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DUET-2: Week 48 results of a Phase III randomized double-blind trial to evaluate the efficacy and safety of etravirine (ETR; TMC125) versus placebo in 591 treatment-experienced HIV-1-infected patients

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Abstract

Background

The Week 24 primary analysis of DUET-2 showed that ETR, a next-generation NNRTI, provides strong antiviral activity and a good tolerability profile in treatment-experienced patients with HIV-1. We present a pre-planned analysis of Week 48 efficacy and safety data.

Methods

DUET-2 is an ongoing 96-week randomized double-blind Phase III trial designed to show superiority of ETR 200mg vs placebo, both given twice daily (bid) with a background regimen (BR) of darunavir/r, investigator-selected NRTI(s) and optional enfuvirtide (ENF), in patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations (November 2005 IAS-USA list). The primary endpoint was the percentage of patients with a confirmed viral load (VL) of <50 copies/mL at Week 24 (time to loss of virologic response; TLOVR). Safety was also assessed throughout the study.

	Week 24			Week 48		
	ETR + BR	Placebo + BR	Difference (95% CI)	ETR + BR	Placebo + BR	Difference (95% CI)
VL <50 copies/mL, %	63	42	21 (13; 29) p<0.0001*	61	41	21 (13; 28) p<0.0001*
VL <400 copies/mL, %	75	53	22 (14; 29) p<0.0001*	72	48	24 (16; 32) p<0.0001*
Mean (SE) change in VL, log_{10} copies/mL	−2.4 (0.08)	−1.7 (0.08)	−0.51[‡] (0.27; 0.74) p<0.0001**	−2.2 (0.08)	−1.5 (0.08)	−0.64[‡] (0.39; 0.89) p<0.0001**
Mean (SE) change in CD4 cell count, cells/mm^3	78 (4.9)	66 (4.7)	6.5[‡] (−7.8; 20.9) p=0.3809**	94 (5.9)	72 (6.4)	20.8[‡] (3.9; 37.8) p=0.0160**

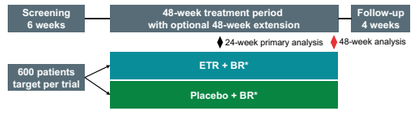
[‡]LS means difference; *Logistic regression model; **ANCOVA model
SE = standard error

Results

The intent-to-treat (ITT) population included 591 patients (median baseline VL was 4.8 log_{10} copies/mL; median CD4 cell count was 105 cells/mm^3, 55% patients were CDC Category C, median number of NNRTI mutations was two, 27% of patients used enfuvirtide *de novo*).

Of patients with a VL of <50 copies/mL at Week 24, 90% of patients maintained a VL of <50 copies/mL at Week 48 with ETR + BR vs 88% with placebo + BR. Furthermore, a significantly increased mean CD4 cell count was observed at Week 48 with ETR + BR vs placebo + BR. Similar to Week 24, Week 48 safety data showed that the incidence and severity of adverse events (AEs) with ETR were similar to placebo: any AE (96% ETR vs 95% placebo), serious AEs (21% vs 22%), grade 3/4 AEs (38% vs 34%), AEs leading to discontinuation (8% vs 4%). The most common AEs were diarrhea (22% vs 23%), rash (any type) (17% vs 11%) and nausea (15% vs 11%). Most rashes were mild to moderate, infrequently led to discontinuation (2.4% vs 0%), occurred early and resolved with continued treatment. The incidences of nervous system (17% vs 18%) and psychiatric disorders (20% vs 21%) with ETR were comparable to placebo.

