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

Effect of food on the oral bioavailability of the phase III formulation of TMC125

M Schöller-Gyüre,[1] R Leemans,[2] V Vyncke,[1] K Vandermeulen,[1] M Peeters,[1] B Baeten,[1] C Debroye,[1] B Woodfall,[1] R Hoetelmans[1]
[1]Tibotec BVBA, Mechelen; [2]Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium

Poster No. 80

Abstract

Objective
TMC125 is an NNRTI with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. With the Phase II formulation of TMC125, intake after a substantial meal (>500kcal) was required due to a 3-fold increase in bioavailability compared to fasted conditions. The objective of this study was to evaluate the effect of various types of meals on the oral bioavailability of TMC125 when administered as the Phase III formulation F060.

Methods
This was a Phase I, open label, randomised, 3-period crossover trial in 2 panels of 12 HIV-negative volunteers each. Panel 1 received a single 100mg dose of TMC125 (F060) on three occasions: after a standard breakfast, in fasted state and after a snack (croissant). Panel 2 received the same treatment after the intake of a standard breakfast, a high-fibre breakfast (fruits) and a high-fat breakfast. There was a washout period of at least 14 days between subsequent periods. For each intake, full pharmacokinetic (PK) profiles of TMC125 were determined up to 96 hours post-dose. PK parameters were determined by non-compartmental analysis and analysed using a linear mixed-effect model for a crossover design.

Results
Twenty-four male HIV-negative volunteers participated in the study (mean age 29 years). The LSmean ratio of AUC_{last} and C_{max} after intake in fasted condition was 49% (90% confidence interval [CI]: 39–61) and 56% (90% CI: 41–77), respectively, versus a standard breakfast. When given after a snack these values were 80% (90% CI: 69–94) and 97% (90% CI: 75–125), respectively. After intake following a high-fibre breakfast these values were 75% (90% CI: 63–90) and 62% (90% CI: 47–83). When given after a high-fat breakfast the LSmean ratio of AUC_{last} and C_{max} were 109% (90% CI: 84–141) and 95% (90% CI: 70–129) versus standard breakfast. The administration of three single doses of 100mg TMC125 was generally safe and well tolerated.

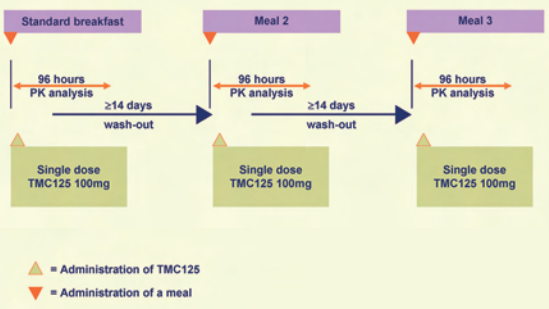
Conclusions
The effect of food on the oral bioavailability of the Phase III formulation of TMC125 was less compared to the Phase II formulation. The lowest exposures were reached when TMC125 was taken in fasted state or after a meal with high-fibre contents. The difference in exposure after a high-fat breakfast or snack compared to a standard breakfast is not considered clinically relevant. TMC125 should be taken with a meal.

Introduction

- TMC125 is an NNRTI that is being evaluated for the treatment of HIV-1 infected individuals[1]
- TMC125 has potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs[1]
- Exposure to the Phase II formulation of TMC125 (TF035) was 3.5 times higher if taken after a substantial meal compared with administration in the fasted state[2]
- A new formulation with improved oral bioavailability was developed (F060) and is being used in Phase III trials
- This study (TMC125-C147) evaluated the effect of different types of meals on the oral bioavailability of the Phase III formulation of TMC125

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Clinical Research Report, Trial TMC125-C137. Data on file, Tibotec

Study design



Study design

- Randomised, open label, 3-period, crossover study
- Two panels, each with 12 HIV-negative, healthy volunteers
- A single dose of 100mg TMC125 (Phase III formulation) was administered to all individuals on three occasions – each time with a different meal – in a random order
  - panel 1: standard breakfast; fasted; croissant
  - panel 2: standard breakfast; high-fat; high-fibre
- All doses were taken within 10 minutes after the meal
- PK characteristics of TMC125 were determined until 96 hours after administration
- Wash-out periods of at least 14 days were applied
- 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

Description of meals

- Standard breakfast (reference treatment)*
  - 4 slices of bread, 2 slices of ham or cheese, butter, jelly, 2 cups of decaffeinated coffee or tea with milk and/or sugar
- No breakfast
  - fasted for at least 10 hours; water intake is allowed until 2 hours before drug administration
- Croissant
  - 1 butter croissant with 1 teaspoon of unsalted butter and 1 teaspoon of jelly, 1 cup of decaffeinated coffee or tea with milk and/or sugar
- High-fat meal
  - 2 large fried eggs, 2 slices of fried bacon, 1 butter croissant, 2 slices of white bread, 1 teaspoon of unsalted butter, 1 bar of semi-sweet chocolate (30g), 1 cup of decaffeinated coffee or tea with milk and/or sugar
- High-fibre meal
  - grapes with skin (80g), raw pineapple (80g), raw pears (80g), raw strawberries (80g), 1 glass of orange juice (225g), 1 raw banana (200g), 2 slices of mixed grain bread, 2 tablespoons (40g) of jelly

