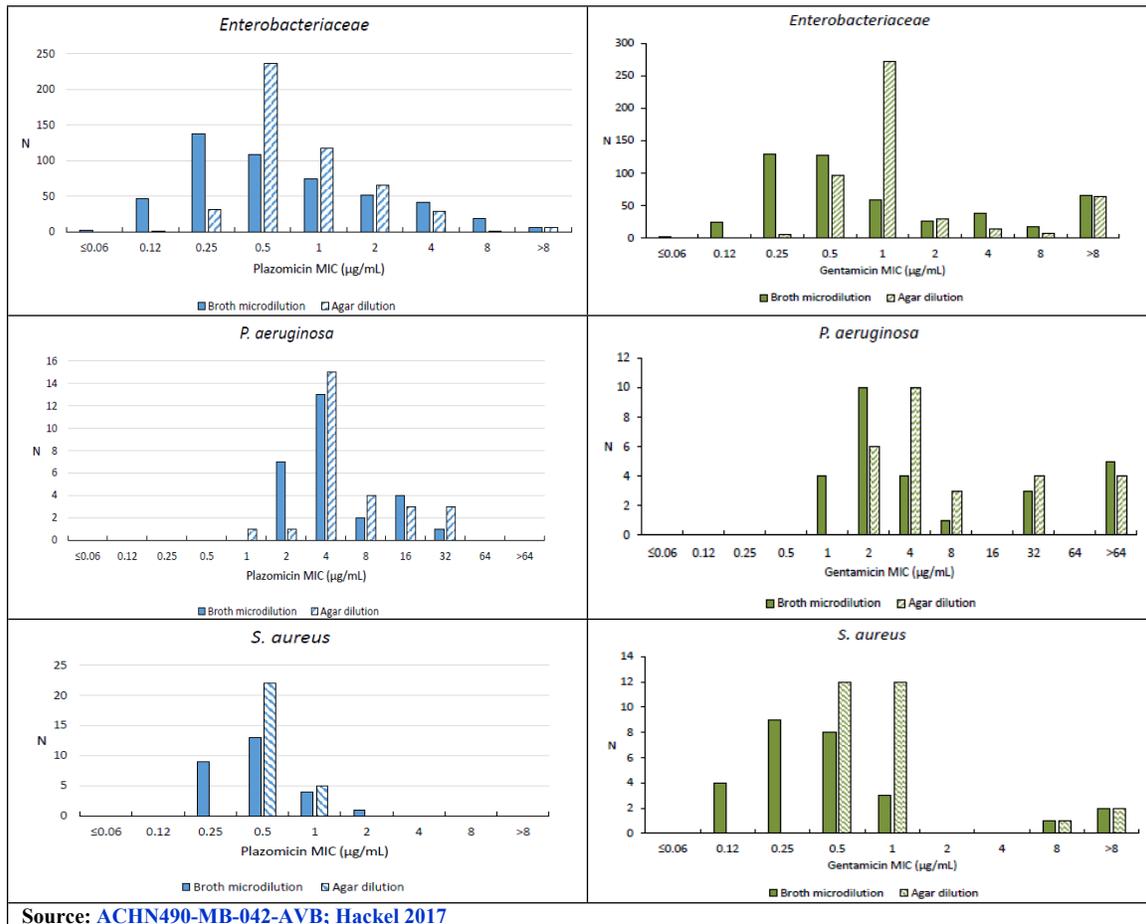
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dilution for the two methods. Most plazomicin MICs (82.6% overall) were within ± 1 dilution for the two test methods, there was a tendency toward higher MICs by agar dilution (Figure 2). This phenomenon of higher MICs by agar dilution was also observed for gentamicin, which had a slightly lower percentage of MICs within ± 1 dilution for the two tests method (72.6%)(ACHN-490-MB-042-AVB).

Figure 2: Frequency distribution of plazomicin MIC against Enterobacteriaceae, *P. aeruginosa* and *S. aureus* tested by broth microdilution and agar dilution



Reviewer's comments:

Plazomicin behaves similarly to amikacin and gentamicin with regards to conditions for testing by the agar dilution method. There was a tendency toward higher MICs by agar dilution method. Based on these results, plazomicin agar dilution assays should be conducted in accordance with CLSI recommended methodology (M07-A11 [2018]),

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3.3. Disk Diffusion method

Disk diffusion testing were performed using a 30-µg plazomicin disk provided by two manufacturers (MAST, Merseyside, UK and BioRad, Steenvorde, France).

3.3.1. Effect of various factors

The optimal disk mass concentration for plazomicin was determined by evaluating the performance of two different disk plazomicin masses (10 and 30 µg). Plazomicin 30-µg disks were manufactured by Mast (Lot# 358109) and 10 µg disks were prepared by (b) (4). Gentamicin (10 µg, BD Lot# 5182686) and amikacin (30µg, BD Lot# 5182692) disk were used as positive controls. Isolates were tested in duplicate by disk diffusion with both the 10µg and 30 µg disks in accordance with CLSI standard methods for disk testing (M02-A12 [2015]) and broth microdilution testing (M07-A10 [2015]) using the same inoculum. QC testing was performed using the reference organisms *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 for broth microdilution and disk diffusion assays. Against the QC strains, plazomicin MICs were all within recommended range by the broth microdilution method (Table 3). Larger zone diameters were observed for the 30-µg disk, compared to the 10-µg disk against QC strains.

Table 3: Comparison of 10- µg and 30- µg disks by disk diffusion and broth microdilution method against QC strains

QC Organism	QC range* (µg/mL)	10 µg-disk Zone Diameters (mm)	30 µg-disk Zone Diameters (mm)
<i>Escherichia coli</i> ATCC 25922	0.25 – 1	20 – 24	22 – 27
<i>Pseudomonas aeruginosa</i> ATCC 27853	2 – 4	13 – 15	18 – 20
<i>S. aureus</i> ATCC 29213	0.25 – 1	20 – 23	22 – 26
<i>Enterococcus faecalis</i> ATCC 29212	32 - 64	NT	NT

NT= not tested

*See Table 1 for the plazomicin QC ranges

Source: ACHN490-MB-033-DMD

Further analyses were performed assessing the correlation between plazomicin disk diffusion and broth microdilution results using 508 gram-negative and gram-positive clinical isolates. A total of 374 Enterobacteriaceae (100 *E. coli*, 103 *K. pneumoniae*, 31 *K. oxytoca*, 32 *E. cloacae*, 24 *E. aerogenes*, 26 *C. freundii*, 26 *P. mirabilis*, 32 indole-positive *Proteae*), 51 *P. aeruginosa*, 11 *A. baumannii*, 53 *S. aureus*, 10 *E. faecalis* and 9 *E. faecium* were tested. Among Enterobacteriaceae isolates, 39 had characterized aminoglycoside resistance mechanisms. Isolates were obtained from global surveillance studies 2014 – 2015 (North America, Latin America and Europe) as well as from patients with bloodstream infections, skin and soft tissue infections and nosocomial and community acquired respiratory tract infections. Data were analyzed by scatterplot analysis, linear regression and error-rate bounding analysis of disk zone diameter results versus MIC results for plazomicin and control agents. Plazomicin MICs for all isolates tested ranged from ≤ 0.06–>128 µg/mL. The 10-µg and 30-µg plazomicin disks were

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both tested in duplicate (replicate A and replicate B). A total of 1016 results (for 508 isolates) were obtained for each disk mass. As expected, larger zone diameters were observed for the 30-µg disk as compared with the 10-µg disk (**Table 4**). The 30-µg disk zone diameters ranged from 6 to 33 mm, with an average size of 21.8 mm, while the 10-µg disk zone diameters ranged from 6 to 28 mm, with an average size of 18.8 mm.

Table 4: Comparison of 10-µg and 30-µg disks by disk diffusion and broth microdilution method against 508 clinical isolates

QC Organism	MIC range* (µg/mL)	10 µg-disk Zone Diameters (mm)	30 µg-disk Zone Diameters (mm)
Enterobacteriaceae	≤0.06 - > 128	6 - 27	6 - 30
<i>Pseudomonas aeruginosa</i>	0.25 - >128	6 - 26	6 - 30
<i>A. baumannii</i>	1 - >128	6 - 21	6 - 24
<i>S. aureus</i>	0.25 - 2	19 - 28	21 - 33
<i>Enterococcus</i> spp.	2 - 128	6 - 19	9 - 24

Source: [ACHN490-MB-033-DMD](#)

When the 10-µg plazomicin disk zone diameter values were compared with the plazomicin MIC values, a clustering of 48 results at 6 mm corresponding to plazomicin MIC values ranging from 16 to >128 µg/mL was observed (**Figure 1**). Furthermore, a total of 83 zone diameter results of <9 mm obtained with the 10-µg disk corresponded to plazomicin MIC results ranging from 8 to >128 µg/mL.

Figure 3: Scatter diagram of plazomicin MIC results and 10-µg disk zone diameter values against 508 Enterobacteriaceae isolates



Source: [ACHN490-MB-033-DMD](#)

In comparison, when the 30 µg disk plazomicin zone diameter values were compared with the plazomicin MIC values, linearity was observed even at diameters associated with higher MIC values (**Figure 4**). MIC values of 16 to > 128 µg/mL corresponded to a wider range of zone diameters (6 to 14 mm). Overall, the results showed wider

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correlation and linearity using the 30- μ g disk compared to the 10- μ g disks. The 30 μ g disk was used for further analyses.

Figure 4: Scatter diagram of plazomicin MIC results and 30- μ g disk zone diameter values against 508 isolates



Source: [ACHN490-MB-033-DMD](#)

Stability studies were conducted to determine conditions under which manufactured disks can continue to provide reliable susceptibility results. The disks manufactured by MAST disk (Merseyside, MK) were used. A production lot of disks were exposed to a range of temperatures (-20°C, 4°C, 25°C, 37°C and 56°C) in accordance with standard quality control methods for antibiotic disks over a 2-year period. Additionally, a set of disks were held at room temperature (~25°C) for 1 month before being returned to 4°C in order to simulate transport and in-use robustness. Results showed disks held at room temperature and 4°C storage conditions were well stable meeting specifications for the 12-month and 18-month batches, indicating a shelf-life of up to (b) (4) months is recommended.

3.3.2. Quality Control parameters

Prior to conduct of the phase 2/3 clinical studies, plazomicin QC limits were determined in a multi-center, tier 2 study which determine disk diffusion zone diameter ranges against 3 standard QC strains (of *S. aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853). The zone diameters were determined in accordance with CLSI M23-A3 (2008) guidelines. Nine independent laboratories in US and Canada were used in these studies. Two different lots of 30- μ g disks were tested from two manufacturers: MAST group, Merseyside, United Kingdom (Lot# 255748) and Bio-Rad, Hercules, CA (Lot# 9H0010). Single lots of amikacin disks were used as a comparator disk manufactured from BD/BBL, Franklin Lakes, NJ (Lot# 9079053). Plates contained three lots of Mueller Hinton Agar (Remel Lot# 806005, Lenexa, KS; BD/BBL Lot# 92010901 and Teknova Lot# M002517C0901). Each laboratory tested 10 replicates of *S. aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. A total of 1,619 zone diameters were reported for the disk diffusion method, plazomicin results are summarized as proposed ranges in **Table 5**:

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- *Escherichia coli* ATCC 25922 ranged from (b) (4) mm (b) (4) mm range), which included 98.9% of the reported results.
- *Pseudomonas aeruginosa* ATCC 27853 ranged from (b) (4) mm (b) (4) mm range) which included 98.3% of the reported results.
- *Staphylococcus aureus* ATCC 25923 ranged from (b) (4) mm (b) (4) mm range) which included 98.7% of the reported results. These results excluded the results from two laboratories which reported diameters that were outside this range (60 results from Lab E and 2 from Lab C). The reasons for these discordant values are unknown.
- There was ≤ 2 mm variation between the lots of disks and ≤ 2 mm variation across all organisms and investigational media.
- Amikacin against QC strains were reported within the published ranges (96.3%) providing a valid internal control for the study.

Table 5: Quality control ranges of plazomicin disk diffusion zone diameters

QC Organism	Proposed range (mm)	Total (N)	% results in proposed range
<i>Escherichia coli</i> ATCC 25922	(b) (4)	540	98.9
<i>Pseudomonas aeruginosa</i> ATCC 27853		539	98.2
<i>S. aureus</i> ATCC 29213		540	98.7
		520 ¹	98.8
		478 ²	98.7

Source: ACHN490-MB-49-QCS

In the phase 3 clinical trials, Kirby-Bauer disks containing 30 µg plazomicin were provided by Mast Group, Ltd. Two different disk lots (Lot# 375428 and 358109) were tested against the QC strains:

- For *E. coli* ATCC25922, 54 distinct zone diameters were obtained and were within range (b) (4) mm).
- For *P. aeruginosa* ATCC 27853, 54 distinct zone diameters were obtained and all were within range (b) (4) mm).
- For *S. aureus* ATCC 29213, there were 54 distinct zone diameters obtained and all were within range (b) (4) mm) except 1 result which produced a zone diameter of (b) (4) mm (Lot# 358109)

Table 6: Plazomicin QC zone diameter results from the phase 3 clinical trials

QC Strain	No. Tested	Zone Diameters (mm)		
		Range	Mode	Median
<i>Escherichia coli</i> ATCC 25922		(b) (4)		
Lot# 375428	22		24	24
Lot# 358109	32		25	25
<i>Pseudomonas aeruginosa</i> ATCC 27853		(b) (4)		
Lot# 375428	22		20	19
Lot# 358109	32		18	18
<i>Staphylococcus aureus</i> ATCC 29213		(b) (4)		
Lot# 375428	22		22	22

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QC Strain	No. Tested	Zone Diameters (mm)		
		Range	Mode	Median
Lot# 358109	32	(b) (4)	1	23

Shading indicates the proposed QC range

Source: [ACHN490-MB-049-QCS](#)

Reviewer's comments:

Good linearity was observed with the plazomicin 30-µg disks when compared with the broth microdilution method.

Based on these results, plazomicin disk diffusion should be conducted in accordance with CLSI recommended methodology (M02-A13[2018]). The following QC zone diameter ranges is acceptable and recommended for:

(b) (4)

The MAST Group Ltd (Merseyside, UK) 30-µg disks is acceptable for testing plazomicin zone diameters by the disk diffusion method.

