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# Bioavailability of the 100mg etravirine tablet dispersed in water and of the 25mg pediatric tablet formulation

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## Abstract

### Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced HIV-infected patients, including those with NNRTI resistance. To support administration in children and in patients with swallowing difficulties, the oral bioavailability of the 100mg tablet dispersed in water and of the compositionally proportional 25mg pediatric tablet was assessed relative to the 100mg tablet swallowed whole.

### Methods

In an open-label, randomized, three-period crossover trial in HIV-negative volunteers, three single doses of ETR were administered as: one 100mg tablet swallowed whole (Treatment A; reference), four 25mg tablets (Treatment B; test 1) and one 100mg tablet dispersed in 100mL water (Treatment C; test 2). All treatments were given following a meal and were separated by 14-day washout periods. Pharmacokinetics of ETR were assessed over 96 hours after each administration. Pharmacokinetic (PK) parameters were obtained by non-compartmental analysis and evaluated by a linear mixed effects model. Safety and tolerability were assessed.

### Results

Thirty-seven volunteers participated (seven females). Least squares means (LSM) ratios (90% confidence interval [CI]) for ETR maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve from time of administration up to the last timepoint with a measurable concentration after dosing ($AUC_{last}$) in Treatment B compared to reference were 0.85 (0.78–0.93) and 0.91 (0.85–0.98), respectively, and in Treatment C compared to reference 0.95 (0.88–1.04) and 0.97 (0.90–1.03), respectively. ETR was generally safe and well tolerated. The most frequently reported adverse event (AE) was headache in eight volunteers. One volunteer discontinued prematurely due to grade 3 lipase increase during Treatment B. No other grade 3 or 4 AEs were reported.

### Conclusions

No relevant change in the oral bioavailability of ETR was demonstrated when the drug was administered as either four 25mg tablets, or as one 100mg tablet dispersed in water, compared to the administration of a 100mg tablet swallowed whole. Patients who are looking for a different option may disperse ETR tablets in a glass of water.

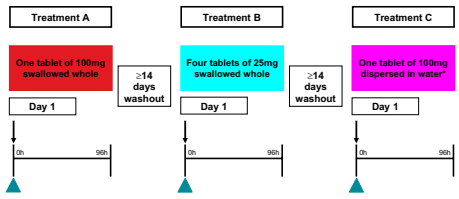
## Introduction

- 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 antiviral 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]
- ETR is administered in adult patients as two 100mg tablets (total 200mg) taken twice daily following a meal
- To support administration in children, a compositionally proportional 25mg tablet was developed
- ETR is stable when dispersed in water at ambient temperatures for up to 6 hours; the dispersion is odorless and tasteless
- The objective of this trial was to assess the single-dose oral bioavailability, relative to one 100mg tablet swallowed whole, of
  - four 25mg tablets
  - one 100mg tablet dispersed in water

## Study design

- TMC125-C173 was a Phase I, open-label, three-period crossover trial in HIV-negative volunteers
- Three treatment sessions (A, B and C) were scheduled for all volunteers, separated by washout periods of at least 14 days as shown in the study design scheme. Twelve volunteers were randomized each to begin the trial with either Treatment A, Treatment B or Treatment C
- In all treatments, 100mg ETR was taken within 10 minutes after a standardized meal
- Safety and tolerability assessments were performed throughout the trial until 31 (±1) days after the last trial medication intake
- 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)




▲ 96-hour PK analysis of ETR on Day 1 of Treatment A, B and C

*One tablet of 100mg was dispersed in 100mL water, stirred well and consumed immediately; the glass was then rinsed twice with 70mL water and each rinse was completely swallowed

## Treatments


## PK analyses

- Plasma concentrations of ETR were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- Primary PK parameters
  - $C_{max}$ (ng/mL)
  - $AUC_{last}$ (ng•h/mL)
- 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 was used for the PK analysis

LC-MS/MS = liquid chromatography-mass spectrometry/mass spectrometry
LLOQ = lower limit of quantification; $AUC_{last}$ = AUC from time of administration to 96 hours after dosing

