O413

# Pharmacokinetics of Once-Daily Etravirine (ETR) Without and With Once-Daily Darunavir/Ritonavir (DRV/r) in Antiretroviral-Naïve HIV-1 Infected Adults

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## Introduction

- With a terminal half-life of 30–40 hours, and formulation improvements leading to a reduced pill burden, etravirine (INTELENCE™; ETR) is a candidate for once daily (qd) dosing
- In previous studies in healthy volunteers
  - ETR AUC was similar, $C_{max}$ was 44% higher and $C_{min}$ was 25% lower for qd versus twice daily (bid) dosing **(Figure 1)**[1]
  - Co-administration of darunavir (PREZISTA™; DRV) with low-dose ritonavir (RTV; /r) 600/100mg bid decreased AUC of ETR 100mg bid by 37%[2]
- Once-daily DRV/r has been shown to be effective and well-tolerated in antiretroviral (ARV)-naïve patients[3]
- This multicenter, open-label phase IIa trial (TMC125-HIV2032) evaluated pharmacokinetic (PK) and short-term safety and efficacy of ETR 400mg qd plus tenofovir/emtricitabine (TDF/FTC) 300/200mg qd without and then with DRV/r 800/100mg qd in ARV-naïve, HIV-1-infected patients

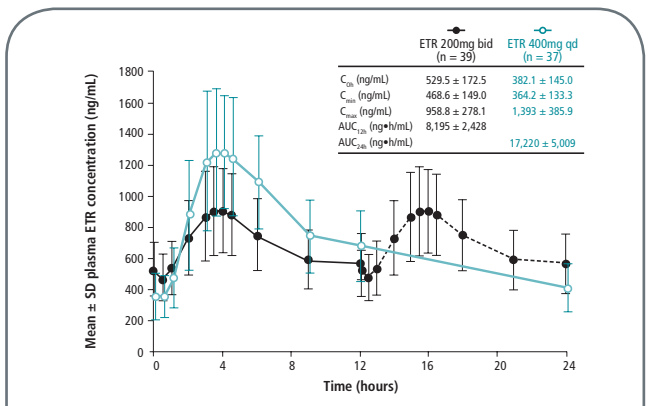



**Figure 1. Comparison of ETR PK qd vs bid in healthy volunteers**

## Methods

- In this phase IIa open label, single arm study, 23 patients enrolled and 20 completed through Day 42
- Key eligibility criteria
  - ARV-naïve adults with HIV-1
  - No evidence of resistance to study drug based on screening or historical resistance assays (presence of <3 ETR resistance-associated mutations [list of 13 RAMs] defined susceptibility to ETR)
  - HBV/HCV co-infection not allowed
- Intensive PK sampling was performed over 24 hours on Day 14 for ETR, and Day 28 for ETR, DRV and RTV **(Figure 2)**
- All doses were administered following a meal
- PK parameters were determined using a noncompartmental model with extravascular input and evaluated by least squares mean (LSM) ratios with 90% confidence interval (CI)
- Patients were offered a 42-week open-label extension with DRV/r 800/100mg qd plus TDF/FTC 300/200mg qd

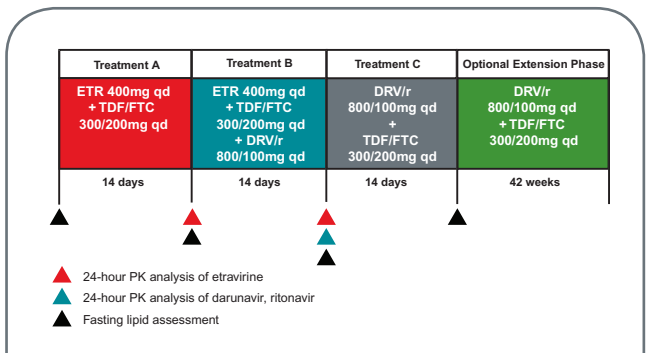



**Figure 2. QD PK study design**

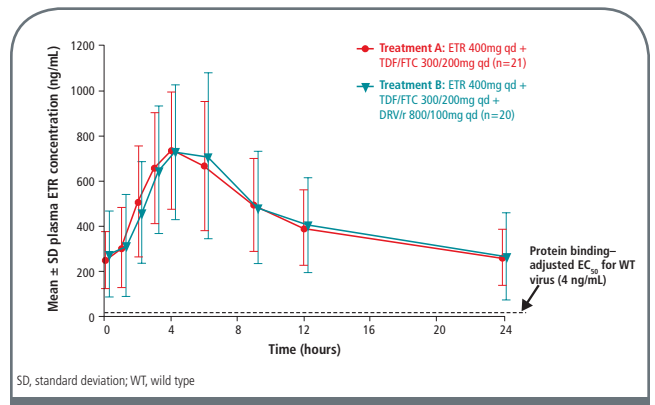
## Results

- Twenty-three patients enrolled **(Table 1)** and 20 completed Day 42 of the study