4. ANIMAL MODELS OF INFECTION

Plazomicin was evaluated in various animal models of infection including septicemia, respiratory tract, urinary tract, neutropenic thigh and lung infections. Many of the isolates tested produced clinically relevant AMEs or characterized β-lactamases and had plazomicin MIC values ranging from 0.25 to 16 µg/mL.

4.1. Mouse septicemia model

Septicemia was established by infecting CD-1 male mice (weighing 24 ± 2 g) with twice the 90-100% lethal dose of *E. coli* ATCC25922 or *Pseudomonas aeruginosa* ATCC 27853. Subcutaneous treatment with plazomicin or comparators was administered at 1 hour post-inoculation and monitored for survival for 7 days. The median effective dose (ED₅₀) was determined that protected 50% of the mice from death.

- Against the *E. coli* ATCC25922 strain (plazomicin MIC, 1 µg/mL), plazomicin ED₅₀ (0.60 - <1 mg/kg) was similar to gentamicin (0.48 – 0.66 mg/kg), while higher ED₅₀ values were observed for amikacin (2.21 – 2.52 mg/kg).
- Against *P. aeruginosa* ATCC 27853 (plazomicin MIC, 2 µg/mL), plazomicin (ED₅₀ 8.3 mg/kg) and gentamicin (ED₅₀ 5.2 mg/kg) were more effective than amikacin (ED₅₀ 22.4 - >30 mg/kg); achieving 100% survival at lower ED₅₀s.
- A higher ED₅₀ was observed for plazomicin against *P. aeruginosa* compared to Enterobacteriaceae, suggesting that plazomicin may show diminished *in vivo* activity against *P. aeruginosa*.

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Table 7: Activity of plazomicin and comparators against gram-negative isolates in mouse septicemia model

Organism (CFU/mouse)	Compound	MIC (µg/mL)	Route of Administration	Dose Range	ED ₅₀
<i>Escherichia coli</i> ATCC 25922 (4.5 x 10 ⁵)	Plazomicin	1	SC	1 – 3	<1
				0.2 – 3	0.6
	Amikacin	4	SC	1 – 10	2.21
				0.8 – 10	2.52
	Gentamicin	0.5	SC	0.3 – 3	0.48
				0.2 – 3	0.66
		IV	0.2 – 3	0.61	
<i>P. aeruginosa</i> ATCC 27853 (5.8 x 10 ⁴)	Plazomicin	2	SC	10 – 30	ND
				2 – 30	8.31
	Amikacin	4	SC	3 – 30	>30
				2 – 60	22.4
	Gentamicin	1	SC	1 – 10	4.19
				0.8 – 30	5.22
		IV	0.8 – 30	5.0	

ED₅₀ = median effective dose; IV = intravenous SC = subcutaneously

Source: Study# ACHN490-PHA001, ACHN490-PHA002, ACHN490-PHA003, ACHN490-PHA004. Reyes (2011)

The activity of plazomicin alone or in combination with meropenem or tigecycline was evaluated against Enterobacteriaceae in an immunocompetent murine septicemia model. A humanized dose of plazomicin was used in this study. Plazomicin alone provided 80 - 100% survival benefit over meropenem or tigecycline alone or in combination with plazomicin. Survival rates for each of the plazomicin-based combinations were generally comparable to survival rates for plazomicin alone. The one exception was against *K. pneumoniae* KP561 isolate which showed higher survival for the combination than plazomicin, meropenem and tigecycline alone. Negative blood cultures were reported for 78/80 animals against all isolates within 4 hours of initiation of treatment, including in animals that did not survive to 96 hours. Overall, higher survival rates were observed in animals treated with plazomicin alone with isolates that had plazomicin MICs ≤ 4 µg/mL (86%) compared to treatment in animals infected with isolates that had plazomicin MIC values ≥ 8 µg/mL (53.3%). One exception was noted with *K. pneumoniae* KP557 (plazomicin MIC 2 µg/mL) in which survival was 60% at 96 hours.

Table 8: Survival rates for plazomicin alone or in combination with meropenem or tigecycline against Enterobacteriaceae isolates in mouse septicemia model.

Organism	Resistance Mechanism	MIC (µg/mL)			Survival by 96 hours				
		PLZ	MEM	TGC	PLZ Alone	PLZ +MEM	PLZ + TGC	MEM Alone	TGC Alone
<i>K. pneumoniae</i> KP557	<i>Aac(6')-Ib</i> , <i>bla</i> _{KPC-2}	2	8	0.5	60%	60%	80%	80%	0%
<i>K. pneumoniae</i> KP558	<i>Aac(3)-IIa</i> , <i>bla</i> _{KPC-3}	2	≥ 32	1	100%	80%	100%	10%	30%
<i>E. coli</i> EC471	Not determined	4	0.03	≤ 0.06	100%	70%	80%	90%	70%
<i>C. freundii</i> CF38	Not determined	4	0.06	0.5	90%	100%	100%	100%	60%
<i>K. oxytoca</i> KO92	Not determined	4	≤ 0.015	0.12	80%	90%	90%	90%	80%
<i>K. pneumoniae</i> KP561	<i>Aac(3)-IIa</i> , <i>aac(6')-Ib</i> , <i>bla</i> _{OXA-48} , reduced	8	≥ 32	2	20%	100%	90%	0%	10%

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	ompK36 expression								
<i>M. morgani</i> MM65	Not determined	8	0.06	1	70%	100%	80%	80%	0%
<i>K. pneumoniae</i> KP559	Aac(3)-IIa, aac(6')-Ib, bla _{OXA-48} , reduced ompK36 expression	16	≥ 32	2	70%	70%	80%	10%	0%

MEM=meropenem; MIC=minimum inhibitory concentration; PLZ=plazomicin; R=resistant; S=susceptible; TGC=tigecycline.

Note: Regimens in humans were plazomicin 15 mg/kg IV q24h as a 30-minute infusion, meropenem 2 g IV q8h as a 3-hour infusion, and tigecycline 50 mg IV q12h.

^a Meropenem MIC ≤1/2/≥4 interpreted as susceptible/intermediate/resistant per CLSI M100-S27 based on 1 g IV q8h regimen.

^b Tigecycline MIC ≤2/4/≥8 interpreted as susceptible/intermediate/resistant per Tygacil 2016.

Source: [Study# A16040-1490-EF-M](#)

4.2. Urinary tract infection model

In a urinary tract infection model (with diuresis induced 6 days before the beginning of and maintained during the course of the study), female C3H/HeJ mice were inoculated transurethrally with 8.8 log₁₀ CFUs of the aminoglycoside-susceptible *E. coli* ATCC 700336. Plazomicin (range 0.125 to 8 mg/kg) was administered subcutaneously twice per day. Gentamicin (0.125 to 2 mg/kg) and levofloxacin (0.125 and 0.5 mg/kg) were used as comparators. Treatment started 4 days after bacterial inoculation for 3 days. Urine, bladders and kidneys were collected 18 hours after final dose and plated for colony enumeration. The difference between the mean log₁₀ CFU reduction were determined as the difference between the mean CFU counts of untreated 7-day controls compared to antibiotic treated groups. Compared with controls, at doses of 1 – 16 mg/kg/day of plazomicin showed significant reduction in bacterial loads in the kidney (3.36 – 4.5 log₁₀ reduction), bladder (1.97 – 4.1 log₁₀ reduction) and urine (3.78 – 4.5 log₁₀ reduction). At doses ≥ 0.5 mg/kg, similar reduction in counts in kidney, bladder and urine were observed with plazomicin as with gentamicin and levofloxacin (2016-06-UTI; Pulse et al., [2010]).

4.3. Neutropenic mouse thigh infection model

The activity of plazomicin was assessed in a series of studies using a neutropenic thigh infection model. Neutropenic mice were infected by an intramuscular injection with Enterobacteriaceae isolates including two aminoglycoside susceptible strains (*Klebsiella pneumoniae* ATCC 43816 and *E. coli* AECO001 strain), two multidrug-resistant strains (*K. pneumoniae* AKPN1073 and *E. coli* AECO1003) and two strains expressing *K. pneumoniae* carbapenemase (KPC; *K. pneumoniae* AKPN1109 and *Serratia marcescens* ASMA1030). In addition, the model was tested with a strain of methicillin-resistant *S. aureus* ATCC33591. Plazomicin MIC values ranged from 0.25 to 4 µg/mL. Plazomicin was administered subcutaneously beginning 2 hours post infection of total doses ranging from 1 to 64 mg/kg per day. Twenty four hours after treatment, mice were euthanized, thigh muscle excised and bacterial load (CFU/g) enumerated. The slope of the dose response curve was calculated and used to predict the static dose (Table 9).

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Against Enterobacteriaceae isolates, plazomicin showed dose-dependent activity depending on the isolate. Against the aminoglycoside susceptible isolates, *K. pneumoniae* ATCC43816 and *E. coli* ATCC25922, plazomicin doses of 7.8 mg/kg/day and 10.6 mg/kg/day reduced the bacterial load to below the static level, respectively. Plazomicin activity was comparable to gentamicin and ciprofloxacin against these isolates, whereas treatment with imipenem using the same dosing schedule was less effective against *K. pneumoniae* ATCC 43816 (static dose >200 mg/kg/day).

Plazomicin showed activity against the MDR Enterobacteriaceae isolates, *K. pneumoniae* AKPN1073 (static dose = 12 mg/kg/day) and *E. coli* AECO1003 (static dose = 25 mg/kg/day). Gentamicin and ciprofloxacin was completely ineffective against these isolates; doses as high as 64 mg/kg/day failed to reduce the bacterial load relative to untreated animals. Imipenem activity was similar to plazomicin against *E. coli* AECO1003 strain; however higher doses of imipenem compared to plazomicin were needed to achieve stasis for the *K. pneumoniae* AKPN1073 strain.

Against the two KPC-positive (β -lactam resistant), *K. pneumoniae* AKPN1109 and *S. marcescens* ASMA1030, imipenem was ineffective against both isolates. Similarly, gentamicin and ciprofloxacin did not inhibit either strain (static dose >64 mg/kg). This was an expected finding since these strains harbor AMEs and mutations in the quinolone resistance determining region. The highest dose of plazomicin needed to reduce the bacterial load to below static level against *S. marcescens* ASMA1030 was 37 mg/kg/day; whereas higher doses were needed against the *K. pneumoniae* AKPN1109 (static dose = 64 mg/kg/day).

Against *S. aureus* ATCC 33591, plazomicin (static dose = 52 mg/kg/day) was comparable to gentamicin (static dose = 53 mg/kg/day). In comparison, lower doses of vancomycin and daptomycin were required to achieve stasis in the model whereas higher doses of arbekacin were needed.

Table 9: Dose required to achieve stasis of plazomicin and comparators in the neutropenic mouse model of thigh infection

Organism	Resistance Mechanism	Antimicrobial Agent	MIC (μ g/mL)	Range of Doses (mg/kg/day)	Dose required for stasis (mg/kg/day)
<i>E. coli</i> ATCC 25922 (AEC001)	None	Plazomicin	1	4 – 64	11
		Gentamicin	0.5	4 – 64	7.8
		Ciprofloxacin	0.008	4 – 64	<4
		Imipenem	0.125	10 – 200	<10
<i>E. coli</i> AECO1003	<i>aac(3)-IIa</i> <i>ant(2'')-Ia</i>	Plazomicin	1	4 - 64	25
		Gentamicin	>64	4 – 64	>64
		Ciprofloxacin	>32	4 – 64	>64
		Imipenem	0.125	10 – 200	23
<i>K. pneumoniae</i> ATCC 43816	None	Plazomicin	0.5	4 – 64	7.8
		Gentamicin	0.5	4 – 64	15
		Ciprofloxacin	0.03	4 – 64	22
		Imipenem	0.5	10 – 200	>200

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Organism	Resistance Mechanism	Antimicrobial Agent	MIC (µg/mL)	Range of Doses (mg/kg/day)	Dose required for stasis (mg/kg/day)
<i>K. pneumoniae</i> AKPN1073	<i>aac(3)-IIa</i> <i>aac(6')-Ib</i>	Plazomicin	0.5	4 – 64	12
		Gentamicin	>64	4 – 64	>64
		Ciprofloxacin	>16	4 – 64	>64
		Imipenem	0.25	10 – 200	97
<i>K. pneumoniae</i> AKPN1109	<i>bla_{KPC}</i>	Plazomicin	0.25 – 0.5	4 – 64	64
		Gentamicin	64	4 – 64	>64
		Ciprofloxacin	2	4 – 64	>64
		Imipenem	32	10 – 200	>200
<i>S. marcescens</i> ASMA1030	<i>bla_{KPC}</i>	Plazomicin	1	4 – 64	37
		Gentamicin	>64	4 – 64	>64
		Ciprofloxacin	>8	4 – 64	>64
		Imipenem	>32	10 – 200	>200
<i>S. aureus</i> ATCC 33591	MRSA	Plazomicin	4	8 – 256	54
		Gentamicin	2 – 4	8 – 256	52
		Arbekacin	4	8 – 256	148
		Vancomycin	1	8 – 128	20
		Daptomycin	NR	4 – 64	<4

Source: Study# AA92320; ACHN490-PHA006; ACHN490-MB-056-MPD, ACHN490-MB-057-MPD, ACHN490-PHA011; ACHN490-PHA012, Reyes et al., [2011]

4.4. Neutropenic lung infection model

Table 10 shows the plazomicin doses and comparators needed to achieve net bacterial stasis, 1-log₁₀ and 2-log₁₀ CFU reduction in the bacterial burden in neutropenic lung infection mouse models.

Against 7 *K. pneumoniae* isolates, plazomicin doses of 0.7 to 5.35 mg/kg/day were sufficient to achieve net stasis. To reduce the bacterial burden in the lungs of mice by 1-log₁₀ kill and 2-log₁₀ kill were achieved with 0.7 – 5.35 mg/kg/day and 1.6 – 17 mg/kg/day of plazomicin, respectively. The doses of plazomicin needed to achieve 1-log₁₀ kill and 2-log₁₀ kill were similar between AME encoding isolates and isolates that did not encode an AME. Plazomicin showed similar activity to gentamicin against aminoglycoside susceptible isolates (ATCC 43816 and AKPN1046); however, higher doses were needed for AME producing isolates (AKPN1066, AKPN1077 and AKPN1087) and multi-drug resistant isolates (AKPN1113).

