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Pharmacokinetics of etravirine (ETR; TMC125) are not affected by sex, age, race, use of enfuvirtide (ENF) or treatment duration in HIV-1-infected subjects

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Abstract

Background
ETR is a recently US Food and Drug Administration-approved next-generation NNRTI. *In vitro*, ETR has potent activity against both wild-type and NNRTI-resistant HIV. ETR 200mg bid was superior to placebo in the proportion of treatment-experienced HIV-1-infected subjects achieving viral load <50 copies/mL at Week 48 from two identical, ongoing Phase III, double-blind, randomized trials (DUET-1 and DUET-2 [TMC125-C206 and C216]).

Methods
Plasma concentrations of ETR over 12 hours were collected at Weeks 4 and 24 in a substudy of both DUET trials; pharmacokinetic (PK) parameters (area under the plasma concentration-time curve over 12 hours [AUC_{12h}] and minimum and maximum plasma concentration [C_{min} and C_{max}, respectively]) were determined using noncompartmental analysis (WinNonlin Professional 4.1). A two-compartment model with sequential zero-order and first-order absorption including lag-time was developed for population pharmacokinetics analyses (NONMEM V level 1.1); AUC_{12h} and predose plasma concentration (C_{0h}) were individually estimated from sparse sampling collected over 48 weeks using Bayesian feedback in DUET subjects randomized to ETR. The effect of sex, age, race, weight, adherence to ETR by pill count, use of ENF or tenofovir (TDF) and hepatitis B and/or C coinfection on ETR AUC_{12h} or C_{0h} was assessed using analysis of covariance (ANCOVA) model. The effect of treatment duration was assessed graphically in the main study and by comparison of PK parameters in the substudy.

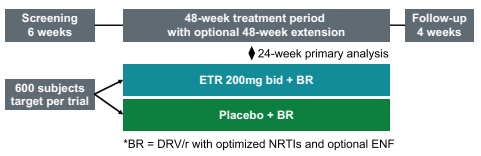
Results
Twenty-five subjects participated in the substudy at Week 4, and 23 subjects remained in the substudy at Week 24. The geometric mean ratio between Week 4 and 24 was 0.98 for AUC_{12h}. DUET-1 and DUET-2 collectively enrolled 1,203 subjects of which 599 were randomized to ETR; population pharmacokinetics were estimated in 575 subjects. Mean (standard deviation [SD]) ETR AUC_{12h} and C_{0h} was 5,506 (4,710) ng•h/mL and 393 (391) ng/mL, respectively. Inter and intrasubject variability was 60% and 40%, respectively. Mean (SD) ETR AUC_{12h} in 57 women was 6,027 (3,591) ng•h/mL compared to 5,449 (4,817) ng•h/mL in 518 men (p=0.20). Mean (SD) ETR in Caucasians (n=360), Blacks (n=67), Hispanics (n=56) and Asians (n=7) was 5,552 (5,264), 5,451 (3,524), 5,183 (2,483) and 10,299 (7,185) ng•h/mL, respectively (p=0.23). ETR exposure (AUC_{12h}) increased with increasing adherence (p=0.0187) or decreasing weight (p=0.0490). Use of ENF had no effect on ETR AUC_{12h} (p=0.80), but as expected, TDF was associated with a 26% decrease in AUC_{12h} (p=0.0005). Hepatitis B and/or C coinfection was associated with a 1.35-fold increase in AUC_{12h} (p=0.0028). There was a trend for higher ETR exposure with higher age (p=0.0645). Visual inspection of plasma concentrations over 24 weeks revealed no treatment duration-dependent effects.

Conclusions
ETR pharmacokinetics do not vary by sex, race, age or use of ENF. TDF decreases ETR exposure, whereas hepatitis B and/or C coinfection was associated with higher ETR exposure. ETR exposures were slightly higher in subjects with lower weight and greater adherence. No dose adjustments for ETR are necessary for these covariates. There was no apparent treatment duration-dependent clearance in ETR pharmacokinetics.

