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Pharmacokinetic interaction between etravirine and fluconazole or voriconazole in HIV-negative volunteers

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Abstract

Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-infected patients. ETR is a substrate and inducer of cytochrome P450 (CYP) CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19. Fluconazole (FLU) and voriconazole (VOR) are inhibitors of CYP3A, 2C9 and 2C19. This study evaluated the pharmacokinetics of ETR and FLU or VOR when co-administered.

Methods

In an open-label, randomized, two-way, three-period crossover trial, 200mg ETR bid was given for 8 days (Treatment A). In Treatments B and C, 200mg FLU qd or 200mg VOR bid, respectively, was administered for 16 days with 14-day washout periods. ETR 200mg bid was co-administered during Days 8–16. ETR pharmacokinetics were assessed on Day 8 of Treatment A and Day 16 of Treatments B and C; FLU and VOR pharmacokinetics on Days 8 and 16 of Treatments B and C, respectively. Pharmacokinetic (PK) parameters were obtained by non-compartmental analyses. Safety and tolerability were assessed.

Results

Eighteen volunteers participated (median age 29 years; three females). PK results are given below.

PK parameter LSM ratio and 90% CI	ETR with/ without FLU (n=16)	ETR with/ without VOR (n=16)	FLU with/ without ETR (n=15)	VOR with/ without ETR (n=14)
C_{min}	2.09 (1.90–2.31)	1.52 (1.41–1.64)	0.91 (0.84–0.98)	1.23 (0.87–1.75)
C_{max}	1.75 (1.60–1.91)	1.26 (1.16–1.38)	0.92 (0.85–1.00)	0.95 (0.75–1.21)
$AUC_{12h/24h}$	1.86 (1.73–2.00)	1.36 (1.25–1.47)	0.94 (0.88–1.01)	1.14 (0.88–1.47)

LSM = least square means; CI = confidence interval; C_{min} = minimum plasma concentration; C_{max} = maximum plasma concentration; $AUC_{12h/24h}$ = area under the plasma concentration-time curve from time of administration to 12/24 hours after dosing

Three volunteers withdrew consent, one discontinued due to leucocyturia when taking FLU alone. The most frequent adverse events (AEs) were headache and blurred vision (11 and eight volunteers, respectively) in the majority during VOR alone treatment. No grade 3 AEs were observed during the treatments. Co-administration of ETR and FLU or VOR was generally safe and well tolerated.

Conclusions

Co-administration of ETR with FLU or VOR resulted in an increase of ETR steady-state concentrations. FLU pharmacokinetics were unchanged and VOR pharmacokinetics were slightly increased when given with ETR, all at steady-state. Combinations of ETR and FLU or VOR were generally safe and well tolerated.

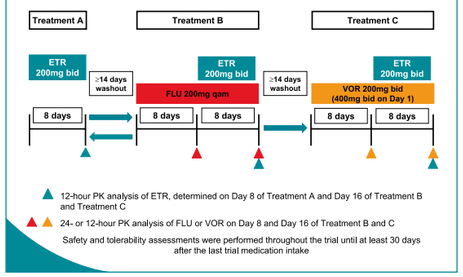
Introduction

- ETR is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to first-generation NNRTIs[1]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit over 96 weeks of treatment with ETR in treatment-experienced patients with resistance to first-generation NNRTIs. Except for a higher incidence of rash, patients treated with ETR had an AE profile similar to placebo[2–4]
- ETR is predominantly metabolized by the CYP enzymes 3A, 2C9 and 2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein
- FLU and VOR are antifungal agents that are used in the clinical management of fungal infections and are frequently administered to HIV-1-infected individuals
- The majority (~80%) of FLU is renally excreted as unchanged drug; VOR is a substrate of CYP3A, 2C9 and 2C19[5]
- FLU and VOR are inhibitors of CYP3A, 2C9 and 2C19 to varying extent[5]
- To support concomitant administration, an interaction study with ETR and FLU or VOR was conducted in healthy volunteers

