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Pooled 48-Week analysis of DUET-1 and DUET-2: durable efficacy and safety results of etravirine (ETR; TMC125) in treatment-experienced HIV-infected patients

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Abstract

Background
The next-generation NNRTI, ETR, provided significant virologic responses and favorable tolerability at 24 weeks in the multinational DUET trials, which included centers in Canada. We present the pooled 48-week analysis of DUET-1 and DUET-2.

Methods
Treatment-experienced patients with documented NNRTI-resistance, ≥3 primary protease inhibitor (PI) mutations and viral loads >5000 copies/mL were randomized 1:1 to receive bid ETR 200mg or placebo, both with a background regimen (BR) of darunavir with low-dose ritonavir (DRV/r), optimized NRTI(s) and optional enfuvirtide (ENF). The primary endpoint for the 48-week analysis was the proportion of patients with confirmed undetectable viral load (<50 copies/mL; intent-to treat/time-to-loss of virologic response [ITT-TLOVR]). The primary analysis tested for an interaction in the viral response rate between randomized groups and ENF use.

Results
1203 patients received ETR or placebo (median baseline viral load 4.8 log_{10} copies/mL; median CD4 cell count 105 cells/mm³). Efficacy and safety analyses at Week 48 confirmed the Week 24 results.

	Week 24			Week 48		
	ETR + BR (n=599)	Placebo + BR (n=604)	Difference (95% CI)	ETR + BR (n=599)	Placebo + BR (n=604)	Difference (95% CI)
Viral load <50 copies/mL, %						
Overall	61	41	20 (14.3, 25.4) p<0.0001*	61	40	21 (15.3, 26.4) p<0.0001*
ENF+	67	61	6 (–4.3, 17.0) p=0.1878*	71	58	13‡ (2.3, 23.2) p=0.0116*
ENF–	58	34	25‡ (18.5, 31.2) p<0.0001*	57	33	24‡ (17.6, 30.3) p<0.0001*
Viral load <400 copies/mL, %	74	52	23‡ (17.2, 27.8) p<0.0001*	72	47	24 (18.7, 29.5) p<0.0001*
Mean change in viral load, log_{10} copies/mL	–2.37	–1.69	–0.54§ (–0.71, –0.37) p<0.0001¶	–2.25	–1.49	–0.64§ (–0.82, –0.46) p<0.0001¶
Mean change in CD4 cell count, cells/mm³	84	65	18.8§ (7.9, 29.8) p=0.0008¶	98	73	24.4§ (10.4, 38.5) p=0.0006¶

CI = confidence interval; ENF+ = patients using de novo ENF; ENF– = patients reusing or not using ENF; *Logistic regression model including the ENF interaction term (<0.2); ‡Value based on rounded data; §Least square mean difference; ¶ANCOVA model

The incidence and severity of adverse events (AEs), serious AEs, laboratory abnormalities and discontinuations due to AEs, were generally comparable between the ETR and placebo groups except for rash. The most common AEs (ETR versus placebo) were rash (19.2% vs 10.9%; p<0.0001 with 2.2% vs 0% stopping due to rash), diarrhea (18.0% vs 23.5%) and nausea (14.9% vs 12.7%). The frequency of nervous system (17.2% vs 19.7%) and psychiatric disorders (16.7% vs 19.5%) were comparable to placebo.

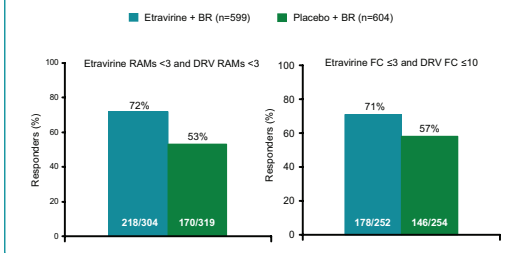
Conclusion
ETR-based antiretroviral (ARV) treatment produced significant and durable improvement in virologic and immunologic parameters after 48 weeks of therapy. With the exception of rash, the safety profile of ETR was generally comparable to placebo.

Note: abstract has been modified.

