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Pharmacokinetic interaction between etravirine and lopinavir/ritonavir in HIV-negative volunteers

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Abstract

Objectives

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-1-infected patients. A previous interaction trial in HIV-negative volunteers demonstrated 17% increase of ETR exposure when co-administered with the soft-gel formulation of lopinavir (LPV) with low-dose ritonavir (LPV/r; RTV). This study re-evaluated the pharmacokinetics of ETR and LPV/r when LPV/r was administered as the Meltrex® formulation in HIV-negative healthy volunteers.

Methods

In an open-label, randomised, two-way, two-period crossover trial, ETR 200mg bid was given for 8 days. After 14 days washout, LPV/r 400/100mg bid was administered for 16 days; ETR 200mg bid was co-administered on days 9–16. Steady-state pharmacokinetics were assessed over 12 hours for ETR, LPV and RTV alone and when co-administered. Pharmacokinetic (PK) parameters were obtained by non-compartmental analysis and analysed by linear mixed-effects model. Safety and tolerability were assessed.

Results

Sixteen volunteers participated (11 male/five female). PK results are given below:

ETR	Alone (mean ± SD) (n=16)	With LPV/r (mean ± SD) (n=16)	LSM ratio (90% CI)
C_{min} (ng/mL)	451 ± 121	253 ± 84	0.55 (0.49–0.62)
C_{max} (ng/mL)	905 ± 187	643 ± 163	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	8,036 ± 1,779	5,250 ± 1,416	0.65 (0.59–0.71)
LPV	**Alone (mean ± SD) (n=16)**	**With ETR (mean ± SD) (n=16)**	**LSM ratio (90% CI)**
C_{min} (µg/mL)	5.3 ± 1.9	4.3 ± 1.5	0.80 (0.73–0.88)
C_{max} (µg/mL)	11.2 ± 2.9	9.8 ± 1.9	0.89 (0.82–0.96)
AUC_{12h} (µg•h/mL)	96.8 ± 21.8	84.5 ± 17.7	0.87 (0.83–0.92)
RTV			
C_{min} (ng/mL)	125 ± 72	107 ± 53	0.86 (0.76–0.97)
C_{max} (ng/mL)	845 ± 452	668 ± 341	0.81 (0.69–0.95)
AUC_{12h} (ng•h/mL)	4,415 ± 1,792	3,925 ± 1,472	0.89 (0.81–0.98)

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

All volunteers completed the trial. The most frequent adverse event (AE) was headache in six volunteers (grade 1). One transient grade 3 increase of triglycerides was reported during co-administration, all other AEs were grade 1 or 2.

Conclusions

In contrast to the results of the study performed with the soft-gel formulation of LPV/r, co-administration of ETR with LPV/r (Meltrex®) resulted in a 30–45% decrease in ETR PK parameters. The decrease of LPV and RTV PK parameters by 11–20% when combined with ETR is similar to earlier reported data and is not considered clinically relevant. Given that the effect of LPV/r on ETR pharmacokinetics is comparable to the effect of darunavir/RTV (DRV/r) on ETR pharmacokinetics shown in previous trials, which demonstrated favourable ETR efficacy and safety, ETR and LPV/r can be co-administered without dose adjustments.

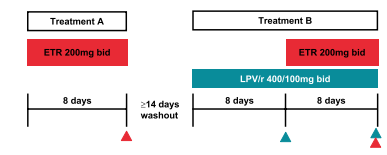
Introduction

- 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 metabolised by the cytochrome P450 (CYP) enzymes 3A, 2C9 and 2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein
- The protease inhibitor LPV/r is indicated for the treatment of HIV-1 infection
- LPV/r is an inducer of CYP1A2, CYP2C9, CYP2C19 and an inhibitor of CYP3A[5]
- A previous interaction trial in HIV-negative volunteers demonstrated increased ETR exposure when an earlier formulation of ETR was co-administered with the soft-gel formulation of LPV/r[6]
- This trial re-evaluated the PK interaction between ETR and LPV/r using the current formulation for both drugs (i.e. ETR spray-dried formulation and LPV/r produced by melt extrusion technology)

Study design

- TMC125-C197 was a Phase I, open-label, two-way, two-period, randomised 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. Half of the volunteers were randomised to start with Treatment A and half were randomised to start with Treatment B
- ETR was administered as 200mg bid; all doses were taken within 10 minutes after breakfast and dinner
- LPV/r was administered as 400/100mg bid of the Meltrex® formulation, within 10 minutes after breakfast and dinner
- Post-treatment safety visits took place 7 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 on Day 8 of Treatment A and Day 16 of Treatment B
▲ 12-hour PK analysis of LPV and RTV, determined on Day 8 and Day 16 of Treatment B

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 LPV and RTV were determined using a validated LC-MS/MS method (LLOQ 10ng/mL and 5ng/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

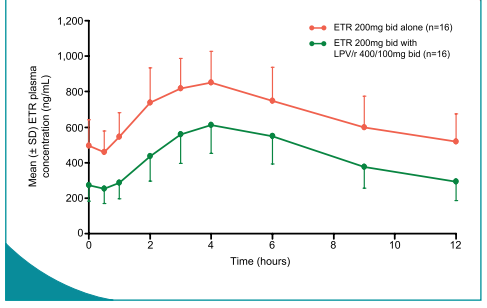
PK and safety parameters and statistical analyses

