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Virological response with fully active etravirine after 48 weeks of treatment: pooled results from the DUET-1 and DUET-2 trials

P023

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Abstract

The NNRTI etravirine (ETR; TMC125) has demonstrated durable antiviral activity and favourable tolerability in treatment-experienced patients in the Phase III DUET trials. We report Week 48 virological response in the subgroup of patients who were fully sensitive to ETR, analysed according to enfuvirtide (ENF) use and number of active background agents. HIV-1-infected, treatment-experienced patients with documented NNRTI-resistance, ≥3 primary protease inhibitor (PI) mutations and viral load >5,000 copies/mL were randomised 1:1 to receive ETR 200mg bid or placebo following a meal plus a background regimen (BR) of darunavir (DRV) with low-dose ritonavir (DRV/r), NRTI(s) and optional ENF. The current analysis included all patients who were fully sensitive to ETR. Phenotypic Sensitivity Score (PSS; Antivirogram®) was used to determine the number of active background agents; ETR was considered active if the fold-change in 50% effective concentration (FC) was ≤3; DRV if FC ≤10; NRTIs if FC was < cut-off defined on Antivirogram® and ENF if used *de novo*. The pooled analysis was pre-specified.

In total, 599 and 604 patients received ETR + BR and placebo + BR, respectively. Baseline demographics and characteristics were similar between treatment groups, with a median viral load of 4.8 $\log_{10}$ copies/mL in both treatment groups and CD4 cell counts of 99 vs 109 cells/mm³ in the ETR and placebo groups, respectively. After 48 weeks of treatment, 61% of patients receiving ETR + BR in the overall population achieved a confirmed virological response (<50 copies/mL) vs 40% in the placebo group (p<0.0001). Virological response by PSS (0, 1 and ≥2 active antiretrovirals [ARVs]) in patients fully sensitive to ETR according to ENF use (*de novo* or not *de novo*) is presented in the table. In the overall and the ENF not de-novo subgroups, virological response increased with increasing number of active agents in the BR. The difference between the treatment groups was most apparent in patients who had no active background agents.

Number of fully active background ARVs*	Viral load <50 copies/mL at Week 48, % (n) ETR + BR	Placebo + BR	p value
Overall	**n=355**	**n=357**	
0	56 (31/55)[‡]	8 (4/51)	<0.0001
1	71 (93/131)	37 (47/127)	<0.0001
≥2	82 (139/169)	68 (122/179)	0.0004
ENF *de novo*	**n=88**	**n=95**	
1	91 (21/23)	41 (9/22)	<0.0001
≥2	83 (54/65)	71 (52/73)	0.0867
ENF not *de novo* [§]	**n=267**	**n=262**	
0	56 (31/55)	8 (4/51)	<0.0001
1	67 (72/108)	36 (38/105)	<0.0001
≥2	82 (85/104)	66 (70/106)	0.0011

*Excluding ETR; [‡]Values in parentheses are number of patients with 0, 1 or ≥2 ARVs with an undetectable viral load over the total number of patients in each ARV category; [§]Includes patients reusing or not using ENF

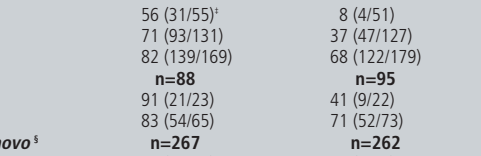
In patients with virus fully sensitive to ETR, the virological response was higher in the ETR + BR group than in the placebo + BR group, irrespective of ENF use or number of active background agents. These results complement current guidelines, which recommend a minimum of two active agents in any treatment regimen.

Data has been updated since abstract submission.

