

Clinical endpoints reduced through etravirine use 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) 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

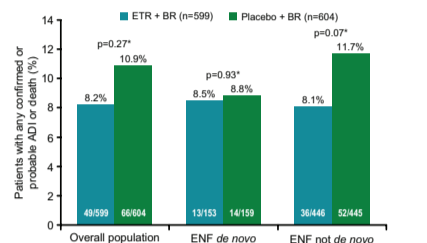
In addition to improving virological endpoints, ETR demonstrated reductions in ADI/D versus placebo through 96 weeks of treatment. In both treatment groups, few patients had new adjudicated ADIs between Weeks 48 and 96.

Assessment of clinical endpoints

- Clinical endpoints (ADIs and deaths) were identified using methods described in the ESPRIT¹ and SMART² trials
- ADIs were identified using reported adverse event (AE) terms appearing as CDC category C illnesses³
- 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])

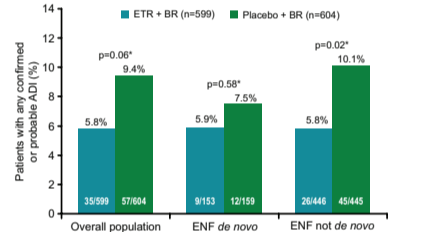
¹Emery S, et al. *Control Clin Trials* 2002;23:198–220; ²SMART Study Group. *N Engl J Med* 2006;356:2283–96; ³From the 1993 revised classification system for HIV issued by the US CDC; ITT = intent-to-treat

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

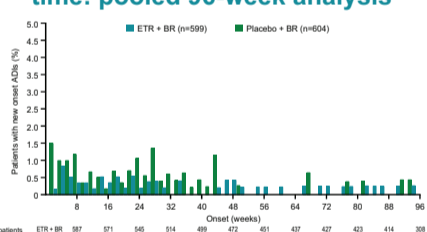
Proportion of patients with any confirmed or probable ADI: pooled 96-week analysis



* 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)

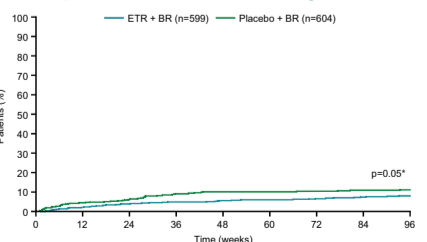
New cases of confirmed or probable ADIs reported between 48- and 96-week analysis

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

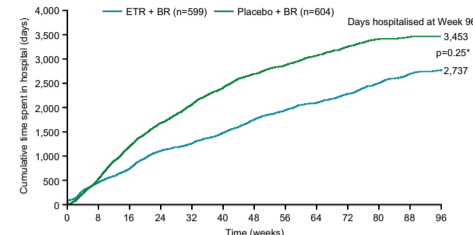
Time to first clinical endpoint: pooled 96-week analysis



* 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

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

Acknowledgements

● We express our gratitude to the patients who participated in the studies, as well as the study centre staff, the data safety and monitoring board, clinical event adjudication panels, Virco, Tibotec personnel and the following principal investigators

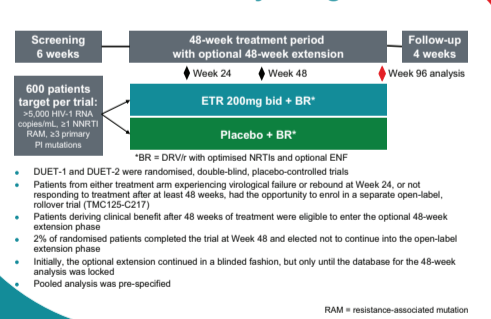
DUET-1

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DUET-2

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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

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/mm ³ , 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	66
DRV, %	4	5
Deletable 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 = 0.1, %	17	16
Active background agents = 1.1, %	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 (Tambyezzer L, et al. *Antiviral Ther* 2008;14:103–9); ‡Assessed by PSS (Antivirogram)

ARVs = antiretrovirals

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