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Paper Poster Session
Cefepime-tazobactam

Safety, tolerability and pharmacokinetics of WCK 4282 (fep-taz) in healthy adult subjects

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Background: WCK 4282 (FEP-TAZ) is an injectable combination of cefepime (FEP) and tazobactam (TAZ). FEP-TAZ is being developed as a new therapeutic option for the treatment of a 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 randomized, double-blind, placebo-controlled, dose escalation study. 30 healthy subjects were enrolled into 3 cohorts with 8 subjects on FEP-TAZ and 2 subjects on placebo in each cohort. Cohort 1 received 1 g FEP + 1 g TAZ or placebo q8h for 7 days; Cohort 2 received 2 g FEP + 2 g TAZ or placebo q12h for 7 days and Cohort 3 received 2 g FEP + 2 g TAZ or placebo q8h for 7 days. Pharmacokinetic (PK) parameters were determined from serial plasma and urine samples collected over a 48-hour interval on the first and seventh dosing day. The measured PK parameters included C_{max}, C_{last}, C_{8h}, C_{12h}, t_{max}, t_{last}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-24}, AUC_{0-inf}, %AUC, CL, Vz and Ae_{urine}. Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events were monitored throughout the study.

Results: The mean FEP AUC_{0-inf} was 164.1 µg.hr/mL, 334 µg.hr/mL, and 329.3 µg.hr/mL on Day 1, following the first dose in Cohorts 1, 2, and 3, respectively. The mean TAZ AUC_{0-inf} was 35.3 µg.hr/mL, 87.0 µg.hr/mL, and 91.8 µg.hr/mL on Day 1, following the first dose in Cohorts 1, 2, and 3, respectively. The AUCs were comparable for TAZ at Day 1 and Day 7, whereas AUCs for FEP were approximately 10-16% higher on Day 7 compared on Day 1. The maximum concentrations (C_{max}) of FEP and TAZ were typically reached at the end of infusion in all cohorts. FEP and TAZ reached steady-state by the second day of dosing. The terminal half-life ($t_{1/2}$) of FEP and TAZ ranged from 1.63 h to 2.62 h and 0.732 h to 2.16 h, respectively, on Day 1. The AEs reported were generally mild in intensity and resolved during the study. One serious adverse event, a femur fracture, was reported which was unrelated to the study drug and occurred after discharge from the clinic. No clinically significant changes in vital signs and ECGs were reported.

Conclusions: There was no significant accumulation of FEP and TAZ following q12h or q8h IV administration of FEP-TAZ for 7 days. Overall, multiple escalating doses of FEP-TAZ were safe and well tolerated by healthy adult human subjects.