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Pharmacokinetic evaluation of the interaction between TMC125 and tenofovir disoproxil fumarate

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Abstract

Background
TMC125 is an NNRTI with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. To support concomitant administration of the NtRTI tenofovir disoproxil fumarate (TDF) and TMC125, an interaction study was conducted with TDF and TMC125 (Phase III formulation) in HIV-negative volunteers.

Methods
TMC125-C177 was an open-label, two-period crossover, randomized trial. In Session I, 200mg TMC125 bid was administered for 7 days followed by a single morning dose on Day 8. After a washout period of 14 days, TDF 300mg qd was given from Day 1 to Day 16 of Session II. TMC125 200mg bid was coadministered during Days 9–15 in 12 volunteers randomized to Panel 1 and during Days 1–7 in 12 volunteers randomized to Panel 2 with a morning dose on Days 16 and 8, respectively. TMC125 and TDF were both administered after food intake. Plasma concentrations of TMC125 and tenofovir were assessed at steady-state over 12 and 24 hours, respectively. Pharmacokinetic (PK) parameters were estimated using non-compartmental methods and analyzed using a linear mixed effect model for a crossover design. Safety and tolerability were assessed.

Results
Twenty four male volunteers participated (median age 26 years). When combined with TDF, TMC125 AUC_{12h} was 81% (90% CI: 75–88%) compared with administration of TMC125 alone. TMC125 C_{max} and C_{min} were 81% (90% CI: 75–88%) and 82% (90% CI: 73–91%), respectively. AUC_{24h}, C_{max} and C_{min} of tenofovir were 115% (90% CI: 109–121%), 115% (90% CI: 104–127%) and 119% (90% CI: 113–126%), respectively, when combined with TMC125 compared with administration of TDF alone. Adverse events (AEs) were mild to moderate. The most common AEs were nasopharyngitis and headache (five subjects each). The concomitant administration of TMC125 and TDF was generally safe and well tolerated in this trial.

Conclusions
The changes in the pharmacokinetics of TMC125 or tenofovir when TMC125 is combined with TDF, are not clinically relevant. TMC125 and TDF can be coadministered without dose modifications.

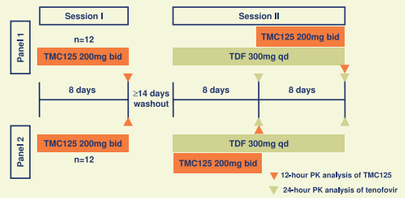
Introduction

- TMC125 is a next generation NNRTI with potent in-vitro activity against both wild-type HIV-1 and HIV-1 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 at 48 weeks significantly more than active control. No dose-related effects on safety and tolerability were noted[2,3]
- TMC125 is predominantly metabolized by CYP3A4, CYP2C and glucuronidation
- TDF is an NtRTI, indicated for the treatment of HIV-infected adults
- Tenofovir is primarily eliminated via the kidney. In-vitro and in-vivo studies conducted previously have demonstrated its limited drug-drug interaction potential
- To support the concomitant administration, an interaction study with TDF and TMC125 (Phase III formulation) was conducted

Study design

- TMC125-C177 was a Phase I, open-label, two-way, two-period crossover trial in which 24 HIV-negative volunteers were randomized in a 1:1 ratio to one of two panels as shown in the study design scheme
- Two treatment sessions (I and II) were scheduled for all volunteers, separated by a washout period of at least 14 days. Within each panel, half the subjects were randomized to start with Session I and half were randomized to start with Session II
- All doses were taken within 10 minutes after a meal, the order of intake was TMC125, then TDF
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication
- The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities, and was conducted in accordance with the Declaration of Helsinki

Study design



- Plasma concentrations of TMC125 were determined for 12 hours on Day 8 in Session I and on Days 8 or 16 in Session II
- Plasma concentrations of tenofovir were determined for 24 hours on Days 8 and 16 in Session II
- Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

Methods

- Plasma concentrations of TMC125 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (LLOQ 2ng/mL)
- Plasma concentrations of tenofovir were determined using a validated HPLC method with fluorescence detection (LLOQ 20ng/mL)
- PK and statistical PK analyses were performed using
  - WinNonlin Professional™ (version 4.1; Pharsight Corporation, Mountain View, CA, USA)
  - Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA)
  - SAS (version 9.1.3 SAS Institute Inc., Cary, NC, USA)
- A non-compartmental model with extravascular input was used for the PK analysis

