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# Etravirine demonstrates a favourable safety and tolerability profile: pooled 96-week results from the Phase III DUET trials

PE7.3/5

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## Abstract

### Background
The next-generation NNRTI etravirine (ETR; TMC125) demonstrated superior efficacy versus placebo, and a tolerability profile generally similar to placebo, at Weeks 24 and 48 in treatment-experienced, HIV-1-infected patients enrolled in the Phase III DUET trials. We report Week 96 safety results from a prespecified pooled analysis of the DUET-1 and DUET-2 trials.

### Methods
Patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations were randomised to ETR 200mg or placebo bid, both with a background regimen (BR) of darunavir with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). Incidence and severity of adverse events (AEs) were recorded. To account for the difference in treatment duration, incidences were adjusted for total patient years of exposure.

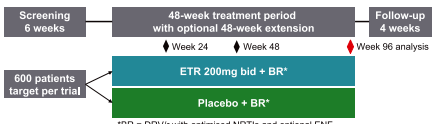
### Results
Five hundred and ninety-nine and 604 patients were randomised to ETR + BR and placebo + BR, respectively. Median treatment duration was 96 vs 70 weeks. The incidence of AEs with ETR + BR was generally comparable to placebo + BR, with the exception of rash. No significant increase in rash occurred from Week 48 to 96 and the incidence of nervous system, psychiatric, and hepatic AEs, and grade 3/4 lipid abnormalities was generally comparable between treatment groups. When adjusted for total patient years of exposure, the incidence of any AE, grade 3/4 AE, serious AE (SAE), AEs leading to discontinuation, death, nervous system and psychiatric AEs, hepatic AEs and lipid abnormalities was similar between the treatment groups.

| Parameter | Overall incidence, % | | Incidence adjusted for difference in exposure time, No. of patients/100 PYE | |
|---|---|---|---|---|
| | ETR + BR (n=599) | Placebo + BR (n=604) | ETR + BR (n=599) | Placebo + BR (n=604) |
| Any AE | 96.7 | 96.4 | 64.7 | 75.9 |
| Any grade 3 AE | 37.1 | 34.8 | 24.8 | 27.4 |
| Any grade 4 AE | 12.7 | 12.1 | 8.5 | 9.5 |
| Any SAE | 26.2 | 25.8 | 17.5 | 20.3 |
| AE leading to permanent discontinuation | 8.5 | 6.1 | 5.7 | 4.8 |
| Death | 3.2 | 3.6 | 2.1 | 2.9 |
| Any rash | 20.5* | 11.8 | 13.7 | 9.3 |
| Grade 1 rash | 12.2 | 7.9 | 8.1 | 6.3 |
| Grade 2 rash | 9.7 | 4.3 | 6.5 | 3.4 |
| Grade 3 rash | 1.3 | 0 | 0.9 | 0 |
| Grade 4 rash | 0 | 0 | 0 | 0 |
| Vesicular rash | 0 | 0.2 | 0 | 0.1 |
| Stevens-Johnson syndrome | 0 | 0.2‡ | 0 | 0.1 |
| Any nervous system event of interest | 18.9§ | 21.4 | 12.6 | 16.8 |
| Any psychiatric event of interest | 19.9¶ | 20.9 | 13.3 | 16.4 |
| Any hepatic event of interest | 8.7# | 7.1 | 5.8 | 5.6 |
| Grade 3 or 4 ALT elevation | 4.4 | 2.3 | 2.9 | 1.8 |
| Grade 3 or 4 AST elevation | 3.9 | 2.5 | 2.6 | 2.0 |
| Grade 3 or 4 lipid abnormalities | | | | |
| Triglycerides | 11.3 | 7.0 | 7.5 | 5.5 |
| Total cholesterol | 9.2 | 6.0 | 6.1 | 4.7 |
| LDL-cholesterol | 9.4 | 8.1 | 6.1 | 6.3 |

PYE = patient years of exposure; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDL = low-density lipoprotein;
*p<0.0001 vs placebo; ‡Grade 4, likely related to an allergic reaction to trimethoprim/sulfamethoxazole; §p=0.3140 vs placebo; ¶p=0.7204 vs placebo; #p=0.3370 vs placebo. All p values were determined by Fisher's exact test

### Conclusions
Consistent with previous results at 24 and 48 weeks, overall rates of AEs were similar between both arms, with the exception of rash which occurred more commonly with ETR treatment. The incidence of AEs adjusted for patient exposure was similar and often lower in the ETR + BR group than the placebo + BR group. Except for rash, ETR + BR demonstrates a tolerability profile similar to placebo over 96 weeks in the DUET trials.

