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Durability of virologic response to etravirine is not affected by time to reach virologic response

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Abstract

Background

Etravirine (ETR; TMC125), a next-generation NNRTI provided durable and statistically superior efficacy versus placebo over 48 weeks in treatment-experienced patients in the DUET trials. This pooled DUET analysis investigates whether time to reach virologic response impacts durability of response.

Methods

The primary endpoint was the percentage of patients with viral load <50 copies/mL (time-to-loss of virologic response [TLOVR] analysis). The intent-to-treat (ITT) population included all patients; the as treated population excluded patients who discontinued for non-virologic reasons.

Results

Five hundred and ninety-nine and 604 patients received ETR and placebo, respectively. Baseline characteristics were comparable between treatment groups with regards to median baseline viral load (4.8 log_{10} copies/mL each), CD4 cell count (99 vs 109 cells/mm^3), overall enfuvirtide (ENF) use (45.4 vs 46.7%), darunavir (DRV) and NRTI sensitivity, and median number of sensitive antiretrovirals (ARVs) at baseline. At Weeks 12, 24 and 48, virologic response (viral load <50 copies/mL) in ETR-treated patients was 47%, 61% and 61%, respectively. The number of responders at Week 48 by the first timepoint on which virologic response was seen is presented below.

Population	First virologic response by Week 12 (ETR)		First virologic response between Weeks 12 and 24 (ETR)		No virologic response by Week 24 (ETR)	
	ITT (n=281)	As treated (n=273)	ITT (n=104)	As treated (n=102)	ITT (n=214)	As treated (n=165)
Responders at Week 48 (<50 copies/mL), n (%)						
	245 (87)	245 (90)	89 (86)	89 (87)	29 (14)	29 (18)

In the ETR group, early responders generally had lower baseline viral load (median 4.6 log_{10} copies/mL) and higher CD4 cell count (median 152 cells/mm^3) than late responders (median viral load: 5.0 log_{10} copies/mL; CD4 cell count: 127 cells/mm^3).

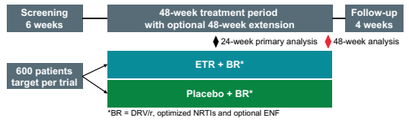
Conclusion

Durable, high virologic response rates were observed up to Week 48 in ETR-treated patients. Virologic response at Week 12 does not fully predict response at Week 48; full suppression of HIV RNA by Week 48 can occur in patients who have not yet suppressed viral load at Week 12.

Introduction

- ETR is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1[1,2]
- Two phase III trials (DUET-1 and DUET-2) demonstrated significant antiretroviral benefit after 48 weeks of treatment with ETR + background regimen (BR) in treatment-experienced patients with NNRTI resistance.[3,4] Aside from a higher incidence of rash, patients treated with ETR + BR had a safety and tolerability profile similar to placebo + BR[3,4]
- This pooled DUET analysis assessed whether time to reach virologic response affected durability of response to ETR

DUET study design and major inclusion criteria



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

- Plasma viral load >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historic genotype
- ≥3 primary PI mutations at screening
- DUET-1 and DUET-2 differ only in geographic 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

DRV/r = DRV with low-dose ritonavir
RAM = resistance-associated mutation; PI = protease inhibitor

Baseline demographics and background ARVs

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Gender		
Male	90	89
Race		
Caucasian	70	70
Black	13	13
Hispanic	11	12
Prior ARV use		
Number of ARVs previously taken (median)	12	13
DRV/r	4	5

Baseline demographics and background ARVs (cont'd)

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Detectable mutations		
≥2 NNRTI RAMs*	70	70
≥3 primary PI RAMs‡	97	97
BR		
Used ENF (total)	45	47
Reused ENF	20	20
Used ENF *de novo*	26	26
ENF not used	55	53
Active background agents (PSS) = 0	17	16
Active background agents (PSS) = 1	36	39

*From extended NNRTI RAM list (Tambuyzer L, et al. EHDRW 2007. Abstract 67); ‡From Johnson M, et al. Top HIV Med 2005;13:125–31

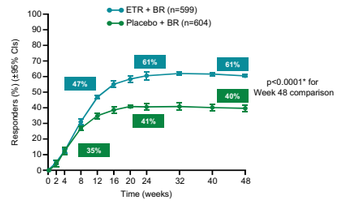
Phenotypic sensitivity score (PSS) was determined by Antivirogram®

Baseline disease characteristics

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Disease characteristics		
Duration of HIV infection, years, median (range)	14 (2.5–25.4)	14 (4.6–26.2)
CDC category C, %	58	59
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)
CD4 cell count category (cells/mm^3)		
<50, %	36	35
50–199, %	35	34
200–349, %	20	21
≥350, %	10	10
Hepatitis B/C co-infection		
Positive, %	13	12

CDC = Centers for Disease Control and Prevention

Patients achieving virologic response (<50 copies/mL) at Weeks 12, 24 and 48 (ITT-TLOVR)



- Durable and significant (versus placebo) responses were observed in the ETR group over the 48 weeks of treatment, regardless of the time it took to achieve <50 copies/mL

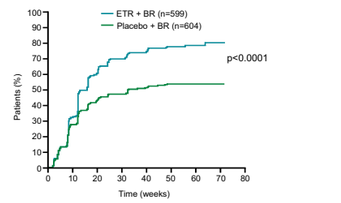
*Logistic regression model; CI = confidence interval

Virologic response (<50 copies/mL) at Week 48 (ITT-TLOVR)

