790

DUET-1: Week 48 results of a Phase III randomized double-blind trial to evaluate the efficacy and safety of etravirine (ETR; TMC125) versus placebo in 612 treatment-experienced HIV-1-infected patients

Richard Haubrich,[1] Pedro Cahn,[2] Beatriz Grinsztejn,[3] Jacob Lalezari,[4] José Valdez Madruga,[5] Anthony Mills,[6] Monika Peeters,[7] Johan Vingerhoets,[7] Kathy Iveson,[8] Goedele De Smedt,[7] on behalf of the DUET-1 study group

[1]University of California San Diego, San Diego, CA, USA; [2]Hospital Juan A. Fernández and Fundación Huesped, Buenos Aires, Argentina; [3]Instituto de Pesquisa Clinica Evandro Chagas, Fiocruz, Brazil; [4]Quest Clinical Research, San Francisco, CA, USA; [5]Centro de Referência e Treinamento DST/AIDS, São Paulo, Brazil; [6]Private Practice, Los Angeles, CA, USA; [7]Tibotec BVBA, Mechelen, Belgium; [8]Tibotec Inc, Yardley, PA, USA

Richard Haubrich, MD
Division of Infectious Diseases
University of California, San Diego
150 West Washington Street
Suite 100
San Diego, CA 92103
USA
Phone: +001 (619) 543 8080
rhaubrich@ucsd.edu

Abstract

Background

New, potent and tolerable antiretrovirals (ARVs) are needed, particularly for treatment-experienced, resistant HIV-1 patients.

Methods

DUET-1 is an ongoing 96-week randomized double-blind Phase III trial evaluating the efficacy and safety of ETR 200mg vs placebo, both given bid. All patients received a background regimen (BR) of darunavir with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) and optional enfuvirtide (ENF). Patients had documented NNRTI resistance and ≥3 primary PI mutations. The primary efficacy endpoint for this Week 48 analysis was the percentage of patients with a confirmed viral load (VL) of <50 copies/mL. Safety was also assessed throughout the study.

Results

A total of 612 patients were included in the intent-to-treat (ITT) population (62% of patients were CDC Category C, the median number of NNRTI mutations was two, 25% of patients used ENF *de novo* [i.e. naïve]) with a median baseline VL of 4.9 $\log_{10}$ copies/mL and a CD4 cell count of 106 cells/mm^3.

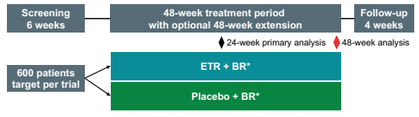
	Week 24			Week 48		
	ETR + BR	Placebo + BR	Diff (95% CI)	ETR + BR	Placebo + BR	Diff (95% CI)
VL <50 copies/mL, %	58	40	19 (11; 26) p=0.0001*	60	39	21 (13; 29) p<0.0001*
VL <400 copies/mL, %	74	51	23 (16; 31) p<0.0001*	71	47	24 (17; 32) p<0.0001*
Mean (SE) change in CD4 cell count, cells/mm^3	89 (5.4)	65 (5.2)	32[‡] (48; 15) p=0.0002**	103 (7.0)	74 (6.3)	32[‡] (52; 11) p=0.0025**

SE = standard error; CI = confidence interval
*Logistic regression model; **ANCOVA model; [‡]LS means difference

Of patients with a VL of <50 copies/mL at Week 24, 94% maintained a VL of <50 copies/mL at Week 48 with ETR + BR versus 89% with placebo + BR. In addition, at Week 48 the mean CD4 cell count was significantly increased in the ETR versus the placebo group.

As at Week 24, safety assessments at Week 48 showed that the incidences of any adverse event (AE) (96% ETR vs 97% placebo), serious AEs (19% vs 25%) and grade 3/4 AEs (29% vs 36%) with ETR were similar to placebo. Most AEs with ETR were mild-to-moderate in severity and infrequently led to discontinuation (7% vs 7%). Rash (any type) (22% vs 11%), diarrhea (14% vs 24%) and nausea (15% vs 15%) were the most common AEs. Nervous system (18% vs 21%) and psychiatric disorders (14% vs 18%) with ETR were comparable to placebo.

