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Clinical endpoints reduced through etravirine use in treatment-experienced, HIV-1-infected patients: pooled 96-week results from the Phase III DUET trials

MOPEB043

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Abstract

Background
Etravirine (ETR; TMC125) showed durable efficacy/safety in the Phase III DUET trials. Pooled 48-week results from DUET showed a significant reduction in adjudicated AIDS-defining illness and/or death (ADI/D) in patients receiving ETR versus placebo. We present pooled Week 96 adjudicated ADI/D results.

Methods
Treatment-experienced patients with documented NNRTI and protease inhibitor (PI) resistance were randomised 1:1 to receive ETR 200mg or placebo, both bid following a meal, plus a background regimen (BR) of darunavir (DRV) with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). ADI/D was adjudicated prior to database lock by an independent four-member panel blinded to study treatment. Analysis outcome 'per 100 patient years' was performed to account for the differences in treatment duration.

Results
Five hundred and ninety-nine and 604 patients received ETR + BR or placebo + BR, respectively with median treatment duration of 96.0/69.6 weeks, respectively. Overall, 57% of ETR patients and 36% of placebo patients achieved viral load <50 copies/mL (time-to-loss of virological response [TLOVR]) at Week 96. Adjudicated clinical endpoints are shown.

Classification	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration, median, weeks	96.0	69.6
Any confirmed or probable ADI/D, %	8.2	10.9
Any confirmed or probable ADI, %	5.8	9.4
Death, %	3.2	3.8
Number of patients with any confirmed or probable ADI/D per 100 patient years*	5.37	8.37
Relative risk (95% CI) ETR versus placebo	0.64 (0.39–0.89)	

*Calculated to account for the differences in treatment duration; CI = confidence interval

In both ETR and placebo groups since the previous analysis at Week 48, the number of patients adjudicated with new ADIs was low (ETR; placebo): herpes zoster multi-dermatomal (3; 3), herpes simplex (3; 0); Hodgkin's disease (2; 0); oesophageal candidiasis (1; 1); diffuse large B-cell lymphoma (1; 0); Kaposi's sarcoma (1; 0); cytomegalovirus gastritis (0; 1); pneumonia (0; 1); pulmonary aspergillosis (0; 1).

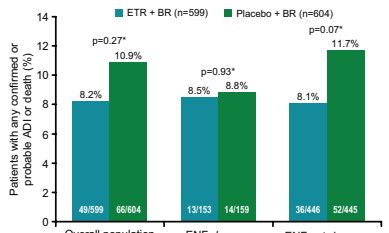
Conclusions
In addition to improving virological endpoints, ETR demonstrated reductions in ADI/D versus placebo through 96 weeks of treatment. In both treatment groups, few patients had new adjudicated ADIs between Weeks 48 and 96.

Assessment of clinical endpoints

- Clinical endpoints (ADIs and deaths) were identified using methods described in the ESPRIT[1] and SMART[2] trials
- ADIs were identified using reported adverse event (AE) terms appearing as CDC category C illnesses*
- ADIs were adjudicated prior to database lock by an independent expert panel blinded to treatment allocation
  - only events adjudicated as confirmed or probable category C events were considered as ADIs
  - analysis outcome 'per 100 patient years' was performed to account for differences in treatment duration
- Primary analysis: all confirmed or probable ADIs or deaths
- At the time of this analysis, all patients had been treated for ≥96 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*])

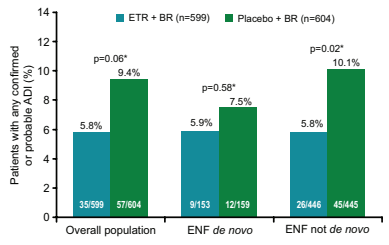
[1]Emery S, et al. Control Clin Trials 2002;23:198–220; [2]SMART Study Group. N Engl J Med 2006;355:2283–96
*From the 1993 revised classification system for HIV issued by the US CDC; ITT = intent-to-treat

Proportion of patients with any clinical endpoint: pooled 96-week analysis



*p values derived from logistic regression model with factors treatment (ETR or placebo), trial (DUET-1 or DUET-2), baseline viral load, ENF use (*de novo* or not *de novo*) and interaction between treatment and ENF use

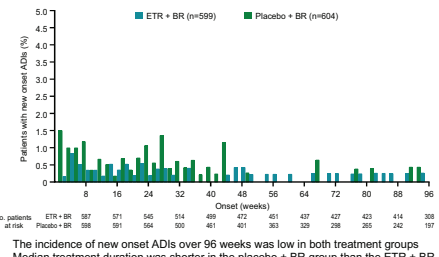
Proportion of patients with any confirmed or probable ADI: pooled 96-week analysis



- ETR + BR significantly reduced the incidence of any confirmed or probable ADI versus placebo + BR in the ENF not de-novo population

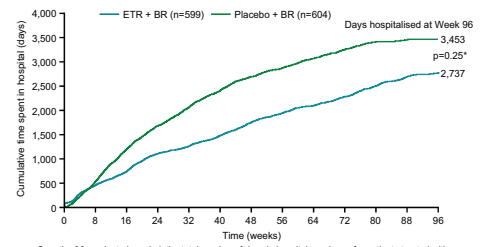
*p values derived from logistic regression model with factors treatment (ETR or placebo), trial (DUET-1 or DUET-2), baseline viral load, ENF use (*de novo* or not *de novo*) and interaction between treatment and ENF use

