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

TMC125 bioavailability is not affected by ranitidine and omeprazole

M Schöller-Gyüre, G De Smedt, H Vanaken, M Peeters, C Debroye, B Woodfall, R Hoetelmans
Tibotec BVBA, Mechelen, Belgium

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Abstract

Background
TMC125 is an NNRTI with potent activity against wild-type and NNRTI-resistant HIV. Proton pump inhibitors and H_2-antagonists are frequently used in the HIV-infected population and drug–drug interactions have been described with other antiretrovirals. The objective of this study was to evaluate the effect of omeprazole and ranitidine on the pharmacokinetics (PK) of TMC125 administered as the Phase III formulation.

Methods
In an open-label, one-way crossover trial, HIV-negative volunteers randomly received in three periods a single dose of 100mg TMC125 alone (Session 1); 11 days of 150mg ranitidine bid (Session 2); and 11 days of 40mg omeprazole qd (Session 3). A single 100mg TMC125 dose was co-administered on Day 8 of Sessions 2 and 3. Sessions were separated by a washout period of 14 days. Ninety-six-hour TMC125 PK were assessed in each session and determined by non-compartmental analysis. Safety and tolerability were assessed.

Results
Nineteen volunteers (7 female/12 male) participated. When a single dose of TMC125 was administered in the presence of steady-state ranitidine, TMC125 AUC_{last} and C_{max} were 86% (90% confidence interval [CI]: 76–97%) and 94% (75–117%), respectively, compared with administration of TMC125 alone. When administered with steady-state omeprazole, these values were 141% (122–162%) and 117% (96–143%), respectively. The co-administration of a single dose of TMC125 and ranitidine or omeprazole was generally safe and well tolerated.

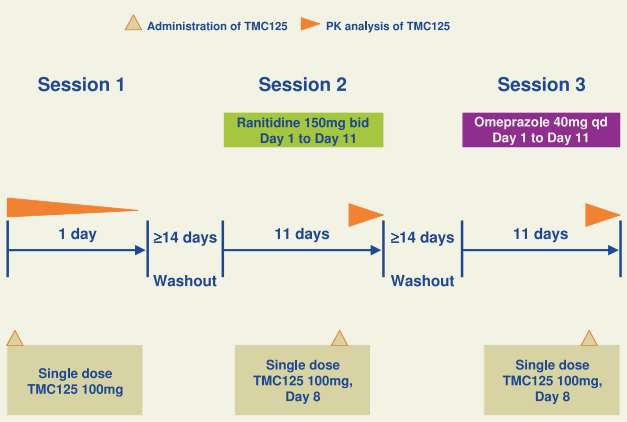
Conclusions
The bioavailability of TMC125 is not decreased when co-administered with the H_2-antagonist ranitidine or the proton pump inhibitor omeprazole. The increased exposure of TMC125 when co-administered with omeprazole is not considered clinically relevant. Based on the results of this study, TMC125 can be co-administered with proton pump inhibitors and H_2-antagonists without dose adjustments.

Introduction

- TMC125 is a novel NNRTI with potent in-vitro activity against both wild-type strains of HIV-1 and those resistant to current NNRTIs[1]
- A Phase IIb trial (TMC125-C223) in treatment-experienced HIV patients demonstrated that TMC125, with an optimized background regimen, reduced viral load significantly more than the standard of care regimen. No dose-related effects on safety and tolerability were noted[2]
- pH modifiers are frequently used in the HIV-infected population.[3] Pharmacodynamic (PD) and/or PK interactions of these agents are described with a number of antiretroviral drugs
- This trial (TMC125-C120) evaluated the effect of the proton pump inhibitor omeprazole, and the H_2-receptor antagonist ranitidine on the oral bioavailability of TMC125 (formulation F060, used in all Phase III trials)

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Cohen C, et al. 12th BHIVA 2006 (Poster 2)
3. Luber A, et al. Drug Therapy in HIV, Glasgow, 2004 (Poster 206)

Study design



Study design (cont'd)

- Randomized, open-label, three-period, crossover study
- One panel of 18 HIV-negative, healthy volunteers
- A single dose of 100mg TMC125 (formulation F060) was administered on three occasions to all individuals in a random order
  - Session 1: single dose of 100mg TMC125
  - Session 2: ranitidine 150mg bid for 11 days, 100mg TMC125 single dose on Day 8
  - Session 3: omeprazole 40mg qd for 11 days, 100mg TMC125 single dose on Day 8
- Ranitidine and omeprazole were administered at clinically relevant doses for up to 11 days to
  - ensure the development of the PD effect on gastric acidity
  - allow the development, if any, of enzyme induction
  - maintain these effects from dosing of TMC125 on Day 8 until the end of PK sampling on Day 11

Study design (cont'd)

- pH modifiers were taken before meals, and TMC125 was administered within 10 minutes after breakfast
- PK characteristics of TMC125 were assessed for 96 hours after administration
- Washout periods of at least 14 days separated each session
- The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and was conducted in accordance with the Declaration of Helsinki