### Table 1. Patient baseline demographics and disease characteristics

| Parameter | N = 23 |
|---|---|
| Baseline demographics | |
| Age, mean (SD), years | 35.7 (13.6) |
| Male, n (%) | 20 (87) |
| Race/ethnicity, n (%) | |
| Black | 9 (39) |
| Caucasian | 9 (39) |
| Hispanic | 5 (22) |
| Disease characteristics | |
| Baseline viral load, mean (SD), $log_{10}$ copies/mL | 4.2 (0.75) |
| Baseline CD4 count, median (range), cells/mm$^3$ | 403 (144–895) |
| ETR fold change[a] ≤1.6, n (%) | 22 (95.7)[b] |
| DRV fold change[a] ≤10, n (%) | 23 (100) |

[a]Predicted fold change in $EC_{50}$ according to VircoTYPE; fold change values were not available for ETR at time of screening
[b]1 subject had ETR fold change of 2.5




SD, standard deviation; WT, wild type

**Figure 3. Plasma concentration-time profile of ETR 400mg qd**

- There was no change in ETR PK following co-administration of DRV/r 800/100mg qd **(Figure 3 and Table 2)**

### Table 2. PK parameters of ETR 400mg qd

| Parameter *Mean (SD); $t_{max}$, median (range)* | Treatment A (Reference) Day 14 ETR + TDF/FTC (n=21) | Treatment B (Test) Day 28 ETR + TDF/FTC + DRV/r (n=20) | LSM ratio[a] (90% CI) |
|---|---|---|---|
| $C_{0h}$, ng/mL | 249.7 (129.0) | 276.3 (191.2) | — |
| $C_{min}$, ng/mL | 232.9 (129.6) | 236.4 (168.0) | 0.96 (0.83–1.10) |
| $C_{max}$, ng/mL | 790.1 (286.9) | 800.7 (327.4) | 1.03 (0.93–1.13) |
| $t_{max}$, h | 4.00 (1.97–6.05) | 4.03 (2.97–9.02) | — |
| $AUC_{24h}$, ng•h/mL | 10,410 (4,186) | 10,720 (5,459) | 0.99 (0.89–1.10) |

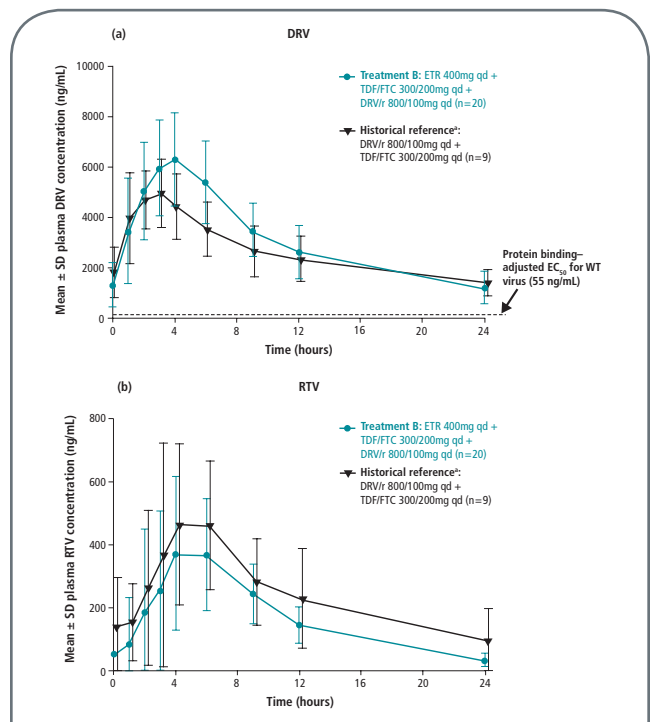
[a]Test/reference; SD, standard deviation; LSM, least squared means; CI, confidence interval