## 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
- 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 |
| **Background regimen** | | |
| Used ENF (total), % | 45 | 47 |
| Used ENF *de novo*, % | 26 | 26 |
| Active background agents = 0*, % | 17 | 16 |
| Active background agents = 1*, % | 37 | 39 |
| **Hepatitis co-infection status** | | |
| Positive hepatitis B surface antigen, % | 7 | 6 |
| Known active HCV infection,‡ % | 6 | 6 |
| Active HBV and/or HCV co-infection,§ % | 13 | 12 |

*Assessed by phenotypic susceptibility score; †Determined based on hepatitis C antibody and hepatitis C RNA results; ‡Defined as having a positive hepatitis B surface antigen test and/or a known active HCV infection

ARVs = antiretrovirals
CDC = Centers for Disease Control and Prevention; HCV = hepatitis C virus; HBV = hepatitis B virus

## 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** | 97 | 96 |
| Grade 3 AE | 37 | 35 |
| Grade 4 AE | 13 | 12 |
| Discontinuation due to AEs | 9 | 6 |
| SAEs | 26 | 26 |
| Death (any cause)* | 3 | 4 |
| **Most common AEs†** | | |
| 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 |

*All deaths in the ETR group were considered not or doubtfully related to ETR; †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

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

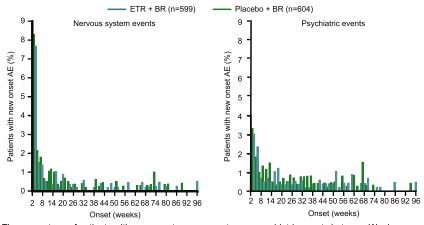
## Rash (any type) overview: pooled 96-week analysis

| 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 (range) onset, days | 15 (1–666) | 64 (1–660) |
| Median (range) duration, days | 15 (1–672) | 19 (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 group (32% vs 19%, respectively; p=0.0290), but similar severity
- History of NNRTI-related rash had no effect on the incidence of rash in either treatment group
- No relationship was evident between baseline CD4 cell count and incidence of rash

## 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

Nervous system and psychiatric events were selected based on the type of AEs commonly reported with other NNRTIs, particularly EFV, and were classified based on the MedDRA system order classes 'nervous system disorders' and 'psychiatric disorders'

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

| Parameter, % | ETR + BR (n=599) | Placebo + BR (n=604) |
|---|---|---|
| **Any 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 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** | | |
| Depression | 7.0 | 7.5 |
| Insomnia | 6.8 | 8.4 |
| 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 psychiatric history 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 group

## Summary of hepatic AEs: pooled 96-week analysis

| Parameter,* % | ETR + BR (n=599) | Placebo + BR (n=604) |
|---|---|---|
| Any hepatic AE | 8.7 | 7.1 |
| Any grade 3 or 4 hepatic AE | 4.2 | 3.0 |
| Grade 3 or 4 hyperbilirubinaemia | 2.0 | 0.7 |
| Permanent discontinuation due to hepatic AEs | 1.3 | 0.7 |

*All comparisons between ETR and placebo were non-significant (except for grade 3 or 4 hyperbilirubinaemia, where p=0.0468). Concomitant treatment with Cytochrome P450 3A4 inducers, inhibitors (except clarithromycin) and substrates with a small therapeutic index was prohibited during the trials

- No hepatic-related deaths were reported

The term hepatic AE includes all AEs reported under the MedDRA system order class 'hepatobiliary disorders' as well as AEs listed in other system order classes with laboratory components (e.g. transaminase elevations)

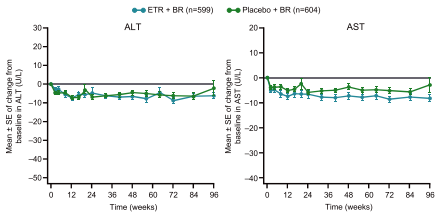
## Most common* hepatobiliary AEs: pooled 96-week analysis

| Hepatobiliary AEs, % | ETR + BR (n=599) | Placebo + BR (n=604) |
|---|---|---|
| Hepatomegaly | 1.0 | 1.0 |
| Jaundice | 1.0 | <1.0 |
| Cholecystitis | 1.0 | <1.0 |
| Hepatic steatosis | 1.0 | <1.0 |
| Cytolytic hepatitis | <1.0 | <1.0 |
| Hepatosplenomegaly | <1.0 | <1.0 |
| Hepatic failure | <1.0 | 0.0 |

- The incidence of hepatobiliary AEs was low and comparable between treatment groups

*Irrespective of grade and reported in >1 patient in the ETR group
Analysis does not include laboratory abnormalities reported as AEs

