Rolf van Heeswijk
Tibotec BVBA
Generaal de Wittelaan L11 B3
B2800, Mechelen
Belgium
rvheesw1@tibbe.jnj.com

The pharmacokinetic interaction between famotidine and TMC278, a next-generation NNRTI, in HIV-negative volunteers

R van Heeswijk,[1] R Hoetelmans,[1] D Kestens,[1] M Stevens,[1] M Peeters,[1] P Williams,[1] B Woodfall,[1] K Boven[2]
[1]Tibotec BVBA, Mechelen, Belgium; [2]Tibotec Inc, Yardley, PA, USA

TUPDB01

Abstract

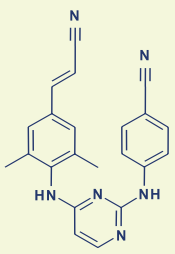
Objectives: TMC278 is a next-generation NNRTI with potent and sustained efficacy in antiretroviral (ARV)-naïve patients (CROI-2007). As TMC278 showed pH-dependent solubility *in vitro* the current study evaluated the interaction between TMC278 and the H_2-antagonist famotidine, as well as dosing strategies to circumvent the anticipated interaction.

Methods: This was a single-dose, open-label, randomised, four-way, crossover trial in 24 HIV-negative volunteers. On four occasions, each separated by a 14-day washout, volunteers received TMC278 150mg alone (Treatment A), TMC278 2 hours after famotidine 40mg (Treatment B), TMC278 4 hours before famotidine (Treatment C), and TMC278 12 hours after famotidine (Treatment D). Intragastric pH was measured over 24 hours during Treatments A and B. PK of TMC278 and famotidine was assessed up to 168 hours and 24 hours post-dose, respectively. TMC278 was administered with food.

Results: When TMC278 was administered 2 hours after famotidine, the TMC278 maximum and plasma concentrations (C_{max}) and area under the curve from time 0 to infinity (AUC_∞) were reduced by 85% (least square means [LSM] ratio 0.15, 90% confidence intervals (CI): 0.12–0.19) and 76% (LSM ratio 0.24, 90% CI: 0.20–0.28), respectively. The TMC278 AUC_∞ was increased by 13% (LSM ratio 1.13, 90% CI: 1.01–1.27) when TMC278 was administered 4 hours before famotidine, and was not affected when TMC278 was administered 12 hours after famotidine (LSM ratio 0.91, 90% CI: 0.78–1.07).
A negative correlation was observed between intragastric pH and exposure to TMC278. The pharmacokinetic (PK) parameters of famotidine were not influenced by TMC278. All treatments were generally well tolerated. Three volunteers (12.5%) experienced adverse events (AEs), all grade 1 or 2. One volunteer was withdrawn with grade 2 mouth ulceration during Treatment C, without rash or other skin events.

Conclusions: TMC278 should not be administered shortly after famotidine. However, no clinically relevant effects on TMC278 exposure were observed when TMC278 was administered either 4 hours before, or 12 hours after famotidine. These results confirm the pH-dependent bioavailability of TMC278 and suggest that separate intake of TMC278 and famotidine 40mg prevents reduced absorption and thus allows co-administration without dose modification.

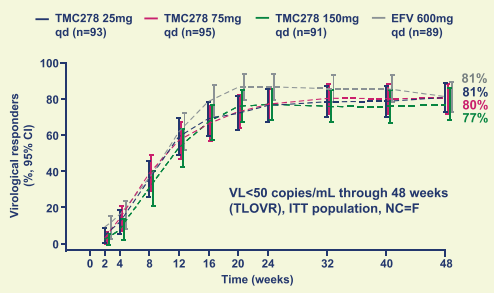
Introduction



- TMC278, a next-generation NNRTI, has demonstrated in-vitro and in-vivo activity against wild-type and NNRTI-resistant isolates[1]
- TMC278 has an increased genetic barrier to the development of resistance compared with efavirenz (EFV) and nevirapine[1]
- 48-week results from a Phase IIb dose-finding study of TMC278 qd in ARV-naïve, HIV-1-infected patients have recently been presented[2]

1. de Béthune MP, et al. 12th CROI 2005. Abstract 556
2. Pozniak A, et al. 14th CROI 2007. Abstract 144LB

Potent and sustained efficacy of TMC278 in ARV-naïve patients



VL = viral load; TLOVR = time to loss of virological response; ITT = intent-to-treat; NC=F = non-completer = failure

Pozniak A, et al. 14th CROI 2007. Abstract 144LB

Background and objective

- Background
  - TMC278 has been shown to have decreased solubility at increased pH *in vitro*
  - co-administration of drugs that modify intragastric pH, such as the H_2-antagonist famotidine, may thus influence the absorption of TMC278
- Objective
  - the current study aimed to investigate the effect of single-dose famotidine on the single-dose pharmacokinetics of TMC278, as well as dosing strategies to circumvent the anticipated interaction

Study design

Four-way, randomised, crossover design

Four different treatments, all with single-dose TMC278 150mg

1. No famotidine (reference)
2. Famotidine 40mg 2 hours before TMC278 150mg
3. Famotidine 40mg 12 hours before TMC278 150mg
4. Famotidine 40mg 4 hours after TMC278 150mg