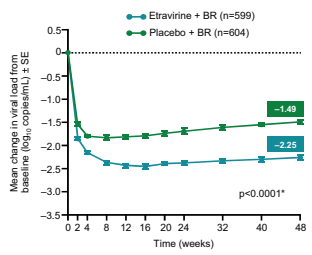
Sustained virologic response (ITT-TLOVR)

Virologic response at Week 24 (copies/mL)	Virologic response at Week 48 (copies/mL)	Etravirine + BR (n=599), %	Placebo + BR (n=604), %
<50	<50	92	89
	50–400	5	6
	≥400	3	6
50–400	<50	35	31
	50–400	53	45
	≥400	12	24
≥400	<50	0	<1
	50–400	3	1
	≥400	97	99

Response (<50 copies/mL) by fully active etravirine and DRV at Week 48 (ITT-TLOVR)



Viral load reduction from baseline at Week 48 (ITT; NC=F)



*ANCOVA model; NC=F = non-completer=failure imputation algorithm: changes below the detection limit (<50 copies/mL) were imputed as 49 copies/mL; SE = standard error

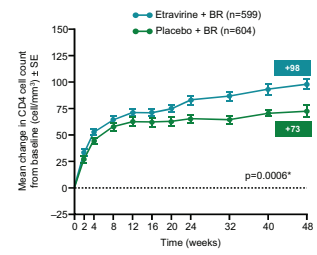
Overview of AEs (regardless of causality) at Week 48

Parameter, %	Etravirine + BR (n=599)	Placebo + BR (n=604)
Any AE (any cause)	96	96
Grade 3 or 4 AE	33	35
Discontinuation due to AE	7	6
Serious AE	20	23
Death (any cause)*	2	3
Most common AEs		
Rash (any type)	19	11
Diarrhea	18	24
Nausea	15	13
Headache	11	13
AEs of interest		
Nervous system disorders	17	20
Psychiatric disorders	17	20
Hepatic AEs	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 etravirine and placebo groups

*All deaths in the etravirine group were considered not or doubtfully related to trial medication. One death in the pooled placebo group was considered possibly related to the BR

Change in CD4 cell count from baseline at Week 48 (ITT; NC=F)

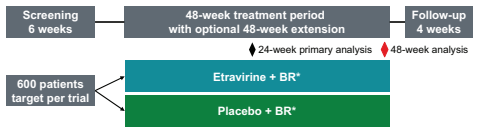


*ANCOVA model

Summary of rash in the etravirine group at Week 48

- **Overall incidence:** 19% in the etravirine group vs 11% in the placebo group (p<0.0001)
- **Early onset:** most frequent in second week of therapy; median onset Day 14
  - after the first 6 weeks of treatment, the incidence of rash was similar between treatment groups, with new onset of rash reported in <2% of patients
- **Duration:** median duration 15 days
- **Usually mild-to-moderate severity:** 1% grade 3 and no grade 4 events
  - in the DUET-2 placebo group, one case of Stevens-Johnson syndrome was observed and was likely related to an allergic reaction to trimethoprim/sulfamethoxazole
- **Infrequently led to discontinuation**
  - 2% of patients permanently discontinued
  - most rashes were self-limiting with continued treatment
- **Relationship to gender**
  - there was a higher incidence of rash in women than men in the etravirine group (30% vs 18%; p=0.0365)
  - no clear differences in severity or treatment discontinuations according to gender
- No increased risk in patients with a history of NNRTI-related rash
- No relationship with baseline CD4 cell count

DUET study design and major inclusion criteria

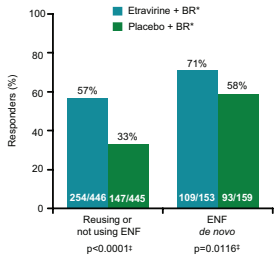


*BR = DRV/r with optimized NRTIs and optional ENF

- Plasma viral load >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
- DUET-1 and DUET-2 differ only in geographic location
  - in DUET-1, patients were recruited from Thailand, Australia, Europe and the Americas
  - in DUET-2, patients were recruited from Europe, Australia, Canada, and the USA
- Pooled analysis was prespecified

RAM = resistance-associated mutation

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



- Virologic response was higher in the ENF *de novo* group compared with the group who were reusing or not using ENF
- Etravirine provided an added benefit to the regimen, which was also observed when ENF was used *de novo*

*Etravirine + BR: n=153 and n=446 for the ENF *de novo* and ENF not *de novo* subgroups, respectively. Placebo + BR: n=159 and n=445 for the ENF *de novo* and ENF not *de novo* subgroups, respectively; ‡Logistic regression

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

Parameter, %	Etravirine + BR (n=599)	Placebo + BR (n=604)
At least one laboratory abnormality		
Grade 3	36	35
Grade 4	10	10
Selected grade 3/4 laboratory abnormalities		
Pancreatic amylase (>2 x ULN)	9	9
Triglycerides (>8.49mmol/L)	9	6
Total cholesterol (>7.77mmol/L)	8	5
LDL-cholesterol (>4.9mmol/L)	7	7
Decreased neutrophils (≤749/mm³)	5	7
ALT (>5 x ULN)	4	2
AST (>5 x ULN)	3	2

