


Pharmacokinetics and Short-term Safety and Efficacy of Once-daily Etravirine Without and With Once-daily Darunavir/ritonavir in Antiretroviral-naïve HIV-1 Infected Adults

**Jacob Lalezari¹, Edwin DeJesus², Olayemi
Osiyemi³, Peter Ruane⁴, Robert Ryan⁵, Bryan
Polsonetti⁶, Thomas N Kakuda⁵, James Witek⁶**

*¹Quest Clinical Research, San Francisco, CA; ²Orlando Immunology Center, Orlando, FL; ³Triple O
Medical Services Inc., West Palm Beach, FL; ⁴Medical Practice of Peter Ruane, Los Angeles, CA;
⁵Tibotec, Inc, Yardley, PA; ⁶Tibotec Therapeutics, Bridgewater, NJ*

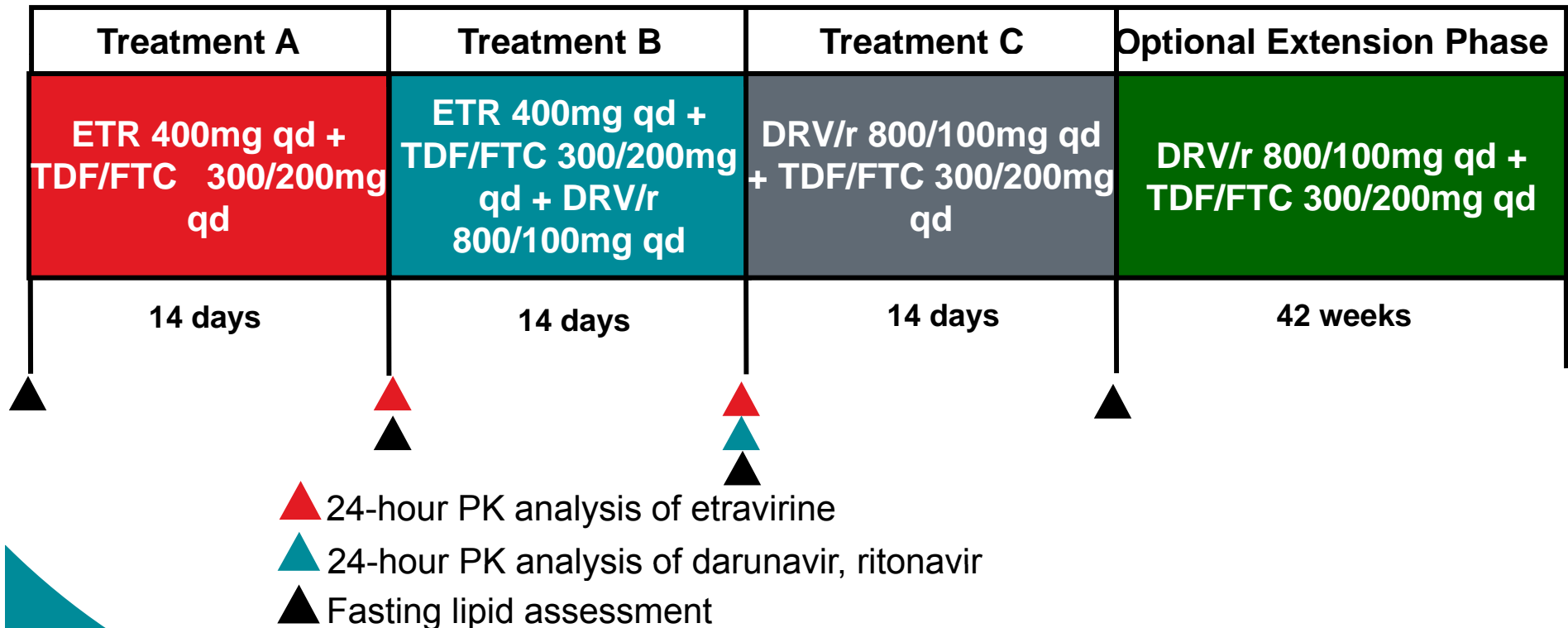


Introduction

- With a terminal half-life of 30-40 hours, and formulation improvements leading to a reduced pill burden, 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) dosing¹
 - Co-administration of DRV/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 ARV-naïve patients³
- This multicenter, open-label Phase IIa trial (TMC125-HIV2032) evaluated PK and short-term safety and efficacy of ETR qd plus TDF/FTC qd without and then with DRV/r qd in ARV-naïve, HIV-1 infected patients

