

Effect of etravirine on cytochrome P450 isozymes assessed by the Cooperstown 5+1 cocktail

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Abstract

Background

Etravirine (ETR; TMC125) is an NNRTI recently approved in the USA, Europe and a number of other countries for HIV-1-infected treatment-experienced patients. This randomized, crossover trial in HIV-negative volunteers evaluated the effect of a single dose and steady-state ETR on five cytochrome P450 (CYP) isozymes.

Methods

The Cooperstown 5+1 cocktail (orally: 150mg caffeine [CYP1A2], 10mg warfarin and 10mg vitamin K [CYP2C9], 40mg omeprazole [CYP2C19], 30mg dextromethorphan [CYP2D6], and 0.025mg/kg midazolam intravenously (iv) [CYP3A]) was administered alone (reference). After 2 weeks washout, 200mg ETR bid was given for 14 days with the cocktail co-administered on Days 1 and 14 (tests). Plasma pharmacokinetic (PK) parameters for ETR and the parent and metabolite compounds for the cocktail were calculated and analyzed by a linear mixed effects model. Parent/metabolite (P/M) ratios were determined. Safety and tolerability were also assessed.

Results

Fourteen male volunteers participated in the trial. On Day 14, the area under the plasma concentration-time curve from time zero to last timepoint with a measurable concentration after dosing (AUC_{last}) least square mean (LSM) ratios (90% confidence interval [CI]) were: caffeine 0.85 (0.78–0.91), S-warfarin 1.05 (0.93–1.19), omeprazole 1.83 (0.78–4.29), dextromethorphan 0.94 (0.72–1.23) and midazolam 0.69 (0.64–0.74). Mean (standard deviation [SD]) AUC_{last} P/M ratios when given alone, and with ETR on Days 1 and 14 are shown below.

Mean P/M ratios (SD)	Cocktail alone (n=12)	Cocktail + ETR Day 1 (n=14)	Cocktail + ETR Day 14 (n=12)
Caffeine/paraxanthine	1.87 (0.66)	1.90 (0.66)	1.67 (0.42)
S-warfarin/7-OH-S-warfarin	19.3 (15.7)	16.8 (6.74)	31.5 (12.9)
Omeprazole/5-OH-omeprazole	1.33 (0.61)	1.72 (0.70)	5.29 (0.90)
Dextromethorphan/dextrorphan	0.007 (0.007)	0.009 (0.009)	0.005 (0.004)
Midazolam/1-OH-midazolam	6.85 (1.67)	6.09 (1.16)	4.30 (0.72)

All adverse events (AEs) were grade 1 or 2. One volunteer discontinued the trial due to sore throat and one for grade 2 rash. The most common AEs were fatigue and hypoesthesia (64% each).

Conclusions

ETR had no clinically relevant effect on CYP1A2 or CYP2D6. At steady-state, ETR was a weak inducer of CYP3A and a weak inhibitor of CYP2C9. An inhibitory effect of ETR on CYP2C19 was observed.

In-vitro interaction potential of ETR and the composition of the Cooperstown 5+1 cocktail

CYP450	Inhibition	Induction	Probe drug	Parent compound	Metabolite
1A2	+	-	Caffeine 150mg orally	Caffeine	Paraxanthine
2C9	++	+	Warfarin 10mg orally	S-warfarin	7-OH-S-warfarin
2C19	+	+	Omeprazole 40mg orally	Omeprazole	5-OH-omeprazole
2D6	+	-	Dextromethorphan 30mg orally	Dextromethorphan	Dextrorphan
3A	+	++	Midazolam 0.025mg/kg iv	Midazolam	1-OH-midazolam

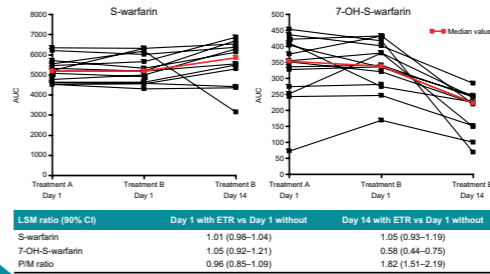
*A single oral dose of 10mg vitamin K was administered to counteract the pharmacodynamic effects of warfarin

PK and safety parameters and statistical analyses

- Primary PK parameters (for the cocktail drugs and the P/M ratios of these parameters)
 - C_{max} (ng/mL)
 - AUC_{last} (ng·h/mL)
- Safety parameters
 - AEs were assessed throughout the entire trial
 - laboratory assessments, electrocardiogram, vital signs assessment and physical examinations were performed at predefined timepoints
 - severity and drug relationship of AEs to ETR and/or cocktail compounds were recorded
- Statistical analyses
 - descriptive statistics were calculated for the PK parameters of all compounds
 - LSM ratios and 90% CIs were calculated with a linear mixed effects model
 - safety parameters were evaluated by descriptive statistics and frequency tabulations

C_{max} = maximum plasma concentration

Warfarin pharmacokinetics (CYP2C9)



Safety summary

- No serious AEs were reported
- The most frequently reported AEs were fatigue and hypoesthesia, in nine volunteers each
- All AEs reported were mild (grade 1) or moderate (grade 2) in severity
- Two volunteers discontinued the trial due to grade 2 AEs, one on Day 6 (sore throat) and one on Day 9 (rash) of Treatment B, respectively
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations

