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Safety and pharmacokinetics of multiple ascending doses of WCK 5107 (zidebactam) and WCK 5222 (cefepime and zidebactam)

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Background: WCK 5107 (zidebactam) is a new chemical entity (NCE) exhibiting a novel mode of action. WCK 5222, a combination of cefepime and β-lactam enhancer, zidebactam, is being developed to provide a therapeutic option for the treatment of infections caused by MDR Gram-negative pathogens including enterics and *Pseudomonas* harbouring metallo-β-lactamases (MBL) as well as carbapenem-hydrolysing (CHDL) Class D β-lactamases in *Acinetobacter spp* and *Klebsiella*. WCK 5222 is based on a novel 'enhancer' mechanism that involves complementary binding to essential PBPs by its constituents, cefepime and zidebactam. Multiple Ascending Doses (MAD) studies were conducted to evaluate the safety, tolerability and pharmacokinetics of zidebactam and WCK 5222 in healthy subjects.

Material/methods: In these double-blind studies, sequential cohorts (n= 8 active and 2 placebo) received multiple q8h intravenous infusions of zidebactam (1 g or 2 g) for 7 days or WCK 5222 (cefepime 2 g and zidebactam 1 g or cefepime 2 g and zidebactam 2 g) for 10 days.

Results: Exposure parameters for zidebactam ($AUC_{(0\text{-}nf)}$ and C_{max}) were comparable for each dosing interval within each dosing day and between dosing days. Summary of exposure parameters for Zidebactam and Cefepime are provided in Table 1.

Table 1: Summary of Exposure Parameters for Zidebactam and Cefepime

Parameter	Zidebactam MAD Study (1 - 2 g q8h for 7 days)	WCK 5222 MAD Study (cefepime 2 g and zidebactam 1 – 2 g q8h for 10 days)	
	Zidebactam	Zidebactam	Cefepime
C_{max} (µg/mL)	59.5 - 129	57.2 - 130	130 - 160
$AUC_{(0\text{-}Inf)}$ (µg*h/mL)	150 - 343	152 - 402	341 - 508

Majority of the administered doses of zidebactam and cefepime were excreted as unchanged in urine. Dose proportional increase was observed in AUCs and C_{max} between 1 g and 2 g administration of zidebactam in both studies. No deaths or SAEs were reported and all treatment-emergent adverse events (TEAEs) were mild in severity.

Conclusions:

- Zidebactam exposures were dose proportional within the 3 g to 6 g dose range.
- No accumulation of zidebactam or cefepime was observed after 10 days of q8h dosing.
- No significant PK interaction was observed when zidebactam and cefepime were co-administered.
- Multiple doses (up to 6 g) of zidebactam and WCK 5222 were well tolerated up to 10 days.