CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210303Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	210303
Link to EDR	\\CDSESUB1\evsprod\NDA210303\0001
Submission Date	10/25/2017
Submission Type	Priority review
Brand Name	ZEMDRI
Generic Name	Plazomicin Sulfate
Dosage Form and Strength	For injection: a single dose vial of 500 mg plazomicin in 10 mL Water for Injection (concentration of 50 mg/mL)
Route of Administration	Intravenous infusion
Proposed Indication	• For the treatment of Complicated Urinary Tract Infection (cUTI) including pyelonephritis in adults • For the treatment of Blood Stream Infection (BSI) in adults • As only limited clinical safety and efficacy data are available, reserve plazomicin for use in patients who have limited or no alternative treatment options
Applicant	Achaogen Inc.
Associated IND	IND 102563
OCP Review Team	Kunyi Wu, Pharm.D. Seong Jang, Ph.D. Luning (Ada) Zhuang, Ph.D. Chao Liu, Ph.D.
OCP Final Signatory	John Lazor, Pharm.D. Director, Division of Clinical Pharmacology IV

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1. EXECUTIVE SUMMARY

Plazomicin sulfate (ZEMDRI®) is an aminoglycoside antibacterial drug proposed for the treatment of complicated urinary tract infection (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli, Klebsiella pneumoniae, Proteus spp.* (including *P. mirabilis* and *P. vulgaris*), and *Enterobacter cloacae*. Plazomicin is also proposed for the treatment of blood stream infection (BSI) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Escherichia coli*. Plazomicin is administered by intravenous (IV) infusion. Due to the difficulty in patient enrollment, only limited number of BSI patients (N=29) were in Study ACHN-490-007. As only limited clinical safety and efficacy data are available, the Applicant proposed that plazomicin be reserved for use in patients who have limited or no alternative treatment options.

The key clinical pharmacology review questions focus on evaluation of the C_{min}-based therapeutic drug monitoring (TDM) in cUTI patients to mitigate nephrotoxicity, (b) (4)

1.1 Recommendations

The clinical pharmacology information in this NDA is acceptable to support the approval of plazomicin for the proposed indications. However, the TDM-based dosing regimens and the final labeling remain to be agreed between the Applicant and the Agency (Table 1.1-1). Due to the limited evidence to support the efficacy in BSI patients, the approvability of BSI indication is still under discussion at the time of this review.

Table 1.1-1 Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Complicated Urinary Tract Infection (cUTI) • The primary evidence of effectiveness for plazomicin in cUTI patients comes from one Phase 3 trial (ACHN-490-009) which demonstrated the non-inferiority of plazomicin to meropenem. • Supportive evidence of effectiveness was provided by the results of one Phase 2 trial in cUTI patients (ACHN-490-002) and the exposure-response (E-R) analyses for efficacy. The results of Phase 2 study and E-R analyses indicated that the exposure of plazomicin was high enough to achieve the efficacy plateau in the two clinical studies.

<table>
<tr><td></td><td>Blood Stream Infection (BSI)
• The Phase 3 study (ACHN-490-007) (b) (4)
• (b) (4)</td></tr>
<tr><td>General dosing instructions</td><td>The proposed initial dosage regimen for patients whose CLcr > 60 mL/min is 15 mg/kg every 24 hours (Q24h) administered by IV infusion over 30 minutes for a total duration of 4 to 7 days for cUTI patients and 7-14 days for BSI patients, respectively. Dosage is calculated using total body weight (TBW). For patients with TBW greater than ideal body weight (IBW) by 25% or more, adjusted body weight (ABW) is used based on the equation: ABW= IBW + 0.4 x (TBW – IBW).

(b) (4)

Refer to Dosing in patient subgroups in this table for dose adjustment in patients with renal impairment.

Subsequent doses should be adjusted based on C_{min} (b) (4) for cUTI (b) (4) (see Other in this table for details).</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>Due to accumulation of plazomicin in patients with renal impairment, dose adjustment is recommended in patients with moderate and severe renal impairment (CLcr[a] from > 15 to 60 mL/min) as shown in the table below.
<table>
<tr><td></td><td>FDA recommendation[b]</td></tr>
<tr><td>Patients with moderate renal impairment (CLcr[a] >30 -60 mL/min)</td><td>10 mg/kg every 24 hours (Q24h)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Patients with severe renal impairment (CLcr[a] >15-30 mL/min)</td><td>10 mg/kg every 48 hours (Q48h)</td></tr>
</table>
[a] CLcr: estimate of CLcr based on Cockcroft-Gault equation using TBW. IBW should be used for patients with TBW greater than IBW by 25% or more.
[b] refer to General dosing instructions
</td></tr>
<tr><td>Labeling</td><td>Generally acceptable. The review team has specific content and formatting change recommendations.</td></tr>
<tr><td>Other (Therapeutic Drug Monitoring (TDM))</td><td>
<table>
<tr><td></td><td>FDA recommendation (Difference highlighted in Bold)</td><td>Applicant’s proposal</td></tr>
<tr><td>Patients with cUTI</td><td>C_{min}-based TDM for patients whose CLcr > 15 to 90 mL/min regardless of the duration of treatment

C_{min} should be maintained at a plasma concentration of less than 3 µg/mL</td><td>(b) (4)

(b) (4)</td></tr>
</table>
(b) (4)
</td></tr>
</table>

1.2 Post-Marketing Requirements and Commitments

Discussions for the following post-marketing requirements are on-going within the review team at the time of this review.

Post-Marketing Requirement 1: Conduct a clinical study in subjects with end stage renal disease (ESRD) receiving hemodialysis to evaluate the pharmacokinetics (b) (4) of plazomicin. The results of this study should be used for dosing strategies in this patient population.

Post-Marketing Requirement 2: (b) (4)

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Plazomicin sulfate is a semi-synthetic aminoglycoside antibacterial drug derived from sisomicin. The molecular weight of plazomicin sulfate is 837.89 g/mol.

Mechanism of Action:
Like other aminoglycosides, the antibacterial action of plazomicin is primarily mediated through inhibition of bacterial protein synthesis.

Distribution:
The human plasma protein binding of plazomicin is approximately 20% (range: 13.9%-24.2%) and concentration independent from 5 to 100 µg/mL. The mean (%CV) volume of distribution is approximately 18.5 L (25.2%) following a single dose of 15 mg/kg IV infusion in healthy volunteers.

Metabolism:
Plazomicin does not appear to be metabolized to any appreciable extent. Unchanged plazomicin was the predominant component in human plasma (about 82% of the total radioactivity) following a single dose of 15 mg/kg IV radiolabeled plazomicin.

Excretion:
Plazomicin is primarily excreted by the kidneys. Approximately 89% of the total radioactivity was recovered as unchanged plazomicin in urine following a single dose of 15 mg/kg IV radiolabeled plazomicin. The geometric mean (%CV) total body clearance of plazomicin and renal clearance in healthy adults (N=6) following a single dose of plazomicin 15 mg/kg were 4.76 L/h (17.1%) and 4.64 (23.5%), respectively. The mean (%CV) half-life of plazomicin in healthy adults was 3.53 hour (14.1%).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The dosage regimen for plazomicin includes two parts, initial dose and dosing based on TDM. Only the initial dose for patients with CLcr > 60 mL/min is discussed in this section. Refer to Section 2.2.2 Therapeutic individualization for doses in patients with renal impairment and TDM discussion in cUTI and BSI patients, respectively.

The Applicant proposed to administer plazomicin 15 mg/kg every 24 hours by intravenous (IV) infusion over 30 minutes in adult patients with CLcr > 60 mL/min. The recommended duration of treatment is 4 to 7 days for patients with cUTI including pyelonephritis and 7 to 14 days for patients with BSI. The review team considers this proposed initial dosage regimen to be acceptable based on the PK, efficacy and safety data from the clinical studies submitted in the NDA.

2.2.2 Therapeutic individualization

cUTI Patients

For cUTI patients, the initial dose should be based on the baseline CLcr and subsequent dose adjustments should be based on the daily CLcr assessment (2.2.1 General dosing and Table 2.2.2-1). The dosing interval should be adjusted based on C_{min} (see below).

Dosage Regimen in cUTI patients with renal impairment

The Applicant identified renal function as one of the key intrinsic factors warranting dose adjustment and proposed dose adjustment in patients whose CLcr ranges from >15 to 60 mL/min. Although six subjects with severe renal impairment (CLcr from 15 to 29 mL/min) were enrolled in Study ACHN-490-004 (a PK study in subjects with renal impairment: see Section 3.3.3 for a summary of the results), only two patients (one BSI patient and one cUTI patient) were enrolled in the Phase 3 Studies ACHN-490-007 and ACHN-490-007-009, respectively. In addition, based on the exposure-response (E-R) analysis for nephrotoxicity, defined as an increase of serum creatinine concentration ≥0.5 mg/dL from baseline, higher risk was identified in patients with mild or moderate renal impairment (CLcr > 30-90 mL/min) compared to patients with CLcr >90 mL/min. These results indicate that the risk of nephrotoxicity may increase with the decrease in renal function. Therefore, patients with CLcr > 15 to 30 mL/min potentially may have a higher risk of nephrotoxicity than patients with CLcr > 30 mL/min.

However, plazomicin may become the last treatment option in patients with CLcr >15 to 30 mL/min. Thus, the proposed initial dose for patients with CLcr >15 to 30 mL/min, 10 mg/kg every 48 hours, was evaluated based on simulated exposures of plazomicin across different renal function groups. The exposure (AUC_{0-48h}) in patients with CLcr >15 to 30 mL/min receiving plazomicin 10 mg/kg q48h was simulated based on the population PK model and compared with that in patients with CLcr >30 mL/min receiving their corresponding doses (refer to Section 3.3.3 for details). A simulation study demonstrated that AUC_{0-48} in patients with CLcr >15 to 30 mL receiving 10 mg/kg q48h would be similar to the ones in other renal function groups. Therefore, the review team recommends using plazomicin in patients with severe renal impairment (i.e., CLcr >15 to 30 mL/min) and agrees with the Applicant's proposed dose adjustments in patients with renal impairment which are summarized in Table 2.2.2-1.

Table 2.2.2-1: Plazomicin Dosing for Patients with Renal Impairment

	FDA recommendation[b]
Patients with moderate renal impairment (CLcr[a] > 30-60 mL/min)	10 mg/kg every 24 hours (Q24h)
Patients with severe renal impairment (CLcr > 15-30 mL/min)	10 mg/kg every 48 hours (Q48h)

[a] CLcr: estimate of CLcr based on Cockcroft-Gault equation using total body weight (TBW). The ideal body weight (IBW) should be used for patients with TBW greater than ideal body weight (IBW) by 25% or more.

[b] Calculate dosage using TBW. For patients with TBW greater than IBW by 25% or more, use adjusted body weight (ABW). ABW= IBW + 0.4 x (TBW – IBW)

TDM in cUTI Patients

The Applicant proposed to conduct C_{min}-based TDM in cUTI patients with moderate or severe renal impairment (CLcr > 15 to 60 mL/min) or in those for whom more than 5 days of plazomicin therapy is anticipated to mitigate the risk of nephrotoxicity. The Applicant also proposed (b) (4) Based on our independent E-R analysis for nephrotoxicity, defined as serum creatinine concentration increase 0.5 mg/dL from baseline, in cUTI patients, the incidence of nephrotoxicity in cUTI patients was independent of the duration of plazomicin treatment. In addition, compared to the comparator arms in cUTI Phase 2 & 3 trials, plazomicin caused substantially higher incidence of nephrotoxicity in patients whose CLcr < 90 mL/min. Moreover, the incidence of nephrotoxicity for patients with CLcr > 90 mL/min was much lower patients with CLcr < 90 mL/min in plazomicin arm. Therefore, we recommend the C_{min}-based TDM be applied to patients with CLcr < 90 mL/min receiving plazomicin treatment. The results of a classification and regression tree (CART) analysis in cUTI patients indicated that $C_{1st, min}$ of 3 μg/mL is a critical cut-off associated with high incidence of nephrotoxicity. Consequently, we recommend C_{min} be maintained less than 3 μg/mL in cUTI patients (see section 3.3.2).

(b) (4)

(b) (4)

(b) (4)

2.3 Outstanding Issues

(b) (4)

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert (Table 2.4-1).

Table 2.4-1 Summary of Labeling Issues Identification and Recommendations

Section/heading	Acceptable to OCP?			Comment
	A	AWE	NA	
Highlights and 2.3 / [redacted] in cUTI Patients	☐	☐	☒	• Apply C_{min}- based TDM to cUTI patients with CLcr < 90 mL/min • Revise the C_{min} value for dose adjustment from [redacted] to 3 µg/mL • Add the instruction to extend the dose interval to 36 hours the patients whose C_{min} > 3 µg/mL at 24 hours • Change [redacted] to Therapeutic Drug Monitoring
5.1 / Nephrotoxicity and 12.2 / Nephrotoxicity	☐	☐	☒	• Delete the statement [redacted] • Revise the statement regarding C_{min} to C_{min} > 3 µg/mL
[redacted]				
12.3/ Membrane transporters	☐	☒	☐	• Add that [redacted] • Add that plazomicin selectively inhibited the MATE1 renal transporter in vitro with an IC50 value of 1300 µg/mL.

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Plazomicin is an aminoglycoside antibacterial drug proposed for the treatment of cUTI including pyelonephritis and BSI caused by susceptible microorganism(s). Due to the difficulty in patient enrollment, only a limited number of patients were in ACHN-490-007, which was a randomized, open-label study to evaluate the efficacy and safety of plazomicin compared with colistin in patients with infection due to carbapenem-resistant Enterobacteriaceae. The Applicant decided to pursue the BSI indication (b) (4). Refer to the Clinical Review by Dr. Shrimant Mishra for details. Due to the limited clinical safety and efficacy data, plazomicin is reserved for use in patients who have limited or no alternative treatment options.

IND 102563, was submitted to the Division of Anti-infective Products (DAIP) on 12/19/2008 for cUTI. Breakthrough Therapy designation was granted to plazomicin on 5/17/2017 for the treatment of BSI caused by the susceptible microorganism(s): *Klebsiella pneumoniae and Enterobacter aerogenes*.

(b) (4)

Multiple milestone meetings have been held between the Division and the Applicant throughout the development process, including the End of Phase 2 meeting (12/17/2012) and the Pre-NDA meeting (4/14/2017).

An Advisory Committee (AC) meeting was held on May 2nd, 2018. Refer to the 2018 Meeting Materials, Antimicrobial Drugs Advisory Committee for details[1]. The committee members support the approval of plazomicin for the treatment of cUTI for patients with limited or no alternative treatment options but do not support the approval of plazomicin for the treatment of BSI.

3.2 General Pharmacology and Pharmacokinetic Characteristics

[1] https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-infectiveDrugsAdvisoryCommittee/ucm587657.htm

Table 3.2-1: Summary of Clinical Pharmacology and Pharmacokinetics

<table>
<tr><td colspan="2">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td>Like other aminoglycosides, the primary mechanism of action of plazomicin is inhibition of key steps in bacterial protein synthesis.</td></tr>
<tr><td>Active Moieties</td><td>Plazomicin</td></tr>
<tr><td>QT Prolongation</td><td>The patch-clamp method hERG inhibition assay showed less than 36.6% inhibition at 3000 µg/mL, which is the highest concentration typically tested in this assay. The upper bound of the 90% 2-sided confidence interval of ΔΔQTcF was less than 10 msec at all time points for both dose groups of plazomicin (i.e., 15 mg/kg and 20 mg/kg). The plasma concentration QTc linear regression model of plazomicin indicated no clear plazomicin plasma concentration effect on QTc (QT-IRT review in DARRTS dated 1/26/2018 under IND 102563).</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td>Bioanalysis</td><td>Validated HPLC/MS/MS methods to determine plazomicin concentrations in human plasma and urine (Refer to Appendix 4.1)</td></tr>
<tr><td>Healthy vs. Patients (population PK model)</td><td>
<table>
<tr><td></td><td>Healthy Subjects</td><td>cUTI Patients</td><td>(b) (4)</td></tr>
<tr><td></td><td>Geometric mean (CV%) N=97</td><td>Geometric mean (CV%) N=87</td><td></td></tr>
<tr><td>CL (L/h)</td><td>4.61 (18.6%)</td><td>5.08 (35.2%)</td><td></td></tr>
<tr><td>Vss (L)</td><td>23.5 (24.3%)</td><td>30.7 (36.3%)</td><td></td></tr>
</table>
*Only including subjects with normal renal function (CLcr > 90 mL/min)</td></tr>
<tr><td>Drug exposure following a single therapeutic dosing regimen</td><td>The geometric mean (CV%) of AUC_{0-24} and C_{max} (µg/mL) were 265 (25.1%) µg·hr/mL and 76 (25.7%), respectively, in healthy subjects (Study ACHN-490-006, N=54).</td></tr>
<tr><td>Range of effective dose or exposure</td><td>• 10 mg/kg and 15 mg/kg IV Q24h for 5 days for cUTI (Study ACHN-490-002)
• 15 mg/kg IV Q24h for 4-7 days then switch to oral antibacterial drug treatment for a total duration of treatment of 7 to 10 days (Study ACHN-490-009)
• 15 mg/kg IV Q24h for 7 to 14 days; AUC_{0-24}- based TDM was conducted with a target AUC_{0-24} range of 210 – 315 µg*h/mL (Study ACHN-490-007)</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>Fifteen mg/kg by IV infusion over 10 minutes caused hypotension in 5 of 15 heathy subjects (Study ACHN-490-003). C_{max} values in</td></tr>
</table>

	these 5 subjects ranged from 132 µg/mL to 228 µg/mL. Note that Cmax following the proposed dose by IV infusion over 30 min ranged from 45.8 to 136 µg/mL.
Dose Proportionality	Both C_{max} and AUC_{0-24} following single IV administration increased in an approximately dose-proportional manner from 1 mg/kg to 15 mg/kg. The C_{max}, C_{min}, and AUC_{0-24}following a repeated daily administration increased in an approximately dose-proportional manner from 4 mg/kg QD to 15 mg/kg QD (Study ACHN-490-001).
Accumulation	There was no appreciable accumulation in plasma exposure (C_{max}, AUC_{0-24}, or C_{min}) at steady-state for once-daily dosing in subjects with normal renal function. The $T_{1/2}$ of plazomicin increased by approximately 2-fold and 4-fold in subjects with moderate (i.e., $T_{1/2}$ = ~7 hours) and severe renal impairment (i.e., $T_{1/2}$ = ~14 hours), respectively, compared to subjects with normal renal function (i.e., $T_{1/2}$ = ~ 3.5 hours). Therefore, accumulation ratio was about 1.2 and 1.7 in subjects with moderate or severe renal impairment, respectively, with Q24h dosage regimen (Study ACHN-490-004).
Variability	For healthy subjects with normal renal function, after a single dose, the inter-subject variability (%CV) in C_{max} and AUC_{0-24} values ranged from 19.1% to 31.3% and 14.7% to 25.1%, respectively (Studies ACHN-490-001, 003, and 006). For subjects with renal impairment, the inter-subject variability (%CV) in C_{max} and AUC_{0-24} increased with the severity of renal impairment and ranged from 13.2% to 18.9% for C_{max}, from 12.6% to 40.0% for AUC_{0-24} (Study ACHN-490-004).
Absorption	
Bioavailability	Plazomicin is administered as IV infusion only.
T_{max}	30 minutes (at the end of IV infusion)
Distribution	
Volume of Distribution	Refer to **Healthy vs. Patients**.
Plasma Protein Binding	The mean percentage protein binding of plazomicin in human plasma was 19.6%, ranged from 13.9% to 24%. The protein binding was not concentration dependent in the plazomicin concentration range from 5 µg/mL to 100 µg/mL (*In Vitro* Study A16098-1490-AD).
Substrate transporter systems [*in vitro*]	Plazomicin is not a substrate of P-gp or BCRP transporters at the concentration up to 17.8 µg/mL which is equivalent to 22.3 µg/mL *in vivo* with 20% protein binding (*In Vitro* Study A15014-1490-AD).
Elimination	
Half-life	The mean apparent half-life of plazomicin in healthy volunteers with normal renal function is 3.5 (14.9%) hours including

	$T_{1/2, \alpha}$=0.3 hr, $T_{1/2, \beta}$= 3.0 hr, and $T_{1/2, \gamma}$= 25.0 hr. See Accumulation above for half-life for subjects with renal impairment.
Metabolism	
Fraction metabolized (% dose)	None
Primary metabolic pathway(s) [*in vitro*]	N/A
Excretion	
Primary excretion pathways (% dose) ±SD	About 97.5% of administered dose were excreted in urine as unchanged parent drug in a human mass balance study (Study ACHN-490-010).
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	• Plazomicin does not inhibit CYP1A2, CYP3A4/5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6., or CYP3A4/5 (Study A15015-1490-AD). • Plazomicin does not induce CYP1A2, CYP3A4, or CYP2B6 (Study A15016-1490-AD).
Inhibition/Induction of transporter systems	Plazomicin is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2, but is an inhibitor of MATE1 and MATE2-K transporters in vitro (Study A15014-1490-AD).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

3.3.1.1 Complicated Urinary Tract Infection (cUTI)

The pivotal evidence of efficacy in the treatment of cUTI was the clinical efficacy results of one Phase 3 study (ACHN-490-009). The results of one Phase 2 study in cUTI patients (Study ACHN-490-002) and the exposure-response analysis for efficacy of Study ACHN-490-009 provided supportive evidences of effectiveness.

Pivotal Evidence

One Phase 3 study was conducted in adult patients with cUTI. Study ACHN-490-009 was a randomized, double-blind study evaluating the efficacy and safety of plazomicin compared with meropenem followed by optional oral (PO) therapy in the treatment of cUTI, including pyelonephritis, in adults. Patients received IV plazomicin or meropenem for 4 to 7 days and then had the option to switch to oral antibacterial drugs, such as levofloxacin, with a total duration of treatment of 7-10 days. Plazomicin initial dose was based on renal function (i.e., CLcr) and subsequent dose adjustments were also made based on patients' daily measured CLcr. Refer to the Clinical review by Dr. Shrimant Mishra for details of the study design. In this study,

plazomicin demonstrated non-inferiority (NI) to meropenem with respect to the co-primary endpoints, the composite cure rates at both Day 5 and the TOC visit, based on a non-inferiority (NI) margin of 15%.

Supportive Evidence

Phase 2 Study (ACHN-490-002)

In the Phase 2 Study, a total of 145 patients were randomized to treatment, as follows: 22 to plazomicin 10 mg/kg, 76 to plazomicin 15 mg/kg, and 47 to levofloxacin 750 mg. The microbiological eradication rates were generally comparable between treatment groups and comparator (levofloxacin) group (Table 3.3.1-1 microbiologically evaluable (ME) populations without substantial adverse events). A numerically lower microbiological eradication rate was observed at the 10 mg/kg arm as compared with 15 mg/kg in the modified intent-to-treat (MITT) populations.

Table 3.3.1-1 Microbiological Response at TOC (MITT and ME Populations in Study ACHN-490-002)) (Adapted from Table 5 in Summary of Clinical Efficacy)

Population	By-Patient Microbiological Response	Plazomicin 10 mg/kg	Plazomicin 15 mg/kg	Levofloxacin 750 mg
MITT	N	12	51	29
	Eradication, n (%)	6 (50.0)	31 (60.8)	17 (58.6)
	95% CI	(21.1, 78.9)	(46.1, 74.2)	(38.9, 76.5)
	Non-eradication, n (%)	1 (8.3)	5 (9.8)	4 (13.8)
	Indeterminate, n (%)	5 (41.7)	15 (29.4)	8 (27.6)
	Difference (95% CI) [a]			2.2 (-22.9, 27.2)
ME	N	7	35	21
	Eradication, n (%)	6 (85.7)	31 (88.6)	17 (81.0)
	95% CI	(42.1, 99.6)	(73.3, 96.8)	(58.1, 94.6)
	Non-eradication, n (%)	1 (14.3)	4 (11.4)	4 (19.0)
	Difference (95% CI) [a]			7.6 (-16.0, 31.3)

Abbreviations: ME=microbiologically evaluable; MITT=modified intent-to-treat; mMITT=microbiological modified intent-to-treat; N=number of patients; TOC= test-of-cure.

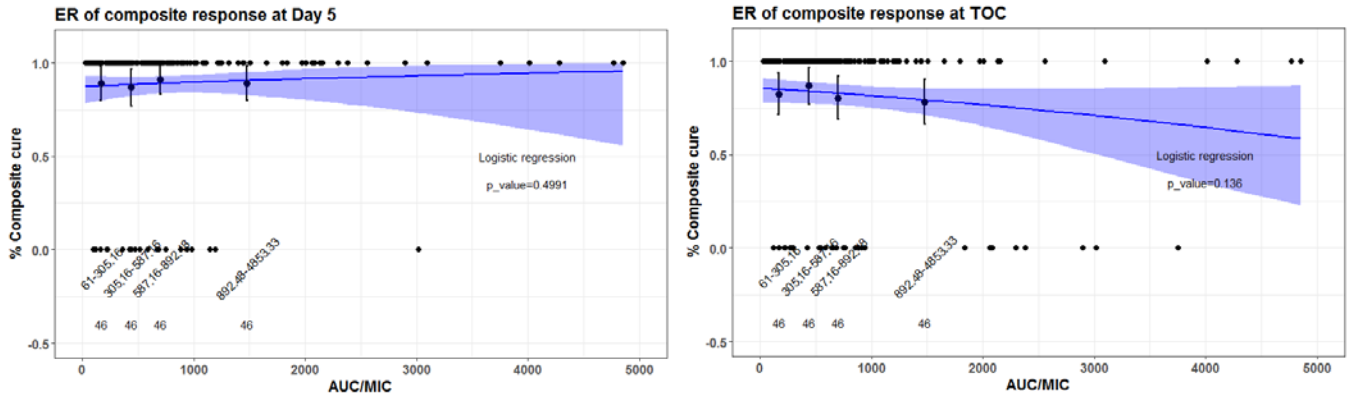
[a] Difference is for the difference in microbiological eradication rates between plazomicin 15 mg/kg and levofloxacin and is calculated as plazomicin 15 mg/kg – levofloxacin. The 95% CI for the difference is based on a normal approximation with a continuity correction.

Exposure-Response (E-R) Analyses

The Applicant did not conduct exposure-response (E-R) analysis for efficacy in cUTI patients. Although doses were adjusted in this study based on patients' daily CLcr, because the AUC_{0-24} values were comparable across different renal function groups with the proposed dosage regimen, plazomicin exposure for each individual patient is expected to be similar during the treatment even with dose adjustment. Therefore, we conducted an independent analysis in cUTI patients for the relationship between total plazomicin AUC_{0-24} / MIC ratio after first dose in Study ACHN-490-009 and four endpoints: 1) composite microbiology and clinical response at Day 5; 2) composite microbiology and clinical response at test of cure (TOC); 3) microbiology response at Day 5; and 4) microbiology at TOC. The exposure of AUC_{0-24} was derived from post hoc analysis from population PK model. A total of 184 patients received plazomicin were included in the E-R dataset. The flat E-R relationship was identified between AUC_{0-24} / MIC

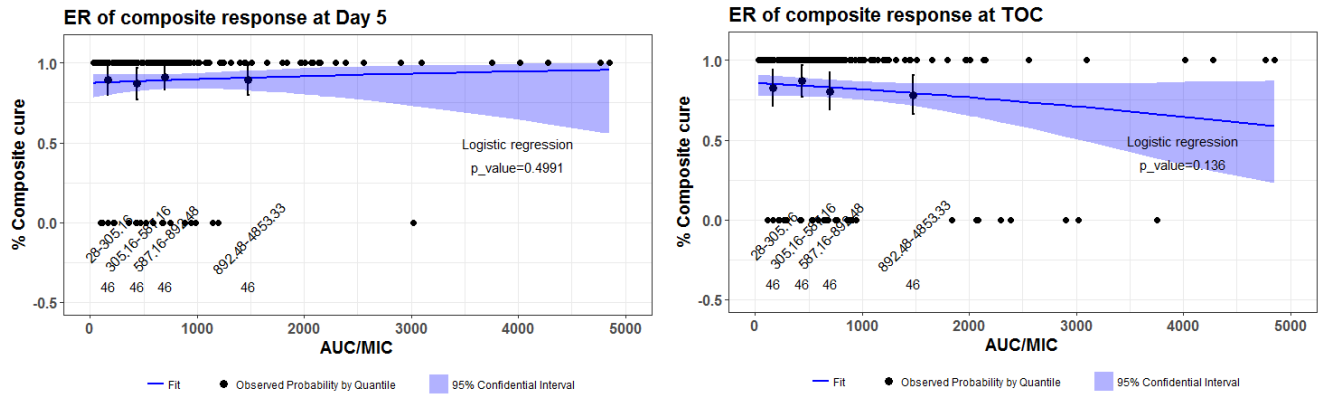
ratio and the four efficacy endpoints (Figures 3.3.1-1 and 3.3.1-2). Refer to APPENDIX 4.3 for details.

Figure 3.3.1-1 E-R analysis using AUC_{0-24}/MIC for composite response at Day 5 (left) and TOC (right) (Adapted from Figure 4.3.1-3 Exposure-Response Analysis)



The numbers on the bottom left corner in the figure represent the range of AUC/MIC and the number of subjects in each AUC/MIC quartile

Figure 3.3.1-2 E-R analysis using AUC/MIC for microbiological response at Day 5 (left) and TOC (right) (Adapted from Figure 4.3.1-4 Exposure-Response Analysis)



The numbers on the bottom left corner in the figure represent the range of AUC/MIC and the number of subject in each AUC/MIC quartile

3.3.1.2 Blood Stream Infection (BSI)

One Phase 3 study (ACHN-490-007) was conducted including BSI patients. Of note, Study ACHN-490-007 was originally designed to be a multicenter, randomized, open-label trial to evaluate the efficacy and safety of plazomicin compared with colistin in patients with Hospital-Acquired Bacterial Pneumonia/ Ventilator- Associated Bacterial Pneumonia (HABP/VABP) or BSI due to CRE. (b) (4)

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3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

For both cUTI and BSI patients, the proposed dosing regimen can be divided into two parts, initial dose and subsequent therapeutic drug monitoring (TDM).

The proposed initial dosing regimen for BSI and cUTI patients with normal renal function shown below is acceptable.

- 15 mg/kg Q24h administered over 30 minutes by IV infusion
  - BSI: 7-14 days
  - cUTI including pyelonephritis: 4-7 days

However, we disagree upon the Applicant's TDM plans for cUTI patients (see Section 3.3.2.1 for details).

- For cUTI patients, Applicant proposed to adjust plazomicin dose to maintain C_{min} (b) (4) (b) (4) 2 µg/mL. We recommend that C_{min} should be maintained at a plasma concentration of less than 3 µg/mL.
- In addition, the Applicant proposed to monitor C_{min} in cUTI patients with moderate or severe renal impairment (CLcr >15 to 60 mL/min) or in those for whom more than 5 days of plazomicin therapy is anticipated. We recommend that TDM should be applied to patients whose CLcr >15 to 90 mL/min regardless of the duration of treatment.

(b) (4)

3.3.2.1 Dosing Regimen in cUTI Patients

Initial Dosing Regimen in General Population with cUTI

The proposed initial dosing regimen for cUTI patients was studied in one Phase 2 trial (ACHN-490-002) and one Phase 3 trial (ACHN-490-009). The evidence of effectiveness for plazomicin in the treatment of cUTI patients has been demonstrated in these two studies (see Section 3.3.1 for details). In addition, the E-R analysis in cUTI patients suggests the exposure achieved by the initial dosing regimen may be sufficient for the desired efficacy outcome (see Section 3.3.1 for details). After initial dose, C_{min}- based TDM is proposed to be used to guide dose adjustment in cUTI patients to mitigate potential nephrotoxicity risk (see TDM in cUTI patients below in this section for details).

TDM in cUTI patients

The dose of plazomicin is proposed to be adjusted daily based on estimated CLcr in all cUTI patients. C_{min}-based TDM is also proposed in cUTI patients to monitor the plazomicin concentrations (b) (4) before administration of the second or third dose to avoid trough concentrations above 2 μg/mL for patients with moderate or severe renal impairment (CLcr >15 to 60 mL/min) or for patients expected to receive more than 5 days of plazomicin treatment. In study ACHN-490-009, daily dose adjustment was conducted in the Phase 3 study while the C_{min}-based TDM was not conducted. The TDM threshold and target population were selected by the Applicant based on univariate analysis and multivariable regression analysis, respectively (refer to APPENDIX 4.3.2 for details). Of note, C_{min}-based TDM is currently used for other approved aminoglycosides to reduce the probability of nephrotoxicity with TDM thresholds derived from clinical experience.

C_{min}-based TDM approach requires a precise, accurate, and reliable bioassay device. The regulatory action on the companion diagnostic device is still pending with CDRH. The current review will discuss dose evaluation for two scenarios: with and without C_{min}-based TDM approach.

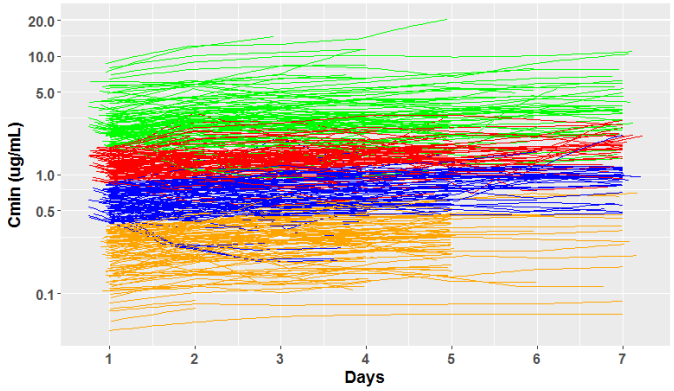
With C_{min}-based TDM approach

We conducted an independent E-R analysis and a classification and regression tree (CART) analysis (refer to APPENDIX 4.3.2 for details) to evaluate the TDM threshold and TDM population, and demonstrated:

- Daily C_{min} was predicted based on the population PK model at the time prior to the next dose or at 24 hours after the last dose
- The predicted daily C_{min} of each patient did not change substantially during the treatment period because plazomicin dose was adjusted based on changes in CLcr, which warranted the use of the estimated C_{min} prior to 2nd dose ($C_{1st,min}$) in the E-R assessment for nephrotoxicity, which was defined as increase of serum creatinine concentration ≥0.5 mg/dL from baseline (Figure 3.3.2-1)

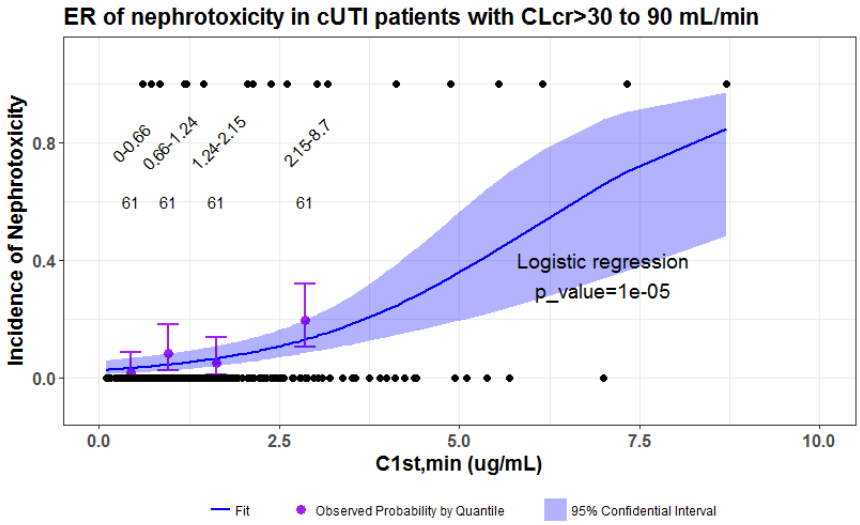
- The nephrotoxicity incidence was lower in plazomicin arm compared to that in active control arm in patients with CLcr >90 mL/min (Table 3.3.2-1)
- Most nephrotoxicity occurred in the patients with renal impairment (CLcr >30 to 90 mL/min) (Table 3.3.2-1), the incidence of nephrotoxicity was significantly associated with an increase in estimated $C_{1st,min}$ ($p<0.0001$, logistic regression) based on data from Studies ACHN-490-002 and ACHN-490-009 (Figure 3.3.2-2).
- The incidence of nephrotoxicity in cUTI patients was independent of the duration of plazomicin treatment
- The $C_{1st, min}$ value of 3 µg/mL is the critical cutoff associated with higher incidence of nephrotoxicity based on CART analysis (Figure 3.3.2-3).