PK and statistical analysis

- Plasma concentrations of TMC125 were determined using a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method
- PK and statistical PK analyses were performed using
  - WinNonlin Professional™ (version 4.1; Pharsight Corporation, Mountain View, California, USA)
  - Microsoft Excel® (version 2000; Microsoft, Redmond, Washington, USA)
- A non-compartmental model with extravascular input was used for the PK analysis. Primary PK parameters were
  - C_{max} (ng/mL): maximum plasma concentration
  - AUC_{last} (ng•h/mL): area under the plasma concentration-time curve from time of administration until the last measurable or measured timepoint, calculated by linear trapezoidal summation
- Descriptive statistics were calculated for the PK parameters of TMC125
- Least square (LS) means were estimated with a linear mixed effects model

Safety analysis

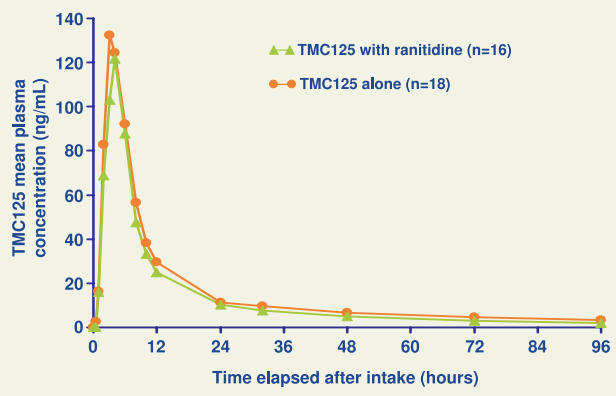
- Volunteers were monitored throughout the trial for the following safety variables
  - adverse events (AEs)
  - laboratory abnormalities
  - cardiovascular changes
  - physical health
  - changes to the skin
- The severity and drug-relatedness of AEs were recorded
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication

Volunteer demographics

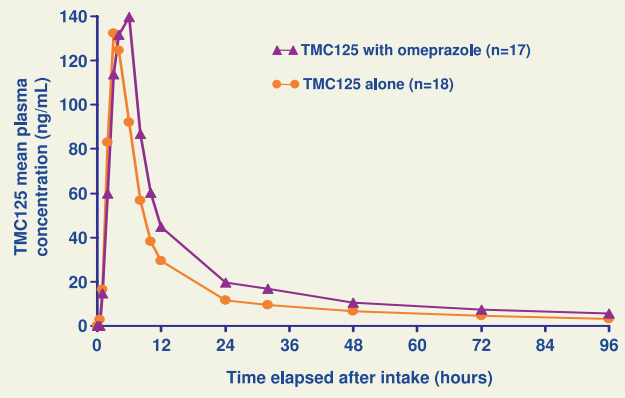
Demographic parameter	Total (n=19) n (%)
Age, years	49 (27–54)*
Height, cm	173 (163–194)*
Weight, kg	81 (58–98)*
BMI, kg/m²	26 (21–30)*
Ethnic origin	
Caucasian/White	16 (84)
Oriental/Asian	1 (5)
Other	1 (5)
Hispanic	1 (5)
Type of smoker	
Non-smoker	19 (100)

*Median (range)

PK profiles of TMC125 if taken alone or if co-administered with steady-state ranitidine



PK profiles of TMC125 if taken alone or if co-administered with steady-state omeprazole



Summary of TMC125 PK results

PK parameters			
PK parameter	TMC125 alone (mean ± SD) n=18	TMC125 + ranitidine (mean ± SD) n=16	TMC125 + omeprazole (mean ± SD) n=17
C_{max} (ng/mL)	146±69	141±78	165±51
AUC_{last} (ng•h/mL)	1,501±686	1,257±653	2,113±670

LS mean ratios		
PK parameter	With ranitidine versus alone % (90% CI)	With omeprazole versus alone % (90% CI)
C_{max}	94 (75–117)	117 (96–143)
AUC_{last}	86 (76–97)*	141 (122–162)*

*$p<0.05$

SD = standard deviation

Summary of safety

- No serious AEs were reported and no volunteers discontinued the trial due to AEs
- No rash was reported, that could be considered as possibly related to TMC125
- The most frequently reported AE was headache in 63% of volunteers, with the highest incidence during the omeprazole alone treatment phase
  - most cases were grade 1 in severity
  - grade 2 headache was reported in four volunteers; for three volunteers this was considered as possibly related to TMC125
- Two grade 3 AEs were reported in two volunteers: elevated lipase during TMC125 plus omeprazole treatment, and diarrhea in the washout period after the TMC125 alone treatment
- The administration of three single doses of TMC125 (alone, with steady-state ranitidine, and with steady-state omeprazole) was generally well tolerated and showed a good safety profile

Conclusions

- Ranitidine has no clinically relevant effect on the oral bioavailability of TMC125.
- Exposure to TMC125 is increased by 41% when co-administered with omeprazole, possibly due to inhibition of CYP2C19
  - given the safety profile of TMC125 and that no PK/safety relationship has been observed so far in clinical studies, this increase is not believed to be clinically relevant.
- TMC125 can be co-administered with ranitidine and omeprazole without dose adjustments.
- Clinically relevant interactions with other proton pump inhibitors and H_2-antagonists are not anticipated.

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