Study design

- TMC125-C187 was a Phase I, open-label, two-way, three-period, partially randomized crossover trial in 18 HIV-negative volunteers
- Three treatment sessions (A, B and C) were scheduled for all volunteers, separated by two washout periods of at least 14 days each, as shown in the study design scheme. Half of the volunteers were randomized to start with Treatment A and half were randomized to start with Treatment B. Treatment C followed for all volunteers in the third period
- ETR was administered as 200mg bid; all doses were taken within 10 minutes after breakfast and dinner
- FLU was administered as 200mg qam, within 10 minutes after breakfast
- VOR was administered as 400mg bid on Day 1 and 200mg bid on and after Day 2. All VOR doses were taken 1.5 hours before breakfast or dinner
- 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 (cont'd)



▲ 12-hour PK analysis of ETR, determined on Day 8 of Treatment A and Day 16 of Treatment B and Treatment C

▲▲ 24- or 12-hour PK analysis of FLU or VOR on Day 8 and Day 16 of Treatment B and C

Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

PK analyses

- Plasma concentrations of ETR were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- Plasma concentrations of FLU and VOR were determined using validated LC-MS/MS methods (LLOQ 20ng/mL and 10ng/mL, respectively)
- A non-compartmental model with extravascular input was used for the PK analysis
- PK and statistical PK analyses were performed using WinNonlin Professional™ (version 4.1, Pharsight Corporation, Mountain View, California, USA) and SAS System for Windows® version 9.1.3 (SAS Institute Inc., Cary NC 27512–8000, USA)

LC-MS/MS = liquid chromatography–tandem mass spectrometry
LLOQ = lower limit of quantification

PK and safety parameters and analyses

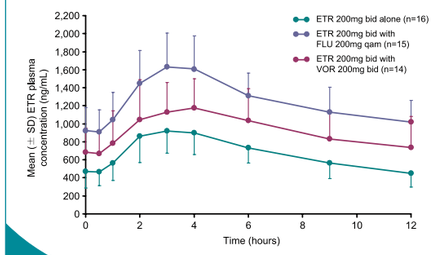
- Primary PK parameters
  - C_{min} (ng/mL)
  - C_{max} (ng/mL)
  - $AUC_{12h/24h}$ (ng•h/mL)
- Safety parameters
  - AEs, laboratory assessments, electrocardiogram, vital signs assessment and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to ETR, FLU and/or VOR were recorded
- Genotyping for CYP2C9 and CYP2C19 was performed in volunteers who provided consent for pharmacogenetic assessment
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of ETR, FLU and VOR
  - LSM ratios and 90% CIs were estimated with a linear mixed-effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

Demographic parameter	All volunteers (N=18)
Age, years, median (range)	29 (18–45)
Height, cm, median (range)	178 (157–198)
Weight, kg, median (range)	80 (56–101)
Body mass index, kg/m², median (range)	24 (21–29)
Gender, n (%)	
Male	15 (83)
Female	3 (17)
Ethnic origin, n (%)	
Caucasian	16 (89)
Black	2 (11)

- Four volunteers discontinued the trial: three due to withdrawal of consent and one due to an AE

ETR plasma PK profile



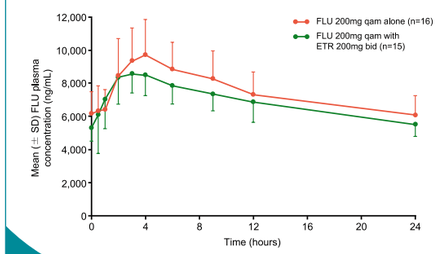
SD = standard deviation

ETR PK parameters

PK parameter	ETR alone (Reference) (mean ± SD) (n=16)	ETR + FLU (Test A) (mean ± SD) (n=15)	ETR + VOR (Test B) (mean ± SD) (n=14)
C_{min} (ng/mL)	426 ± 154	889 ± 242	648 ± 237
C_{max} (ng/mL)	984 ± 250	1,723 ± 395	1,251 ± 366
AUC_{12h} (ng•h/mL)	8,105 ± 2,173	15,160 ± 3,204	11,230 ± 3,794

