Absorption, Distribution, and Excretion of [14C]Rezafungin after Single-Dose Intravenous Administration in Rats and Monkeys

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INTRODUCTION AND PURPOSE
Rezafungin (RZF) is a novel echinocandin antifungal in development for the treatment as well as prevention (prophylaxis) of invasive fungal infections. RZF is differentiated from previous echinocandins by greater stability and efficacy-enhancing, front-loaded pharmacokinetics (PK) with once-weekly dosing.

METHODS
Male Sprague-Dawley (SD) albino (intact and bile duct–cannulated) as well as Long-Evans (LE) pigmented rats were administered a single IV bolus dose of [14C]RZF. Urine and feces samples were collected for up to 30 days post-dose.

RESULTS
In the intact SD rat, mean cumulative recovery of [14C]RZF radioactivity in rats was 95% of the dose. The primary route of elimination was in feces, which accounted for 70% of the dose (predominantly parent drug) after 2 weeks. An average of 14% and 3% of the administered dose was recovered in the urine and cage residues, respectively, with 8% remaining in the carcass.

In the monkey, a similar pattern of elimination to that in the rat was observed but at a lower elimination rate, with 74% cumulative recovery after 30 days. As in the rat, the primary route of elimination was in feces (60%) with 10% and 4% recovered in urine and cage residue, respectively.

METHODS (con’t)
In bile duct-cannulated rats, 35% of the dose was recovered in feces suggesting intestinal secretion of RZF, while 17%, 14%, 30%, and 1% was recovered in the bile, urine, carcass, and cage residues, respectively, for a cumulative recovery of 97%.

RESULTS (con’t)
In the LE rat, [14C]RZF radioactivity was extensively distributed throughout the body within 1 hour following a single IV dose.

Similar radioactivity distribution trends and exposures were observed in pigmented LE and non-pigmented SD skin indicating that [14C]RZF was not specifically associated with melanin.

RESULTS (con’t)
In the monkey, a similar pattern of elimination to that in the rat was observed but at a lower elimination rate, with 74% cumulative recovery after 30 days. As in the rat, the primary route of elimination was in feces (60%) with 10% and 4% recovered in urine and cage residue, respectively.

Low-level oxidative metabolites (2, 3-, di-hydroxypentyl CD101, and despentyl-CD101) were observed during metabolite profiling at later (≥4 hr) timepoints, with greater levels detected in rat than in monkey plasma/excreta.

REFERENCES
2. Ong V., et al., “CD101 Lung Epithelial Lining Fluid (ELF) Concentrations Substantiate Its Use For Prophylaxis (predominantly as parent drug), RZF has the potential to be used as treatment and prophylaxis against invasive fungal infections.

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CONCLUSIONS
As [14C]RZF is extensively distributed throughout the entire body and is cleared slowly primarily via excretion in feces (predominantly as parent drug), RZF has the potential to be used as treatment and prophylaxis against invasive fungal infections.

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