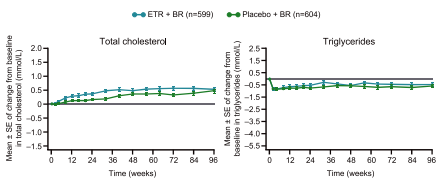
## Mean change from baseline in ALT and AST: pooled 96-week analysis




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

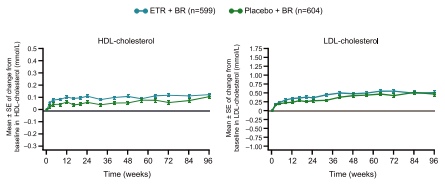
SE = standard error; U/L = units per litre

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




- Grade 3 or 4 total cholesterol increase: 9.2% vs 6.0% in the ETR and placebo groups, respectively
- Grade 3 or 4 triglycerides increase: 11.3% vs 7.0% in the ETR and placebo groups, respectively

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




- Grade 3 or 4 LDL-cholesterol increase: 9.4% vs 8.1% in the ETR and placebo groups, respectively

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

## Incidences adjusted for difference in treatment exposure: pooled 96-week analysis

- These analyses were performed to account for the differences in treatment duration
  - median treatment duration longer in the ETR group than the placebo group (96.0 vs 69.6 weeks, respectively)
  - total exposure was higher in the ETR group than the placebo group (695.4 vs 766.7 patient-years, respectively)

| Parameter | Number of patients/100 patient years of exposure | |
|---|---|---|
| | ETR + BR (n=599) | Placebo + BR (n=604) |
| **Any AE** | **64.7** | **75.9** |
| Grade 3 AE | 24.8 | 27.4 |
| Grade 4 AE | 8.5 | 9.5 |
| Discontinuation due to AEs | 5.7 | 4.8 |
| Serious AEs | 17.5 | 20.3 |
| Death | 2.1 | 2.9 |
| **Dermatological AEs** | | |
| Rash (any type)* | 13.7 | 9.3 |
| Grade 1 | 8.1 | 6.3 |
| Grade 2 | 6.5 | 3.4 |
| Grade 3 | 0.9 | 0 |
| Grade 4 | 0 | 0 |
| Vesicular rash | 0 | 0.1 |
| Stevens-Johnson syndrome | 0 | 0.1 |
| **AEs of interest** | | |
| Nervous system disorders | 12.6 | 16.8 |
| Psychiatric disorders | 13.3 | 16.4 |
| Hepatic AEs | 5.8 | 5.6 |
| **Grade 3 or 4 treatment-emergent laboratory abnormalities** | | |
| ALT elevation | 2.9 | 1.8 |
| AST elevation | 2.6 | 2.0 |
| Triglycerides | 7.5 | 5.5 |
| Total cholesterol | 6.1 | 4.7 |
| LDL-cholesterol | 6.1 | 6.3 |

*Relative risk (95% confidence interval [CI]) = 1.48 (1.02–1.95)

## Conclusions

- Consistent with previous results at 24 and 48 weeks, the incidence of AEs was similar in both treatment groups, with the exception of rash, which occurred more commonly in the ETR group
  - no safety signals were associated with longer treatment with ETR and there were no unexpected safety concerns between Weeks 48 and 96
  - <1% of patients in both groups experienced new onset of rash between 48 and 96 weeks and there were no new discontinuations after Week 48
- The incidence of nervous system, psychiatric and hepatic AEs was low and comparable between the ETR and placebo groups
- The incidence of laboratory abnormalities, including lipid abnormalities, was low and similar in the two groups
- The incidence of AEs adjusted for patient exposure was similar and often lower in the ETR group than the placebo group
- Apart from rash, ETR demonstrates a tolerability profile generally similar to placebo in treatment-experienced, HIV-1-infected patients over 96 weeks

## Acknowledgements and disclosures

- We express our gratitude to the patients who participated in the studies, as well as the study centre staff, data safety and monitoring board, members of the cardiac events/death adjudication panel (Jens Lundgren [chair], Christian Funck-Brentano, Annette Sjøl), members of the clinical events/death adjudication panel (Joe Eron, Peter Reiss, Melanie Thompson and Rainer Weber), 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, JV Madruga, 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, C Katlama, 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 Wilkin, T Wills, M Wohlfeiler, K Workowski

**DUET-2**
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- Editorial support was provided by Karen Runcie of Gardiner-Caldwell Communications, Macclesfield, UK; this support was funded by Tibotec
- PMG has participated as an expert or speaker for Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Tibotec; BG has served as an investigator for, and received research support from, Janssen Pharmaceutica Inc, Merck & Company, Inc. Schering-Plough Corporation; AR has no conflicts of interest; SN and JW are full-time employees of Tibotec

Presented at the 12th European AIDS Conference, Cologne, Germany, 11–14 November 2009.

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