DUET study design and major inclusion criteria

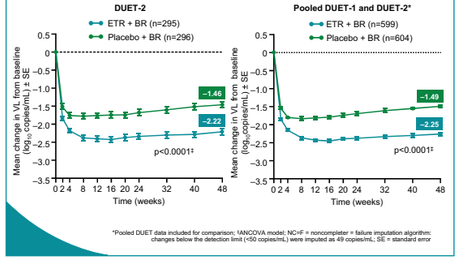


*BR = DRV/r with optimized NRTIs and optional ENF

- 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-2, patients were recruited from Europe, Australia, Canada, and the USA
- DUET-1 and DUET-2 differed only in geographic location; pooled analysis was prespecified

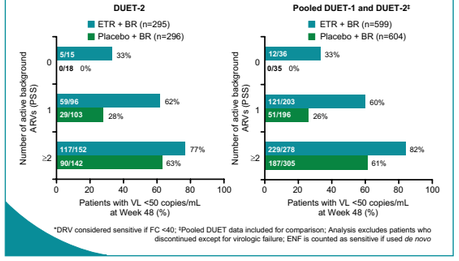
DRV/r = darunavir with low-dose ritonavir; RAM = resistance-associated mutation

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; SE = standard error

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



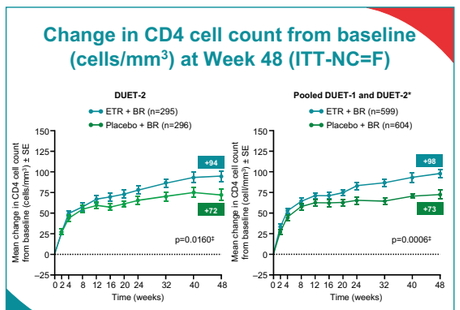
*DRV considered sensitive if FC <40; †Pooled DUET data included for comparison; ‡Analysis excludes patients who discontinued except for virologic failure; ENF is counted as sensitive if used *de novo*

Baseline characteristics and background ARVs

Parameter		DUET-2 ETR + BR (n=295)	DUET-2 Placebo + BR (n=296)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
Patient demographics	Male (%)	94	92	90	89
	Caucasian (%)	77	76	70	70
Disease characteristics	VL (log_{10} copies/mL)	4.8 (3.0–6.8)	4.8 (2.2–6.3)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	CD4 cells (cells/mL)	100 (1.0–708)	108 (0–912)	99 (1–789)	109 (0–912)
	CDC category C (%)	55	55	58	59
Prior ARV use	10–15 ARVs (%)	67	62	66	65
	DRV/r (%)	3	4	4	5
Detectable mutations	≥2 ETR RAMs (%)	27	27	31	28
	≥2 NNRTI RAMs†,¶ (%)	68	67	69	69
	≤3 primary PI RAMs (%)	35	34	38	37
BR	NNRTIs in screening (%)	9	10	12	12
	Used ENF (total) (%)	52	52	46	47
	Used ENF *de novo* (%)	27	27	26	26
	Active background agents = 0§ (%)	17	16	17	16
	Active background agents = 1§ (%)	35	43	37	39

*Pooled DUET data included for comparison; †From extended NNRTI RAM list
‡Assessed by phenotypic sensitivity score (PSS); ARVs = antiretrovirals

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



*Pooled DUET data included for comparison; †ANCOVA model

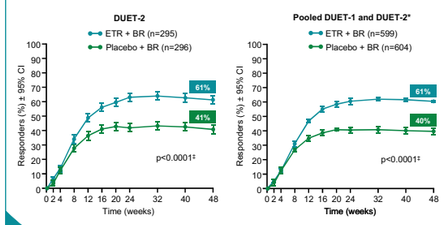
Overview of AEs (regardless of causality) at Week 48

Parameter, %		DUET-2 ETR + BR (n=295)	DUET-2 Placebo + BR (n=296)	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	95	96	96
Grade 3 or 4 AE		38	34	33	35
Discontinuation due to AE		8	4	7	6
Serious AE		21	22	20	23
Death (any cause)†		2	3	2	3
Most common AEs	Rash (any type)	17	11	19	11
	Diarrhea	22	23	18	24
	Nausea	15	11	15	13
	Headache	10	12	11	13
AEs of interest	Nervous system disorders	17	18	17	20
	Psychiatric disorders	20	21	17	20
	Hepatic AEs	6	4	7	6

