27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: P060 News on relebactam and vaborbactam

Category: 5c. New antibacterial agents: clinical trials

24 April 2017, 12:30 - 13:30
P1289

Clinical Outcomes in Adults with Complicated Urinary Tract Infections (cUTI), including Acute Pyelonephritis (AP) in TANGO 1, a Phase 3 Randomized, Double-blind, Double-dummy Trial Comparing Meropenem-Vaborbactam (M-V) with Piperacillin-Tazobactam (P-T)

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Background: The fixed combination of meropenem 2g and vaborbactam 2g by intravenous (IV) infusion is being developed to treat serious gram-negative infections, such as complicated urinary tract infections (cUTIs), including those infections caused by multidrug resistant (MDR) bacteria, which includes those resistant to currently available carbapenems.

Material/methods: We conducted a Phase 3, multicenter, double-blind, double-dummy, randomized, parallel-group study (TANGO 1) evaluating efficacy, safety, and tolerability of meropenem-vaborbactam (M-V) compared with piperacillin-tazobactam (P-T) for treatment of adults (≥ 18 years) with cUTI or acute pyelonephritis (AP). Patients meeting inclusion criteria for cUTI or AP were randomized 1:1 to receive either M-V or P-T. Randomization was stratified by geographic region and type of infection (AP, cUTI with removable source of infection, and cUTI with a non-removable source). After a minimum of 15 doses, patients in both arms could be switched to oral levofloxacin if they met pre-specified criteria. Primary efficacy endpoint for the FDA was proportion of subjects in the Microbiological Modified Intent-to-Treat (m-MITT) population who achieved overall success at End of IV Treatment (EOIVT), a composite endpoint that includes both clinical and microbiologic outcomes. A

clinical outcome of Cure or Improvement and a microbiologic outcome of eradication (FDA's CFU/mL criterion) at the EIOIVT visit were necessary to achieve overall success.

Results: Of 550 subjects randomized, 545 received at least one dose of study drug (272 in M-V group and 273 in P-T group). Overall, a similar percentage of subjects with AP (59.2% and 59.0%) and cUTI (40.8% and 41.0%) were enrolled in each group. At EOIVT (mMITT population), overall success rates were higher in the M-V group compared to the P-T group in subjects with AP (97.5% vs 94.1%), in subjects with cUTI and a removable source of infection (100% vs 92.1%), and in subjects with cUTI and a non-removable source of infection (100% vs 95.3%). The lower limit of the 95% CI was > -15% in each infection type. In the M-V and P-T groups, eradication rates at Test of Cure (TOC; m-MITT population) were 74.2% and 63.4% in subjects with AP compared to 60.0% and 52.6% in subjects with cUTI and a removable source of infection and 48.6% and 48.8% in subjects with cUTI and a non-removable source.

Conclusions: M-V is noninferior to P-T for overall success in subjects with AP and subjects with cUTI and either a removable or non-removable source of infection. M-V is non-inferior to P-T for microbial eradication at the TOC visit in patients with cUTI or AP. Eradication rates in both groups were highest in AP patients and lowest in cUTI patients with a non-removable source of infection. M-V appears to be a viable treatment for AP and cUTIs.