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Long-term safety profile of etravirine in treatment-experienced, HIV-1-infected patients: pooled 96-week results from the Phase III DUET trials

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Abstract

Background
Etravirine (ETR; TMC125) is a next-generation NNRTI with superior efficacy versus placebo in treatment-experienced, HIV-1-infected patients in the DUET-1 and DUET-2 trials. Previous analyses of 48-week data from DUET showed that, except for rash, the incidence/severity of adverse events (AEs) with ETR were similar to placebo. We report the safety profile of ETR at 96 weeks.

Methods
Patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations were randomised to ETR 200mg or placebo bid with a background regimen (BR) of darunavir (DRV) with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). Safety data from DUET-1 and DUET-2 were pooled and the frequency, severity and type of AEs were compared between arms by Fisher's exact test.

Results
One thousand, two hundred and three patients were randomised to ETR or placebo (599 and 604, respectively). Overall median age was 45 years; 10.7% were female. Median duration of treatment was 96 vs 70 weeks. The most common reasons for treatment discontinuation were virological endpoints (16% vs 40%) and AEs (9% vs 7%). Serious AEs occurred in 26% of both arms, death in 3% vs 4%.

Clinical and laboratory AEs

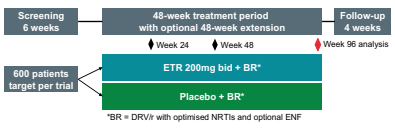
Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Rash, any, %	21*	12
Grade 3	1	0
Grade 4	0	0
Median time to rash onset, days (range)	15 (1–666)	64 (1–660)
Median duration of rash, days (range)	15 (1–672)	26 (1–687)
Discontinuation due to rash, %	2	0
Rash by gender, %		
Males (n=539 vs 535, ETR vs placebo)	19	12
Females (n=60 vs 69, ETR vs placebo)	32**	12
Rash by previous history of NNRTI-related rash, %		
With previous history (n=46 vs 82, ETR vs placebo)	22	15
Without previous history (n=553 vs 522, ETR vs placebo)	20	11
Any nervous system event of interest, %	19***	21
Any psychiatric event, %	20****	21
Any hepatic event, %	9*****	7
Treatment-emergent laboratory abnormalities, %		
Grade 3	42	40
Grade 4	11	11

*p<0.0001 vs placebo; **p=0.0290 vs males; ***p=0.3140 vs placebo; ****p=0.7204 vs placebo; *****p=0.3370 vs placebo (all p-values from Fisher's exact test)

Rash in the ETR + BR group was mild-to-moderate, occurred early with 2 weeks median duration and led to discontinuation in 2.2% of patients. The occurrence of nervous system, psychiatric and hepatic AEs was low in both arms. Grade 3/4 treatment-emergent laboratory abnormalities were similar between groups.

Conclusions
ETR was well tolerated in treatment-experienced, HIV-1-infected adults over 96 weeks and continues to demonstrate a tolerability profile similar to placebo. Rash, which was mostly mild-to-moderate and occurred early, was the only AE associated with ETR treatment.

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

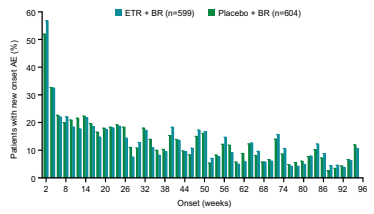
Baseline characteristics and background ARVs

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

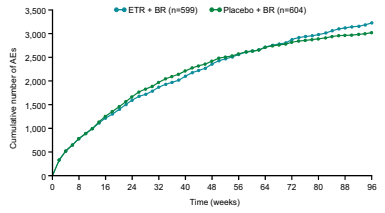
ARVs = antiretrovirals
CDC = Centers for Disease Control and Prevention; PSS = phenotypic sensitivity score

AEs incidence over time: pooled 96-week analysis



- The overall incidence of AEs with ETR + BR was similar to placebo + BR across 96 weeks

Cumulative AEs: pooled 96-week analysis



- Median treatment duration was 96 weeks in the ETR + BR group and 70 weeks in the placebo + BR group

Overview of AEs (regardless of causality): pooled 96-week analysis

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration, median (weeks)	**96**	**70**
Any AE (any cause)	**97**	**96**
Grade 3 AE	37	35
Grade 4 AE	13	12
Discontinuation due to AEs	9	6
Serious AEs	26	26
Death (any cause)[2]	3	4
Most common AEs[1]		
Rash (any type)	21*	12
Diarrhoea	19	24
Nausea	15	14
Nasopharyngitis	14	12
Headache	12	14
Cough	11	9
Herpes simplex	10	10
AEs of interest		
Nervous system disorders	19**	21
Psychiatric disorders	20***	21
Hepatic AEs	9****	7
Treatment-emergent laboratory abnormalities		
Grade 3	42	40
Grade 4	11	11

[1]All deaths in the ETR group were considered not or doubtfully related to ETR; [2]Occurring in at least 10% of patients in the ETR group; *p<0.0001 vs placebo; **p=0.3140 vs placebo; ***p=0.7204 vs placebo; ****p=0.3370 vs placebo, all Fisher's exact test

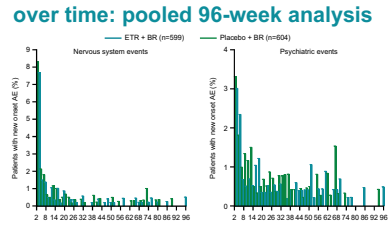
Rash (any type) overview: pooled 96-week analysis

