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Incidence and severity of nervous system and psychiatric events are similar with etravirine versus placebo: pooled 48-week data from the Phase III DUET studies

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Abstract

Background

Neuropsychiatric events have been associated with other NNRTIs. The next-generation NNRTI etravirine (ETR; TMC125) provided durable and statistically superior efficacy versus placebo over 48 weeks in treatment-experienced patients in the Phase III DUET trials. This preplanned, pooled analysis of DUET-1 and DUET-2 focuses on a comparison of nervous system events of interest and psychiatric events observed with ETR versus placebo after patients had received at least 48 weeks of treatment or discontinued.

Methods

Patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations received ETR 200mg or placebo, both bid, with a background regimen (BR) of darunavir/with low-dose ritonavir (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). Specific events were identified by a physician blinded to treatment assignment, prior to database lock, based on the type of events commonly reported with NNRTIs, specifically efavirenz.

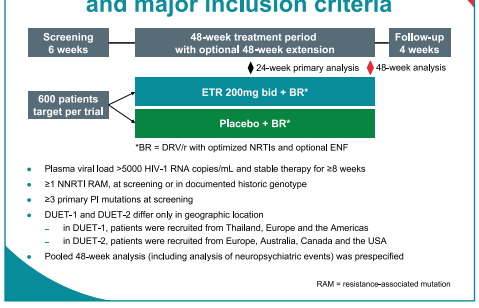
Results

The intent-to-treat population included 1203 patients; 599 vs 604 patients received ETR versus placebo, respectively (median age 45 years, 10.7% female, median baseline viral load 4.8 $\log_{10}$ copies/mL, median CD4 cell count 105 cells/mm^3). Incidences of nervous system (17.2% vs 19.7%, p=0.2660) and psychiatric disorders (16.7% vs 19.5%, p=0.2042) with ETR were comparable to placebo. The most frequent nervous system events were headache (10.9% ETR vs 12.7% placebo), dizziness (3.2% vs 4.3%) and somnolence (1.8% vs 2.3%). The most frequent psychiatric events were insomnia (7.2% vs 8.3%), depression (4.2% vs 6.6%), anxiety (3.8% vs 4.1%) and sleep disorder (1.3% vs 0.8%). All other events were reported in <1% of patients. Incidences of grade 3 nervous system (0.2% vs 0.8%) and psychiatric (0.3% vs 1.3%) events were low; there were no grade 4 nervous system or psychiatric events in the ETR group. Nervous system and psychiatric events leading to discontinuation were 0% vs 0.5% and 0.2% vs 0.2%, respectively.

Conclusions

The incidence and severity of neuropsychiatric events observed with ETR was similar to placebo over 48 weeks in the DUET trials.

DUET study design and major inclusion criteria



Baseline characteristics and background ARVs

Parameter		ETR + BR (n=599)	Placebo + BR (n=604)
Patient demographics	Male, %	90	89
	Caucasian, %	70	70
Patient history	Psychiatric symptoms (any type), %	46	44
Disease characteristics	Viral load, $\log_{10}$ copies/mL (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	CD4 cells, cells/mL (range)	99 (1–789)	109 (0–912)
	CDC category C, %	58	59
Prior therapy	NNRTIs used in screening period, %	12	12
	NRTIs used in screening period, %	97	98
	10–15 ARVs, %	66	65
	DRV/r, %	4	5
	Psycholeptics used in screening period, %	21	21
	Psychoanaleptics used in screening period, %	20	20

ARV = antiretroviral

Concomitant use of psycholeptics and psychoanaleptics during treatment

Concomitant therapy use, %	ETR + BR (n=599)	Placebo + BR (n=604)
Psycholeptics	**32**	**32**
Used in >2% of patients in both treatment groups		
Alprazolam	5	5
Bromazepam	3	3
Diazepam	3	2
Hydroxyzine	5	4
Lorazepam	5	6
Temazepam	3	3
Zolpidem	3	4
Zolpidem tartrate	5	6
Psychoanaleptics	**26**	**25**
Used in >2% of patients in both treatment groups		
Amitriptyline	4	2
Citalopram hydrobromide	2	2
Sertraline	2	2
Venlafaxine	2	3

Summary of AEs (regardless of causality) over 48 weeks

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Any AE (any cause)	**96**	**96**
Grade 3 or 4 AE	33	35
Discontinuation due to AE	7	6
Serious AE	20	23
Death (any cause)*	2	3
Most common AEs†		
Rash (any type)	19	11
Diarrhea	18	24
Nausea	15	13
Headache	11	13
Nasopharyngitis	11	10
AEs of interest (by class)		
Nervous system AEs of interest	17	20
Psychiatric AEs	17	20
Hepatic AEs	7	6

*All deaths in the ETR group were considered not or doubtfully related to trial medication; One death in the placebo group was considered possibly related to the investigational medication; †Occurring in at least 10% of patients in the ETR group; 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'

- No consistent or clinically relevant trends in laboratory abnormalities, vital signs or electrocardiogram data
- The incidence and severity of laboratory abnormalities, including hepatic and lipid parameters, were generally similar between the ETR and placebo groups

