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Cefiderocol Compared with Imipenem/Cirastatin in the Treatment of Adults with Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis: Results from a Multicenter, Double-blind, Randomized Study

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Background: Cefiderocol (S-649266) is a novel siderophore cephalosporin with potent activity against Gram-negative bacteria (Enterobacteriaceae and non-fermenters) including multidrug-resistant (MDR) pathogens, and is being developed to treat serious MDR Gram-negative infections. The primary objective of this study was to compare cefiderocol with imipenem/cilastatin (IPM/CS) on the composite endpoint of clinical and microbiologic outcome in a patient population at risk for MDR Gram-negative pathogens.

Material/methods: This was a multicenter, double-blind, randomized trial in patients with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis (AUP). AUP was limited to 30% of the patient population. Hospitalized patients 18 years and older were randomized 2:1 to receive intravenous (IV) cefiderocol (2 g) or IPM/CS (1/1 g) over 1 hour, every 8-hours for 7 to 14 days. No IV to oral antibiotic step down was permitted. The primary composite endpoint was clinical and

microbiological response at test of cure (TOC, 7 days following the end of treatment) in the Microbiological Intent to Treat (MITT) population. A sensitivity analysis was performed in the Microbiologically Evaluable (ME) population. The study was designed to demonstrate non-inferiority to IPM/CS within a margin of 15%. One of the key secondary endpoints was per-patient microbiological response at TOC in the MITT population.

Results: Of 452 randomized patients, 371 had Gram-negative pathogens at baseline (MITT). The median treatment duration was 9.0 days in both treatment arms. In the MITT population, 100 (27 %) patients had AUP. Noninferiority of cefiderocol vs IPM/CS was demonstrated for the primary composite endpoint of clinical and microbiologic response at TOC: 72.6 % (183 / 252) in cefiderocol vs 54.6 % (65 / 119) in the IPM/CS group (adjusted difference of 18.58%, 95% CI : 8.23, 28.92). Per-patient microbiological response at TOC was 73.0 % (184/252) in the cefiderocol and 56.3% (67/119) in the IPM/CS group (adjusted difference of 17.25%, 95% CI: 6.92, 27.58). Both composite and microbiologic results showed superiority of cefiderocol for both MITT and ME patient populations. Adverse events were reported in 120 (40.0 %) patients receiving cefiderocol vs 74 (50.0 %) on IPM/CS, the majority being mild or moderate in severity. Serious adverse events were reported in 14 (4.7 %) receiving cefiderocol vs 12 (8.1 %) on IPM/CS. One death, not considered drug related, was reported in a subject exposed to cefiderocol.

Conclusions: Treatment with cefiderocol resulted in the superiority over IPM/CS in patients with cUTI at risk of MDR Gram-negative infections. Cefiderocol was generally well tolerated with no safety concerns identified.