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Etravirine demonstrates durable efficacy in treatment-experienced patients in the DUET trials: pooled 96-week results

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Abstract

Background
The 24- and 48-week efficacy and safety of etravirine (ETR; TMC125) in treatment-experienced, HIV-1-infected patients have been demonstrated in the Phase III DUET trials. We report detailed efficacy results from a pooled analysis at 96 weeks.

Methods
Patients were randomised 1:1 to either ETR 200mg or placebo, both bid following a meal, in combination with a background regimen (BR) of darunavir (DRV) with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). Phenotypic Sensitivity Score (PSS; Antivirogram®) was used to determine the number of active agents; ETR was considered active if the fold-change in 50% effective concentration (FC) was ≤3.

Results
Five hundred and ninety-nine and 604 patients received ETR + BR or placebo + BR, respectively. Baseline characteristics were comparable between the treatment groups. Overall, 57% of ETR patients achieved viral load <50 copies/mL at Week 96 compared with 36% of placebo patients. Of patients who achieved viral load <50 copies/mL with ETR + BR at Week 48 (60%), 91% remained undetectable at Week 96. Response was consistently higher in the ETR group, irrespective of gender, race, age and region. Detailed efficacy results by baseline PSS, ETR FC and weighted genotypic score are shown in the table.

Viral load <50 copies/mL, %	ETR + BR (n=599)	Placebo + BR (n=604)
Overall	**57***	**36**
Number of active agents at baseline (PSS)‡		
0	46	6
1	61	29
2	75	55
≥3	77	64
Baseline ETR FC		
≤3	73	42
3 <FC ≤13	54	35
>13	44	24
Baseline ETR weighted genotypic score		
[0; 2]	76	42
[2.5; 3.5]	60	33
≥4	43	32

*p<0.0001 vs placebo; ‡DRV FC ≤10 and de-novo ENF use counted as active, excluding ETR in calculation

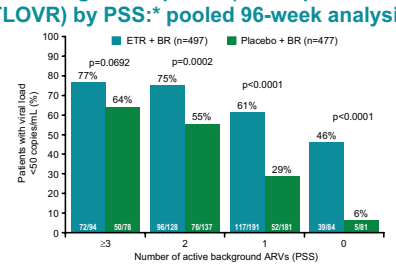
Conclusions
The results from the pooled DUET 96-week analysis demonstrate the superior durable efficacy of ETR over placebo. Patients in the ETR group maintained undetectable viral load through 96 weeks, with only a 3% drop from Week 48 (57% vs 60%). In addition, higher responses were observed with ETR versus placebo, irrespective of number of active agents, baseline ETR FC or weighted score.

Sustained virological response in DUET (confirmed TLOVR)

Viral load, %	ETR + BR (n=599)	Placebo + BR (n=604)
<50 copies/mL at Week 24		
<50 copies/mL at Week 96	83	78
50–<400 copies/mL at Week 96	9	10
≥400 copies/mL at Week 96	8	12
<50 copies/mL at Week 48		
<50 copies/mL at Week 96	91	88
50–<400 copies/mL at Week 96	6	7
≥400 copies/mL at Week 96	3	5

- 91% and 83% of responding ETR + BR patients at Weeks 48 and 24, respectively, maintained virological response to Week 96

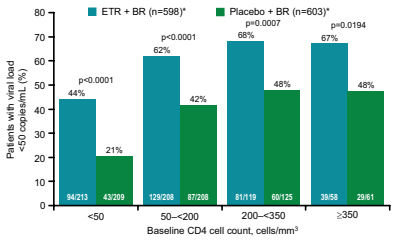
Virological response (<50 copies/mL TLOVR) by PSS:* pooled 96-week analysis



- Patients in the ETR + BR group achieved consistently higher response rates than patients in the placebo + BR group, irrespective of number of active background agents; the difference was most apparent in patients with no active background agents

*DRV considered sensitive if FC ≤10; ENF counted as sensitive if used *de novo*; ETR not included in the PSS calculation; Analysis excludes patients who discontinued except for virological failure (VF)

