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Pharmacokinetics and pharmacodynamics of etravirine in treatment-experienced HIV-1-infected patients: pooled 48-week results of DUET-1 and DUET-2

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Abstract

Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with potent activity against both wild-type and NNRTI-resistant HIV. DUET-1 and DUET-2 are identically designed, ongoing, Phase III, double-blind, randomized trials of ETR versus placebo, both with an investigator-selected background regimen (BR) including ritonavir-boosted darunavir (DRV/r). The relationship between ETR pharmacokinetics and pharmacodynamics over 48 weeks from these trials was investigated.

Methods

Population pharmacokinetics for area under the plasma concentration-time curve (AUC) and predose plasma concentration (C_{0h}) were estimated using Bayesian feedback. Analysis of covariance (ANCOVA) and logistic regression with generalized additive modeling (GAM) were used to analyze pharmacokinetic/pharmacodynamic (PK/PD) relationships with efficacy endpoints and safety.

Results

Of the 1203 patients enrolled, 599 were randomized to ETR, and PK data from 575 were available. Mean (standard deviation [SD]) ETR AUC and C_{0h} were 5506 (4710) ng•h/mL and 393 (391) ng/mL, respectively. In the GAM analysis, ETR AUC or C_{0h} was not significantly associated with reaching viral load <50 copies/mL at Week 48. Other factors, including baseline viral load and CD4 cell count, phenotypic sensitivity score (PSS), adherence, baseline fold-change in EC_{50} (FC) to DRV and ETR, age and use of enfuvirtide (ENF) or tenofovir (TDF), were more important determinants than pharmacokinetics. Antiviral activity of ETR was observed in patients with PSS=0 irrespective of pharmacokinetics. No apparent relationships were seen between ETR pharmacokinetics and laboratory changes or adverse events, including rash.

Conclusions

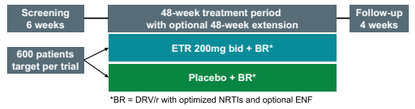
ETR demonstrated superior activity compared with placebo in the DUET trials at Week 48. Achieving viral load <50 copies/mL at Week 48 in these trials was not influenced by ETR pharmacokinetics, but rather by other drug-, disease- and patient-related factors. Furthermore, no relationship between ETR pharmacokinetics and safety was observed.

Introduction

- ETR 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 ~50% under fasting conditions
  - highly protein bound (99.9%) to both albumin and α_1-acid glycoprotein (orosomucoid)
  - substrate and inducer of CYP3A
  - substrate and inhibitor of CYP2C9 and 2C19
  - inhibitor of P-glycoprotein, but not a substrate
  - minimal (<1.2%) renal excretion
  - mean terminal elimination half-life of 41 hours

AUC_{12h} = AUC from time of administration to 12 hours after dosing

DUET study design and major inclusion criteria[3]

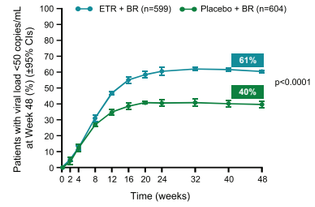


*BR = DRV/r with optimized NRTIs and optional ENF

- DUET-1 and DUET-2 differ only in geographic location; pooled analysis was prespecified at Weeks 24 (primary analysis), 48 and 96 (final analysis)
- Major inclusion criteria
  - plasma viral load >5000 copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI mutation at screening or in documented historic genotype
  - ≥3 primary PI mutations at screening
- Patients recruited from Thailand, Australia, Europe and the Americas

PI = protease inhibitor

Response (viral load <50 copies/mL) at Week 48 (ITT-TLOVR)



- 92% of subjects randomized to ETR who were undetectable (viral load <50 copies/mL) at Week 24 remained undetectable at Week 48

ITT = intent-to-treat; TLOVR = time-to-loss of virologic response
CI = confidence interval; p value ETR versus placebo from logistic regression model

Population PK methods

- Sparse sampling
  - trough and ≥1 hour post dose at Week 4
  - random sample at Weeks 8, 12, 24 and 48
  - second random sample at Weeks 8 and 24
- Bioanalysis
  - ETR plasma concentrations were measured using a validated LC-MS/MS assay with a LLOQ of 2ng/mL
- ETR PK model
  - two-compartmental model with sequential zero-order and first-order absorption including lag-time 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})

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

PK/efficacy analysis: GAM

- Prognostic factors
  - study (DUET-1 or DUET-2)
  - study arm (placebo or ETR)
  - age
  - weight
  - sex (male or female)
  - race (Caucasian, Black, Hispanic, Asian or Other/Not allowed to ask)
  - hepatitis B and/or C co-infection status (positive or negative)
  - baseline viral load
  - baseline CD4 cell count
  - baseline PSS
  - number of NRTIs with phenotypic sensitivity
  - use of TDF (none, use and phenotypic sensitivity, use and no phenotypic sensitivity)
  - use of ENF (none, de-novo use or re-use)
  - ETR AUC_{12h}
  - ETR C_{0h}
  - DRV AUC_{12h}
  - DRV C_{0h}
  - phenotypic FC to ETR (set to 5000 for placebo)
  - phenotypic FC to DRV
  - adherence based on 48-week pill count

→ Linear, spline or loess smoother ← Viral load <50 copies/mL

→ Automated stepwise GAM search (S-Plus 6.1, Insightful Corporation, Seattle, WA, USA)

→ Akaike's information criterion (AIC)
- AIC used to select final model
- low AIC = best model