Viral load at Week 24 (n, ETR, placebo)	Viral load at Week 48	ETR + BR (n=599), %	Placebo + BR (n=604), %
<50 copies/mL (n=363, 246)	<50	92	89
	50–<400	5	6
	≥400	3	6
50–<400 copies/mL (n=83, 67)	<50	35	31
	50–<400	53	45
	≥400	12	24
≥400 copies/mL (n=153, 291)	<50	0	<1
	50–<400	3	1
	≥400	97	99

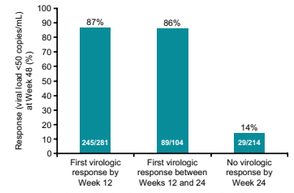
- The majority of patients achieving undetectability (<50 copies/mL) at Week 24 maintained this response to Week 48
- Some patients with a viral load of 50–<400 at Week 24, displayed an improved virologic response at Week 48, while the majority of patients with viral load ≥400 at Week 24 had a similar response at Week 48

Time to confirmed virologic response (<50 copies/mL) in overall population



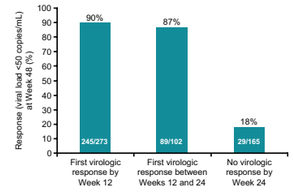
- Patients in the ETR group achieved virologic response earlier than patients in the placebo group
  - median time to virologic response was 15.7 and 32.7 weeks in the ETR and placebo groups, respectively

Undetectability at Week 48 by time to first virologic response (<50 copies/mL) (ETR group, ITT population)



- A high proportion of patients achieving virologic response in the first 12 weeks of treatment maintained this response out to 48 weeks
- Similarly, the majority of patients achieving virologic response between 12 and 24 weeks displayed a durable response

Undetectability at Week 48 by time to first virologic response (<50 copies/mL) (ETR group, as-treated population*)



- Consistent with the ITT analysis, the analysis on the as-treated population showed that patients achieving virologic response over the first 24 weeks of treatment maintained this response at Week 48

*Excludes patients who discontinued for non-virologic reasons

Effect of baseline characteristics on time to first virologic response (<50 copies/mL)

Baseline characteristic by time to first virologic response	Time of first response: <50 copies/mL at Week 12 (N=281)	<50 copies/mL at Week 24 (N=104)	No response at Week 24 (N=214)
Baseline viral load, median (range)	4.6 (2.7–6.3)	5.0 (3.5–6.2)	5.1 (3.0–6.8)
Baseline CD4 cell count, median (range)	152 (1–744)	127 (5–760)	32 (1–789)
Use of ENF in BR, % (n)*			
De-novo use	27 (75)	30 (31)	22 (47)
Re-use	17 (48)	20 (21)	23 (50)
Not used	56 (158)	50 (52)	55 (117)
Use of active NRTIs in BR, % (n)*			
0	50 (141)	45 (46)	64 (135)
1	31 (87)	32 (33)	25 (53)
≥2	18 (53)	23 (24)	11 (24)

- In the ETR group, early responders generally had lower baseline viral load and higher CD4 cell count than late responders
- ENF use in the BR was comparable across subgroups irrespective of time to response
- Patients who were non-responders at Week 24 tended to have low baseline CD4 cell counts and fewer active NRTIs in their BR

*Proportion of responders with class of ENF use/NRTI use in the BR

Summary of other efficacy endpoints at Week 24 and 48

Endpoint	Week 24: ETR + BR (N=599)	Week 24: Placebo + BR (N=604)	Week 48: ETR + BR (N=599)	Week 48: Placebo + BR (N=604)
Response (<50 copies/mL) by ENF use, % (n)				
Overall ENF	61 (363)	41 (246)	61 (363)	40 (240)
ENF *de novo*	67 (103/153)	61 (97/159)	71 (109/153)	58 (93/159)
ENF not *de novo*	58 (260/446)	33 (149/445)	57 (254/446)	33 (147/445)
Response (<50 copies/mL) by PSS, % (n)				
0	45 (39/87)	7 (6/83)	46 (40/87)	6 (5/83)
1	61 (122/200)	32 (64/201)	63 (125/200)	32 (64/201)
≥2	78 (197/252)	68 (172/252)	78 (197/252)	67 (169/252)
Change from baseline in log_{10} viral load, mean (SE)	−2.37 (0.05)	−1.69 (0.06)	−2.25 (0.06)	−1.49 (0.06)
Change in CD4 cell count from baseline (cells/mm^3), mean (SE)	83.5 (3.6)	65.0 (3.5)	98.2 (4.6)	72.9 (4.5)

SE = standard error

Conclusions

- In DUET, durable, high virologic response rates (<50 copies/mL) were observed up to Week 48 in patients receiving ETR plus BR
  - virologic responses obtained at Week 48 were comparable to those observed at Week 24
  - patients in the ETR plus BR group reached virologic response significantly earlier than those in the placebo plus BR group (p<0.0001)
  - the proportion of ETR patients achieving virologic response was 47%, 61% and 61% at 12, 24 and 48 weeks, respectively
- Durability of response is not affected by time to reach first virologic response
- Patients with viral load ≥400 copies/mL at Week 24 were unlikely to be virologic responders at Week 48
- Virologic response by Week 24 was highly predictive of durability of response through Week 48, but not fully predictive
- Full suppression of viral load (<50 copies/mL) by Week 48 can occur in patients who have not yet achieved a virologic response (viral load <50 copies/mL) at Week 12

References

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3. Trottier B, et al. CAHR 2008. Poster P167.
4. De Smedt G, et al. ISHEID 2008.

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DUET-1
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DUET-2
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