Pharmacokinetic interaction between TMC125 and rifabutin

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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. TMC125 and rifabutin are substrates and inducers of CYP3A4. To support concomitant administration, an interaction study was conducted.

Methods
TMC125-C156 was an open-label, randomized, two-period, crossover trial. In Treatment A, 300mg rifabutin qd was administered for 14 days. After a washout period of 14 days, 800mg TMC125 bid (Phase II formulation) was given for 21 days, co-administered with 300mg rifabutin qd on Days 8–21 (Treatment B). The 12-hour pharmacokinetic (PK) profile of TMC125 was assessed on Day 7 and Day 21 of Treatment B. The 24-hour PK profiles of rifabutin and its active metabolite 25-O-desacetyl rifabutin were determined on Day 14 of Treatment A and Day 21 of Treatment B. PK parameters were analyzed using a linear mixed effect model for crossover design. Safety and tolerability were assessed.

Results
Sixteen HIV-negative volunteers (15 male, median age 34 years) participated. When combined with rifabutin, TMC125 AUC_12h was 63% (90% CI: 54–74%) compared with administration of TMC125 alone. TMC125 Cmax and Cmin were 63% (90% CI: 53–74%) and 65% (90% CI: 56–74%), respectively, when combined with rifabutin compared with administration alone.

PK and safety parameters and analyses

- **Primary PK parameters:** TMC125: Cmax, Cmin, and AUC_12h. Rifabutin: Cmax, AUC_24h, and its active metabolite, 25-O-desacetyl rifabutin, Cmax, and AUC_24h.
- **Safety parameters:** adverse events, laboratory assessments, ECG, vital signs and physical examinations were evaluated throughout the study.

Study design

- **Study design:** TMC125-C156 was a Phase II, open-label, two-way, parallel, randomized, two-period, crossover trial. In Treatment A, 300mg rifabutin qd was administered for 14 days. After a washout period of 14 days, 800mg TMC125 bid (Phase II formulation) was given for 21 days, co-administered with 300mg rifabutin qd on Days 8–21 (Treatment B). The 12-hour pharmacokinetic profile of TMC125 was assessed on Day 7 and Day 21 of Treatment B. The 24-hour PK profiles of rifabutin and its active metabolite 25-O-desacetyl rifabutin were determined on Day 14 of Treatment A and Day 21 of Treatment B. PK parameters were analyzed using a linear mixed effect model for crossover design. Safety and tolerability were assessed.

Conclusions

- The decrease of rifabutin and 25-O-desacetyl rifabutin exposures by 17% is not clinically relevant.
- The decrease in TMC125 exposure by 37% is comparable with interactions observed with boosted PIs in Phase II trials. Rifabutin can be co-administered with TMC125 without dose adjustments. The effect of all co-administered drugs should be taken into account.

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