Abstract

Background

TMC125 is an NNRTI with potent activity against wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs. TMC125 is an inducer of CYP3A4 and an inhibitor of both CYP2C9 and 2C19, all involved in the metabolism of oral contraceptives. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone. This study assessed the effect of TMC125 on the pharmacokinetics of ethinylestradiol and norethindrone.

Methods

The oral contraceptive Ortho-Novum® 1/35 was given for three cycles of 28 days: a run-in cycle followed by two cycles with pharmacokinetic (PK) assessments.

In the third cycle, 200mg TMC125 bid (Phase III formulation) was co-administered from Day 1 to Day 15. On Day 15 of Cycles 2 and 3, the 24-hour pharmacokinetics of ethinylestradiol and norethindrone were assessed. The 12-hour pharmacokinetics of TMC125 were evaluated on Day 15 of Cycle 3. PK parameters were calculated by non-compartmental methods. The pharmacokinetics of ethinylestradiol and norethindrone were analysed using a linear, mixed-effects model. Safety and tolerability were evaluated.

Results

Thirty HIV-negative female volunteers participated (median age 24 years). When combined with TMC125, ethinylestradiol AUC24h was 122% (90% CI: 113–131%) compared with administration of oral contraceptives alone, Cmax and Cmin were 133% (90% CI: 121–146%) and 109% (90% CI: 101–118%), respectively. AUC24h, Cmax and Cmin of norethindrone were 95% (90% CI: 90–99%), 105% (90% CI: 98–112%) and 78% (90% CI: 68–89%), respectively, when combined with TMC125 compared with administration of oral contraceptives alone. The concomitant administration of TMC125 and oral contraceptives was generally safe and well tolerated. Ten adverse events (AEs) led to trial discontinuation: seven grade 2 rashes, one grade 2 pyrexia, one grade 3 herpes simplex and one grade 2 lymphadenopathy.

Conclusions

No clinically relevant changes in the pharmacokinetics of ethinylestradiol and norethindrone were observed when TMC125 was given concomitantly with Ortho-Novum® 1/35. No loss in the efficacy of oral contraceptives are expected when TMC125 is co-administered.