LSM ratio (Test/Reference) (90% CI)	ETR alone (Reference) (mean ± SD) (n=16)	ETR + FLU (Test A) (mean ± SD) (n=15)	ETR + VOR (Test B) (mean ± SD) (n=14)
C_{min}	–	2.09 (1.90–2.31)	1.52 (1.41–1.64)
C_{max}	–	1.75 (1.60–1.91)	1.26 (1.16–1.38)
AUC_{12h}	–	1.86 (1.73–2.00)	1.36 (1.25–1.47)

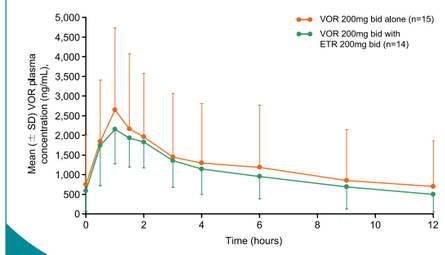
FLU plasma PK profile



FLU PK parameters

PK parameter	FLU alone (Reference) (mean ± SD) (n=16)	FLU + ETR (Test) (mean ± SD) (n=15)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	5,786 ± 1,089	5,240 ± 765	0.91 (0.84–0.98)
C_{max} (ng/mL)	9,834 ± 2,115	9,209 ± 1,819	0.92 (0.85–1.00)
AUC_{24h} (ng•h/mL)	176,000 ± 29,290	165,900 ± 23,780	0.94 (0.88–1.01)

VOR plasma PK profile

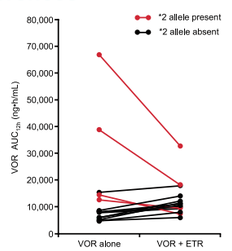


VOR PK parameters

PK parameter	VOR alone (Reference) (mean ± SD) (n=15)	VOR + ETR (Test) (mean ± SD) (n=14)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	692 ± 1,161	494 ± 455	1.23 (0.87–1.75)
C_{max} (ng/mL)	2,871 ± 1,952	2,455 ± 799	0.95 (0.75–1.21)
AUC_{12h} (ng•h/mL)	14,740 ± 17,390	12,660 ± 6,767	1.14 (0.88–1.47)

VOR PK – pharmacogenetic differences

- Four volunteers had one CYP2C19 *2 allele each, no homozygous volunteers for CYP2C19 (*2/*2, poor metabolizers) were identified
- Nine volunteers were identified without CYP2C19 *2 allele
- High inter-individual variability of VOR PK was due to differences in CYP2C19 metabolizer status
- In carriers of CYP2C19 *2 allele, the net effect of ETR is possibly induction rather than inhibition
- Co-administration of ETR decreased VOR concentrations in carriers of CYP2C19 *2 allele and increased them in volunteers without *2 allele, resulting in lower inter-individual variability of VOR PK



Safety summary

- No serious AEs were reported
- The most frequently reported AEs were headache and blurred vision, most of these events were observed during treatment with VOR alone (47% and 53%, respectively), consistent with the safety profile of VOR
- All AEs reported during the treatment periods were mild (grade 1) or moderate (grade 2) in severity
- One volunteer discontinued the trial on Day 6 of treatment with FLU alone due to grade 2 leucocyturia
- Grade 3 laboratory abnormalities were observed in one volunteer during the follow-up period (increased pancreatic amylase and lipase) and in one volunteer on Day 8 of ETR treatment (increased partial thromboplastin time)
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations

Conclusions

- When co-administered with FLU or VOR, ETR steady-state plasma concentrations were increased
  - post-hoc analysis of AEs in DUET-1 and DUET-2 over 96 weeks in patients with and without co-administration of FLU showed no difference in safety profile (data on file)
- ETR had no effect on the pharmacokinetics of FLU when these two drugs were co-administered at steady-state
- VOR pharmacokinetics were slightly increased when co-administered with ETR; no increase was observed in carriers of CYP2C19 *2 allele
- Co-administration of ETR with FLU or VOR in HIV-negative volunteers was generally safe and well tolerated

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