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The pharmacokinetic (PK) interaction between omeprazole and TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI)

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Purpose of the study

TMC278 is a next-generation investigational NNRTI with potent and sustained efficacy through 96 weeks in ARV-naïve patients [1]. The current trial evaluated the PK interaction between omeprazole and TMC278. Omeprazole increases gastric pH, which can affect the solubility and gastro-intestinal absorption of TMC278. Furthermore, TMC278 has been shown to induce CYP2C19 *in vitro*, which may influence the omeprazole PK.

Methods

This was an open-label, randomized, 2-way crossover trial in 16 HIV-negative volunteers. In two sessions, separated by a 14-day washout, participants received TMC278 150 mg QD alone (11 days), and omeprazole 20 mg QD (22 days) with co-administration of TMC278 150 mg QD (day 12–22). All treatments were taken following breakfast. Steady-state 24-hr PK profiles of TMC278 were assessed on the last day of each session and steady-state 24-hr PK profiles of omeprazole and its metabolite 5-hydroxy(OH)-omeprazole (formed via CYP2C19) were assessed without (day 11) and with (day 22) co-administration of TMC278. PK parameters were calculated using non-compartmental analysis. The $AUC_{24\,h}$ ratio of 5-OH-omeprazole to omeprazole was used as a surrogate marker of CYP2C19 activity. Least square (LS) means and associated 90% CI of treatment ratios (test/reference) were calculated based on log-transformed PK parameters.

When combined with omeprazole, the TMC278 steady-state $AUC_{24\,h}$ decreased by 40% (LS mean ratio 0.60, 90% CI 0.51–0.71) compared to administration of TMC278 alone, and the steady-state C_{max} and C_{min} decreased by 40% (0.60, 90% CI 0.48–0.73) and 33% (0.67, 90% CI 0.58–0.78), respectively. TMC278 at steady state decreased the omeprazole $AUC_{24\,h}$ by 14% (0.86, 90%CI 0.76–0.97). Repeated doses of TMC278 resulted in a 27% increase of the $AUC_{24\,h}$ ratio of 5-OH-omeprazole to omeprazole (1.27, 90%CI 1.18–1.36). The latter suggests weak induction of CYP2C19 by TMC278 150 mg QD, an effect which will likely be less at lower doses, and is unlikely to result in clinically relevant interactions. TMC278 alone or in combination with omeprazole was generally well tolerated. No grade 3 or 4 adverse events (AEs) and no serious AEs were reported. There were no discontinuations due to AEs.

Conclusion

These results confirm the pH-dependent bioavailability of TMC278 and indicate that proton pump inhibitors and TMC278 25 mg QD (selected dose for Phase III) should not be co-administered. As an alternative, H_2-antagonists can be used, if taken 12 hours before or 4 hours after TMC278 [2].

References

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