QD PK Study Design

- Phase IIa, open label, single arm study (23 subjects enrolled)
- Key eligibility criteria
 - ARV-naïve adults with HIV-1 infection
 - No evidence of resistance to study drugs^a
 - HBV/HCV co-infection not allowed



^aBased on screening or historical resistance assays; presence of <3 ETR resistance-associated mutations (list of 13 RAMs) defined susceptibility to ETR

Demographics and Baseline Characteristics

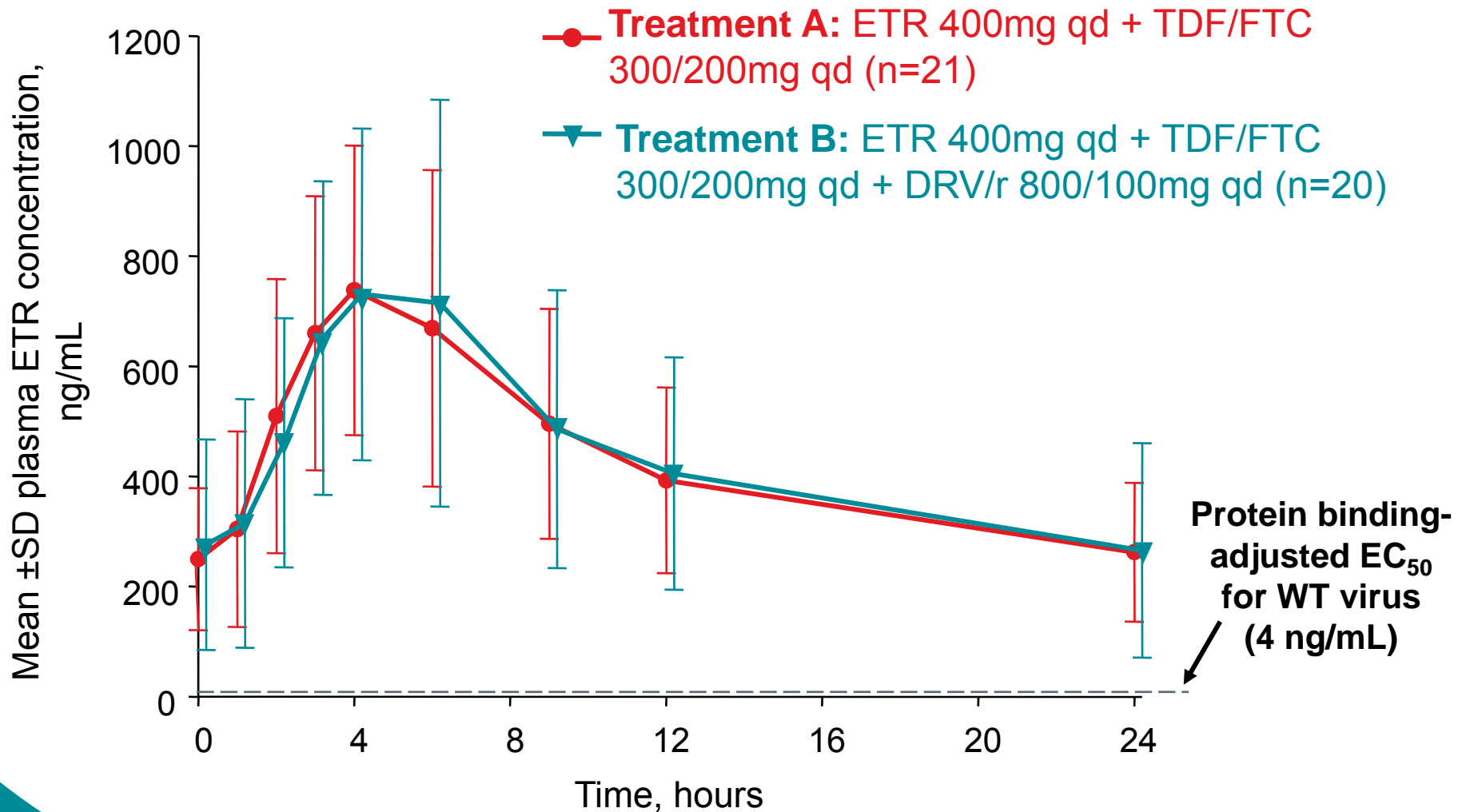
Parameter	N=23
Demographics	
Age, mean (SD), y	35.7 (13.6)
Male, n (%)	20 (87)
Race/ethnicity, n (%)	
Black	9 (39)
Caucasian	9 (39)
Hispanic	5 (22)
Disease characteristics	
Viral load, mean (SD), log ₁₀ copies/mL	4.2 (0.75)
CD4 count, median (range), cells/mm ³	403 (144-895)
ETR fold change ^a ≤1.6, n (%)	22 (95.7) ^b
DRV fold change ^a ≤10, n (%)	23 (100)