- In general, ETR $C_{max}$ was higher, $C_{min}$ was lower, and AUC was similar when comparing qd dosing in the current study to bid dosing in treatment-experienced patients (reference: DUET PK sub-study; n=24)[4] **(Table 3)**
  - Evaluations were at Week 4 in DUET versus Day 14 for current study
  - In DUET-1 and DUET-2, all patients were treatment-experienced and received DRV/r 600/100mg bid

### Table 3. ETR PK in HIV-infected patients: qd and bid

| Parameter *Median (range)* | QD PK Study (Current Study) ETR 400mg qd Day 14 (n=21) | HISTORICAL REFERENCE[1] (DUET PK Sub-study) ETR 200mg bid Week 4 (n=25) |
|---|---|---|
| $C_{0h}$, ng/mL | 224 (58–503) | 260 (110–3,960) |
| $C_{min}$, ng/mL | 197 (58–480) | 195 (109–3,900) |
| $C_{max}$, ng/mL | 765 (254–1,410) | 525 (285–4,980) |
| $t_{max}$, h | 4 (2–6) | 4 (0–6) |
| $AUC_{12h}$, ng•h/mL | — | 4,307 (2,284–53,870) |
| $AUC_{24h}$, ng•h/mL | 9,778 (3,364–18,650) | — |

- DRV PK was slightly higher and RTV PK was lower when compared to historical controls (ARTEMIS week 4 PK substudy) **(Figure 4a and 4b, and Table 4)**




[a]ARTEMIS PK substudy (Week 4); SD, standard deviation; WT, wild-type

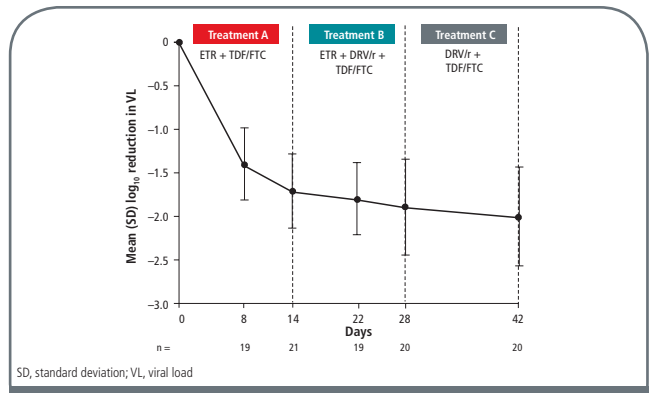
**Figure 4. Plasma concentration-time profile of (a) DRV (DRV/r 800/100mg qd) and (b) RTV (100mg qd) compared to historical controls[5,6]**

### Table 4. Pharmacokinetic parameters of DRV and RTV on Day 28

| Parameter *Mean (SD); $t_{max}$, median (range)* | DRV (n=20) | RTV (n=20) |
|---|---|---|
| $C_{0h}$, ng/mL | 1,335 (867) | 53 (70) |
| $C_{min}$, ng/mL | 1,049 (616) | 27 (21) |
| $C_{max}$, ng/mL | 7,008 (1,514) | 465 (231) |
| $t_{max}$, h | 4 (2–6) | 6 (2–9) |
| $AUC_{24h}$, ng•h/mL | 76,130 (22,080)[a] | 4,128 (1,854)[a] |

[a]n=19

- The mean viral load (VL) decline was 1.7 $log_{10}$ copies/mL at Day 14, 1.8 $log_{10}$ at Day 28 and 2.0 $log_{10}$ copies/mL at Day 42 **(Figure 5)**




SD, standard deviation; VL, viral load

**Figure 5. Short-term virologic response**

- The median increase in CD4 cell count was 56 cells/mm$^3$ at Day 42 (n=19)
- Most common treatment-emergent AEs were nausea, headache, rash, and flatulence **(Table 5)**
- Of the 3 cases of rash, none were considered serious or were grade 3 or 4
- No serious or grade 3 or 4 AEs were reported
- No AEs led to discontinuation
- There were no grade 3 or 4 AST, ALT or lipid elevations
- One case of grade 3 neutropenia was reported during Treatment A