Introduction

- Etravirine (ETR, formerly TMC125) is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1[1]
- PK characteristics[2]
  - ETR must be administered following a meal
    - AUC_{12h} decreased 51% under fasting conditions
  - highly protein bound (99.9%) to both albumin and α_1-acid glycoprotein (orosomucoid)
  - substrate and weak inducer of CYP3A
  - substrate and weak inhibitor of CYP2C9 and 2C19
  - not a substrate, but a weak inhibitor of P-glycoprotein (P-gp)[3]
  - mild-to-moderate hepatic impairment has no effect on PK
  - minimal (<1.2%) renal excretion
  - mean terminal elimination half-life ($t_{1/2}$) of 41 hours

DUET study design and major inclusion criteria[4,5]

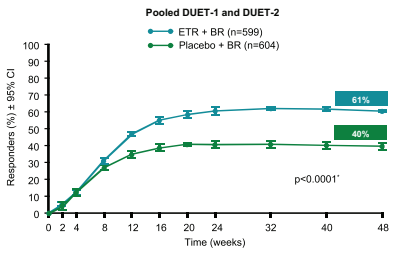


*BR = DRV/r with optimized NRTIs and optional ENF

- DUET-1 and DUET-2 differed only in geographical location; pooled analysis was prespecified
- Major inclusion criteria
  - plasma viral load >5,000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI mutation at screening or in documented historical genotype
  - ≥3 primary PI mutations at screening
- Subjects recruited from Thailand, Australia, Europe and the Americas

BR = background regimen; DRV/r = darunavir with low-dose ritonavir; ENF = enfuvirtide

Subjects with viral load <50 copies/mL at Week 48 (ITT-TLOVR)[4,5]



*Logistic regression model; ITT = intent-to-treat; TLOVR = time-to-loss of virologic response; CI = confidence interval

PK and bioanalysis

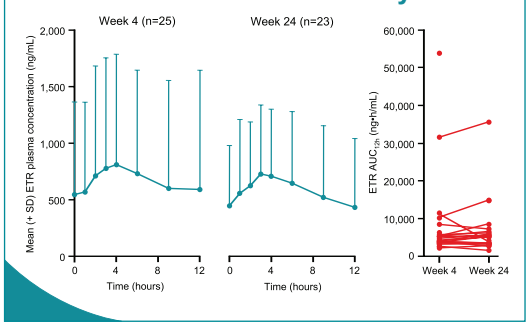
- Main study
  - sparse sampling in all subjects
    - trough and ≥1 hour post-dose at Week 4
    - random sample at Weeks 8, 12, and 24
    - second random sample at Weeks 8 and 24
- Substudy
  - optional participation at Weeks 4 and 24
  - intensive PK sampling over 12 hours
    - predose, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose
- Bioanalysis
  - ETR plasma concentrations were measured using a validated LC-MS/MS assay with a LLOQ 2.00ng/mL

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

Statistical analysis methods

- ETR PK model
  - a two-compartmental model with sequential zero and first-order absorption including lag-time was implemented in NONMEM V level 1.1 (Icon Development Solutions, Ellicott City, MD, USA)
  - Bayesian feedback on individual PK parameters (AUC_{12h} and C_{0h})
- Effect of covariates on log-transformed ETR AUC_{12h} or C_{0h}
  - univariate and multivariate ANCOVA with the following covariates: age, weight, sex, race, viral hepatitis coinfection status, adherence (as measured by pill count), use of ENF and use of TDF

Steady-state pharmacokinetics of ETR: DUET substudy



PK parameters of ETR: DUET substudy

	Week 4		Week 24	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
C_{0h} (ng/mL)	545 (819)	260 (110–3,960)	446 (533)	297 (75–2,710)
C_{12h} (ng/mL)	590 (1,055)	240 (142–4,850)	432 (609)	275 (81–2,980)
C_{max} (ng/mL)	880 (1,030)	525 (285–4,980)	797 (668)	586 (199–3,130)
t_{max} (hours)	–	4 (0–6)	–	4 (1–6)
AUC_{12h} (ng•h/mL)	7,964 (11,180)	4,307 (2,284–53,870)	7,034 (7,238)	5,253 (1,709–35,570)

- GMR (range) for AUC_{12h} (Week 4: Week 24): 0.98 (0.61–2.75)

t_{max} = time to maximum concentration; GMR = geometric mean ratio

Population pharmacokinetics of ETR: DUET main study

- Parameter estimates of the PK model
  - apparent oral clearance (CL/F): 43.7L/h
  - volume of the central compartment: 422L
    - intersubject variability on CL/F: 60%
    - intrasubject variability on fraction absorbed: 40%
- Population PK estimates
  - n=575