DUET study design and major inclusion criteria

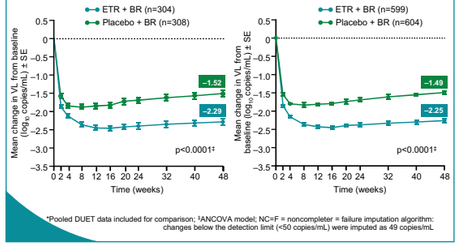


*BR = DRV/r with optimized NRTIs and optional ENF

- Plasma VL >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historic genotype
- ≥3 primary PI mutations at screening
- In DUET-1, patients were recruited from Thailand, Australia, Europe and the Americas
- DUET-1 and DUET-2 differed only in geographic location; pooled analysis was prespecified

RAM = resistance-associated mutation

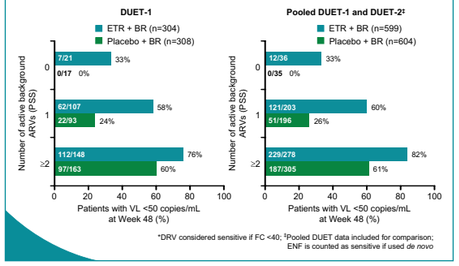
VL reduction from baseline at Week 48 (ITT NC=F)



*Pooled DUET data included for comparison; ‡ANCOVA model; NC=F = noncompleter = failure imputation algorithm: changes below the detection limit (<50 copies/mL) were imputed as 49 copies/mL

Response (<50 copies/mL) by PSS (DRV FC <40)* at Week 48

(Analysis excludes patients who discontinued except for virologic failure)



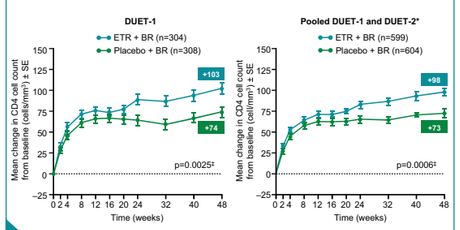
*DRV considered sensitive if FC <40; ‡Pooled DUET data included for comparison; ENF is counted as sensitive if used *de novo*

Baseline characteristics and background ARVs

Parameter		DUET-1 ETR + BR (n=304)	DUET-1 Placebo + BR (n=308)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
Patient demographics	Male (%)	87	86	90	89
	Caucasian (%)	65	65	70	70
Disease characteristics	VL ($\log_{10}$ copies/mL)	4.8 (2.7–6.2)	4.9 (2.4–6.5)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	CD4 cells (cells/mL)	99 (1–789)	109 (1–694)	99 (1–789)	109 (0–912)
	CDC category C (%)	61	64	58	59
Prior ARV use	10–15 ARVs (%)	65	67	66	65
	DRV/r (%)	5	5	4	5
Detectable mutations	≥2 ETR RAMs (%)	35	30	31	28
	≥2 NNRTI RAMs[†] (%)	70	70	69	69
	≤3 primary PI RAMs (%)	40	41	38	37
BR	NNRTIs in screening (%)	14	14	12	12
	Used ENF (total) (%)	40	41	46	47
	Used ENF *de novo* (%)	24	26	26	26
	Active background agents = 0[§] (%)	17	16	17	16
	Active background agents = 1[§] (%)	38	35	37	39

*Pooled DUET data included for comparison; [†]From extended NNRTI RAM list [§]Assessed by phenotypic sensitivity score (PSS)

Change in CD4 cell count from baseline (cells/mm^3) at Week 48 (ITT NC=F)



*Pooled DUET data included for comparison; ‡ANCOVA model

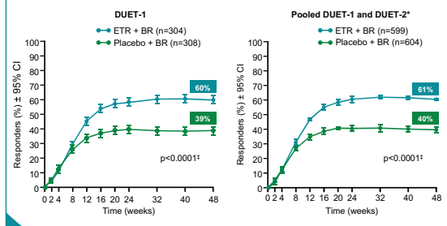
Overview of AEs (regardless of causality) at Week 48

Parameter, %		DUET-1 ETR + BR (n=304)	DUET-1 Placebo + BR (n=308)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
Any AE (any cause)		96	97	96	96
Grade 3 or 4 AE		29	36	33	35
Discontinuation due to AE		7	7	7	6
Serious AE		19	25	20	23
Death (any cause)[‡]		2	4	2	3
Most common AEs	Rash (any type)	22	11	19	11
	Diarrhea	14	24	18	24
	Nausea	15	15	15	13
	Headache	12	14	11	13
AEs of interest	Nervous system disorders	18	21	17	20
	Psychiatric disorders	14	18	17	20
	Hepatic AEs	7	8	7	6

- No consistent or clinically relevant trends in laboratory, vital signs or ECG data were observed
- The incidence and severity of laboratory abnormalities, including hepatic and lipid parameters, was generally similar between the ETR and placebo groups

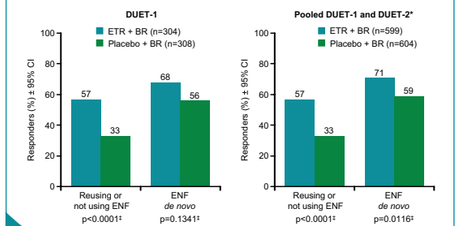
*Pooled DUET data included for comparison; [‡]All deaths in the ETR group were considered not or doubtfully related to trial medication. One death in the pooled placebo group was considered possibly related to the BR

Patients with VL <50 copies/mL at Week 48 (ITT-TLOVR)