Figure 3.3.2-1 C_{min} over time for cUTI patients from Studies 002 and 009 (Adapted from Figure 4.3.3-1 in APPENDIX 4.3.3)



Each line represents C_{min} over days for each subject; Orange, blue, red, and green represent 1^{st}, 2^{nd}, 3^{rd}, and 4^{th} quartiles of $C_{1st,min}$, respectively.

Figure 3.3.2-2 Exposure-response analysis for nephrotoxicity in cUTI/AP patients with CLcr >30 to 90 mL/min (Adapted from Figure 4.3.3-3 in APPENDIX 4.3.3)



The line and the shaded area represent the predicted relationship between $C_{1st,min}$ and incidence of nephrotoxicity and their 95% confidence interval (CI). Closed circles and bars represent the observed

incidence of nephrotoxicity and 95% CI, respectively, at each $C_{1st,min}$ quartile. Occurrence of nephrotoxicity in each patient (i.e., 1 or 0 for yes or no, respectively) were plotted at estimated $C_{1st,min}$ in each patient. The numbers on the upper left corner represent the range of concentrations (µg/mL) and number of patients in each $C_{1st,min}$ quartile.

Figure 3.3.2-3 CART analysis for nephrotoxicity in cUTI/AP patients with CLcr >30 to 90 mL/min (Adapted from Figure 4.3.3-4 in APPENDIX 4.3.3)

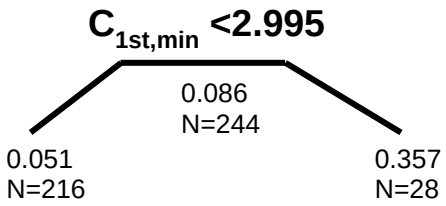


Table 3.3.2-1 Percentage of cUTI patients with nephrotoxicity by CLcr and arm (Adapted from Table 4.3.3-1 in Section 4.3.3)

	% Nephrotoxicity (n/N)*	
	CLcr >30 to 90 mL/min	CLcr >90 mL/min
Plazomicin	8.6% (21/244)	0.8% (1/123)
Active Control[#]	4.1% (10/243)	3.1% (3/97)

**n is the number of patients with nephrotoxicity; N is the number of patients*
[#]Meropenem or levofloxacin

The proposed TDM threshold of 2 µg/mL appears to be not appropriate due to the following reasons:

(b) (4)

(b) (4)

Table 3.3.2-2 Summary of incidence of nephrotoxicity in cUTI patients with CLcr >30 to 90 mL/min by $C_{1st,min}$ range (Adapted from Table 4.3.3-4 in Section 4.3.3)

$C_{1st, min}$ Range	% Nephrotoxicity (n/N)*
≥ 4 µg/mL	40.0% (6/15)
≥ 3, and <4 µg/mL	30.8% (4/13)
≥ 2 and < 3 µg/mL	9.8% (4/41)
≥ 1 and < 2 µg/mL	5.0% (4/80)
< 1 µg/mL	3.2% (3/95)
Total	8.6% (21/244)

**n is the number of subjects with nephrotoxicity; N is the number of all the subjects*

Table 3.3.2-3 Comparison of two $C_{1st, min}$ cutoffs in patients with CLcr >30 to 90 mL/min (Adapted from Table 4.3.2-7 in Section 4.3.3)

Cutoffs	% Patients with $C_{1st, min}$ ≥ cutoff (n/N)*	% Nephrotoxicity in patients with $C_{1st, min}$ ≥ cutoff (n/N)	% Nephrotoxicity in patients with $C_{1st, min}$ < cutoff (n/N)
3 µg/mL	11.5% (28/244)	35.7% (10/28)	5.1% (11/216)
2 µg/mL	28.3% (69/244)	20.3% (14/69)	1.0% (7/175)

**n represents number of patients with nephrotoxicity; N represents number of patients*

Table 3.3.2-4 Sensitivity and specificity comparison by TDM cutoffs in patients with CLcr >30 to 90 mL/min (Adapted from Table 4.3.3-8 in Section 4.3.3)

$C_{1st, min}$ cutoffs	Sensitivity*	Specificity[#]
3 µg/mL	48%	92%
2 µg/mL	67%	75%

**Sensitivity is defined the percentage of patients with nephrotoxicity who can be correctly classified as dose adjustment is needed (*$C_{1st, min}$ ≥ cutoff*).*

[#]The specificity is defined as the percentage of patients without nephrotoxicity who can be correctly classified as no dose adjustment is needed ($C_{1st, min}$ < cutoff*).*

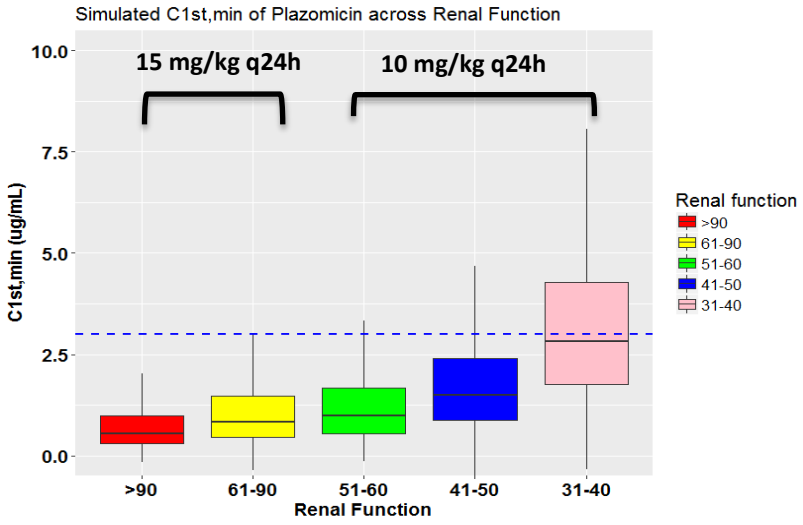
In brief, $C_{1st, min}$ ≥3 µg/mL is an option if overall efficacy loss is a major concern for TDM since less patients may have dose adjustment while $C_{1st, min}$ ≥2 µg/mL is an option if overall safety is a major concern for TDM since more patients with nephrotoxicity may have dose adjustment. Specifically, dose reductions for patients with $C_{1st, min}$ between 2 and 3 µg/mL may raise concern for efficacy loss and no dose reduction for patients with $C_{1st, min}$ between 2 and 3 µg/mL may raise safety concern. However, considering that the Phase 3 study was a non-inferiority study without TDM and there was a signal that efficacy may be compromised with lower exposure based on the Phase 2 dose-ranging study, the higher cutoff may prevent potential efficacy loss by reducing the percentage of patients with the dose adjustment. In addition, treatment duration is short and nephrotoxicity is reversible (13 out of 22 cUTI patients with nephrotoxicity had their serum creatinine concentration back to normal at the end of the study). Therefore, $C_{1st, min}$ ≥3

µg/mL appears to be more reasonable than $C_{1st, min} \geq 2$ µg/mL as the TDM cutoff in cUTI patients.

Without C_{min}-based TDM approach

Since the device for TDM may not be ready when plazomicin is available for patients, the dosing strategy with dose adjustment based on daily CLcr measure but without C_{min}-based TDM was evaluated. As mentioned above, the nephrotoxicity incidence was low in patients with CLcr >90 mL/min who received plazomicin. Thus, C_{min}-based TDM may not be needed in patients with CLcr >90 mL/min. It is also known that daily dose adjustment based on CLcr without C_{min}-based TDM was unable to mitigate the nephrotoxicity in patients with Clcr >30 to 90 mL/min. Adjusting the initial dose may be the only approach to reduce the potential delayed nephrotoxicity in cUTI patients. However, the proposed initial dose is either the same as the studied dose or lower than the studied dose in most of the patients except the patients with CLcr >30 to 40 mL/min who received 8 mg/kg q24h in the Phase 3 study, which is 20% lower than what was proposed in the label (10 mg/kg q24h). Therefore, adjusting initial dose may be only appropriate in patients with CLcr >30 to 40 mL/min without the potential efficacy loss. The plot of $C_{1st, min}$ across renal function (Figure 3.3.2-4) shows that $C_{1st, min}$ increased with a decrease in CLcr based on the proposed initial dose. The percentages of patients with $C_{1st, min} \geq 3$ µg/mL were 2%, 5%, 6%, 15%, and 46% for CLcr >90 mL/min, CLcr > 60 to 90 mL/min, CLcr >50 to 60 mL/min, CLcr >40 to 50 mL/min, and CLcr >30 to 40 mL/min. It appears that adjusting the initial dose for patients with CLcr >30 to 40 mL/min may potentially reduce the nephrotoxicity incidence because $C_{1st, min}$ would be decreased. The simulation showed that around 46% patients with CLcr >30 to 40 mL/min would have $C_{1st, min} \geq 3$ µg/mL based on an initial dose of 10 mg/kg while the percentage would be reduced to 33% based on an initial dose of 8 mg/kg. The limitation is the CLcr range is too narrow to propose a reduced initial dose considering the high variability of CLcr measure.

Figure 3.3.2-4 $C_{1st, min}$ across renal function based on the proposed initial dose



The blue dash line represents the $C_{1st,\ min}$ equals to 3 μg/mL

TDM scheme in cUTI patients

The Applicant also provided the details of TDM scheme using C_{min} ≥2 μg/mL as the TDM cutoff for cUTI patients:

- If the measured trough level is ≥2 μg/mL, increase the dosing interval by 1.5-fold
- If trough concentrations continue to persist ≥2 μg/mL, discontinue or increase the dosing interval by additional 24 hours

The proposed TDM scheme appears to be consistent with other aminoglycosides. However, the treatment duration (5 to 7 days) is relatively short for cUTI patients and concentration values will be available at 24 to 36 hours after blood samples are collected, two dose adjustments may not be clinically feasible. We evaluated the effect of one dose adjustment (increase the dosing interval by 1.5-fold) on the distribution of $C_{1st,min}$. Based on simulation using population PK model, around 97% patients are predicted to have C_{min} <3 μg/mL after one dose adjustment with $C_{1st,\ min}$ ≥3 μg/mL as the TDM cutoff (refer to APPENDIX 4.3.3 for details).

Limited efficacy and safety data were available in patients with CLcr >15 to 30 mL/min, thus, the TDM scheme was proposed (b) (4) . As the dosing interval is 48 hours in patients with CLcr >15 to 30 mL/min, the $C_{1st,\ min}$ at 48 hours instead of 24 hours will be used for TDM. Considering the short treatment duration, multiple dose adjustments may not be clinically feasible either in this patient population. Based on simulation using population PK model, around 88% patients would have a reasonable dosing interval based on one dose adjustment (increase the dosing interval by 1.5-fold) using $C_{1st,\ min}$ ≥3 μg/mL as the TDM cutoff (refer to APPENDIX 4.3.3 for details).

(b) (4)

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Figure 3.3.2-6 (b) (4)

3.3.2.4 Susceptibility Breakpoints for Plazomicin

Antibacterial susceptibility test interpretive criteria (breakpoints hereafter) are discriminatory antimicrobial concentrations used in the interpretation of results of susceptibility testing to define isolates as Susceptible, Intermediate or Resistant. The Applicant's proposed susceptibility breakpoints are in Table 3.3.2-10. The results of our probability of target attainment analyses (PTA) in cUTI patients support the susceptibility breakpoint of 1 µg/mL for plazomicin. However, it should be noted that the determination of breakpoints involves multiple disciplines including clinical and microbiological perspectives in addition to the nonclinical PK/PD considerations. The ultimate determination of the plazomicin breakpoint will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

Table 3.3.2-10 Applicant's Proposed Susceptibility Breakpoints for Plazomicin

Pathogen	**Minimum Inhibitory Concentration (µg/mL)**		
	S	I	R
Enterobacteriaceae	(b) (4)		

The PK/PD index for plazomicin is total AUC_{0-24} / MIC which is closely correlated to plazomicin antibacterial activity for Enterobacteriaceae based on animal infection models. Due to the similar plasma protein binding in humans (i.e., 19.6%) and mice (i.e., 19.9%), total

$AUC_{0\text{-}24}$ / MIC from a neutropenic murine thigh model can be applied to humans for PTA analysis without adjusting for free drug exposure.

The Applicant conducted a probability of target attainment (PTA) analysis in cUTI patients using the non-clinical PK/PD targets (i.e., 18 for bacterial stasis and 73 for 1-$\log_{10}$ CFU reduction) against *Enterobacteriaceae* based on a neutropenic murine thigh model in Study UFL-2016-001. In this study, mice were infected by nine *Enterobacteriaceae* strains with MIC range from 0.25 to 4 µg/mL, two of them were Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates.

However, we noted that another dose-fractionation study to determine non-clinical PK/PD target (Study UFL-2012-009) was included in this application using a similar neutropenic murine thigh model infected by another eight CRE isolates with MIC ranging from 0.19 to 0.46 µg/mL. The PK/PD targets derived from this study were used to support the clinical dose selection in Phase 3 studies. Because these two studies used very similar neutropenic murine thigh model, same amount of bacterial inoculation, and similar study design., to include more *Enterobacteriaceae* strains for the PK/PD target determination, the reviewer combined individual PK/PD targets of each strain from two studies together (see APPENDIX 4.5.1 for details). Consequently, a total of 17 *Enterobacteriaceae* were included to determine PK/PD targets for plazomicin. The results from PK/PD studies in the neutropenic murine thigh model indicated median values of $AUC_{0\text{-}24}$/ MIC of 24 (range: 5.7 to 65) for bacterial stasis and 89 (range: 8.1 to 518.3) for 1 $\log_{10}$ CFU reduction, respectively. Refer to Table 3.3.2-11 below for the summary.

Table 3.3.2-11 Summary of $AUC_{0\text{-}24}$ / MIC Ratios for Plazomicin against 17 *Enterobacteriaceae* Strains in a Neutropenic Murine Thigh Infection Model

	$AUC_{0\text{-}24}$/MIC Ratio for Net Bacterial Stasis	**AUC/MIC Ratio for 1 logCFU Reduction**
Median	24	89
75% Quantile	39	152
25% Quantile	12	48

PTA analyses were conducted for the median, 75% quantile value of $AUC_{0\text{-}24}$/MIC ratios for net bacterial stasis and median value for 1 log CFU reduction using the proposed dose. Refer to Table 3.3.2-12 below for the PTA analysis results.

Due to the severity of the infection in cUTI patients, historically the median value of PK/PD targets for 1 log10 CFU reduction was utilized to determine the breakpoint. Based on the results in Table 3.3.2-12, the PTA analysis supports 1 µg/mL as the breakpoint for Susceptible when the target bacteria killing is 1 log10 CFU reduction from baseline (i.e., 89 of $AUC_{0\text{-}24}$/MIC).

Table 3.3.2-12 PTA Results in Simulated cUTI Patients with Different Renal Function

PTA by MIC using AUC/MIC of 24 as a PK/PD target					
CLcr	*MIC Values*				
	1 µg/mL	*2 µg/mL*	*4 µg/mL*	*8 µg/mL*	*16 µg/mL*
CLcr>90 mL/min	*100%*	*100%*	*98%*	*54%*	*3%*
CLcr>30 to 90 mL/min	*100%*	*100%*	*99%*	*64%*	*6%*
CLcr>15 to 30 mL/min	*100%*	*100%*	*99%*	*66%*	*7%*
PTA by MIC using AUC/MIC of 39 as a PK/PD target					
CLcr	*MIC Values*				
	1 µg/mL	*2 µg/mL*	*4 µg/mL*	*8 µg/mL*	*16 µg/mL*
CLcr>90 mL/min	*100%*	*100%*	*75%*	*10%*	*0*
CLcr>30 to 90 mL/min	*100%*	*100%*	*82%*	*16%*	*0*
CLcr>15 to 30 mL/min	*100%*	*100%*	*83%*	*18%*	*0*
PTA by MIC using AUC/MIC of 89 as a PK/PD target					
CLcr	*MIC Values*				
	1 µg/mL	*2 µg/mL*	*4 µg/mL*	*8 µg/mL*	*16 µg/mL*
CLcr>90 mL/min	*99%*	*62%*	*5%*	*0*	*0*
CLcr>30 to 90 mL/min	*99%*	*70%*	*9%*	*0*	*0*
CLcr>15 to 30 mL/min	*99%*	*73%*	*10%*	*0*	*0*

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, an alternative dosing regimen proposed by the Applicant for patients with renal impairment (Table 2.2.2-1) for (b) (4) cUTI (b) (4) appears to be reasonable.

Based on the Applicant's analysis of a PK study in subjects with renal impairment (Study ACHN-490-004 APPENDIX 4.5.4), total plazomicin exposure in plasma consistently increased with decreasing renal function. After a 30 minute 7.5 mg/kg plazomicin infusion, geometric mean AUC_{0-24} values for the severe (15-29 mL/min) and moderate (30-59 mL/min) renal impairment group were 4.4-fold and 2.0 higher, respectively, than the corresponding exposure observed for the normal renal function group. The study results suggested that a dose adjustment was necessary for patients with moderate or severe renal impairment.

Based on the population pharmacokinetic analysis, renal function and body size were identified to have clinically significant impact on PK parameters of plazomicin (See APPENDIX 4.2). Therefore, plazomicin is dosed by weight and dose adjustment is recommended in patients with renal impairment based on the final population PK model.

However, the dose adjustment algorithm for patients with renal impairment in two Phase 3 studies (Table 3.3.3-2) was different from the one proposed by the Applicant in the draft labeling (Table 3.3.3-1). We simulated exposure (AUC_{0-24h}) for plazomicin across different renal function categories based on the patient demographics in Study ACHN-490-009 under two dosing regimens, proposed by the Applicant in the labeling and studied in Study ACHN-490-009

(Figure 3.3.3-1). The results illustrate that the proposed initial dose by Applicant in the labeling would result in slightly lower exposure (20% lower) in the group of CLcr between 50 and 60 mL/min and slightly higher exposure (20% higher) in the group of CLcr between 30 and 40 mL/min. However, the exposure in patients with CLcr >30-40 mL/min based on the proposed initial dose was still lower than the upper bound of 95% quantile of $AUC_{0\text{-}24h}$ in cUTI patients from Study ACHN-490-009.

(b) (4)

Table 3.3.3-2 Dose Chart for Phase 3 cUTI Study (ACHN-490-009) (b) (4)

Baseline Creatinine Clearance or Type of Renal Replacement Therapy		Dose Interval	Dose (mg/kg; per Injection) [a]
CLcr >60 mL/min		q24h ± 2h	15
CLcr >50–60 mL/min			12
CLcr >40–50 mL/min			10
CLcr >30–40 mL/min			8
CLcr >25–30 mL/min		q48h ± 2h	12
CLcr >20–25 mL/min			10
CLcr >15–20 mL/min			8
CLcr ≤15 mL/min [b]		q48h ± 2h	8
CRRT	Slow [c]	q24h ± 2h	11
	Fast [d]	q12h ± 2h	10

CLcr=creatinine clearance; CRRT=continuous renal replacement therapy; q12h=every 12 hours; q24h=every 24 hours; q48h=every 48 hours; TDM=therapeutic drug management.

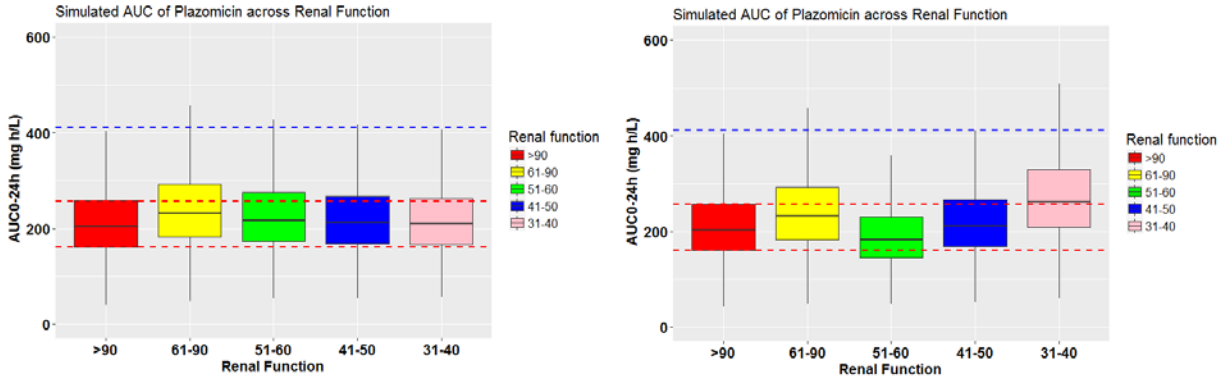
[a] Adjusted dosing weight was applied as needed.

[b] For patients with CLcr ≤15 mL/min who were not on renal replacement therapy, a single initial dose of 8 mg/kg was given and TDM samples were drawn as indicated below. Independent pharmacology support was contacted for further dosing recommendations once TDM data was available. If TDM data was not available prior to the next scheduled dose (q48h), a single maintenance dose of 5 mg/kg was given.

[c] Assumes residual plazomicin renal clearance of 0 mL/min and clearance attributed to CRRT of 2.4 L/h when using slow dialysate and ultrafiltrate flow rates (5–15 mL/min) and blood flow rate of 150 mL/min.

[d] Assumes residual plazomicin renal clearance of 0 mL/min and clearance attributed to CRRT of 4.8 L/h when using fast dialysate and ultrafiltrate flow rates (30–40 mL/min) and blood flow rate of 150 mL/min.

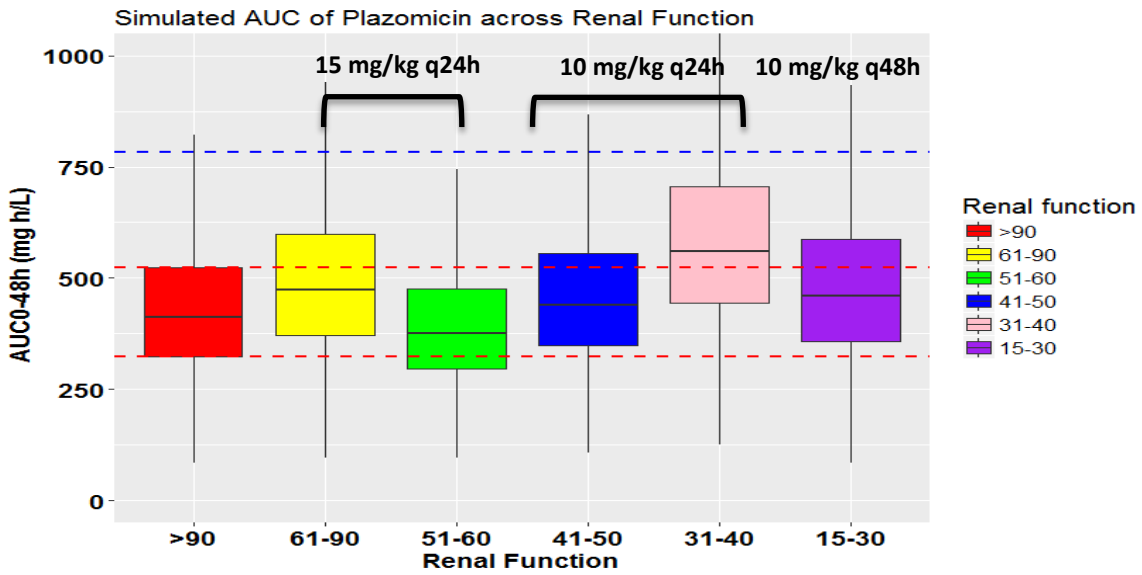
Figure 3.3.3-1 Exposure comparison across renal function in cUTI patients from Study ACHN-490-009 with the studied doses (left) and the proposed doses (right) (Adapted from Figure 5 in APPENDIX 4.2)



The red dash lines represent the 25% and 75% quantile of $AUC_{0\text{-}24h}$ in cUTI patients with CLcr > 90 mL/min; the blue dash lines represent the 95% quantile of $AUC_{0\text{-}24h}$ (411 mg·h/L) in cUTI patients from Study ACHN-490-009.

There were only two patients with CLcr >15 to 30 mL/min enrolled in Phase 3 studies (i.e., one in BSI study and the other in cUTI study). Moreover, the E-R analysis for nephrotoxicity in cUTI patients indicates that higher risk of nephrotoxicity is expected in patients with CLcr >15 to 30 mL/min. However, considering that plazomicin is indicated for limited use, the patients with CLcr >15 to 30 mL/min may have limited treatment option. Therefore, we evaluated the initial dose for patients with CLcr >15 to 30 mL/min. The exposure ($AUC_{0\text{-}48h}$) in patients with CLcr >15 to 30 mL/min administered an initial dose of 10 mg/kg q48h was simulated based on the population PK model and compared with that in patients with CLcr >30 mL/min receiving their corresponding doses (Figure 3.3.3-2). The simulated $AUC_{0\text{-}48}$ in patients with CLcr >15 to 30 mL appears to be similar to the ones in other renal function groups.

Figure 3.3.3-2 Exposure comparison across renal function in cUTI patients



The red dash lines represent the 25% and 75% quantile of $AUC_{0\text{-}48h}$ in cUTI patients with CLcr >90 mL/min; the blue dash lines represent the 95% quantile of $AUC_{0\text{-}48h}$ (783 mg·h/L) in cUTI patients from Study ACHN-490-009.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

3.3.4.1 Food Effect

Because plazomicin is administered by IV infusion only, there are no food-drug interactions.

3.3.4.2 Drug-drug Interaction

Based on in vitro study results, plazomicin may be an inhibitor to MATE1 and/or MATE2-K transporters (APPENDIX 4.5.2). Metformin is a substrate for both MATE1 and MATE2-K. Therefore, a clinical DDI study (APPENDIX 4.5.6 Study ACHN-490-011) was conducted by co-administering metformin, a MATE transporter substrate, with plazomicin. The study results demonstrated that 90% CIs for the GLSM ratios of plasma metformin $AUC_{0\text{-inf}}$, and C_{max}, following a single oral dose of metformin with plazomicin relative to a single oral dose of metformin alone, were within the 80.00 - 125.00% interval, indicating that there is no effect of plazomicin on the plasma PK of metformin.

Serum creatinine (Scr) is primarily filtered through the kidneys, but a small proportion (~10%–20%) undergoes active secretion into the renal proximal tubules. MATE transporters mediate the active secretion of Scr. Consequently, inhibition of MATE transporters can increase Scr in the

absence of clinically meaningful alteration in renal function[6,7]. The negative PK results from the clinical DDI study between plazomicin and metformin are not able to 100% exclude the potential inhibition of plazomicin of creatinine secretion. Because the Scr increase of 0.5 mg/dL was used as an indicator for potential nephrotoxicity in this application, it is critical to distinguish clinically relevant increases in Scr due to renal toxicity from the non-pathologic increase in Scr attributed to inhibition of renal transporters

Literature evidence suggests that the increase of Scr caused by the inhibition of the renal transporters (i.e., OCT2, MATE1, and MATE2-K, respectively) usually occur early in therapy with prompt return to baseline and with a maximum observed Scr increase of about 0.38 mg/dL [5, 6]. Therefore, the increase Scr of 0.5 mg/dL may indicate a potential nephrotoxicity caused by plazomicin.

[6] Arya V, Yang X, Balimane P, et al. Creatinine as an endogenous marker for renal function—emerging role of transporters in the overall assessment of renal toxicity. Presented at: ASCPT Annual Meeting; March 18-22, 2014; Atlanta, GA.

[7] Zhang Y, Warren MS, Zhang X, et al. Impact on creatinine renal clearance by the interplay of multiple renal transporters: a case study with INCB039110. Drug Metab Dispos. 2015;43(4):485-9.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Two validated assays as listed below were used for quantification of plazomicin (ACHN-490) in plasma and urine including one validated assay for quantification of Iothalamate in human plasma. Please refer to Table 4.1-1 for details. Because no proposed indications were related to lung penetration, the validated assay for quantification of plazomicin in epithelial lining fluid (ELF) was not reviewed.

When concentrations exceeded the standard curve range, samples were diluted and, then, assayed. Dilution integrity was verified within each clinical pharmacology study when sample dilutions were performed. The sample preparation, stability, analysis accuracy, and precision in each clinical pharmacology study were reported in its individual bioanalytical report and reviewed by the Clinical Pharmacology reviewer.

Based on the method validation and description of the run acceptance criteria, both analytical methods and runs met the acceptable criteria specified in the FDA Guidance to Industry: Bioanalytical Method Validation.

Table 4.1-1 Summary of Good Laboratory Practice Method Validation and Bioanalytical Study Reports (Adapted from Table 2 in Summary of Biopharmaceutical Studies)

Method Validation Report Number	Method Validation Report Title	Species and Matrix	Range of Quantitation (µg/mL)	Bioanalytical Study Reports	Clinical Protocol Numbers
AV08-ACHN490-02	HPLC/MS/MS Assay Validation for the Determination of ACHN-490 from Human Plasma and Urine and Iothalamate from Human Plasma [a]	Human plasma	0.010–5.00	AD09-216 AD12-298 AD17-633	ACHN-490-001 ACHN-490-004 ACHN-490-010
		Human urine	0.500–50.0		
AV10-ACHN490-01	HPLC/MS/MS Assay Validation for the Determination of ACHN-490 in Human Plasma	Human plasma	0.010–5.00	AD12-312 AD10-249 AD12-298 AD12-299 AD15-492 AD16-568 AD17-633 AD17-643	ACHN-490-002 ACHN-490-003 ACHN-490-004 ACHN-490-006 ACHN-490-007 ACHN-490-009 ACHN-490-010 ACHN-490-011

Abbreviations: HPLC/MS/MS = high-performance liquid chromatography-tandem mass spectrometry.

[a] Iothalamate clearance was measured to estimate the glomerular filtration rate to assess renal function.

The performance validation parameters in human plasma and urine for the validated assay methods were summarized in Table 4.1-2 and Table 4.1-3, respectively.

Table 4.1-2 Summary of Validation Performance Parameters for the Quantitation of Plazomicin From Human Plasma (Adapted from Table 4 in Summary of Biopharmaceutical Studies)

QC Level	QC Concentration (µg/mL)	Intrabatch Accuracy (% Bias)	Intrabatch Precision (% CV)	Interbatch Accuracy (% Bias)	Interbatch Precision (% CV)
AV08-ACHN490-02 (adult plasma)					
LLOQ	0.010	−13.0	6.4	−3.3	13.0
LQC	0.030	2.0	8.6	−2.7	7.9
MQC	0.300	−4.7	5.2	−3.0	7.8
HQC	4.00	−11.5	7.4	−6.7	5.8
ULOQ	5.00	−12.6	2.1	−6.0	5.6
AV10-ACHN490-01 (adult plasma)					
LLOQ	0.010	−0.1	5.6	3.0	9.5
LQC	0.030	−6.0	2.0	0.7	8.9
MQC	0.300	−7.7	2.2	−1.0	5.7
HQC	4.00	−5.0	3.7	−2.0	4.1
ULOQ	5.00	−3.6	1.9	−0.6	3.9

Table 4.1-3 Summary of Validation Performance Parameters for the Quantitation of Plazomicin From Urine and Epithelial Lining Fluid and Iothalamate From Plasma (Adapted from Table 5 in Summary of Biopharmaceutical Studies)

QC Level	QC Concentration (µg/mL)	Intrabatch Accuracy (% Bias)	Intrabatch Precision (% CV)	Interbatch Accuracy (% Bias)	Interbatch Precision (% CV)
Urine					
LLOQ	0.500	−14.6	5.6	−9.6	9.2
LQC	1.50	−12.7	7.6	−12.7	9.2
MQC	8.00	−14.1	7.4	−9.4	6.2
HQC	40.0	−12.0	3.4	−8.0	8.0
ULOQ	50.0	−5.6	2.1	−4.6	5.6
Epithelial lining fluid					
LLOQ	0.010	5.0	7.5	−1.9	9.1
LQC	0.030	−0.7	3.5	−3.0	3.9
MQC	0.300	1.3	2.0	−0.3	2.3
HQC	4.00	2.0	2.1	−0.5	3.0
ULOQ	5.00	3.8	3.0	2.6	2.8
Iothalamate from plasma					
LLOQ	1.00	−12.6	5.9	−4.7	8.6
LQC	3.00	−7.0	3.2	−1.7	7.8
MQC	30.0	−6.7	2.0	−7.0	5.5
HQC	400	−5.5	4.1	−8.5	7.3
ULOQ	500	−0.2	2.5	−5.6	6.4

Abbreviations: CV=coefficient of variation; HQC=high-level quality control; LLOQ=lower limit of quantitation; LQC=low-level quality control; MQC=mid-level quality control; QC=quality control; ULOQ=upper limit of quantitation.

The sample stability data were summarized in Table 4.1-4.

Table 4.1-4 Summary of Proven Plazomicin and Iothalamate Sample Stability

Species and Matrix	Hours of Sample Collection Stability	Hours of Benchtop Stability at Ambient Conditions	Cycles of Freeze-Thaw Stability	Hours of Autosampler Stability at Ambient Conditions	Days of Proven Long-Term Frozen Stability
Plazomicin					
Human plasma (AV08-ACHN490-02)	0.5 at ambient temperature [a]	6	3	61	99 at –70°C
Human plasma (AV10-ACHN490-01)	3 at 4°C [a] 96 at ambient temperature [a]	20	12	37	≥ 480 at –70°C 213 at –20°C
Human epithelial lining fluid	— [b]	6	4	54	27 at –70°C
Human urine	26 at 4°C	6	3	89	64 at –70°C
Human serum	— [b]	264	4	— [b]	≥ 463 at –70°C
Iothalamate					
Human plasma	0.5 at ambient temperature [a]	6	3	61	99 at –70°C

[a] Plazomicin or iothalamate stability in dipotassium ethylenediaminetetraacetic acid whole blood before being processed to plasma. Whole blood sample collection stability states that the mean concentration of the samples at each concentration must not change by more than 20% from the control concentration (t=0).

[b] Per the assay validation protocol, experiment was not performed.

4.2 Population PK Analyses

Applicant's analysis

A population PK model was developed by Applicant based on pooling data from four Phase 1 studies, Studies ACHN-490-001, ACHN-490-003, ACHN-490-004, and ACHN-490-006, one Phase 2 study, Study ACHN-490-002, and two Phase 3 studies, Studies ACHN-490-007 and ACHN-490-009.

Study ACHN-490-001 was a Phase 1 study conducted in healthy volunteers to assess the safety, tolerability, and PK following ascending single and multiple doses of plazomicin. A total of 30 subjects were enrolled in the study receiving plazomicin while 28 subjects were included in the population PK analysis. Single doses of 1, 4, 7, 11, and 15 mg/kg infused over 10 minutes and daily doses of 4, 7, 11, and 15 mg/kg infused over 10 minutes were tested. PK samples were collected during the single-dose phase and on the first and last dosing days during the multiple-dose phase at the following times: pre-dose and at 5, 10, 15, 20, 30 and 45 minutes and 1, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours after the start of the infusion. Additional PK samples were obtained pre-dose for up to three days prior to the last dose for subjects who received once-daily dosing more than 5 days.

ACHN-490-003 was a Phase 1 study conducted in healthy volunteers to assess the safety, tolerability, plasma PK, and lung penetration following single and multiple IV doses of plazomicin. A total of 30 subjects were enrolled in the study receiving plazomicin and all of them were included in the population PK analysis. Subjects in Cohort 1 received a 15 mg/kg IV dose of plazomicin or placebo over 10 minutes once daily for five consecutive days. Blood samples for PK analysis of plazomicin were collected prior to dosing on Days 1 through 5 and at 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after the start of the infusion on Day 5. Subjects in Cohort 2 received a single IV dose of either 10.7 mg/kg or 15 mg/kg of plazomicin over 10 minutes. Blood samples for PK analysis of plazomicin were collected at pre-dose and at 10, 15, 30, 45 minutes and 1, 1.5, 2, 3, 6, and 10 hours after the start of the infusion.

Study ACHN-490-004 was a Phase 1 study conducted in healthy subjects with normal renal function and subjects with varying degrees of renal dysfunction to assess the PK, safety, and tolerability of plazomicin. A total of 24 subjects were enrolled in the study receiving plazomicin and all of them were included in the population PK analysis. Subjects were divided into four groups based on the mean of two CLcr values calculated using the Cockcroft-Gault equation and each received a single-dose of plazomicin (7.5 mg/kg) administered IV over 30 minutes.

- Group I: Normal renal function: CLcr ≥ 90 mL/min
- Group II: Mild renal dysfunction: CLcr = 60 to 89 mL/min
- Group III: Moderate renal dysfunction: CLcr = 30 to 59 mL/min

- Group IV: Severe renal dysfunction: CLcr = 15 to 29 mL/min, and if possible, two subjects were to have CLcr < 20 mL/min

Blood samples for PK analysis were collected prior to dosing and at 36 and 45 minutes and at 1, 1.5, 3, 6, 10, 16, 24, 36, 48, 72, and 96 hours after the start of the infusion.