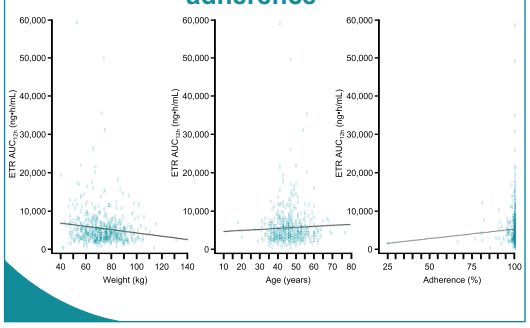
Parameter	Mean (SD)	Median (range)
AUC_{12h} (ng•h/mL)	5,506 (4,710)	4,380 (458–59,084)
C_{0h} (ng/mL)	393 (391)	298 (2–4,852)

Effect of covariates on ETR AUC_{12h}: multivariate ANCOVA

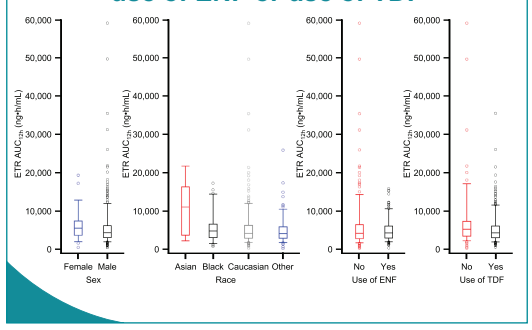
		n	Mean (SD)	p value
Sex	Male	518	5,449 (4,817)	0.1976
	Female	57	6,027 (3,591)	
Age (years)		575	–	0.0645
Race	Caucasian	360	5,552 (5,264)	0.2272
	Black	67	5,451 (3,524)	
	Hispanic	56	5,183 (2,483)	
	Asian	7	10,299 (7,185)	
	Other	20	5,946 (5,475)	
Weight (kg)		575	–	0.0490
Adherence		575	–	0.0187
Use of ENF	Yes	260	5,093 (2,674)	0.8048
	No	315	5,847 (5,865)	
Use of TDF	Yes	436	5,079 (3,471)	0.0005
	No	139	6,846 (7,205)	
HBV or HCV	Positive	69	7,207 (7,588)	0.0028
	Negative	475	5,333 (4,221)	

HBV = hepatitis B virus; HCV = hepatitis C virus

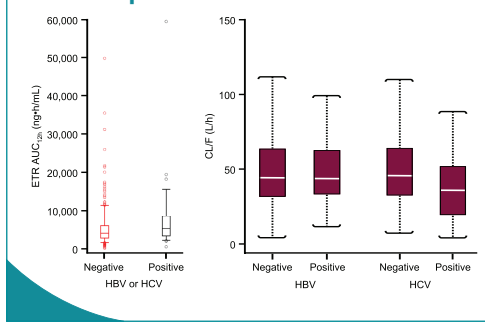
ETR AUC_{12h} by weight, age and adherence



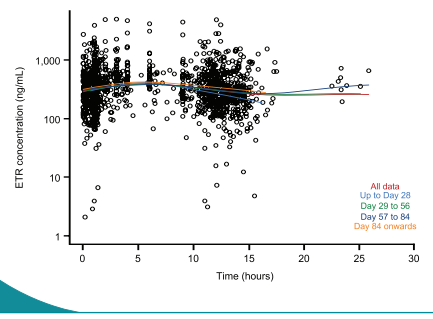
ETR AUC_{12h} by sex, race, use of ENF or use of TDF



ETR AUC_{12h} and CL/F by hepatitis coinfection status



No evidence of PK changes over treatment duration



Discussion and conclusions

- ETR has moderate-to-high inter and intrasubject variability
  - intersubject variability probably due to metabolism via multiple CYP isozymes (i.e. CYP3A, 2C9 and 2C19), adherence, concomitant medications (e.g. TDF) and/or hepatitis coinfection status
  - intrasubject variability probably due to CYP2C19,[6,7] adherence, concomitant medications and/or food effects.
- ETR pharmacokinetics do not vary by sex, age, race, use of ENF or treatment duration.
- TDF decreases ETR AUC_{12h} by ~26%
  - consistent with interaction studies in healthy volunteers
  - mechanism unknown
  - effect of TDF on CYP2C19?
- Hepatitis coinfection increases ETR AUC_{12h} ~1.35-fold
  - change in CL/F was negligible (+8.3%) in subjects with HBV, whereas a 24% decrease in CL/F was observed in subjects with HCV
  - no obvious difference in concomitant medications or baseline demographics
  - mechanism unknown.
- ETR AUC_{12h} was slightly higher with decreasing weight or increasing adherence.
- No relationship between pharmacokinetics and efficacy or safety have been demonstrated in the DUET trials[8]
  - no dose adjustments are needed for TDF, hepatitis coinfection status or weight.

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