*Pooled DUET data included for comparison; ‡Logistic regression model; TLOVR = time-to-loss of virologic response imputation algorithm. CI = confidence interval

Response (<50 copies/mL) according to ENF use at Week 48



*Pooled DUET data included for comparison; ‡Logistic regression model

DUET-1: summary of rash in the ETR group

- **Overall incidence:** 22% in ETR group versus 11% in placebo group (p=0.0003)*
- **Early onset:** most frequent in second week of therapy; median onset Day 12
  - after the first 6 weeks of treatment, the incidence of rash was similar between treatment groups and the incidence of new cases of rash remained stable, with new onset of rash reported in <1% of patients
- **Duration:** median duration 14 days
- **Usually mild-to-moderate severity:** 1% grade 3 and no grade 4 events
  - no rashes with mucosal involvement
- **Infrequently lead to discontinuation**
  - 2% of patients permanently discontinued
  - most rashes were self-limiting with continued treatment
- Higher incidence in women, but no clear difference in severity or treatment discontinuations according to gender

*Fisher's exact test

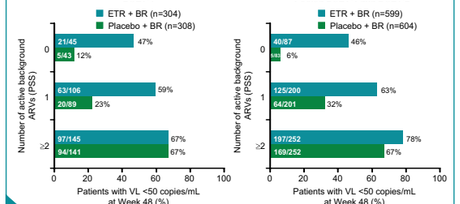
Durability of response (VL <50 copies/mL) at Weeks 24 and 48

Parameter, %	DUET-1 ETR + BR (n=304)	DUET-1 Placebo + BR (n=308)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
Overall				
Week 24	58	40	61	41
Week 48	60	39	61	40
ENF *de novo*				
Week 24	61	56	67	61
Week 48	68	56	71	59
ENF not *de novo* (reused or not used)				
Week 24	57	34	58	34
Week 48	57	33	57	33

*Pooled DUET data included for comparison

Response (<50 copies/mL) by PSS (DRV FC <10)* at Week 48

(Analysis excludes patients who discontinued except for virologic failure)



*DRV considered sensitive if FC <10; ‡Pooled DUET data included for comparison; ENF is counted as sensitive if used *de novo*

Grade 3 and 4 treatment-emergent laboratory abnormalities at Week 48

Parameter, %	DUET-1 ETR + BR (n=304)	DUET-1 Placebo + BR (n=308)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
At least one lab abnormality				
Grade 3	34	34	36	35
Grade 4	12	12	10	10
Most common grade 3/4 lab abnormalities[‡]				
LDL-cholesterol (>190mg/dL)	4	5	7	7
Total cholesterol (>300mg/dL)	7	5	8	5
Triglycerides (>751mg/dL)	10	6	9	6
Pancreatic amylase (>2 x ULN)	10	10	9	9
Decreased neutrophils (≤749/mm^3)	6	9	5	8

*Pooled DUET data included for comparison; [‡]≥5% in TMC125 group in either trial
LDL = low-density lipoprotein; ULN = upper limit of laboratory normal range

DUET-1: conclusions

- ETR + BR demonstrated superior virologic responses over placebo in treatment-experienced patients
  - 60% of patients in the ETR group achieved confirmed undetectable (<50 copies/mL) VLs compared with 39% in the placebo group
  - in the ETR group 71% of patients achieved a VL <400 copies/mL compared to 47% in the placebo group
- Virologic and immunologic responses with ETR were sustained
  - 94% of patients receiving ETR + BR achieving <50 copies/mL at Week 24 maintained virologic suppression at Week 48
- The safety and tolerability of ETR was comparable to placebo, with the exception of rash
- ETR provides superior efficacy over placebo and extends and enhances the therapeutic options available for treatment-experienced HIV-infected patients

Reference

1. Tambuyzer L, et al. 5th EHDRW 2007. Abstract 67.

Acknowledgments

We express our gratitude to the patients that participated in the study, as well as the study center staff, data safety and monitoring board, clinical event adjudication panel, Virco, Tibotec personnel and the following principal investigators

Argentina: HA Ariza, J Benetucci, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso,P Patterson, RA Teijeiro

Brazil: CA da Cunha, EG Kallas, EM Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman

Chile: J Ballesteros, R Northland

Costa Rica: AA Alvilés Montoya, G Herrera Martinez, A Solano Chinchilla

France: M Dupon, C Katlama, JM Livrozet, P Morlat, G Pialoux, C Piketty, I Poizot-Martin

Mexico: J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero

Panama: A Canton, A Rodriguez, N Sosa

Puerto Rico: JO Morales Ramirez, JL Santana Bagur, R Soto-Malave

Thailand: T Anekthananon, P Mootsikapun, K Ruxrungtham

USA: M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, WJ Fessel, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Leider, D McDonough, K Mounzer, J Nadler, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wills, M Wohlfeiler, K Workowski

Supported by Tibotec

Presented at the 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 3–6 February 2008.

This poster is available on-line at www.tibotec.com