- 23 patients enrolled; 20 completed through Day 42

^a Predicted fold change in EC₅₀ according to VircoTYPE; fold change values were not available for ETR at time of screening

^b 1 patient had ETR fold change of 2.5

Plasma Concentration-time Profile of ETR 400 mg qd



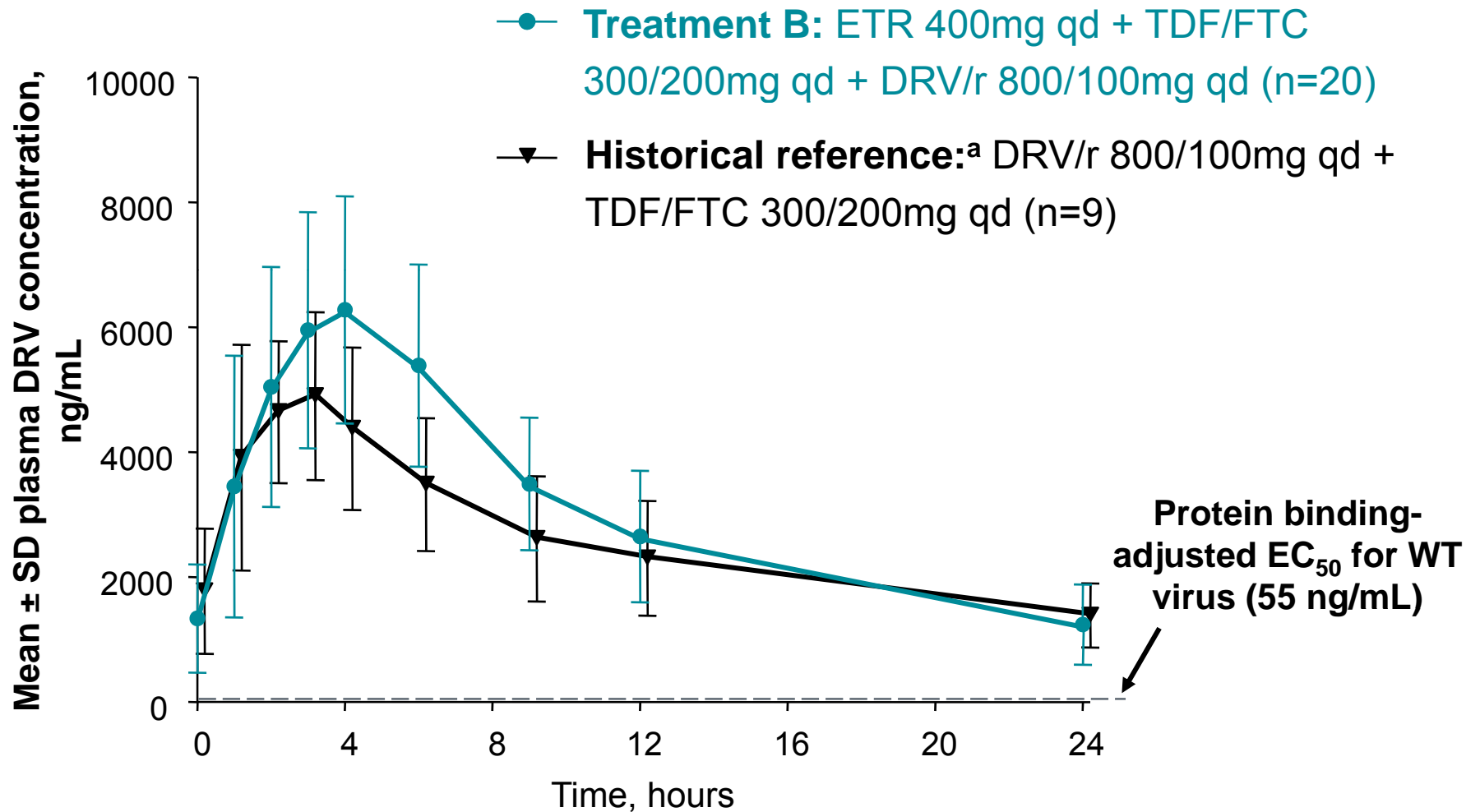
ETR PK in HIV-infected Patients: 400mg qd and 200mg bid

- Historical reference: PK sub-study from DUET-1 and DUET-2
 - Treatment-experienced patients also receiving DRV/r 600/100mg bid
- Evaluations at Day 14 in current study vs. Week 4 in DUET