Study design

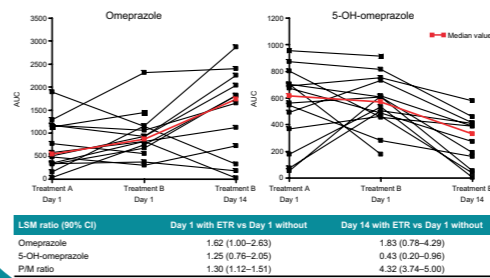
- TMC125-C174 was a Phase I, open-label, one-way, two-period, crossover trial in 14 HIV-negative volunteers
- Two treatment sessions (A and B) were scheduled for all volunteers, separated by a washout period of at least 14 days as shown in the study design scheme. Half of the volunteers were randomized to start with Treatment A and the other half were randomized to start with Treatment B
- A single oral dose of the cocktail drugs was administered on Day 1 of Treatment A and Days 1 and 14 of Treatment B
- ETR was administered as 200mg bid for 14 days in Treatment B; all doses were taken within 10 minutes after a meal
- 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

Demographics

Demographic parameter	All volunteers (N=14)
Age, years, median (range)	34 (21–49)
Height, cm, median (range)	181 (171–193)
Weight, kg, median (range)	81 (60–97)
Body mass index, kg/m ² , median (range)	24 (19–30)

- All volunteers were non-smoking male Caucasians
- Poor metabolizers for CYP2C9 and/or CYP2C19 were not allowed to participate

Omeprazole pharmacokinetics (CYP2C19)

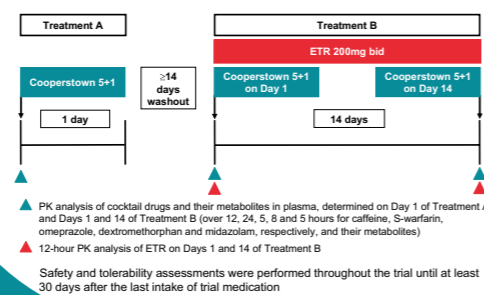


Conclusions

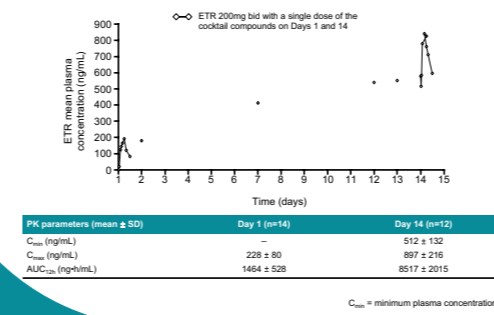
The co-administration of representative validated probes with ETR in steady state demonstrated:

- No clinically relevant induction or inhibition of CYP1A2
- Weak inhibition of CYP2C9, based on the decrease in the warfarin metabolite plasma concentrations, leading to an increased P/M ratio
- Inhibition of CYP2C19, shown both on Days 1 and 14 by increased omeprazole and decreased metabolite concentrations
- No clinically relevant induction or inhibition of CYP2D6
- Weak induction of CYP3A4, demonstrated by the decrease in the midazolam plasma concentrations on Day 14
- These results are consistent with the results of drug–drug interaction studies conducted with ETR and known substrates for these isozymes

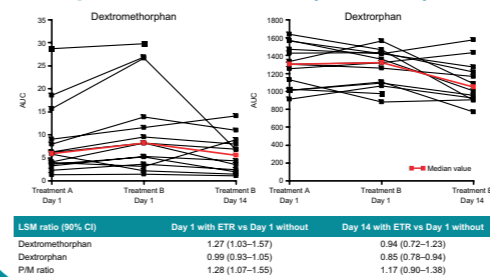
Study design (cont'd)



ETR pharmacokinetics



Dextromethorphan pharmacokinetics (CYP2D6)



References

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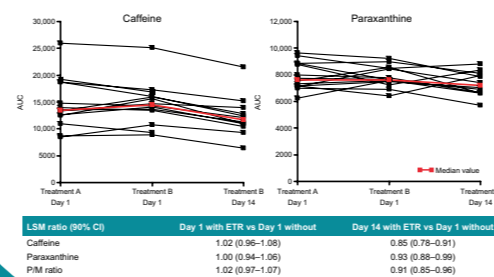
Introduction

- ETR is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1^{1,2}
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiretroviral benefit after 48 weeks of treatment with ETR in treatment-experienced patients with NNRTI resistance. Except for a higher incidence of rash, patients treated with ETR had an AE profile similar to placebo^{3,4}
- The 'Cooperstown 5+1' cocktail is a validated and generally safe combination of single-dose probe drugs for simultaneous assessment of the activity of a number of relevant drug metabolizing enzymes⁵
- A PK study in HIV-negative volunteers was undertaken with the concomitant administration of the drug cocktail and a single dose of ETR followed by the co-administration of the drug cocktail after 2 weeks of treatment with ETR, in order to assess the inhibitory and induction potential of ETR, respectively

PK analyses

- Plasma concentrations of ETR, caffeine, paraxanthine, S-warfarin, 7-OH-S-warfarin, omeprazole and 5-OH-omeprazole, dextromethorphan, dextrorphan, midazolam and 1-OH-midazolam, were determined using validated LC-MS/MS methods (LLOQ were 2ng/mL, 25ng/mL, 25ng/mL, 5ng/mL, 5ng/mL, 1ng/mL, 2ng/mL, 0.05ng/mL, 0.8ng/mL, 0.1ng/mL, 0.1ng/mL and 1ng/mL, respectively)
 - 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, USA)
 - a non-compartmental model with extravascular input (iv bolus for midazolam and 1-OH-midazolam) was used for the PK analysis
- LC-MS/MS = liquid chromatography-tandem mass spectrometry
LLOQ = lower limit of quantification

Caffeine pharmacokinetics (CYP1A2)



Midazolam pharmacokinetics (CYP3A4)