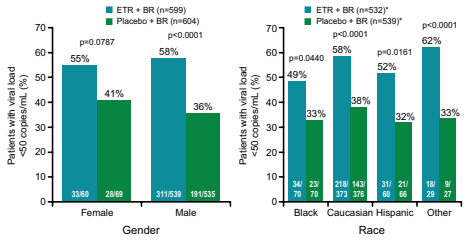
Virological response (<50 copies/mL TLOVR) by baseline CD4 cell count: pooled 96-week analysis



- Higher baseline CD4 cell count resulted in higher virological response rates in both treatment groups, however, response was consistently higher in the ETR + BR group irrespective of baseline CD4 cell count

*CD4 cell counts before or at baseline were not available for two patients (one in each group)

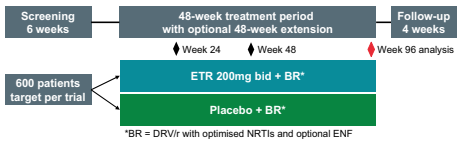
Virological response (<50 copies/mL TLOVR) by gender and race: pooled 96-week analysis



- ETR + BR provided numerically higher virological response rates than placebo + BR, irrespective of gender or race

*Local regulations prevented collection of race data for 67 ETR and 65 placebo patients

DUET study design and major inclusion criteria



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

- Plasma viral load >5,000 HIV-1 RNA 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
  - in DUET-1, patients were recruited from Thailand, Europe and the Americas
  - in DUET-2, patients were recruited from Europe, Australia, Canada, and the USA
- Pooled analysis was pre-specified
- 2% of randomised patients completed the trial at Week 48 and elected not to continue into the open-label extension phase

RAM = resistance-associated mutation; PI = protease inhibitor

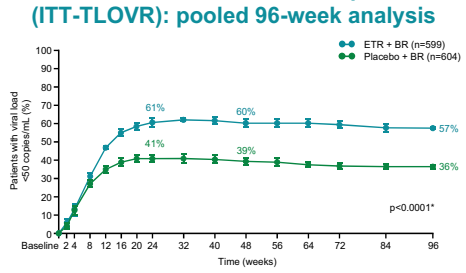
Baseline characteristics and background ARVs

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Patient demographics		
Male, %	90	89
Caucasian, %	70	70
Disease characteristics		
Viral load, $\log_{10}$ copies/mL, median (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
CD4 cells, cells/mm³, median (range)	99 (1–789)	109 (0–912)
CDC category C, %	58	60
Prior ARV use		
NNRTIs in screening, %	12	12
10–15 ARVs, %	66	65
DRV/r, %	4	5
Detectable mutations		
≥3 ETR RAMs, %	18	15
≥2 NNRTI RAMs,* %	70	70
≤3 primary PI RAMs, %	31	31
BR		
Used ENF (total), %	45	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. Antiviral Ther 2009;14:103–9); †Assessed by PSS

ARVs = antiretrovirals; CDC = Centers for Disease Control and Prevention

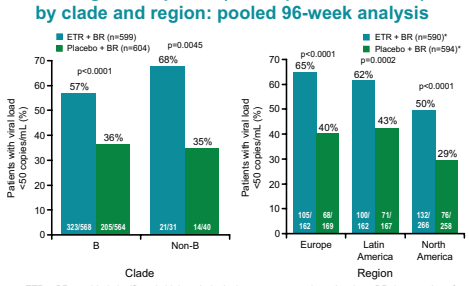
Patients with viral load <50 copies/mL (ITT-TLOVR): pooled 96-week analysis



- Mean change in CD4 cell count was 128 cells/mm³ in the ETR + BR arm versus 86 cells/mm³ in the placebo + BR arm (p<0.0001)

*Logistic regression model controlling for baseline viral load, ENF use and study number
ITT = intent-to-treat; TLOVR = time-to-loss of virological response algorithm

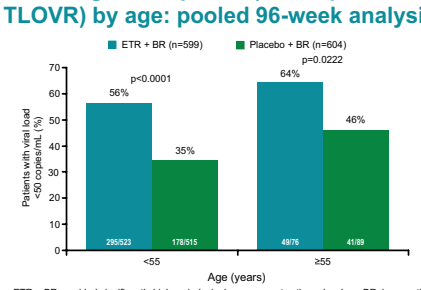
Virological response (<50 copies/mL TLOVR) by clade and region: pooled 96-week analysis



