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Pharmacokinetics of TMC125 in HIV-negative volunteers with mild or moderate hepatic impairment

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Abstract

Background: TMC125 (etravirine; ETR) is a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs. TMC125 is mainly eliminated via the hepatobiliary route. This study aimed to assess the pharmacokinetics of TMC125 in HIV-negative volunteers with and without hepatic impairment.

Methods: This was an open-label trial including volunteers with mild or moderate hepatic impairment (Child-Pugh[1] A or B, respectively) and healthy volunteers matched for age, gender, race, and body mass index (BMI). All volunteers received TMC125 200mg twice-daily (bid) following a meal for 7 days with a morning dose on Day 8. TMC125 pharmacokinetics over 12 hours on Days 1 and 8 were determined using non-compartmental methods and analyzed by a linear mixed effect model. Safety and tolerability were assessed.

Results: Eight volunteers with mild hepatic impairment (five males; median age 57 years), eight with moderate hepatic impairment (six males; median age 54 years) and 16 matched healthy volunteers participated. Pharmacokinetic (PK) results are shown below.

LS mean ratios (90% confidence intervals [CIs])

	PK parameter	Mild hepatic impairment versus healthy	Moderate hepatic impairment versus healthy
Day 1	C_{max}	0.92 (0.69–1.21)	0.63 (0.47–0.85)
	AUC_{12h}	0.99 (0.75–1.29)	0.77 (0.55–1.08)
Day 8	C_{min}	0.87 (0.65–1.17)	0.98 (0.68–1.42)
	C_{max}	0.79 (0.63–1.00)	0.72 (0.54–0.96)
	AUC_{12h}	0.87 (0.69–1.09)	0.82 (0.60–1.11)

LS = least square; C_{max} = maximum plasma concentration; AUC_{12h} = area under the plasma concentration-time curve from time of administration to 12 hours after dosing; C_{min} = minimum plasma concentration

All treatment emergent adverse events (AEs) were mild or moderate. The most common AEs were headache, fatigue and nausea. No clinically significant changes in laboratory parameters were observed.

Conclusions: TMC125 was generally safe and well tolerated. The systemic exposure to TMC125 in volunteers with hepatic impairment was comparable to that in healthy volunteers. Dose adjustment of TMC125 in patients with mild or moderate hepatic impairment is not required.

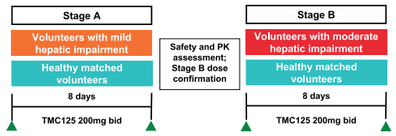
Introduction

- TMC125 is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently available NNRTIs[2]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to current NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an AE profile similar to placebo[3,4]
- TMC125 is predominantly metabolized by the cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19
- Antiretroviral treatment in patients with hepatic impairment may lead to enhanced liver toxicity and/or altered pharmacokinetics of the administered drugs[5,6]
- To support administration of TMC125 in patients with hepatic impairment, a PK study in this population was conducted

Study design

- TMC125-C125 was a Phase I, open-label, multiple dose PK trial in two sequential stages in HIV-negative volunteers with mild (Stage A, Child-Pugh[1] score 5–6) or moderate (Stage B, Child-Pugh[1] score 7–9) hepatic impairment
- In both stages healthy HIV-1 negative control volunteers were also included, matched by age, gender, race and BMI
- Concomitant medication for the management of hepatic impairment was allowed
- All volunteers received TMC125 200mg bid (Phase III formulation) following a meal for 7 days with a morning dose on Day 8
- 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 1 and Day 8

- Plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method for TMC125 (lower limit of quantification 2ng/mL)

Parameters and analyses

- Primary PK parameters
  - C_{max} (ng/mL)
  - C_{min} (ng/mL)
  - AUC_{12h} (ng•h/mL), calculated by linear trapezoidal summation
- Safety parameters
  - AEs, laboratory assessments, electrocardiograms, vital signs assessments and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to TMC125 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 WinNonLin Professional™ 4.1 (Pharsight Corporation, Mountain View, CA, USA) and Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA), and/or SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA)
  - descriptive statistics were calculated for the PK parameters of TMC125, LS means for volunteers with hepatic impairment and their matched healthy controls were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

