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Pharmacokinetics of amprenavir and TMC125 in HIV-infected volunteers receiving TMC125 with fosamprenavir/ritonavir

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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. TMC125 is a substrate and inducer of CYP3A4. The protease inhibitor (PI) amprenavir (APV), administered as fosamprenavir (fosAPV) with low-dose ritonavir (RTV), is a substrate and inducer of CYP3A4. This study was conducted to investigate the effect of TMC125 on the pharmacokinetic (PK) profile of APV when administered as fosAPV with low-dose RTV (fosAPR/r).

Methods
TMC125-C117 was an open-label, add-on, one-way interaction trial in HIV-infected volunteers, being treated with a stable antiretroviral (ARV) regimen consisting of fosAPV/r 700/100mg bid and NRTIs. On Days 1–13, 800mg bid of TMC125 (Phase II formulation) was added, with a morning dose on Day 14. Steady-state 12h PK profiles of APV and RTV were assessed on Days –1 and 14, and for TMC125 on Day 14. Plasma concentration data was analyzed by non-compartmental methods. PK parameters of APV were analyzed using a linear mixed effect model. PK parameters of TMC125 were compared with historical controls. Safety and tolerability were assessed during the trial.

Results
One female and seven males participated (median age 42 years). APV AUC_{12h}, C_{max} and C_{min} were 169% (90% CI: 153–186%), 162% (90% CI: 147–179%) and 177% (90% CI: 139–225%), respectively, when combined with TMC125 compared with administration without TMC125. Least square (LS) mean ratios for AUC_{12h}, C_{max} and C_{min} of RTV were 100% (90% CI: 81–123%), 102% (90% CI: 79–131%) and 93% (90% CI: 70–124%), respectively, when combined with TMC125. Plasma concentrations of TMC125 were in the range of those observed in HIV-positive volunteers receiving TMC125 without the coadministration of a boosted PI. The short-term concomitant administration of TMC125 and fosAPV/r was generally safe and well tolerated.

Conclusions
Plasma concentrations of APV are significantly increased when fosAPV/r is coadministered with TMC125, without relevant changes in RTV PK parameters. Dose adjustment of fosAPV might be considered when combined with TMC125. No apparent effect of APV on TMC125 PK was noted.

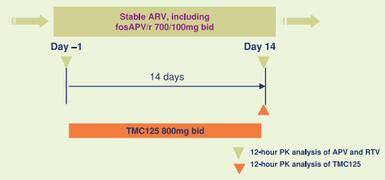
Introduction

- 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 a substrate and inducer of CYP3A4 and a substrate and inhibitor of CYP2C
- FosAPV is a prodrug of the PI APV, administered with low-dose RTV (fosAPV/r) and indicated for the treatment of HIV-infected adults
- APV is a substrate and inhibitor of CYP3A4
- To investigate the effect of TMC125 on the pharmacokinetics of APV when administered as fosAPV/r, an interaction study with fosAPV/r and TMC125 (Phase II formulation) was conducted in HIV-infected volunteers

Study design

- TMC125-C117 was a Phase I, open-label, add-on, one-way interaction trial in HIV-infected volunteers, being treated with a stable ARV regimen consisting of fosAPV/r 700/100mg bid and ≥2 NRTIs, who had documented NNRTI resistance and viral load <50 copies/mL
- On Days 1 to 13, 800mg bid of TMC125 (Phase II formulation) was added to the above regimen, with a morning dose on Day 14
- All doses were taken concomitantly within 10 minutes after a meal. On Days –1 and 14 a standardized breakfast was served
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication

Study design



- Plasma concentrations of APV and RTV were determined for 12 hours on Days –1 and 14
- Plasma concentrations of TMC125 were determined for 12 hours on Day 14
- Safety and tolerability of TMC125 and fosAPV/r were assessed throughout the trial until at least 30 days after the last trial medication intake

Methods

- Plasma concentrations of TMC125, APV and RTV were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (LLOQ: 2ng/mL for TMC125, 50mg/mL for APV and 5ng/mL for RTV)
- PK and statistical PK analyses were performed using SAS System for Windows, (version 8.2, SAS Institute Inc., Cary, NC, USA)
- A non-compartmental model with extravascular input was used for the PK analysis
- 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

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

PK and safety parameters and statistical analyses

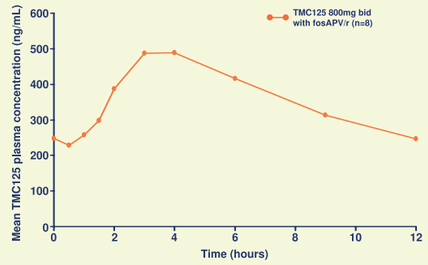
- Primary PK parameters
  - C_{max} (ng/mL): maximum plasma concentration
  - C_{min} (ng/mL): minimum plasma concentration
  - AUC_{12h} (ng·h/mL): area under the plasma concentration-time curve over 12-hour period, calculated by linear trapezoidal summation
- Safety parameters
  - AEs, laboratory assessments, ECG, vital signs and physical examinations were evaluated throughout the study
  - Severity and drug relationship of AEs to fosAPV/r and/or TMC125 were recorded
- Statistical analysis
  - Descriptive statistics were calculated for the PK parameters of TMC125, APV and RTV
  - PK parameters of TMC125 (AUC_{12h} and C_{0h}) were compared with those obtained in historical controls (HIV-infected volunteers using the same dose and formulation of TMC125)
  - LS means were estimated with a linear mixed effects model for APV and RTV
  - Safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