Parameter <i>Median (range)</i>	QD PK Study (Current Study)	HISTORICAL REFERENCE ¹ (DUET PK Sub-study)
	ETR 400mg qd (n=21)	ETR 200mg bid (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)	--

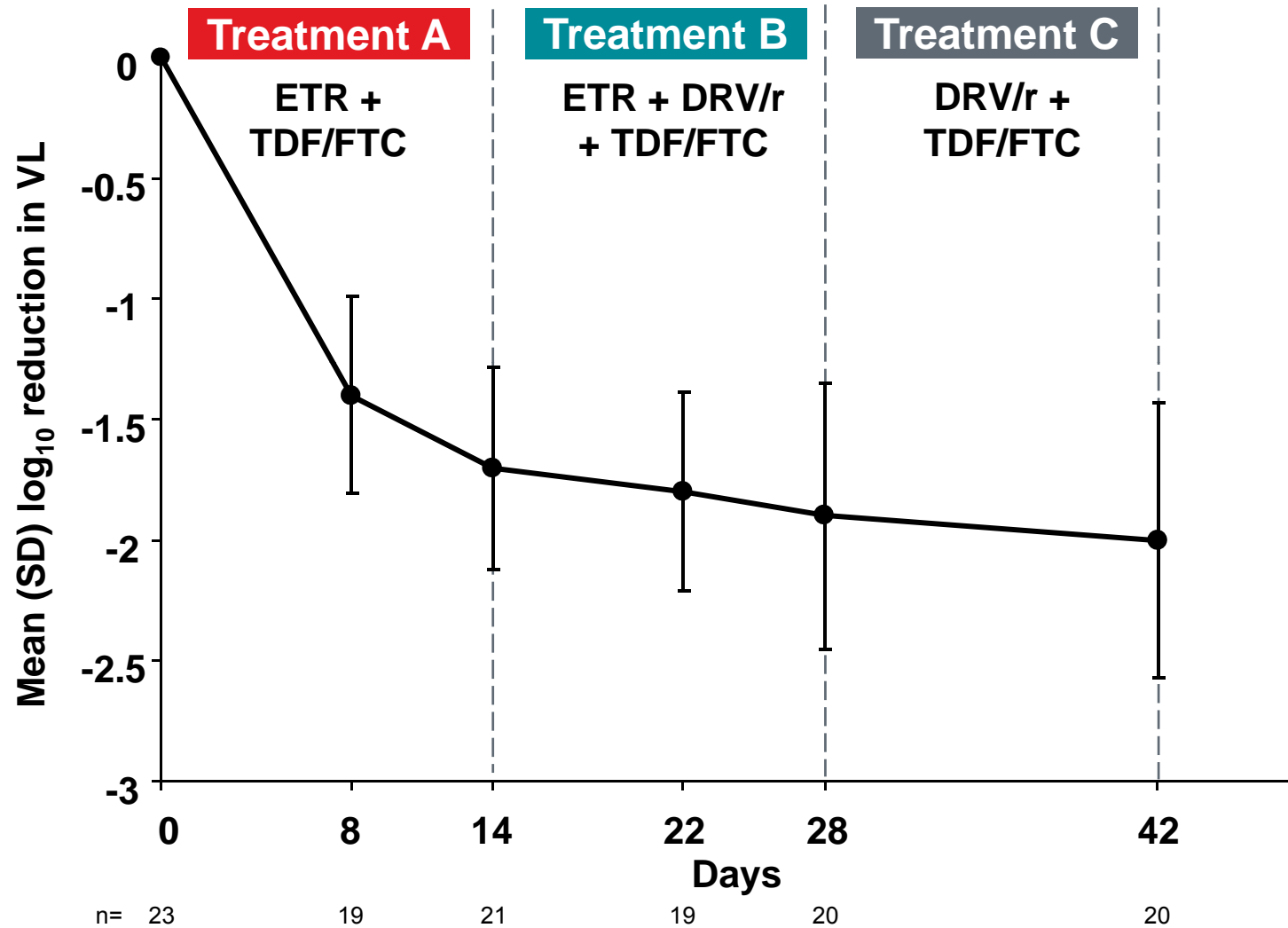
1. Kakuda, TN, *et al.* 9th International Workshop on Clin Pharm of HIV 2008; Poster P34.

Plasma Concentration-time Profile of DRV (DRV/r 800/100mg qd)



^aARTEMIS PK sub-study (Week 4); DeJesus, E, et al. Oral presentation at 47th ICAAC 2007; Abstract H-718b.

