Monika Schöller-Gyüre
Tibotec BVBA
Generaal de Wittelaan L11 B3
B2800, Mechelen
Belgium
mscholle@tibbe.jnj.com

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

P4.3/01

M Schöller-Gyüre,[1] TN Kakuda,[2] S Bollen,[1] G De Smedt,[1] B Woodfall,[1] M Peeters,[1] K Vandermeulen,[1] RM Hoetelmans[1]
[1]Tibotec BVBA, Mechelen, Belgium; [2]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 primarily metabolised by CYP2D6. TMC125 is a substrate of CYP3A4 and CYP2C 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 qd 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) ratios and 90% confidence intervals (CI) for the primary PK parameters AUC_{12h} (area under the plasma concentration-time curve over 12- or 24-hour period, calculated by linear trapezoidal summation), maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) 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_{24h} was 1.03 (90% CI: 0.9–1.18), C_{max} was 1.06 (90% CI: 0.95–1.20) and C_{min} was 0.87 (90% CI: 0.75–1.02) compared to administration alone. The concomitant administration of TMC125 and paroxetine 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.

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

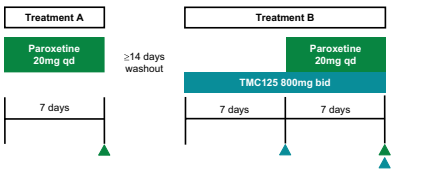
Introduction

- TMC125 is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to current NNRTIs[1]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to currently approved NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an AE profile similar to placebo[2,3]
- TMC125 is predominantly metabolised by the cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19
- Paroxetine is a selective serotonin reuptake inhibitor (SSRI) that is used in the clinical management of depression and anxiety and is frequently administered in HIV-1-infected individuals
- Paroxetine is primarily metabolised by CYP2D6[4,5] and partly by CYP3A4, and subsequently conjugated into its pharmacologically inactive metabolites. Paroxetine is also an inhibitor of CYP2D6
- To support concomitant administration, an interaction study with paroxetine and TMC125 was conducted

Study design

- TMC125-C165 was a Phase I, open-label, two-way, two-period crossover trial in 16 HIV-negative volunteers
- Two treatment sessions (A and B) were scheduled for all volunteers, separated by a washout period of at least 14 days as shown in the study design scheme. Half of the volunteers were randomised to start with Treatment A and half were randomised to start with Treatment B
- TMC125 was administered as 800mg bid of Phase II formulation (TF035), which provides comparable exposure to that obtained with 200mg bid of Phase III formulation (F060)
- All doses were taken within 10 minutes after a standardised meal
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication
- The trial protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities; the trial was conducted in accordance with the Declaration of Helsinki

Study design (cont'd)



- 12-hour PK analysis of TMC125, determined on Day 7 and Day 14 of Treatment B
- 24-hour PK analysis of paroxetine, determined on Day 7 of Treatment A and Day 14 of Treatment B
- Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

PK analyses

- Plasma concentrations of TMC125 were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- Plasma concentrations of paroxetine were determined using a validated LC-MS/MS method (LLOQ 0.10ng/mL)
- PK and statistical PK analyses were performed using
  - SAS System for Windows® version 8.2 (SAS Institute Inc., Cary NC 27512-8000, USA)
  - a non-compartmental model with extravascular input was used for the PK analysis

LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = lower limit of quantification

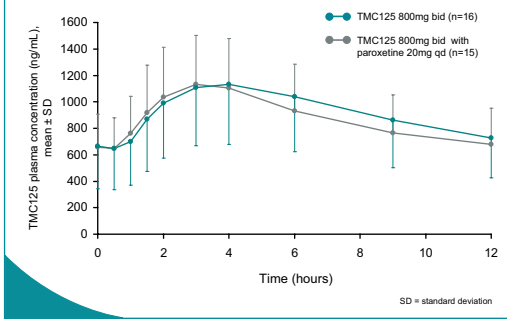
PK and safety parameters and analyses

- Primary PK parameters
  - C_{max} (ng/mL)
  - C_{min} (ng/mL)
  - $AUC_{12h/24h}$ (ng•h/mL)
- Safety parameters
  - AEs, laboratory assessments, electrocardiogram (ECG), vital signs assessment and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to TMC125 and/or paroxetine were recorded
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of TMC125 and paroxetine
  - LSM ratios and 90% CIs were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

Demographic parameter	All volunteers (N=16)
Age, years, median (range)	29 (21–38)
Height, cm, median (range)	182 (163–194)
Weight, kg, median (range)	75 (64–107)
Body mass index, kg/m², median (range)	24 (20–30)
Male gender, n (%)	16 (100)
Ethnic origin, n (%)	
Caucasian	12 (75)
Black	4 (25)

TMC125 plasma PK profile

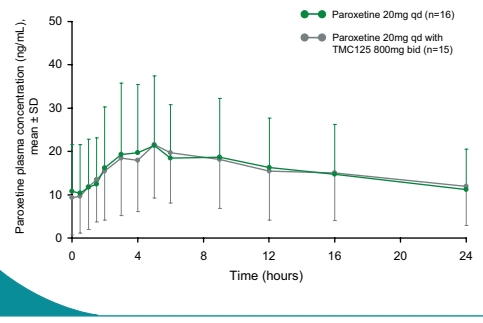


SD = standard deviation

TMC125 PK parameters

PK parameter	TMC125 alone (reference) (mean ± SD) (n=16)	TMC125 + paroxetine (test) (mean ± SD) (n=15)	LSM ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	11,099 ± 4,524	10,529 ± 3,808	1.01 (0.93–1.10)
C_{max} (ng/mL)	1,161 ± 449	1,149 ± 377	1.05 (0.96–1.15)
C_{min} (ng/mL)	637 ± 305	626 ± 241	1.07 (0.98–1.17)

Paroxetine plasma PK profile



Paroxetine PK parameters

PK parameter	Paroxetine alone (reference) (mean ± SD) (n=16)	Paroxetine + TMC125 (test) (mean ± SD) (n=15)	LSM ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	376 ± 283	375 ± 252	1.03 (0.90–1.18)
C_{max} (ng/mL)	22.7 ± 16.3	22.8 ± 13.1	1.06 (0.95–1.20)
C_{min} (ng/mL)	9.52 ± 8.47	8.63 ± 8.12	0.87 (0.75–1.02)

Safety summary

- No serious AEs were reported
- The most frequently reported AE was grade 1 nausea in two volunteers, both reported during co-administration of TMC125 and paroxetine
- All AEs reported were mild (grade 1) or moderate (grade 2) in severity
- One volunteer discontinued the trial on Day 9 of Treatment B (TMC125 co-administered with paroxetine) due to grade 2 rash, possibly related to TMC125 and paroxetine
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations. One volunteer had a grade 3 elevation of amylase during both TMC125 alone and paroxetine alone treatments

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

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. Madruga JV, et al. Lancet 2007;370:29–38.
3. Lazzarin A, et al. Lancet 2007;370:39–48.
4. Basu S, et al. AIDS 2005;19:2057–67 .
5. Hemeryck, et al. Curr Drug Metab 2002;1:13–37.

Acknowledgements

The authors would like to express their gratitude to the volunteers. We also acknowledge:
- MP Bouche, J&J Pharmaceutical Research and Development, Beerse, Belgium
- T Duvauchelle, Aster Clinical Unit, Paris, France.

Supported by Tibotec

Presented at the 11th European AIDS Conference, Madrid, Spain, 24–27 October 2007.

This poster is available on-line at www.tibotec.com