ACHN-490-006 was a Phase 1 study conducted in healthy volunteers to evaluate the effect of IV plazomicin injection on the QT/QTc interval. A total of 61 subjects were enrolled in the study receiving plazomicin and all of them were included in the population PK analysis. Subjects received a single IV infusion dose of plazomicin 20 mg/kg infused over 30 minutes. PK samples were collected from each subject at the following times: pre-dose and at 36 and 45 minutes and 1, 2, 3, 6, 12, and 24 hours after the start of the infusion.

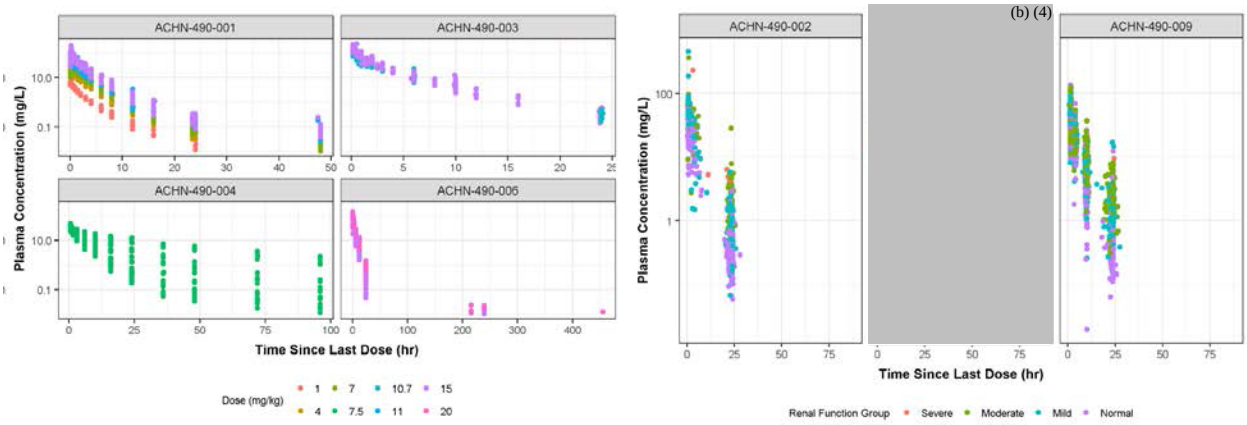
ACHN-490-002 was a Phase 2 Study to assess the PK as well as the safety and efficacy of plazomicin in hospitalized patients with Complicated urinary tract infection (cUTI) or Acute pyelonephritis (AP). A total of 98 subjects were enrolled in the study receiving plazomicin while 92 subjects were included in the population PK analysis. Subjects received plazomicin (10 or 15 mg/kg) over either 10 or 30 minutes for up to five consecutive days. Blood samples were collected at the following time intervals after the start of infusion: 35 to 55 minutes, 1.5 to 3 hours, and 4 to 8 hours on Day 1. Samples were also collected immediately prior to the start of infusion on Days 2 to 5.

Study ACHN-490-007 was a Phase 3 study conducted to evaluate the efficacy and safety of plazomicin compared with colistin in patients with bloodstream infection (BSI), hospital-acquired bacterial pneumonia (HABP), ventilator-acquired bacterial pneumonia (VABP), cUTI, or AP due to carbapenem resistant Enterobacteriaceae (CRE). (b) (4)

Study ACHN-490-009 was a Phase 3 study conducted to evaluate the efficacy and safety of plazomicin compared with meropenem for the treatment of cUTI, including AP, in adult patients. A total of 306 subjects were enrolled in the study receiving plazomicin while 281 subjects were included in the population PK analysis. Patients received up to 15 mg/kg IV over 30 minutes once daily based on renal function as shown in Table 4.2-1. Plazomicin was dosed using either TBW or ABW (TBW if TBW/IBW <125% or ABW if TBW/IBW ≥ 125%). A minimum of four days and maximum of 7 days of IV study drug were required, and patients could switch to open-label oral levofloxacin for an additional three to six days to complete a total of seven to 10 days of therapy. Plasma PK samples were collected on Day 3 (±1 day) of study drug administration for all patients. The sampling time points were listed as follows: just prior to infusion, 90 minutes (±15 minutes), 4 hours (±1 hour), and 10 hours (±1 hour) after initiation of study drug infusion.

A total of 564 subjects and 4990 plasma concentration records from the seven studies were used to establish the population PK model. Semi-log scatterplots of plazomicin plasma concentrations versus time, stratified by study and dose for the Phase 1 studies and renal function category for the Phase 2/3 studies are provided in Figure 4.2-1.

Figure 4.2-1 Semi-log scatterplots of plazomicin plasma concentrations versus time, stratified by dose and presented by study (Phase 1, 2 and 3)



Source: Applicant's population PK report (icpd-00462_1), Page 60-61, Figure 4-5

A three-compartment model with zero-order input and first-order elimination best described the pooled plasma plazomicin concentration-time data from the Phase 1, 2, and 3 studies. CLcr was normalized to a body surface area (BSA) of 1.73 m^2 and evaluated as a time-varying covariate for plazomicin CL in the base structural model and it was determined that a sigmoidal Hill-type function best described the relationship. To prevent calculation of abnormally high CLcr values, serum creatinine (Scr) was capped to a lower bound of 0.50 mg/dL during the calculation of CLcr. Clearance due to CRRT was set to the sum of the actual patient-specific ultrafiltrate flow rate (DFR) and dialysate flow rate (UFR) and multiplied by an estimate of the sieving coefficient (SC, which represents the membrane permeability of the drug) on the study days when CRRT was utilized. DFR and UFR were fixed based on the source data and the sieving coefficient was estimated during the base model establishment.

Body weight and infection type were identified as statistically significant covariates on CL. For plazomicin Vc, the covariates of body surface area and infection type were statistically significant predictors. For plazomicin distributional clearance to peripheral compartment 1 (CLd1), only the covariate of infection type was a statistically significant predictor. For plazomicin volume of distribution for peripheral compartment 1 (Vp1), the covariates BSA, age, and infection type were statistically significant predictors. For plazomicin distributional clearance to peripheral compartment 2 (CLd2), the covariates height and infection type were statistically significant predictors. For plazomicin volume of distribution for peripheral compartment 2 (Vp2), the covariates body weight and concomitant vasopressors were statistically significant predictors. The population PK parameter estimates and their associated precision for the fit of the three-compartment model are provided in Table 4.2-3.

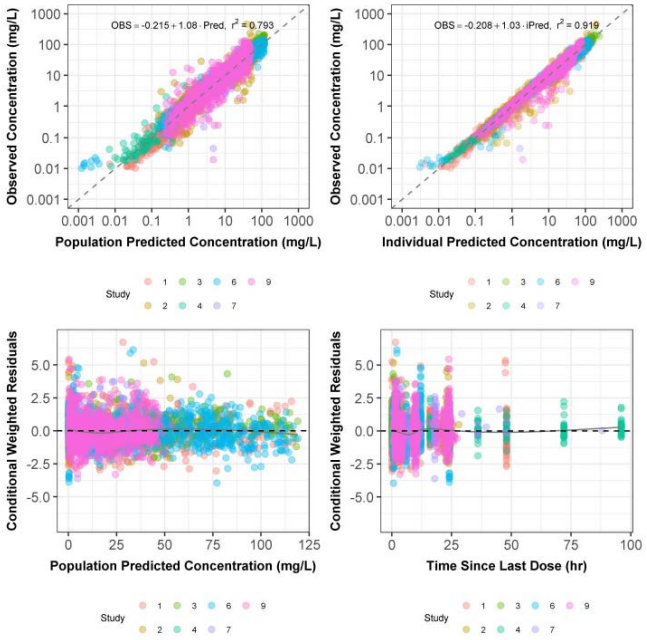
Table 4.2-3 Final population PK model parameter estimates and associated standard errors

Parameter	Final estimate	%SEE
CL (L/hr)		
Non-renal CL (L/hr)	0.491	24.9
CL_R maximum (L/hr)	4.80	7.39
Baseline $CLcr_{50}$ (mL/min/1.73 m^2)	45.3	5.27
Hill coefficient	2.49	13.9
CL-weight power	0.529	14.0
Proportional increase for AP patients	0.130	22.9
[redacted]		(b) (4)
Vc (L)		
Coefficient	9.10	4.07
Vc-BSA power	1.23	17.5
Proportional increase for AP and cUTI patients	1.05	10.6
[redacted]		(b) (4)
CLd1 (L/hr)		
Coefficient	8.05	7.97
Proportional increase for AP and cUTI patients	-0.831	4.85
Vp1 (L)		
Coefficient	8.71	3.97
Vp1-BSA power	1.17	22.2
Vp1-age slope	0.00954	11.1
Proportional increase for AP and cUTI patients	-0.437	14.6
CLd2 (L/hr)		
Coefficient	0.199	3.64
CLd2-HTCM power	3.38	17.5
Proportional increase for AP and cUTI patients	-0.299	46.0
[redacted]		(b) (4)
Vp2 (L)		
Coefficient	6.98	9.21
Vp2-weight power	1.62	20.8
Proportional increase for patients on vasopressors	3.90	36.0
CL_{CRRT} (L/hr)		
Sum of UFR and DFR (L/hr)	1.14 to 1.8	NA
Sieving coefficient	0.734	94.7
ω^2 for CL	0.103 (32.0 %CV)	9.52
ω^2 for Vc	0.211 (46.0 %CV)	14.8
ω^2 for CLd1	0.0661 (25.7 %CV)	47.8
ω^2 for Vp1	0.0678 (26.0 %CV)	20.9
ω^2 for CLd2	0.0350 (18.7 %CV)	24.2
ω^2 for Vp2	0.170 (41.3 %CV)	34.9
IOV on CL	0.00129 (3.59 %CV)	61.1
Covariance between CL and Vc	0.0931 (r^2=0.398)	15.6
Covariance between CL and Vp1	0.0734 (r^2=0.772)	15.1
Covariance between Vc and Vp1	0.0649 (r^2=0.295)	19.6
Residual variability (σ^2)		
Additive component	4.14e-05 (0.00897 mg/L)	51.5
CCV component for Phase 1 studies	0.0297 (17.2 %CV)	8.99
CCV component for Phase 2 studies	0.168 (40.9 %CV)	14.9
CCV component for Phase 3 studies	0.0846 (29.1 %CV)	8.78

Source: Applicant's population PK report (icpd-00462_1), Page 76, Table 13

Goodness-of-fit plots for the final model are shown in Figure 4.2-2. There was a good agreement between the observed plasma plazomicin concentrations and the population predicted concentrations from the final population PK model

Figure 4.2-2 Goodness-of-fit plots for the final population PK model for plazomicin



Source: Applicant's population PK report (icpd-00462_1), Page 78, Figure 9

The visual predictive check (VPC) was provided in Figure 4.2-3. There appears to be reasonable agreement between the observed concentrations and the 5th, 50th, and 95th percentiles of the individual simulated concentrations across time intervals.

Figure 4.2-3 Prediction-corrected visual predictive check for the final population PK model for plazomicin over the first 48 hours after a dose, stratified by infection type

(b) (4)

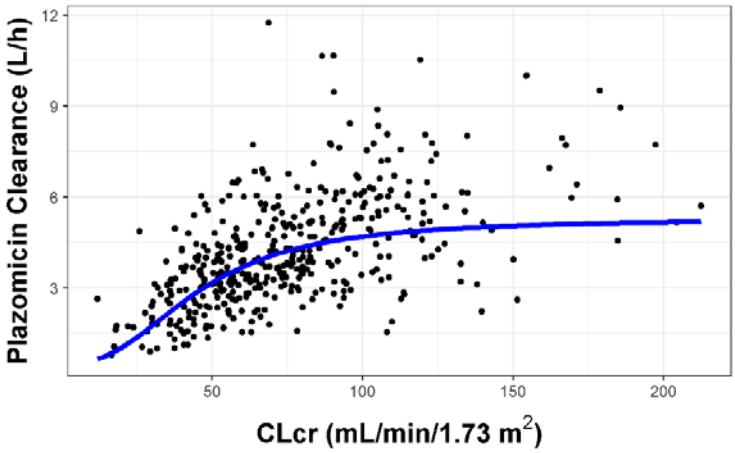
Source: Applicant's population PK report (icpd-00462_1), Page 86, Figure 15

The plazomicin exposure estimates relative to patient covariates of interest were examined based on the final population PK model.

1. Renal impairment

The relationship between clearance and renal function (BSA normalized CLcr in mL/min/1.73 m^2) was plotted in Figure 4.2-4. The nature of this relationship is such that clearance increases in an approximately linear fashion up until a CLcr of approximately 50 mL/min/1.73 m^2, at which point the relationship starts to be less pronounced until the relationship is essentially flat by a CLcr of approximately 150 mL/min/1.73 m^2.

Figure 4.2-4 Relationship between individual post-hoc estimates of plazomicin clearance and CLcr in healthy subjects and infected patients



Source: Applicant's population PK report (icpd-00462_1), Page 102, Figure 19

2. Body size

Three different measures of body size were identified as significant covariates in relation to various parameters in the population PK model: body weight was significant for CL and Vp2, BSA was significant for Vc and Vp1, and height was significant for CLd2. Given that plazomicin is dosed by body weight and the relationship between CL and body weight is less than linear, it is expected that there were slight trends for exposure to increase with increasing body weight. The use of the adjusted body weight to calculated dose in patients with TBW/IBW ≥ 125% results in relatively consistent plazomicin exposure relative to those patients whose TBW/IBW is less than 125% where TBW was used.

3. Age

Age was identified as a statistically significant predictor of the IIV in plazomicin Vp1. Given the correlation between age and renal function, the exposure trends with age are most likely due to age-related changes in renal function as opposed to an independent effect of age.

4. Infection type

Infection type was identified as a statistically significant predictor of the IIV in all the plazomicin PK parameters, except for Vp2. CL was increased by 13.0% in patients with AP (b) (4) Vc was increased by (b) (4) 105% in cUTI patients relative to healthy volunteers.

5. Concomitant Vasopressor Use

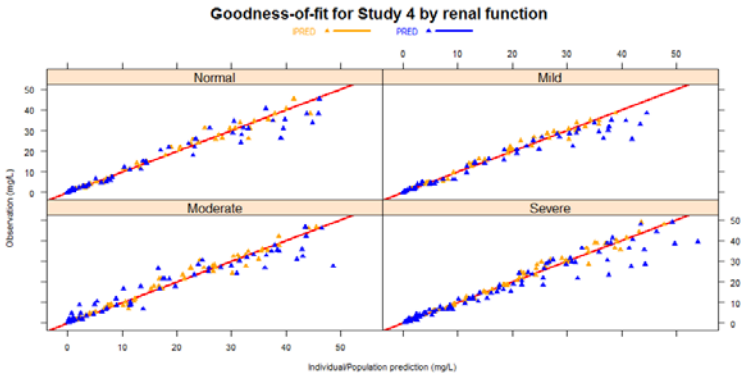
Concomitant vasopressor use was identified as a statistically significant predictor of the IIV in Vp2. Vasopressors were evaluated as a yes/no categorical covariate based on administration at any time a patient was on study, does not guarantee that the vasopressor and plazomicin were concomitantly administered. (b) (4)

Reviewer's comments

The Reviewer verified the population PK model developed by Applicant. The population PK model can reasonably describe the PK data pooled from 7 clinical trials in both healthy volunteers and patients. No additional covariate was identified. The reviewer conducted an independent population PK analysis for plazomicin using capped creatinine clearance (serum creatinine concentrations was capped to 0.5 mg/dL or above) instead of capped creatinine clearance normalized by BSA. The parameter estimates were consistent with Applicant's result.

As renal function was a significant covariate for PK of plazomicin and dose reduction is proposed for patients with moderate and severe renal impairment, the goodness-of-fit for PK profile in study ACHN-490-004 (Dedicated renal impairment study) was independently evaluated (Figure 4.2-5) to ensure that the population PK model accurately describes exposures in patients with reduced renal function.

Figure 4.2-5 Diagnostic Plots for Study ACHN-490-004 by Renal Function



Source: Reviewer's independent analysis.

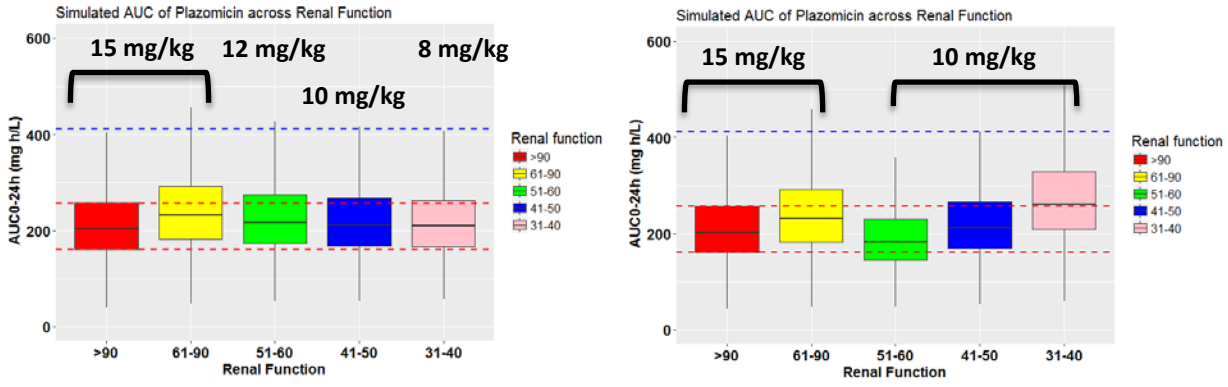
The plots show that the population PK model can generally describe the data and can be used to predict the exposure in patients with different levels of renal function.

Therefore, the Reviewer's population PK model using capped CLcr other than capped CLcr normalized by BSA was utilized to simulate exposure in cUTI and BSA patients to facilitate dose/TDM evaluation and exposure-response analysis for efficacy and safety.

4.2.1 Evaluation of initial dose

The proposed initial dose by Applicant is simplified from what was studied in the Phase 3 study (Study ACHN-490-009). The proposed initial doses were 15 mg/kg for patients with CLcr >60 mL/min and 10 mg/kg for patients with CLcr >30 to 60 mL/min, whereas the studied doses were 15 mg/kg for patients with CLcr >60 mL/min, 12 mg/kg for patients with CLcr >50 to 60 mL/min, 10 mg/kg for patients with CLcr >40 to 50 mL/min, and 8 mg/kg for patients with CLcr >30 to 40 mL/min. The Reviewer simulated exposure ($AUC_{0\text{-}24h}$) for plazomicin across different renal function categories based on the patient demographics in Study ACHN-490-009 under two dosing regimens: proposed by Applicant in the labeling and studied in Study ACHN-490-009 (Figure 4.2-6). The results illustrate that the proposed initial dose by Applicant in the labeling would result in slightly lower exposure in the group of CLcr between 50 and 60 mL/min and higher exposure in the group of CLcr between 30 and 40 mL/min. However, the predicted exposure in patients with CLcr of 31-40 mL/min based on proposed initial dose is still lower than the upper bound of 95% quantile of $AUC_{0\text{-}24h}$ in cUTI patients from Study ACHN-490-009. The simulated mean, 5% and 95% quantiles of AUC values are listed in Table 4.2-4. The proposed initial dose in the label appears to be reasonable.

Figure 4.2-6 Exposure comparison across renal function in cUTI patients from Study ACHN-490-009 with studied doses (left) and proposed doses (right)



The red dash lines represent the 25% and 75% quantile of $AUC_{0\text{-}24h}$ in cUTI patients with CLcr > 90 mL/min; the blue dash lines represent the 95% quantile of $AUC_{0\text{-}24h}$ (411 mg·h/L) in cUTI patients from Study ACHN-490-009.

Source: Reviewer's independent analysis.

Table 4.2-4 Summary of exposure (AUC_{0-24h}) across renal function in cUTI patients from Study ACHN-490-009 with studied doses and proposed doses

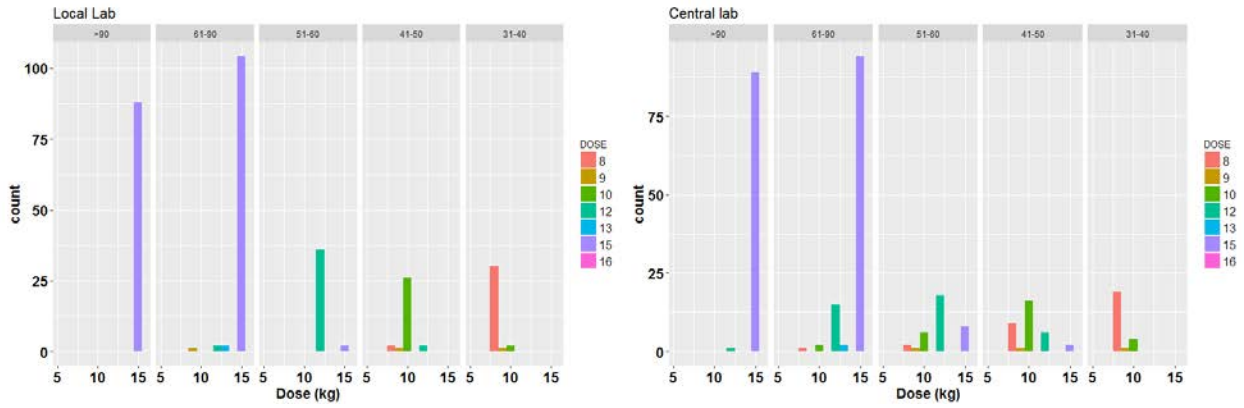
Renal function	*Studied doses (mean, 5-95% quantile)*	*Proposed doses (mean, 5-95% quantile)*
CLcr> 90 mL/min	*216 (113-360)*	*215 (113-359)*
CLcr >60, ≤90 mL/min	*245 (129-407)*	*245 (130-407)*
CLcr >50, ≤60 mL/min	*231 (124-380)*	*193 (103-319)*
CLcr >40, ≤50 mL/min	*224 (119-369)*	*223 (121-365)*
CLcr >30, ≤40 mL/min	*221 (121-359)*	*277 (150-455)*

Source: Reviewer's independent analysis.

4.2.2 Dose discrepancy by CLcr from central lab and local lab

The dose in Study ACHN-490-009 was given based on CLcr from local lab, while the CLcr listed in the population PK dataset was from central lab. Dose discrepancy was identified by using CLcr from central lab and local lab. However, the difference between central lab and local lab was relatively small and not expected to impact the result of dose comparison between studied dose and proposed dose (Figure 4.2-7). It is thus acceptable to use CLcr from central lab for population PK analysis and exposure-response analysis for efficacy and safety in this review for (b) (4) *cUTI* (b) (4)

Figure 4.2-7 Dose distributions across renal function in cUTI patients from Study ACHN-490-009 using CLcr from central lab (left) or local lab (right)



Source: Reviewer's independent analysis.

4.3 Exposure-Response Analyses

4.3.1 Exposure-Response Analysis for Efficacy in cUTI patients

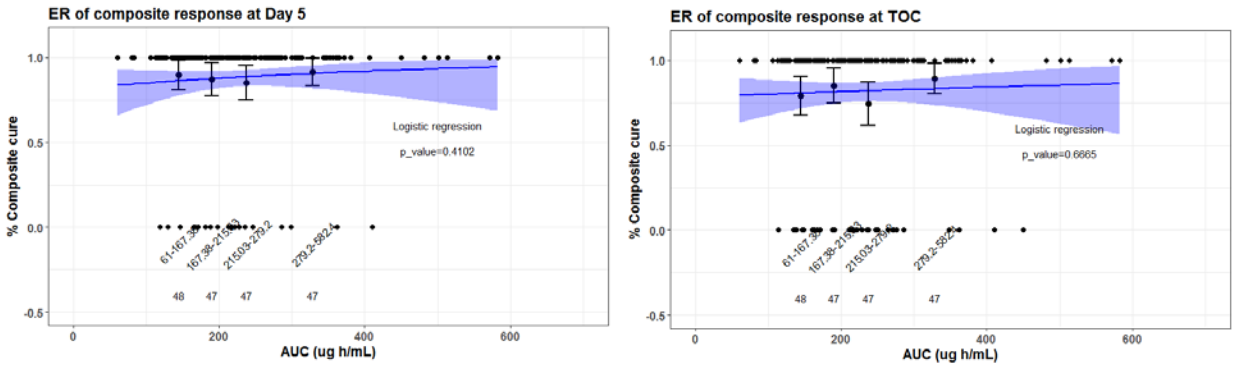
The Applicant did not conduct exposure-response (E-R) analysis for efficacy.

A Phase 2 dose ranging study (Study ACHN-490-002) was conducted in patients with cUTI. In Study ACHN-490-002, patients were randomized to receive plazomicin 10 or 15 mg/kg Q24h dose as 30-minute IV infusion for 5 days. The co-primary efficacy endpoint was the microbiological eradication (MBE) at the test-of-cure (TOC) visit in the modified intent-to-treat (MITT) population and in the microbiologically evaluable (ME) population. For the mITT population, MBE was achieved for 6 of 12 patients (50%) in the plazomicin 10 mg/kg group and 31/51 (60.8%) in the plazomicin 15 mg/kg group. In the ME population, MBE at the TOC visit was 6 of 7 patients (85.7%) in the plazomicin 10 mg/kg group and 31 of 35 patients (88.6%) in the plazomicin 15 mg/kg group. The dose of 15 mg/kg Q24h was further evaluated in two Phase 3 studies for patients with cUTI or BSI, respectively.

The Reviewer conducted an independent E-R analysis in cUTI patients from Study ACHN-490-009 using four endpoints: 1) composite microbiology and clinical response at Day 5; 2) composite microbiology and clinical response at test of cure (TOC); 3) microbiology response at Day 5; and 4) microbiology at TOC. The exposure of $AUC_{0\text{-}24h}$ after first dose was derived from post hoc analysis from population PK model since is not expected to change substantially due to daily dose adjustment based on CLcr. A total of 189 patients administered plazomicin were included in the E-R dataset.

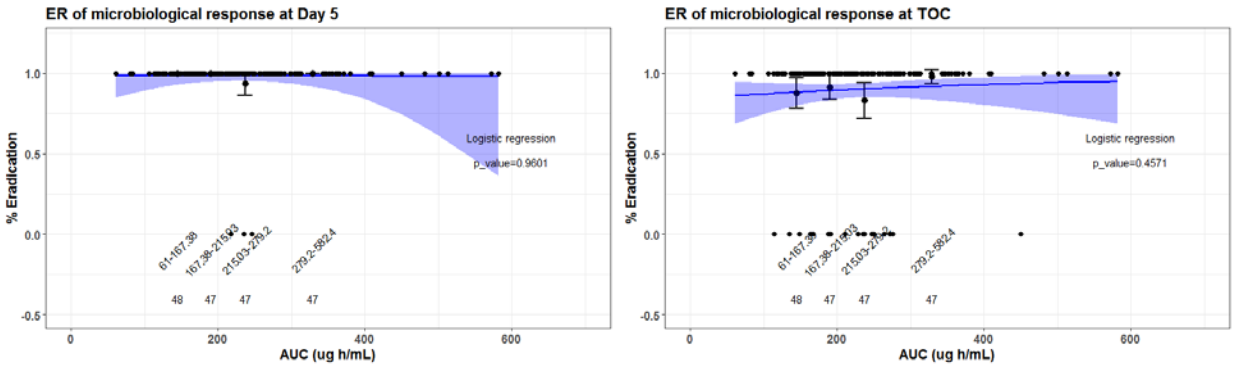
No E-R relationship was identified between exposure and the four efficacy endpoints as shown in Figures 4.3.1-1 and 4.3.1-2. E-R analysis was also conducted using $AUC_{0\text{-}24h}$/MIC as PK surrogate. A total of 184 patients with susceptibility information was included in the analysis. Similarly, no E-R relationship was identified between $AUC_{0\text{-}24h}$/MIC and four efficacy endpoints as shown in Figures 4.3.1-3 and 4.3.1-4.

Figure 4.3.1-1 E-R analysis for composite response at Day 5 (left) and TOC (right)



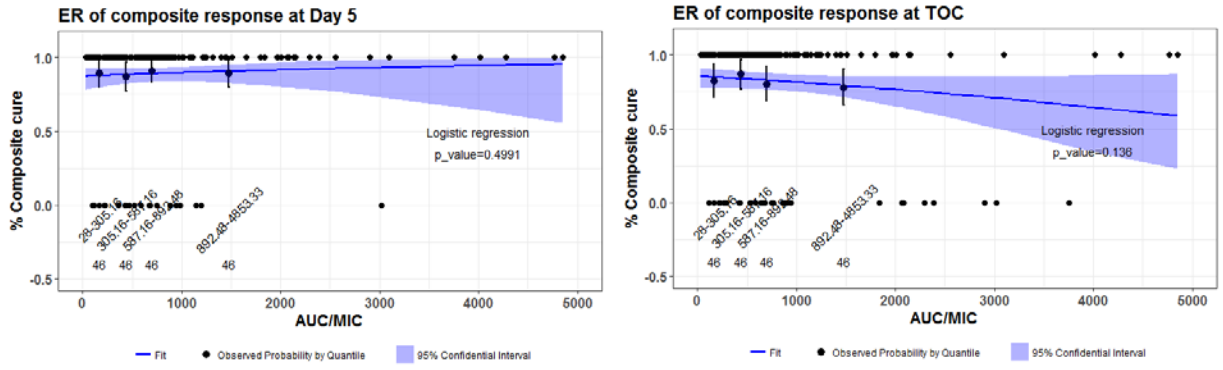
Source: Reviewer's independent analysis.

Figure 4.3.1-2 E-R analysis for microbiological response at Day 5 (left) and TOC (right)



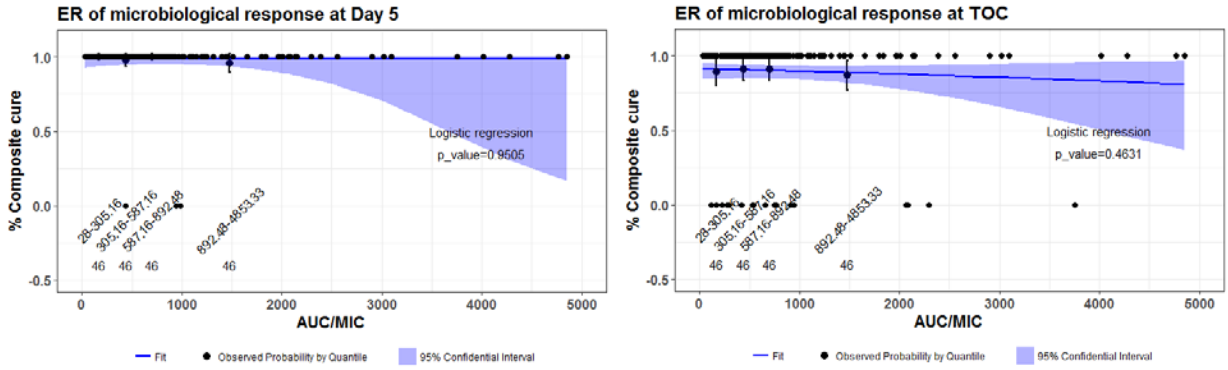
Source: Reviewer's independent analysis.

Figure 4.3.1-3 E-R analysis using AUC/MIC for composite response at Day 5 (left) and TOC (right)



Source: Reviewer's independent analysis.

Figure 4.3.1-4 E-R analysis using AUC/MIC for microbiological response at Day 5 (left) and TOC (right)



Source: Reviewer's independent analysis.

4.3.1.1 E-R analysis for efficacy in cUTI patients with bacteremia

The exposure-response relationship for efficacy was also evaluated in the cUTI patients with bacteremia. A total of 25 cUTI patients received plazomicin had bacteremia at baseline. Due to the small sample size, the statistical analysis for efficacy was not conducted. The relationship between exposure (AUC_{0-24h}) and efficacy was summarized the Table 4.3.1-1 and the relationship between AUC_{0-24h}/MIC and efficacy was summarized in the Table 4.3.1-2. No relationship between exposure and efficacy was identified. In addition, there was no significant signal of comprised efficacy in terms of bacterial eradication in this subpopulation.

Table 4.3.1-1 Relationship between AUC_{0-24h} and composite and microbiological response at Day 5 or TOC

AUC_{0-24h}	1st Quartile N=7	2nd Quartile N=6	3rd Quartile N=6	4th Quartile N=6
	61-147	147-172	172-220	220-410
% composite cure at Day 5	71%	83%	67%	83%
% composite cure at TOC	71%	83%	50%	83%
% microbiological cure at Day 5	100%	100%	100%	100%
% microbiological cure at TOC	86%	100%	83%	100%

Source: Reviewer's independent analysis.

Table 4.3.1-2 Relationship between AUC_{0-24h}/MIC and composite and microbiological response at Day 5 or TOC

AUC_{0-24h}/MIC	1st Quartile N=6	2nd Quartile N=6	3rd Quartile N=6	4th Quartile N=6
	121-365	365-550	550-661	661-2153
% composite cure at Day 5	100%	89%	100%	83%
% composite cure at TOC	83%	67%	67%	83%
% microbiological cure at Day 5	100%	100%	100%	100%
% microbiological cure at TOC	100%	83%	100%	83%

Source: Reviewer's independent analysis.

4.3.1.2 E-R analysis by renal function

The response rate including composite response, clinical response, and microbiological response in patients with different renal function was evaluated (Tables 4.3.1-3 to 4.3.1-5). The composite response rate and microbiological response rate at TOC were decreased in patients with renal impairment, while the microbiological response rate at Day 5 was not impacted by renal function. A similar trend was found in patients receiving meropenem (comparator) (Tables 4.3.1-6 to 4.3.1-8).

Table 4.3.1-3 Composite response across renal function in patients receiving plazomicin

CLcr (mL/min)	No. of Subjects	% composite cure at Day 5	% composite cure at TOC
> 90	58	94.8	91.4
> 60, ≤90	70	87.1	84.3
> 30, ≤60	63	82.5	69.8
≤ 30	-	-	-

Source: Reviewer's independent analysis.

Table 4.3.1-4 Clinical response across renal function in patients receiving plazomicin

CLcr (mL/min)	No. of Subjects	% clinical cure at Day 5	% clinical cure at TOC
> 90	58	96.6	94.8
> 60, ≤90	70	88.6	90.0
> 30, ≤60	63	84.1	82.5
≤ 30	-	-	-

Source: Reviewer's independent analysis.

Table 4.3.1-5 Microbiological response across renal function in patients receiving plazomicin

CLcr (mL/min)	No. of Subjects	% eradication at Day 5	% eradication at TOC
> 90	58	98.3	94.8
> 60, ≤90	70	98.6	91.4
> 30, ≤60	63	98.4	82.5
≤ 30	-	-	-

Source: Reviewer's independent analysis.

Table 4.3.1-6 Composite response across renal function in patients receiving meropenem

CLcr (mL/min)	No. of Subjects	% composite cure at Day 5	% composite cure at TOC
> 90	48	93.8	77.1
> 60, ≤90	84	92.9	66.7
> 30, ≤60	77	90.9	62.3
≤ 30	3	66.7	66.7

Source: Reviewer's independent analysis.

Table 4.3.1-7 Clinical response across renal function in patients receiving meropenem

CLcr (mL/min)	No. of Subjects	% clinical cure at Day 5	% clinical cure at TOC
> 90	48	93.8	85.7
> 60, ≤90	84	94.0	91.7
> 30, ≤60	77	92.2	85.7
≤ 30	3	66.7	100

Source: Reviewer's independent analysis.

Table 4.3.1-8 Microbiological response across renal function in patients receiving meropenem

CLcr (mL/min)	No. of Subjects	% eradication at Day 5	% eradication at TOC
> 90	48	97.9	79.2
> 60, ≤90	84	98.8	71.4
> 30, ≤60	77	98.7	71.4
≤ 30	3	100	66.7

Source: Reviewer's independent analysis.

4.3.2 Exposure-Response Analysis for Safety in cUTI patients

Applicant's analysis

An exposure-response analysis for safety was conducted by Applicant using creatinine clearance (CLcr) normalized to a BSA of 1.73 m^2 as a biomarker based on data from Studies ACHN-490-002 and ACHN-490-009. Data from levofloxacin-treated patients from Study ACHN-490-002 and meropenem-treated patients from Study ACHN-490-009 were also considered to represent zero plazomicin exposure. All evaluable patients were required to have baseline CLcr and at least one CLcr measurement during treatment up to and including end-of-therapy (EOT) or end-of-IV-therapy (EOIV).