Introduction

- ETR is a next-generation NNRTI recently approved for use in treatment-experienced, HIV-1-infected patients
- ETR + BR showed significant antiretroviral benefit versus placebo + BR in two Phase III trials (DUET-1 and DUET-2)[1,2]
- This pooled DUET analysis assessed virological response after 48 weeks of treatment with ETR + BR or placebo + BR in the subgroup of patients who were fully sensitive to ETR
  - results were analysed according to ENF use and number of active agents in the BR

DUET study design and major inclusion criteria



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

- Plasma viral load >5,000 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 prespecified

RAM = resistance-associated mutation

DUET 48-week pooled analysis: baseline characteristics

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration at time of analysis (weeks)	52.3	51.0
Patient demographics		
Male, %	90	89
Caucasian, %	70	70
Age, years (range)	46 (18–77)	45 (18–72)
Disease characteristics		
Viral load, $\log_{10}$ copies/mL, median (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
Viral load >100,000 copies/mL, %	38	36
CD4 cell count, cells/mm³, median (range)	99 (1.0–789)	109 (0.0–912)
CD4 cells <50 cells/mm³, %	36	35
CDC category C, %	58	59
Prior ARV use		
10–15 ARVs, %	66	65
DRV/r, %	4	5

- Baseline characteristics were well balanced across treatment groups

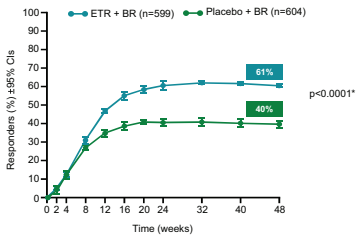
CDC = Centers for Disease Control and Prevention

DUET 48-week pooled analysis: background ARVs

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Number of active background agents (PSS)*		
0	17	16
1	36	39
2	27	28
3	16	13
4	4	4
5	0	<1
Number of NRTIs[‡] used in BR		
0	<1	0
1	3	3
2	44	49
3	45	42
4	7	6
5	<1	0
ENF use in BR		
ENF *de novo*	26	26
ENF re-used	20	20
ENF not used	55	53

*PSS determined by Antivirogram®
[‡]Most commonly used NRTIs (in 30% of ETR and placebo patients) were tenofovir, lamivudine and zidovudine

Virological response (viral load <50 copies/mL) at Week 48 (ITT-TLOVR)



- 61% of patients in the ETR group achieved a confirmed undetectable viral load (<50 copies/mL) at Week 48 compared with 40% in the placebo group (p<0.0001)

ITT = intent-to-treat; TLOVR = time-to-loss of virological response
CI = confidence interval; *Logistic regression model

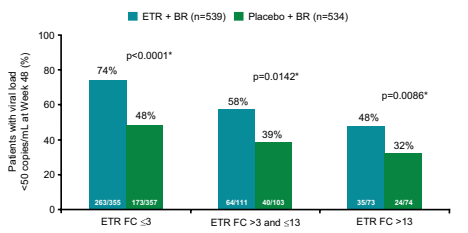
Analysis of impact of ETR activity on virological response

- The current analysis assessed the impact of ETR activity on virological response and included all patients who were fully sensitive to ETR (i.e. ETR FC ≤3)
  - analyses were carried out on the non-VF excluded population (i.e. patients who discontinued for reasons other than VF were excluded)
  - 65% of patients were fully sensitive to ETR and response in these patients was analysed according to ENF use and number of active background agents
- PSS was used to determine the number of active background ARVs; ARVs were considered active as highlighted below

ARV	Definition of active
ETR	FC ≤3
DRV	FC ≤10
NRTIs	FC < cut-off defined on Antivirogram®
ENF	Used *de novo*

VF = virological failure

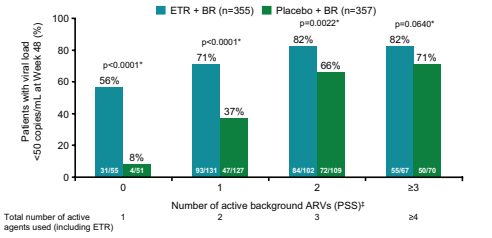
Virological response at Week 48 by ETR FC at baseline



- Virological response decreased with increasing ETR FC, but in all three ETR FC categories, ETR + BR produced a greater virological response than placebo + BR

*p values vs placebo using logistic regression modelling
Analysis excludes patients who discontinued for reasons other than VF

