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Reduction in AIDS-defining events/deaths with etravirine compared to placebo: pooled DUET 48-week results

P027

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Abstract

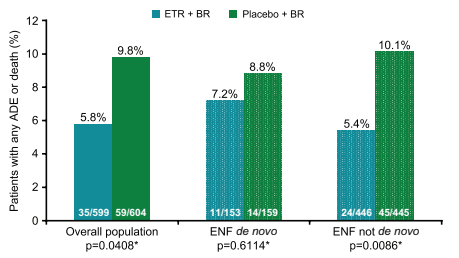
The benefit of newer antiretroviral (ARV) regimens on clinical endpoints for treatment-experienced, HIV-1-infected patients remains to be determined. Etravirine (ETR; TMC125) demonstrated durable efficacy and safety in HIV-1-infected, treatment-experienced patients in the Phase III DUET trials. We report adjudicated clinical endpoints from a prespecified pooled analysis of DUET-1 and DUET-2 after 48 weeks of treatment.

Patients were randomised 1:1 to receive either ETR 200mg bid or placebo, both in combination with a background regimen (BR) of darunavir (DRV) with low-dose ritonavir (DRV/r), investigator-selected NRTIs and optional enfuvirtide (ENF). AIDS-defining events/deaths (ADE/D) were adjudicated by a four-member independent panel masked to treatment assignment. All events were adjudicated, and only those confirmed or probable ADE/D were included in the analysis. Prespecified analyses were stratified by de novo or not de novo (including recycled ENF or ENF not used) ENF use.

Five hundred and ninety-nine and 604 patients received ETR and placebo, with median treatment duration of 52.3 vs 51.0 weeks, respectively. At baseline, median CD4 cell count was 105 cells/mm^3, $\log_{10}$ HIV RNA was 4.8, and 59% had clinical Centers for Disease Control and Prevention (CDC) C classification. Overall, 35 ETR patients (5.8%) and 59 placebo patients (9.8%) had an ADE/D (p=0.041). In total, 22 ADE/D occurred in the first 30 days (six in the ETR group, 16 in the placebo group). Time to ADE/D was significantly shorter for patients in the placebo group compared with ETR (see figure). The most common ADEs were Candida esophagitis (one ETR, nine placebo), Pneumocystis pneumonia (three ETR, six placebo), Mycobacterium avium complex (MAC; two ETR, five placebo), herpes simplex virus (HSV; four ETR, four placebo), cytomegalovirus (CMV) retinitis (one ETR, five placebo) and Kaposi's sarcoma (KS; two ETR, four placebo). In the de-novo ENF sub-group (ETR n=153; placebo n=159), events were similar, with an ADE/D reported for 11 patients in the ETR group (7.2%) and 14 patients in the placebo group (8.8%). However, in those not receiving de-novo ENF (ETR n=446; placebo n=445), more events among patients in the placebo group were reported than among those in the ETR group (45 patients [10.1%] vs 24 patients [5.4%]; p=0.0086).

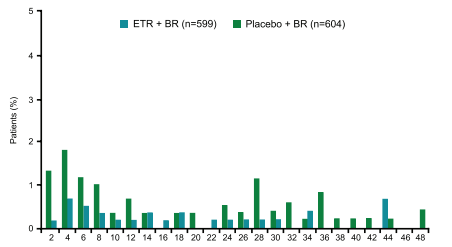
In addition to virological and immunological benefits, use of ETR was associated with a reduction in ADE/D and a significantly longer time to ADE/D than placebo in treatment-experienced, HIV-1-infected patients.

