Pharmacokinetic evaluation of the interaction between TMC125 and tenofovir disoproxil fumarate

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Abstract

Background
TMC125 is an NNRTI with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. To support concomitant administration of the NtRTI tenofovir disoproxil fumarate (TDF) and TMC125, an interaction study was conducted with TDF and TMC125 (Phase III formulation) in HIV-negative volunteers.

Methods
TMC125-C177 was an open-label, two-period, crossover, randomized trial. In Session I, 200mg TMC125 bid was administered for 7 days followed by a single morning dose on Day 8. After a washout period of 14 days, TDF 300mg qd was given from Day 1 to Day 16 of Session II. TMC125 200mg bid was coadministered during Days 9–15 in 12 volunteers randomized to Panel 1 and during Days 1–7 in 12 volunteers randomized to Panel 2 with a morning dose on Days 16 and 8, respectively. TMC125 and TDF were both administered after food intake. Plasma concentrations of TMC125 and tenofovir were assessed at steady-state over 12 and 24 hours, respectively. Pharmacokinetic (PK) parameters were estimated using non-compartmental methods and analyzed using a linear mixed effect model for a crossover design. Safety and tolerability were assessed.

Results
Twenty-four male volunteers participated (median age 26 years). When combined with TDF, TMC125 AUC_{12h} was 81% (90% CI: 75–88%) compared with administration of TMC125 alone. TMC125 C_{max} and C_{min} were 81% (90% CI: 75–88%) and 82% (90% CI: 73–91%), respectively; AUC_{0-12h}, C_{max} and C_{min} of tenofovir were 115% (90% CI: 109–121%), 115% (90% CI: 104–127%) and 119% (90% CI: 113–126%), respectively, when combined with TMC125 compared with administration of TDF alone. Adverse events (AEs) were mild to moderate. The most common AEs were nasopharyngitis and headache (five subjects each). The concomitant administration of TMC125 and TDF was generally safe and well tolerated in this trial.

Conclusions
The changes in the pharmacokinetics of TMC125 or tenofovir when TMC125 is combined with TDF, are not clinically relevant. TMC125 and TDF can be coadministered without dose modifications.

Study design
- TMC125-C177 was a Phase III, open-label, randomized, two-period crossover trial in which 24 healthy volunteers were randomized to receive TMC125 and TDF in sequence.
- TMC125 200mg bid was administered for 7 days followed by a single morning dose on Day 8. After a washout period of 14 days, TDF 300mg qd was given from Day 1 to Day 16 of Session II. TMC125 200mg bid was coadministered during Days 9–15 in 12 volunteers randomized to Panel 1 and during Days 1–7 in 12 volunteers randomized to Panel 2 with a morning dose on Days 16 and 8, respectively.
- Plasma concentrations of TMC125 and tenofovir were assessed at steady-state over 12 and 24 hours, respectively. Pharmacokinetic (PK) parameters were estimated using non-compartmental methods and analyzed using a linear mixed effect model for a crossover design. Safety and tolerability were assessed.

Safety summary
- No serious AEs or grade 3 or 4 AEs were reported.
- All reported AEs were mild in severity, except for one case of moderate hyperuricemia, not related to TMC125 or TDF.
- The most frequent AEs were nasopharyngitis (six volunteers) and headache (five volunteers).
- Four volunteers developed mild mucosal rash during TMC125 alone treatment and discontinued the study; all cases resolved without treatment within 10 days after discontinuation.
- No constant or relevant changes were found in laboratory or cardiovascular safety parameters, or physical examinations.

Conclusions
- When coadministered with TDF 300mg qd, TMC125 200mg bid exposure was decreased by 19% with similar decreases in C_{max} and C_{min}; these effects are not clinically relevant.
- The 15% increase of tenofovir exposure after the coadministration of TDF 300mg qd with TMC125 200mg bid is not clinically relevant.
- Short-term coadministration of TMC125 with TDF in healthy volunteers was generally safe and well tolerated.
- TMC125 can be coadministered with TDF without dose adjustments.

Acknowledgments
The authors would like to acknowledge:
- M-P Bouche, J&J Pharmaceutical Research and Development, Beerse, Belgium
- Demeyer, Adial Hospital Research Unit, Aalst, Belgium.

References