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Safety and Pharmacokinetics of Single and Multiple Intravenous Doses of WCK 4282 (Cefepime and Tazobactam) in Healthy Volunteers

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Background: WCK 4282 is an injectable combination product consisting of cefepime (FEP) and tazobactam (TAZ), in a 1:1 proportion (FEP 2g + TAZ 2g). It is being developed as a new therapeutic option for the treatment of a wide range of Gram-negative infections prevalent in hospital settings such as complicated urinary tract infections (cUTI), nosocomial pneumonia, and complicated intra-abdominal infections (cIAI).

Material/methods: This was a Phase 1, double-blind, randomized, multiple-dose, and single-dose crossover, 2-part study in healthy male and female subjects.

Part 1 (N=36): 30 subjects were administered multiple intravenous (IV) doses of FEP-TAZ 4g (2g FEP + 2g TAZ) [N=15] or FEP-TAZ 3g (2g FEP + 1g TAZ) [N=15] q8h for 10 days; 6 received placebo in a blinded manner.

Part 2 (N=9): 9 subjects were administered single IV doses of FEP-TAZ 4g (2g FEP + 2g TAZ), 2g FEP, and 2g TAZ based on a double-blind randomization schedule in a 3-period cross-over manner.

Results: After multiple doses, the ratio of $AUC_{0-24}(\text{Day } 10)$ to $AUC_{0-24}(\text{Day } 1)$ for FEP was 1.02 and 1.04 for FEP-TAZ 3g and FEP-TAZ 4g respectively whereas, the ratio of $AUC_{0-24}(\text{Day } 10)$ to $AUC_{0-24}(\text{Day } 1)$ for TAZ was 0.80 and 0.78 respectively. In the cross-over cohort, the AUC_{0-24} and C_{max} values were similar for FEP and TAZ, when administered alone and as FEP-TAZ. The summary of exposure parameters for FEP and TAZ are provided in Table 1.

Table 1: Summary of Exposure Parameters for FEP and TAZ

Study part	Parameter	FEP		TAZ	
		Day 1	Day 10	Day 1	Day 10
Part 1 FEP-TAZ 4g	C _{max} , µg/mL	90.79	95.91	55.9	40.33
	AUC ₀₋₂₄ , µg.h/mL	930.48	960.23	311.54	235.47
Part 1 FEP-TAZ 3g	C _{max} , µg/mL	79.52	87.09	23.2	17.68
	AUC ₀₋₂₄ , µg.h/mL	812.55	828.82	120.07	98.11
Part 2 (Crossover) FEP 2g TAZ 2g FEP-TAZ 4g	C _{max} , µg/mL	84.77 (FEP 2g alone)		57.26 (TAZ 2g alone)	
		81.99 (FEP 2g in FEP-TAZ 4g)		57.58 (TAZ 2g in FEP-TAZ 4g)	
Part 2 (Crossover) FEP 2g TAZ 2g FEP-TAZ 4g	AUC ₀₋₂₄ , µg.h/mL	274.81 (FEP 2g alone)		96.17 (TAZ 2g alone)	
		260.54 (FEP 2g in FEP-TAZ 4g)		100.44 (TAZ 2g in FEP-TAZ 4g)	

There were no deaths, serious or severe adverse events (AEs) observed in the study. Infusion site reaction was the most commonly reported AE. All AEs were mild except one (increased transaminases), which was of moderate intensity and unrelated to study drug, and recovered at the follow-up.

Conclusions: There was no evidence of pharmacokinetic interaction between FEP and TAZ after administration in a cross-over manner.

Overall, 10-day multiple repeated IV doses of FEP-TAZ (4g and 3g) and single doses of FEP-TAZ 4g, FEP 2g, and TAZ 2g were safe and well tolerated.