Mass Balance, Metabolism, and Excretion of [14C]-Plazomicin in Healthy Human Subjects

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INTRODUCTION

• Plazomicin is an aminoglycoside (AG) that was engineered to overcome AG-resistance mechanisms, the most common of which involves modification of the ribosomes, which results in decreased binding to the primary site of action.

• Plazomicin is approved by the FDA and drug administration for the treatment of complicated skin and skin structure infections, including polymicrobial infections.

• This work characterizes the mass balance, excretion, and metabolism of [14C]-plazomicin in healthy human subjects.

METHODS

Study Design

• This was a single-center, open-label, nonrandomized study (NCT03177278).

• Six healthy male subjects were administered a single 30-minute intravenous (IV) infusion of [14C]-plazomicin sulfate (50 mg/mL).

• Participants were confined to the clinical research unit (CRU) for in-house observation for 14 days following the study treatment administration (Figure 1).

• Subjects were discharged from the CRU starting on Day 7 if following criteria were met:
  - ≤ 8% of the radiolabeled dose was recovered.
  - ≥ 90% of the radiolabeled dose was recovered.

• Plasma samples were pooled across all subjects according to the Hamilton method.2

• For plasma and whole blood total radioactivity, the total [14C]-plazomicin radioactivity was collected as a series of 15-second to 1-minute fractions of the radioactivity dose.

Sample Preparation and Analysis

• Plasma, urine, and fecal homogenates were mixed with sodium hydroxide (1 M) at 6.5 ± 0.2.

• Sodium hydroxide (1 M) was used to adjust the drug solution pH to 6.5 ± 0.2.

• Plazomicin was predominantly eliminated renally, with 97.5% of the dose recovered as parent drug in urine by the end of the last sampling interval (Figure 2).

• Approximately 56% of the total administered radioactivity was recovered in urine within 72 hours post-dose.

• The plasma pharmacokinetic (PK) parameters were generally consistent with those generated in other phase 1 studies.3

• Plazomicin pharmacokinetic parameters were generally consistent with those conclude with those generated in other phase 1 studies.4

• Plazomicin does not appear to be metabolized to any appreciable extent as no plasma metabolites were observed.5

• The 14C-[plazomicin] radiolabeled material contained 14C-labeled impurities.

• Results are consistent with nonclinical and clinical data for plazomicin and with the 14C-labeling.

CONCLUSIONS

• Drug development on plazomicin continues with the aim of identifying an unchanged drug in vivo and a marginable amount (≤ 5%) in plasma.

• Plazomicin does not appear to be metabolized in vivo or excreted in urine, confirming the potential for [14C]-plazomicin clinical evaluation in vivo.

REFERENCES


5. Taylor Choi; Julie D. Seroogy; Mitesh Sanghvi; Shyeilla V. Dhuria; Taylor Choi; Julie D. Seroogy; Mitesh Sanghvi; Shyeilla V. Dhuria 1 Achaogen Inc., South San Francisco, CA, USA; 2Xceleron, a Pharmaron company, Germantown, MD, USA

MS is an employee of Xceleron, a Pharmaron company.

TC, JDS, and SVD are employees or former employees of and stockholders in Achaogen; TC and SVD are employees or former employees of and stockholders in Health and Human Services, under Contract No. HHSO100201000046C.

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DISCLOSURES

None of the authors have any financial ties or other potential conflicts of interest to declare.

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Figure 1. Structure of Plazomicin

Figure 2. Screening, Treatment, and Follow-up

Table 1. Demographic Summary

Table 2. Summary of Plasma and Whole Blood Total Radioactivity and Plazomicin (PK)

Figure 3. Mean Cumulative Percent of [14C]-Plazomicin Dose Excreted Based on Total Radioactivity in urine, Feces, and Total Viscous Samples at the Collection Interval

Figure 4. Mean Plasma and Whole Blood Total Radioactivity (ng eq/mL) vs Time

Figure 5. Mean Plasma Radioactivity- Equivalent Concentration (ng/mL) vs Time

Figure 6. Radiochromatogram of [14C]-Plazomicin-related Molecules in Urine

Figure 4. Radiochromatogram of [14C]-Plazomicin-related Molecules in Urine

Figure 5. Mean Plasma Radioactivity- Equivalent Concentration (ng/mL) vs Time

Figure 6. Radiochromatogram of [14C]-Plazomicin-related Molecules in Urine