No pharmacokinetic interaction between TMC125 (etravirine; ETR) and paroxetine in HIV-negative volunteers

Monika Schöller-Gyüre
Tibotec BVBA
General de Wittelaan L11 83
B2800, Mechelen
Belgium
mscholle@tibbe.jnj.com

M Schöller-Gyüre,1 TN Kakuza,1 S Bollen,1 G De Smedt,1 B Woodfall,1 M Peeters,1 V Vandermeulen,1 RM Hoetelmans1
Tibotec BVBA, Mechelen, Belgium; ’Tibotec Inc., Yardley, PA, USA

Abstract

Objectives: TMC125 is a next-generation NNRTI with demonstrated activity in treatment-experienced HIV-infected patients, including those with NNRTI resistance. Paroxetine is widely used for the treatment of psychiatric disorders and is pharmacologically metabolised by CYP2D6. TMC125 is a substrate of CYP3A4 and CYP2C5 and does not affect CYP2D6 in vitro. This study aimed to assess the pharmacokinetics of TMC125 and paroxetine when co-administered in HIV-negative volunteers.

Methods: This was an open-label, randomised, two-way, two-period crossover trial in 16 HIV-negative volunteers. In Treatment A, 20mg paroxetine qd was given for 7 days. After 14 days washout, 800mg TMC125 bid (Phase II formulation) was administered during Days 1–14 (Treatment B). Paroxetine 20mg was co-administered on Days 8–14. Pharmacokinetics of TMC125 were assessed over 12 hours on Day 7 and 14 of Treatment B, and of paroxetine over 24 hours on Day 7 of Treatment A and Day 14 of Treatment B. Pharmacokinetic (PK) parameters were obtained by non-compartmental analysis and summarised using a linear mixed effects model. Safety and tolerability were assessed.

Results: 16 male volunteers participated (median age 29 years). Least square mean (LSM) ratio and 90% confidence intervals (CI) for the primary PK parameters AUC∞C165 (area under the plasma concentration-time curve over 12- or 24-hour period, calculated by linear trapezoidal summation), maximum plasma concentration (Cmax) and minimum plasma concentration (Cmin) obtained for TMC125 during combined administration with paroxetine versus TMC125 treatment alone were all within the limits 0.80–1.25. When co-administered with TMC125, paroxetine LSM ratio for AUC∞ was 1.03 (90% CI: 0.90–1.18), Cmax was 1.06 (90% CI: 0.95–1.20) and Cmin was 0.87 (90% CI: 0.75–1.02) compared to administration alone.

Conclusions: TMC125 and paroxetine pharmacokinetics are not affected when given concomitantly. TMC125 and paroxetine can be co-administered without dose adjustments.

Introduction

TMC125 is a next-generation NNRTI. Its activity in treatment-experienced HIV-infected patients, including those with NNRTI resistance, has been demonstrated in clinical trials. TMC125 has a low potential to induce or inhibit CYP enzymes. TMC125 is predominantly metabolised by the cytochrome P450 enzymes CYP3A4 and CYP2C5, while paroxetine in HIV-negative volunteers was not affected. Short-term co-administration of TMC125 with paroxetine in HIV-negative volunteers was generally safe and well tolerated; one volunteer discontinued due to grade 2 rash. The most common adverse event (AE) was grade 1 nausea, which occurred in two volunteers.

Study design

Study design (cont’d)

Safety summary

• No serious AEs were reported
• The most frequently reported AE was grade 1 nausea in both volunteers, both reported during co-administration of TMC125 and paroxetine
• All AEs reported were grade 1 or 2 in intensity
• One volunteer discontinued the trial on Day 9 of Treatment B (TMC125 co-administered with paroxetine) due to grade 2 rash

Conclusions

• When co-administered with paroxetine, TMC125 pharmacokinetics were not altered.
• TMC125 had no effect on the pharmacokinetics of paroxetine.
• Short-term co-administration of TMC125 with paroxetine in HIV-negative volunteers was generally safe and well tolerated.
• TMC125 and paroxetine can be co-administered without dose adjustments.

References


Acknowledgements

The authors would like to express their gratitude to the volunteers. We also acknowledge – MP Bouche, JJPharmaceutical Research and Development, Beersel, Belgium – T Duvauchelle, Astor Clinical Unit, Paris, France.