The analysis was carried out using multivariate linear regression for repeated measures. Time, exposure measures prior to specific CLcr values and a random intercept for each patient was incorporated in the model. Several exposures (AUC and C_{min}) over varying duration prior to each serum creatinine (Scr) measurement were predicted by the population PK model including the prior 24-hour AUC, prior 48-hour average AUC (average 24-hour AUC over 48 hours), prior 72-hour average AUC (average 24-hour AUC over 72 hours), prior 96-hour average AUC(average 24-hour AUC over 96 hours), cumulative average AUC (average 24-hour AUC over the time after first dose), prior 24 hours C_{min}, prior 48-hour average C_{min} (average 24-hour C_{min} over 48 hours), prior 72-hour average C_{min} (average 24-hour C_{min} over 72 hours), prior 96-hour average C_{min} (average 24-hour C_{min} over 96 hours), and cumulative average C_{min} (average 24-hour C_{min} over the time after first dose). A square root transformation was considered for the AUC and C_{min} to achieve distributions with reduced skewness. A base-2 logarithmic transformation was applied to CLcr to help achieve approximate normal distribution for residual errors.

Other potential variables were considered including the administration of concomitant nephrotoxic medications and vasopressor (a surrogate for shock). A list of 20 nephrotoxic medication categories (Table 4.3.2-1) was constructed. Individual drugs belonging to the 20 different categories were assessed for concomitant administration with plazomicin, levofloxacin, or meropenem in the 48-hour period prior to each Scr measurement.

Table 4.3.2-1 List of nephrotoxic medication categories included in the E-R for safety analysis

Concomitant medication category number	Concomitant medication category
1	ACE-inhibitors/ARBs
2	Aminoglycosides
3	Amphotericin
4	Analgesics
5	Rifampin/Rifampicin
6	Antiepileptics
7	Antineoplastic agents
8	Antivirals and anti-retrovirals
9	Beta-lactams[a]
10	Colistin
11	Diuretics
12	H2-antagonist
13	Iodinated contrast
14	NSAIDs[b]
15	Proton-pump inhibitors
16	Quinolones[c]
17	Sulfonamide antibiotics
18	Tubulotoxins
19	Uric acid reducer
20	Vancomycin

Source: Applicant's E-R report (icpd-00462-2), Page 94

Additional independent variables that were considered were age, body mass index (BMI), sex, and infection type. These variables potentially modified the degree of the relationship between the plazomicin exposure measure and CLcr.

A stepwise available selection process based on Akaike's information criterion (AIC) was employed to reduce the model to only include the interactions and main effects that demonstrate predictive benefit. The fit of the repeated measures multivariate linear regression model was assessed visually with scatterplots of model-predicted values of CLcr versus observed value of CLcr. The final model was used to characterize the nephrotoxicity of plazomicin.

The demographics of patients in the E-R analysis for safety are listed in Table 4.3.2-2 and 4.3.2-3.

Table 4.3.2-2 Summary statistics for patient demographics – Categorical baseline

Baseline characteristic		% (n/N)
		Analysis Population
Age (years)	<65	59.8 (422/706)
	≥65	40.2 (284/706)
BMI (kg/m^2)	≤30	73.1 (516/706)
	>30	26.9 (190/706)
CLcr (mL/min/1.73 m^2)	>16 to 30	2.1 (15/706)
	>30 to 60	34.4 (243/706)
	>60 to 90	37.1 (262/706)
	>90	26.3 (186/706)
Race		
African American		2.7 (19/706)
American Indian or Alaskan Native		7.4 (52/706)
Asian		5.5 (39/706)
Unknown		0.28 (2/706)
White		83.9 (592/706)
Sex (male)		42.6 (301/706)
Atherosclerotic vascular disease		17.3 (122/706)
Congestive heart failure		7.1 (50/706)
History of diabetes		14.4 (102/706)
Hypertension		40.1 (283/706)
Infection Type		
AP		42.8 (302/706)
cUTI		57.2 (404/706)
Number of patients per baseline concomitant nephrotoxic medication categories	0	49.9 (352/706)
	1	32.2 (227/706)
	>1	18.0 (127/706)

Source: Applicant's E-R report (icpd-00462-2), Page 48, Table 7

Table 4.3.2-3 Summary statistics for patient demographics – Continuous baseline

Baseline characteristic	Analysis Population (n=706)	
	Mean (%CV)	Median (min, max)
Age (years)	55.9 (33.2)	60 (18, 90)
BMI (kg/m^2)	27.0 (19.3)	26.5 (14.5, 51.4)
BSA (m^2)	1.84 (11.7)	1.83 (1.23, 2.48)
CLcr (mL/min/1.73 m^2)	74.3 (40.4)	69.2 (22.2, 212)
Scr (mg/dL)[a]	0.94 (33.5)	0.88 (0.3, 3)
IBW (kg)	60.9 (16.4)	59.6 (32.5, 87.7)
Weight (kg)	75.7 (21.5)	75.0 (39.0, 135)

Source: Applicant's E-R report (icpd-00462-2), Page 50, Table 8

The models containing prior 24-hour AUC or C_{min} were selected to be the final models taking both AIC and precision into consideration. The final parameter estimates are shown in Table 4.3.2-4 and 4.3.2-5.

Table 4.3.2-4 Final model for CLcr with prior 24-hour AUC

Variable	Parameter estimate	SE	Means ratio (95% CI)	P-value
Intercept	7.934	0.0747	-	-
Time (per 1 day increase)	0.0318	0.0017	1.022 (1.020, 1.025)	<0.001
Prior 24-hour AUC (mg•h/L)[a]	0.0018	0.0007	1.001 (1.000, 1.002)	0.005
Age (per 10 year increase)	-0.2003	0.0079	0.870 (0.861, 0.880)	<0.001
Sex (male)	0.1704	0.0286	1.125 (1.083, 1.170)	<0.001
BMI (per 5 kg/m^2 increase)	-0.1402	0.0133	0.907 (0.891, 0.924)	<0.001
Number of concomitant nephrotoxicity medication categories	-0.0355	0.0068	0.976 (0.967, 0.985)	<0.001
Time and prior 24-hour AUC interaction	-0.0034	0.0002	0.998 (0.997, 0.998)	<0.001

Source: Applicant's E-R report (icpd-00462-2), Page 61, Table 16

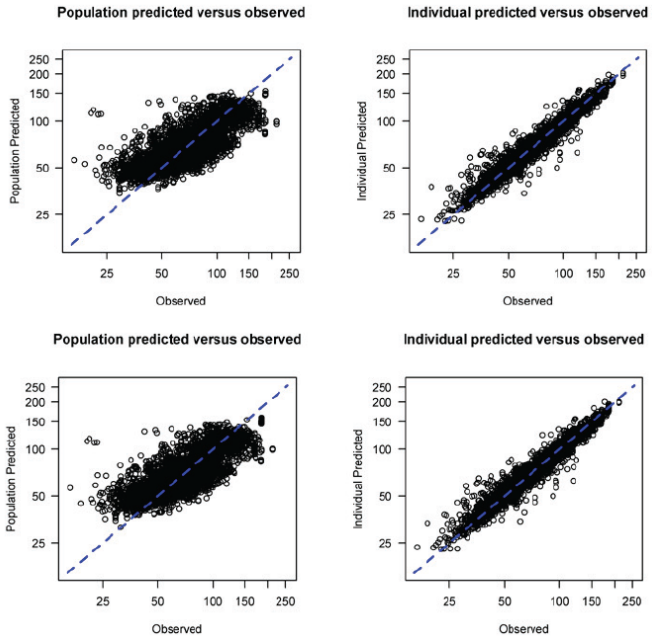
Table 4.3.2-5 Final model for CLcr with prior 24-hour Cmin

Variable	Parameter estimate	SE	Means ratio (95% CI)	P-value
Intercept	7.913	0.0735	-	-
Time (per 1 day increase)	0.0284	0.0016	1.020 (1.018, 1.022)	<0.001
Prior 24-hour C_{min} (mg/L)[a]	0.0114	0.0069	1.008 (0.999, 1.017)	0.10
Age (per 10 year increase)	-0.1964	0.0078	0.873 (0.864, 0.882)	<0.001
Sex (male)	0.1713	0.0281	1.126 (1.084, 1.170)	<0.001
BMI (per 5 kg/m^2 increase)	-0.1409	0.0131	0.907 (0.891, 0.923)	<0.001
Number of concomitant nephrotoxicity medication categories	-0.0297	0.0068	0.980 (0.971, 0.989)	<0.001
Time and prior 24-hour C_{min} interaction	-0.0367	0.0018	0.975 (0.972, 0.977)	<0.001

Source: Applicant's E-R report (icpd-00462-2), Page 63, Table 18

The goodness of fit for two final models are plotted in Figure 4.3.2-1. There was a good agreement between observations and predictions.

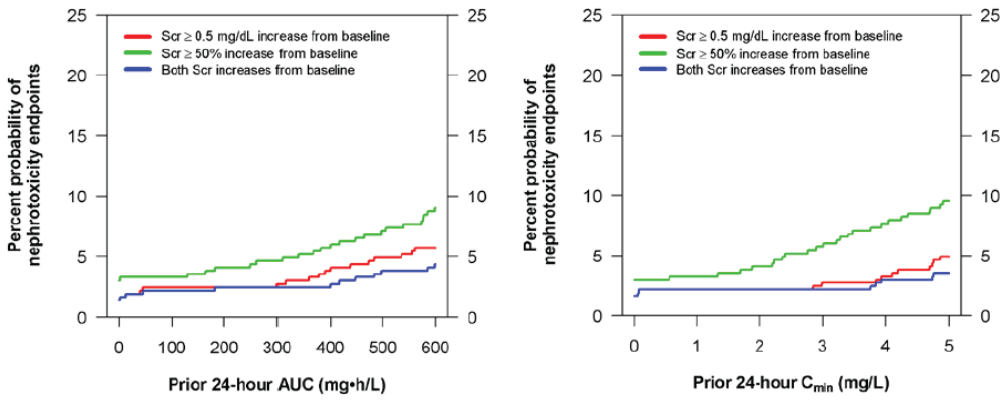
Figure 4.3.2-1 Goodness of fit for final model using prior AUC (upper) and final model using prior Cmin (bottom)



Source: Applicant's E-R report (icpd-00462-2), Pages 170 and 172

The E-R models for CLcr were applied to simulate percent probabilities of nephrotoxicity using three endpoints, an increase in serum creatinine (Scr) from baseline ≥ 0.5 mg/dL, an increase in Scr from baseline ≥ 50%, and both an increase in Scr from baseline ≥ 0.5 mg/dL and an increase in Scr from baseline ≥ 50%. The simulated patient population (N=3000) was generated by replicating the demographics for each patient from Study ACHN-490-002 and ACHN-490-009. The results are presented in Figure 4.3.2-2.

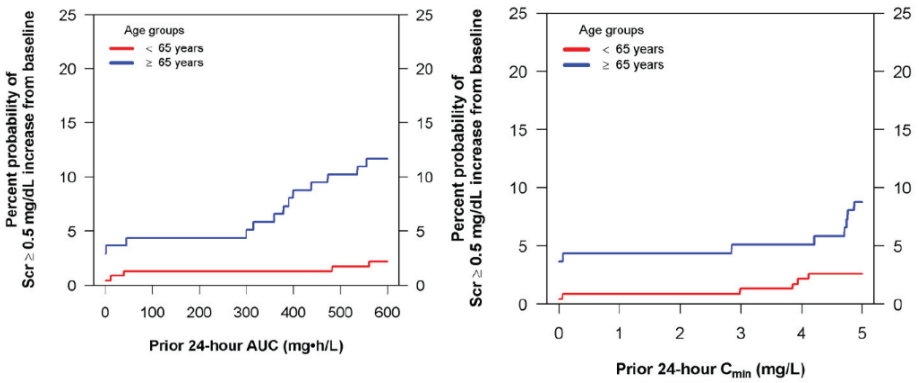
Figure 4.3.2-2 Probability of nephrotoxicity endpoints among simulated patients with cUTI/AP using prior 24-hour AUC (left) and Prior 24-hour C_{min} (right)



Source: Applicant's E-R report (icpd-00462-2), Page 68, Figure 3.

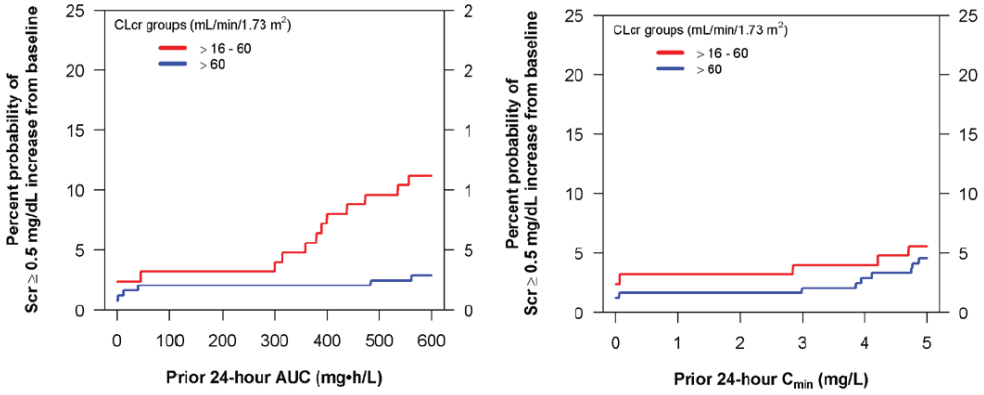
A subgroup analysis for the percent probability of nephrotoxicity using an increase in Scr from baseline ≥ 0.5 mg/dL among simulated patients with cUTI or AP stratified by age, CLcr and treatment duration was conducted and the results are shown in Figure 4.3.2-3 to 4.3.2-5. The percent probabilities of nephrotoxicity were predicted to be increased for patients aged 65 years or older, with a baseline CLcr ranged 16 to 60 mL/min/1.73 m^2, or a treatment duration >5 days.

Figure 4.3.2-3 Probabilities of Scr ≥ 0.5 mg/dL increase from baseline among simulated patients with cUTI/AP by age using prior 24-hour AUC (left) and Prior 24-hour C_{min} (right)



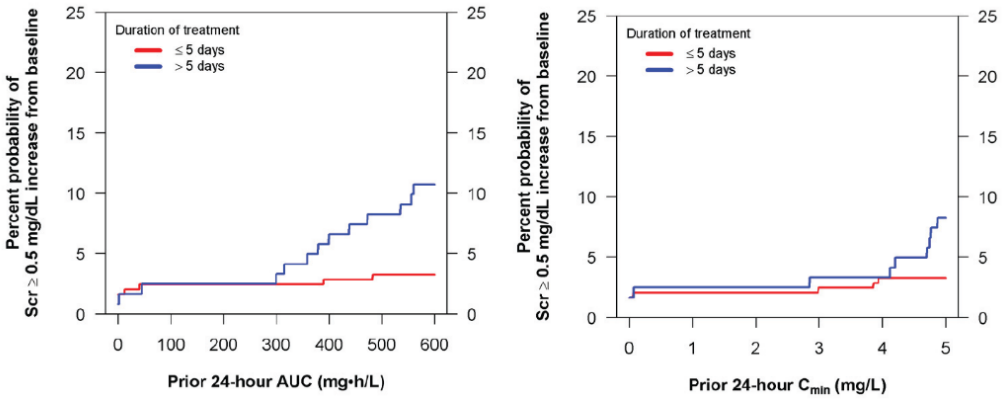
Source: Applicant's E-R report (icpd-00462-2), Pages 73 and 78, Figures 4 and 7.

Figure 4.3.2-4 Probabilities of Scr ≥ 0.5 mg/dL increase from baseline among simulated patients with cUTI/AP by CLcr using prior 24-hour AUC (left) and Prior 24-hour C_{min} (right)



Source: Applicant's E-R report (icpd-00462-2), Pages 74 and 79, Figures 5 and 8.

Figure 4.3.2-5 Probabilities of Scr ≥ 0.5 mg/dL increase from baseline among simulated patients with cUTI/AP by treatment duration using prior 24-hour AUC (left) and Prior 24-hour Cmin (right)



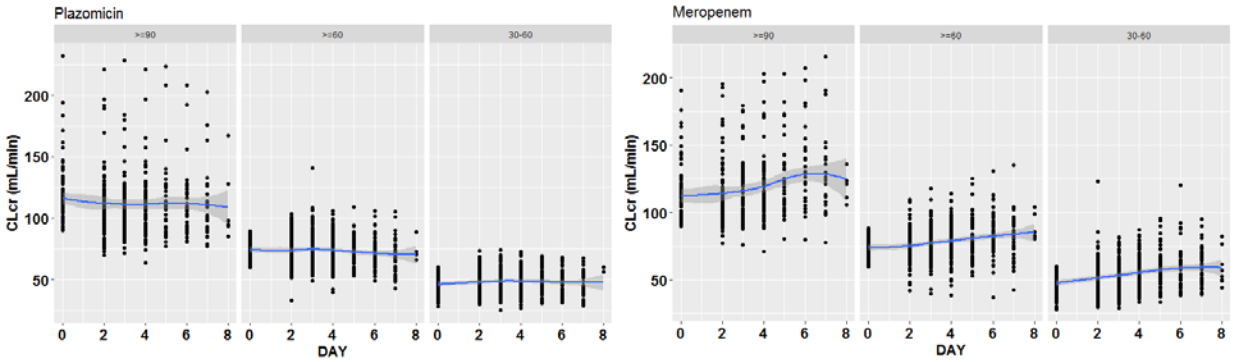
Source: Applicant's E-R report (icpd-00462-2), Pages 75 and 80, Figures 6 and 9.

Based on the results of exposure-nephrotoxicity analysis, the Applicant proposed that TDM is (b) (4)

Reviewer's comments

The Reviewer plotted the CLcr (estimated by Cockcroft-gault equation) versus time for both treatment arm and active control arm based on data from Study ACHN-490-009. The results showed that the CLcr did not change substantially over time for treatment arm, while the CLcr was increased over time for active control arm (Figure 4.3.2-6).

Figure 4.3.2-6 CLcr change over time for plazomicin and meropenem by renal function (Clcr ≥90 mL/min, CLcr ≥60 to 90 mL/min and CLcr ≥30 to 60 mL/min)



A total of 300 patients were in plazomicin arm and a total of 298 patients were in meropenem arm.

Source: Reviewer's independent analysis.

The increased CLcr over time in active control arm observed for meropenem arm indicated that the renal function was improved due to the drug efficacy when no nephrotoxicity was introduced. The flat CLcr over time in treatment arm observed in plazomicin arm suggested that the nephrotoxicity of plazomicin did exist and the current flat CLcr over time reflected the net effect from both drug efficacy and nephrotoxicity. The Applicant's model included data from active control arm to evaluate the impact of both time and exposure on nephrotoxicity appears to be reasonable since the impact of efficacy can be captured by the data from active control arm by using time as a covariate.

(b) (4)

(b) (4)

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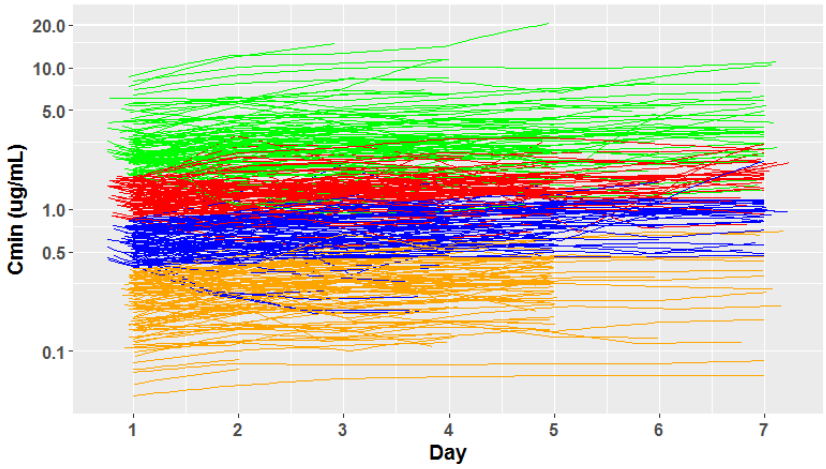
(b) (4)

4.3.3 C_{min}-based TDM evaluation in cUTI patients by Reviewer

4.3.3.1 Selection of PK measure

The plot of C_{min} over time (Figure 4.3.3-1) suggests that C_{min} of each cUTI patient was not changed substantially during the treatment period due to the dose being titrated daily based on CLcr in Study ACHN-490-009 and relatively stable CLcr in Study ACHN-490-002. The C_{min} values of each cUTI patient from Studies ACHN-490-002 and ACHN-490-009 were estimated for each day based on the population PK model (details in Section 4.2) and the last C_{min} was estimated at the 24 hours post the last dose.

Figure 4.3.3-1 C_{min} over time for cUTI patients from Study ACHN-490-002 and ACHN-490-009



Each line represents C_{min} over days for each subject; Orange, blue, red, and green represent 1st, 2nd, 3rd, and 4th quartiles of $C_{1st,min}$, respectively.

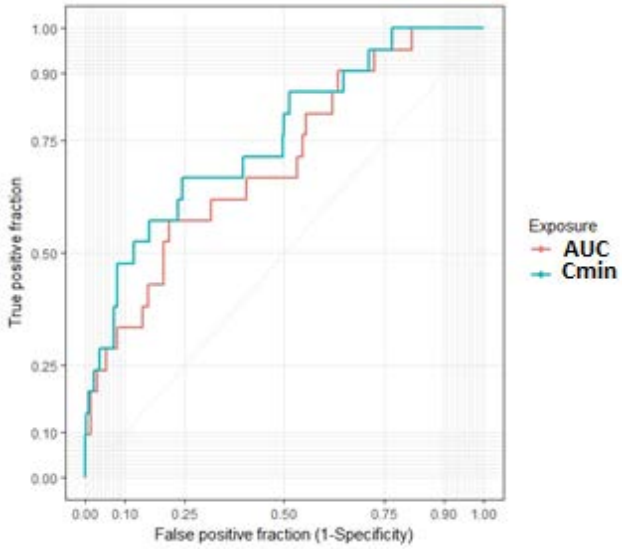
Source: Reviewer's independent analysis.

Therefore, it appears that C_{min} prior to 2nd dose ($C_{1st, min}$) derived from population PK model can be a good PK measure to conduct exposure-response analysis for nephrotoxicity. The patients with an increase in Scr from baseline ≥ 0.5 mg/dL at any time up to late follow-up (LFU) were considered in the analysis. A total of 367 cUTI patients with available PK and serum creatinine information were included in the exposure-response analysis for nephrotoxicity.

Both PK measure, AUC_{0-24h} (estimated based on population PK model) and $C_{1st, min}$, were evaluated in the exposure-nephrotoxicity analysis. According to the receiver operating

characteristics (ROC) analysis (Figure 4.3.3-2), C_{min} outperforms AUC_{0-24h} in predicting nephrotoxicity, based on the comparison of the area under the curve in the ROC plot. Therefore, $C_{1st, min}$ was used in the further exposure-response analysis.

Figure 4.3.3-2 Comparison of AUC_{0-24h} and $C_{1st, min}$ in terms of predicting nephrotoxicity



Source: Reviewer's independent analysis.

4.3.3.2 E-R analysis for nephrotoxicity by the Reviewer

The data show that most nephrotoxicity occurred in cUTI patients with renal impairment (CLcr >30 to 90 mL/min). The nephrotoxicity rate in patients with CLcr >90 mL/min who received plazomicin was even lower than those who received active controls (meropenem or levofloxacin). Only 1 out of 123 patients with CLcr >90 mL/min had nephrotoxicity. The E-R analysis was not conducted in patients with normal renal function.

Table 4.3.3-1 Comparison of nephrotoxicity incidence by renal function

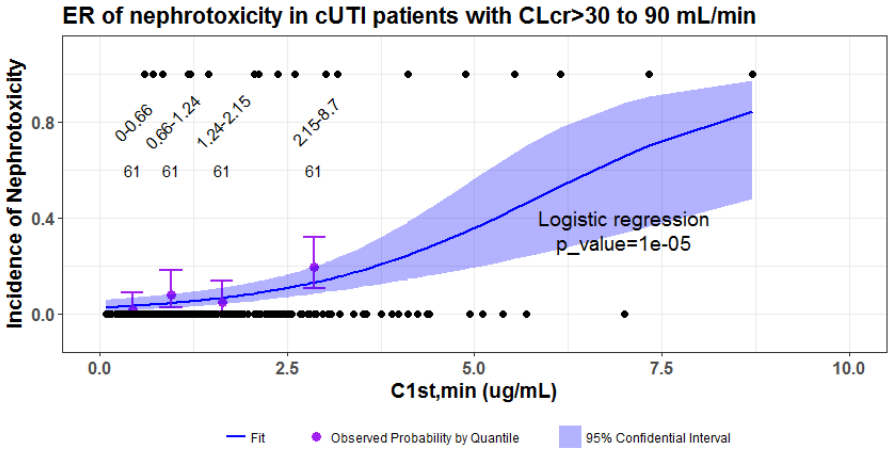
	*% Nephrotoxicity (n/N)**	
	CLcr >30 to 90 mL/min	*CLcr >90 mL/min*
Plazomicin	*8.6% (21/244)*	*0.8% (1/123)*
Active Control[#]	*4.1% (10/243)*	*3.1% (3/97)*

** n is the number of patients with nephrotoxicity; N is the number of patients*
[#]Meropenem or levofloxacin

Source: Reviewer's independent analysis.

For patients with CLcr >30 to 90 mL/min, a significant exposure-response relationship was identified between $C_{1st, min}$ and nephrotoxicity. Therapy duration was categorized by more than 5 days (coded as 1) and equal to or less than 5 days (coded as 0), which was shown to be not associated with incidence of nephrotoxicity.

Figure 4.3.3-3 Exposure-response analysis for nephrotoxicity in cUTI patients with CLcr >30 to 90 mL/min



Source: Reviewer's independent analysis.

The observed percentage of patients with nephrotoxicity was summarized by $C_{1st,\ min}$ quartile as shown in Table 4.3.3-2.

Table 4.3.3-2 Percentage of patients with nephrotoxicity by $C_{1st,\ min}$ quartile

CLcr	*1st Quartile*	*2nd Quartile*	*3rd Quartile*	*4th Quartile*	*Active Control*
>30 to 90 mL/min	*1.6%*	*8.2%*	*4.9%*	*19.7%*	*4.1%*

Source: Reviewer's independent analysis.

As concomitant nephrotoxic medications may be a potential confounding factor for the E-R analysis, the summary of maximum number of daily concomitant nephrotoxic medications of each subject was summarized by exposure quartile and renal function and listed below. It appears that patients with CLcr >30 to 90 mL/min received more concomitant nephrotoxic medications compared to those with CLcr >90 mL/min.The maximum number of daily concomitant nephrotoxic medications were similar in the first three $C_{1st,\ min}$ quartiles and a little bit higher in the last $C_{1st,\ min}$ quartile, indicating minimal impact on the E-R relationship.

Table 4.3.3-3 Summary of maximum number of concomitant nephrotoxic medications by $C_{1st,\ min}$ quartile and renal function

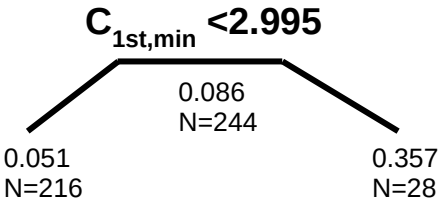
CLcr	*Max No. of concomitant nephrotoxic medications, mean, min-max*			
	1st Quartile	*2nd Quartile*	*3rd Quartile*	*4th Quartile*
>30 to 90 mL/min	*0.8 (0-4)*	*0.9 (0-3)*	*1.0 (0-4)*	*1.3 (0-5)*
>90 mL/min	*0.5 (0-2)*	*0.5 (0-2)*	*0.5 (0-2)*	*0.9 (0-3)*

Source: Reviewer's independent analysis.

4.3.3.3 Classification and regression tree (CART) analysis

A CART analysis was conducted in the cUTI patients to identify potential cutoffs for $C_{1st, min}$, which may be associated with higher incidence of nephrotoxicity. The results are shown in Figure 4.3.3-4.

Figure 4.3.3-4 CART analysis in cUTI patients for incidence of nephrotoxicity



Source: Reviewer's independent analysis.

$C_{1st, min}$ of 3 µg/mL is predicted to be the critical cutoff associated with higher incidence of nephrotoxicity. To further confirm if the cut-off for $C_{1st, min}$ is reasonable, the $C_{1st, min}$ ranges of cUTI patients with CLcr >30 to 90 mL/min from Studies ACHN-490-002 and ACHN-490-009 and the corresponding incidence of nephrotoxicity are summarized in Table 4.3.3-4.

Table 4.3.3-4 Summary of incidence of nephrotoxicity in cUTI patients with CLcr >30 to 90 mL/min from Studies ACHN-490-002 and ACHN-490-009 by $C_{1st, min}$ and CLcr

$C_{1st, min}$ Range	*% Nephrotoxicity (n/N)**
≥ 4 µg/mL	*40.0% (6/15)*
≥ 3, and <4 µg/mL	*30.8% (4/13)*
≥ 2 and < 3 µg/mL	*9.8% (4/41)*
≥ 1 and < 2 µg/mL	*5.0% (4/80)*
< 1 µg/mL	*3.2% (3/95)*
Total	*8.6% (21/244)*

**n is the number of patients with nephrotoxicity; N is the number of patients*

Source: Reviewer's independent analysis.

The results in Table 4.3.3-4 aligned with the CART analysis; nephrotoxicity incidence is dramatically increased with $C_{1st, min}$ ≥3 µg/mL. According to a publication by Neugarten, et. al. (Clinical Nephrology, 2016), nephrotoxicity occurs in 5 to 15% of patients treated with aminoglycosides. For patients with $C_{1st, min}$ ≥3 µg/mL, the nephrotoxicity incidence is higher than 15%. It appears that $C_{1st, min}$ ≥3 µg/mL is a reasonable TDM threshold with high specificity.

More details of nephrotoxicity incidence across renal function based on Phase 2 and 3 studies are summarized in Table 4.3.3-5 and the similar information based on Phase 3 study only is listed in Table 4.3.3-6.

Table 4.3.3-5 Nephrotoxicity incidence across renal function based on Phase 2 and 3 studies

	*% Nephrotoxicity (n/N)**			
$C_{1st, min}$ (μg/mL)	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
≥ 4	*6/17 (35.3%)*	*4/9 (44.4%)*	*2/6 (33.3%)*	*0/2 (0)*
≥ 3	*10/32 (31.3%)*	*7/19 (36.8%)*	*3/9 (33.3%)*	*0/4 (0)*
≥ 2	*14/76 (18.4%)*	*10/46 (21.7%)*	*4/23 (17.4%)*	*0/7 (0)*
≥ 1	*18/166 (10.8%)*	*12/78 (15.4%)*	*6/71 (8.5%)*	*0/17 (0)*
$C_{1st, min}$ (μg/mL)	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
≥ 3 – 4	*4/15 (26.7%)*	*3/10 (30.0%)*	*1/3 (33.3%)*	*0/2 (0)*
≥ 2 -3	*4/44 (9.1%)*	*3/27 (11.1%)*	*1/14 (7.1%)*	*0/3 (0)*
≥ 1 -2	*4/90 (4.4%)*	*2/32 (6.3%)*	*2/48 (4.2%)*	*0/10 (0)*
≥ 0 -1	*4/201 (26.7%)*	*1/26 (3.8%)*	*2/69 (2.9%)*	*1/106 (0.9%)*
Treatment	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
Plazomicin	*22/367 (6%)*	*13/104 (12.5%)*	*8/140 (5.7%)*	*1/123 (0.8%)*
Comparator[#]	*13/340 (3.8%)*	*5/114 (4.4%)*	*5/129 (3.9%)*	*3/97 (3.1%)*

**n is the number of patients with nephrotoxicity; N is the number of patients*
[#]Meropenem or levofloxacin

Source: Reviewer's independent analysis.

Table 4.3.3-6 Nephrotoxicity incidence across renal function based on Phase 3 study

	*% Nephrotoxicity (n/N)**			
$C_{1st, min}$ (μg/mL)	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
≥ 4	*4/15 (26.7%)*	*3/8 (37.5%)*	*1/5 (20.0%)*	*0/2 (0)*
≥ 3	*7/29 (24.1%)*	*5/17 (29.4%)*	*2/8 (25.0%)*	*0/4 (0)*
≥ 2	*11/66 (16.7%)*	*8/39 (20.5%)*	*3/20 (15.0%)*	*0/7 (0)*
≥ 1	*15/142 (10.6%)*	*10/66 (15.2%)*	*5/60 (8.3%)*	*0/16 (0)*
$C_{1st, min}$ (μg/mL)	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
≥ 3 – 4	*3/14 (21.4%)*	*2/9 (22.2%)*	*1/3 (33.3%)*	*0/2 (0)*
≥ 2 -3	*4/37 (10.8%)*	*3/22 (13.6%)*	*1/12 (8.3%)*	*0/3 (0)*
≥ 1 -2	*4/76 (5.3%)*	*2/27 (7.4%)*	*2/40 (5.0%)*	*0/9 (0)*
≥ 0 -1	*2/136 (1.5%)*	*1/20 (5.0%)*	*1/47 (2.1%)*	*0/69 (0)*
Treatment	*Overall*	*CLcr >30 to 60 mL/min*	*CLcr >60 to 90 mL/min*	*CLcr >90 mL/min*
Plazomicin	*17/278 (6.1%)*	*11/86 (12.8%)*	*6/107 (5.6%)*	*0/85 (0)*
Comparator[#]	*12/297 (4.0%)*	*4/106 (3.8%)*	*5/111 (4.5%)*	*3/80 (3.8%)*

**n is the number of patients with nephrotoxicity; N is the number of patients*
[#]Meropenem or levofloxacin

Source: Reviewer's independent analysis.

4.3.3.4 Comparison of TDM cutoffs

The comparison of TDM cutoffs of 3 μg/mL and 2 μg/mL in patients with CLcr >30 to 90 mL/min is shown in Table 4.3.3-7. Patients with $C_{1st, min}$ ≥3 μg/mL may have a higher nephrotoxicity incidence than those with $C_{1st, min}$ ≥2 μg/mL. Moreover, less patients may have $C_{1st, min}$ ≥3 μg/mL compared to $C_{1st, min}$ ≥2 μg/mL. Since the Phase 3 study was a non-inferiority

study without dose adjustment, the higher cutoff would impact less patients, thus, the probability of efficacy loss is minimized

Table 4.3.3-7 Comparison of two $C_{1st, min}$ cutoffs in patients with CLcr >30 to 90 mL/min

Cutoffs	*% Patients with $C_{1st, min} \geq$ Cutoff (n/N)**	*% Nephrotoxicity in patients with $C_{1st, min} \geq$ Cutoff (n/N)*	*% Nephrotoxicity in patients with $C_{1st, min}$ < Cutoff (n/N)*
3 µg/mL	*11.5% (28/244)*	*35.7% (10/28)*	*5.1% (11/216)*
2 µg/mL	*28.3% (69/244)*	*20.3% (14/69)*	*1.0% (7/175)*

**n represents number of patients with nephrotoxicity; N represent number of patients*

Source: Reviewer's independent analysis.

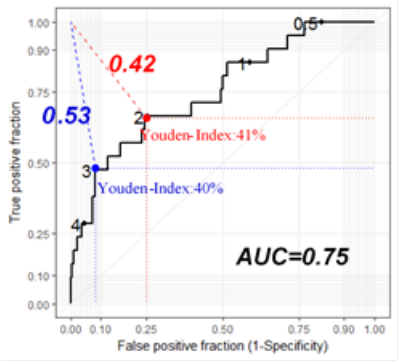
The sensitivity and specificity were compared for the two TDM cutoffs. The specificity was defined as the percentage of patients without nephrotoxicity who can be correctly classified as no dose adjustment is needed ($C_{1st, min} \geq$ cutoff) Sensitivity was defined the percentage of patients with nephrotoxicity who can be correctly classified as dose adjustment is needed ($C_{1st, min}$ < cutoff)). The TDM cutoff of 3 µg/mL provides a high specificity while the TDM of 2 µg/mL provides a good sensitivity in cUTI patients with CLcr >30 to 90 mL/min. The recever operating characteristic (ROC) curve shows that the TDM cutoff of 2 µg/mL has a shorter distance to point (0, 1) and higher Youden index (Figure 4.3.3-5), which is favored from safety perspective without considering the potential efficacy loss caused by dose adjustment.