Against 4 *P. aeruginosa* isolates, stasis was achieved at plazomicin doses ranging from 26 to 251 mg/kg/day for all isolates; however, 1-log₁₀ kill and 2-log₁₀ kill was achieved in only two of four isolates (ATCC27853 and APAE1178). Higher doses of plazomicin were required to achieve stasis for *P. aeruginosa* compared to doses required to achieve stasis in Enterobacteriaceae.

Against *A. baumannii*, plazomicin doses required to achieve stasis ranged from 8.6 to 50 mg/kg/day. Plazomicin doses for 1-log₁₀ kill and 2-log₁₀ kill ranged from 19 to 91 mg/kg/day and 36 to 237 mg/kg/day, respectively.

Against *S. aureus*, plazomicin doses required to achieve stasis, 1-log₁₀ kill and 2-log₁₀ kill

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were 3.4 to 6.7 mg/kg/day, 6.1 to 25 mg/kg/day and 23 to >256 mg/kg/day, respectively. Higher doses of plazomicin were required for stasis against *S. aureus* in the thigh model as compared to the lung model.

Table 10: Dose levels required for net bacterial stasis, 1-log₁₀ and 2-log₁₀ reductions in bacterial burden in neutropenic mouse lung infection model

Organism	Strain	Resistance Mechanism	Test Article	MIC (µg/ml)	Dose (mg/kg/day) to achieve			
					Stasis	1-Log ₁₀ Reduction	2-Log ₁₀ Reduction	
<i>K. pneumoniae</i>	ATCC 43816	None	Plazomicin	0.25	1.6	3.5	9.0	
			Amikacin	0.80	16	24	36	
			Gentamicin	0.21	1.9	2.7	7.5	
	AKPN1025*	ND	Plazomicin	0.19	0.5	1.3	3.5	
			Amikacin	12	26	50	>87.5	
			Gentamicin	37.3	34	>87.5	>87.5	
	AKPN1046	None	Plazomicin	0.5	0.8	3.3	11	
			Amikacin	2	<10.9	<10.9	27	
			Gentamicin	0.25	<2.7	<2.7	4.6	
	AKPN1066*	<i>Ant(2'')-Ia</i>	Plazomicin	0.38	0.6	1.3	4.2	
			Amikacin	1.5	2.2	5	15.8	
			Gentamicin	24	69	151	>175	
	AKPN1077	<i>Aac(3)-IV, Aac(6')-Ib</i>	Plazomicin	0.19	1.1	4.3	17	
			Amikacin	64	109	>175	>175	
			Gentamicin	9.3	<43.8	<43.8	43.8	
	AKPN1087	<i>Aac(6')-Ib</i>	Plazomicin	0.21	0.4	0.7	1.6	
			Amikacin	1.7	<10.9	<10.9	10.9	
			Gentamicin	3	<10.9	<10.9	10.9	
	AKPN1113*	<i>Bla_{NDM-1}, Bla_{CTX-M-15}, bla_{SHV-11}, bla_{oxa-1}</i>	Plazomicin	0.19	2.1	5.35	15.5	
			Amikacin	2.7	49	87	>175	
			Gentamicin	>64	>175	>175	>175	
	<i>P. aeruginosa</i>	ATCC27853	None	Plazomicin	1.2	26	32	40
				Gentamicin	0.39	8.9	16	31
		APAE1006	<i>Aac(3)-II, Aac(6')-Ib</i>	Plazomicin	3.7	251	>256	>256
Imipenem				6.7	<50	<50	<50	
APAE1123		<i>Ant(2'')-Ia</i>	Plazomicin	3.5	249	>256	>256	
			Amikacin	2.9	196	>256	>256	
APAE1178		Not determined	Plazomicin	11	133	164	240	
			Amikacin	12	137	172	212	
<i>A. baumannii</i>		AABA1088	None	Plazomicin	8.7	50	91	237
				Amikacin	3.0	9.4	74	>256
	AABA1047	<i>Ant(2'')-Ia</i>	Plazomicin	1.5	8.6	19	36	
			Amikacin	2.3	5.1	25	256	
	AABA1092	<i>Ant(2'')-Ia</i>	Plazomicin	1.3	18	27	42	
			Imipenem	12	>256	>256	>256	
AABA1100	<i>Ant(2'')-Ia</i>	Plazomicin	1.3	24	35	55		

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Organism	Strain	Resistance Mechanism	Test Article	MIC (µg/ml)	Dose (mg/kg/day) to achieve		
					Stasis	1-Log ₁₀ Reduction	2-Log ₁₀ Reduction
<i>S. aureus</i>	ATCC 33591	MRSA	Imipenem	12	>256	>256	>256
			Plazomicin	4.3	4.5	25	>256
			Amikacin	16	43	>256	>256
			Vancomycin	1.5	6.6	22	>128
			Linezolid	1.5	4.2	25	>256
	ASAU1029	MRSA	Plazomicin	0.38	3.4	6.1	13
			Amikacin	4.3	73	92	>256
			Vancomycin	0.80	34	39	>128
			Linezolid	1.6	13	20	>256
	ASAU1103	MRSA	Plazomicin	0.56	6.7	12	23
			Amikacin	27	315	>512	>512
			Vancomycin	0.5	53	112	>128
Linezolid			4.0	57	256	>256	

Source: Study# ORI-2011-004; *Study# ORI-2010-003; Louie 2012; ACHN490-MB-054-MPD; Reyes (2011b; ACHN490-MB-055-MPD; ACHN490-MB-053-MPD

4.5. Granulocyte-replete mouse model of pneumonia

A dose-ranging study was evaluated against *P. aeruginosa* ATCC 27853 in a granulocyte-replete murine pneumonia model. Plazomicin was administered as humanized doses in decrementing doses 5 times over 24 hours, mimicking a human daily administration profile. Pharmacokinetic profiling was performed in plasma and epithelial lining fluid. Mouse cohorts were treated for 24 hours whereas another cohort was treated with the same therapy and observed for another 24 hours after therapy cessation, allowing enumeration of therapeutic effect necessary to reduce the bacterial burden to a level below the half saturation point. No animals in the untreated control group or the lowest dosing group of plazomicin survived up to 50 hours post-infection. Stasis was achieved at plazomicin doses ranging from 18.2 to 21.9 mg/kg/day; plazomicin doses \geq 43.8 mg/kg/day were required for further reduction in bacterial load. Plazomicin concentrations at 26-hours post-infection were <0.61 mg/L in plasma and <0.56 mg/L in epithelial lining fluid. The difference in log₁₀ reduction between 26 hours and 50 hours post-infection reflects granulocytes affecting an additional 1 – 1.5 log₁₀ kill in the period post-treatment. The data suggest that plazomicin-mediated bacterial load reduction enables additional pathogen clearance by immune system components (Drusano et al., [2014]).

Reviewer's comments:

Plazomicin demonstrated activity in various animal models of infections including septicemia, UTI, lung and thigh infection. Many of the isolates tested produced clinically relevant AMEs or characterized β -lactamases and had plazomicin MIC values ranging from 0.25 to 16 µg/mL.

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- In a mouse septicemia model, plazomicin demonstrated activity against Enterobacteriaceae isolates including ESBL-producing, CRE and aminoglycoside non-susceptible isolates (*K. pneumoniae*, *E. coli*, *C. freundii*, *K. oxytoca* and *M. morgani*). Plazomicin alone provided 80 to 100% survival benefit against isolates with MIC values ≤ 4 $\mu\text{g/mL}$, and reduced survival against isolates with MIC values ≥ 8 $\mu\text{g/mL}$.
- In UTI model, plazomicin showed similar activity to gentamicin and levofloxacin in reducing the bacterial load in kidney, bladder and urine against aminoglycoside susceptible *E. coli*.
- In neutropenic mouse thigh infection models, doses of plazomicin required to achieve stasis ranged from 11 to 64 mg/kg/day against Enterobacteriaceae (plazomicin MICs range, 0.25 – 1 $\mu\text{g/mL}$). Plazomicin was similar in activity to amikacin and gentamicin against aminoglycoside-susceptible Enterobacteriaceae. However, plazomicin was generally more active than gentamicin or amikacin against Enterobacteriaceae isolates encoding different AMEs. Against methicillin-resistant *S. aureus* (plazomicin MIC 4 $\mu\text{g/mL}$), plazomicin doses of 53 mg/kg/day were required to achieve stasis.
- In neutropenic mouse lung infection models, total daily dose ranging from 0.7 to 5.35 mg/kg/day and 1.6 to 17 mg/kg was sufficient to reduce the bacterial burden by 1- \log_{10} kill and 2- \log_{10} kill, respectively against *K. pneumoniae* isolates (plazomicin MICs 0.25 – 8 $\mu\text{g/mL}$). The doses of plazomicin needed to achieve 1- \log_{10} kill and 2- \log_{10} kill were similar between AME encoding isolates and isolates that did not encode an AME. Against non-fermentative gram-negative aerobes, *P. aeruginosa* and *A. baumannii*, higher doses were required to achieve stasis compared to doses required to achieve stasis in Enterobacteriaceae.

The Applicant has provided the activity of plazomicin in a mouse model and non-human primate model in tularemia. In addition, the activity of plazomicin in a mouse and non-human primate model in plague. However, these models are not presented in this review since it is not relevant to the indications sought in this NDA.

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5. PHARMACOKINETICS/PHARMACODYNAMICS

The aminoglycosides demonstrate concentration-dependent killing; as the dose increases the rate of antibacterial kill also increases. The ratio of the area under the concentration-time curve from 0 to 24 hours to MIC (AUC_{0-24h}/MIC) or C_{max}/MIC as the PK/PD index most closely associated with efficacy. For aminoglycosides, an AUC/MIC ratio of 50 – 70 is associated with a 24h static effect for aerobic gram negative bacteria (*Enterobacteriaceae* and *Pseudomonas aeruginosa*) (Craig et al., 2011).

Similar to other aminoglycosides, the AUC_{0-24h}/MIC is the PK/PD parameter most closely associated with plazomicin efficacy ($r^2 = 0.876$) compared to C_{max}/MIC ($r^2 = 0.783$) or $T > MIC$ ($r^2 = 0.712$) against *K. pneumoniae* AKPN001 (ATCC 43816) in the neutropenic mouse thigh model. Plasma protein binding in mouse ($19.9 \pm 10.5\%$) was comparable to human ($19.6 \pm 8.8\%$) species (UFL-2016-001, ORI-2011-008).

Data from neutropenic murine thigh infection model following humanized dose of plazomicin were studied to determine the PK/PD targets associated with net-bacterial stasis, 1- \log_{10} reduction and 2- \log_{10} reduction compared to baseline. Isolates tested included 17 *Enterobacteriaceae* with a variety of AMEs and β -lactamases with plazomicin MIC values ranging from 0.19 to 4 $\mu\text{g/mL}$ (Table 11). Net bacterial stasis was achieved for all bacterial strains with median AUC_{0-24h}/MIC values of 23.6 (mean = 27.4) based on total drug plasma concentration. Against the 8 carbapenem-resistant *K. pneumoniae*, the median plazomicin AUC_{0-24h}/MIC target to achieve stasis in the model was 26. It was noted that 1- \log_{10} kill was not consistently achieved against all isolates tested; the magnitudes could not be estimated or were in the highest quartile for 4 isolates (AEAE1034, AECO1173, AKPN1113, AKPN1077). A 2- \log_{10} reduction was not achieved for any of the bacterial isolates; plazomicin doses as high as 225 mg/kg/day were tested.

Table 11: Target values of plazomicin AUC_{0-24h}/MIC for stasis and 1- \log_{10} kill against *Enterobacteriaceae* isolates in neutropenic mouse thigh infection models

Strain	Resistance Mechanism	Plazomicin MIC	Total-Drug Plasma $AUC_{0-24h}:MIC$ based on Neutropenic Mouse Thigh Model	
			Stasis	1- \log_{10} Kill
<i>K. pneumoniae</i> AKPN001 (ATCC 43816)	None	0.29	26	48
<i>K. pneumoniae</i> KPN1106	KPC-2	0.29	6	29
<i>K. pneumoniae</i> AKPN1118	KPC-2	0.19	34	95
<i>K. pneumoniae</i> AKPN1114	KPC	0.38	65	131
<i>K. pneumoniae</i> AKPN1116	KPC-3	0.21	17	135
<i>K. pneumoniae</i> AKPN1113	NDM-1 (methylase-negative), CTX-M-15, SHV-11, OXA-1	0.19	62	263
<i>K. pneumoniae</i> AKPN1117	KPC-2, SHV-12	0.29	30	89
<i>K. pneumoniae</i> AKPN1077	KPC	0.19	52	158
<i>K. pneumoniae</i> AKPN1169	Bla_{KPC-3}	2	20.2	152
<i>K. pneumoniae</i> AKPN1170	$Aac(6')-Ib$, bla_{KPC-2}	2	23.6	85.0

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Strain	Resistance Mechanism	Plazomicin MIC	Total-Drug Plasma AUC _{0-24h} :MIC based on Neutropenic Mouse Thigh Model	
			Stasis	1-Log ₁₀ Kill
<i>K. pneumoniae</i> AKPN1171	Not determined	4	15.9	NA
Median			26	113
Mean			32.0	118.5
<i>E. coli</i> AECO1133	KPC-2, TEM-1	0.46	13	59
<i>E. coli</i> AECO1173	<i>Aac(3)-IIa</i>	0.25	43.5	518
<i>E. coli</i> AECO1176	<i>Aac(6')-Ib</i>	1	33.0	60.7
<i>E. coli</i> AECO1179	<i>Aac(3)-IIa</i> <i>Aac(6')-Ib</i>	2	7.57	11.3
<i>E. coli</i> AECO1180	<i>Aac(3)-IIa</i>	4	5.67	8.09
Median			13	59
Mean			20.5	131.4
<i>E. aerogenes</i> AEAE1034	Not determined	1	10.9	NA
Total Number of Isolates Tested			17	17
Median			23.6	89
Mean			27.4	122.8
25% Quartile			12	48
75% Quartile			38.8	152.1

Source: Study# UFL-2012-009; ICPD – 00211-2

Pooled data from neutropenic murine pneumonia models were studied to determine the PK/PD targets associated with net-bacterial stasis, 1-log₁₀ and 2-log₁₀ reduction compared to baseline. Isolates tested included 15 Enterobacteriaceae with a variety of AMEs and β-lactamases with plazomicin MIC values ranging from 0.19 to 4 μg/mL (Table 12). Net bacterial stasis, 1-log₁₀ kill and up to 2-log₁₀ kill was achieved in the lung model. Net bacterial stasis was achieved for 14 of the 15 bacterial strains with median AUC_{0-24h}/MIC values of 2.87. The median AUC_{0-24h}/MIC values for 1-log₁₀ kill and 2-log₁₀ kill were 2.87, 8.45 and 25.4, respectively. Requisite exposures for stasis and 1-log₁₀ kill trended lower in the ELF than in plasma.

