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Pharmacokinetic interaction between the non-nucleoside reverse transcriptase inhibitors (NNRTI) TMC125 and atorvastatin in HIV-negative volunteers

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Abstract

Objectives: TMC125 is a next-generation NNRTI with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. TMC125 is a substrate and inducer of CYP3A4. Atorvastatin is primarily metabolised by CYP3A4. This study aimed to assess the pharmacokinetics of TMC125 and atorvastatin when co-administered to HIV-negative volunteers.

Methods: This was an open-label, randomised, two-period, crossover trial. In Treatment A, 40mg atorvastatin once daily (qd) was given for 4 days. After 14 days washout, 800mg TMC125 twice daily (bid; Phase II formulation) was administered during Days 1–13 (Treatment B). Atorvastatin 40mg qd was co-administered on Days 8–11. TMC125 pharmacokinetics were assessed on Day 7 and Day 11 of Treatment B over 12 hours; pharmacokinetics of atorvastatin and metabolites were assessed on Day 4 of Treatment A and Day 11 of Treatment B over 24 hours. Pharmacokinetic (PK) parameters were analysed using a linear mixed effects model. Safety and tolerability were assessed during the trial.

Results: 16 volunteers participated (14 males, median age 40 years). Least square (LS) mean ratios and 90% confidence intervals (CIs) for the primary PK parameters obtained during combined administration versus treatment alone are given below.

Test compound	TMC125	Atorvastatin	2-hydroxy-atorvastatin	Atorvastatin lactone
Co-administered drug	Atorvastatin	TMC125	TMC125	TMC125
C_{min} (ng/mL)	1.10 (1.02–1.19)	NA	NA	NA
C_{max} (ng/mL)	0.97 (0.93–1.02)	1.04 (0.84–1.30)	1.76 (1.60–1.94)	0.62 (0.56–0.69)
$AUC_{12h/24h}$ (ng•h/mL)	1.02 (0.97–1.07)	0.63 (0.58–0.68)	1.27 (1.19–1.36)	0.38 (0.34–0.42)

LS mean ratios and 90% CIs (n=16); NA = not assessed

Most plasma concentrations of 4-hydroxy-atorvastatin were below lower limit of quantification (LLOQ). All volunteers completed the trial. Most adverse events (AEs) were mild in severity. Short-term co-administration of TMC125 and atorvastatin was generally safe and well tolerated.

Conclusions: TMC125 pharmacokinetics are not affected by concomitant administration of atorvastatin. Co-administration with TMC125 decreased exposure to atorvastatin by 37% and increased exposure to its active metabolite by 27%. TMC125 and atorvastatin can be co-administered without dose adjustment.

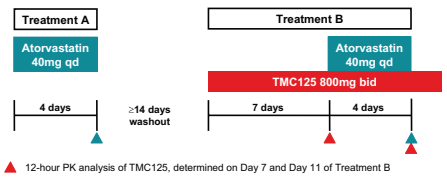
Introduction

- TMC125 (etravirine, ETR) is a next-generation NNRTI with potent in-vitro activity against both wild-type HIV-1 and HIV-1 resistant to currently available NNRTIs[1]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant and sustained antiviral benefit after 24 weeks' treatment with TMC125 in treatment-experienced patients with NNRTI resistance. Except for a higher incidence of rash, patients treated with TMC125 had a side effect profile similar to placebo[2,3]
- TMC125 is predominantly metabolised by the cytochrome P450 enzymes CYP3A4 and CYP2C19; it is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19
- Atorvastatin is an HMG-coenzyme A reductase inhibitor that efficiently decreases serum cholesterol and triglyceride concentrations and is frequently administered to patients with lipid disturbances and/or metabolic syndrome
- Atorvastatin is primarily metabolised by CYP3A4[4,5] to its hydroxylated, pharmacologically equipotent metabolites 2- and 4-hydroxy-atorvastatin and to the inactive atorvastatin lactone. Atorvastatin is also a weak inhibitor of CYP3A4, P-glycoprotein and Breast Cancer Resistance Protein (BCRP)
- To support concomitant administration, an interaction study with atorvastatin and TMC125 was conducted

Study design

- TMC125-C164 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 below. 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 the Phase II formulation, which provides comparable exposure to that obtained with 200mg bid of the Phase III formulation
- All doses were taken within 10 minutes after a standardised meal
- Safety and tolerability assessments were performed throughout the trial. 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 scheme and PK analyses



▲ 12-hour PK analysis of TMC125, determined on Day 7 and Day 11 of Treatment B

▲ 72-hour PK analysis of atorvastatin, 2- and 4-hydroxy-atorvastatin and atorvastatin lactone, determined up to 72 hours on Day 4 of Treatment A and Day 11 of Treatment B

- Plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for TMC125 (LLOQ 2ng/mL), atorvastatin, 2- and 4-hydroxy-atorvastatin and atorvastatin lactone (LLOQ 0.5ng/mL for each)

Parameters and analyses

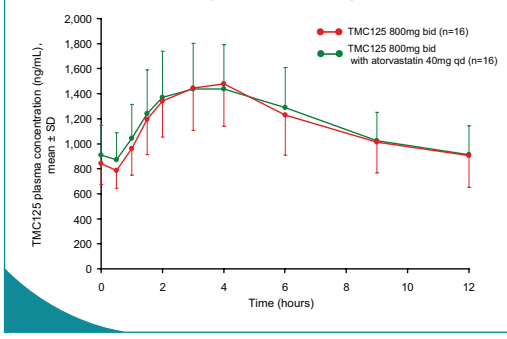
- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration (TMC125 only)
  - $AUC_{12h/24h}$ (ng•h/mL): area under the plasma concentration-time curve over 12- or 24-hour period, calculated by linear trapezoidal summation
- Safety parameters
  - AEs, laboratory assessments, ECGs, vital signs assessments and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to TMC125 and/or atorvastatin were recorded
- PK and statistical analyses
  - a non-compartmental model with extravascular input was used for PK analyses; PK and statistical analyses were performed using SAS System for Windows® version 8.2 (SAS Institute Inc., Cary, NC, USA)
  - descriptive statistics were calculated for the PK parameters of TMC125, atorvastatin and its metabolites; LS means were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