Table 4.3.3-8 Sensitivity and specificity comparison by TDM cutoffs

$C_{1st, min}$ cutoffs	*Sensitivity*	*Specificity*
3 µg/mL	*48%*	*92%*
2 µg/mL	*67%*	*75%*

Source: Reviewer's independent analysis.

Figure 4.3.3-5 ROC curve for patients with CLcr >30 to 90 mL



Source: Reviewer's independent analysis

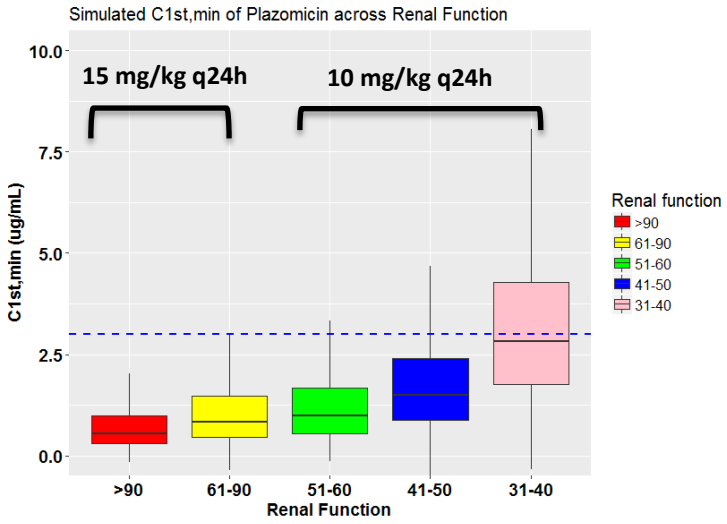
In brief, $C_{1st, min} \geq$3 µg/mL is an option if overall efficacy loss is a major concern for TDM since less patients may have dose adjustment while $C_{1st, min} \geq$2 µg/mL is an option if overall safety is a

major concern for TDM since more patients with nephrotoxicity may have dose adjustment. Specifically, dose reductions for patients with $C_{1st, min}$ between 2 and 3 µg/mL may raise concern for efficacy loss and no dose reduction for patients with $C_{1st, min}$ between 2 and 3 µg/mL may raise safety concern.

4.3.3.5 Dosing strategy in cUTI patients without C_{min}-based TDM

Of note, C_{min}-based TDM requires a precise, accurate, and reliable bioassay. The Reviewer also evaluated the dosing strategy with the scenario that bioassay device would not be available for C_{min}-based TDM. As mentioned above, the nephrotoxicity incidence was lower in in patients with CLcr >90 mL/min who received plazomicin. Therefore, TDM may not be needed in patients with normal renal function. The findings from the Phase 3 study show that the dose adjustment daily based on CLcr was not sufficient to prevent the nephrotoxicity in patients with Clcr >30 to 90 mL/min. Adjusting the initial dose may be the only approach to reduce the potential nephrotoxicity in cUTI patients. However, the proposed initial dose is either same as the studied dose or lower than the studied dose in most of the patients except the patients with CLcr >30 to 40 mL/min who received 8 mg/kg q24h in the Phase 3 study, which is 20% lower than what is proposed in the labeling (10 mg/kg q24h). Therefore, adjusting initial dose may be only appropriate in patients with CLcr >30 to40 mL/min without concern for potential efficacy loss. The $C_{1st, min}$ is plotted across renal function based on the proposed initial dose as shown in Figure 4.3.3-6.

Figure 4.3.3-6 $C_{1st, min}$ across renal function based on the proposed initial dose



The blue dash line represents the $C_{1st, min}$ equals to 3 µg/mL

Source: Reviewer's independent analysis.

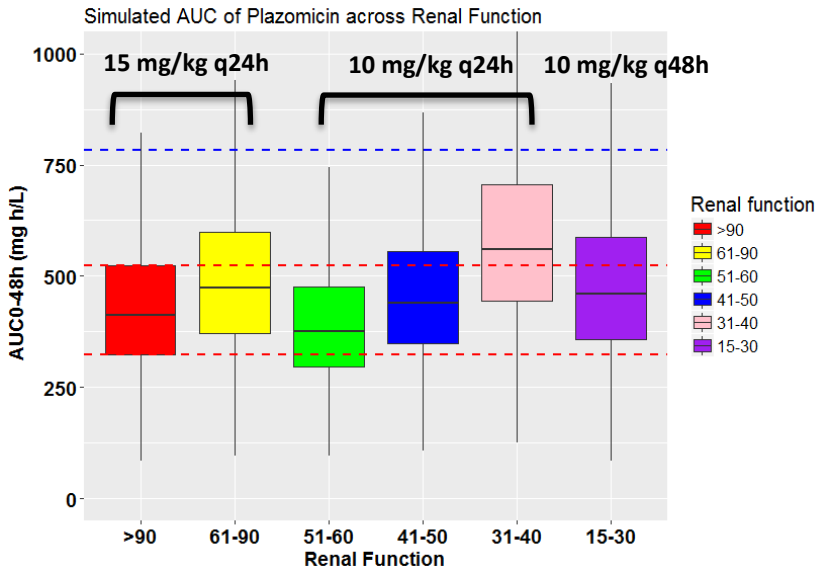
Although the predicted AUC_{0-24h} is comparable based on the proposed initial dose (Figure 4.2-5), the $C_{1st, min}$ increased with decreased CLcr. The percentages of patients with $C_{1st, min}$ ≥3 µg/mL

were 2%, 5%, 6%, 15%, and 46% for CLcr >90 mL/min, CLcr > 60 to 90 mL/min, CLcr >50 to 60 mL/min, CLcr >40 to 50 mL/min, and CLcr >30 to 40 mL/min. It appears that adjusting the initial dose for patients with CLcr >30 to 40 mL/min may potentially reduce the nephrotoxicity incidence. The simulation showed that around 46% patients with CLcr >30 to 40 mL/min would have $C_{1st, min} \geq 3$ μg/mL based on an initial dose of 10 mg/kg while the percentage would be reduced to 33% based on an initial dose of 8 mg/kg. The limitation is that the CLcr range is too narrow to propose a reduced initial dose considering the high variability of CLcr estimation.

4.3.3.6 Dosing strategy in cUTI patients with CLcr >15 to 30 mL/min

Limited efficacy and safety data are available for cUTI patients with CLcr ≤30 mL/min (N=1 patient). As exposure-nephrotoxicity relationship differs with renal function, greater risk of nephrotoxicity is expected in cUTI patients with CLcr ≤30 mL/min. However, considering that plazomicin is indicated for limited use, the patients with CLcr >15 to 30 mL/min may have limited treatment option. Therefore, the initial dose for patients with CLcr >15 to 30 mL/min was evaluated by the Reviewer. The exposure (AUC_{0-48h}) in patients with CLcr >15 to 30 mL/min administered an initial dose of 10 mg/kg q48h was simulated based on the population PK model and compared with that in patients with CLcr >30 mL/min receiving their corresponding doses (Figure 4.3.3-7).

Figure 4.3.3-7 AUC_{0-48h} across renal function



The red dash lines represent the 25% and 75% quantile of AUC_{0-48h} in cUTI patients with CLcr >90 mL/min; the blue dash lines represent the 95% quantile of AUC_{0-48h} (783 mg·h/L) in cUTI patients from Study ACHN-490-009.

Source: Reviewer's independent analysis.

A comparable exposure would be achieved for patients with CLcr >15 to 30 mL/min using an initial dose of 10 mg/kg q48h to patients with CLcr > 30 mL/min using the proposed initial dose of 10 mg/kg q 24h. It appears that the proposed initial dose for patients with Clcr > 15 to 30 mL/min is reasonable.

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4.3.4 TDM scheme in cUTI patients

Applicant's analysis

The applicant did not provide the details of the TDM scheme using $C_{min} \geq 2$ μg/mL in the original submission. More information was provided in Applicant's IR responses received on Feb 12th, 2018 and March 7th, 2018. The proposed TDM scheme using $C_{min} \geq 2$ μg/mL for cUTI patients is described as follows:

(b) (4)

Simulation was conducted by Applicant using population PK model (b) (4) to predict the daily exposure (C_{min} and AUC) taking the interaction between exposure and CLcr into consideration. Plazomicin doses (mg/kg) were not adjusted based on CLcr postbaseline. A predose C_{min} sample was obtained 30 minutes before administration of each plazomicin dose, starting with 2nd Dose. To mimic the clinical application of TDM, a 24-hour lag was implemented between collection of the C_{min} sample and availability of the C_{min} value.

Summary statistics for plazomicin C_{min} and $AUC_{0–24h}$ over the duration of each plazomicin dose, with and without TDM, were compared among simulated patients (Tables 4.3.4-1 to 4.3.4-3). C_{min} was predicted immediately before the start of infusion. $AUC_{0–24h}$ was derived from AUC over the dose interval (AUC_{0-t}) and the number of hours in the dosing interval (τ) as follows: $AUC_{0–24h} = (AUC_{0-t}/\tau) \times 24$. The target range of AUC_{0-24h} (121-368 μg·h/mL) was defined as the 5th and 95th percentile $AUC_{0–24h}$ values for cUTI patients in the PK analysis population

Table 4.3.4-1 C_{min} and $AUC_{0–24h}$ summary in patients with normal renal function or mild renal impairment

Variable	C_{min} (mcg/mL)													
	No TDM							With TDM						
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
Patients	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	2990	2850	2680
5th percentile	0.144	0.168	0.181	0.191	0.198	0.202	0.200	0.144	0.168	0.181	0.191	0.196	0.197	0.191
95th percentile	1.95	2.15	2.30	2.43	2.60	2.66	2.72	1.95	1.72	1.63	1.63	1.61	1.59	1.58
Mean	0.739	0.816	0.876	0.920	0.976	1.01	1.02	0.739	0.725	0.731	0.744	0.753	0.739	0.731
%CV	85.9	85.3	86.9	89.0	107	117	122	85.9	65.4	60.6	59.7	60.2	57.4	57.6
% ≥ 2 mcg/mL	4.73	6.17	7.50	8.47	9.57	9.97	10.3	4.73	1.60	0.633	0.367	0.401	0.105	0.00
Variable	AUC_{0-24h} (mcg·h/mL)													
	No TDM							With TDM						
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
Patients	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	2990	2850	2680
5th percentile	120	124	124	124	124	124	124	120	124	124	123	124	122	121
95th percentile	357	368	376	382	388	392	395	357	348	342	342	341	338	335
Mean	221	225	227	229	232	233	234	221	220	218	218	218	217	216
% CV	33.9	34.3	35.0	35.8	37.3	38.9	39.7	33.9	32.1	31.4	31.3	31.3	31.1	31.0
% within target range[a]	90.7	90.5	89.8	89.4	89.2	88.8	88.5	90.7	91.9	92.3	92.4	92.5	92.6	92.5
% above target range[a]	4.13	4.97	5.73	6.20	6.50	6.77	7.00	4.13	3.53	3.23	3.07	2.94	2.67	2.46

Source: Applicant's IR response received on March, 7, 2018, Page 13, Table 3

Table 4.3.4-2: C_{min} and $AUC_{0–24h}$ summary statistics in patients with moderate renal impairment

Variable	C_{min} (mcg/mL)													
	No TDM							With TDM						
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
Patients	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	2670	1990	1580
5th percentile	0.344	0.370	0.356	0.360	0.361	0.373	0.385	0.344	0.365	0.336	0.316	0.316	0.310	0.302
95th percentile	4.88	5.98	6.24	6.56	7.03	7.61	8.67	4.88	2.87	1.87	1.81	1.79	1.75	1.71
Mean	1.87	2.11	2.15	2.23	2.38	2.53	2.75	1.87	1.35	1.01	0.974	0.993	0.948	0.957
% CV	78.6	86.8	89.9	93.1	95.8	98.7	104	78.6	64.7	47.2	47.9	46.9	46.9	45.8
% ≥ 2 mcg/mL	34.1	38.3	38.3	38.8	41.2	42.9	45.6	34.1	15.7	2.40	1.67	1.31	0.955	0
Variable	AUC_{0-24h} (mcg·h/mL)													
	No TDM							With TDM						
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
Patients	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	2670	1990	1580
5th percentile	106	108	108	106	106	106	108	106	108	104	100	99.5	98.0	98.3
95th percentile	369	406	417	427	442	456	486	369	318	274	261	262	260	258
Mean	214	227	228	229	235	239	248	214	199	178	172	173	170	171
%CV	39.0	40.8	42.1	43.8	45.4	47.1	49.4	39.0	32.6	28.8	29.4	29.2	29.7	29.6
% within target range[a]	84.9	82.8	81.8	80.8	79.6	78.6	77.1	84.9	89.4	88.6	84.8	85.0	83.5	83.8
% above target range[a]	5.17	8.73	9.47	9.77	11.2	12.2	14.6	5.17	1.73	0.167	0.200	0.0749	0.151	0.252

Source: Applicant's IR response received on March, 7, 2018, Page 14, Table 4

Table 4.3.4-3: C_{min} and $AUC_{0–24h}$ summary statistics in patients with severe renal impairment

Variable	C_{min} (mcg/mL)							
	No TDM				With TDM			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
Patients	3000	3000	3000	3000	3000	3000	3000	1320
5th percentile	0.414	0.335	0.303	0.332	0.414	0.334	0.298	0.208
95th percentile	5.47	7.18	8.38	9.67	5.47	3.91	2.85	1.95
Mean	2.34	2.79	3.18	3.54	2.34	1.72	1.42	1.03
%CV	72.4	83.7	88.4	90.2	72.4	72.3	63.8	53.4
% ≥ 2 mcg/mL	49.1	53.4	56.9	60.1	49.1	29.5	16.2	3.34
Variable	AUC_{0-24h} (mcg·h/mL)							
	No TDM				With TDM			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
Patients	3000	3000	3000	3000	3000	3000	3000	1320
5th percentile	115	110	103	105	115	110	101	90.0
95th percentile	393	441	474	516	393	340	293	254
Mean	230	247	257	271	230	209	188	165
% CV	38.6	44.2	48.1	49.7	38.6	36.1	33.0	30.6
% within target range[a]	86.8	80.0	75.1	72.4	86.8	88.1	87.8	80.6
% above target range[a]	6.77	11.8	15.5	19.2	6.77	3.40	1.30	0.0759

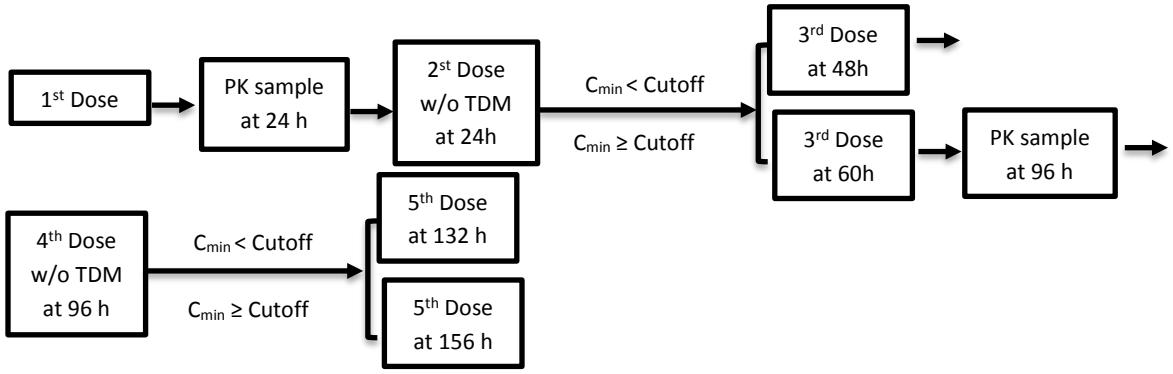
Source: Applicant's IR response received on March, 7, 2018, Page 15, Table 5

The results showed that the proposed dose adjustments in cUTI patients following C_{min}-based TDM decreased the percentages of patients with C_{min} values ≥2 µg/mL and AUC_{0-24h} values above the target range while increasing the percentages of patients with $AUC_{0–24h}$ values within the target range.

Reviewer's comments

The Reviewer conducted an independent analysis to evaluate the appropriate C_{min}-based TDM scheme using the TDM threshold of 3 µg/mL instead of 2 µg/mL. (b) (4) *Considering the short treatment duration (5 to 7 days) and delayed PK sample results (~24 to 36 hours), it may not be an appropriate approach. The dosing and TMD scheme based on two dose adjustments for patients with CLcr >30 mL/min are summarized in Figure 4.3.4-1.*

Figure 4.3.4-1 Dosing and TDM scheme in cUTI patients using C_{min}-based TDM



Source: Reviewer's independent analysis.

Briefly, two doses were assumed to be given on Day 1 (0 hour) and 2 (24 hours), respectively based on body weight (15 mg/kg for patients with CLcr >60 mL/min and 10 mg/kg for patients with CLcr>30 to 60 mL/min) assuming the TDM occurred on Day 3 (C_{min} sample was taken prior to the 2nd dose and was available before the 3rd dose due to the 24 to 36 hours delay). Once the information of C_{min} at 24 hours was available prior to Day 3, the subjects with C_{min} < cutoff at 24 hours would have their next dose at 48 hours and daily dosing regimen thereafter, while the subjects with C_{min} ≥ cutoff at 24 hours would extend their dosing interval to 36 hours and have their next dose at 60 hours instead of 48 hours. The second PK sample would be taken at 96 hours for the subjects with C_{min} ≥ cutoff at 24 hours. The dose at 96 hours was not adjusted due to the delayed PK sample results. The information of C_{min} at 96 hours was available at 120 hours, the subjects with C_{min} < cutoff at 96 hours would continue with 36 hours dosing interval thereafter (next dose would be on Day 6 (132 hours)) and the subject with C_{min} ≥ cutoff at 60 hours would extend the dosing interval to 60 hours, which means they would receive the last dose on Day 7 (156 hours) as shown in Figure 4.3.3-1.

The population PK model was used to simulate the C_{min} for virtual cUTI patients (N=19100) at 24, 60, and 72 hours after receiving the first and second doses at 0 and 24 hours. The results using both 2 and 3 μg/mL as cutoffs are presented Table 4.3.4-4.

Table 4.3.4-4 Summary of results for C_{min}-based TDM scheme in subjects with CLcr >30 to 90 mL/min

C_{min} Cutoff	No. of Subjects (%)			
	C_{min} < cutoff at 24 h	C_{min} ≥ cutoff at 24 h but <cutoff at 60 h	C_{min} ≥ cutoff at 60 h	Total
3 μg/mL	165991 (86.9%)	18623 (9.8%)	6386 (3.3%)	191000
2 μg/mL	142646 (74.7%)	33287 (17.4%)	15067 (7.9%)	191000

Source: Reviewer's independent analysis.

The simulation showed that approximately 86.9% subjects may have C_{min} <3 μg/mL at 24 hours after first dose and do not need TDM. About 13.1% subjects may have C_{min} ≥3 μg/mL at 24 hours and need to extend their dosing interval to 36 hours. These 13.1% subjects would have their 3rd dose at 60 hours. Around 9.8% subjects may have C_{min} predicted to be below 3 μg/mL at 60 hours and continue with their 36 hours dosing interval routinely. Around 3.3% subjects may have their C_{min} ≥3 μg/mL at 60 hours and may have to further extend the dosing interval if two dose adjustments are implemented. However, this percentage would be increased to 7.9% using $C_{1st, min}$ ≥2 μg/mL as the cutoff.

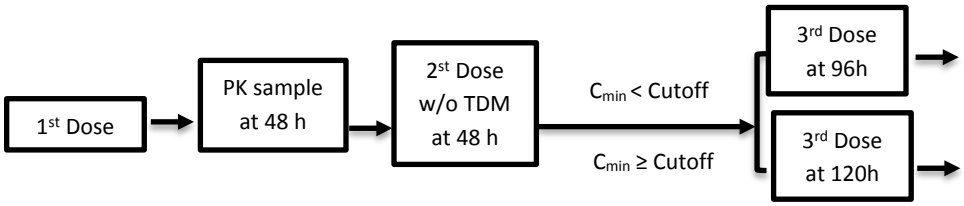
It appears to be reasonable to extend the dosing interval to 36 hours for subjects who have C_{min} ≥3 μg/mL at 24 hours. However, it appears to be not clinically feasible to further extend the dosing interval again as the treatment duration is only 4-7 days. The subjects who don't receive more than a 4-day treatment would not have the opportunity to have the second dose adjustment. Moreover, only around 3% subjects would have a C_{min} ≥3 μg/mL at 60 hours; therefore TDM may not be worthwhile. PTA analysis was conducted to evaluate if there maybe potential efficacy loss with C_{min}-based dose adjustment (details in Section 4.4). The proposed TDM would reduce nephrotoxicity by extending the dosing interval resulting in their C_{min} below 3 μg/mL.The C_{min}-based TDM can only be used to determine the appropriate dosing interval. At the same time, the daily dose can be determined based on daily measured CLcr.

It is worth noting that the recommended C_{min}-based TDM used a single threshold ($C_{1st, min}$ ≥3 μg/mL) without further considering the impact of magnitude of $C_{1st, min}$. The patients with $C_{1st, min}$ of 3.5 μg/mL would have the same extended dosing interval with those with $C_{1st, min}$ of 10 μg/mL. It is possible that the patients with $C_{1st, min}$ of 3.5 μg/mL and extended their dosing intervals may have exposure (AUC) lower than target therapeutic range while the patients with $C_{1st, min}$ of 10 μg/mL and extended their dosing intervals may have C_{min} still higher than 3 μg/mL. However, based on Table 4.3.4-4, around 10% patients may have lower AUC due to dose adjustment. PTA analysis was conducted by the Reviewer to evaluate the potential efficacy loss due to TDM (Section 4.4.1). Based on Table 4.3.4-4, few patients (3%) may have C_{min} still higher than 3 μg/mL. Also more than one dose adjustment may not be practical due to the short treatment duration (4-7 days). Therefore, these patients may experience higher risk of nephrotoxicity due to the limitation of TDM strategy.

In patients with CLcr >15 to 30 mL/min, limited efficacy and safety data were available, thus, the TDM scheme was proposed using the modeling and simulation approach based on findings from patients with CLcr >30 mL/min. As dosing interval is 48 hours in this population, the $C_{1st, min}$ at 48 hours instead of 24 hours will be used for TDM. The PK samples would be collected at 48 hours and PK results may be available at 72 to 84 hours (24 to 36 hours delay). The second dose would be given at 48 hours without TDM for all the subjects. When PK results were available, the subjects with $C_{1st, min}$ < cutoff at 48 hours would have their 3rd dose at 96 hours, while subjects with $C_{1st, min}$ ≥ cutoff at 48 hours are proposed to have their 3rd dose at 120 hours (Day 6) instead of 96 hours (one dose adjustment by increasing the dosing interval to 1.5-fold

(72 hours)). Two dose adjustment may not be clinically feasible either in this population considering the short treatment duration (4-7 days). The dosing and TDM scheme based on one dose adjustment for patients with CLcr >15 to 30 mL/min are summarized in Figure 4.3.4-2.

Figure 4.3.4-2 Dosing and TDM scheme in cUTI patients using C_{min}-based TDM



The population PK model was used to simulate the Cmin for virtual cUTI patients with CLcr >15 to 30 mL/min (N=95500) at 48, 96, and 120 hours after receiving the first and second doses at 0 and 48 hours. The results using both 2 and 3 μg/mL as cut-offs are presented Table 4.3.4-5.

Table 4.3.4-5 Summary of results for C_{min}-based TDM scheme in subjects with CLcr >15 to 30 mL/min

	No. of Subjects (%)			
C_{min} cutoff	*C_{min} < cutoff at 48 h*	*C_{min} ≥ cutoff at 48 h but < cutoff at 120 h*	*C_{min} ≥ cutoff at 120 h*	*Total*
3 μg/mL	*66736 (69.9%)*	*17438 (18.2%)*	*11326 (11.9%)*	*95500*
2 μg/mL	*48501 (50.8%)*	*24403 (25.6%)*	*22596 (23.6%)*	*95500*

Source: Reviewer's independent analysis.

Approximately 88% patients would have C_{min} <TDM threshold based on one dose adjustment strategy using $C_{1st, min}$ ≥3 μg/mL as the TDM threshold. This percentage would be reduced to 76% using $C_{1st, min}$ ≥2 μg/mL as the TDM threshold.

Therefore, it is recommended to have one dose adjustment by increasing dosing interval to 1.5-fold in cUTI patients based on their $C_{1st, min}$ using the threshold of 3 μg/mL.

4.4 Target Attainment Analyses

Applicant's analysis

Probability of target analysis (PTA) was conducted by Applicant in cUTI patients using non-clinical PK/PD targets based on neutropenic murine thigh infection models (Table 4.4-1) and parameter estimates from a population PK model describing the PK characteristics of plazomicin in humans,.

Table 4.4-1 Summary of $AUC_{0\text{-}24h}$/MIC ratio targets for plazomicin against Enterobacteriaceae based on studies with neutropenic murine thigh infection model

Isolate	Plasma $AUC_{0\text{-}24h}$/MIC ratio targets	
	Net bacterial stasis	1-log10 CFU reduction
Enterobacteriaceae	18	73

Source: Applicant's report (ICPD 00462-3), Page 32, Table 5

The final population PK model (*details in Section 4.2*) was used to generate the $AUC_{0\text{-}24h}$ of plazomicin in cUTI patients by Monte Carlo simulation based on the demographic information from Studies ACHN-490-002 and ACHN-490-009 with exception of CLcr. Baseline CLcr was randomly assigned for each simulated patient using a uniform distribution from one of the following seven CLcr intervals:

- > 120 to ≤ 240 mL/min
- > 90 to ≤ 120 mL/min
- > 60 to ≤ 90 mL/min
- > 50 to ≤ 60 mL/min
- > 40 to ≤ 50 mL/min
- > 30 to ≤ 40 mL/min
- > 16 to ≤ 30 mL/min

Since CLcr was a time-varying covariate in the population PK analysis, the initial concentration-time profiles were generated based on the population PK model and baseline CLcr, and the subsequent concentration-time profiles were generated based on the population PK model and the follow-up CLcr predicted from the direct exposure-nephrotoxicity model (*details in Section 4.3.2*). The concentration-time profiles from 0 to 48 hours were simulated and AUC was calculated using numerical integration. The average 24-hour plazomicin AUC value was calculated by dividing the $AUC_{0\text{-}48h}$ by 2.

(b) (4) the PTA results are shown below.

Table 4.4-2 PTA result in simulated cUTI patients by CLcr group

(b) (4)

Source: Applicant's report (ICPD 00462-3), Page 18, Table 1

Reviewer's comments

4.4.1 PTA in cUTI patients

The reviewer conducted an independent PTA analysis in cUTI patients. The AUC_{0-24} after first dose instead of steady state AUC_{0-24} generated by population PK model was used due to the complexity of dose adjustment in cUTI patients. The PK/PD targets of 24 (median value for bacterial stasis), 39(75% quantile for bacterial stasis) and 89 (median value for 1-log kill) were used in the PTA analysis. The results are shown in Table 4.4-3.

Table 4.4-3 PTA result in simulated cUTI patients by CLcr group

CLcr	*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*
CLcr>90 mL/min	*100%*	*100%*	*98%*	*54%*	*3%*
CLcr>30 to 90 mL/min	*100%*	*100%*	*99%*	*64%*	*6%*
CLcr>15 to 30 mL/min	*100%*	*100%*	*99%*	*66%*	*7%*
CLcr	*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*
CLcr>90 mL/min	*100%*	*100%*	*75%*	*10%*	*0*
CLcr>30 to 90 mL/min	*100%*	*100%*	*82%*	*16%*	*0*
CLcr>15 to 30 mL/min	*100%*	*100%*	*83%*	*18%*	*0*
CLcr	*PTA by MIC using AUC/MIC of 89 as a PK/PD target*				
	1 μg/mL	*2 μg/mL*	*4 μg/mL*	*8 μg/mL*	*16 μg/mL*
CLcr>90 mL/min	*99%*	*62%*	*5%*	*0*	*0*
CLcr>30 to 90 mL/min	*99%*	*70%*	*9%*	*0*	*0*
CLcr>15 to 30 mL/min	*99%*	*73%*	*10%*	*0*	*0*

Source: Reviewer's independent analysis.

The PTA results show the breakpoint can be up to 4 μg/mL in cUTI patients for all the renal groups based on PK/PD target of 24 for AUC/MIC. The breakpoint is predicted to be down to 2

and 1 μg/mL in CUTI patients for all the renal groups based on PK/PD target of 39 and 89 for AUC/MIC, respectively.

*The PTA analysis was also conducted in patients receiving one dose adjustment using both 2 μg/mL and 3 μg/mL as TDM threshold was implemented. The PK/PD target of 24, 39, and 89 for AUC/MIC was used. The $AUC_{0\text{-}24h}$ after second dose was simulated for patients without dose adjustment based on population PK model and the normalized $AUC_{0\text{-}24}$ after second dose using $AUC_{0\text{-}36h}$*24/36 was simulated and calculated for patients with dose adjustment based on population PK model.*

Table 4.4-4 PTA analysis to evaluate the one dose adjustment using different TDM threshold

TDM threshold	*Probability of target attainment by MIC using AUC/MIC of 24 as a PK/PD target*		
	1 μg/mL	*2 μg/mL*	*4 μg/mL*
2 μg/mL	*100%*	*100%*	*99.0%*
3 μg/mL	*100%*	*100%*	*99.0%*
TDM threshold	*Probability of target attainment by MIC using AUC/MIC of 39 as a PK/PD target*		
	1 μg/mL	*2 μg/mL*	*4 μg/mL*
2 μg/mL	*100%*	*99.8%*	*83.4%*
3 μg/mL	*100%*	*99.8%*	*85.5%*
TDM threshold	*Probability of target attainment by MIC using AUC/MIC of 89 as a PK/PD target*		
	1 μg/mL	*2 μg/mL*	*4 μg/mL*
2 μg/mL	*99.4%*	*71.7%*	*6.1%*
3 μg/mL	*99.4%*	*75.7%*	*8.4%*

Source: Reviewer's independent analysis.

The PTA result supports that efficacy may not be significantly compromised after one dose adjustment using the TDM threshold of both 2 μg/mL and 3 μg/mL. However, it should be noted that PTA analysis is based on PK/PD target derived from animal model, which may not be conservative enough to predict a potential efficacy loss. As a numerically decrease of microbiological response with a lower dose was observed in the Phase 2 dose-ranging study, it is uncertain if dose adjustment may be associated with compromised efficacy.

(b) (4)


(b) (4)

4.5 Individual Clinical Pharmacology Study Report Reviews

	Study Number	Study Type / Population
4.5.1		Animal models to determine the PK/PD target
4.5.2		In Vitro study reports
4.5.3	ACHN-490-001	Single dose and Multiple dose escalation PK / Healthy adults
4.5.4	ACHN-490-004	Single dose PK, renal impairment / Healthy adults
4.5.5	ACHN-490-010	Mass balance / Healthy male adults
4.5.6	ACHN-490-011	Drug-drug interaction PK, metformin / Healthy adults

4.5.1 Animal Models to Determine the PK/PD Target for Plazomicin

The PK/PD Index of plazomicin, AUC_{0-24}/ MIC ratio, was determined by an early dose-fractionation study in a neutropenic murine pneumonia model (Study ORI-2011-008) and a neutropenic murine thigh infection model (Study UFL-2016-001).

Several dose-fractionation-studies were conducted to determine the PK/PD target of plazomicin against *Enterobacteriaceae* in both neutropenic murine thigh infection (Studies UFL-2016-001 and UFL-2012-009) and neutropenic murine pneumonia models (Studies UFL-2016-001, UFL-2012-003 and UFL-2011-004). Due to the low plasma protein binding in both mice and humans (i.e., approximately 20% for both), the total (i.e., unbound plus bound) AUC of plazomicin was used to determine the PK/PD target. Of note, the AUC/MIC in Study UFL-2016-001 and Study UFL-2012-009 is for AUC_{0-24}/MIC.

Neutropenic Murine Thigh Infection Model

Study UFL-2016-001

Dose-fractionation studies were conducted using eight *Enterobacteriaceae* strains (four *E. coli*, three *K. pneumoniae*, and one *E. aerogenes*) in neutropenic murine thigh infection model to determine the PK/PD target. Among them, six strains were resistant to carbapenem antibiotics and/or to the legacy aminoglycosides, gentamicin and/or tobramycin. Strain AKPN001 was only used in early dose fractional study for PK/PD index determination. Please refer to Table 1 for the details of each strain.

Table 1. Activities of plazomicin and comparator antibiotics against the study bacteria (Adapted from Table 8.1.1 in report of Study UFL-2016-001)

		Mode MIC (µg/mL)					
Strain Code	Resistance Phenotype	Plazomicin	Amikacin	Gentamicin	Tobramycin	Meropenem	Ceftazidime
AKPN001[1]	none	0.5	1	0.25	0.25	0.03	0.25
AECO1176	aac(6)-Ib[2]	1	32	1	>8	≤ 0.015	2
AECO1179[3]	aac(3)-IIa, aac6-Ib	2	32	>32	>8	0.03	>32
AKPN1171	Not reported	4	8	4	4	0.03	0.5
AKPN1169	KPC-3[4]	2	32	>32	>8	>32	>32
AEAE1034	Not reported	1	4	0.5	1	0.06	>32
AECO1173	aac(3)-IIa	0.25	1	>32	8	≤ 0.015	0.25
AECO1180	aac(3)-IIa	4	8	>32	>8	0.03	>32
AKPN1170	aac(6)-Ib, KPC-2	2	32	4	>8	8	>32

1. AKPN001 was used only in the dose-fractionation study for plazomicin.
2. Resistance phenotypes that begin with "aac" are aminoglycoside resistance mechanisms.
3. This strain was used in the dose-range study in the neutropenic murine thigh infection model. It was not used in the dose-range study in the neutropenic murine pneumonia model because this microbe self-cleared from the lungs of control animals.
4. KPC: *Klebsiella pneumoniae* carbapenemase.

To induce transient neutropenia (defined as neutrophil count <100 cells/mL of blood) each mouse was injected via the intraperitoneal route with 150 mg/kg cyclophosphamide 4 days prior to infection and 100 mg/kg cyclophosphamide 1 day prior to infection.

For the neutropenic murine thigh infection model, neutropenic mice were inoculated with one of nine strains in Table 1 at 10^5 CFU to each posterior thigh muscle. The Sponsor stated that this inoculum was shown to produce a progressive infection in neutropenic mouse thigh muscles in the in vivo growth curve experiments.

There were three additional vehicle control groups. One saline vehicle group was euthanized at the end of 26 hours after infection. Another vehicle group was euthanized 2-hours post infection, prior to dosing. The third one was euthanized at 0 hour, immediately after bacterial inoculation into the posterior thigh muscles.

Twenty-four hours after the start of dosing (26 h post infection), the posterior thigh muscles were aseptically collected from mice following euthanasia. The thigh tissues from a mouse were combined and weighed. The specimens were homogenized in 10 ml sterile saline. There were five specimens (mice) per group. Additional groups of animals were euthanized immediately after bacterial inoculation and 2 h post infection (just prior to the start of treatment) to validate

that the bacterial were replicating within the thigh muscle prior to treatment initiation and to determine the bacterial burden before therapy began.

Results

Please refer to Table 2 for the AUC/MIC ratios of plazomicin needed to achieve net bacterial stasis, 1-$\log_{10}$, and 2-$\log_{10}$ CFU/g reduction from baseline. The median values are 18 and 73, for stasis and 1-log CFU reduction, respectively. A 2-log CFU/g reduction was not achieved for any of the bacterial isolates in the neutropenic murine thigh infection model for plazomicin dosages as high as 225 mg/kg/day.

Table 2. Calculated doses (mg/kg/day) and AUC/MIC ratios of plazomicin needed to achieve bacterial stasis and 1-log and 2-log (CFU/g) reductions in the bacterial densities of 8 *Enterobacteriaceae* strains in a neutropenic murine thigh infection model (Adapted from Table 16.2.1 in the report of Study UFL-2016-001)

				Plazomicin Dose (mg/kg/day)			Plazomicin Exposure (AUC/MIC ratio)		
Strain	Plazomicin MIC (µg/mL)	Amikacin MIC (µg/mL)	Challenge Inoculum (CFU/thigh)	Stasis	1 Log (CFU/g) Reduction	2 Log (CFU/g) Reduction	Stasis	1 Log (CFU/g) Reduction	2 Log (CFU/g) Reduction
AECO1176	1	32	10^5	14.4	26.5	------[a]	33.0	60.7	------[a]
AECO1179	2	32	10^5	7.0	10.0	------	7.6	11.34	------[a]
AKPN1171	4	8	10^5	27.4	------[a]	------[a]	15.9	------[a]	------[a]
AKPN1169	2	32	10^5	18.0	135.0	------[a]	20.2	152.1	------[a]
AEAE1034	1	4	10^5	4.9	------[a]	------[a]	10.9	------[a]	------[a]
AECO1173	0.25	1	10^5	4.9	58.5	------[a]	43.5	518.3	------[a]
AECO1180	4	8	10^5	10.1	14.4	------[a]	5.7	8.1	------[a]
AKPN1170	2	32	10^5	20.8	75.0	------[a]	23.6	85.0	------[a]
a: ------ = end point not achieved with plazomicin 225 mg/kg/d.									