Proportion of patients with any ADE or death



*p values derived from logistic regression model with factors treatment, trial, baseline viral load, ENF use and interaction between treatment and ENF

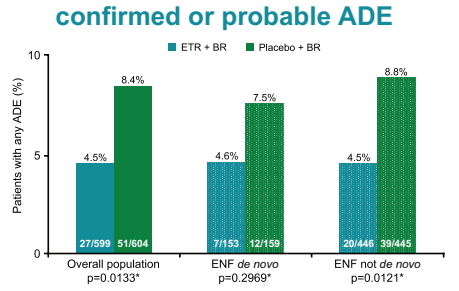
Incidence of ADEs over time



- Twenty-one ADEs occurred in the first 30 days of treatment (16 in the placebo + BR group and five in the ETR + BR group)

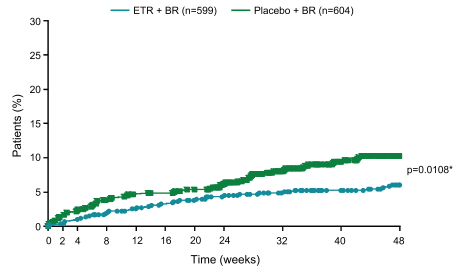
*2 = Week 1–2; 4 = Week 3–4; 6 = Week 5–6, etc

Proportion of patients with any confirmed or probable ADE



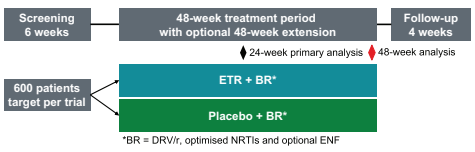
*Logistic regression with factors treatment, trial, baseline viral load, ENF use and interaction between treatment and ENF

Time to first confirmed/probable ADE or death: overall



*p value derived from log-rank test

DUET study design and major inclusion criteria

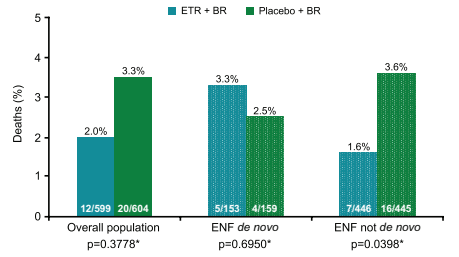


*BR = DRV/r, optimised NRTIs and optional ENF

- Major inclusion criteria
  - plasma viral load >5,000 copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI RAM, at screening or in documented historical genotype
  - ≥3 primary PI mutations at screening
- DUET-1 and DUET-2 differ only in geographical location
- Pooled analysis was prespecified

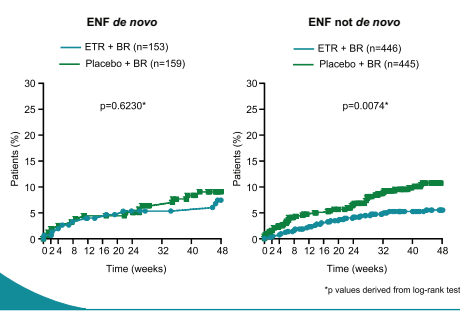
RAM = resistance-associated mutation; PI = protease inhibitor

Proportion of deaths in the treatment period



*Logistic regression with factors treatment, trial, baseline viral load, ENF use and interaction between treatment and ENF

Time to first confirmed/probable ADE or death: ENF subgroups



*p values derived from log-rank test

Pooled 48-week DUET analysis: baseline characteristics

Parameter, % or median (range)	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration at time of analysis, weeks	52.3 (1.6–85)	51.0 (3.4–80)
Patient demographics		
Male	90	89
Caucasian	70	70
Age, years	46 (18–77)	45 (18–72)
Disease characteristics		
Viral load, $\log_{10}$ copies/mL	4.8 (2.7–6.8)	4.8 (2.2–6.5)
Viral load ≥100,000 copies/mL	38	36
CD4 cells, cells/mm^3	99 (1.0–789)	109 (0.0–912)
CD4 cells <50 cells/mm^3	36	35
Baseline CDC category		
CDC category A	21	21
CDC category B	21	19
CDC category C	58	59

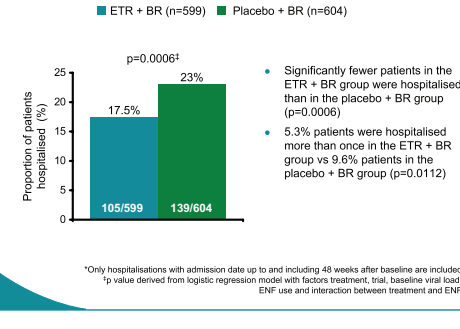
Summary of clinical outcomes over 48 weeks of treatment

