**ABSTRACT**

Plazomicin (PLZ) is a next generation aminoglycoside (AG) that overcomes common AG resistance mechanisms and retains activity against extended spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant Enterobacteriaceae (CRE). Phase 3 studies in complicated urinary tract infections and in serious infections due to CRE have been completed. To better understand the tissue distribution of PLZ, quantitative whole-body autoradiography (QWBA) was conducted in male Sprague-Dawley (SD) and Long-Evans (LE) rats administered [14C]-PLZ. Six SD and LE rats were administered a single 30-minute IV infusion dose of 80 mg/kg [14C]-PLZ (100 μCi/kg). One animal was euthanized per time point (up to 100 and 504 h post-dose for SD and LC rats, respectively) for blood collection and carcass analysis. At each time point, one animal was euthanized by CO2 inhalation (5% CO2). Radio-HPLC and LC/MS/MS analyses of plasma and urine samples from SD rats showed that plazomicin parent compound represented the entirety of the radioactivity.

**RESULTS**

- The [14C]-PLZ radioactivity was widely distributed to all SD tissues analyzed. The whole body autoradiogram (WBA) indicated that PLZ substrate is not partitioning into the red blood cells. Tissue plasma AUC0-t: plasma AUC0-t ratios for radioactivity in kidney, large intestine (wall), liver, spleen, bone marrow (femur), and adrenal gland. Radio-HPLC and LC-MS/MS analyses of plasma and urine samples confirmed that the radioactivity derived from [14C]-PLZ exhibited minimal to no affinity to melanin.

- Following a single IV administration of [14C]-PLZ rats, radioactivity was widely distributed to all SD tissues analyzed. As expected for AG drugs, [14C]-PLZ radioactivity was highest in the kidney at all time points analyzed, with 10%, 1.8%, and 0.6% of the administered dose in the kidney at 0.083, 24, and 168 h post-dose, respectively.

**CONCLUSIONS**

- The radiotherapy derived from intravenously administered [14C]-plazomicin exhibited minimal to no affinity to melanin, suggesting plazomicin is not likely to be retained in pigmented tissues.

- The potential contribution of sustained plazomicin exposure in the kidneys to the high and sustained microbiological eradication rates observed in the Phase 3 cUTI study warrants further investigation.

**REFERENCES**


**ACKNOWLEDGMENTS**

Thank you to Charles River Laboratories for medical writing support and sponsor preparation support. This work was supported by Achaogen (Inglewood, CA) under the terms of a master services agreement with Charles River Laboratories under Study Director Justin Godsey.

**Tissue Distribution of [14C]-Plazomicin in Rats**

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**INTRODUCTION**

- Plazomicin (PLZ) is a next-generation aminoglycoside (AG) that overcomes common AG resistance mechanisms and retains activity against extended spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant Enterobacteriaceae (CRE).

- Plazomicin is under development for the treatment of complicated urinary tract infections (cUTIs) and other serious bacterial infections that affect critically ill patients, especially those due to multidrug-resistant (MDR) CRE.

- The objective of this study was to determine the tissue distribution of radioactivity after a single intravenous (IV) administration of [14C]-plazomicin.

**METHODS**

- [14C]-Plazomicin was administered to instrumented Sprague-Dawley (SD) and noninstrumented Long-Evans (LE) rats by 30-minute IV infusion at a dose of 80 mg/kg (100 μCi/kg). Tissue distribution was determined by quantitative whole-body autoradiography at the following time points: SD rats—0.083, 0.5, 1, 24, and 168 h post IV infusion (EOIV); LE rats—0.083, 0.5, 1, 24, 168, 336, and 504 h post-EOIV. At each time point, one animal was euthanized by CO2 inhalation (5% CO2). Radio-HPLC and LC/MS/MS analyses of plasma and urine samples confirmed that the radioactivity derived from [14C]-PLZ exhibited minimal to no affinity to melanin.

- Following a single IV administration of [14C]-PLZ rats, radioactivity was widely distributed to all LE tissues analyzed. As expected for AG drugs, [14C]-PLZ radioactivity was highest in the kidney at all time points analyzed, with 6%, 1.8%, and 0.6% of the administered dose in the kidney at 0.083, 24, and 168 h post-dose, respectively.

**RESULTS**

- The [14C]-plazomicin radioactivity was widely distributed to all tissues analyzed. Tissue plasma AUC0-t: plasma AUC0-t ratios for radioactivity in kidney, large intestine (wall), liver, spleen, bone marrow (femur), and adrenal gland. Radio-HPLC and LC-MS/MS analyses of plasma and urine samples confirmed that the radioactivity derived from [14C]-plazomicin exhibited minimal to no affinity to melanin.

- The radiotherapy derived from intravenously administered [14C]-plazomicin exhibited minimal to no affinity to melanin, suggesting plazomicin is not likely to be retained in pigmented tissues.

- The potential contribution of sustained plazomicin exposure in the kidneys to the high and sustained microbiological eradication rates observed in the Phase 3 cUTI study warrants further investigation.

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