Meropenem-vaborbactam (M-V) versus piperacillin-tazobactam (P-T) in the treatment of adults with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP) in TANGO 1, a phase 3 randomized, double-blind, double-dummy trial

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Background: Meropenem-vaborbactam (formerly RPX7009) is a new carbapenem/beta-lactamase inhibitor combination designed to have enhanced in vitro activity against select carbapenemase-producing carbapenem-resistant Enterobacteriaceae, and is a potential new option for the treatment of severe gram-negative infections. The efficacy and safety of meropenem-vaborbactam (M-V) was assessed in a Phase 3 randomized trial in complicated urinary tract infections (cUTI).

Methods: We conducted a Phase 3, randomized, double-blind, double-dummy trial (TANGO 1) in adult patients (≥ 18 years) with cUTI, including acute pyelonephritis (AP). Patients meeting the inclusion criteria for cUTI or AP were randomized 1:1 to receive M-V (2g/2g via 3-hr infusion) or P-T (4g/0.5g via 30-min infusion) every 8 hrs. Enrollment 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 could switch to oral levofloxacin if they met pre-specified criteria, so as to complete 10 days of total treatment. The primary endpoint for the European Medicines Agency (EMA) was the proportion of patients with microbial eradication (reduction of the baseline pathogen to <10^3 CFU/ml) at the Test of Cure visit ([TOC] 5-9 days after completion of treatment). We analyzed this endpoint in two primary analysis populations (popn) -- the microbiologic modified intent-to-treat
(mMITT) and the microbiologic evaluable (ME). There was a pre-specified non-inferiority (NI) margin of 15%. Both adverse events (AEs) and serious AEs (SAEs) were recorded.

**Results:** 550 patients were enrolled; 374 (68%) had at least 1 baseline pathogen and comprised the mMITT popn while 347 (63.1%) were included in the ME popn. In the mMITT popn, 221 (59.1%) patients were enrolled with AP, and 153 (40.9%) with cUTI. Among the mMITT cohort, microbiologic eradication with M-V occurred in 128/192 (66.7%) compared to 105/182 (57.7%) with P-T. For the ME popn, microbiologic eradication was noted in 118/178 (66.3%) for M-V vs 102/169 (60.4%) for P-T. The treatment effect differences (95% CI) between the groups were 9.0% (-0.9, 18.7) and 5.9% (-4.2, 16.0) favoring M-V for the two popns, respectively. AEs were reported in 106/272 (39.0%) patients on M-V vs 97/273 (35.5%) on P-T. Discontinuations from study drug due to an AE occurred in 7 patients (2.6%) on M-V and 14 (5.1%) on P-T. SAEs were reported in 11 patients (4.0%) receiving M-V vs 12 patients (4.4%) on P-T. Two deaths occurred in each group.

**Conclusions:** M-V proved to be non-inferior to P-T for the EMA primary endpoint of microbial eradication at the TOC visit in the treatment of patients with cUTI/AP. M-V was well tolerated, with an adverse event profile similar to P-T. M-V appears to be a safe and efficacious treatment for cUTIs.