Table 12: Target values of plazomicin AUC_{0-24h}/MIC for stasis, 1-log₁₀ kill and 2-log₁₀ kill against Enterobacteriaceae isolates in neutropenic mouse pneumonia models

Strain	Resistance Mechanism	Plazomicin MIC	ELF AUC _{0-24h} :MIC Targets		
			Stasis	1-Log ₁₀ Kill	2-Log ₁₀ Kill
<i>K. pneumoniae</i> AKPN001 (ATCC 43816)	None	0.25	7.0	15.2	39.1
<i>K. pneumoniae</i> KPN1025	--	0.19	3.3	8.6	23.2
<i>K. pneumoniae</i> AKPN1046	--	0.5	2.0	8.3	27.7
<i>K. pneumoniae</i> AKPN1066	--	0.38	2.0	4.3	13.9
<i>K. pneumoniae</i> AKPN1077	KPC	0.19	7.3	28.5	113
<i>K. pneumoniae</i> AKPN1087	--	0.21	2.4	4.2	9.6
<i>K. pneumoniae</i> AKPN1113	NDM-1 (methylase-negative), CTX-M-15, SHV-11, OXA-1	0.5	13.9	35.8	106
<i>K. pneumoniae</i> AKPN1169	<i>Bla</i> _{KPC-3}	2	4.6	10.6	_ a
<i>K. pneumoniae</i> AKPN1170	<i>Aac(6')-Ib</i> , <i>bla</i> _{KPC-2}	2	2.44	9.65	33.7
<i>K. pneumoniae</i> AKPN1171	Not determined	4	4.4	31.0	_ a
Median			3.85	8.45	30.7
Mean			4.29	12.34	45.78
<i>E. coli</i> AECO1173	<i>Aac(3)-IIa</i>	0.25	0.1	0.6	4.9
<i>E. coli</i> AECO1176	<i>Aac(6')-Ib</i>	1	4.6	4.9	5.3

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Strain	Resistance Mechanism	Plazomicin MIC	ELF AUC _{0-24h} :MIC Targets		
			Stasis	1-Log ₁₀ Kill	2-Log ₁₀ Kill
<i>E. coli</i> AECO1179	<i>Aac(3)-IIa</i> <i>Aac(6')-Ib</i>	2	_ a	_ a	_ a
<i>E. coli</i> AECO1180	<i>Aac(3)-IIa</i>	4	5	6.26	8.1
Median			4.6	4.9	5.3
Mean			3.2	3.92	6.1
<i>E. aerogenes</i> AEAE1034	Not determined	1	1.0	4.9	35.1
Total Number of Isolates Tested			14	14	12
Median			2.87	8.45	25.4
Mean			4.0	12.25	34.97

Development of plazomicin resistance was also assessed in an *in vitro* chemostat model. Aminoglycoside pharmacokinetics is best described using tri-phasic elimination (alpha, beta and gamma). The significance of drug concentrations during gamma elimination phase was investigated in terms of prolonged low concentration on the impact on the bacterial growth after initial killing and the potential for emergence of resistance. Drugs were assessed using a once daily or twice daily dose scheme against 5 *E. coli* and 5 *K. pneumoniae* isolates with different resistance mechanisms. Emergence of resistance mutants were determined by plating samples onto agar plates containing no plazomicin and plazomicin at 1X, 2X, 4X and 8X the MIC at time zero (pre-exposure) and at 24-hour and 48-hour intervals. Development of resistance was defined as a post-exposure MIC >4 µg/mL in isolates that had MIC ≤ 4 µg/mL at baseline and a ≥4-fold increase in MIC relative to that of untreated control. No colonies were observed at time zero (pre-exposure) on 4X or 8X containing plates in all isolates tested (**Table 13**). Increased plazomicin MICs were observed for in 4 of the 5 *E. coli* isolates and 5 of the *K. pneumoniae* isolates selected on 4X and 8X plazomicin MIC plates ranging from 2 to 32-fold. Stability of elevated plazomicin MICs and molecular characterization in these isolates were not assessed. Mutants were detected at maximum of AUC/MIC concentrations ratios < 132 in *E. coli* AECO1175 and *K. pneumoniae* AKPN1171 isolates. No growth was observed on 4X or 8X MIC plates from *E. coli* or *K. pneumoniae* isolate tested after exposure to plazomicin at AUC/MIC ratios ≥ 132.

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Table 13: Relationship between development of resistance and plazomicin exposure against Enterobacteriaceae strains in an in vitro chemostat model

Strain	Original MIC (µg/ml)	AUC/MIC ratio	Pre-exposure MIC (µg/ml)	Post-Exposure MIC (µg/ml)	Fold Change in MIC	Resistant Organism
<i>Escherichia coli</i>						
AECO1174	0.5	16.5	0.5	16	32	Y
		33	2	8	4	Y
		33	1	8	8	Y
		100	0.25	8	32	Y
		132	2	16	8	Y
AECO1175	1	16.5	1	4	4	Y
		16.5	8	64	8	Y
		33	2	8	4	Y
		50	2	8	4	Y
		64	ND	ND	ND	ND
		66	1	16	16	Y
		132	1	8	8	Y
AECO1177	1	- a	- a	- a	- a	- a
64979	2	33	0.5	16	32	Y
64982	4	8.25	4	16	4	Y
		16.5	ND	32	ND	Y
<i>Klebsiella pneumoniae</i>						
AKPN1169	1	33	2	8	4	Y
		66	2	8	4	Y
		132	2	4	2	N
AKPN1170	1	16.5	1	8	8	Y
		33	2	8	4	Y
AKPN1171	2	33	8	16	2	Y
		132	4	32	8	Y
41965	0.5	16.5	0.5	2	4	Y
		33	0.5	8	16	Y
		66	0.5	1	2	N
41966	0.5	16.5	0.5	4	8	Y

^aDead on subculture;

Source: Study# A15082-1490

The proposed clinical dosing regimens were designed to target steady state AUC_{0-24h} equivalent to the mean AUC for a subject with normal creatinine clearance (≥ 90 mL/min 1.73 m²) who is administered 15 mg/kg/day. Pharmacokinetic studies in healthy volunteers showed that the maximum plasma concentration (C_{max}), trough concentration (C_{min}) and AUC for plazomicin increase in proportion to doses within the single dose range of 4 to 15 mg/kg. No appreciable accumulation of plazomicin was observed following multiple IV infusion of 15 mg/kg administered every 24 hours in subjects with normal renal function. The geometric mean (CV%) of AUC₀₋₂₄ and C_{max} were 265 µg*h/mL (25.1%) and 76 µg/mL (25.7%), respectively in healthy subjects (Study ACHN-490-006). Exposure for cUTI^{(b) (4)} patients were extremely variable with changes in dose and renal function during the treatment.

The probability of target attainment among simulated patients was determined for patients with normal renal function and varying degrees of renal impairment (mild, moderate and severe). **Table 14** provides the probability of target attainment of plazomicin in cUTI patients based on renal function. The targets from the mouse thigh infection model were chosen in target attainment assessment, since it provides a conservative PK/PD target for a given exposure. The PK/PD target attainment of an AUC/MIC ratio of 24 (stasis) using a 15 mg/kg dose (in patients with normal to moderate renal function) will be achieved in more than 98% of patients with normal to severe renal impairment with isolates that having MIC values ≤ 4 µg/mL. Using the 75th percentile target for stasis (AUC/MIC ratio of 39), attainment rates will be achieved in 100% of the patients with normal to severe renal impairment with isolates that having MIC values ≤ 2 µg/mL.

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Table 14: Probability of target attainment analyses of plazomicin in cUTI patients against Enterobacteriaceae based on renal function

Creatinine Clearance	PTA by MIC using AUC/MIC of 24 as a PK/PD target				
	1 µg/mL	2 µg/mL	4 µg/mL	8 µg/mL	16 µg/mL
>90 mL/min	100%	100%	98%	54%	3%
>30 to 90 mL/min	100%	100%	99%	64%	6%
>15 to 30 mL/min	100%	100%	99%	66%	7%
Creatinine Clearance	PTA by MIC using AUC/MIC of 39 as a PK/PD target				
	1 µg/mL	2 µg/mL	4 µg/mL	8 µg/mL	16 µg/mL
>90 mL/min	100%	100%	76%	10%	0
>30 to 90 mL/min	100%	100%	82%	16%	0
>15 to 30 mL/min	100%	100%	83%	18%	0

^a Plazomicin 15 mg/kg q24h infused over 30-minutes

^b Based on creatinine clearance (in mL/min) mild to normal renal impairment => 60 to ≥ 90 mL/min; moderate renal impairment => 45 to ≥ 60; severe renal impairment => 30 to ≥ 45

Target attainment rate for AUC/MIC of 24 to achieve bacterial stasis

Source: see [FDA Clinical Pharmacologist Review](#)

(b) (4)

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(b) (4)

Reviewer's comments:

Similar to other aminoglycosides, the ratio of the area under the concentration-time curve from 0 to 24-hours to the MIC for the target organism (AUC_{0-24h} /MIC) is the best predictor of microbiologic outcome. For plasma, the median AUC/MIC targets to achieve stasis and 1-log₁₀ kill was 24 and 89, respectively. For ELF, the median *f*AUC/MIC targets to achieve stasis, 1-log₁₀ kill and 2-log₁₀ kill was 2.87, 8.45 and 25.4, respectively. Development of plazomicin resistance was not detected after exposure to plazomicin at AUC/MIC ratios > 132 in murine thigh infection models.

The targets from the mouse thigh infection model were chosen in target attainment assessment, since it provides a relative conservative PK/PD target for a given exposure. A PK/PD target attainment of an AUC/MIC ratio of >24 (stasis) is recommended for treatment in cUTI patients. (b) (4)

6. CLINICAL STUDIES

6.1. Complicated Urinary Tract Infection including Acute Pyelonephritis

The clinical development program supporting the efficacy and safety of plazomicin in the treatment of cUTI includes one Phase 3 study (ACHN-490-009) with supportive data from a phase 2 dose finding study (ACHN-490-002).

6.1.1. Phase 2 Clinical Study (ACHN490-002)

The Phase 2 study compared plazomicin to levofloxacin in 145 patients with documented or protocol-specified clinical signs and symptoms of cUTI or AP. Early in the study, patients were randomized 1:1:1 to receive intravenous plazomicin 10 or 15 mg/kg every 24 hours or intravenous levofloxacin 750 mg once daily for 5 days. Later in the study, the 10 mg/kg arm was eliminated and patients were randomized 2:1 to plazomicin 15 mg/kg or levofloxacin 750 mg. The primary outcome measure was the proportion of patients who attained microbiological eradication at test-of-cure (7 ± 2 days after the last treatment).

A total of 145 patients were randomized to treatment, 5 patients did not receive study drug and 15 were prematurely withdrawn from the study. Randomized patients had a mean age of approximately 43 years and 80% were female. Seventy-nine patients

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(54.5%) had AP and 66 patients (45.5%) had cUTI. Clinical signs and symptoms most often included pyuria, urinary frequency, abdominal pain, urinary urgency and dysuria. Of the 145 patients, 92 patients (63.4%) had an acceptable urine specimen that contained at least 1 organism that was quantified at $\geq 10^5$ CFU/mL. Only one patient (randomized to plazomicin 15 mg/kg group) had two isolated organisms quantified at $\geq 10^5$ CFU/mL; both organisms were gram-negative.

The clinical cure rates were 67% and 71% for the lower and higher dose of plazomicin and 66% for the levofloxacin group in the MITT population. Microbiological eradication rates were 86%, and 89% for the lower and higher dose of plazomicin and 81% in the levofloxacin group.

Microbiological eradication at the TOC visit was 50% in the plazomicin 10 mg/kg arm, 60.8% in the plazomicin 15 mg/kg arm compared to 58.6% in the levofloxacin treatment arm in the MITT population. The treatment difference between the levofloxacin and plazomicin 15 mg/kg group was -2.2. In the ME population, the microbiological eradication occurred in 85.7% in the plazomicin 10 mg/kg group, 88.6% in the plazomicin 15 mg/kg arm compare to 81% in the levofloxacin treatment arm. The treatment difference between the levofloxacin and plazomicin 15 mg/kg groups was -7.6%. Overall, there was a lower microbiological eradication rate in the MITT population compared to the ME population. The Applicant attributed this low response to the number of samples that had a microbiological outcome of indeterminate due to improper specimen collection or handling at the TOC.

Most patients had a gram-negative pathogen isolated at baseline. *Enterobacteriaceae* were the predominant pathogens isolated in 90% of cases with 74.2% of the patients had an *Escherichia coli* isolated whereas the remaining cases were *K. pneumoniae* (7.5%), other *Enterobacteriaceae* (9.7%), *P. aeruginosa* (2.2%) and gram-positive aerobes (6.5%).

The plazomicin MICs values of the causative pathogen isolated from urine at baseline ranged from ≤ 0.125 $\mu\text{g/mL}$ to 256 $\mu\text{g/mL}$ with MIC_{50/90} values of 1 $\mu\text{g/mL}$ and 2 $\mu\text{g/mL}$, respectively. Of the 38 baseline pathogens in the plazomicin treatment groups, 35 (92%) had plazomicin MICs ≤ 4 $\mu\text{g/mL}$. Among these isolates, 32/35 were associated with microbiological eradication. The microbiological eradication was 0% (0/1) at an MIC of 8 $\mu\text{g/mL}$ and 100% (1/1) at plazomicin MICs of 128 $\mu\text{g/mL}$ and 256 $\mu\text{g/mL}$, respectively. Against *E. coli*, none of the isolates had plazomicin MICs > 8 $\mu\text{g/mL}$. More than 10% of strains identified were resistant to ceftazidime (17.6%), gentamicin (14.7%), levofloxacin (27.9%) or trimethoprim/sulfamethoxazole (39.7%) using the CLSI criteria among *Enterobacteriaceae*.