### Table 5. Adverse events

| Parameter, n (%) | N = 23 |
|---|---|
| Serious adverse events | 0 |
| Grade 3/4 clinical adverse events | 0 |
| Adverse events leading to discontinuation | 0 |
| Adverse events at least possibly related to study drug, ≥ 5%[a] | |
| Related to ETR | |
| Nausea | 4 (17.4) |
| Headache | 3 (13.0) |
| Flatulence | 2 (8.7) |
| Rash | 2 (8.7) |
| Related to DRV | |
| Nausea | 3 (13.0) |
| Rash | 2 (8.7) |

[a]Any grade; individual adverse events could be assigned dual causality by investigator

- The impact on metabolic parameters was small when ETR was given with or without DRV/r **(Table 6)**

### Table 6. Change in metabolic parameters and laboratory abnormalities

| Parameter, Median (range) | Baseline (n=23) | Median (range) change from BL: Day 14 (A) (n=21)[a] ETR + TDF/ FTC | Day 28 (B) (n=21)[b] ETR + TDF/FTC + DRV/r | Day 42 (C) (n=20)[c] DRV/r + TDF/FTC |
|---|---|---|---|---|
| Triglycerides, | | | | |
| mmol/L | 0.79 (0.40, 2.81) | 0.01 (–1.40, 1.16) | 0.27 (–0.90, 1.17) | 0.37 (–0.99, 1.87) |
| mg/dL | 70 (35, 249) | 1 (–124, 103) | 24 (–80, 104) | 33 (–88, 166) |
| Total cholesterol, | | | | |
| mmol/L | 3.75 (2.84, 5.74) | –0.08 (–1.16, 1.14) | 0.03 (–1.32, 1.22) | 0.28 (–1.66, 1.50) |
| mg/dL | 145 (110, 222) | –3 (–45, 44) | 1 (–51, 47) | 11 (–64, 58) |
| Direct LDL cholesterol, | | | | |
| mmol/L | 2.38 (1.53, 3.59) | –0.21 (–1.11, 0.75) | –0.16 (–0.93, 0.83) | 0.04 (–1.01, 1.27) |
| mg/dL | 92 (59, 139) | –8.0 (–43, 29) | –6.0 (–36, 32) | 1.5 (–39, 49) |
| HDL cholesterol, | | | | |
| mmol/L | 1.06 (0.78, 1.55) | 0 (–0.31, 0.44) | –0.05 (–0.67, 0.36) | –0.03 (–0.78, 0.21) |
| mg/dL | 41 (30, 60) | 0 (–12, 17) | –2 (–26, 14) | –1 (–30, 8) |
| TC/HDL ratio | 3.67 (2.20, 4.95) | –0.05 (–1.00, 0.72) | 0.10 (–0.58, 4.82) | 0.36 (–0.38, 7.65) |
| Glucose, | | | | |
| mmol/L | 5.05 (4.16, 5.94) | –0.11 (–2.00, 2.33) | –0.11 (–1.72, 0.67) | –0.08 (–1.22, 2.39) |
| mg/dL | 91 (75, 107) | –2 (–36, 42) | –2 (–31, 12) | –2 (–22, 43) |
| Insulin/U/mL | 5 (1.9, 23.0) | –0.8 (–13.3, 11.3) | 0 (–16.0, 20.0) | 0 (–10.0, 32.2) |

LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol.
[a]n=20 for trilycerides; [b]n=20 for HDL cholesterol, direct LDL cholesterol, total cholesterol, total cholesterol/HDL and n=19 for triglycerides; [c]n=19 for insulin

## Conclusions

- Addition of once-daily DRV/r to once-daily ETR did not have a clinically significant impact on ETR pharmacokinetics
- In general, $C_{max}$ was higher, $C_{min}$ was lower and AUC was similar for once-daily ETR in treatment-naïve patients relative to twice-daily ETR in treatment-experienced patients (historical reference)
  - Mean $C_{min}$ for ETR dosed once-daily was >50-fold higher than the protein binding-adjusted $EC_{50}$ for wild-type HIV, with and without co-administration of DRV/r qd
  - No relationship between PK and efficacy or safety was observed in the DUET studies
- Once daily ETR was associated with good short term safety and minimal impact on metabolic parameters
- PK data combined with short-term safety and efficacy support further clinical investigation of ETR 400 mg qd in HIV-1 infected patients

## References

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