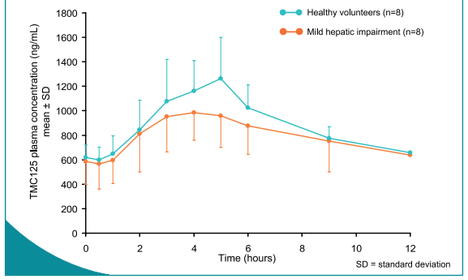
Demographics

Demographic parameter, median (range) unless indicated	Stage A: Mild hepatic impairment (n=8)	Stage A: Healthy (n=8)	Stage B: Moderate hepatic impairment (n=8)	Stage B: Healthy (n=8)
Age, years	57 (41–65)	56 (44–66)	54 (44–64)	51 (42–63)
Height, cm	171 (160–183)	172 (157–181)	174 (158–198)	175 (155–190)
Weight, kg	74 (58–101)	72 (57–89)	79 (60–125)	82 (55–96)
BMI, kg/m²	26 (20–32)	26 (23–29)	26 (22–32)	27 (23–31)
Male/female, n	5/3	5/3	6/2	6/2
Caucasian, n (%)	8 (100)	8 (100)	8 (100)	8 (100)

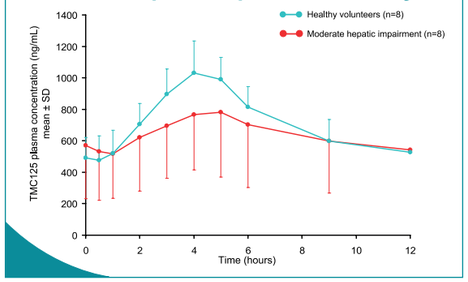
- Etiology of hepatic impairment was alcoholic cirrhosis except one case of HCV cirrhosis and one case of HCV plus alcoholic cirrhosis

HCV = hepatitis C virus

TMC125 plasma PK profile in mild hepatic impairment on Day 8



TMC125 plasma PK profile in moderate hepatic impairment on Day 8



TMC125 PK parameters (mean ± SD) in mild hepatic impairment

PK parameter		Mild hepatic impairment	Healthy	LS mean ratio (90% CI)
Day 1	C_{max} (ng/mL)	467 ± 158	499 ± 149	0.92 (0.69–1.21)
	AUC_{12h} (ng•h/mL)	2903 ± 816	2972 ± 1105	0.99 (0.75–1.29)
Day 8	C_{min} (ng/mL)	550 ± 192	594 ± 100	0.87 (0.65–1.17)
	C_{max} (ng/mL)	1060 ± 268	1339 ± 357	0.79 (0.63–1.00)
	AUC_{12h} (ng•h/mL)	9546 ± 2630	10650 ± 1688	0.87 (0.69–1.09)

TMC125 PK parameters (mean ± SD) in moderate hepatic impairment

PK parameter		Moderate hepatic impairment	Healthy	LS mean ratio (90% CI)
Day 1	C_{max} (ng/mL)	268 ± 101	414 ± 123	0.63 (0.47–0.85)
	AUC_{12h} (ng•h/mL)	1846 ± 808	2293 ± 664	0.77 (0.55–1.08)
Day 8	C_{min} (ng/mL)	499 ± 293	462 ± 128	0.98 (0.68–1.42)
	C_{max} (ng/mL)	818 ± 394	1054 ± 194	0.72 (0.54–0.96)
	AUC_{12h} (ng•h/mL)	7665 ± 4122	8584 ± 1560	0.82 (0.60–1.11)

Safety summary

- All volunteers completed the trial
- The most frequently reported AEs for volunteers with mild hepatic impairment were nausea and fatigue (both in two volunteers with mild hepatic impairment and one healthy volunteer)
- Dizziness and muscle spasms were the most common AEs for volunteers with moderate hepatic impairment (both in two volunteers compared to none in the healthy volunteers)
- Headache was reported for four healthy volunteers (none of the volunteers with hepatic impairment)
- No rash was reported

Safety summary (cont'd)

- All AEs reported were mild or moderate (grade 1 and 2) in severity
- No serious AEs were reported, except one case of tachyarrhythmia with cardiac failure in a volunteer with moderate hepatic impairment and pre-existing cardiomyopathy, which occurred 36 days after the last intake of TMC125
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or the results of physical examinations
- Grade 3 or 4 laboratory abnormalities were reported in one volunteer with mild hepatic impairment (hypercholesterolemia) and two volunteers with moderate hepatic impairment (low hemoglobin and hypophosphatemia in one, and increased lipase in another volunteer)

Conclusions

- No clinically relevant difference was observed between the pharmacokinetics of TMC125 when administered in HIV-negative volunteers with and without hepatic impairment (mild or moderate).
- Short-term administration of TMC125 in HIV-negative volunteers with and without hepatic impairment was generally safe and well tolerated.
- TMC125 can be administered in patients with mild or moderate hepatic impairment without dose adjustment.

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