PK/efficacy analysis: GAM (cont'd)

- Dataset bootstrapped 1000 times
- Probability of response (viral load <50 copies/mL) was predicted 1000 times for each subject in the original database using the bootstrapped dataset
  - response rate was predicted for each study arm with and without the addition of residual error to each of the individual predictions
  - residual error was added by sampling a random value between zero and one for each subject, assuming a uniform distribution, and comparing this sampled value with the predicted probability of response in that subject
  - if the sampled value was below the predicted probability, the response was considered to have occurred; otherwise the response was considered not to have occurred

PK/safety analysis

- Presence or absence of adverse event by DRV or ETR AUC_{12h}
  - rash, skin events of interest, nervous system, psychiatric or gastrointestinal disorders, or the individual events of headache, dizziness, tachycardia, palpitations or blurred vision
- Maximum change from baseline in laboratory parameter by DRV or ETR AUC_{12h}
  - pancreatic amylase, lipase, ALT, AST, AP, direct, indirect, total bilirubin, cholesterol, LDL-C, HDL-C, triglycerides and PT or PTT

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol
PT = plasma prothrombin time; PTT = partial thromboplastin time

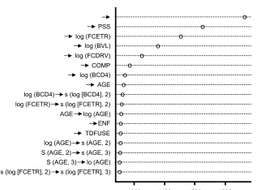
ETR population PK and covariate analysis

- Parameter estimates of the PK model
  - apparent oral clearance (CL/F): 43.7L/hour
  - volume of the central compartment: 422L
    - intersubject variability on CL/F: 60%
    - intrasubject variability on fraction absorbed: 40%
- Population PK estimates at Week 48 (n=575)

Parameter	Mean (SD)	Median (range)
AUC_{12h}, ng•h/mL	5506 (4710)	4380 (458–59,084)
C_{0h}, ng/mL	393 (391)	298 (2–4852)

  - use of TDF was associated with a ~26% decrease in AUC_{12h}
  - hepatitis co-infection increased AUC_{12h} ~1.35-fold
  - no relevant effect of sex, age, race, use of ENF or treatment duration on AUC_{12h}[4]

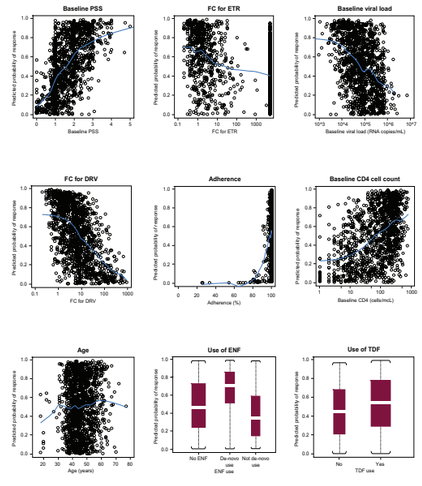
Selection of final GAM



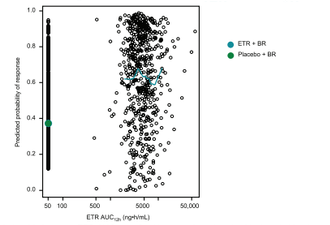
- Effect of prognostic factors on virologic response (viral load <50 copies/mL)
  - VL50 ~ log (BVL) + PSS + COMP + s (log [BCD4], 2) + lo (AGE) + log (FCDRV) + s (log [FCETR], 3) + ENF + TDFUSE

FCETR = FC in ETR; BVL = baseline viral load; FCDRV = FC in DRV
BCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load

Viral load <50 copies/mL at Week 48 by prognostic factors in the final model



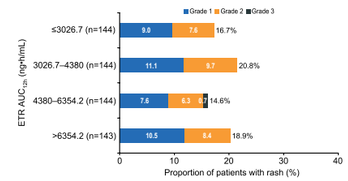
Viral load <50 copies/mL at Week 48 by ETR AUC_{12h} or C_{0h}



- No apparent relationship between ETR AUC_{12h} or C_{0h} (data not shown) and achieving viral load <50 copies/mL over the range of observed exposures

Pharmacokinetics and safety

- Safety and tolerability of ETR was similar to placebo except for rash over 48 weeks[5]
  - rash (any type) was more commonly reported with ETR (19%) than with placebo (11%)
  - no apparent association between rash and baseline CD4 cell count, previous history of NNRTI-related rash or ETR AUC_{12h}



Numbers have been rounded to one decimal place

Pharmacokinetics and safety (cont'd)

- no apparent relationship between ETR AUC_{12h} and any of the other adverse events
- no apparent relationship between ETR AUC_{12h} and maximum change from baseline in any of the laboratory parameters, including hepatic and lipid parameters

Conclusions

- ETR 200mg bid demonstrated superior activity than placebo in this treatment-experienced patient population
- Moderate-to-high inter and intrapatient variability in ETR pharmacokinetics
  - ETR pharmacokinetics do not vary by sex, age or race
  - changes in ETR pharmacokinetics due to TDF or hepatitis co-infection are not clinically relevant
- ETR AUC_{12h} or C_{0h} was not associated with viral load <50 copies/mL at Week 48
  - prognostic factors retained in the final model (baseline CD4 cell count, baseline viral load, use of active agents,[6] adherence, age and FC to DRV and ETR) are more important determinants than pharmacokinetics
- No apparent relationships were seen between pharmacokinetics and adverse events or laboratory changes
  - rash does not appear to be related to ETR AUC_{12h}

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