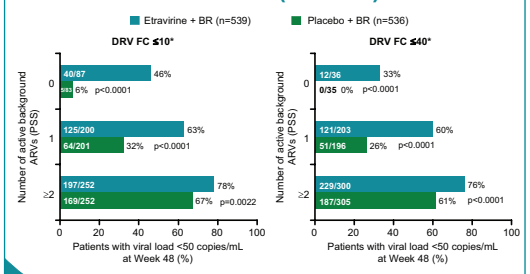
ULN = upper limit of laboratory normal range; LDL = low-density lipoprotein
ALT = alanine aminotransferase; AST = aspartate aminotransferase

Baseline characteristics and background ARVs

Parameter		Etravirine + BR (n=599)	Placebo + BR (n=604)
Patient demographics	Male, %	90	89
	Caucasian, %	70	70
Disease characteristics	Viral load, log_{10} copies/mL (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	CD4 cells, cells/mL (range)	99 (1–789)	109 (0–912)
	CDC category C, %	58	59
Prior ARV use	NNRTIs in screening, %	12	12
	10–15 ARVs, %	66	65
	DRV/r, %	4	5
Detectable mutations	≥3 etravirine RAMs, %	14	13
	≥2 NNRTI RAMs,* %	69	69
	≤3 primary PI RAMs, %	38	37
BR	Used ENF (total), %	46	47
	Used ENF *de novo*, %	26	26
	Active background agents = 0,‡ %	17	16
	Active background agents = 1,‡ %	37	39

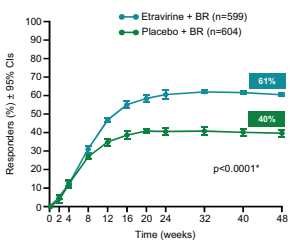
*From extended NNRTI RAM list (Tambuyzer L, et al. EHDRW 2007. Abstract 67)
‡Assessed by phenotypic sensitivity score (PSS)

Response (<50 copies/mL) by PSS at Week 48 (TLOVR)*



*DRV considered sensitive if fold-change (FC) ≤10 or ≤40; Analysis excludes patients who discontinued except for virologic failure; ENF is counted as sensitive if used *de novo*

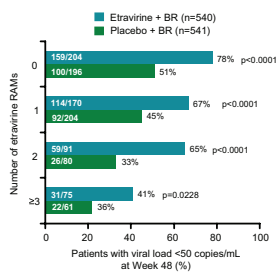
Patients with viral load <50 copies/mL at Week 48 (ITT-TLOVR)



- 61% of patients in the etravirine group achieved confirmed undetectable viral load (<50 copies/mL) compared with 40% in the placebo group

*Logistic regression model

Response (<50 copies/mL) by etravirine RAMs* at Week 48 (ITT-TLOVR)



*Etravirine RAMs are defined as V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S

Conclusions

- At 48 weeks, etravirine + BR demonstrated superior virologic responses over placebo in treatment-experienced patients
  - 61% of patients in the etravirine group achieved confirmed undetectable (<50 copies/mL) viral load compared with 40% in the placebo group.
- Virologic and immunologic responses with etravirine were sustained
  - 92% of patients receiving etravirine + BR achieving <50 copies/mL at Week 24 maintained virologic suppression at Week 48.
- Virologic response rates in both treatment groups increased with increasing number of active agents in the BR
  - the difference in response rate between the etravirine and placebo groups was most apparent in patients with no active agents in the BR.
- The safety and tolerability profile of etravirine was comparable to placebo, with the exception of rash which occurred early in treatment.
- Etravirine provides durable immunologic and virologic responses and extends and enhances the therapeutic options available for treatment-experienced HIV-infected patients.

Acknowledgments

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

DUET-1
Argentina: HA Ariza, J Benetucci, P Cahn, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso, P Patterson, RA Teijeiro; **Brazil:** CA da Cunha, B Grinsztejn, 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, 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, R Haubrich, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Lalezari, J Leider, D McDonough, A Mills, 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.

DUET-2
Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, CM Tsoukas; **France:** C Arvieux, L Cotte, JF Delfraissy, PM Girard, B Marchou, JM Molina, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arasteh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, A Moll, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, B Clotet, G Garcia, JM Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, T Campbell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, AE Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch, W Towner.

Supported by Tibotec

Presented at the 17th Annual Canadian Conference on HIV/AIDS Research (CAHR), Montréal, Canada, April 24–27 2008.

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

BT, MJ, CK and J-VM participated in the recruitment of patients and reporting of data for those patients.
RK, DM, MPdB, MP and BW are full-time employees of the trial sponsor, Tibotec Pharmaceuticals Ltd.