LLOQ = lower limit of quantification; HPLC = high performance liquid chromatography

PK and safety parameters and statistical analyses

- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - AUC_{12h} and AUC_{24h} (ng•h/mL): area under the plasma concentration-time curve over 12 and 24-hour period, respectively, calculated by linear trapezoidal summation
- Safety parameters
  - AEs, laboratory assessments, ECG, vital signs and physical examinations were evaluated throughout the study
  - Severity and drug relationship of AEs to TDF or TMC125 were recorded
- Statistical analyses
  - Descriptive statistics were calculated for the PK parameters of TMC125 and tenofovir
  - Least square (LS) means were estimated with a linear mixed effects model
  - Safety parameters were evaluated by descriptive statistics and frequency tabulations

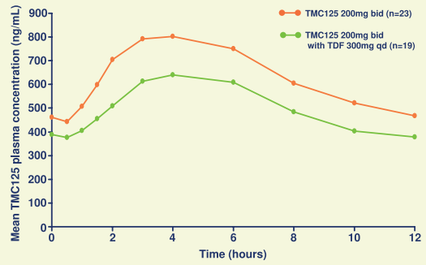
Demographics

Demographic parameter	All volunteers (n=24)
Age, years (median [range])	26 (19–54)
Height, cm (median [range])	182 (174–188)
Weight, kg (median [range])	77 (58–102)
BMI, kg/m² (median [range])	24 (18–30)
Ethnic origin, n (%)	
Caucasian/White	23 (96)
Hispanic	1 (4)
Male gender, n (%)	24 (100)
Type of smoker	
Light smoker*, n (%)	9 (38)
Non-smoker, n (%)	15 (62)

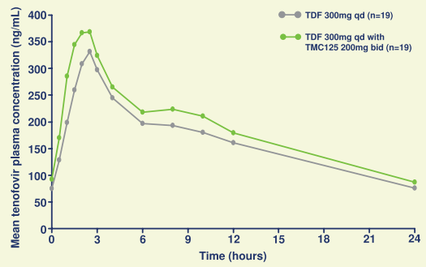
Demographic data were similar in Panel I and Panel II

*Light smoker was defined as smoking no more than 10 cigarettes, two cigars, or two pipes per day

PK profiles of TMC125



PK profiles of tenofovir



TMC125 PK parameters (mean ± SD)

PK parameter	TMC125 alone (reference) (n=23)	TMC125 + TDF (test) (n=19)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng•h/mL)	7,638±2,254	6,040±1,557	0.81 (0.75–0.88)
C_{max} (ng/mL)	876±233	695±144	0.81 (0.75–0.88)
C_{min} (ng/mL)	426±155	338±114	0.82 (0.73–0.91)

SD = standard deviation

Tenofovir PK parameters (mean ± SD)

PK parameter	TDF alone (reference) (n=19)	TDF + TMC125 (test) (n=19)	LS mean ratio (test/reference) (90% CI)
AUC_{24h} (ng•h/mL)	3,946±778	4,511±828	1.15 (1.09–1.21)
C_{max} (ng/mL)	389±97	443±99	1.15 (1.04–1.27)
C_{min} (ng/mL)	70±16	82±17	1.19 (1.13–1.26)

SD = standard deviation

Safety summary

- No serious AEs or grade 3 or 4 AEs were reported
- All reported AEs were mild in severity, except for one case of moderate hyperuricemia, not related to TMC125 or TDF
- The most frequent AEs were nasopharyngitis (six volunteers) and headache (five volunteers)
- Four volunteers developed mild macular rash during TMC125 alone treatment and discontinued the study; all cases resolved without treatment within 10 days after discontinuation
- No consistent or relevant changes were found in laboratory or cardiovascular safety parameters, or physical examinations

Conclusions

- When coadministered with TDF 300mg qd, TMC125 200mg bid exposure was decreased by 19% with similar decreases in C_{max} and C_{min}; these effects are not clinically relevant.
- The 15% increase of tenofovir exposure after the coadministration of TDF 300mg qd with TMC125 200mg bid is not clinically relevant.
- Short-term coadministration of TMC125 with TDF in healthy volunteers was generally safe and well tolerated.
- TMC125 can be coadministered with TDF without dose adjustments.

References

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. Nadler J, et al. 10th European AIDS Conference 2005 (Poster LBPS3/7A).
3. Cohen C, et al. XVI International AIDS Conference 2006 (Poster TUPE0061).

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