Safety, tolerability and pharmacokinetics of nacubactam, a novel β-lactamase inhibitor, administered alone and with meropenem in healthy volunteers

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Background: Nacubactam (OP0595, RG6080) is a novel β-lactamase inhibitor with activity encompassing β-lactamases in Ambler Classes A, C and D, but also possessing direct antibacterial activity through inhibition of PBP2. A previous clinical study had demonstrated that single nacubactam doses up to 2000 mg were well tolerated by healthy volunteers. Here we report a second clinical study to assess the safety, tolerability, and pharmacokinetics of Q8h repeat dosing with nacubactam, administered alone and co-administered with 2g Q8h meropenem.

Materials/methods: A randomized, double-blind, placebo controlled, three part, ascending dose study. Parts 1 and 2 evaluated nacubactam alone; Part 3 evaluated nacubactam co-administered with meropenem. Healthy volunteers were enrolled in sequential cohorts, and within each cohort subjects were randomized to either active treatment or placebo Q8h for up to 7 days.

Results: Nacubactam doses up to 4000 mg Q8h, and single doses up to 8000 mg, administered as 1.5 hr IV infusions were well tolerated. Nacubactam 2000 mg Q8h co-administered with meropenem 2000 mg Q8h was also considered to be safe and well tolerated. There were no SAEs or withdrawals because of AEs from dosing with nacubactam. There was no apparent relationship with dose in the pattern, incidence, or severity of AEs, and no dose limiting AEs were identified. The most common AEs reported were associated with the intravenous access, and the AEs during treatment with meropenem plus nacubactam were consistent with the known safety profile of meropenem. Nacubactam dosing had no effect on heart rate-corrected QT interval duration or other ECG and vital signs parameters. There were no apparent trends in laboratory tests, and no changes in established measures of renal function.

Nacubactam pharmacokinetics were linear, and plasma exposures were dose-proportional. Renal elimination was the principal route of clearance. There was no accumulation from a Qh8 dosing regimen. There were also no pharmacokinetic drug drug interactions between nacubactam and meropenem.

Conclusions: Nacubactam, alone or co-administered with meropenem, was well tolerated by healthy volunteers, and no significant safety signals were identified. The favourable safety and pharmacokinetic profile supports continued clinical development of nacubactam.