Reviewer's Comments

- *The median value of AUC/MIC ratios for net stasis determined in a neutropenic murine thigh model infected with eight Enterobacteriaceae strains was 18, ranging from 5.7 to 43.5. The 25th and 75th percentiles were 8.4 and 30.7, respectively.*
- *The median value of AUC/MIC ratios for 1-$\log_{10}$ CFU reduction determined in a neutropenic murine thigh model infected with six Enterobacteriaceae* strains was 73, *ranging from 8.1 to 518.3. The 25th and 75th percentiles were 10.5 and 243.7, respectively.*

Study UFL-2012-009

Neutropenic BALB/c mice were inoculated intramuscularly in both posterior thigh muscles with 10^5 CFU of one of nine *Enterobacteriaceae* isolates. These included eight CRE isolates consisting of seven *K. pneumoniae* isolates and one *E. coli* (AECO1133) isolate and one broadly susceptible *K. pneumoniae* control strain (AKPN001); plazomicin MIC values for these isolates ranged from 0.19 to 0.46 mg/L. Plazomicin treatment was initiated after two hours of inoculation. Same as Study UFL-2016-001, the treated animals were sacrificed 24 hours after the

initiation of therapy and the bacterial burden was determined as CFU per gram of thigh tissue. Separate cohorts of control animals were assessed for bacterial burden at baseline prior to (0 hours) and 24-hours after treatment initiation with vehicle. Antibiotic effect was calculated as the change in log10 CFU from baseline (0 hours).

Results

Refer to Table 3 for the AUC/MIC ratios for net stasis and 1-$\log_{10}$ CFU reduction.

Table 3. Summary of plasma plazomicin AUC/MIC ratios for *K. pneumoniae* or *E. coli* isolates based on data from a neutropenic murine-thigh infection model (Adapted from Table 3-1 in Report # ICPD 00211-2)

Isolate	Plasma AUC:MIC ratio targets	
	Net bacterial stasis	1-$\log_{10}$ CFU reduction
K. pneumoniae, AKPN001	26	48
K. pneumoniae, AKPN1116	17	135
K. pneumoniae, AKPN1117	30	89
K. pneumoniae, AKPN1118	34	95
K. pneumoniae, AKPN1077	52	158
K. pneumoniae, AKPN1113	62	263
K. pneumoniae, AKPN1106	6	29
K. pneumoniae, AKPN1114	65	131
E. coli, AECO1133	13	59
Median	30	95
Minimum	6	29
Maximum	65	263

Neutropenic Murine Pneumonia Model

Study UFL-2016-001

For the neutropenic murine pneumonia model, the anesthetized mice were inoculated in each nostril with 10^6 CFU of a bacterial isolate (seven of nine strains in Table 1). The bacterium was administered in volumes of 15 µL/nostril. However, as an inoculum of 10^6 CFU/nostril in the neutropenic murine pneumonia model was not sufficient to establish a progressive infection in the lungs for four of the bacterial strains, the inoculum was increased to 10^7 CFU/ nostril for these strains.

For each experiment, nine total daily (dose range from 1.37 to 225 mg/kg/day) doses of plazomicin were administered to different groups of female BALB/c mice as a humanized series

of 5 subcutaneous (SC) injections over a 20-hour period after the mice were infected with a bacterium.

Refer to Table 4 for the AUC/MIC ratios of plazomicin needed to achieve net bacterial stasis, 1-$\log_{10}$, and 2-$\log_{10}$ CFU/g. The median values are 1.6 and 73, for net stasis and 1-$\log_{10}$ CFU reduction, respectively.

Table 4. Calculated doses (mg/kg/day) and AUC/MIC Ratios of plazomicin needed to achieve net bacterial stasis and 1-log and 2-log (CFU/g) reductions in the bacterial densities of 7 *Enterobacteriaceae* strains in a neutropenic murine pneumonia model (Adapted from Table 16.2.2 in the report for Study UFL-2016-001)

				Plazomicin Dose (mg/kg/day)			Plazomicin Exposure (AUC/MIC ratio)		
Strain	Plazomicin MIC (µg/mL)	Amikacin MIC (µg/mL)	Challenge Inoculum (CFU/nare)	Stasis	1 Log (CFU/g) Reduction	2 Log (CFU/g) Reduction	Stasis	1 Log (CFU/g) Reduction	2 Log (CFU/g) Reduction
AECO1176	1	32	10^6	4.6	4.9	5.3	5.6	6.0	6.5
AKPN1171	4	8	10^6	4.4	31.0	------[a]	2.3	16.4	------[a]
AKPN1169	2	32	10^7	4.6	10.6	------[a]	2.7	6.3	------[a]
AEAE1034	1	4	10^7	1.0	4.9	35.1	1.2	5.6	40.3
AECO1173	0.25	1	10^7	0.1	0.6	4.9	0.9	2.9	23.7
AECO1180	4	8	10^7	5.0	6.26	8.1	1.4	1.7	2.2
AKPN1170	2	32	10^6	2.44	9.65	33.7	1.6	6.2	21.6
a: the end point was not achieved with plazomicin doses as high as 225 mg/kg/d.									

Reviewer's Comments:

- *The median value of AUC/MIC ratios for net stasis determined in a neutropenic murine pneumonia model infected with seven Enterobacteriaceae strains was 1.6, ranging from 0.9 to 5.6. The 25th and 75th percentiles were 1.2 and 2.7, respectively.*
- *The median value of AUC/MIC ratios for 1-$\log_{10}$ CFU reduction determined in a neutropenic murine pneumonia model infected with seven Enterobacteriaceae strains was 6, ranging from 1.7 to 16.4. The 25th and 75th percentiles were 2.9 and 6.3, respectively.*
- *The median value of AUC/MIC ratios for 2-$\log_{10}$ CFU reduction determined in a neutropenic murine pneumonia model infected with five Enterobacteriaceae strains was 21.6, ranging from 2.2 to 40.3. The 25th and 75th percentiles were 4.4 and 32, respectively.*

Studies ORI-2011-008, UFL-2012-003, and UFL-2011-004

The Applicant combined three neutropenic murine-pneumonia model study results (Studies ORI-2011-008, UFL-2012-003 and UFL-2011-004) to support the AUC/MIC ratios for net bacterial stasis, 1-log10 CFU reduction, and 2-log10 CFU reduction for bacterial pneumonia. Female Balb/c mice were infected intra-nasally with the *K. pneumoniae* isolates. Two hours after

infection, plazomicin dosing regimens were initiated. To determine the impact of drug therapy on the bacterial burden, treated animals were sacrificed 24 hours after the initiation of therapy and the bacterial burden was determined as CFU per gram of lung tissue. Separate cohorts of control animals were assessed for bacterial burden at baseline prior to (0 hours) and 24 hours after treatment initiation with vehicle. Antibiotic effect was calculated as the change in $\log_{10}$ CFU from baseline (0 hours). The MIC range for *K. pneumoniae* strains was 0.19 to 0.5 µg/mL.

Refer to Table 5 for the AUC/MIC ratios for net bacterial stasis, 1-$\log_{10}$ CFU reduction, and 2-$\log_{10}$ CFU reduction.

Table 5. Summary of plasma and ELF plazomicin AUC: MIC ratio targets for *K. pneumoniae* based on data from a neutropenic murine-pneumonia infection model (Adapted from Table 3-2 in Report # ICPD 00211-2)

K. pneumoniae isolates	Plasma AUC:MIC ratio targets			ELF AUC:MIC ratio targets		
	Net bacterial stasis	1-$\log_{10}$ CFU reduction	2-$\log_{10}$ CFU reduction	Net bacterial stasis	1-$\log_{10}$ CFU reduction	2-$\log_{10}$ CFU reduction
AKPN001	7.6	16.7	43.0	7.0	15.2	39.1
AKPN1025	3.6	9.5	25.5	3.3	8.6	23.2
AKPN1046	2.2	9.2	30.5	2.0	8.3	27.7
AKPN1066	2.2	4.7	15.3	2.0	4.3	13.9
AKPN1077	8.0	31.4	124	7.3	28.5	113
AKPN1087	2.6	4.6	10.6	2.4	4.2	9.6
AKPN1113	15.3	39.4	117	13.9	35.8	106
Median	3.6	9.5	30.5	3.3	8.6	27.7
Minimum	2.2	4.6	10.6	2.0	4.2	9.6
Maximum	15.3	39.4	124	13.9	35.8	113

Reviewer's Comments

- *It appears that the AUC/MIC ratios in the neutropenic murine pneumonia model were lower compared to the ones in the neutropenic murine thigh model. It may be due to the higher plazomicin penetration to the lung than to the muscle in mice. The plasma AUC/ ELF AUC in mice was reported to be 1.1 in Study ICPD 00211-2.*
- *The reviewer did not review individual animal study reports for early murine neutropenic pneumonia model but reviewed the summary of these studies (Studies ORI-2011-008, UFL-2012-003 and UFL-2011-004) in report of Study ICPD 00211-2.*
- *To guarantee the antibacterial activity of plazomicin in cUTI* (b) (4) *patients, it is reasonable to use the high AUC/MIC ratios derived from a neutropenic murine thigh*

infection model. In addition, the PK/PD targets for cUTI are usually determined by the neutropenic murine thigh infection model.

- *It appears that the PK/PD targets for net bacterial stasis and 1-log CFU reduction in study UFL-2012-009 using the same murine model were higher than the one derived from Study UFL-2016-001. It may be due to different strain combination (i.e. more E. coli strains (4/9) in Study UFL-2016-001 but only one E. coli (1/9) strain in Study UFL-2012-009 and more CRE strains in Study UFL-2012-009)*
- *The MIC range (0.25 – 4 mg/L) in Study UFL-2016-001 was broader compared to Study UFL-2012-009 (0.19 to 0.46 mg/L). The wider range of MIC covered MIC50 (0.5 mg/L) and MIC90 (1-2 mg/L) of plazomicin based on surveillance data. Additionally, Study UFL-2016-001 included more E. coli strains which are important for* (b) (4) *cUTI* (b) (4) *Therefore, it is more reasonable to use the results from Study UFL-2016-001 for PK/PD target determination if only one study can be selected. Studies UFL-2016-001 and UFL-2012-009 had the similar study design (same inoculation amount, sample collection time, and same mouse strain). Therefore, to avoid information loss the reviewer combined results of two neutropenic murine thigh infection model studies together. Refer to Table 6 for the combined results.*
- *PTA analyses were conducted using the median value and 75th percentile of AUC/MIC ratios for net bacterial stasis as well as the median value of AUC/MIC ratios for1 log_{10} CFU reduction. Refer to Section 3.3.2 for details.*

Table 6. *Summary of Plasma Plazomicin AUC/ MIC ratios from a Neutropenic Murine-Thigh Infection Model*

strains	***Phenotype***	***Plazomicin MIC (mg/L)***	***AUC: MIC Ratio for Net Stasis***	***AUC: MIC Ratio for 1 log_{10} CFU Reduction***
AKPN001	*ATCC 43816 susceptible*	*0.29*	*26*	*48*
AKPN1116	*KPC-3*	*0.21*	*17*	*135*
AKPN1117	*KPC-2, SHV-12*	*0.29*	*30*	*89*
AKPN1118	*KPC-2*	*0.19*	*34*	*95*
AKPN1077	*KPC*	*0.19*	*52*	*158*
AKPN1113	*(methylase (methylase negative), CTX-M15, SHV-11, OXA-1*	*0.19*	*62*	*263*
AKPN1106	*KPC-2*	*0.29*	*6*	*29*
AKPN1114	*KPC*	*0.38*	*65*	*131*
AECO1133	*KPC-2 TEM-1*	*0.46*	*13*	*59*
AECO1176	*aac (6)-lb*	*1*	*33*	*60.7*
AECO1179	*aac (3)-lla, ac6-lb*	*2*	*7.6*	*11.34*
AKPN1171	*not reported*	*4*	*15.9*	
AKPN1169	*KPC-3*	*2*	*20.2*	*152.1*
AEAE1034	*not reported*	*1*	*10.9*	
AECO1173	*aac (3)-lla*	*0.25*	*43.5*	*518.3*
AECO1180	*aac (3)-lla*	*4*	*5.7*	*8.1*
AKPN1170	*aac (6)-lb, KPC-2*	*2*	*23.6*	*85*
MEDIAN			*23.6*	*89*
75% Quartile			*38.8*	*152.1*
25% Quartile			*12*	*48*

4.5.2 In Vitro Study Reports

A total of nine *in vitro* studies were conducted to address the metabolism characterization, transporter characterization, distribution, and drug-drug interaction (DDI) of plazomicin in the drug development program. Refer to Table 1 below for the list of *in vitro* studies included and reviewed in this submission.

Table 1. In Vitro Studies Included and Reviewed in the Plazomicin Development Program

In Vitro Studies	Comments
ACH-011008-C001490-PS	To evaluate plazomicin plasma stability
A16091-1490-AD	To evaluate plazomicin stability in human liver microsomes
A16092-1490-AD	To evaluate plazomicin stability in human hepatocytes
A15014-1490-AD	To evaluate plazomicin as an inhibitor and a substrate of human transporters
A17022-1490-ETI	To evaluate plazomicin as an inhibitor of human BSEP and OCT1
A16098-1490-AD	To evaluate protein binding of plazomicin in plasma
A16093-1490-AD	To evaluate red blood cell/plasma partitioning of plazomicin in fresh whole blood
A15015-1490-AD	To evaluate the ability of plazomicin to inhibit the major CYP enzymes in human liver microsomes
A15016-1490-AD	To evaluate the ability of plazomicin to induce the major CYP enzymes in primary cultures of cryopreserved human hepatocytes

Individual Study Review

Study Title: Plasma Stability of C001490 (Plazomicin) (Study ACH-011008-C001490-PS)

This study was conducted to determine the stability of plazomicin (ACHN-490) in plasma. Plazomicin (50 µg/mL) was incubated in mouse, rat, rabbit, dog, monkey, and human plasma at 37ºC for 0, 0.25, 0.5, 1, and 2 h. Chloroprocaine was used as a positive control. The amount of plazomicin remaining in plasma after 0, 0.25, 0.5, 1, and 2 h incubation at 37ºC are shown in Figure 1 and Table 2. The Sponsor stated that chloroprocaine, the positive control, exhibited marked instability in mouse, rabbit, monkey, and human plasma. Chloroprocaine is relatively stable (>70%) in dog and rat plasma. However, no detailed results of positive control were included in the study report.

Figure 1. Stability of Plazomicin (ACHN-490) in Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma Expressed as Percentage Remaining in Plasma Relative to the Initial Concentration after Incubation at 37ºC over 2 hours (Adapted from Figure 1 in the study report)

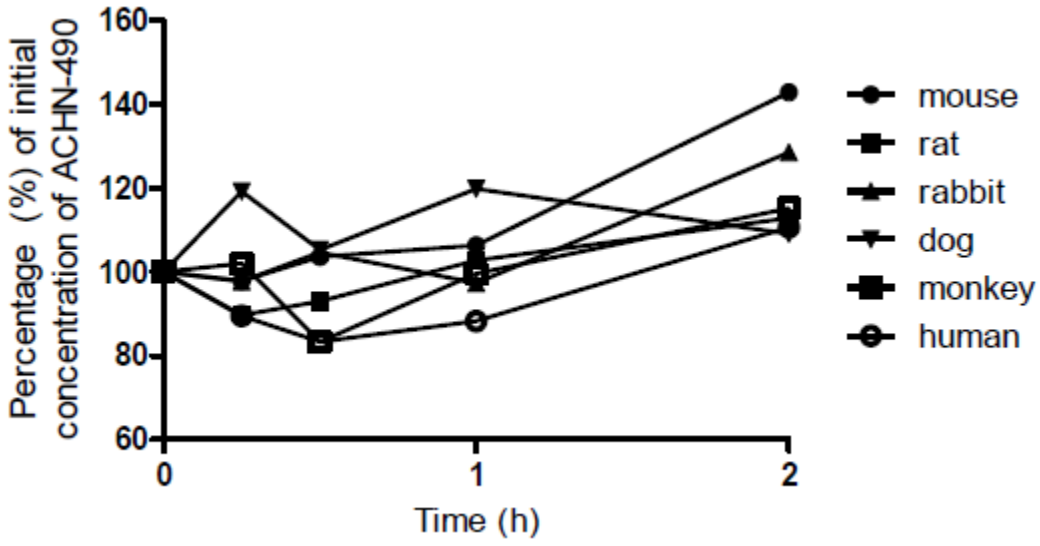


Table 2. Percentage (%) of Plazomicin Remaining in Plasma Relative to the Initial Concentration after Incubation at 37ºC over 2 hours (Adapted from Table 1 in the study report)

Species	0 hour	0.25 hour	0.5 hour	1 hour	2 hour
Mouse	100	97.9	104	106	143
Rat	100	89.7	93.0	103	113
Rabbit	100	97.8	105	97.4	129
Dog	100	119	105	120	109
Monkey	100	102	83.4	99.6	115
Human	100	89.5	83.4	88.3	111

Reviewer's Comments:

- *It was observed that the concentration of plazomicin at 2 hr time point was higher than 0 and 1 hr. It may be due to the assay variability of the internal standard (IS) for the LC-MS/MS at 2 h relative to the one at other time points. According to LC-MS/MS peak area response in Appendix 8.1 in this report, the IS peak area at 2 h is approximately 20% lower compared to the IS response at other time points. Therefore, the concentration of analyte vs. concentration of IS determined by the ratio of peak area of analyte vs. IS is expected to increase about 20%.*

- *The percentage of plazomicin remaining in plasma relative to the initial concentration after 2 hours of incubation in human plasma was above 80% when calculated without internal standard.*
- *Per the draft label,* (b) (4) *. The concentration used in this study was 50 µg/mL, which is acceptable.*
- *Plazomicin appears to be stable in human plasma up to 2 hours at 37 ºC.*

Study Title: Assessment of Metabolic Stability of ACHN-490 in Liver Microsomes (Study A16091-1490-AD)

The study was conducted to assess the metabolic stability of plazomicin (ACHN-490) in human, mouse, rat, dog, rabbit, and cynomolgus monkey liver microsomes. Plazomicin was incubated at 50 µg/mL in duplicates in 1 mg/mL of liver microsomes for 0, 15, 30, and 60 minutes at 37°C. Verapamil was included as a positive control to verify assay performance. It was tested at 1 µM. Refer to Table 3 for the study results. There were duplicated samples for each concentration.

Table 3. Percent of Plazomicin (ACHN-490) and Positive Control Remaining in the Liver Microsomes of Human, Mouse, Rat, Dog, Rabbit, and Cynomolgus Monkey (Adapted from Table 2 in the study report)

Species	Compound	[Compound]	0 min		30 min		60 min		120 min	
			%Remaining	Mean	%Remaining	Mean	%Remaining	Mean	%Remaining	Mean
Human	Verapamil	1 µM	101.3	100.0	21.5	22.3	5.2	5.3	0.3	0.4
			98.7		23.2		5.4		0.4	
	ACHN-490	50 µg/mL	97.3	100.0	87.4	90.3	80.0	80.1	86.7	85.2
			102.7		93.2		80.2		83.6	
Mouse	Verapamil	1 µM	102.7	100.0	3.1	3.1	0.3	0.4	0.1	0.1
			97.3		3.2		0.4		0.1	
	ACHN-490	50 µg/mL	102.8	100.0	90.5	92.7	86.9	86.4	87.3	82.3
			97.2		94.9		85.9		77.4	
Rat	Verapamil	1 µM	102.9	100.0	4.3	4.5	0.6	0.6	0.1	0.1
			97.1		4.7		0.6		0.1	
	ACHN-490	50 µg/mL	102.4	100.0	81.3	84.7	76.1	78.9	87.8	82.9
			97.6		88.2		81.8		78.1	
Dog	Verapamil	1 µM	98.2	100.0	34.9	35.3	11.6	12.0	1.0	0.9
			101.8		35.6		12.4		0.9	
	ACHN-490	50 µg/mL	99.6	100.0	95.9	96.2	91.3	94.8	85.2	87.8
			100.4		96.4		98.3		90.3	
Rabbit	Verapamil	1 µM	100.5	100.0	22.2	23.1	2.1	2.2	0.2	0.1
			99.5		24.1		2.4		0.1	
	ACHN-490	50 µg/mL	105.6	100.0	79.3	88.7	81.6	83.2	92.0	89.1
			94.4		98.1		84.8		86.2	
Cynomolgus Monkey	Verapamil	1 µM	102.8	100.0	0.6	0.6	0.1	0.1	0.0	0.0
			97.2		0.6		0.1		0.0	
	ACHN-490	50 µg/mL	94.7	100.0	92.6	93.1	94.7	93.1	86.2	86.8
			105.3		93.7		91.5		87.5	

Reviewer's Comments:

- *It seems that plazomicin was stable (>78.9% remaining) in liver microsomes incubated for up to 2 h at 37°C.*

Study Title: Assessment of Metabolic Stability of ACHN-490 in Hepatocytes (Study A16092-1490-AD)

This study assessed the metabolic stability of plazomicin (ACHN-490) in human, mouse, rat, dog, rabbit, and cynomolgus monkey hepatocytes. Plazomicin was incubated at 5 µg/mL or 100 µg/mL in duplicate in 1 million cells/mL of hepatocyte suspension for up to 2 hr at 37°C in a tissue culture incubator in the presence of 5% CO_2. Midazolam was included as a positive control to verify assay performance. Refer to Table 4 for the study results. There were duplicated samples for each concentration.

Table 4. Percent of Plazomicin (ACHN-490) and Positive Control Remaining in the Hepatocytes of Human, Mouse, Rat, Dog, Rabbit, and Cynomolgus Monkey (Adapted from Table 1 in the study report)

Species	Compound	[Compound]	0 min		30 min		60 min		120 min	
			%Remaining	Mean	%Remaining	Mean	%Remaining	Mean	%Remaining	Mean
Human	Midazolam	1 µM	100.5	100.0	58.7	63.5	30.2	30.2	8.5	8.6
			99.5		68.4		30.1		8.8	
	ACHN-490	5 µg/mL	108.5	100.0	86.1	89.4	90.8	90.1	94.7	88.4
			91.5		92.7		89.4		82.0	
	ACHN-490	100 µg/mL	97.0	100.0	92.2	91.4	105.8	103.7	109.7	101.1
			103.0		90.6		101.5		92.4	
Mouse	Midazolam	1 µM	101.6	100.0	86.0	74.8	71.9	72.8	54.8	58.7
			98.4		63.6		73.7		62.6	
	ACHN-490	5 µg/mL	96.2	100.0	93.2	95.9	104.2	107.0	97.4	99.0
			103.8		98.6		109.9		100.5	
	ACHN-490	100 µg/mL	96.6	100.0	100.2	101.9	102.5	105.9	97.6	102.2
			103.4		103.7		109.2		106.7	
Rat	Midazolam	1 µM	100.4	100.0	33.5	33.8	17.1	20.7	21.6	19.9
			99.6		34.0		24.2		18.3	
	ACHN-490	5 µg/mL	101.9	100.0	98.7	104.4	95.6	99.0	109.4	107.8
			98.1		110.0		102.4		106.2	
	ACHN-490	100 µg/mL	97.1	100.0	98.8	98.8	105.0	105.8	99.6	101.0
			102.9		98.7		106.6		102.5	
Dog	Midazolam	1 µM	101.4	100.0	41.1	40.2	23.3	22.0	9.7	11.0
			98.6		39.3		20.7		12.4	
	ACHN-490	5 µg/mL	98.5	100.0	106.1	97.6	110.7	107.1	92.8	93.8
			101.5		89.1		103.5		94.9	
	ACHN-490	100 µg/mL	103.1	100.0	109.2	104.9	115.1	102.4	107.1	102.6
			96.9		100.6		89.6		98.2	
Rabbit	Midazolam	1 µM	99.4	100.0	36.3	36.7	12.1	13.9	4.6	5.1
			100.6		37.2		15.7		5.6	
	ACHN-490	5 µg/mL	94.9	100.0	100.7	97.5	114.4	110.3	93.7	100.7
			105.1		94.3		106.2		107.6	
	ACHN-490	100 µg/mL	101.2	100.0	96.7	92.8	116.8	110.6	101.6	108.1
			98.8		89.0		104.4		114.6	
Cynomolgus Monkey	Midazolam	1 µM	100.0	100.0	33.4	38.3	16.7	16.3	5.2	5.1
			100.0		43.2		15.9		5.1	
	ACHN-490	5 µg/mL	101.2	100.0	98.2	101.3	108.2	110.8	106.0	103.6
			98.8		104.4		113.4		101.2	
	ACHN-490	100 µg/mL	92.5	100.0	93.8	95.6	102.0	100.5	93.1	93.5
			107.5		97.4		98.9		93.8	

Reviewer's Comments:

- *It seems that plazomicin was stable in human (>80% remaining) hepatocytes incubated for up to 2 h at 37°C.*
- *The results of this study are consistent with the findings in Study A16091-1490-AD.*

Study Title: In Vitro Evaluation of Plazomicin as an Inhibitor of Human P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K Transporters (Study A15014-1490-AD)

This study was designed to evaluate plazomicin as an inhibitor and/or a substrate of human transporters.

Evaluation of plazomicin as an inhibitor

Methods:

- P-gp and BCRP: The ability of plazomicin at tested concentrations (17.8, 59.3, 178, 593, 1780 and 5930 μg/mL) to inhibit human ABC transporters (namely, P-gp and BCRP) was evaluated by measuring the bidirectional permeability of a probe substrate (digoxin [P-gp] or prazosin [BCRP]) across a monolayer of Caco-2 and MDCKII-BCRP cells in the presence of plazomicin.
- MRP2: The ability of plazomicin at tested concentrations (5.93, 17.8, 59.3, 178, 593, 1780 and 5930 μg/mL) to inhibit human MRP2 was evaluated by measuring the accumulation of a probe substrate (estradiol-17β-glucuronide) in vesicles with inserted MRP2 transporter proteins in the presence of plazomicin.
- OATP1B1, OATP1B3, OAT1, OAT3 and OCT2: The ability of plazomicin at tested concentrations (5.93, 17.8, 59.3, 178, 593, 1780 and 5930 μg/mL) to inhibit human transporters including OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 was evaluated by measuring the accumulation of probe substrates (estradiol-17β-glucuronide [OATP1B1 and OATP1B3], p-aminohippurate [OAT1], estrone-3-sulfate [OAT3] and metformin [OCT2]) in transporter-expressing and control HEK293 cells in the presence of plazomicin.
- MATE1 and MATE2-K: The ability of plazomicin at tested concentrations (5.93, 17.8, 59.3, 178, 593, 1780 and 5930 μg/mL) to inhibit human MATE1 and MATE2-K was evaluated by measuring the accumulation of probe substrate (metformin) into transporter-expressing and control HEK293 cells.
- Positive control: Known inhibitors were included as positive controls in all experiments.

Results

- **P-gp and BCRP inhibition: Bidirectional permeability of probe substrate across Caco-2 cells and MDCKII-BCRP and control cells in the presence of plazomicin**
    - P-gp: in the presence of plazomicin (17.8 to 5930 μg/mL) the net flux of digoxin (10 μM) was not reduced; accordingly, an IC50 was not calculated. The positive control inhibitors valspodar (1 μM) and verapamil (60 μM) reduced the net flux of digoxin from 16.0 to 1.00 and 2.26 (94 and 86% inhibition), respectively, indicating the test system functioned as expected.

- BCRP: in the presence of plazomicin (17.8 to 5930 μg/mL) the corrected efflux ratio of prazosin (1 μM) was not reduced; accordingly, an IC50 was not calculated. The positive control inhibitor Ko143 (1 μM) reduced the corrected efflux ratio of prazosin from 6.44 to 0.987 (complete inhibition) indicating the test system functioned as expected.

- **MRP2 inhibition: Accumulation of estradiol-17β-glucuronide by MRP2-expressing vesicles in the presence of plazomicin**
  - The ATP-dependent accumulation of [^{3}H]-estradiol-17β-glucuronide in MRP2 expressing vesicles was not inhibited more than 15% by plazomicin (5.93 to 5930 μg/mL); accordingly, an IC50 was not calculated. The results suggest that plazomicin is not an inhibitor of MRP2. In the presence of the positive control inhibitor benzbromarone (100 μM), the ATP-dependent uptake of estradiol-17β-glucuronide was reduced from 8740 to 596 pmol/mg protein (93% inhibition), indicating the test system functioned as expected.

- **OATP, OAT and OCT inhibition:**
  - OATP1B1: in the presence of plazomicin (5.93 to 5930 μg/mL) the transporter-dependent uptake rate of [^{3}H]-estradiol-17β-glucuronide into OATP1B1-expressing cells was not reduced more than 9%; accordingly, an IC50 was not calculated. In the presence of the positive control inhibitors rifampin (10 μM) and cyclosporine (1 μM) the transporter-dependent uptake rate was reduced from 4.44 to 0.231 and 0.114 pmol/mg/min, respectively (95% and 97% inhibition, respectively), indicating the test system functioned as expected.
  - OATP1B3: in the presence of plazomicin (5.93 to 5930 μg/mL) the transporter-dependent uptake rate of [^{3}H]-estradiol-17β-glucuronide into OATP1B3-expressing cells was not reduced; accordingly, an IC50 was not calculated. In the presence of the positive control inhibitors rifampin (10 μM) and cyclosporine (1 μM) the transporter-dependent uptake rate was reduced from 0.407 to -0.00330 and -0.00132 pmol/mg/min, respectively (complete inhibition), indicating the test system functioned as expected.
  - OAT1: at lower concentrations (5.93 to 59.3 μg/mL) plazomicin did not inhibit the uptake of [^{3}H]-p-aminohippurate. In the presence of higher concentrations of plazomicin (178 to 5930 μg/mL) the transporter-dependent uptake rate of p-aminohippurate into OAT1-expressing cells was reduced in a concentration-dependent manner from 46.3 pmol/mg/min at 0 μM to 31.5 pmol/mg/min at the highest concentration evaluated (32% inhibition); accordingly, an IC50 was not calculated. In the presence of the positive control inhibitors probenecid (100 μM) and novobiocin (300 μM) the transporter-dependent uptake rate was reduced from 46.3 to 4.15 and 0.805 pmol/mg/min, respectively (91 and 98% inhibition,

respectively), indicating the test system functioned as expected. Refer to Table 5 for detail.

Table 5. OAT1 inhibition: Accumulation of p-aminohippurate into OAT1 cells in the presence of plazomicin, probenecid and novobiocin (Adapted from Table 8 of the study report)

Substrate	Inhibitor	[Inhibitor]	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OAT1			
[^{3}H]-*p*-Aminohippurate (1 µM)	Solvent control	0	2.25 ± 0.15	48.5 ± 2.6	46.3	100	IC_{50}: > 5930 µg/mL
	Plazomicin (µg/mL)	5.93	1.73 ± 0.08	50.4 ± 3.3	48.7	105	
		17.8	1.75 ± 0.14	50.9 ± 2.3	49.1	106	
		59.3	2.21 ± 0.36	48.6 ± 3.3	46.4	100	
		178	0.778 ± 0.050	40.5 ± 1.7	39.7	85.8	
		593	1.13 ± 0.35	39.9 ± 2.4	38.8	83.7	
		1780	1.47 (n = 2)	36.0 ± 1.4	34.6	74.7	
		5930	1.56 ± 0.52	33.1 ± 2.0	31.5	68.1	
	Probenecid (µM)	100	0.608 ± 0.259	4.76 ± 1.16	4.15	9.0	NA
	Novobiocin (µM)	300	0.343 (n = 2)	1.15 ± 0.54	0.805	1.7	

n Number of replicates
NA Not applicable
Values are triplicate determinations rounded to three significant figures with standard deviations rounded to the same degree of accuracy.
Percentages are rounded to one decimal place except percentages ≥ 100, which are rounded to the nearest whole number.
A Dixon Q Test was used to determine statistical outlying data points for the n = 2 number of replicates, where reported.

- OAT3: in the presence of plazomicin (5.93 to 5930 µg/mL) the transporter-dependent uptake rate of [^{3}H]-estrone-3-sulfate into OAT3-expressing cells was not reduced more than 8%; accordingly, an IC50 was not calculated. In the presence of the positive control inhibitors probenecid (100 µM) and ibuprofen (100 µM) the transporter-dependent uptake rate was reduced from 1.35 to 0.104 and 0.0685 pmol/mg/min, respectively (92 and 95% inhibition, respectively), indicating the test system functioned as expected.
- OCT2: at lower concentrations (5.93 to 178 µg/mL) plazomicin did not inhibit the uptake of metformin. In the presence of plazomicin (593 to 5930 µg/mL) the transporter-dependent uptake rate of [^{14}C]-metformin into OCT2-expressing cells was reduced from 77.1 at 0 µM to 38.1 pmol/mg/min at the highest concentration evaluated (51% inhibition). The calculated IC50 was 5120 µg/mL. In the presence of the positive control inhibitors quinidine (300 µM) and cimetidine (1000 µM) the transporter-dependent uptake rate was reduced from 77.1 to 5.46 and 8.85 pmol/mg/min, respectively (93 and 89% inhibition, respectively), indicating the test system functioned as expected. Refer to Table 6 for details. Per FDA DDI Draft Guidance 2017 [1], the investigational drug has the potential to inhibit OCT2 transporters in vivo if the Imax, u/IC50 value is ≥0.1. For plazomicin, Imax,u / IC50 is approximately 0.007 for patients with cUTI (b) (4) Therefore, based on in vitro study results, plazomicin is not likely to inhibit OCT2. Consequentially, the increase of creatinine may not attribute to the inhibition of OCT2 by plazomicin.

Table 6. OCT2 inhibition: Accumulation of metformin into OCT2 cells in the presence of plazomicin, quinidine and cimetidine (Adapted from Table 10 in the study report)

Substrate	Inhibitor	[Inhibitor]	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OCT2			
[^{14}C]-Metformin (10 µM)	Solvent control	0	6.74 ± 1.55	161 ± 11	77.1	100	IC_{50}: 5120 µg/mL Slope: 0.904 Min: 0% Max: 101%
	Plazomicin (µg/mL)	5.93	13.4 (n = 1)	169 ± 12	77.7	101	
		17.8	7.38 ± 2.54	157 ± 8	74.7	96.9	
		59.3	5.58 (n = 2)	155 ± 7	74.6	96.8	
		178	5.05 ± 1.50	161 ± 11	78.1	101	
		593	5.56 ± 0.55	146 ± 12	70.4	91.3	
		1780	4.51 ± 1.10	108 ± 8	51.8	67.2	
		5930	4.21 (n = 2)	80.3 ± 3.4	38.1	49.4	
	Quinidine (µM)	300	2.32 ± 0.16	13.2 ± 1.5	5.46	7.1	NA
	Cimetidine (µM)	1000	2.46 ± 0.55	20.2 ± 1.2	8.85	11.5	

n Number of replicates
NA Not applicable
Values are triplicate determinations rounded to three significant figures with standard deviations rounded to the same degree of accuracy.
Percentages are rounded to one decimal place except percentages ≥ 100, which are rounded to the nearest whole number.
A Dixon Q Test was used to determine statistical outlying data points for the n = 2 number of replicates, where reported.
Two control values for plazomicin (5.93 µg/mL) were excluded from data processing due to analyst error, resulting in an n =1 of replicates.

- **MATE1 and MATE2-K inhibition:**
  - MATE1: in the presence of plazomicin (5.93 to 5930 µg/mL) the transporter-dependent rate of the background corrected cleared volume of [^{14}C]-metformin (10 µM) was reduced from 4.14 to 0.920 µL/mg/min protein (78% inhibition). The calculated IC50 was 1300 µg/mL. In the presence of the positive control inhibitors cimetidine (10 µM) and pyrimethamine (0.3 µM) the transporter-dependent rate of the background corrected cleared volume was reduced from 4.14 to 0.708 and 0.394 µL/mg protein, respectively (83 and 90% inhibition, respectively), indicating the test system functioned as expected. Refer to Table 7 for details.
  - MATE2-K: in the presence of plazomicin (5.93 to 5930 µg/mL) the transporter-dependent rate of the background corrected cleared volume of [^{14}C]-metformin (10 µM) was reduced from 2.75 to 0.175 µL/mg protein (94% inhibition). The calculated IC50 was 338 µg/mL. In the presence of the positive control inhibitors, cimetidine (100 µM) and pyrimethamine (0.3 µM), the transporter-dependent rate of the background corrected cleared volume of metformin was reduced from 2.75 to 0.306 and 0.181 µL/mg protein, respectively (89 and 93% inhibition, respectively), indicating the test system functioned as expected. Refer to Table 8 for details.