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At the long term follow-up (LTFU) visit in the ME population, clinical relapse (defined as return of clinical signs and symptoms requiring antibiotic therapy) had occurred in 14.3% (4/28) patients in the plazomicin 15 mg/kg group and 6.3% (1/16) in the levofloxacin group; none were reported in the plazomicin 10 mg/kg group. Microbiological recurrence (defined as eradication of the original pathogens but regrowth at levels > 10⁵ CFU/mL) had occurred in 6.5% (2/31) in the plazomicin 15 mg/kg group and 23.5% (4/17) in the levofloxacin group; none were reported in the plazomicin 10 mg/kg group. No information was provided on the MICs or PK among patients with clinical relapse and microbiological recurrence.

Super-infections were reported in 2 patients in the plazomicin 10 mg/kg group and 3 in the plazomicin 15 mg/kg group, none were reported in the levofloxacin treated group. The two isolates that grew in the 10 mg/kg plazomicin group were *C. freundii*. In the 15 mg/kg group, the 3 isolates were *E. coli*, *P. mirabilis* and *P. aeruginosa*. No information was provided on the MICs or PK in patients with super-infections or new infections.

New infections were reported in 1 patient treated with plazomicin 15 mg/kg (*P. aeruginosa*) and 1 patient in the levofloxacin group (*P. mirabilis*). No information was provided on the MICs or PK in patients with super-infections or new infections.

6.1.2. Phase 3 Clinical Study (ACHN490-009)

The Phase 3 study compared plazomicin to meropenem in 609 patients with documented cUTI or AP. Patients were randomized 1:1 to receive intravenous plazomicin administered 15 mg/kg IV over 30-minute infusion once daily or 1 g meropenem IV administered every 8 hours for 5 days. The primary outcome was the composite cure endpoint of microbiological eradication and clinical cure at Day 5 and Test-of-Cure (TOC; Day 15 – 19) visits in the microbiological modified intent-to-treat (mMITT) population.

Microbiological and clinical outcomes definitions are summarized in the Table below

Outcome	Definition
Microbiological Outcomes	
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	No urine culture was done at Day 5 or EOIV visit and 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 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.
Clinical Outcome	
Cure	Complete resolution or return to pre-morbid levels of core symptoms of cUTI

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	and no new symptoms develop and no use of non-study antibiotic therapy for the current cUTI.
Failure	Persistence of one or more core symptom of infection or reappearance or development of new core symptoms that require alternative non-study therapy for the current cUTI.
Indeterminate	Insufficient data are available to allow an evaluation of clinical outcome for any reason.

The composite cure (microbiological eradication and clinical cure) was defined as noted in the table below:

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

A total of 609 hospitalized patients were enrolled, 388 (64%) qualified for the mMITT population with 191 in the plazomicin group and 197 in the meropenem group. In the mMITT population, 99.5% of patients were white with a mean age of 59.4 years (range, 18 – 88) and approximately equal representation of males (47.2%) and females (52.8%). There were very few patients from United States (1%) with the majority from Europe (98.5%). More patients had cUTI (58.2%) than AP (41.8%) and 13.1% of patients had cUTI with an indwelling catheter at baseline. The median treatment duration of IV study drug was 6.0 days in both groups.

The composite cure rate at Day 5 was 88.0% for plazomicin compared with 91.4% in the meropenem treatment arm in the mMITT population. The difference between the composite cure rates (plazomicin minus meropenem) was -3.4% with a 2-sided 95% CI of -10.0% to 3.1%. At the TOC visit, the composite cure rate for plazomicin and meropenem was 93.7% and 94.9%, respectively (95% CI, -6.5% to 4.0%). Thus, results of the primary analysis show that the lower bound of the 2-sided 95% CI around the treatment difference was greater than or equal to -15% which met the protocol definition of NI margin. The lower limits of the 95% CI for the EOIV and LFU visits was also larger than the pre-specified NI margin.

At Day 5, the composite cure rates were lower in the plazomicin group compared to the meropenem group (**Table 16**). Composite failures in both treatment groups at Day 5 were due to more to clinical failures than persistence of the baseline pathogen. At the EOIV

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visit, plazomicin achieved higher composite cure rates than meropenem, driven primarily by a higher microbiological eradication rate which was sustained at TOC in the plazomicin group. The microbiological eradication rates were sustained at LFU and was significantly higher in the plazomicin group (84.3%) compared with meropenem (65.0% [difference 19.3%; 95% CI, 10.4% to 27.9%]). Similar results were observed in the ME populations (data not shown).

Table 16: Primary and key secondary analyses: composite responses (clinical cure and microbiological eradication) at different visits in cUTI Phase 3 trial in the mMITT population

Analysis	Plazomicin (N =191) n (%)	Meropenem (N=197) n (%)	Treatment Difference ^a (95% CI)
Composite Response			
Composite Cure at Day 5	168/191 (88.0)	180/197 (91.4)	-3.4 (-10.0, 3.1)
Composite Cure at EOIV	179/191 (93.7)	187/197 (94.9)	-1.2 (-6.5, 4.0)
Composite Cure at TOC	156/191 (81.7)	138/197 (70.1)	11.6 (2.7, 20.3)
Composite Cure at LFU	147/191 (77.0)	119/197 (60.4)	16.6 (7.0, 25.7)
Programmatically-Determined Clinical Response			
Clinical Cure at Day 5	171 (89.5)	182 (92.4)	-2.9 (-9.1, 3.3)
Clinical Cure at EOIV	184 (96.3)	190 (96.4)	-0.1 (-4.6, 4.3)
Clinical Cure at TOC	170 (89.0)	178 (90.4)	-1.4 (-7.9, 5.2)
Clinical Cure at LFU	169 (88.5)	168 (85.3)	3.2 (-4.0, 10.3)
Microbiological Response			
Microbiological Eradication at Day 5	188 (98.4)	193 (98.0)	0.5 (-3.1, 4.1)
Microbiological Eradication at EOIV	186 (97.4)	192 (97.5)	-0.1 (-4.1, 3.9)
Microbiological Eradication at TOC	171 (89.5)	147 (74.6)	14.9 (7.0, 22.7)
Microbiological Eradication at LFU	161 (84.3)	128 (65.0)	19.3 (10.4, 27.9)

Abbreviations: CI = confidence interval; EOIV = end of intravenous therapy; TOC = test-of-cure; LFU = late follow-up

^a Treatment difference is ZEMDRI – meropenem. CI = 95% confidence interval based on Newcombe method with continuity correction.

Source: Study Report ACHN490-009 Tables 14.2.1.1, 14.2.3.1, 14.2.4.1.1, 14.2.9.1.1

For patients with cUTI compared to AP at Day 5, the composite cure rates for plazomicin were similar; however, the composite cure rate for plazomicin was lower with cUTI than for patients with AP at TOC (**Table 17**). Consistent with the overall results, plazomicin demonstrated higher composite cure rates compared to meropenem at the TOC visit for each infection types. The composite cure rates for plazomicin were consistent between patients with and without indwelling catheters. The composite cure rate for plazomicin at TOC was lower for patients with an indwelling catheter relative to those without.

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Table 17: Composite response at different visits in cUTI Phase 3 trial by infection types in the mMITT population

Analysis	Plazomicin (N =191) n (%)	Meropenem (N=197) n (%)	Treatment Difference ^a (95% CI)
AP	n = 84	N =78	
Composite Cure at Day 5	73 (86.9)	72 (92.3)	-5.4 (-16.0, 5.4)
Composite Cure at TOC	72 (85.7)	56 (71.8)	13.9 (0.4, 27.1)
cUTI	n = 107	n = 119	
Composite Cure at Day 5	95 (88.8)	108 (90.8)	-2.0 (-11.0, 6.7)
Composite Cure at TOC	84 (78.5)	82 (68.9)	9.6 (-2.6, 21.3)
With Indwelling Catheter	n = 29	n = 29	
Composite Cure at Day 5	25 (86.2)	28 (96.6)	-10.3 (-29.4, 8.3)
Composite Cure at TOC	18 (62.1)	15 (51.7)	10.3 (-16.6, 35.5)
Without Indwelling Catheter	n = 162	n = 168	
Composite Cure at EOIV	143 (88.3)	152 (90.5)	-2.2 (-9.5, 5.0)
Composite Cure at LFU	138 (85.2)	123 (73.2)	12.0 (2.8, 20.9)

Abbreviations: CI = confidence interval; EOIV = end of intravenous therapy; TOC = test-of-cure; LFU = late follow-up

^a Treatment difference is ZEMDRI – meropenem. CI = 95% confidence interval based on Newcombe method with continuity correction.

Source: [Study Report ACHN490-009 Tables 14.2.1.3, 14.2.1.4](#)

Microbiological Response by pathogen

Most patients had a gram-negative pathogen isolated at baseline, with *E. coli* as the predominant uropathogen, followed by *K. pneumoniae*, *P. mirabilis* and *E. cloacae*. Most patients had monomicrobial infections (95.3% [182/191] plazomicin group; 91.9% [181/197] meropenem group); 25 patients had two uropathogens isolated at baseline (**Table 18**). There were too few gram positive isolates in the study, plazomicin showed activity against the 2 methicillin susceptible *S. aureus* isolates.

Table 18: Per-pathogen Microbiological Eradication Rate at TOC by Baseline Pathogen in Phase 3 cUTI Trial (mMITT Population)

Baseline Uropathogen	Plazomicin (N =191) n/N (%)	Meropenem (N=197) n/N (%)	Treatment Difference ^a (95% CI)
Enterobacteriaceae	177/198 (89.4)	157/208 (75.5)	13.9 (6.2, 21.5)
<i>Escherichia coli</i>	120/128 (93.8)	106/142 (74.6)	19.1 (10.0, 27.9)
<i>Klebsiella pneumoniae</i>	27/33 (81.8)	32/43 (74.4)	7.4 (-13.9, 26.5)
<i>Enterobacter cloacae</i>	13/16 (81.3)	3/3 (100)	-18.8 (-46.3, 51.6)
<i>Proteus mirabilis</i>	9/11 (81.8)	4/7 (57.1)	24.7 (-21.4, 64.5)

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Baseline Uropathogen	Plazomicin (N =191) n/N (%)	Meropenem (N=197) n/N (%)	Treatment Difference ^a (95% CI)
<i>Citrobacter freundii</i>	2/3 (66.7)	2/3 (66.7)	--
<i>Morganella morganii</i>	2/2 (100.0)	1/1 (100.0)	
<i>Serratia marcescens</i>	1/2(50.0)	2/3 (66.7)	
<i>Klebsiella oxytoca</i>	1/1 (100.0)	3/3 (100.0)	--
<i>Proteus vulgaris</i>	1/1 (100.0)	0/1 (0.0)	
<i>Providencia rettgeri</i>	1/1 (100.0)	--	--
<i>Providencia stuartii</i>	--	1/1 (100.0)	--
Enterobacteriaceae- Aminoglycoside R^b	41/52 (78.8)	33/51 (68.6)	10.2 (-8.1, 27.8)
<i>Escherichia coli</i>	20/23 (87.0)	16/26 (61.5)	25.4 (-2.4, 48.3)
<i>Klebsiella pneumoniae</i>	14/18 (77.8)	15/20 (75.0)	2.8 (-27.3, 31.4)
<i>Enterobacter cloacae</i>	4/6 (66.7)	1/2 (50.0)	--
<i>Proteus mirabilis</i>	3/5 (60.0)	2/3 (66.7)	--
Enterobacteriaceae- Carbapenem R	7/9 (77.8)	5/6 (83.3)	-5.6 (-46.3, 44.7)
<i>Klebsiella pneumoniae</i>	--	1/1 (100)	--
<i>Morganella morganii</i>	2/2 (100.0)	--	--
<i>Proteus mirabilis</i>	5/7 (71.4)	4/5 (80.0)	--
Enterobacteriaceae- ESBL^c	42/51 (82.4)	45/60 (75.0)	7.4 (-9.6, 23.1)
<i>Escherichia coli</i>	18/20 (90.0)	19/28 (67.9)	22.1 (-5.7, 44.0)
<i>Klebsiella pneumoniae</i>	15/20 (75.0)	20/26 (76.9)	-1.9 (-29.7, 24.1)
<i>Enterobacter cloacae</i>	6/8 (75.0)	1/2 (50.0)	--
<i>Proteus mirabilis</i>	3/3 (100.0)	1/1 (100.0)	--
<i>Citrobacter freundii</i>	--	1/1 (100.0)	--
<i>Serratia marcescens</i>	--	1/2 (50.0)	--
AME gene positive	45/58 (77.6)	47/68 (69.1)	
β- lactamase gene positive	55/70 (78.6)	51/74 (68.9)	
Gram positive			
<i>Staphylococcus aureus</i>	2/2 (100)	3/5 (60.0)	
MRSA	--	1/2 (50.0)	
MSSA	2/2 (100)	2/3 (66.7)	

Abbreviations: CI = confidence interval; EOIV = end of intravenous therapy; TOC = test-of-cure;

LFU = late follow-up; ESBL = extended-spectrum β-lactamase

^a Treatment difference is ZEMDRI – meropenem. CI = 95% confidence interval based on Newcombe method with continuity correction.

^b Non-susceptible to amikacin, gentamicin, or tobramycin.

^c Non-susceptible to ceftazidime, ceftriaxone or aztreonam

Source: CSR ACHN-490-009 Table 14.2.11.1. Integrated Summary of Microbiology Table 1 and 2

Microbiological Eradication by MIC

The range of plazomicin MIC observed in the mMITT population was ≤ 0.06 to 4 µg/mL,

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with MIC_{50/90} values of 0.5 and 1 µg/mL, respectively (Table 18). The MIC values were similar for Enterobacteriaceae collected in Global Surveillance during 2014 through 2016 in all regions (MIC_{50/90} 0.5 µg/mL and 1 to 2 µg/mL, respectively). As expected, the *Proteae* species (*Proteus*, *Morganella* and *Providencia* spp.) had higher plazomicin values than other Enterobacteriaceae species. None of the patients' isolates had MIC values > 4 µg/mL; patients were excluded from the primary analysis population in the phase 3 study with plazomicin MICs > 4 µg/mL. There were 6 Enterobacteriaceae, from 6 different patients, with MICs at 4 µg/mL. All isolates with MIC of 4 µg/mL were eradicated at Day 5 and at the TOC visit, and all 6 patients were clinical cures at these visits. Overall no trends in favorable outcomes were observed based on plazomicin MICs.