Short-term Clinical Response



- Median increase in CD4 cell count was 56 cells/mm³ at Day 42 (n=19)

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, $\geq 5\%$ ^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)

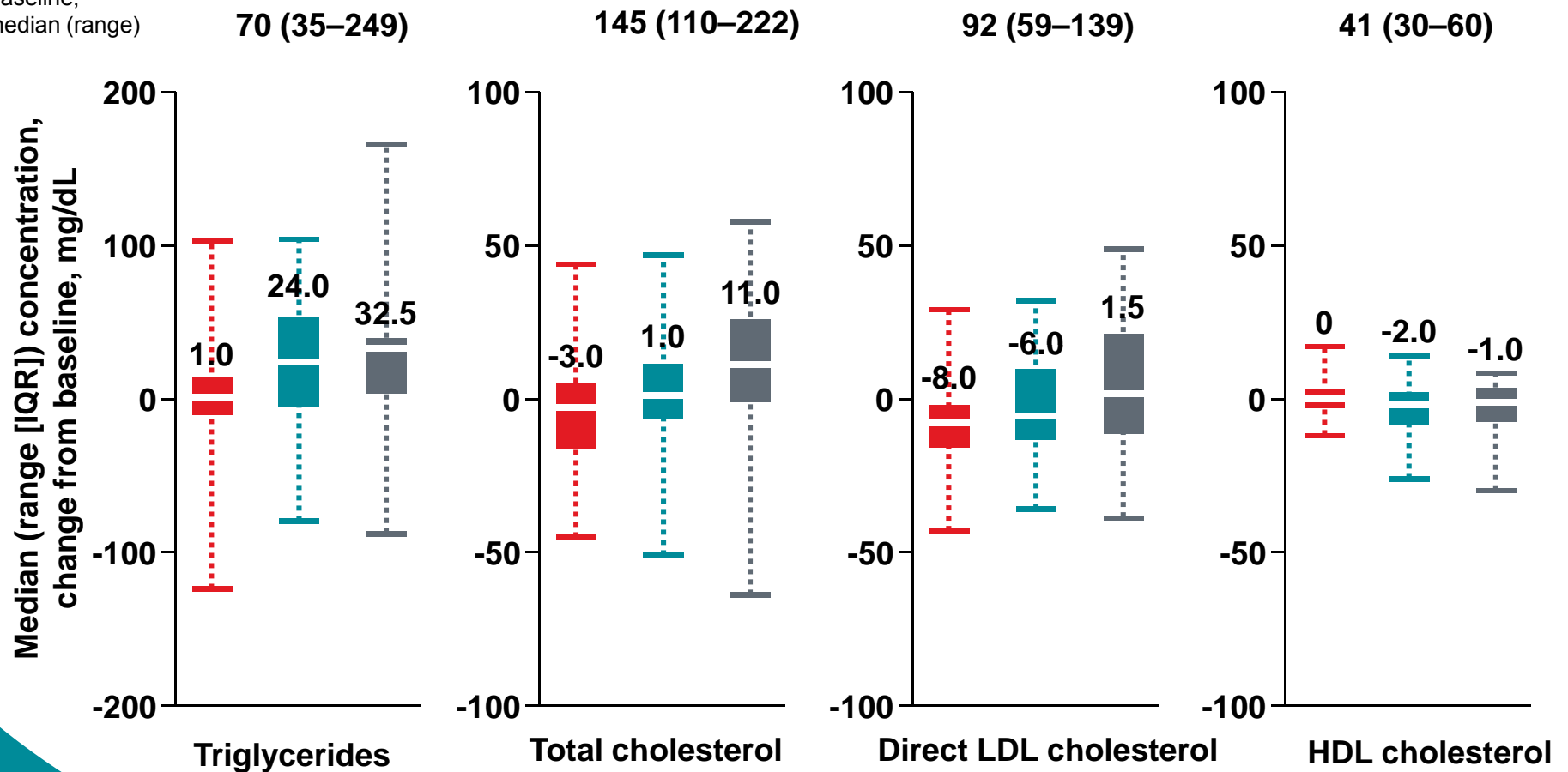
- No Grade 3/4 AST, ALT or lipid elevations
- One Grade 3 neutropenia during Treatment A

^aAny grade; Individual adverse events could be assigned dual causality by investigator

Changes in Lipid Parameters from Baseline

- Treatment A: ETR + TDF/FTC (Day 14)
- Treatment B: ETR + DRV/r + TDF/FTC (Day 28)
- Treatment C: DRV/r + TDF/FTC (Day 42)

Baseline,
median (range)



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 (DUET)
 - Mean C_{\min} for ETR dosed once-daily was 58- to 59-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 400mg qd in HIV-1-infected patients

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