Parameter, n (%)	ETR + BR	Placebo + BR
Overall population	**n=599**	**n=604**
Any confirmed or probable ADE/death	35 (5.8)*	59 (9.8)
Any confirmed or probable ADE	27 (4.5)	51 (8.4)
Any confirmed ADE	20 (3.3)	30 (5.0)
Any probable ADE	8 (1.3)	25 (4.1)
Death	12 (2.0)	20 (3.3)
ENF *de novo*	**n=153**	**n=159**
Any confirmed or probable ADE/death	11 (7.2)‡	14 (8.8)
Any confirmed or probable ADE	7 (4.6)	12 (7.5)
Any confirmed ADE	4 (2.6)	8 (5.0)
Any probable ADE	3 (2.0)	4 (2.5)
Death	5 (3.3)	4 (2.5)
ENF not *de novo*	**n=446**	**n=445**
Any confirmed or probable ADE/death	24 (5.4)§	45 (10.1)
Any confirmed or probable ADE	20 (4.5)	39 (8.8)
Any confirmed ADE	16 (3.6)	22 (4.9)
Any probable ADE	5 (1.1)	21 (4.7)
Death	7 (1.6)	16 (3.6)

Thirty-two patients died during the treatment period (12 and 20 patients in the ETR + BR and placebo + BR groups, respectively); All deaths in the ETR + BR group were considered not or doubtfully related to ETR; One death in the placebo + BR group was considered possibly related to the BR

*p=0.0408; ‡p=0.6114; §p=0.0086; Logistic regression with factors treatment, trial, baseline viral load, ENF use and interaction between treatment and ENF

Proportion of patients hospitalised by Week 48*



- Significantly fewer patients in the ETR + BR group were hospitalised than in the placebo + BR group (p=0.0006)
- 5.3% patients were hospitalised more than once in the ETR + BR group vs 9.6% patients in the placebo + BR group (p=0.0112)

*Only hospitalisations with admission date up to and including 48 weeks after baseline are included
‡p value derived from logistic regression model with factors treatment, trial, baseline viral load, ENF use and interaction between treatment and ENF

Assessment of clinical outcomes (ADEs and deaths)

- Clinical endpoints were defined as a combination of ADEs and deaths and were identified using methods described in the ESPRIT[1] and SMART[2] trials
- ADEs were identified using reported adverse event (AE) terms appearing as category C illnesses*
- ADEs were reviewed, certified and validated by an independent expert adjudication panel blinded to treatment allocation
  - events adjudicated as confirmed or probable category C events were considered as ADEs
  - events adjudicated as not category C events or not enough information were not considered as ADEs
- Primary analysis: all confirmed or probable ADEs or deaths
- At the time of this analysis, all patients were treated for ≥48 weeks or had discontinued
- Statistical analyses were performed on the overall ITT population and according to ENF use (re-use/no use [not *de novo*], or use for the first time [*de novo*])

*From the 1993 revised classification system for HIV issued by the US CDC; ITT = intent-to-treat
[1]Emery S, et al. Control Clin Trials 2002;23:198–220; [2]SMART Study Group. N Engl J Med 2006;355:2283–96

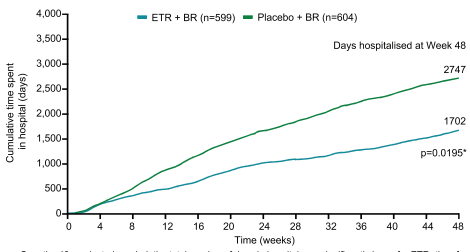
Most commonly reported confirmed or probable ADE*