Table 19: Favorable per-pathogen microbiological response for baseline Enterobacteriaceae pathogens at TOC by plazomicin MIC (micro-ITT population)

Baseline Plazomicin MIC (µg/mL)	Enterobacteriaceae	<i>C. freundii</i>	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. oxytoca</i>	<i>K. pneumoniae</i>	<i>M. morganii</i>	<i>P. mirabilis</i>	<i>P. vulgaris</i>	<i>P. rettgeri</i>	<i>S. marcescens</i>
≤ 0.06	2/2(100)		1/1(100)	0/0(0)		1/1(100)					
0.12	22/27(81.5)	2/2(100)	3/5(60.0)	5/6(83.3)		12/14(85.7)					
0.25	58/66(87.9)	0/1(0)	8/9(88.9)	39/42(92.9)		11/14(78.6)					
0.5	59/64(92.2)		1/1(100)	55/59(93.2)	1/1(100)	2/3(66.7)					
1	17/19(89.5)			12/12(100)		1/1(100)		2/3(66.7)	1/1(100.0)		1/2(50.0)
2	11/12(91.7)			6/6(100)			1/1(100)	3/4(75.0)		1/1(100.0)	
4	6/6(100)			1/1(100)			1/1(100)	4/4(100)			
MIC ₅₀	0.5	--	0.25	0.5	--	0.25	--	2	--	--	--
MIC ₉₀	1	--	0.25	1	--	0.5	--	4	--	--	--
Range	≤0.06 - 4	0.12 - 0.25	≤0.06 - 0.5	0.12 - 4	0.5	≤0.06 - 1	2 - 4	1 - 4	1	2	1

Source: ACHN490-009 Table 14.1.14.1; Table 14.2.13.1.1

Aminoglycoside resistance (defined as non-susceptible to gentamicin, amikacin or tobramycin) was detected in 101 of 388 (26%) patients with an Enterobacteriaceae baseline pathogen. Resistance to other aminoglycosides were higher among *K. pneumoniae*, *P. mirabilis* and *E. cloacae* isolates than among *E. coli* isolates. The plazomicin MIC_{50/90} against aminoglycoside-non-susceptible isolates were 0.25 µg/mL and 2 µg/mL, respectively (Table 20). Microbiological eradication rates at the TOC visit in this subset were 78.8% (41/52) in the plazomicin group and 68.6% (33/51) in the meropenem group. Genotypic testing of baseline Enterobacteriaceae non-susceptible to amikacin, gentamicin, or tobramycin identified at least one AME gene. The most commonly detected AME gene was *aac(6')-Ib-cr* (71 isolates positive) with 10 isolates positive for other variants of *aac(6')-Ib* (*aac(6')-Ib-cr-like* and *aac(6')-Ib*). The next common AME genes detected were *aac(3)-IIa* (49 isolates), *aph(6)-Ia* (41 isolates) and *aph(6)-Id* (34 isolates), *aadA5* (33 isolates), *aac(3)-IId* (23 isolates) and *ant(3'')-Ia* (20 isolates). This is consistent with the 2016 Global Surveillance which found that the most frequently observed clinically relevant genes were *aac(6')-Ib* variants and *aac(3)-IIa*. No baseline uropathogens were positive for 16S rRNA methyltransferase gene.

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ESBL positive isolates (defined as ceftriaxone, ceftazidime or aztreonam MIC ≥ 2 $\mu\text{g/mL}$) were detected in 107 of 388 (27.6%) patients. The most commonly detected β -lactamase genes were the ESBL *bla*_{CTX-M-15} (87 isolates) and *bla*_{OXA-1/OXA-30} (72 isolates); the narrow spectrum β -lactamase gene *bla*_{TEM-1} (69 isolates) was also frequently detected. The plazomicin MIC_{50/90} against ESBL producing Enterobacteriaceae isolates were 0.25 $\mu\text{g/mL}$ and 0.5 $\mu\text{g/mL}$, respectively

Carbapenem resistant (defined as non-susceptible to doripenem or imipenem) were detected in 15 of 388 (3.9%) patients. No baseline uropathogens were positive for a carbapenemase gene. All baseline isolates were susceptible to meropenem (MIC < 1 $\mu\text{g/mL}$) due to exclusion of patients with isolates confirmed to be non-susceptible to meropenem from the analysis population.

Table 20: Favorable per-pathogen microbiological response for baseline Enterobacteriaceae pathogens by resistance profile at TOC by plazomicin MIC (micro-ITT population)

Baseline Plazomicin MIC ($\mu\text{g/mL}$)	Aminoglycoside-Resistant					Carbapenem-Resistant			ESBL-producing				
	Enterobacteriaceae	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	Enterobacteriaceae	<i>M. morganii</i>	<i>P. mirabilis</i>	Enterobacteriaceae	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>
≤ 0.06													
0.12	10/14(71.4)	1/3(33.3)	1/1(100)	8/10 (80.0)					11/15(73.3)	1/3(33.3)		10/12(83.3)	
0.25	13/16(81.3)	3/3(100)	7/8(87.5)	3/5 (60.)					14/17(82.4)	4/4(100)	7/8(87.5)	3/5(60.0)	
0.5	11/13(84.6)		9/11(81.8)	2/2 (100.)					12/14(85.7)	1/1(100)	10/11(90.9)	1/2(50.0)	
1	1/2(50.0)			1/1 (100.0)	0/1(0)	2/3(66.7)		2/3(66.7)	2/2(100)			1/1(100)	1/1(100)
2	5/6(83.3)		3/3(100)		2/3(66.7)	3/4(75.0)	1/1(100)	2/3(66.7)	2/2(100)		1/1(100)		1/1(100)
4	1/1(100)				1/1(100)	2/2 (100)	1/1(100)	1/1(100)	1/1(100)				1/1(100)
MIC ₅₀	0.25	--	0.5	0.12	--	--	--	--	0.25	--	0.5	0.12	--
MIC ₉₀	2	--	2	0.5	--	--	--	--	0.5	--	0.5	0.5	--
Range	0.12 - 4	0.12 - 0.5	0.12 - 2	0.12 - 1	1 - 4	1 - 4	2 - 4	1 - 4	0.12 - 4	0.12 - 0.5	0.25 - 2	0.12 - 1	1 - 4

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Development of resistance to plazomicin was defined as ≥ 4 -fold increase in plazomicin MIC compared to baseline and a plazomicin MIC $> 4 \mu\text{g/mL}$. This occurred in 7 isolates from 6 plazomicin-treated patients; all 7 isolates were considered resistant with plazomicin MICs $> 4 \mu\text{g/mL}$ (Table 21). Five of the 7 isolates with decreased plazomicin susceptibility (MICs $> 4 \mu\text{g/mL}$) 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.

- Patient# (b) (6) – isolate detected at screening was *K. pneumoniae* isolate with plazomicin MIC of $0.12 \mu\text{g/mL}$. At the LFU visit, the isolate showed decreased susceptibility to plazomicin (MIC $8 \mu\text{g/mL}$). This patient was clinical failure at TOC. No additional AMEs or 16S ribosomal methyltransferase genes were detected in the isolate.
- Patient# (b) (6) – isolate detected at screening was *P. mirabilis* with plazomicin MIC of $4 \mu\text{g/mL}$. On or before EOIV visit, the isolate showed decreased susceptibility to plazomicin (MIC $32 \mu\text{g/mL}$). No additional AMEs or 16S ribosomal methyltransferase genes were detected in the isolate. This patient was clinical cure at Day 5 and EOIV visit.
- Patient# (b) (6) – isolate detected at screening was *E. cloacae* with plazomicin MIC of $0.12 \mu\text{g/mL}$. At the TOC visit, the isolate showed decreased susceptibility to plazomicin (MIC $> 128 \mu\text{g/mL}$). A 16S ribosomal methyltransferase gene (*rmtC*), was detected at TOC as well as other resistant genes such as the *bla*_{NDM-1}, that was not present at baseline. The patient had unresolved frequency that met the programmatic definition for clinical failure at TOC, however, was not treated with non-study antibiotics.
- Patient# (b) (6) – isolate detected at screening was *K. pneumoniae* with plazomicin MIC of $0.25 \mu\text{g/mL}$. On or before EOIV visit, the isolate showed decreased susceptibility to plazomicin (MIC $64 \mu\text{g/mL}$) and increased further at LFU ($> 128 \mu\text{g/mL}$). A 16S RMTase (*armA*) as well as AME genes *aac(6')-Ib-cr*, *aadA2* was detected at TOC that was not present at baseline. This patient was clinical cure at Day 5 and EOIV visit.
- Patient# (b) (6) – isolate detected at screening was *Enterobacter cloacae* with plazomicin MIC of $0.12 \mu\text{g/mL}$. Prior to EOIV visit (Day 2, Day 3) and on EOIV, the isolate showed decreased susceptibility to plazomicin (MIC $> 128 \mu\text{g/mL}$). A 16S RMTase (*rmtB*) was detected on Day 2 that was not present at baseline. The patient was clinical cure at Day 5 and EOIV visit and was treated with non-study antibiotics prior to the TOC visit.

The presence of additional resistance genes in post-baseline isolates in most cases suggest that the genes may have been encoded on mobile elements (e.g. plasmids or transposons). These mobile elements may have been acquired horizontally during the treatment course or the baseline culture may have contained a low frequency subpopulation carrying these

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elements that was selected for upon exposure to plazomicin. It is not possible to distinguish between these two hypotheses with the available data.

Table 21: Listing of 6 plazomicin-treated patients with uropathogens that developed resistance to plazomicin (mMITT population)

Patient ID	Treatment Group	Visit	Isolate Accession Number	Organism	Plazomicin MIC (µg/mL)	Plazomicin Zone Diameter (mm)	Meropenem MIC (µg/mL)	Resistance Mechanisms	Related to Baseline
(b) (6)	Plazomicin	Screening	AC8916806-1	<i>Escherichia coli</i>	0.25	25	0.008	Negative	Baseline
		Day 5	AC8917506-1	<i>Escherichia coli</i>	>128	6	0.008	<i>aadA2, armA, blaCTX-M-3</i>	No
		EOIV	AC8918006-1	<i>Escherichia coli</i>	>128	6	0.008	<i>aadA2, armA, blaCTX-M-3</i>	No
		Screening	AC8916805-1	<i>Klebsiella pneumoniae</i>	0.25	22	0.015	<i>blaSHV-11</i>	Baseline
		Day 5	AC8917505-1	<i>Klebsiella pneumoniae</i>	>128	6	0.03	<i>aadA2, armA, blaCTX-M-3, blaSHV-11</i>	Yes
		EOIV	AC8918005-1	<i>Klebsiella pneumoniae</i>	>128	6	0.015	<i>aadA2, armA, blaCTX-M-3, blaSHV-11</i>	Yes
	Plazomicin	Screening	AE7839705-1	<i>Klebsiella pneumoniae</i>	0.12	21	0.015	<i>aac(3)-IIa, aac(6)'Ib-cr, blaOXA-1/OXA-30, blaSHV-1, blaCTX-M-15, blaNDM-1</i>	Baseline
		LFU	AE7839006-1	<i>Klebsiella pneumoniae</i>	8	19	0.015	<i>aac(3)-IIa, aac(6)'Ib-cr, blaOXA-1/OXA-30, blaSHV-1, blaCTX-M-15</i>	Yes
	Plazomicin	Screening	AC7812205-1	<i>Proteus mirabilis</i>	4	18	0.03	<i>aph(3')-Ia</i>	Baseline
		EOIV	AC7812405-1	<i>Proteus mirabilis</i>	32	10	0.12	<i>aph(3')-Ia</i>	Yes
	Plazomicin	Screening	AG2825105-1	<i>Enterobacter cloacae</i>	0.12	25	0.015	<i>aph(6)-Ia, aph(6)-Id, aac(3)-IIa, aac(6)'Ib-cr, blaOXA-1/OXA-30, blaTEM-1, blaACT-16-IIIe</i>	Baseline
		TOC	AG2825405-1	<i>Enterobacter cloacae</i>	>128	6	16	<i>aph(6)-Ia, aph(6)-Id, aac(6)'Ib-cr, rmtC, blaOXA-1/OXA-30, blaTEM-1, blaACT-16-IIIe, blaNDM-1</i>	Yes
LFU		AI8185205-1	<i>Enterobacter cloacae</i>	128	6	16	<i>aph(6)-Ia, aph(6)-Id, aac(3)-IIa, aac(6)'Ib-cr, rmtC, blaOXA-1/OXA-30, blaCTX-M-15, blaTEM-1, blaACT-16-IIIe, blaNDM-1</i>	Yes	
Plazomicin	Screening	AE6778305-1	<i>Klebsiella pneumoniae</i>	0.25	27	0.06	<i>blaCTX-M-15, blaSHV-11</i>	Baseline	
	EOIV	AE6778405-1	<i>Klebsiella pneumoniae</i>	64	18	0.06	Not Tested	Not Tested	
	TOC	AE6779705-1	<i>Klebsiella pneumoniae</i>	64	6	0.06	<i>aac(6)'Ib-cr, aadA2, armA, blaOXA-1/OXA-30, blaCTX-M-15, blaSHV-11</i>	Yes	
	LFU	AE6780805-1	<i>Klebsiella pneumoniae</i>	>128	6	0.06	<i>aac(6)'Ib-cr, aadA2, armA, blaOXA-1/OXA-30, blaCTX-M-15, blaSHV-11</i>	Yes	
	Screening	AF8968605-1	<i>Enterobacter cloacae</i>	0.12	25	0.06	<i>aac(6)'Ib-cr, blaOXA-1/OXA-30, blaCTX-M-15, blaTEM-1, blaACT-16</i>	Baseline	
	Day 2	AF8967805-1	<i>Enterobacter cloacae</i>	>128	6	0.06	<i>aac(6)'Ib-cr, rmtB, blaOXA-1/OXA-30, blaCTX-M-15, blaTEM-1, blaACT-16, blaVEB-3</i>	Yes	
	Day 2	AF8967807-1*	<i>Enterobacter cloacae</i>	>128	6	0.06	Not Tested	Not Tested	
	Day 2	AF8967844-1	<i>Enterobacter cloacae</i>	128	6	0.06	<i>aac(6)'Ib-cr, rmtB, blaOXA-1/OXA-30, blaCTX-M-3, blaTEM-1, blaACT-16, blaVEB-3</i>	Yes	
Plazomicin	Day 3	AF8968505-1	<i>Enterobacter cloacae</i>	128	6	0.06	<i>aac(6)'Ib-cr, rmtB, blaOXA-1/OXA-30, blaCTX-M-15, blaTEM-1, blaACT-16, blaVEB-3</i>	Yes	
	EOIV	AF8967905-1	<i>Enterobacter cloacae</i>	>128	6	0.06	<i>aac(6)'Ib-cr, rmtB, blaOXA-1/OXA-30, blaCTX-M-15, blaTEM-1, blaACT-16, blaVEB-3</i>	Yes	
	TOC	AF5352505-1	<i>Enterobacter cloacae</i>	>128	6	0.06	<i>aac(3)-IIa, aadA2, rmtB, blaCTX-M-15, blaTEM-1, blaACT-16, blaVEB-3</i>	Yes	
	Meropenem	Screening	AF5355605-1	<i>Escherichia coli</i>	0.5	21	0.008	<i>aph(6)-Ia, aph(6)-Id, blaCTX-M-3</i>	Not Tested
(b) (6)	Meropenem	Day 3	AF5354905-1	<i>Escherichia coli</i>	0.25	25	16	Not Tested	Not Tested