Table 7. MATE1 inhibition: Accumulation of metformin into MATE1 cells in the presence of plazomicin, cimetidine and pyrimethamine (Adapted from Table 11 in the study report)

Probe substrate	Inhibitor	[Inhibitor]	Cleared volume (µL/mg protein)		Background corrected cleared volume (mg/min)	Percent of control (%)	IC_{60} parameters
			Control	MATE1			
[^{14}C]-Metformin (10 µM)	Solvent control	0	1.08 ± 0.30	21.8 ± 1.1	4.14	100	IC_{50}: 1300 µg/mL
	Plazomicin (µg/mL)	5.93	0.985 ± 0.173	26.0 ± 1.1	5.00	121	
		17.8	1.50 ± 0.35	25.3 ± 0.9	4.76	115	
		59.3	0.785 ± 0.033	21.8 ± 0.8	4.20	101	
		178	0.698 ± 0.157	18.3 ± 0.9	3.52	85.0	
		593	0.751 ± 0.121	17.8 ± 1.4	3.41	82.3	
		1780	1.16 ± 0.23	10.5 ± 0.5	1.87	45.1	
		5930	0.798 ± 0.083	5.40 ± 0.43	0.920	22.2	
	Cimetidine (µM)	10	0.471 ± 0.157	4.01 ± 0.30	0.708	17.1	NA
	Pyrimethamine (µM)	0.3	0.641 ± 0.222	2.61 ± 0.45	0.394	9.5	

NA Not applicable
Values are triplicate determinations rounded to three significant figures with standard deviations rounded to the same degree of accuracy.
Percentages are rounded to one decimal place except percentages ≥ 100, which are rounded to the nearest whole number.

Table 8. MATE2-K inhibition: Accumulation of metformin into MATE2-K cells in the presence of plazomicin, cimetidine and pyrimethamine (Adapted from Table 12 in the study report)

Probe substrate	Inhibitor	[Inhibitor]	Cleared volume (µL/mg protein)		Background corrected cleared volume (mg/min)	Percent of control (%)	IC_{60} parameters
			Control	MATE2-K			
[^{14}C]-Metformin (10 µM)	Solvent control	0	1.07 ± 0.06	14.8 ± 1.9	2.75	100	IC_{50}: 338 µg/mL
	Plazomicin (µg/mL)	5.93	1.00 ± 0.08	18.0 ± 1.5	3.40	124	
		17.8	0.922 ± 0.048	17.8 ± 0.5	3.38	123	
		59.3	0.957 ± 0.113	16.3 ± 1.2	3.07	112	
		178	1.12 ± 0.02	12.1 ± 0.9	2.20	80.0	
		593	1.07 ± 0.10	6.97 ± 0.73	1.18	43.0	
		1780	1.25 ± 0.06	4.02 ± 0.14	0.554	20.2	
		5930	0.703 ± 0.042	1.58 ± 0.09	0.175	6.4	
	Cimetidine (µM)	100	0.312 ± 0.024	1.84 ± 0.08	0.306	11.1	NA
	Pyrimethamine (µM)	0.3	0.316 ± 0.041	1.22 ± 0.15	0.181	6.6	

NA Not applicable
Values are triplicate determinations rounded to three significant figures with standard deviations rounded to the same degree of accuracy.
Percentages are rounded to one decimal place except percentages ≥ 100, which are rounded to the nearest whole number.

Evaluation of plazomicin as a substrate

Methods

- P-gp and BCRP: To determine if plazomicin at tested concentrations (0.593, 1.78, 5.93 and 17.8 µg/mL; equivalent to 1, 3, 10, and 30 µM) is a substrate of human ABC transporters (namely, P-gp and BCRP), the bidirectional permeability of plazomicin across MDCKII-MDR1 and MDCKII-BCRP cells was measured.
- Known substrates and inhibitors were included as positive controls in all experiments.

Results

- P-gp and BCRP substrate determination: Bidirectional permeability of plazomicin across MDCKII-MDR1 and control cells and MDCKII-BCRP and control cells
    - P-gp: the efflux ratio of plazomicin (0.593, 1.78, 5.93 and 17.8 µg/mL, equivalent to 1, 3, 10, and 30 µM) was below two in the presence and absence of the

inhibitor valspodar (10 μM). The results suggest that plazomicin is not a substrate of P-gp. The corrected efflux ratio of the positive control digoxin (10 μM) was reduced by the inhibitor, valspodar, from 27.4 to 1.35 (99% inhibition), indicating the test functioned as expected.

- BCRP: the efflux ratio of plazomicin (0.593, 1.78, 5.93 and 17.8 μg/mL, equivalent to 1, 3, 10, and 30 μM) was below two in the absence and presence of the inhibitor Ko143 (1 μM). The results suggest that plazomicin is not a substrate of BCRP. The corrected efflux ratio of the positive control prazosin (1 μM) was reduced by the inhibitor Ko143 from 6.22 to 0.908 (complete inhibition), indicating the test system functioned as expected.

Reviewer's Comments:

- *The methods used to evaluate whether plazomicin is an inhibitor and/or substrate of these transporters are acceptable*[8]*.*
- *Study results indicate that plazomicin is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1 or OAT3.*
- *Study results indicate that plazomicin inhibited OCT2, MATE1 and MATE2-K with calculated IC50 values of 5120, 1300 and 338 μg/mL, respectively.*
- *Per FDA DDI Draft Guidance 2017* [1]*, the investigational drug has the potential to inhibit MATEs in vivo if the* $I_{max,u}/IC_{50}$ *value is ≥0.02. Per MATE1,* $I_{max,u} / IC_{50}$ *is 0.028 for patients with cUTI* (b) (4) *Per MATE2-K,* $I_{max,u} / IC_{50}$ *is 0.11 for patients with cUTI* (b) (4) *Metformin is a substrate for both MATE1 and MATE2-K. The Sponsor conducted an in vivo DDI study by co-administering metformin and plazomicin. The study results indicate that plazomicin is not a MATE transporter inhibitor in vivo.*
- *Because OCT1 is responsible for metformin uptake in the liver, the Division suggested that the Sponsor investigate whether plazomicin is an inhibitor of OCT1in the final meeting minutes for the Type B meeting held on April 14, 2017. Following the Agency's suggestion, the Sponsor conducted an in vitro study whose results indicated that plazomicin is unlikely to inhibit OCT1 at clinically relevant concentrations. Refer to the individual study review for in vitro Study A17022-1490-ETI for detail.*
- *Study results indicate that plazomicin was not a substrate of P-gp or BCRP transporters at the concentration up to 17.8 μg/mL which is equivalent to 22.3 μg/mL in vivo with 20% protein binding. Per the draft label,* (b) (4) *It seems that plazomicin concentrations*

[8] FDA Draft Guidance for Industry In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies 2017
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf

did not cover the range of clinically relevant concentrations. However, the Clinical Pharmacology reviewer thinks the results of this study are acceptable for the Labeling statement "In vitro study results indicate plazomicin is not a substrate of P-gp or BCRP transporters (b) (4) *and no further in vivo DDI study is needed based on the rationale provided below.*

- *P-gp and BCRP are expressed in various tissues including the gastrointestinal tract, liver, kidney, and brain.*
- *Because plazomicin is administered as an IV infusion, the effects of P-gp and BCRP on absorption are not important.*
- *Because plazomicin is mainly eliminated by the kidney as unchanged drug, the potential impact of P-gp and BCRP on plazomicin in the liver is neglectable.*
- *Plazomicin, an aminoglycoside antibacterial drug, usually has low CNS penetration.*
- *Based on the Sponsor's submission on 9/6/2017 under IND 102563 (SDN 185), active renal secretion is not significant for plazomicin (Table 8). Therefore, P-gp and BCRP are unlikely to be involved in plazomicin renal excretion.*

- *Per the FDA draft DDI Guidance[1], if the investigational drug's ADME data suggest that active renal secretion is significant for a drug (i.e. active secretion of the parent drug by the kidney is ≥ 25% of the total clearance), the Sponsor should evaluate the drug in vitro to determine whether it is a substrate of OAT1/2, OAT2 and MATE1 and MATE2-K. Based on the Sponsor's submission on 9/6/2017 under IND 102563 (SDN 185), active renal secretion is not significant for plazomicin. Therefore, no in vitro study was conducted to investigate whether plazomicin is a substrate to OAT1/2, OAT2, or MATE1 or MATE2-K. Refer to Table 9 regarding the approach for the assessment of active renal secretion. The Clinical Pharmacology reviewer agrees with the Sponsor's approach and conclusion.*

Table 9. *Assessment of Active Renal Secretion of Plazomicin (Adapted from Table 1 from the Request for Comment: Drug-Drug Interactions 9-6-2017)*

	Criteria	Equation	Conclusion
FDA (2012)	% active renal secretion is estimated from (CL_R - f_u x GFR) / CL_T	(CL_R - f_u x GFR) / CL_T = (68.0-0.804 x 90)/76.2 = negative	Renal active secretion is < 25%; therefore, renal active secretion is not major
EMA (2013)	The importance of renal secretion is estimated by comparing total renal clearance to the renal filtration clearance	GFR x f_u = 90 x 0.804 =72.4	CL_R would need to be > 72.4 mL/min for renal secretion to be significant; therefore, renal secretion is not important
ITC (2010)	Secretory clearance is an important route of NME elimination if CL_R > 1.5 x f_u x GFR	CL_R > 1.5 x f_u x GFR --> 68.0 > 1.5 x 0.804 x 90 False	Secretory clearance is not an important route of elimination

Abbreviations: CL_R: renal clearance (4.08 L/h or 68.0 mL/min); CL_T: total systemic clearance (4.57 L/h or 76.2 mL/min) from population PK report (Institute for Clinical Pharmacodynamics [ICPD] Study ICPD 00462); fu: fraction unbound (0.804) from Study A16098-1490-AD; GFR: glomerular filtration rate (assumed to be 90 mL/min)

- *Since Plazomicin is mainly eliminated by the kidneys, the Clinical Pharmacology reviewer agrees with the Sponsor that it is not necessary to determine whether plazomicin is a substrate of OATP1B1 or OATP1B3.*

Study Title: In Vitro Evaluation of Plazomicin as an Inhibitor of Human BSEP and OCT1 (Study A17022-1490-ETI)

The objective of this study was to evaluate plazomicin as an inhibitor of the human ABC transporter BSEP and the human SLC transporter OCT1. BSEP is mainly expressed in the canalicular membrane of hepatocytes where it facilitates excretion into the bile. OCT1 is expressed on the sinusoidal membrane of hepatocytes and facilitates the accumulation of endogenous and xenobiotic compounds into hepatocytes for further metabolism or excretion into the bile.

Methods

Refer to the table below for the test system and probe substrates.

Transporter	Test system	Probe substrate	Experimental design
BSEP	Vesicles	[^{3}H]-Taurocholate	Accumulation of the probe substrate into transporter-expressing and control vesicles in the presence and absence of ATP
OCT1	HEK293	[^{14}C]-Tetraethylammonium bromide	Accumulation of the probe substrate into transporter-expressing and control cells

Results

- **BSEP inhibition:**
  - In the presence of plazomicin (10, 30, 100, 300, 1,000, 3,000 and 10,000 µM) the ATP-dependent uptake of [^{3}H]-taurocholate in BSEP-expressing vesicles was not reduced (IC50 of > 10,000 µM). The positive control inhibitors, cyclosporine (20 µM) and glyburide (100 µM), reduced the ATP-dependent uptake by 95 and 98%, respectively, showing the positive control and test system functioned as expected.
- **OCT1 inhibition:**
  - In the presence of plazomicin (10, 30, 100, 300, 1,000, 3,000 and 10,000 µM), the uptake rate of [^{14}C]-tetraethylammonium bromide (5 µM) into OCT1-expressing cells was reduced from 21.2 to 8.60 pmol/mg/min (59% inhibition), resulting in an IC50 of 3,930 µM. In the presence of the positive control inhibitors quinidine (100 µM) and verapamil (10 µM) the uptake rate of [^{14}C]-tetraethylammonium bromide was reduced by 92 and 93%, respectively, indicating the positive controls and test system functioned as expected.

Reviewer's Comments:

- *It seems that BSEP is unlikely to be inhibited by plazomicin.*
- *The IC50 of plazomicin to OCT1 was 3930 µM which is equivalent to 3292.9 µg/mL (molecular weight of plazomicin is 837.89 g/mol). This concentration is more than 500 times higher than the Cmax of plazomicin in vivo with 15 mg/kg IV infusion for 30 minutes. Therefore, plazomicin is unlikely to inhibit OCT1 in vivo.*

Study Title: Assessment of Protein Binding of ACHN-490 in Plasma (Study A16098-1490-AD)

This study assessed the protein binding of plazomicin (ACHN-490) in human, mouse, rat, dog, rabbit, and cynomolgus monkey plasma. Plazomicin at 5, 50, and 100 µg/mL was incubated in human, mouse, rat, dog, rabbit, and cynomolgus monkey plasma via equilibrium dialysis for 15 hours at 37°C. Please refer to Table 10 for the results.

Table 10. Individual and Mean Protein Binding of Plazomicin (ACHN-490) in Human, Mouse, Rat, Dog, Rabbit, and Cynomolgus Monkey Plasma (Adapted from Table 1 in the study report)

Species		Human		Mouse		Rat		Dog		Rabbit		Cynomolgus Monkey	
[ACHN-490]	Assay Date	% Bound	Mean % Bound	% Bound	Mean % Bound	% Bound	Mean % Bound	% Bound	Mean % Bound	% Bound	Mean % Bound	% Bound	Mean % Bound
5 µg/mL	08-Feb-2017	41.1	24.2	26.7	29.2	35.0	29.9	38.2	33.3	10.2	9.6	22.7	22.4
		21.7		37.5		26.7		42.1		7.3		25.9	
		18.4		38.7		26.7		39.0		6.8		34.0	
	14-Mar-2017	22.6		18.2		30.1		26.6		18.6		24.0	
		24.7		31.5		34.7		34.0		5.6		13.8	
		16.5		22.4		26.1		20.0		8.8		13.7	
50 µg/mL	14-Mar-2017	11.2	13.9	18.6	16.4	15.8	20.9	30.1	30.3	23.2	17.1	18.7	22.1
		13.8		9.2		24.4		29.3		17.3		25.3	
		16.7		21.2		22.3		31.3		10.6		22.2	
100 µg/mL	08-Feb-2017	21.2	17.9	23.2	12.5	18.0	12.6	26.2	22.1	11.3	13.9	18.4	12.1
		24.2		11.8		9.7		23.0		16.8		15.8	
		21.4		17.8		18.5		20.5		8.7		0	
	14-Mar-2017	0		10.1		12.5		20.8		12.3		0	
		15.9		7.7		1.7		24.9		18.4		19.3	
		24.9		4.3		15.0		17.0		15.6		18.9	
Overall Mean		**19.6**		**19.9**		**21.2**		**28.2**		**12.8**		**18.2**	
SD		8.8		10.5		9.4		7.6		5.2		9.0	

Reviewer's Comments:

- *It seems that the protein binding of plazomicin in human plasma was low (about 20%) and concentration independent from 5 to 100 µg/mL*

Study Title: Assessment of Red Blood Cell/Plasma Partitioning of ACHN-490 in Fresh Whole Blood (Study A16093-1490-AD)

The objective of this study is to assess the red blood cell (RBC)/plasma partitioning of plazomicin (ACHN-490) in fresh human, rat, and dog whole blood.

Methods

Plazomicin was incubated at 0.3 μg/mL or 3 μg/mL in triplicate in both whole blood and reference plasma for 60 minutes at 37°C. After the 60-min incubation, whole blood and reference plasma samples were centrifuged at 2,000g for 10 minutes at 4°C. Top layer plasma fraction was collected. Samples were analyzed by LC/MS/MS.

RBC-to-plasma ratio (KRBC/PL) was subsequently calculated as follows:

$K_{RBC/PL}=(1/H)\ (Cp/Cb-1)+1$

- H is the hematocrit (percent of total red blood cells in whole blood sample, v/v, values for the human, rat, and dog whole blood were 0.45, 0.42, and 0.44, respectively, in the current experiment)
- Cp is the ratio of peak areas of the analyte over internal standard in the reference plasma
- Cb is the average ratio of peak areas of the analyte over internal standard in the plasma fraction prepared following incubation with whole blood. Note it is not the concentration in the blood, but in the plasma layer after centrifugation of the blood samples.

Results

- The mean whole blood to plasma ratio, Cp/Cb for human, rat, and dog ranged from 0.55 to 0.65 across the concentrations tested.
- The mean red blood cell partitioning, $K_{RBC/PL}$ for human, rat, and dog ranged from -0.01 to 0.22 across the concentrations tested. No concentration dependence was observed.
- $K_{RBC/PL}$ values were less than 1, indicating low partitioning in the human, rat, and dog red blood cells.

Study Title: In Vitro Evaluation of Plazomicin as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes (Study A15015-1490-AD)

This study was designed to evaluate the ability of plazomicin to inhibit, in vitro, the major CYP enzymes in human liver microsomes (namely CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 [using two different substrates]) in a direct, time-dependent, and/or metabolism-dependent manner.

To evaluate plazomicin as a direct, time-dependent and metabolism-dependent inhibitor of CYP activity, human liver microsomes from a pool of 200 individuals were incubated with marker substrates in the presence or absence of plazomicin. To distinguish between time-dependent and metabolism-dependent inhibition, plazomicin was preincubated with human liver microsomes for 30 min without and with an NADPH-generating system, respectively, prior to the incubation with the marker substrate. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls in all experiments, as applicable.

Results

Please refer to Table 11 for the summary of results.

- For CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (as measured by midazolam 1´-hyroxylation and testosterone 6β-hydroxylation) there was no evidence of direct, time- or metabolism-dependent inhibition by plazomicin up to the highest concentration evaluated (12,000 μg/mL).
- Under the experimental conditions examined, plazomicin directly inhibited CYP1A2 and CYP2C8, with IC50 values of 7,300 and 7,500 μg/mL, respectively.
- There was little or no evidence of time- or metabolism-dependent inhibition of CYP1A2 or CYP2C8 by plazomicin.
- There was a concentration dependent increase in CYP2B6 and CYP2C19 activity of 1.3-fold (from 400 to 4000 μg/mL) and 1.8-fold (at 1200 μg/mL), respectively, followed by a decrease in activity.
- There was a concentration dependent increase in activity of 2.3-fold (at 4000 μg/mL) for CYP2C9, and 1.3-fold for CYP2D6 and CYP3A4/5 (as measured by testosterone 6β-hydroxylation) at plazomicin concentrations of 4,000 μg/mL, followed by a decrease in activity.
- There was a concentration dependent increase in CYP3A4/5 (as measured by midazolam 1´-hydroxylation) activity of 1.2-fold up to 12,000 μg/mL in the zero-minute and 30-minute preincubation with NADPH samples; there was also a concentration dependent increase in activity of 1.2-fold up to 4,000 μg/mL followed by a decrease in activity in the 30-minute preincubation without NADPH samples.

Table 11. Summary of results: In vitro evaluation of plazomicin as an inhibitor of human CYP enzymes (Adapted from Table 3 in the study report)

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-min preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (µg/mL) [a]	Inhibition observed at 12,000 µg/mL (%) [b]	IC_{50} (µg/mL) [a]	Inhibition observed at 12,000 µg/mL (%) [b]	IC_{50} (µg/mL) [a]	Inhibition observed at 12,000 µg/mL (%) [b]	
CYP1A2	Phenacetin	7,300 ± 1,100	62	6,100 ± 700	70	> 12,000	45	Little or no
CYP2B6	Efavirenz	> 12,000	4.3	> 12,000	16	> 12,000	24	ND
CYP2C8	Amodiaquine	7,500 ± 600	71	5,600 ± 1,100	80	7,500 ± 600	64	Little or no
CYP2C9	Diclofenac	> 12,000	NA	> 12,000	NA	> 12,000	NA	ND
CYP2C19	S-Mephenytoin	> 12,000	2.9	> 12,000	30	> 12,000	1.7	ND
CYP2D6	Dextromethorphan	> 12,000	NA	> 12,000	10	> 12,000	NA	ND
CYP3A4/5	Midazolam	> 12,000	NA	> 12,000	3.7	> 12,000	NA	ND
CYP3A4/5	Testosterone	> 12,000	NA	> 12,000	NA	> 12,000	NA	ND

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.

b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures):
Inhibition observed (%) = 100% − Percent solvent control.

c Metabolism-dependent inhibition was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC_{50} plots.

NA Not applicable. No value was obtained as the rates at the highest concentration of plazomicin evaluated (12,000 µg/mL) were higher than the control rates.

ND Not determined. It is unknown whether the decrease in activity that follows an apparent concentration-dependent increase in marker substrate activity is due to inhibition by plazomicin or if it is a return to control-level activity.

Reviewer's Comments:

- *Due to the high plazomicin IC50 value for CYP1A2 (7300 µg/mL) and CYP2C8 (7500 µg/mL), plazomicin is unlikely to inhibit these two CYP enzymes at a clinically relevant concentration (Cmax was about 46 µg/mL for cUTI patients).*
- *The Sponsor stated that the increase in CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 activity may be allosteric activation in which marker substrate activity gains efficiency with increasing concentrations of plazomicin. No in vitro and in vivo relationship has been established to further investigate this observation yet. The plazomicin concentrations relating to this observation were all above 400 µg/mL which is about 10- fold higher than Cmax with the therapeutic dose. Therefore, plazomicin is not expected to stimulate the CYP enzymes under the therapeutic dose.*

Study Title: In Vitro Evaluation of Plazomicin as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes (Study A15016-1490-AD)

The objective of this study was to investigate the effects of treating primary cultures of cryopreserved human hepatocytes with plazomicin on the expression of cytochrome P450 (CYP) enzymes.

Methods

Three preparations of cryopreserved human hepatocytes (HC10-10, HC10-8 and HC7-5, respectively) supplied internally by (b) (4) were treated with plazomicin (0.05, 0.1, 0.5, 1, 3, or 5.7 mg/mL) for three consecutive days. The vehicle control, negative, and positive controls are listed in the table below.

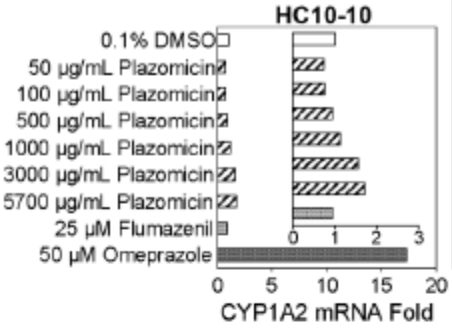
Controls	Compound name
Vehicle control	DMSO
Negative control	Flumazenil
CYP1A2 inducer	Omeprazole
CYP2B6 inducer	Phenobarbital
CYP3A4 inducer	Rifampin

Approximately 24 hours after the last treatment, hepatocytes were lysed in Buffer RLT reagent containing β-mercaptoethanol (100:1), and cell lysates were stored at −80 ± 10 °C.

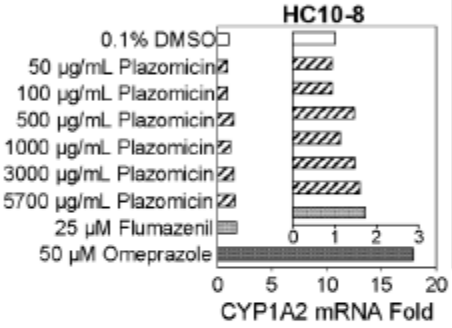
Results

Please refer to Figures 2, 3, and 4 for the changes in mRNA levels after plazomicin treatment for CYP1A2, CYP2B6, and CYP3A4.

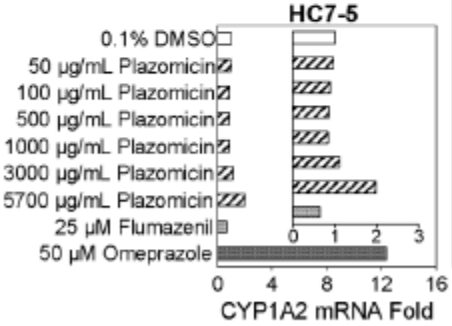
Figure 2. CYP1A2 fold change: The effect of treating cultured human hepatocytes with plazomicin on CYP1A2 mRNA levels (Adapted from Figure 5 in the study report)



mRNA Fold Change	n
1.00	3
0.734	3
0.758	3
0.934	3
1.13	3
1.55	3
1.70	3
0.953	3
17.3	3



mRNA Fold Change	n
1.00	2
0.916	3
0.921	3
1.46	3
1.14	3
1.48	3
1.60	3
1.73	3
17.9	3



mRNA Fold Change	n
1.00	3
0.973	3
0.881	3
0.848	3
0.832	3
1.12	3
1.99	3
0.636	3
12.3	3

n Number of replicates

Fold change values are relative to vehicle control, normalized to GAPDH.

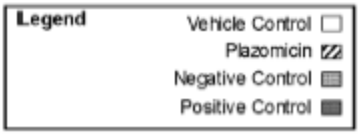
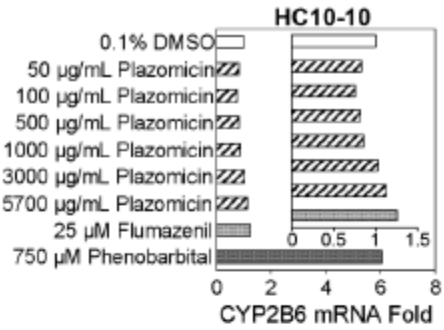
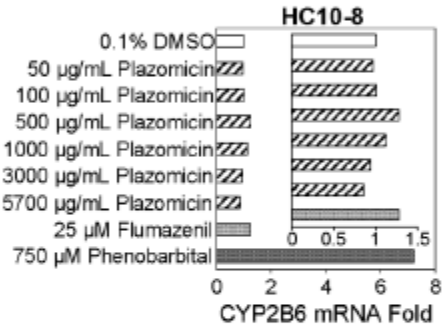


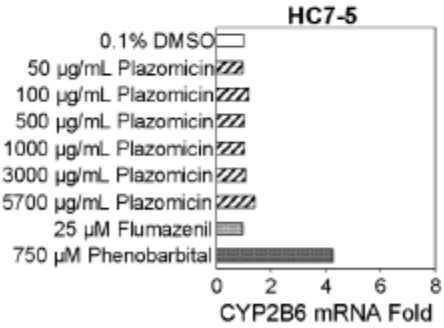
Figure 3. CYP2B6 fold change: The effect of treating cultured human hepatocytes with plazomicin on CYP2B6 mRNA levels (Adapted from Figure 7 in the study report)



mRNA Fold Change	n
1.00	3
0.833	3
0.755	3
0.823	3
0.850	3
1.03	3
1.12	3
1.25	3
6.04	3



mRNA Fold Change	n
1.00	3
0.974	3
1.01	3
1.27	3
1.13	3
0.937	3
0.846	3
1.27	3
7.20	3



mRNA Fold Change	n
1.00	3
0.965	3
1.14	3
1.04	3
1.04	3
1.08	3
1.40	3
0.954	3
4.28	3

n Number of replicates

Fold change values are relative to vehicle control, normalized to GAPDH.

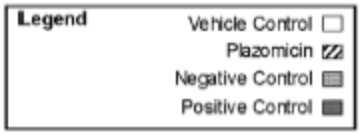
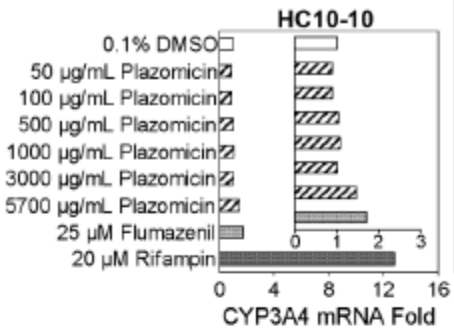
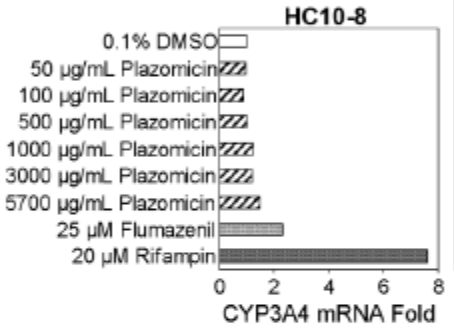


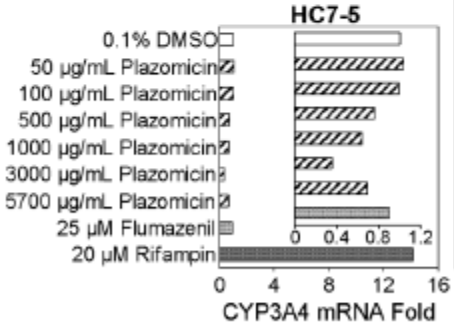
Figure 4. CYP3A4 fold change: The effect of treating cultured human hepatocytes with plazomicin on CYP3A4 mRNA levels (Adapted from Figure 9 in the study report)



mRNA Fold Change	n
1.00	3
0.883	3
0.886	3
1.02	3
1.08	3
1.02	3
1.47	3
1.71	3
12.8	3



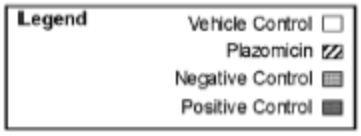
mRNA Fold Change	n
1.00	3
0.952	3
0.845	3
0.998	3
1.22	3
1.18	3
1.49	3
2.30	3
7.59	3



mRNA Fold Change	n
1.00	3
1.04	3
0.991	3
0.761	3
0.634	3
0.349	3
0.689	3
0.900	3
14.2	3

n Number of replicates

Fold change values are relative to vehicle control, normalized to GAPDH.



Reviewer's Comment:

- *Per the FDA draft DDI guidance 2017[1], a ≥ 2- fold increase in mRNA level relative to vehicle control and a ≥ 20% of the response of the positive control in the presence of an investigational drug are interpreted as a positive result. It seems that plazomicin caused little or no increase in CYP1A2, CYP2B6, and CYP3A4 mRNA levels in all three human donor hepatocyte cultures tested.*

- *Because CYP3A4/5 share the same nuclear receptor, PXR, with CYP2C, the negative result for CYP3A4 induction eliminated the need for additional in vitro induction studies for CYP2C8, CYP2C9, and CYP2C19.*
- *The in vitro inducers and duration of treatment for the hepatocytes in this study are acceptable.*

4.5.3 Study Title and Number: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Single and Multiple Dose-Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of ACHN-490 (Plazomicin) Injection Administered Intravenously in Healthy Subjects (ACHN-490-001)

Study Design

This study was designed to enroll 8 subjects into each of 4 cohorts (Cohorts 1 [1a and 1b components], 2, 3, and 4), for a planned minimum of 32 subjects overall. Within each cohort, 6 subjects were to receive plazomicin injection and 2 subjects were to receive placebo. Planned plazomicin injection dose levels were 1 mg/kg in Cohort 1a, 4 mg/kg in Cohort 1b, 7 mg/kg in Cohort 2, 11 mg/kg in Cohort 3, and 15 mg/kg in Cohort 4. The same subjects were enrolled in cohort 1a and 1b. Different groups of subjects were enrolled into each of Cohorts 2, 3, and 4.

In Cohort 1b and in each of Cohorts 2, 3, and 4, subjects first received a single-dose infusion; subsequently, after safety data for the single dose infusion for the given cohort had been reviewed (after an intervening period of at least 7 days after the single-dose infusion had been received by the last subject in that cohort), subjects then received multiple daily infusions (at the same dose level identified for the cohort) during a multiple-dose treatment segment. During the multiple-dose segment, infusions were administered once daily for 10 days in Cohort 1b (4 mg/kg) and Cohort 2 (7 mg/kg), 5 days in Cohort 3 (11 mg/kg), or 3 days in Cohort 4 (15 mg/kg). Throughout the study, each dose of plazomicin or placebo was administered as an IV infusion over 10 minutes. Safety was assessed in an ongoing manner throughout the study.

For Cohorts 1a, 1b, and 2, eighteen plasma samples for PK per subject were collected over 48 hours after the start of infusion on Day 1, Day 8, and Day 17, respectively. For Cohorts 3 and 4, eighteen plasma samples for PK per subject were collected over 48 hours after the start of infusion on Day 1, Day 8, Day 10 (Cohort 4 only), and Day 12 (Cohort 3 only), respectively.

Renal function was assessed at selected time points by estimating GFR via measurement of iothalamate clearance, measurement of creatinine clearance based on serum and urine creatinine, and calculated creatinine clearance based on serum creatinine. The GFR estimation by measurement of iothalamate clearance was performed before administration of the single-dose plazomicin infusion, before administration of the first plazomicin infusion of the multiple-dose segment, and after the final plazomicin infusion of the multiple dose segment. A sub-report regarding iothalamate study was submitted separately. A review for the iothalamate study is included at the end of this review.

PK Evaluation

Pharmacokinetic parameter estimates for plazomicin were calculated by standard noncompartmental methods, based upon actual specimen collection times.

Tables 1 and 2 summarize the plasma and urine plazomicin PK parameters following a single IV dose and following the last daily repeat IV dose of plazomicin, respectively.

Table 1. Mean (SD) Plasma and Urine Plazomicin Pharmacokinetic Parameters following a Single Intravenous Injection of plazomicin (Adapted from Table 1 in APPENDIX PK Study Report in Clinical Study Report ACHN-490-001)

	Plazomicin Dose				
PK Parameter	1 mg/kg (N=5)	4 mg/kg (N=5)	7 mg/kg (N=5)	11 mg/kg (N=6)	15 mg/kg (N=6)
AUC0-inf (µg*h/mL)	14.5 (1.2)	64.8 (8.8)	88.8 (11.2)	181 (35.6)	246 (39.2)
Cmax (µg/mL)	8.1 (0.7)	43.1 (6.5)	45.5 (6.8)	114 (26.5)	144 (45.1)
T1/2 (hr)	4.02 (0.75)	3.65 (0.37)	3.10 (0.40)	3.33 (0.52)	3.37 (0.82)
Ae (%)	87.3 (4.1)	85.4 (6.5)	92.1 (5.0)	85.2 (6.9)*	88.9 (5.5)

**n=5*

Ae (%): urinary excretion

Table 2. Mean (SD) Plasma and Urine Plazomicin Pharmacokinetic Parameters following the Last Daily Repeat Dose Intravenous Injection of plazomicin (Adapted from Table 2 in APPENDIX PK Study Report in Clinical Study Report ACHN-490-001)

	Plazomicin Dose			
PK Parameter	4 mg/kg daily x 10 days (N=6)	7 mg/kg daily x 10 days (N=6)	11 mg/kg daily x 5 days (N=6)	15 mg/kg daily x 3 days (N=6)
AUC0-24 (µg*h/mL)	53.7 (4.8)	88.5 (8.1)	145 (14.4)	224 (37.4)
Cmax (µg/mL)	31.0 (2.5)	43.0 (6.8)	86.5 (19.5)	117 (28.1)
T1/2 (hr)	4.27 (1.03)	4.06 (0.91)	4.08 (0.68)	4.06 (0.71)
Ae (%)	99.5 (6.3)	91.9 (4.4)	96.8 (5.2)	77.8 (9.1)

Conclusion

- The PK of plazomicin [AUC (0-24), Cmax, and Cmin] was approximately dose proportional in a range from 4 mg/kg to 15 mg/kg. It appears that no dose accumulation was observed after repeated once daily dose from 4 mg/kg to 15 mg/kg.
- The Sponsor submitted their bioanalytical report entitled "HPLC/MS/MS Bioanalysis of ACHN490 from Human Plasma and Urine and Iothalamate from Human Plasma" in the Clinical Study Report Amendment to support Study ACHN-490-001. The method was validated by (b) (4) and described in the final validation report AV08-ACHN-490-02 (module 5.3.1.4). Please refer to QBR 4.1 Summary of Bioanalytical

Method Validation and Performance for details. Based on the description in the bioanalytical report for Study ACHN-490-001, the performance of the bioanalysis is acceptable.