## Safety parameters and statistical analyses

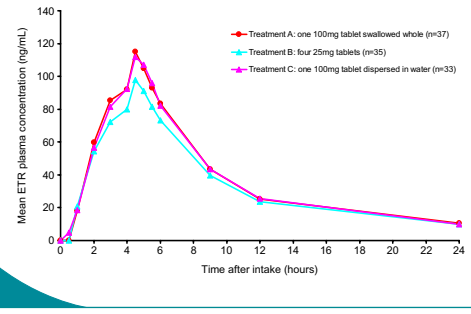
- Safety parameters
  - AEs were assessed throughout the entire trial
  - vital signs and laboratory assessments, electrocardiogram (ECG), and physical examinations were performed at predefined timepoints
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of ETR
  - LSM ratios and 90% CIs were calculated with a linear mixed effects model
  - reference: Treatment A
  - test 1: Treatment B
  - test 2: Treatment C
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

## Demographics

| Demographic parameter | All volunteers (n=37*) |
|---|---|
| Age, years, median (range) | 39 (22–56) |
| Height, cm, median (range) | 177 (160–194) |
| Weight, kg, median (range) | 80 (55–105) |
| Body mass index, kg/m², median (range) | 26 (20–30) |
| Male gender, n (%) | 30 (81) |
| Ethnic origin, n (%) | |
| Caucasian | 35 (95) |
| Hispanic | 1 (3) |
| Other | 1 (3) |

*Four volunteers prematurely discontinued the trial: two withdrew consent during the trial, one was non-compliant and one discontinued due to an AE

## Mean PK profiles




## ETR PK parameters (mean ± SD)

| PK parameters | Treatment A One 100mg tablet swallowed whole | Treatment B Four 25mg tablets swallowed whole | Treatment C One 100mg tablet dispersed in water |
|---|---|---|---|
| n | 37 | 35 | 33 |
| $AUC_{last}$ (ng•h/mL) | 1241 ± 642 | 1126 ± 542 | 1219 ± 712 |
| $AUC_{inf}$ (ng•h/mL) | 1412 ± 885 | 1286 ± 751 | 1409 ± 1109 |
| $C_{max}$ (ng/mL) | 130 ± 50 | 113 ± 44 | 131 ± 62 |
| **LSM ratios (90% CI)** | | **B vs A** | **C vs A** |
| $AUC_{last}$ (ng•h/mL) | | 0.91 (0.85–0.98) | 0.97 (0.90–1.03) |
| $C_{max}$ (ng/mL) | | 0.85 (0.78–0.93) | 0.95 (0.88–1.04) |

SD = standard deviation
$AUC_{inf}$ = AUC from time zero extrapolated to the infinite time

## Safety summary

- No serious AEs were reported
- The most frequently reported AE was headache in eight volunteers (two events in Treatment A, four in Treatment B and three in Treatment C)
- One volunteer discontinued prematurely due to grade 3 lipase increase during Treatment B, which resolved within 2 days
- All other AEs reported were mild (grade 1) or moderate (grade 2) in severity
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations
- Note
  - practicalities with the preparation of the dispersion or its intake (e.g. taste, odor or texture) were not reported

## Conclusions

- The pharmacokinetics of an equivalent dose of ETR administered as either one 100mg tablet or four 25mg tablets swallowed whole, or as one 100mg tablet dispersed in water are comparable.
- The compositionally proportional 25mg tablet of ETR is suitable for pediatric use. The decrease of $C_{max}$ by 15% when given as four 25mg tablets is not considered clinically relevant.
- Patients who are looking for an alternative to swallowing tablets can disperse ETR tablets in a glass of water. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed.
- The stability of ETR in liquids other than water has not been determined.

## References

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. INTELENCE™ US package insert.
3. Haubrich R, et al. CROI 2008. Poster 790.
4. Johnson M, et al. CROI 2008. Poster 791.

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