Abbreviations: EOIV=end-of-intravenous-therapy; LFU=late follow-up; MIC=minimum inhibitory concentration from the central laboratory; TOC=test-of-cure. Note: Decreased susceptibility is defined as a post-baseline MIC >4 µg/mL and a ≥4-fold increase in MIC relative to that of the baseline pathogen. Development of resistance to plazomicin is defined as post-baseline non-susceptibility to plazomicin (ie, MIC >4 µg/mL) in pathogens susceptible to plazomicin (ie, MIC ≤4 µg/mL) at baseline; development of resistance to meropenem is defined as post-baseline non-susceptibility to meropenem (ie, MIC >1 µg/mL) in pathogens susceptible to meropenem (ie, MIC ≤1 µg/mL) at baseline. All isolates with decreased susceptibility to study drug were also considered resistant to study drug. * *Enterobacter cloacae* with accession number AF89678-07-01 is not considered a pathogen for any analyses since it is a back-up isolate for *Enterobacter cloacae* with accession number AF89678-05-01.

Source: CSR ACHN-490-009, Table 14.2.15.1 and Table 14.2.15.2. Resistance mechanisms were determined by whole genome sequencing as detailed in Report ACHN490-MB-059-MCR and results are listed in Integrated Summary of Microbiology (ISM) Tables 1 and 2. Post-baseline relatedness to baseline isolate was determined in Report ACHN-490-MB-063-MCR.

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Bacteremia

Concomitant bacteremia was identified in 25 (13.1%) and 23 (11.7%) patients at baseline in the plazomicin and meropenem groups, respectively (Table 22). At Day 5, the composite cure rate was lower in the plazomicin group compared to meropenem, which were due to lack of clinical improvement of core signs and symptoms as microbiological eradication of the baseline uropathogen was achieved in all patients by Day 5. At the EOIV visit, the composite cure rates for plazomicin and meropenem were comparable. At the TOC visit, the composite cure rate in favor of plazomicin was maintained with greater treatment difference observed. Documented microbiological eradication were very high in both treatment groups on Day 5 and EOIV.

Table 22: Composite responses (clinical cure and microbiological eradication) by bacteremia in cUTI Phase 3 trial in the mMITT population

Analysis	Plazomicin (N =25) n (%)	Meropenem (N=23) n (%)	Treatment Difference ^a (95% CI)
Composite Response			
Composite Cure at Day 5	19 (76.0)	21 (91.3)	-15.3 (-38.0, 9.7)
Composite Cure at EOIV	23 (92.0)	20 (87.0)	5.0 (-16.7, 27.7)
Composite Cure at TOC	18 (72.0)	13 (56.5)	15.5 (-13.7, 41.9)
Programmatically-Determined Clinical Response			
Clinical Cure at Day 5	19 (76.0)	21 (91.3)	-15.3 (-38.0, 9.7)
Clinical Cure at EOIV	23 (92.0)	21 (91.3)	0.7 (-20.1, 22.5)
Clinical Cure at TOC	19 (76.0)	18 (78.3)	-2.3 (-27.6, 24.1)
Microbiological Response			
Microbiological Eradication at Day 5	25 (100)	22 (95.7)	4.3 (-12.7, 24.0)
Microbiological Eradication at EOIV	25 (100)	21 (91.3)	8.7 (-9.4, 29.5)
Microbiological Eradication at TOC	23 (92.0)	15 (65.2)	26.8 (0.5, 50.1)

Abbreviations: CI = confidence interval; EOIV = end of intravenous therapy; TOC = test-of-cure; LFU = late follow-up

^a Treatment difference is ZEMDRI – meropenem. CI = 95% confidence interval based on Newcombe method with continuity correction.

Source: Study Report ACHN490-009 Tables 14.2.1.3, 14.2.4.1.2, 14.2.9.1.2

The most common blood pathogen was *E. coli* followed by *K. pneumoniae*, *E. Clearance* of baseline blood pathogens was confirmed in 21 of 25 (84.0%) patients in the plazomicin group and 18 of 23 (78.3%) in the meropenem group on or before Day 5 (Table 23). By TOC visit, clearance of baseline blood pathogens was confirmed in all patients in the plazomicin group and 95.7% patients in the meropenem group.

Table 23: Per pathogen microbiological eradication on or before Day 5 and TOC by baseline blood pathogen (mMITT population)

	DAY 5	TOC

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Baseline Uropathogen	Plazomicin (N =25) n/N (%)	Meropenem (N=23) n/N (%)	Plazomicin (N =25) n/N (%)	Meropenem (N=23) n/N (%)
All Isolates	21/25 (84.0)	18/23 (78.3)	25/25 (100.0)	22/23 (95.7)
Enterobacteriaceae	21/23 (91.3)	17/22 (77.3)		
<i>Escherichia coli</i>	16/19 (84.2)	14/17 (82.4)	19/19 (100.0)	16/17 (94.1)
<i>Klebsiella pneumoniae</i>	3/3 (100)	3/5 (60.0)	3/3 (100.0)	5/5 (100.0)
<i>Enterobacter cloacae</i>	1/1 (100.0)	--	1/1 (100.0)	--
<i>Citrobacter sakazakii</i> group	1/1 (100.0)	--	1/1 (100.0)	--
Enterobacteriaceae- Aminoglycoside R^b				
<i>Escherichia coli</i>	0/1 (0.0)	--	1/1 (100.0)	--
<i>Klebsiella pneumoniae</i>	2/2 (100.0)	2/3 (66.7)	2/2 (100.0)	3/3 (100.0)
Enterobacteriaceae- ESBL^c				
<i>Escherichia coli</i>	0/1 (0.0)	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)
<i>Klebsiella pneumoniae</i>	2/2 (100.0)	2/3 (66.7)	2/2 (100.0)	3/3 (100.0)
Gram positive				
<i>Staphylococcus aureus</i>	1/2 (50.0)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)
MSSA	1/2 (50.0)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)

Source: ACHN-490-009 Table 14.2.17.1 and 14.2.17.2.1

The plazomicin MICs ranged from 0.12 to 0.5 µg/mL (Table 24).

Table 24: Microbiological Eradication at TOC visit by baseline pathogen and MIC of plazomicin – patients with baseline bacteremia (mMITT population)

Baseline Plazomicin MIC (µg/mL)	All isolates				Aminoglycoside non-susceptible			ESBL-producing isolates		
	Enterobacteriaceae	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	Enterobacteriaceae	<i>E. coli</i>	<i>K. pneumoniae</i>	Enterobacteriaceae	<i>E. coli</i>	<i>K. pneumoniae</i>
≤ 0.06								1/1 (100.0)		
0.12	3/3 (100.0)		2/2 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)		1/1 (100.0)
0.25	13/13 (100.0)	1/1 (100.0)	7/7 (100.0)	5/5 (100.0)	1/1 (100.0)		1/1 (100.0)	2/2 (100.0)		1/1 (100.0)
0.5	10/10 (100.0)		10/10 (100.0)		1/1 (100.0)			1/1 (100.0)	1/1 (100.0)	
1										
2										
4										
MIC ₅₀	0.5	0.25	0.5	0.25	--	2	--	--	--	--
MIC ₉₀	1	0.25	1	0.5	--	4	--	--	--	--
Range	≤0.06 - 4	≤0.06 - 0.5	0.12 - 4	≤0.06 - 1	2 - 4	1 - 4	1	2	1	

Source: ACHN490-009 Table 14.1.14.1; Table 14.2.8.2.1

Persistence

At the LFU visit, persistence of the baseline isolate was more likely observed in the meropenem-treated patients than in plazomicin-treated patients (Table 25). Plazomicin demonstrated high sustained microbiological eradication rates at the LFU visit. There were 7 patients (3.7%) in the plazomicin group and 16 patients (8.1%) in the meropenem group had a relapse with the same baseline pathogen.

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Table 25: Per-patient microbiological response at the LFU visit (mMITT population)

Response	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)	Difference (95% CI)
Sustained Eradication	161 (84.3)	128 (65.0)	19.3 (10.4, 27.9)
Persistence	21 (11.0)	57 (28.9)	
Persistence at TOC	14 (7.3)	41 (20.8)	
Recurrence at LFU	7 (3.7)	16 (8.1)	
Indeterminate	9 (4.7)	12 (6.1)	
Indeterminate at TOC	6 (3.1)	9 (4.6)	
Indeterminate at LFU	3 (1.6)	3 (1.5)	

LFU=late follow-up; mMITT=microbiological modified intent-to-treat; N=number of patients in the mMITT Population; n=number of patients in the specified category; TOC=test of cure.

Notes: Difference=Difference in cure rate (Plazomicin minus Meropenem). CI is calculated using the Newcombe method with continuity correction.

Source: Table 14.2.14.1.

Emergent Infections

Superinfection was low and comparable between treatment groups. Twelve (6.3%) patients in the plazomicin group and 6 (3.0%) patients in the meropenem group had a superinfection (**Table 26**). The most common superinfections in both treatment groups were due to *Enterococcus* spp. This was expected since all *Enterococcus* spp are intrinsically resistant to plazomicin (MICs, range) and most *E. faecium* are resistant to meropenem. The gram negative organisms causing superinfection were *C. braakii*, *C. freundii*, *E. cloacae*, *E. coli* and *P. aeruginosa*, of which most had a plazomicin MIC > 4 µg/mL.

New infections occurred in 24 (12.6%) patients in the plazomicin group and 38 (19.3%) patients in the meropenem group. Similar to superinfections, the most common pathogen causing new infections was *Enterococcus faecalis*, occurring in 12 (6.3%) patients in the plazomicin group and 23 (11.7%) in the meropenem group. In the 13 plazomicin treated patient who had a new gram-negative infection, 6 had isolates with plazomicin MIC > 4 µg/mL in the plazomicin group and 3 had isolates with a meropenem MIC > 1 µg/mL. Most cases of a new infection or superinfection were asymptomatic and did not require treatment with non-study antibiotics.

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Table 26: Patients with superinfection and/or new infections (mMITT population)

Organism	Plazomicin (N=191) n (%)	Meropenem (N=197) n (%)
Patients with a Superinfection ^a	12 (6.3)	6 (3.0)
<i>Enterococcus faecalis</i>	6 (3.1)	1 (0.5)
<i>Enterococcus faecium</i>	2 (1.0)	4 (2.0)
<i>Citrobacter freundii</i>	2 (1.0)	0 (0)
<i>Citrobacter braakii</i>	1 (0.5)	0 (0)
<i>Enterobacter cloacae</i>	1 (0.5)	0 (0)
<i>Enterococcus gallinarum</i>	1 (0.5)	0 (0)
<i>Escherichia coli</i>	1 (0.5)	0 (0)
<i>Pseudomonas aeruginosa</i>	1 (0.5)	0 (0)
<i>Klebsiella pneumoniae</i>	0 (0)	1 (0.5)
Patients with a New Infection ^b	24 (12.6)	38 (19.3)
<i>Enterococcus faecalis</i>	12 (6.3)	23 (11.7)
<i>Pseudomonas aeruginosa</i>	2 (1.0)	5 (2.5)
<i>Klebsiella pneumoniae</i>	3 (1.6)	2 (1.0)
<i>Enterococcus faecium</i>	1 (0.5)	4 (2.0)
<i>Proteus mirabilis</i>	3 (1.6)	3 (1.5)
<i>Escherichia coli</i>	2 (1.0)	2 (1.0)
<i>Citrobacter freundii</i>	1 (0.5)	2 (1.0)
<i>Enterococcus gallinarum</i>	2 (1.0)	0 (0)
<i>Acinetobacter baumannii</i> complex	1 (0.5)	1 (0.5)
<i>Morganella morganii</i>	1 (0.5)	1 (0.5)
<i>Providencia stuartii</i>	1 (0.5)	0 (0)
<i>Enterobacter aerogenes</i>	0 (0)	1 (0.5)
<i>Enterobacter cloacae</i>	0 (0)	1 (0.5)

Abbreviations: CFU=colony-forming units, IV=intravenous; N=number of patients in the specified population; n=number of patients in the specified category.

Note: Percentages are calculated as 100 x (n/N). Patients with >1 of the same uropathogen were counted once. Some patients had more than one different uropathogen.

^a A superinfection is defined as a urine culture that grows $\geq 10^5$ CFU/mL of a uropathogen other than the baseline uropathogen during the course of study therapy (IV or oral).

^b A new infection is defined as a urine culture that grows $\geq 10^5$ CFU/mL of a uropathogen other than the baseline uropathogen at any time after end of all study therapy (IV or oral).

Source: CSR ACHN-490-009, Table 14.2.16.1.