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Any rash AE, %	**21***	**12**
Grade 1	12	8
Grade 2	10	4
Grade 3	1	0
Grade 4	0	0
Discontinuation due to rash, %	2	0
Median onset, days (range)	15 (1–666)	64 (1–660)
Median duration, days (range)	15 (1–672)	26 (1–687)

Percentages have been rounded to the nearest whole number; *p<0.0001 vs placebo, Fisher's exact test

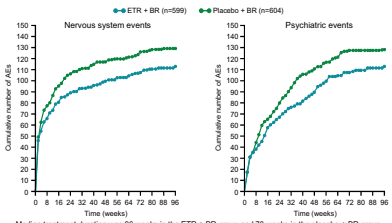
- Less than 1% of patients in both treatment groups experienced **new onset** rash between 48 and 96 weeks
- There were no new grade 3 or 4 rashes or discontinuations due to rash after Week 48
- One patient in the placebo group developed grade 4 vesicular rash in the first 48 weeks (Stevens-Johnson syndrome), thought to be related to an allergic reaction to trimethoprim/sulfamethoxazole
- There was a higher incidence of rash in females, compared with males, in the ETR + BR group (32% vs 19%, respectively), but similar severity. In the ETR + BR group, a higher proportion of females discontinued due to rash than males (5% vs 2%); no patients discontinued due to rash in the placebo + BR group
- History of NNRTI-related rash had no effect on the incidence of rash in either treatment group

Neuropsychiatric AEs incidence over time: pooled 96-week analysis



- The percentage of patients with new onset nervous system or psychiatric events between Weeks 48 and 96 was low and generally comparable between the treatment groups

Cumulative neuropsychiatric AEs: pooled 96-week analysis



- Median treatment duration was 96 weeks in the ETR + BR group and 70 weeks in the placebo + BR group

Summary of nervous system and psychiatric events: pooled 96-week analysis

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Any grade nervous system AE	**18.9***	**21.4**
Grade 3	0.3	1.0
Grade 4	0	0
Discontinuations due to nervous system events	0	0.5
Any grade psychiatric AE	**19.9****	**20.9**
Grade 3	0.3	1.5
Grade 4	0.2	0.2
Discontinuations due to psychiatric events	0.3	0.2

*p=0.3140 vs placebo; **p=0.7204 vs placebo, both Fisher's exact test

- There were no significant differences in the incidence of nervous system and psychiatric AEs between the treatment groups

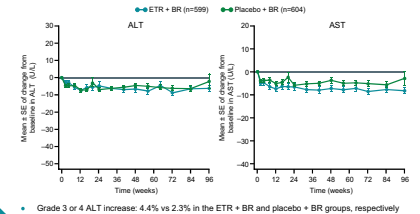
Most common* nervous system and psychiatric events: pooled 96-week analysis

AE, %	ETR + BR (n=599)	Placebo + BR (n=604)
Nervous system		
Headache	11.9	13.7
Dizziness	3.3	4.6
Somnolence	1.8	2.5
Psychiatric		
Insomnia	6.8	8.4
Depression	7.0	7.5
Anxiety	3.8	4.1
Sleep disorder	1.3	0.8

- There were no differences in the incidence of the most common nervous system and psychiatric AEs between the treatment groups
- Previous history of psychiatric AEs increased the incidence of nervous system and psychiatric AEs in both treatment groups, but there was no difference between ETR + BR and placebo + BR

*In >1% of patients in the ETR + BR group

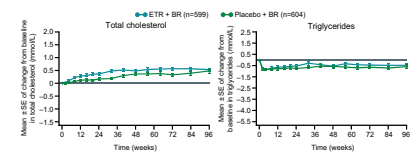
Mean change from baseline in ALT and AST: pooled 96-week analysis



- Grade 3 or 4 ALT increase: 4.4% vs 2.3% in the ETR + BR and placebo + BR groups, respectively
- Grade 3 or 4 AST increase: 3.9% vs 2.5% in the ETR + BR and placebo + BR groups, respectively

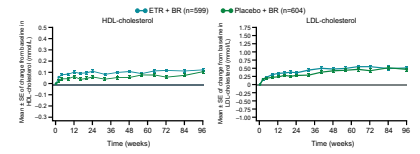
ALT = alanine aminotransferase; AST = aspartate aminotransferase; SE = standard error

Mean change from baseline in lipids: pooled 96-week analysis



Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Grade 3/4 laboratory abnormalities		
Total cholesterol	9.2	6.0
Triglycerides	11.3	7.0

Mean change from baseline in lipids: pooled 96-week analysis (cont'd)



Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Grade 3/4 laboratory abnormalities		
LDL-cholesterol	9.4	8.1

HDL = high density lipoprotein; LDL = low-density lipoprotein, calculated

Conclusions

- No new safety signals were identified between 48 and 96 weeks in either treatment group
- Less than 1% of patients in both treatment groups experienced new onset of rash between 48 and 96 weeks
- Discontinuation due to rash between 48 and 96 weeks remained low
- The incidence of nervous system, psychiatric and hepatic AEs was low and comparable between the ETR + BR and placebo + BR groups
  - the proportion of patients experiencing these AEs did not increase between 48 and 96 weeks
- Apart from rash, ETR + BR continues to demonstrate a safety and tolerability profile generally similar to placebo + BR in treatment-experienced, HIV-1-infected patients

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DUET-1
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DUET-2
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