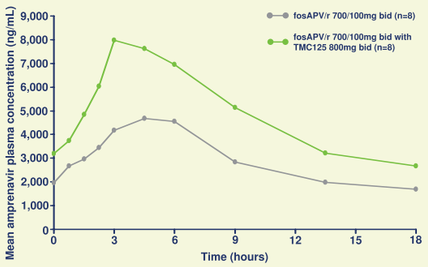
Demographic parameter	All volunteers (n=8)
Age, years (median[range])	42 (33–45)
Height, cm (median [range])	171 (165–186)
Weight, kg (median [range])	66 (54–110)
BMI, kg/m² (median [range])	22 (19–40)
Gender	
Male, n (%)	7 (88)
Female, n (%)	1 (12)
Ethnic origin, n (%)	
Caucasian/White	5 (63)
Black	3 (37)
Type of smoker	
Light smoker*, n (%)	1 (12)
Non-smoker, n (%)	7 (88)

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

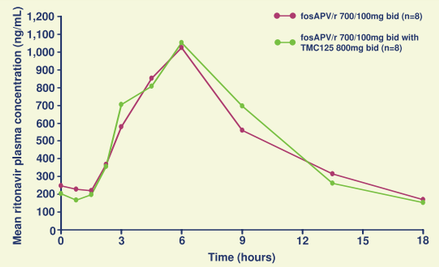
PK profile of TMC125



PK profile of APV



PK profile of RTV



TMC125 PK parameters compared with historical HIV-infected controls

PK parameter	n	AUC_{12h} (ng·h/mL) (median, range)	C_{max} (ng/mL) (median, range)	C_{0h} (ng/mL) (median, range)
TMC125 + fosAPV/r (this trial)	8	8,018 1,982–16,347	869 237–2,140	505 109–928
TMC125 + PIs (historical controls)*	40	3,556 1,157–28,077	NA	196 59–1,533
TMC125, no PIs (historical controls)*	34	6,056 1,564–24,445	NA	386 87–1,575

*In the Phase IIb trial TMC125-C223, HIV-infected volunteers with previous NNRTI experience were treated with 800mg bid of TMC125 (Phase II formulation) and NRTIs, with or without lopinavir/RTV in the background regimen, PK parameters were obtained in the primary analysis at 24 weeks by Bayesian feedback (C_{max} was not determined).
NA = not available

APV PK parameters (mean ± SD)

PK parameter	fosAPV/r alone (reference) (n=8)	fosAPV/r + TMC125 (test) (n=8)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng·h/mL)	35,270±11,115	58,645±17,120	1.69 (1.53–1.86)
C_{max} (ng/mL)	5,505±1,152	8,983±2,369	1.62 (1.47–1.79)
C_{min} (ng/mL)	1,538±700	2,595±1,135	1.77 (1.39–2.25)

SD = standard deviation

RTV PK parameters (mean ± SD)

PK parameter	fosAPV/r alone (reference) (n=8)	fosAPV/r + TMC125 (test) (n=8)	LS mean ratio (test/reference) (90% CI)
AUC_{12h} (ng·h/mL)	5,889±2,153	6,077±3,189	1.00 (0.81–1.23)
C_{max} (ng/mL)	1,073±422	1,158±664	1.02 (0.79–1.31)
C_{min} (ng/mL)	140±65	130±60	0.93 (0.70–1.24)

Safety summary

- No serious AEs or grade 3 or 4 AEs were reported
- No volunteer discontinued the trial prematurely
- All reported AEs were mild to moderate in severity, except for one case of a grade 3 influenza, doubtfully related to TMC125
- The most frequent AE was headache (three volunteers), of mild to moderate severity, possibly related to TMC125
- No rash was reported
- No consistent or relevant changes were found in laboratory or cardiovascular safety parameters, or physical examinations

Conclusions

- When coadministered with fosAPV/r 700/100mg bid, TMC125 exposure was in the range observed after the administration of the same dose and formulation in historical controls without boosted PI use.
- The PK parameters of APV showed significant increases after the addition of TMC125 to the ARV regimen, without any changes observed in the pharmacokinetics of ritonavir.
- Short-term coadministration of TMC125 with fosAPV/r in HIV-infected volunteers was generally safe and well tolerated.
- TMC125 can be coadministered with fosAPV/r without dose adjustment.
- Dose adjustment of fosAPV (administered with low-dose RTV) might be considered when combined with TMC125.

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).

Acknowledgments

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