(b) (4)

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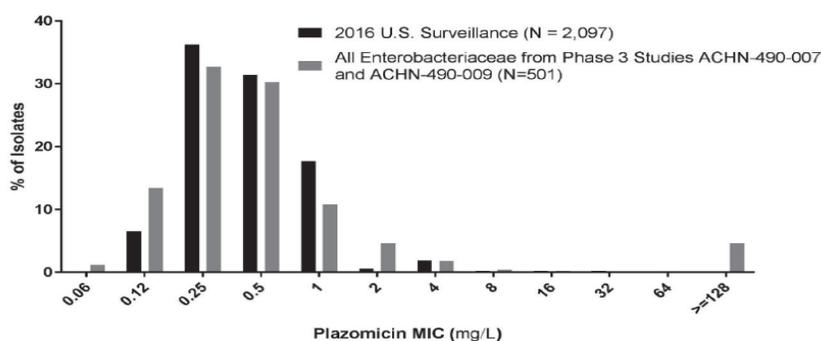
7. SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA

7.1. cUTI or AP

Based on the cUTI clinical trials, the Applicant proposes as the “first list” of microorganisms to include the gram-negative bacteria – *Escherichia coli*, *Klebsiella pneumoniae*, (b) (4) *P. mirabilis*) and *Enterobacter cloacae*. The “second list” include the gram-negative bacteria *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Providencia stuartii* and *Serratia marcescens*. (b) (4)

Surveillance and clinical studies show that the upper bound of the wild-type portion of the MIC distribution is 4 µg/mL. US Surveillance studies (2014 – 2016) showed that plazomicin MIC values ranged from ≤ 0.06 to 32 µg/mL with MIC_{50/90} values of 0.5 and 2 µg/mL, respectively and 99.4 % of the isolates were ≤ 4 µg/mL. Plazomicin MIC distribution was typically bimodal, with very few MICs observed between 4 and 64 µg/mL, particularly for *E. coli* and *Klebsiella* spp. Most strains had plazomicin MICs ≥ 128 µg/mL usually expressed 16S RMTases; which are rare and varies considerably worldwide. Plazomicin MIC₉₀ values were 0.5 µg/mL from the cUTI trial (198 isolates), with MIC₉₀ values of 1 µg/mL for *E. coli* isolates (128 isolates), 0.5 µg/mL *K. pneumoniae* (33 isolates), 0.25 µg/mL for *Enterobacter cloacae* (16 isolates) and 4 µg/mL for *P. mirabilis* (11 isolates). Overall, the plazomicin MIC₉₀ values from the clinical trials were comparable to the MIC₉₀ values of 2,097 Enterobacteriaceae isolates (1 µg/mL) collected from the US Surveillance studies (2014 – 2016).

Figure 5: MIC Frequency distributions of Enterobacteriaceae from 2016 US surveillance from studies ACHN-490-007 and ACHN-490-009 combined



Based on PK-PD, target attainment analyses showed that an AUC₀₋₂₄/MIC of 24 to achieve bacterial stasis against the Enterobacteriaceae, (b) (4)

Plazomicin is intended for intravenous administration at a dose of 15 mg/kg every 24 hours infused over 30 minutes. The area under the concentration-time curve from 0 to 24

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hours to MIC (AUC_{0-24h}/MIC) best correlated with reduction in bacterial count (\log_{10} CFU/mL) for plazomicin. Though TDM dosing is recommended for treatment of cUTIs, the AUC-based TDM dosing is not applicable. The targets from the mouse thigh infection model were chosen in target attainment assessment, since it provides a conservative PK/PD target for a given exposure. For Enterobacteriaceae isolates, the PK/PD target attainment of a $fAUC_{0-24h}/MIC$ ratio of >24 showed that with plazomicin MIC values ≤ 4 $\mu\text{g/mL}$ more than 98% of patients with normal to severe renal impairment (Table 35). Based upon MIC distributions against Enterobacteriaceae, greater than 95% of the isolates had MICs ≤ 4 $\mu\text{g/mL}$, including aminoglycoside non-susceptible and carbapenem-resistant Enterobacteriaceae.

Table 35: Probability of target attainment analyses of plazomicin in cUTI patients against Enterobacteriaceae based on renal function in terms of MIC values.

Creatinine Clearance	PTA by MIC using AUC/MIC of 24 as a PK/PD target				
	1 $\mu\text{g/mL}$	2 $\mu\text{g/mL}$	4 $\mu\text{g/mL}$	8 $\mu\text{g/mL}$	16 $\mu\text{g/mL}$
>90 mL/min	100%	100%	98%	54%	3%
>30 to 90 mL/min	100%	100%	99%	64%	6%
>15 to 30 mL/min	100%	100%	99%	66%	7%

^a Plazomicin 15 mg/kg q24h infused over 30-minutes

^b Based on creatinine clearance (in mL/min) mild to normal renal impairment => 60 to ≥ 90 mL/min; moderate renal impairment => 45 to ≥ 60 ; severe renal impairment => 30 to ≥ 45

Target attainment rate for AUC/MIC of 24 to achieve bacterial stasis

Source: see [FDA Clinical Pharmacologist Review](#)

Clinical evidence shows a high microbiological eradication rate in cUTI caused by Enterobacteriaceae with MIC values ≤ 4 $\mu\text{g/mL}$. By study design in the cUTI clinical trials, there were no isolates in patients with plazomicin MIC values > 4 $\mu\text{g/mL}$; since these isolates were excluded from the study. There were 6 Enterobacteriaceae, from 6 different patients, with MICs at 4 $\mu\text{g/mL}$. All isolates with MIC of 4 $\mu\text{g/mL}$ were eradicated at Day 5 and at the TOC visit, and all 6 patients were clinical cures at these visits. Though, there were no trends in favorable outcomes based on plazomicin MICs; at MICs ≤ 4 $\mu\text{g/mL}$ the microbiological eradication and composite cure were 89.4% and 79.3%, respectively.

Table 36: Clinical and microbiological outcomes for plazomicin against Enterobacteriaceae in cUTI clinical studies

Plazomicin MIC ($\mu\text{g/mL}$)	cUTI		cUTI with bacteremia	
	Microbiological Eradication n/N [%]	Composite Cure n/N [%]	Microbiological Eradication n/N [%]	Composite Cure n/N [%]
All tested	177/198 (89.4)	157/198 (79.3)	26/26 (100.0)	
≤ 0.06	2/2 (100)	2/2(100)		
0.12	22/27 (81.5)	18/27(66.7)	3/3 (100.0)	
0.25	58/66 (87.9)	50/64(78.1)	13/13 (100.0)	
0.5	59/64 (92.2)	57/64(89.1)	10/10 (100.0)	
1	17/19 (89.5)	15/19(78.9)		

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Plazomicin MIC (µg/mL)	cUTI		cUTI with bacteremia	
	Microbiological Eradication n/N [%]	Composite Cure n/N [%]	Microbiological Eradication n/N [%]	Composite Cure n/N [%]
2	11/12 (91.7)	9/12(75.0)		
4	6/6 (100)	6/6(100)		

Animal model studies show that a favorable outcome (survival or CFU reduction) were observed in Enterobacteriaceae isolates with plazomicin MICs ≤ 4 µg/mL compared with MICs > 4 µg/mL. There were not many Enterobacteriaceae isolates tested with plazomicin MICs > 4 µg/mL in the different animal models. In the mouse septicemia model, three isolates (*K. pneumoniae* KP561 [MIC, 8 µg/mL], *K. pneumoniae* KP559 [MIC, 16 µg/mL] and *M. morgani* MM65 [MIC, 8 µg/mL] showed survival rates of 20%, 70% and 70%, respectively. Negative blood cultures were reported for most of the animals within 4 hours of initiation of treatment, including in animals that did not survive to 96 hours.

By the disk diffusion method, the proposed zone diameters (b) (4) Kirby Bauer disks containing 30 µg plazomicin were provided by Mast Group Ltd for disk diffusion testing. Based on the error rate bounded method, the zone diameters were compared to the susceptibility testing criteria of plazomicin MICs by the broth microdilution method (b) (4). No very major errors, 0.2% major errors and 0.8% minor errors were observed when compared to the zone diameters. The single major error isolate was a *P. mirabilis* isolate in Study# ACHN-490-009 with a plazomicin MIC of 2 µg/mL with a disk diameter of 7 mm.

Figure 6: Plazomicin MICs vs. zone diameters for Enterobacteriaceae isolates from Study ACHN-490-009



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Reviewer's comments:

Based on surveillance, PK (without TDM), animal and clinical studies for the cUTI indication, (b) (4)
(b) (4)
by the broth microdilution method. For the corresponding zone diameters using the 30- µg
plazomicin disk (Mast Group Ltd, Meyersville UK), (b) (4)

The "first list" of microorganisms includes the following gram-negative bacteria – *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.

The "second list" includes the following gram-negative bacteria *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Providencia stuartii* and *Serratia marcescens*.

(b) (4)

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(b) (4)

8. REVIEW OF LABELING

The Applicant has provided the proposed labeling, only the microbiology subsection of the labeling is discussed below.

8.1. Labeling Comments

The following comments and edits were recommended to the Applicant for the microbiology section of the labeling:

- **FORMAT**
 - (1) The current format of the microbiology section of the US Package Insert along with the language was revised to the recommended Microbiology format of the labeling in accordance with the Guidance document “**Microbiology Data for Systemic Antibacterial Drug Products – Development, Analysis and Presentation.**”
- **CHANGES TO MICROBIOLOGY LABELING TEXT**
 - (2) ^{(b) (4)} *Resistance* – Added information that highlights ^{(b) (4)}

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- (3) *Mechanisms* – [REDACTED] (b) (4)
- (4) [REDACTED] (b) (4) *Resistance* – [REDACTED] (b) (4)
- (5) *Interaction with other Antimicrobials* – Enterobacteriaceae isolates [REDACTED] (b) (4) no antagonistic [REDACTED] (b) (4) for plazomicin in combination with [REDACTED] (b) (4) levofloxacin, tigecycline, colistin, phosphomycin, daptomycin, linezolid, clindamycin rifampin and vancomycin. Few isolates showed synergy with meropenem, ceftazidime and piperacillin-tazobactam. [REDACTED] (b) (4)

LIST OF MICROORGANISMS

- (6) [REDACTED] (b) (4) It is recommended that *P. vulgaris* be placed in the 2nd list.
- (7) [REDACTED] (b) (4)
- (8) [REDACTED] (b) (4). It should not be included in the 2nd list.

SUSCEPTIBILITY TESTING METHODS

- (9) This section has been formatted in accordance with Section 3044 of Cures Act, Section 511A(b) of the FD&C Act for the new labeling requirements for susceptibility test interpretive criteria (STIC) for antimicrobial drugs. In lieu of the STIC and related information, it is recommended that this section reference the FDA Interpretive Criteria web page. For more information about AST interpretive criteria labeling can be found in the following documents:

Guidance for Industry: Susceptibility Test Interpretive Criteria Labeling for Systemic Antibacterial and Antifungal Drugs

Guidance for Industry: Microbiology Data for Systemic Antibacterial Drugs – Development, Analysis and Presentation.

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8.2. FDA Version of Labeling

The Agency's proposed format of the microbiology subsection (12.4) and related sections should read as follows (Additions to the labeling are noted by double underline and deletions by strikethrough in red):

12.1. Mechanism of Action

ZEMDRI is an antibacterial drug [*see Microbiology (12.4)*].

12.4. Microbiology

(b) (4)

Mechanism of Action

Plazomicin is an aminoglycoside, that acts by binding to the bacterial 30S ribosomal subunit inhibiting (b) (4) protein synthesis. Plazomicin has concentration-dependent bacterial activity as measured by time kill studies.

Resistance

(b) (4) Resistance to aminoglycosides (b) (4) includes production of aminoglycoside modifying enzymes (AMEs); (b) (4) alteration of the ribosomal target through production of 16S rRNA methyltransferases; up-regulation of efflux pumps and reduced permeability into bacterial cell due to loss of outer membrane porins (b) (4)

(b) (4)

Plazomicin may have reduced activity against Enterobacteriaceae that overexpress certain efflux pumps (eg, *acrAB-tolC*) or have reduced expression of porins (eg, *ompF* or *ompK36*). **(See Labeling Comment 2)**

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

Interaction With Other Antimicrobials

In vitro studies have demonstrated that (b) (4) against (b) (4) -Enterobacteriaceae isolates, (b) (4) no antagonism was observed (b) (4) for plazomicin (b) (4) in combination with, clindamycin, colistin, daptomycin, fosfomicin, (b) (4) levofloxacin, linezolid, rifampin, (b) (4) tigecycline, and vancomycin; few isolates showed synergy with ceftazidime, meropenem and piperacillin-tazobactam. The clinical significance of these findings is unknown. **(See Labeling Comment 5)**

(b) (4) Animal Infection Models

Plazomicin (b) (4) demonstrated activity in animal models of infection (e.g., thigh infection, lung infection, urinary tract infection, and septicemia) caused by amikacin- and gentamicin-nonsusceptible, and beta-lactamase producing Enterobacteriaceae.

Antimicrobial Activity

ZEMDRI (b) (4) has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections [*see Indications and Usage (1.1)*]

(b) (4)

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Aerobic Bacteria

Gram-negative Bacteria

Escherichia coli

Klebsiella pneumoniae

(b) (4) *Proteus mirabilis* (b) (4) (See Labeling Comment 6)

Enterobacter cloacae

(b) (4)

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria (b) (4) exhibit in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for plazomicin against isolates of similar genus or organism group. (b) (4)

(b) (4) However, the (b) (4) efficacy of ZEMDRI (b) (4) in treating clinical infections (b) (4) caused by these bacteria (b) (4) has not been established in adequate and well-controlled clinical trials. (See Labeling Comment 1)

Aerobic Bacteria

Gram-negative Bacteria

Citrobacter freundii

Citrobacter koseri

Enterobacter aerogenes

Klebsiella oxytoca

Morganella morganii

Providencia stuartii

Serratia marcescens

(b) (4)

Susceptibility Test Methods (See Labeling Comment 9)

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see <https://www.fda.gov/STIC>

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(b) (4)



9. RECOMMENDATIONS

The NDA is approvable, pending an accepted version of the labeling.

Simone M. Shurland, PhD.
Clinical Microbiology Reviewer
DAIP HFD-520
May 17, 2018

Concurrence: Avery Goodwin, PhD, Acting Clinical Microbiology Team Leader

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/s/

SIMONE SHURLAND
05/17/2018

AVERY C GOODWIN
05/17/2018