*Used in other Phase I trials

Composition of meals

Treatment	Weight (g)	Calories (cal)	Fat (%)	Carbs (%)	Protein (%)	Fibre (g)
Standard	486	561	24	61	16	8.1
Fasted	0	0	0	0	0	0
Croissant	213	345	45	49	6	1.3
High-fibre	855	685	4	89	8	16.1
High-fat	468	1,160	54	32	14	2.2

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

PK and statistical analysis

- Primary PK parameters
  - 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
- LSmeans were estimated with a linear mixed effects model

Safety analysis

- Adverse events (AEs), laboratory assessments, cardiovascular safety, and physical and skin examinations were monitored throughout the study
- Severity and drug relationship of AEs towards TMC125 were recorded
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication

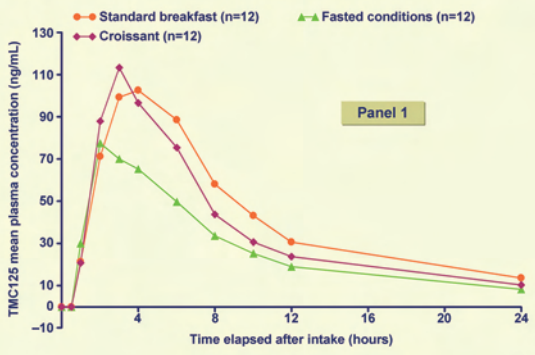
Participant demographics and disposition

Demographic parameter	Total (n=24)
Age, years	28 (20–51)*
Height, cm	181 (171–192)*
Weight, kg	83 (62–115)*
Ethnic origin	
Caucasian/White	23 (96)**
Black	1 (4)**
BMI, kg/m²	25 (20–31)*
Type of smoker	
Smoker	10 (42)**
Non-smoker	14 (58)**

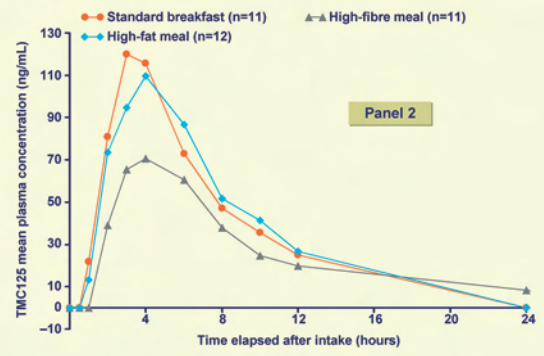
*median (range); **n (%)

- Study population: 24 HIV-negative men were randomised and received at least one dose of TMC125
- Twenty individuals completed the study
- One volunteer dropped out during the study (panel 2) and three withdrew consent during follow-up

PK profiles of TMC125 if taken after a standard breakfast, a croissant or in fasted state



PK profiles of TMC125 if taken after a standard breakfast, a high-fat or high-fibre meal



Summary of PK parameters (mean ± SD)

Panel 1

PK parameter	Standard breakfast (n=12)	Fasted (n=12)	Croissant (n=12)
C_{max} (ng/mL)	129±64	89±68	128±73
AUC_{last} (ng·h/mL)	1,417±1,140	921±1,024	1,189±1,106

Panel 2

PK parameter	Standard breakfast (n=11)	High-fat meal (n=12)	High-fibre meal (n=11)
C_{max} (ng/mL)	138±61	130±64	85±40
AUC_{last} (ng·h/mL)	1,191±700	1,202±586	864±407

Comparison of PK parameters LSmean ratio, % (90% CI)

Panel 1

PK parameter	Fasted versus standard breakfast	Croissant versus standard breakfast
C_{max}	56 (41–77)*	97 (75–125)
AUC_{last}	49 (39–61)*	80 (69–94)*

Panel 2

PK parameter	High-fat versus standard breakfast	High-fibre versus standard breakfast
C_{max}	95 (70–129)	62 (47–83)*
AUC_{last}	109 (84–141)	75 (63–90)*

*p<0.05

Summary of safety

- No serious AEs were reported
- No grade 3 or 4 AEs were reported. All AEs were of grade 1 in severity
- The most frequently reported AE was headache (12.5%)
- Two treatment-emergent grade 3 cases of hypoglycaemia were reported during the follow-up phase
- No volunteers dropped out due to AEs
- The administration of three single doses of TMC125 was generally safe and well tolerated

Conclusions

- The oral bioavailability of the Phase III formulation of TMC125 is less affected by food intake compared with the Phase II formulation.
- Lower exposures are obtained if TMC125 is taken in a fasted state or after a high-fibre meal.
- The differences in exposures of TMC125 if taken after a high-fat meal, standard breakfast or a croissant are not clinically relevant.
- TMC125 should be taken with a meal.

Acknowledgements

The authors would like to express their gratitude to the patients. We also acknowledge:

- M-P Bouche, J&J Pharmaceutical Research and Development, Beerse, Belgium
- A Pozniak and M Boffito, St Stephens Centre, Chelsea and Westminster Hospital, London, UK

Presented at the 7th International Workshop of Clinical Pharmacology, 20–22 April 2006, Lisbon, Portugal.