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Delpazolid population pharmacokinetics in patients with pulmonary tuberculosis

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DElpazolid dose-finding and COmbination DEvelopment (DECODE)

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Abstract

Background Linezolid is currently recommended for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the WHO. However, this drug is associated with severe adverse effects such as myelosuppression and peripheral neuropathy [1]. Delpazolid, a new oxazolidinone, has demonstrated early bactericidal activity with a favorable safety profile when administered up to 14 days [2]. Therefore, if shown effective and with a lower risk of adverse effects over longer treatment durations [3], delpazolid could be a promising alternative for linezolid in MDR-TB treatment.

Methods The DECODE study was a phase 2b, open-label, randomized, controlled dose-ranging trial performed in South Africa and Tanzania. A total of 76 patients with newly diagnosed, drug sensitive pulmonary tuberculosis (TB) were included. Delpazolid was administered in combination with standard-dose bedaquiline, delamanid and moxifloxacin over 16 weeks. Patients were randomized into one of the five arms receiving 0 mg, 400 mg, 800 mg, 1200 mg once daily or 800 mg twice daily, respectively. Intensive pharmacokinetic (PK) sampling was conducted in all patients on day 14 of treatment, with samples taken at 0 (pre-dose) and 1, 2, 4, 8, 12, and 24 hours after dosing. Drug concentrations in plasma were determined using a validated LC-MS/MS combination assay covering all analytes. Sputum samples were collected every week during the treatment period. A population PK model was developed using non-linear mixed effects methodology implemented is software NONMEM. The model will be used to generate individual exposure metrics for evaluating delpazolid efficacy characterized by the change in mycobacterial load over time on treatment.

Results The dataset for the population PK model included 402 plasma concentrations from 60 patients (14 women and 46 men). A two-compartment model with first-order absorption, first-order elimination and a proportional error best described delpazolid PK. The final model included allometric scaling with weight and an effect of sex on bioavailability as covariates. Delpazolid clearance was 40.3 L/h (95% CI 33.2-47.4) for a 70kg person, with an interindividual variability of 10% coefficient of variation (relative standard error 28%). The bioavailability in women was estimated to be 54% higher (95% CI 8.4-99 %) than in men. Based on individual predictions, median $AUC_{0\text{-}24}$ (mg/L*h) values were 10.2 for 400 mg, 28.3 for 800 mg, 44.7 for 1200 mg (all once daily), and 68.1 for 800mg twice daily.

Conclusion and discussion Delpazolid exposures increased linearly with dose. The biological rational for the higher bioavailability in women is unclear, the proportion females was relatively low (23%) and the magnitude of the estimate uncertain. The exposure-response analysis based on this population PK model is currently ongoing.

References

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