168h PK = PK sampling up to 168 hours post-dose

Study methods

- TMC278 150mg was administered orally after an overnight fast for at least 10 hours, and within 10 minutes after completion of a standard breakfast (533kcal; 35% fat, 50% carbohydrates, 14% protein)
- Famotidine 40mg was administered orally in three different treatments, as described in the previous slide
- Intragastric pH was monitored for 24 hours when famotidine was administered 2 hours before TMC278, and after intake of TMC278 alone
- Bioanalysis was carried out by validated LC-MS/MS methods
- Non-compartmental PK analysis was performed (C_{max} and AUC extrapolated to infinity; AUC_∞)
- Statistical analysis was by linear mixed effects modelling (LSM ratio and 90% CI)
- The study protocols were reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and were conducted in accordance with the Declaration of Helsinki

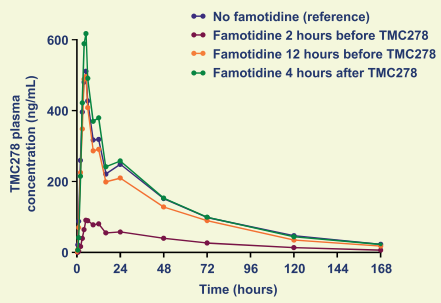
LC-MS/MS = liquid chromatography-mass spectrometry/mass spectrometry

Study population

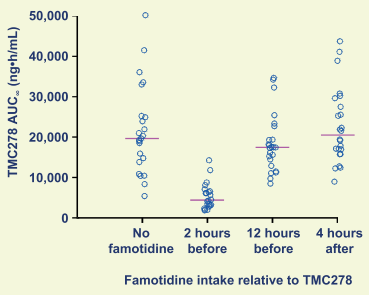
Characteristic	Value
N	24 (all male)
Age,* years	26.5 (20–53)
Weight,* kg	75.0 (59–92)
BMI,* kg/m²	23.0 (19–30)
Ethnic origin, n	
Caucasian	14
Black	4
Asian	1
Other†	5

*Median and range †Volunteers from the West Indies
BMI = body mass index

TMC278 mean PK profiles



Individual TMC278 AUCs by treatment



TMC278 mean (SD) PK parameters

	No famotidine	Famotidine 2 hours before TMC278	Famotidine 12 hours before TMC278	Famotidine 4 hours after TMC278
n	23	23*	24	24
AUC_∞ (ng•h/mL)	21,630 ± 11,070	5,349 ± 3,221	18,740 ± 7,217	22,660 ± 9,306
C_{max} (ng/mL)	564 ± 212	108 ± 110	553 ± 194	665 ± 221

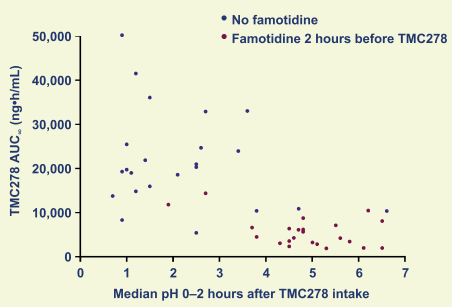
*n=22 for AUC_∞
SD = standard deviation

TMC278 statistical analysis

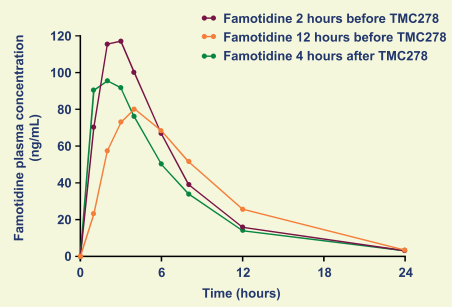
LSM ratio (TMC278 + famotidine/TMC278 alone) + 90% CI

Famotidine intake	AUC_∞	C_{max}
2 hours before TMC278	0.24 (0.20–0.28)	0.15 (0.12–0.19)
12 hours before TMC278	0.91 (0.78–1.07)	0.99 (0.84–1.16)
4 hours after TMC278	1.13 (1.01–1.27)	1.21 (1.06–1.39)

Relationship between pH and TMC278 AUC



Famotidine mean PK profiles



Famotidine mean (SD) PK parameters

	Famotidine 2 hours before TMC278	Famotidine 12 hours before TMC278	Famotidine 4 hours after TMC278
n	23	24*	24*
AUC_∞ (n•hg/mL)	860 ± 215	816 ± 235	743 ± 212
C_{max} (ng/mL)	125 ± 35	91 ± 29	106 ± 32

- Exposure to famotidine was similar between the different treatments

*n=23 for AUC_∞

Safety and tolerability

- Single-dose TMC278 alone, and in combination with single-dose famotidine was generally safe and well tolerated
- Three volunteers (12.5%) experienced AEs
- All AEs were grade 1 or 2 in severity
- One volunteer discontinued the study due to a grade 2 mouth ulceration, which was not associated with fever, hepatic parameter elevation, rash or other skin events. The event was judged to be probably related to TMC278 and possibly related to famotidine

Conclusions

- When famotidine was administered 2 hours before TMC278, absorption of TMC278 was reduced compared with administration of TMC278 alone, resulting in reduced plasma concentrations.
- This interaction is most probably explained by a reduced solubility of TMC278 at increased intragastric pH.
- TMC278 can be combined with famotidine without dosage adjustment when
  - famotidine is administered 12 hours before TMC278
  - famotidine is administered 4 hours after TMC278.
- Similar findings are expected with other H_2-antagonists.

Acknowledgements

- We would like to express gratitude to
  - the study volunteers
  - all the TMC278 team members at Tibotec
  - M-P Bouche (J&J Pharmaceutical Research and Development, Beerse, Belgium)
  - the investigator: T Duvauchelle MD, Aster, Paris, France.

Supported by Tibotec

Presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 22–25 July 2007.

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