Incidence of new onset ADIs over time: pooled 96-week analysis



- The incidence of new onset ADIs over 96 weeks was low in both treatment groups
- Median treatment duration was shorter in the placebo + BR group than the ETR + BR group (69.6 vs 96.0 weeks, respectively)

Cumulative days in hospital over 96 weeks



- Over the 96-week study period, the total number of days in hospital was lower for patients treated with ETR + BR than placebo + BR
  - the median duration of hospitalisation per patient was lower in the ETR + BR group than in the placebo + BR group (10 vs 11 days, respectively)

*p value derived from t-test

Analyses per 100 patient years: pooled 96-week analysis

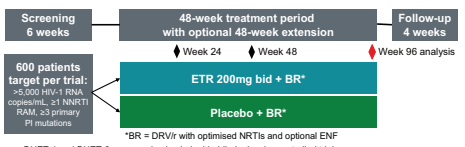
	ETR + BR (n=599)	Placebo + BR (n=604)	Relative risk (95% CI)
Number of patients with any confirmed or probable ADI/D per 100 patient-years of exposure			
Overall population	5.37	8.37	0.64 (0.39–0.89)
ENF de-novo population	5.21	5.76	0.90 (0.19–1.62)
ENF not de-novo population	5.43	9.53	0.57 (0.32–0.82)
Number of patients with hospitalisation per 100 patient-years of exposure			
Overall population	16.3	20.6	0.79 (0.59–0.99)
ENF de-novo population	11.9	20.3	0.58 (0.29–0.88)
ENF not de-novo population	18.0	20.8	0.87 (0.61–1.12)

- These analyses were performed to account for the differences in treatment duration
  - median treatment duration: 96.0 weeks vs 69.6 weeks in the ETR + BR and placebo + BR groups, respectively
- ETR + BR reduced the incidence of ADI or death versus placebo + BR in the overall and ENF not de-novo populations
- ETR + BR reduced the number of patients hospitalised versus placebo + BR in the overall and ENF de-novo populations

Conclusions

- ETR + BR reduced the incidence of any confirmed or probable ADI versus placebo in the ENF not de-novo population, with a trend towards reduction in the overall group (p=0.06)
- In both treatment groups, the incidence of new ADIs between Weeks 48 and 96 was low
- The time to a new ADI or death was significantly prolonged for patients receiving ETR + BR compared with placebo + BR
- Fewer cumulative days in hospital occurred in patients receiving ETR + BR than in the placebo + BR group

DUET study design



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

- DUET-1 and DUET-2 were randomised, double-blind, placebo-controlled trials
- Patients from either treatment arm experiencing virological failure or rebound at Week 24, or not responding to treatment after at least 48 weeks, had the opportunity to enrol in a separate open-label, rollover trial (TMC125-C217)
- Patients deriving clinical benefit after 48 weeks of treatment were eligible to enter the optional 48-week extension phase
- 2% of randomised patients completed the trial at Week 48 and elected not to continue into the open-label extension phase
- Initially, the optional extension continued in a blinded fashion, but only until the database for the 48-week analysis was locked
- Pooled analysis was pre-specified

RAM = resistance-associated mutation

New cases of confirmed or probable ADIs reported between 48- and 96-week analysis

New confirmed or probable ADI, n	ETR + BR (n=599)	Placebo + BR (n=604)
Any confirmed or probable ADI	8	6
Herpes zoster multi-dermatomal	3	3
Herpes simplex	3	0
Hodgkin's disease	2	0
Oesophageal candidiasis	1	1
Diffuse large B-cell lymphoma	1	0
Kaposi's sarcoma	1	0
Cytomegalovirus gastritis	0	1
Pneumonia	0	1
Pulmonary aspergillosis	0	1

Individual patients may have experienced more than one ADI between 48 and 96 weeks

- The incidence of specific new onset ADIs since the Week 48 analysis was low in both treatment groups

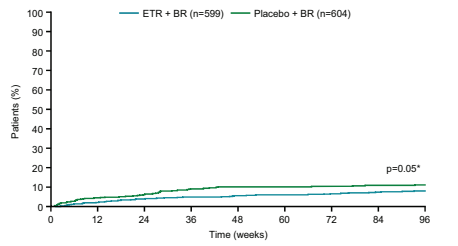
Treatment duration, baseline characteristics and background ARVs

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration, median, weeks	**96.0**	**69.6**
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 *de novo*, %	26	26
Active background agents = 0,§ %	17	16
Active background agents = 1,§ %	37	39

*ETR RAMs are defined as those associated with a decreased virological response to ETR at Week 24 in the DUET trials and if present in at least five patients at baseline; †From extended NNRTI RAM list (Tambuyzer L, et al. Antiviral Ther 2009;14:103–9); §Assessed by PSS (Antivirogram®)

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

Time to first clinical endpoint: pooled 96-week analysis



- Time to first confirmed or probable ADI or death was significantly prolonged in the ETR + BR group compared with the placebo + BR group

*p value derived from log-rank test

Acknowledgements

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DUET-1
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DUET-2
Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, B Trottier, CM Tsoukas, S Walmsley; **France:** C Arvieux, L Cotte, JF Delfraissy, C Katlama, PM Girard, B Marchou, A Rachlis, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arasteh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, B Clotet, G Garcia, JM Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, M Johnson, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, T Campbell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, RN Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch, W Towner

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