Parameter, n (%)	Pooled DUET overall		Pooled DUET ENF *de novo*		Pooled DUET ENF not *de novo*	
	ETR + BR (n=599)	Placebo + BR (n=604)	ETR + BR (n=153)	Placebo + BR (n=159)	ETR + BR (n=446)	Placebo + BR (n=445)
Any confirmed or probable ADE	27 (4.5)	51 (8.4)	7 (4.6)	12 (7.5)	20 (4.5)	39 (8.8)
Death as a first event	8 (1.3)	7 (1.2)	4 (2.6)	2 (1.3)	4 (0.9)	5 (1.1)
Candida oesophagitis	1 (0.2)	9 (1.5)	1 (0.7)	1 (0.6)	0	8 (1.8)
Pneumocystis jiroveci pneumonia	3 (0.5)	6 (1.0)	1 (0.7)	2 (1.3)	2 (0.4)	4 (0.9)
HSV	4 (0.7)	4 (0.7)	0	2 (1.3)	4 (0.9)	2 (0.4)
MAC	2 (0.3)	5 (0.8)	0	1 (0.6)	2 (0.4)	4 (0.9)
CMV retinitis	1 (0.2)	5 (0.8)	0	0	1 (0.2)	5 (1.1)
KS	2 (0.3)	4 (0.7)	1 (0.7)	0	1 (0.2)	4 (0.9)

Other commonly reported ADE (in ≥2 patients in the ETR + BR or placebo + BR group) included gastroenteritis cryptosporodial, meningitis cryptococcal, HIV wasting syndrome, pneumonia bacterial and non-Hodgkin's lymphoma

*In ≥6 patients in the pooled overall ETR + BR and placebo + BR groups

Cumulative hospital days over 48 weeks



- Over the 48-week study period, the total number of days in hospital was significantly lower for ETR- than for placebo-treated patients
  - the median duration of hospitalisation per patient was lower in the ETR + BR group than in the placebo + BR group (9 vs 10 days, respectively)

*p value derived from a t-test correcting for treatment

Pooled 48-week DUET analysis: efficacy and safety overview

- Primary efficacy endpoint – confirmed virological response
  - patients receiving ETR + BR achieved significantly greater virological response rates (viral load <50 copies/mL) than with placebo + BR (61% and 40%, respectively; p<0.0001)[1,2]
- Safety and tolerability
  - aside from rash, ETR displayed a favourable safety and tolerability profile when compared to placebo[1,2]
    - rash was mild-to-moderate, occurred within the first few weeks of treatment, resolved with continued use and infrequently led to discontinuation

[1]Trottier B, et al. CAHR 2008. Poster P167; [2]De Smedt G, et al. ISHEID 2008. Oral presentation

Description of deaths

- In the ETR + BR group, all fatal AEs were considered not or doubtfully related to treatment
- In the placebo + BR group, one patient had a fatal serious AE considered possibly related to treatment (acute renal failure)
- Forty-one patients died in the pooled DUET trials
  - eight due to an AE during screening, 32 during the treatment period (ETR, n=12; placebo, n=20) and one during follow-up (ulcerative colitis)
- Treatment-emergent AEs leading to death were mainly associated with disease progression or HIV-related complications
  - the most common fatal AEs were related to infections (ETR + BR group, 1% [n=6]; placebo + BR, 2% [n=12])
- During the treatment period, 13 out of 20 and four out of 12 patients in the placebo + BR and ETR + BR groups, respectively, presented with an ADE prior to death

Conclusions

- There was a significant reduction in clinical endpoints (ADE or death) in ETR + BR-treated patients compared with placebo + BR in the pooled DUET trials – significant benefit was also observed in the sub-group who did not use ENF *de novo*
- The time to a new ADE or death was significantly prolonged for patients receiving ETR + BR compared with placebo + BR
- Significantly fewer cumulative hospital days occurred in patients receiving ETR + BR than in the placebo + BR group (p=0.0195)
- These results add to the previously demonstrated significant benefit of ETR in achieving HIV RNA suppression and augmenting CD4 cell count recovery
- The clinical endpoint data validates and expands the surrogate marker data by demonstrating a reduction in HIV clinical disease progression when ETR is added to DRV/r + BR

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DUET-1
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, B Grinsztejn, EG Kallas, JV Madruga, EM Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** AA Alvalés Montoya, G Herrera Martínez, A Solano Chinchilla; **France:** M Dupon, C Katlama, JM Livrozet,P Morlat, G Pialoux, C Piketty, I Pozet-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 Lesher, D McDonough, A Mills, R Mounzer, J Nadler, D Norris, W O'Brien, G Perrone, K Raben, B Reinbaum, M Rawlings, B Rodvick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wilkin, T Wills, M Wohlfeiler, K Workowski

DUET-2
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