- ETR + BR provided significantly higher virological response rates than placebo + BR, irrespective of clade or region

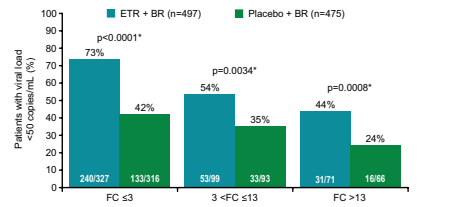
*Patient numbers for Australia and Asia were small and are not included

Virological response (<50 copies/mL TLOVR) by age: pooled 96-week analysis



- ETR + BR provided significantly higher virological response rates than placebo + BR, irrespective of age

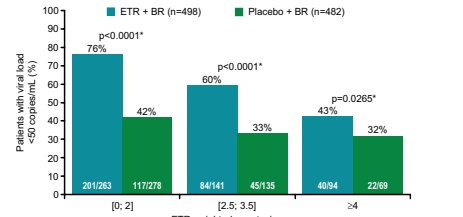
Virological response (<50 copies/mL TLOVR) by baseline ETR FC: pooled 96-week analysis



- ETR + BR provided significantly higher virological response rates than placebo + BR, irrespective of baseline ETR FC
- ETR FC is a marker for other prognostic factors (treatment experience, increased resistance to other ARV classes and lower PSS). In multivariate analyses, ETR FC was a predictor of response in the ETR + BR group, but not in the placebo + BR group

*From logistic regression model with $\log_{10}$ baseline viral load, number of sensitive NRTIs in the BR, $\log_{10}$ baseline DRV FC, study ID [C206 or C216], ENF use, treatment [ETR or placebo], ETR FC; Non-VF excluded population

Virological response (<50 copies/mL TLOVR) by baseline ETR weighted genotypic score:[1] pooled 96-week analysis

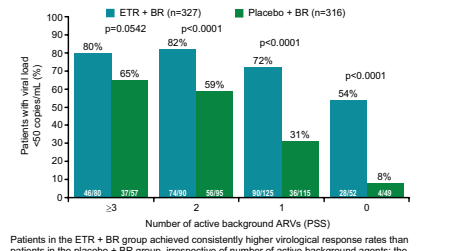


- Lower baseline ETR weighted genotypic score resulted in higher response rates; in patients with ETR weighted genotypic score <4, response rates in the ETR + BR group were higher than the overall response (57%)
- Responses were always higher in the ETR + BR group than in the placebo + BR group

[1]Vingerhoets et al. IHDRW 2008. Abstract 24

*From logistic regression model with $\log_{10}$ baseline viral load, number of sensitive NRTIs in the BR, $\log_{10}$ baseline DRV FC, study ID, ENF use, treatment, ETR weighted genotypic score; Non-VF excluded population

Virological response by baseline PSS with fully active ETR (FC ≤3; TLOVR): pooled 96-week analysis



- Patients in the ETR + BR group achieved consistently higher virological response rates than patients in the placebo + BR group, irrespective of number of active background agents; the difference was most apparent in patients with no active background agents

DRV considered sensitive if FC ≤10; ENF counted as sensitive if used *de novo*
ETR not included in the PSS calculation; Analysis excluded patients who discontinued except for VF

Conclusions

- The results from the pooled DUET 96-week analysis demonstrate the durable and superior virological efficacy of ETR + BR versus placebo + BR in treatment-experienced, HIV-1-infected patients
  - 57% of patients in the ETR + BR group achieved confirmed undetectable (<50 copies/mL) viral load compared with 36% in the placebo + BR group (p<0.0001)
- Virological response was sustained through Week 96
  - 91% of patients with viral load <50 copies/mL at Week 48, and 83% of patients with viral load <50 copies/mL at Week 24, remained undetectable at Week 96
  - virological response remained stable from Week 48 to Week 96
- ETR + BR provided significantly higher virological response rates at Week 96 than placebo + BR, irrespective of race, clade, age, region, ETR FC and ETR weighted genotypic score

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DUET-1
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DUET-2
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