Demographic parameter, median (range) unless indicated	All volunteers (N=16)
Age, years	40 (19–53)
Height, cm	181 (159–191)
Weight, kg	77 (60–98)
BMI, kg/m²	24 (19–29)
Male gender, n (%)	14 (88)
Ethnic origin, n (%)	
Caucasian	14 (88)
Black	1 (6)
Other	1 (6)

BMI = body mass index

TMC125 plasma PK profile

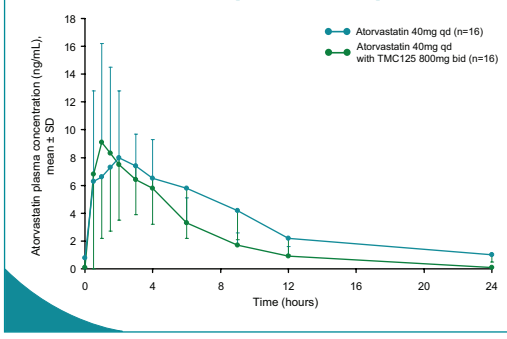


TMC125 PK parameters (mean ± SD)

PK parameter	TMC125 alone (reference) (n=16)	TMC125 + atorvastatin (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	13,816 ± 3,044	14,098 ± 3,290	1.02 (0.97–1.07)
C_{max} (ng/mL)	1,548 ± 339	1,514 ± 367	0.97 (0.93–1.02)
C_{min} (ng/mL)	760 ± 139	847 ± 207	1.10 (1.02–1.19)

SD = standard deviation

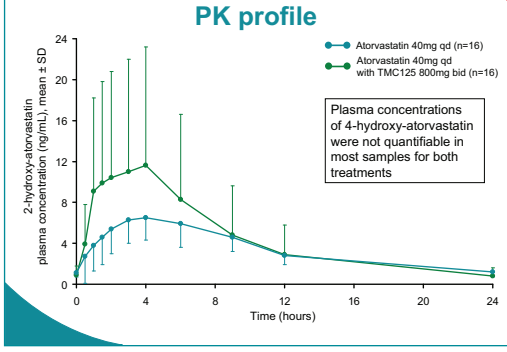
Atorvastatin plasma PK profile



Atorvastatin PK parameters (mean ± SD)

PK parameter	Atorvastatin alone (reference) (n=16)	Atorvastatin + TMC125 (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	82.7 ± 40.3	52.6 ± 29.4	0.63 (0.58–0.68)
C_{max} (ng/mL)	11.0 ± 5.86	11.5 ± 6.04	1.04 (0.84–1.30)

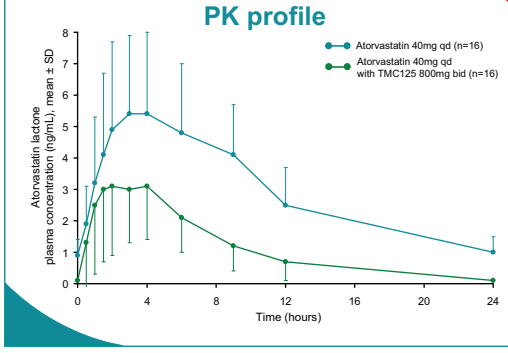
2-hydroxy-atorvastatin plasma PK profile



2-hydroxy-atorvastatin PK parameters (mean ± SD)

PK parameter	Atorvastatin alone (reference) (n=16)	Atorvastatin + TMC125 (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	82.9 ± 26.4	109.8 ± 46.8	1.27 (1.19–1.36)
C_{max} (ng/mL)	7.40 ± 2.25	13.66 ± 6.14	1.76 (1.60–1.94)

Atorvastatin lactone plasma PK profile



Atorvastatin lactone PK parameters (mean ± SD)

PK parameter	Atorvastatin alone (reference) (n=16)	Atorvastatin + TMC125 (test) (n=16)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	70.9 ± 30.4	28.6 ± 17.2	0.38 (0.34–0.42)
C_{max} (ng/mL)	6.04 ± 2.87	3.86 ± 2.13	0.62 (0.56–0.69)

Safety summary

- No serious AEs were reported
- The most frequently reported AE was headache in 12 volunteers, of which one event was possibly related to TMC125
- All AEs reported were mild (grade 1) in severity, except for moderate (grade 2) headache in five volunteers
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or the results of physical examinations
- All volunteers completed the trial

Conclusions

- When co-administered with atorvastatin 40mg qd, TMC125 pharmacokinetics were not altered.
- The decrease of atorvastatin exposure by 37% and the increased exposure to its active metabolite 2-hydroxy-atorvastatin by 27% when co-administered with TMC125, is likely caused by the induction of CYP3A4 by TMC125.
- Short-term co-administration of TMC125 with atorvastatin in HIV-negative volunteers was generally safe and well tolerated.
- TMC125 and atorvastatin can be co-administered. No a priori dose adjustment of atorvastatin is recommended; the dose of atorvastatin may be tailored, based on the clinical response.

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