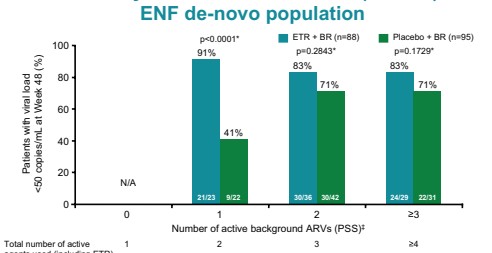
Virological response by baseline PSS with fully active ETR at Week 48 (TLOVR): overall population



- ETR + BR provides higher response rates than placebo + BR, irrespective of the number of active agents in the BR

Fully active ETR = patients with ETR FC ≤3; ETR was not included in the PSS calculation
Analysis excludes patients who discontinued for reasons other than VF
*Logistic regression; [‡]According to Antivirogram®

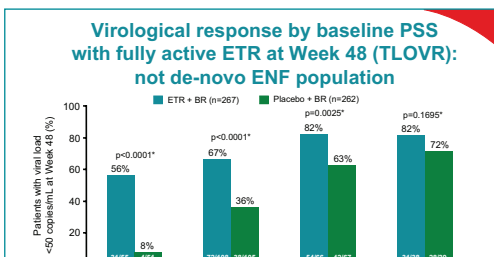
Virological response by baseline PSS with fully active ETR at Week 48 (TLOVR): ENF de-novo population



- Consistent with findings in the overall population, in the ENF de-novo subgroup, ETR + BR provides higher response rates than placebo + BR, irrespective of the number of active agents in the BR; responses to ETR were greatest with one active ARV in the BR

Fully active ETR = patients with ETR FC ≤3; ETR was not included in the PSS calculation
Analysis excludes patients who discontinued for reasons other than VF
*Logistic regression; [‡]According to Antivirogram®; N/A = not applicable

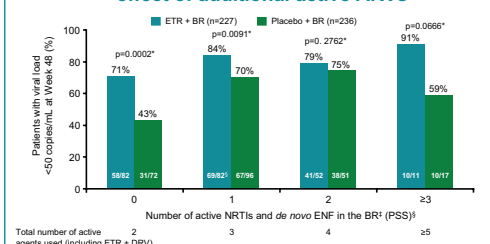
Virological response by baseline PSS with fully active ETR at Week 48 (TLOVR): ENF de-novo population



- Consistent with findings in the overall population, in the ENF not de-novo subgroup, ETR + BR provides higher response rates than placebo + BR, irrespective of the number of active agents in the BR; responses were greatest with two or more active ARVs in the BR

Fully active ETR = patients with ETR FC ≤3; ETR was not included in the PSS calculation
Analysis excludes patients who discontinued for reasons other than VF and includes patients re-using or not using ENF; *Logistic regression; [‡]According to Antivirogram®

Virological response at Week 48 (TLOVR) with fully active ETR and fully active DRV: effect of additional active ARVs



Fully active ETR = patients with ETR FC ≤3; DRV = patients with DRV FC ≤10; ETR and DRV were not included in the PSS calculation; Analysis excludes patients who discontinued for reasons other than VF
*Logistic regression; [‡]56/82 patients had an NRTI and 26/82 ENF as their additional active ARV
[§]According to Antivirogram®

Conclusions

- In the 48-week pooled DUET analysis, ETR + BR achieved a significantly greater virological response than placebo + BR (p<0.0001)
- Higher virological responses were achieved with ETR + BR than with placebo + BR irrespective of number of active agents in the BR, ENF use, or across different ETR FC values
- In patients with virus fully sensitive to ETR (i.e. ETR FC ≤3), virological response was higher in the ETR + BR group irrespective of ENF use or number of active ARVs in the BR
  - difference in virological response was most significant in the subgroup of patients with no active background ARVs
  - 71–91% of patients (depending on the number of additional background active agents) using active ETR and a BR including fully active DRV achieved viral suppression <50 copies/mL
- These results complement current HIV treatment guidelines which recommend the use of at least two active ARVs in a treatment regimen

References

1. Trottier B, et al. CAHR 2008. Poster P167.
2. De Smedt G, et al. ISHEID 2008. PS1/5.

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DUET-1

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DUET-2

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