- Primary PK parameters
  - C_{min} (ng/mL)
  - C_{max} (ng/mL)
  - AUC_{12h} (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, LPV and/or RTV were recorded
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of ETR, LPV and RTV
  - 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=16)
Age, years, median (range)	45 (20–53)
Height, cm, median (range)	175 (158–193)
Weight, kg, median (range)	70 (53–94)
Body mass index, kg/m², median (range)	23 (19–29)
Gender, n (%)	
Male	11 (69)
Female	5 (31)
Ethnic origin, n (%)	
Caucasian	16 (100)

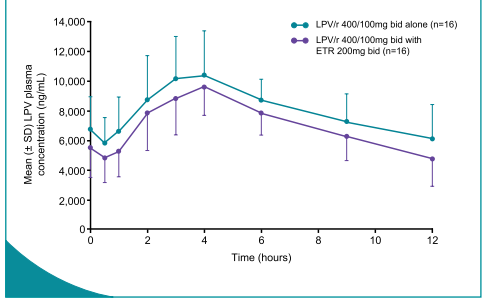
ETR plasma PK profile



ETR PK parameters

PK parameter	ETR alone (Reference) (mean ± SD) (n=16)	ETR + LPV/r (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	451 ± 121	253 ± 84	0.55 (0.49–0.62)
C_{max} (ng/mL)	905 ± 187	643 ± 163	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	8,036 ± 1,779	5,250 ± 1,416	0.65 (0.59–0.71)

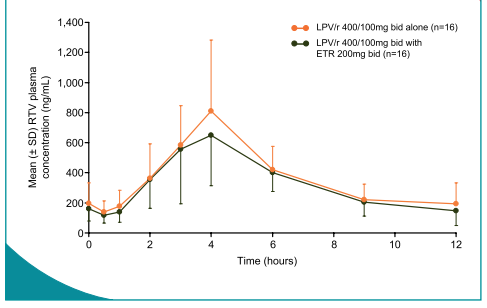
LPV plasma PK profile



LPV PK parameters

PK parameter	LPV alone (Reference) (mean ± SD) (n=16)	LPV + ETR (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	5,333 ± 1,850	4,322 ± 1,527	0.80 (0.73–0.88)
C_{max} (ng/mL)	11,170 ± 2,909	9,792 ± 1,906	0.89 (0.82–0.96)
AUC_{12h} (ng•h/mL)	96,790 ± 21,790	84,520 ± 17,710	0.87 (0.83–0.92)

RTV plasma PK profile



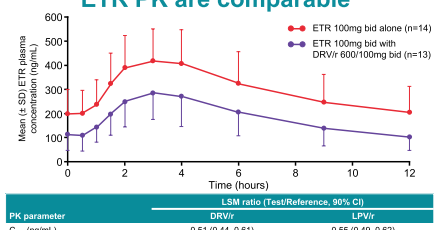
RTV PK parameters

PK parameter	RTV alone (Reference) (mean ± SD) (n=16)	RTV + ETR (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	125 ± 72	107 ± 53	0.86 (0.76–0.97)
C_{max} (ng/mL)	845 ± 452	668 ± 341	0.81 (0.69–0.95)
AUC_{12h} (ng•h/mL)	4,415 ± 1,792	3,925 ± 1,472	0.89 (0.81–0.98)

Safety summary

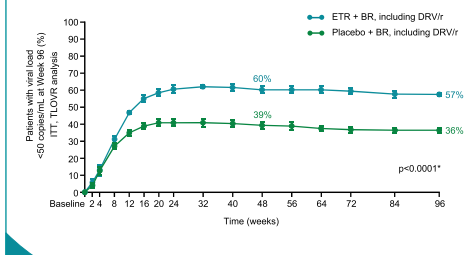
- No serious AEs were reported
- None of the volunteers discontinued the trial
- The most frequently reported AE was headache (six volunteers)
- All AEs reported during the treatment periods were mild (grade 1) or moderate (grade 2) in severity except for a grade 3 increase of triglycerides during co-administration of ETR and LPV/r; two other grade 3 laboratory abnormalities were observed during the co-administration phase (increase of total cholesterol and low-density lipoprotein)
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations

Effects of LPV/r and DRV/r on ETR PK are comparable[7]



PK parameter	LSM ratio (Test/Reference, 90% CI) DRV/r	LPV/r
C_{min} (ng/mL)	0.51 (0.44–0.61)	0.55 (0.49–0.62)
C_{max} (ng/mL)	0.68 (0.57–0.82)	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	0.63 (0.54–0.73)	0.65 (0.59–0.71)

Efficacy of ETR co-administered with DRV/r at Week 96[4]



*Logistic regression model controlling for baseline viral load, enfuvirtide use and study number; ITT = intent-to-treat; TLOVR = time-to-loss of virological response imputation algorithm; BR = background regimen

Conclusions

- ETR had no clinically relevant effect on the pharmacokinetics of LPV and RTV
- When co-administered with the Meltrex® formulation of LPV/r, ETR PK parameters decreased by 30–45%
- The effect of the Meltrex® formulation of LPV/r on ETR is comparable to that seen with DRV/r[7]
  - efficacy and safety of ETR in the presence of DRV/r was demonstrated in DUET-1 and DUET-2[4] up to 96 weeks
- Co-administration of ETR and LPV/r was generally safe and well tolerated
- ETR can be co-administered with LPV/r without dose adjustments

References

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. Madruga JV, et al. Lancet 2007;370:29–38.
3. Lazzarin A, et al. Lancet 2007;370:39–48.
4. Mills A, et al. IAS 2009. Abstract MOPEB036.
5. Yeh RF, et al. JAIDS 2006;42:52–60.
6. Piscitelli S, et al. ICAAC 2002. Abstract A-1824.
7. Schöller-Gyüre M, et al. Antiviral Ther 2007;12:789–96.

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