- The percentages of unchanged plazomicin excreted in urine in this study are lower than the mass balance study results. (APPENDIX 4.5.5) (i.e., 88.9% *versus* 97% after a 15 mg/kg single dose). It may be due to the relatively short urine collection time in his study compared to the mass balance study (i.e., 48 hours *versus* up to 7 days).

IOTHALAMATE CLEARANCE STUDY REPORT

Objective

- To evaluate the effect of plazomicin on renal function as assessed by plasma iothalamate clearance after single-dose intravenous (IV) administration of iothalamate.

Endpoint

- Change in plasma iothalamate clearance from baseline

Study Design

Subjects in Cohort 1a and 1b received iothalamate as a 10-minute IV push of 4 mL/kg, up to a maximum of 300 mL (90 g). Subjects in Cohort 2-4 received iothalamate as a 5-minute IV push of 30 mL (9 g).

Blood samples for measurement of iothalamate in plasma were drawn relative to dosing as follows:

- Cohort 1a (1 mg/kg ACHN-490 or placebo): Day -1 and 7: predose, and 1, 2, 4, and 8 hours after the start of the infusion
- Cohorts 1b (4 mg/kg ACHN-490 or placebo) and 2 (7 mg/kg ACHN-490 or placebo): Days -1, 7, and 18: predose, and 1, 2, 4, and 8 hours after the start of the infusion
- Cohort 3 (11 mg/kg ACHN-490 or placebo): Days -1, 7, and 13: predose, and 1, 2, 4, and 8 hours after the start of the infusion
- Cohort 4 (15 mg/kg ACHN-490 or placebo): Days -1, 7, and 11: predose, and 1, 2, 4, and 8 hours after the start of the infusion

The analytical method (LC/MS/MS) was developed and validated at (b) (4) (b) (4) (AV08-ACHN490-02).

Plasma iothalamate clearance was calculated using standard noncompartmental methods of analysis using a constant infusion model, based upon the actual collection times, and is reported in clearance units (mL/min). Change from baseline (CFB) was calculated using baseline clearance values on Day -1 and Day 7 utilizing the following the equation below:
Change from baseline (mL/min) = CLio following multiple dose of plazomicin – CLio baseline

Results

Data for all 31 subjects who received iothalamate were included in the PK analysis.

Table 3 provides a summary of iothalamate clearance values at baseline (Day -1 and Day 7) and 24-hours post plazomicin treatment (Day 11, Day 13, and Day 18).

Table 3. Arithmetic Mean (SD) Plasma Iothalamate Clearance at Baseline (Day -1 and Day 7) and 24 Hours following the Last Once-Daily Intravenous Infusion of Plazomicin (Day 11, 13, or 18)

	Iothalamate Clearance (mL/min)				
	ACHN-490 Dose Group				
Study Day	All Placebo N=8	4 mg/kg N=6	7 mg/kg N=6	11 mg/kg N=6	15 mg/kg N=5
Baseline, Day -1	231 [c] (41.5)	202 (46.5)	183 [b] (31.0)	261 [b] (35.3)	258 (42.5)
Baseline, Day 7	236 (42.0)	224 (41.8)	200 (21.7)	266 (24.4)	259 (28.7)
Post Last Dose Day 11, 13, or 18	249 (32.3)	246 (59.0)	239 (33.1)	263 (22.3)	222 (29.4)

b. N=4

c. N=7

Table 4 and Table 5 provide a summary of change from baseline (Day -1 and Day 7, respectively) in plasma iothalamate clearance values at the end of multiple dosing.

Table 4. Summary (Mean ±SD) of Iothalamate Plasma Clearance Change from Baseline (Day -1) to 24 Hours following the Last Once-Daily Intravenous Infusion of Plazomicin or Placebo [Days 11 (15 mg/kg), 13 (11 mg/kg), or 18 (4 mg/kg and 7 mg/kg)) (Adapted from Table 3 in the report of sub-Study Iothalamate Clearance under protocol # ACHN-490-001)

Change from Baseline (mL/min)[a]						
		Plazomicin Dose Group				
Post Last Dose versus Day -1		All Placebo (N=7)	4 mg/kg (N=4)	7 mg/kg (N=4)	11 mg/kg (N=4)	15 mg/kg (N=5)
CFB* 24-hr post plazomicin treatment	Mean (SD)	18.8 (41.6)	43.8 (20.5)	51.3 (5.79)	7.56 (26.8)	-36.2 (14.2)
CFB 24-hr post placebo treatment	Value 1		62.8	54.1	-16.9	-14
	Value 2		NA	66.2	10.9	-31.4

[a]*Change from Baseline (mL/min) = CLio following plazomicin – CLio baseline.*

*Change from Baseline (%) = [(CLio following plazomicin – CLio baseline)/CLio baseline] * 100*
**CFB: change from baseline*

Table 5. Summary (Mean ±SD) of Iothalamate Plasma Clearance Change from Baseline (Day 7) to 24 Hours following the Last Once-Daily Intravenous Infusion of Plazomicin (Day 11, 13, or 18) (Adapted from Table 4 in the report of sub-Study Iothalamate Clearance under protocol # ACHN-490-001)

Change from Baseline (mL/min)						
		Plazomicin Dose Group				
Post Last Dose versus Day -1		All Placebo (N=8)	4 mg/kg (N=6)	7 mg/kg (N=4)	11 mg/kg (N=4)	15 mg/kg (N=5)
CFB* 24-hr post plazomicin treatment	Mean (SD)	12.7 (34.8)	22.2 (24.2)	39.4 (22.3)	-2.86 (26.4)	-36.9 (9.91)
CFB 24-hr post placebo treatment	Value 1		28.4	35.9	-11.9	-45.1
	Value 2		35.4	64.9	-1.52	-4.13

Reviewer's Comments:

- *The plasma iothalamate clearance values summarized in Table 3 are much higher than the normal GFR (~100 mL/min). Given that plasma iothalamate clearance is calculated by dividing the dose administered by the AUC, the higher than expected iothalamate CL values may be due to an underestimated AUC. The half-life of iothalamate is about 1 hr and plasma samples were collected to 8 hours for the estimation of iothalamate PK parameters, thus long enough[9, 10]. However, plasma samples were only collected at four time points at baseline, and post plazomicin treatment and iothalamate plasma concentration were estimated using non-compartment analysis, which may result in the inaccurate estimation of AUC.*
- *Per the Summary of Analytical Batches for Iothalamate in the Bioanalysis Report for Study ACHN-490-001, different cohorts were analyzed separately. Therefore, to correct the impact of assay factors to the results, the reviewer subtracted the arithmetic mean of Placebo CFB from ACHN-490 CFB for each cohort. The results are summarized in table below.*
- *Because the values of baseline iothalamate clearance were above 200 mL/min in this study and the variability of CFB values in most cohorts are large, it is not possible to conclude whether plazomicin treatment has an impact on GFR based on the change of iothalamate clearance.*

[9] Agarwal R et al. Clin J am Soc Nephrol. 2009 Jan; 4(1):77-85
[10] Dowling T et al. Pharmacotherapy 1999 Nov; Vol 19: 943-950

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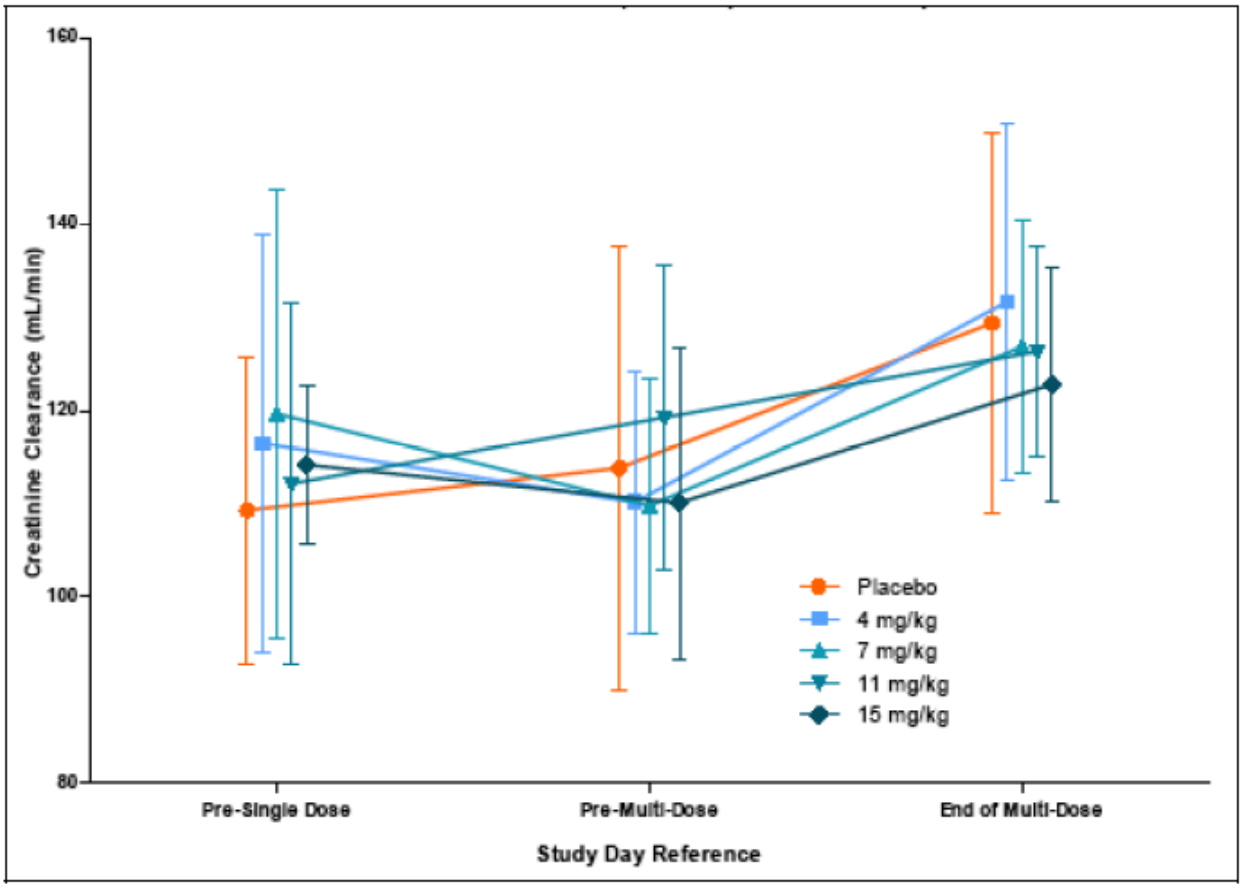
- *Measured creatinine clearance was assessed by calculation of creatinine clearance from 24-hour urine samples collected before administration of the plazomicin on Day 1 of both the single-dose and multiple-dose segments, and on the day after the last dose. No individual calculated creatinine clearance data based on measured urine creatinine were identified in this application. Therefore, it is not possible to calculate the individual creatinine clearance change from baseline following plazomicin treatment. Based on the summary of measured creatinine clearance from the 24-hour urine data in Study ACHN-490-001, Creatinine clearance did not decrease significantly post plazomicin treatment (Figure 1). Therefore, it appears that the renal function did not change significantly at the end of plazomicin treatment in healthy adults with normal renal function at baseline. However, the treatment duration of plazomicin 15mg/kg in this study is only for three days.*

	4 mg/kg (10 days)	**7 mg/kg (10 days)**	**11 mg/kg (5 days)**	**15 mg/kg (3 days)**
Mean CFB 24-hr post plazomicin treatment minus mean placebo CFB in the same cohort (Day -1)	-19	-8.85	10.56	-13.5
Mean CFB 24-hr post plazomicin treatment minus mean placebo CFB in the same cohort (Day 7)	-9.7	-11.0	3.85	-12.29

Figure 1. Measured Creatinine Clearance (mL/min) based on 24-hour Urine Collection by Treatment Group (Adapted from Figure 12-3 from the report of Study ACHN-490-001)



Conclusion

Differences among dose cohorts in change from baseline in iothalamate clearance were observed, however, there was no consistent trend in these changes from baseline that might be suggestive of a drug effect.

4.5.4 Study Title and Number: A Phase 1 Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intravenous ACHN-490 (Plazomicin) Injection in Volunteers with Varying Degrees of Renal Dysfunction Compared to Healthy Volunteers (ACHN-490-004)

Study Design

A total of 24 subjects were enrolled, with 6 subjects in each of four groups (Table 1) based on renal function as determined by CrCl, calculated using the Cockcroft-Gault equation:

$$\text{Calculated CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} (\times 0.85 \text{ for females})$$

Table 1. Renal Function Groups Based on Creatinine Clearance

Group	Renal function group	Calculated CrCl
I	Normal renal function	≥ 90 mL/min
II	Mild renal dysfunction	60–89 mL/min
III	Moderate renal dysfunction	30–59 mL/min
IV	Severe renal dysfunction	15–29 mL/min

All subjects received a single, 7.5 mg/kg dose of plazomicin injection, which was administered by intravenous infusion over 30 minutes on Day 1. Blood and urine samples for laboratory and/or PK assessments were obtained starting on Day 1 and ending on Day 5. Thirteen plasma samples for PK per subject were collected over 96 hours after the start of infusion. Pooled urine samples were collected from the start of the infusion to 48 hours. Safety laboratory testing was repeated on Day 14 (follow-up) if any clinically significant changes from baseline had occurred following dosing. Subject participation completed upon a follow-up visit on Day 14.

Pharmacokinetic Results

Table 2 summarizes plazomicin PK parameters across different renal function groups.

Table 2. Plazomicin Plasma Pharmacokinetic Parameters (Selected) by Renal Function (PK Analysis Population) (Adapted from Table 7 in the report of Study ACHN-490-004)

Plasma Parameter	Normal renal function (N=6)	Mild renal dysfunction (N=6)	Moderate renal dysfunction (N=6)	Severe renal dysfunction (N=6)
C_{max} (mg/L), mean (SD)	37.9 (5.01)	32.8 (4.30)	39.2 (6.43)	41.4 (7.83)
T_{max} (h), median (min, max)	0.6 (0.6, 1.0)	0.6 (0.6, 0.75)	0.6 (0.6, 0.75)	0.6 (0.6, 0.62)
$AUC_{0-\infty}$ (mg × h/L), mean (SD)	136 (17.2)	138 (23.7)	281 (96.0)	647 (259)
$t_{1/2}$ (h), median (min, max) [a]	33.8 (28.1, 62.4)	26.6 (22.9, 32.7)	20.3 (16.3, 32.4)	24.7 (15.6, 33.5)
CL_T (L/h), mean (SD)	4.64 (1.17)	3.98 (0.481)	2.25 (0.685)	0.96 (0.379)
V_{ss} (L), mean (SD)	36.0 (7.76)	28.5 (2.17)	25.8 (6.96)	25.1 (7.89)

[a] terminal elimination $t_{1/2}$.

Please refer to Table 3 for the mean plazomicin urine PK parameters by renal function.

Table 3. Mean (SD) Plazomicin Urine Pharmacokinetic Parameters by Renal Function (PK Analysis Population) (Adapted from Table 9 in the report of Study ACHN-490-004)

Urine Parameter	Normal renal function (N=6)	Mild renal dysfunction (N=6)	Moderate renal dysfunction (N=6)	Severe renal dysfunction (N=6)
Ae_{0-48} (mg)	398 (168)	447 (84.7)	449 (77.2)	317 (88.5)
Ae%	62.8 (20.4)	82 (9.71)	77 (5.37)	58.0 (12.9)
CL_R (L/h)	3.11 (1.60)	3.29 (0.165)	1.82 (0.592)	0.703 (0.315)

Reviewer's Comment: It was observed that the renal clearance (CL_R) of plazomicin was lower in the subjects with normal renal function (67% of the CL_T) compared to the one from population PK model (89%) and other renal function groups. The Sponsor stated it may due to lower than expected urinary recovery of plazomicin (39%, 43.9%, and 53.6%) in three of the six subjects in normal renal function group. Scrutiny of the clinical and analytical information from these subjects failed to identify a reason that could be directly attributed to recording of data or sample assay errors, although errors in sample collection could not be ruled out.

Conclusion

- It appears that Cmax of plazomicin was not significantly different across renal function groups.
- The plazomicin CL_T for subjects with moderate or severe renal impairment was about 50% and 20% of the one for subjects with normal renal function, respectively. Consequently, their corresponding $AUC_{0-\infty\ was}$ 1.98- and 4.42-fold higher than the one for subjects with normal renal function, respectively.
- Given the results of this study, dose adjustments will be required for subjects with moderate or severe renal dysfunction.
- Based on the description in the bioanalytical report (see QBR 4.1 Summary of Bioanalytical Method Validation and Performance), the performance of the bioanalysis in this study is acceptable.

4.5.5 Study Title and Number: A Phase 1, Open-Label Study to Assess the Metabolism, Excretion, and Mass Balance of [^{14}C]-Plazomicin Following a Single IV Infusion in Healthy Adult Male Subjects (Study ACHN-490-010)

Objectives

Primary:

- To determine the major route(s) of elimination and the overall mass balance of plazomicin following a single 30-minute IV infusion of 15 mg/kg of [^{14}C]-plazomicin in healthy adult male subjects;

Exploratory:

- To examine the metabolic profile of plazomicin and identify major metabolites in plasma, urine and feces.

Study Design

The study consisted of a screening period of up to 21 days, a check-in day (Day -1) on the day before study treatment administration, a single dose of study treatment on Day 1, followed by bio-specimen collection until Day 7 or 8 (Twenty-two plasma samples per subject were collected until Day 7 and urine and feces samples were collected until Day 8).

The investigational drug product was prepared by the (b) (4) as a 50 mg/mL plazomicin (5.49 μCi/mL) solution for IV injection by mixing [^{14}C]-plazomicin sulfate powder with unlabeled plazomicin powder and dissolving in sterile water.

There was 1 major protocol deviation related to missing urinalysis sample collection observed during this study:

- Urine samples were not collected in error on Day 4 for urinalysis testing for all subjects. The protocol did not require urinalysis labs to be run after Day 4, so no post-dose urine labs were reported for subjects on the study.

The profiles of plazomicin metabolites were provided in a sub-study report entitled "Metabolite Profiling of Samples Derived from Humans Intravenously Administered [^{14}C]-Plazomicin by HPLC and Accelerator Mass Spectrometry (HPLC+AMS) (Protocol 167/001)" prepared by (b) (4) The urine pool sample was analyzed directly by high-performance liquid chromatography (HPLC) and the plasma pool sample underwent protein precipitation extraction, prior to HPLC fractionation. Full profiles were generated by collecting HPLC fractions during the entire length of the run and then analyzing each fraction, or fractions pooled across an HPLC region, by Accelerator Mass Spectrometry (AMS). The total radioactivity recovered from each fraction or fraction pool was converted to a percentage of the total collected from all fractions to determine the relative amounts of [^{14}C]-plazomicin related analytes present in each pooled sample.

Results

Figure 1 is the plasma and whole blood total radioactivity concentration equivalents and plasma plazomicin concentration *versus* time curve. Table 1 describes the summary of PK parameters of plasma total radioactivity and plasma plazomicin concentrations. The mean plasma plazomicin / mean plasma total radioactivity ratio based on AUC 0-∞ (68.10%) is lower than the one based on AUC $_{0\text{-}t}$ or AUC $_{0\text{-}24}$ (about 82%). This may due to the long PK sample collection time (7 days) and higher assay sensitivity of liquid scintillation counting (LSC) compared to LC/MS/MS. The terminal elimination half-life reported in this study is longer than the ones in other PK studies. This also may be due to the long PK sample collection time (i.e., 7 days) and assay method (i.e., LSC).

Table 2 describes the total radioactivity and plazomicin recovered in urine. The total radioactivity recovered in the urine (89.2%) was lower than the cumulative amount of plazomicin excreted unchanged in urine (97.2%) for unknown reason(s).

Figure 1. Arithmetic Mean Plasma and Whole Blood Total Radioactivity Concentration Equivalents and Plasma Plazomicin Concentrations *versus* Time Following a Single IV Infusion of 15 mg/kg [^{14}C]-Plazomicin (Semi-Log Scale) (Adapted from Figure 11-2 in the report of Study ACHN-490-010)

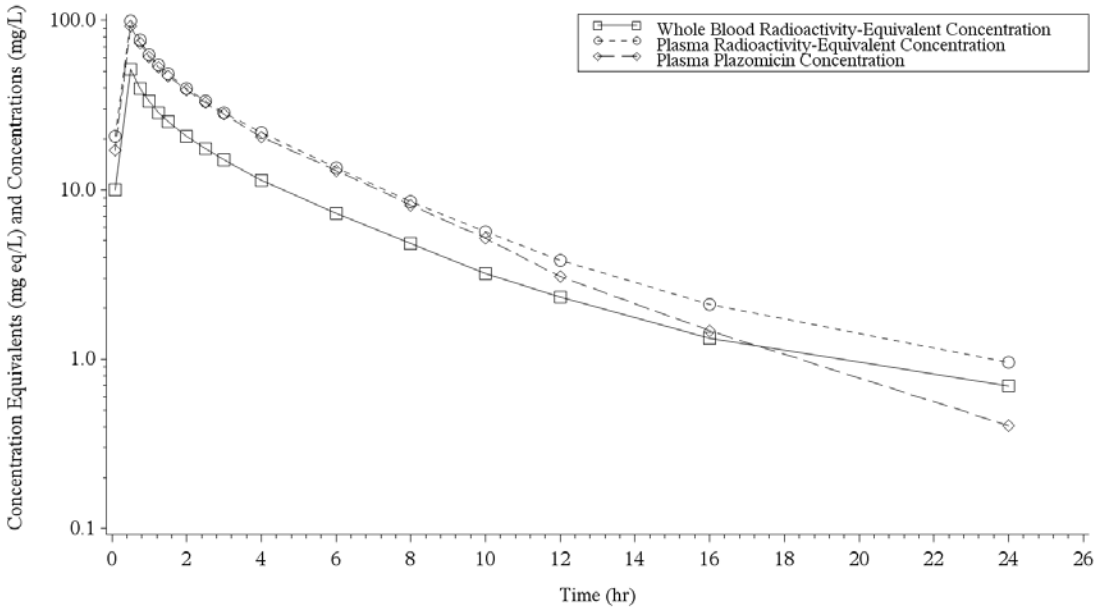


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Table 1. Summary of Plasma Total Radioactivity and Plasma Plazomicin Pharmacokinetics Following a Single IV Infusion of 15 mg/kg [14C]-Plazomicin (Adapted from Table 11-2 in the report of Study ACHN-490-010)

PK Parameters	**Plasma Total Radioactivity (CV%)**	**Plasma Plazomicin (CV%)**	**Mean Plasma Plazomicin/ Mean Plasma Total Radioactivity**
AUC_{0-t} (mg·hr/L or mg eq*hr/L)	325 (12.1)	266 (11.5)	81.85
AUC_{last} (mg·hr/L or mg eq*hr/L)	325 (12.1)	267 (11.4)	82.15
$AUC_{0-\infty}$ (mg·hr/L or mg eq*hr/L)	395 (24.0)	269 (11.4)	68.10
Cmax (mg/L or mg eq/L)	99.0 (5.8)	92.1 (8.4)	93.03
Tmax (hr)*	0.513 (0.513, 0.516)	0.504 (0.503, 0.505)	
CL_T (L/hr)		4.76 (17.1)	
V_{ss} (L)		33.4 (21.0)	
$t_{1/2}$** (hr)	93.5 (100.2)	70.6 (31.8)	

Parameters are presented as geometric mean and geometric CV%.
*Tmax is presented as Median (Minimum, Maximum)
N=6 for all parameters and n=5 for plasma total radioactivity estimates of $AUC_{0-\infty}$ and $t_{1/2}$
**terminal elimination half life

Table 2. Summary of Urinary Total Radioactivity and Plazomicin Pharmacokinetics Following a Single IV Infusion of 15 mg/kg [^{14}C]-Plazomicin (Adapted from Table 11-4 in the report for Study ACHN-490-010)

Pharmacokinetic Parameters	**Urine Total Radioactivity**	**Urine Plazomicin**
CumAe (mg or mg eq)	1140 (17.7)	1250 (16.6)
Cum%Dose (%)	89.1 (8.3)	97.5 (7.4)
CLr (L/hr)	.	4.64 (23.5)

Parameters are presented as geometric mean and geometric CV %.

Figure 2. Total Radioactivity in Urine, Feces, and Urine + Feces *Versus* Collection Interval Following a Single IV Infusion of 15 mg/kg [^{14}C]-Plazomicin (Linear Scale) (Adapted from Figure 11-3 in report of Study ACHN-490-010)

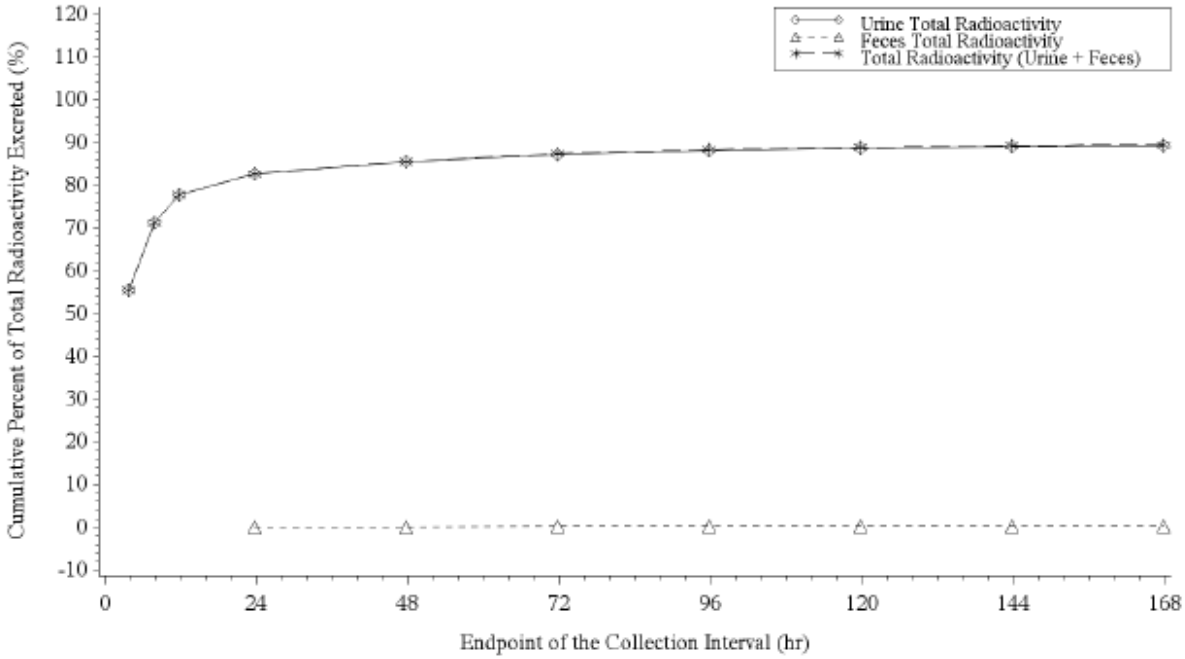


Figure 2 shows arithmetic mean cumulative percent of [^{14}C]-plazomicin dose excreted based on total radioactivity in urine, feces. The cumulative geometric mean of total radioactivity recovered in feces was 2.08 mg eq or 0.162% of the total radioactivity dose. Due to the trace level of radioactivity in feces, metabolite profiling was conducted in plasma and urine only.

In the plasma (pooled samples from different time points, N=6) profile, 94.3% of the radioactivity was in fractions from 13.75-14.5 min, which co-eluted with the spiked unlabeled plazomicin reference standard. Of the remaining radioactivity recovered in the plasma profile, no region contained levels of radioactivity higher than 2.2% or exhibited a peak on the radio chromatogram. In the urine profile (pooled samples, N=6), 93.6% of the recovered radioactivity was attributed to plazomicin. Of the remaining radioactivity recovered in the urine profile, no region had radioactivity higher than 1.3% or exhibited a peak on the radio-chromatogram.

Reviewer's comments:

- *The mass balance study was performed by* (b) (4) *plazomicin plasma and urine drug concentrations were measured using LC/MS/MS by* (b) (4) *the profiles of plazomicin metabolites were provided by* (b) (4) *The assays for all parts appear to be acceptable.*

Conclusion

Plazomicin was eliminated as unchanged drug by the kidney and thus did not appear to be metabolized to any appreciable extent.

4.5.6 Study Title and Number: A Phase 1, Open Label, Randomized, 2-Period, 2-Treatment, Crossover Study to Assess the Effect of Plazomicin on the Pharmacokinetics of Metformin in Healthy Subjects (ACHN-490-011)

Study Objectives

Primary

To evaluate the effect of a single dose of plazomicin (15 mg/kg administered as a 30-minute IV infusion) on the single dose plasma PK of metformin in healthy subjects.

Secondary

- To assess the safety and tolerability of plazomicin when administered in combination with metformin.
- To evaluate metformin urine PK when administered with and without plazomicin.
- To evaluate plazomicin plasma PK when administered in combination with metformin.

Study Rationale

Based on the *in vitro* study results, plazomicin is a potential inhibitor of MATE1 and MATE2-K transporters (APPENDIX 4.5.2). Therefore, an *in vivo* DDI study was conducted using metformin as a substrate.

Study Design

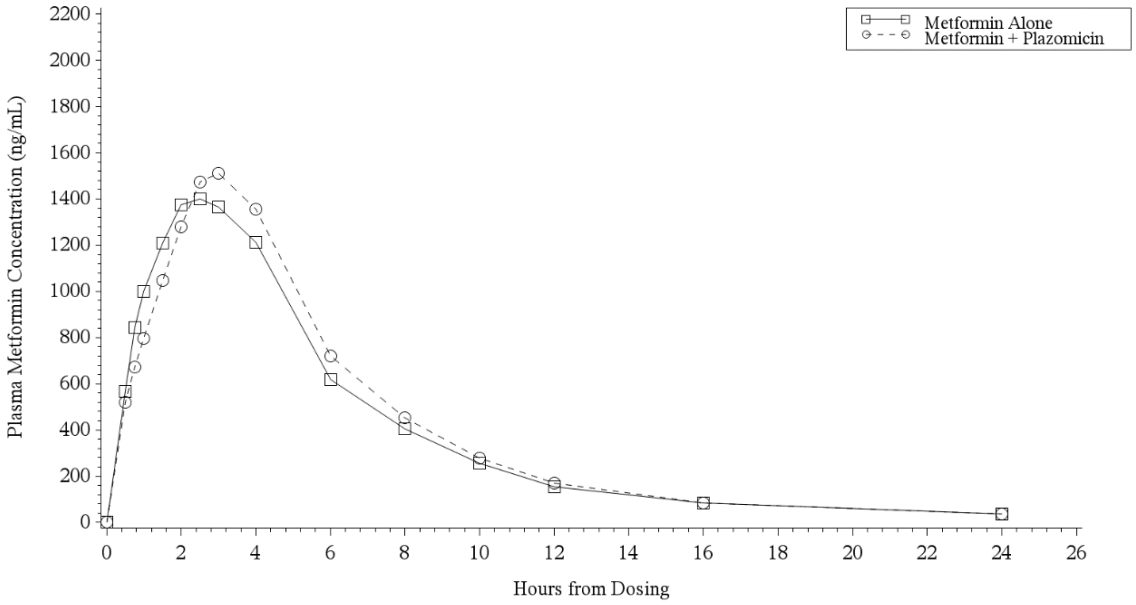
Subjects randomized to Sequence 1 received a single oral dose of immediate-release metformin tablet (850 mg) on Day 1 (Treatment Period 1). Following a 7-day washout period between doses, subjects concurrently received a single oral dose of metformin (850 mg) and a single 30-minute IV infusion of plazomicin (15 mg/kg) on Day 8 (Treatment Period 2). In both periods, fifteen blood samples per subject were collected to measure plasma metformin or metformin and plazomicin concentrations for up to 24 hours post-dose of metformin. Urine samples were collected for up to 24 hours post-dose after each metformin dose for determination of metformin renal clearance. Subjects randomized to Sequence 2 concurrently received a single dose of metformin (850 mg) and a single 30-minute IV infusion of plazomicin (15 mg/kg) on Day 1 (Treatment Period 1) and received a single dose of metformin (850 mg) on Day 8 (Treatment Period 2) after a 7-day washout period.

Results

Pharmacokinetic Results

Refer to Figure 1 for the mean plasma metformin concentration time profile with and without plazomicin, Table 1 for the summary of metformin PK parameters with and without plazomicin, Table 2 for statistical results of the metformin parameter comparisons.

Figure 1. Mean Plasma Metformin Concentration-Time Curves Following a Single Oral Dose of Metformin (850 mg) Alone and Single Oral Dose of Metformin (850 mg) With an IV Infusion of Plazomicin (15 mg/kg)



Source: Tables 14.2.1.1 and 14.2.1.2
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Table 1. Summary of Plasma Metformin Pharmacokinetics Following a Single Oral Dose of Metformin (850 mg) Alone and Single Oral Dose of Metformin (850 mg) With an IV Infusion of Plazomicin (15 mg/kg) (Adapted from Table 11-2 from the report for Study ACHN-490-011)

Pharmacokinetic Parameters	Metformin Alone	Metformin + Plazomicin
AUC0-tlast (hr*ng/mL)	8740 (32.2) [n=16]	9060 (35.6) [n=16]
AUC0-inf (hr*ng/mL)	9010 (31.6) [n=16]	9370 (34.3) [n=16]
Cmax (ng/mL)	1430 (29.0) [n=16]	1490 (34.5) [n=16]
Tmax (hr)	2.50 (1.50, 4.00) [n=16]	3.00 (1.50, 4.00) [n=16]
CL/F (L/hr)	73.6 (31.6) [n=16]	70.8 (34.3) [n=16]
Vz/F (L)	459 (28.8) [n=16]	406 (31.6) [n=16]
Kel (1/hr)	0.160 (23.5) [n=16]	0.174 (22.7) [n=16]
T1/2 (hr)	4.33 (23.5) [n=16]	3.98 (22.7) [n=16]

Parameters are presented as Geometric Mean (Geom CV%)

.

Table 2. Statistical Analysis Results of Metformin Pharmacokinetic Parameters Following a Single Oral Dose of Metformin (850 mg) With an IV Infusion of Plazomicin (15 mg/kg) *Versus* a Single Oral Dose of Metformin (850 mg) Alone (Adapted from Table 11-3 in report of Study ACHN-490-011)

Parameter	n	GLSM* Ratio % (metformin+plazomicin/metformin only)	90% CI
AUC0-inf	16	103.95	94.16-114.76
Cmax	16	104.49	95.05-114.87

**Geometric least-squares means (GLSM) are calculated by exponentiating the LSMs derived from the ANOVA.*
Ratio of geometric least-squares means (GLSM) = 100(test/reference)*

The total cumulative percentage of metformin excreted in urine reached approximately 40% of the administered dose by the end of the sample collection interval. A similar urinary excretion profile was also observed following a single oral dose of metformin (850 mg) with an IV infusion of plazomicin (15 mg/kg), the Geometric Mean maximal metformin excretion was achieved between 0 to 8 hours post-dose and 40% of the administered metformin dose was recovered in urine by 24 hours post-dose. Please refer to Table 3 for details.

Table 3. Summary of Metformin Urinary Pharmacokinetic Parameters Following a Single Oral Dose of Metformin (850 mg) Alone and Single Oral Dose of Metformin (850 mg) With an IV Infusion of Plazomicin (15 mg/kg) Recovered within 24 hours Post-dose (Adapted from Table 11-4 in report of Study ACHN-490-011)

Urine Parameters	Metformin Alone	Metformin + Plazomicin
CumAe (mg)	265 (25.1) [n=16]	276 (25.8) [n=16]
CumFe (%)	40.0 (25.1) [n=16]	41.7 (25.8) [n=16]

CumAe: Cumulative amount of analyte excreted in the urine, calculated for each collection interval
CumFe: Cumulative percentage of administered dose recovered in the urine, calculated for each collection interval.

Following a single oral dose of metformin (850 mg) with an IV infusion of plazomicin (15 mg/kg), the geometric mean $AUC_{0-\infty}$ values of plazomicin was 245 hr*mg/L. Geometric mean clearance and apparent volume of distribution were 4.64 L/hr and 17.3 L, respectively. The geometric mean half-life of plazomicin was 3.81 hours.

Conclusion

- The study design appears acceptable to evaluate the DDI between metformin and plazomicin. Plazomicin did not affect the PK of metformin, indicating that plazomicin is not a MATE transporter inhibitor *in vivo*.

- The plazomicin PK parameters in this study were in line with the ones for healthy subjects receiving same dose in other studies.

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