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

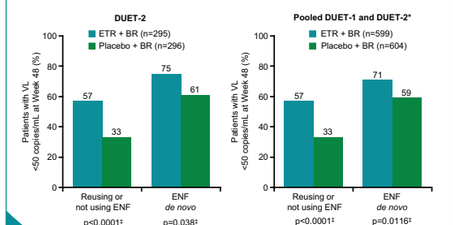
*Pooled DUET data included for comparison; †All deaths in the ETR group were considered not or doubtfully related to trial medication. One death in the pooled placebo group was considered possibly related to the BR

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



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

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



*Pooled DUET data included for comparison; ‡Logistic regression

DUET-2: summary of rash in the ETR group at Week 48

- Overall incidence: 17% in ETR group versus 11% in placebo group (p=0.0577)*
- Early onset: most frequent in second week of therapy; median onset Day 17
- Duration: median duration 18 days
- Usually mild-to-moderate severity: 1.4% grade 3 and no grade 4 events
  - incidence of new cases of rash remained stable after 6 weeks, with new onset of rash reported in <1.5% of patients
  - in DUET-2 one case of SJS was observed in the placebo group and was likely related to an allergic reaction to trimethoprim/sulfamethoxazole
- Infrequently lead to discontinuation
  - 2.4% of patients permanently discontinued
  - most rashes were self-limiting with continued treatment
- In DUET-2, incidence of rash was similar in men and women, with no clear differences in severity or treatment discontinuations according to gender
- No increased risk in patients with a history of NNRTI-related rash

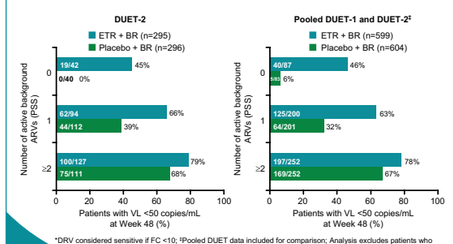
*Fisher's exact test; SJS = Stevens Johnson Syndrome

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

	DUET-2 ETR + BR (n=295)	DUET-2 Placebo + BR (n=296)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
Overall				
Week 24	63	42	61	41
Week 48	61	41	61	40
ENF *de novo*				
Week 24	73	66	67	61
Week 48	75	61	71	59
ENF not *de novo* (*reused or not used*)				
Week 24	59	33	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



*DRV considered sensitive if FC <10; †Pooled DUET data included for comparison; Analysis excludes patients who discontinued except for virologic failure; ENF is counted as sensitive if used *de novo*

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

Parameter, %	DUET-2 ETR + BR (n=295)	DUET-2 Placebo + BR (n=296)	Pooled DUET-1 and DUET-2* ETR + BR (n=599)	Pooled DUET-1 and DUET-2* Placebo + BR (n=604)
At least one laboratory abnormality				
Grade 3	38	35	36	35
Grade 4	9	8	10	10
Most common grade 3/4 laboratory abnormalities†				
LDL-cholesterol	10	8	7	7
Total cholesterol	9	5	8	5
Triglycerides	9	6	9	6
Pancreatic amylase	8	9	9	9
Decreased neutrophils	5	6	5	8

*Pooled DUET data included for comparison; †≥5% in ETR group in either trial
LDL = low-density lipoprotein

DUET-2: Conclusions

- At 48 weeks, in treatment-experienced patients, ETR provided durable and superior virologic and immunologic benefits over placebo
  - in DUET-2 61% of patients achieved undetectable VL (<50 copies/mL) compared with 41% in the placebo group
    - in the pooled analysis, 61% of patients achieved undetectable VL (<50 copies/mL) compared with 40% in the placebo group
  - a statistically significant greater number of patients who received ETR achieved an undetectable VL (<50 copies/mL) than those who received placebo, irrespective of previous ENF use
- Virologic and immunologic responses were well maintained from 24 to 48 weeks
  - of the patients achieving undetectable VL (<50 copies/mL) with ETR plus BR at Week 24, 90% had maintained virologic suppression at Week 48
- ETR was well tolerated in patients over 48 weeks
  - with the exception of rash, incidence and severity of AEs with ETR were similar to placebo
- ETR provides a new effective and well-tolerated treatment option for treatment-experienced patients

Reference

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

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