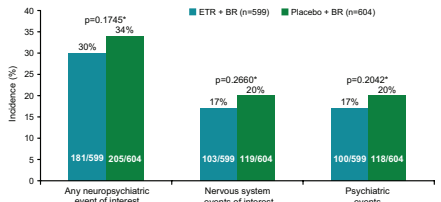
AEs = adverse events; EFV = efavirenz

Summary of neuropsychiatric events of interest over 48 weeks

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Any neuropsychiatric event of interest*	**30**	**34**
Any grade 1 or 2 neuropsychiatric AE	**30**	**33**
Grade 1	21	23
Grade 2	12	15
Any grade 3 or 4 neuropsychiatric AE	**<1**	**2**
Grade 3	<1	2
Grade 4	0	<1
Treatment-related neuropsychiatric AE†	**11**	**14**
Any neuropsychiatric serious AE	**<1**	**2**
Discontinuations due to neuropsychiatric events	**<1**	**<1**
Temporary treatment interruption due to neuropsychiatric events	**<1**	**1**

*Neuropsychiatric events of interest were identified based on the type of events commonly seen with other NNRTIs, particularly EFV, and were classified based on the MedDRA system order class 'neuropsychiatric events'
†Possibly, probably or very likely related to the investigational medication

Neuropsychiatric events of interest over 48 weeks



- Incidence of nervous system and psychiatric events did not differ significantly between treatment groups

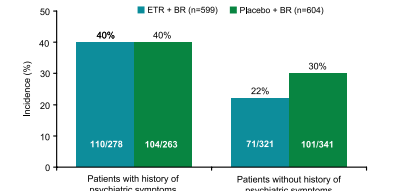
*Fisher's exact test

Summary of neuropsychiatric events of interest over 48 weeks by psychiatric history

Parameter, %	Patients with history of psychiatric symptoms: ETR + BR (n=278)	Patients with history of psychiatric symptoms: Placebo + BR (n=263)	Patients without history of psychiatric symptoms: ETR + BR (n=321)	Patients without history of psychiatric symptoms: Placebo + BR (n=341)
Any neuropsychiatric AE of interest	**40**	**40**	**22**	**30**
Severity				
Grade 1	26	26	17	21
Grade 2	19	20	7	11
Grade 3	1	3	<1	1
Grade 4	0	<1	0	0
Neuropsychiatric event reported as serious AE	**1**	**3**	**<1**	**1**
Permanent discontinuations	**<1**	**1**	**0**	**<1**
Temporary treatment interruptions	**1**	**1**	**1**	**1**

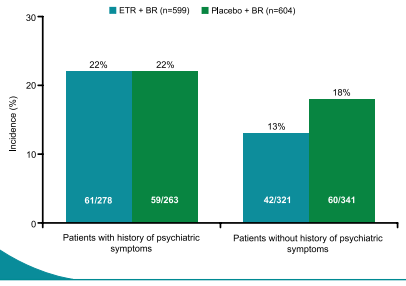
- Overall, 46% of patients in the ETR group and 44% of patients in the placebo group had a history of psychiatric events
- Although psychiatric history was associated with an increased frequency of neuropsychiatric events of interest, incidences were comparable in both treatment groups

Neuropsychiatric AEs of interest over 48 weeks by psychiatric history

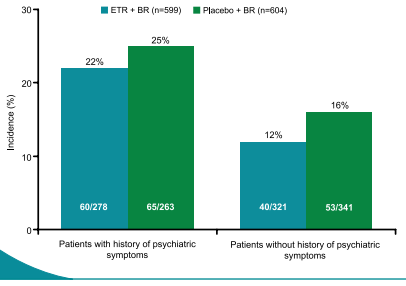


- Incidence of nervous system and psychiatric events although higher in patients with a history of psychiatric symptoms did not differ significantly between treatment groups

Nervous system AEs of interest over 48 weeks by psychiatric history



Psychiatric AEs over 48 weeks by psychiatric history



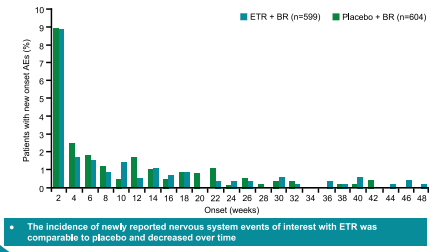
Nervous system events of interest over 48 weeks

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Nervous system disorders*	**17**	**20†**
Headache	11	13
Dizziness	3	4
Somnolence	2	2
Memory impairment	1	1
Amnesia	1	1
Disturbance in attention	<1	1
Grade 3 or 4 nervous system AE	**<1**	**1**
Discontinuation due to nervous system AE	**0**	**<1**

*Most common nervous system events are listed (reported in at least 0.3% of patients in the ETR group); Nervous system events of interest were selected based the type of AEs commonly reported with other NNRTIs, particularly EFV, and were classified based on the MedDRA system order class ‚nervous system disorders'; †p=0.2660; Fisher's exact test

- All nervous system events of interest were reported in ≤1% of ETR-treated patients, with the exception of headache, dizziness and somnolence

Nervous system events of interest: incidence of newly emerging AEs over 48 weeks



- The incidence of newly reported nervous system events of interest with ETR was comparable to placebo and decreased over time

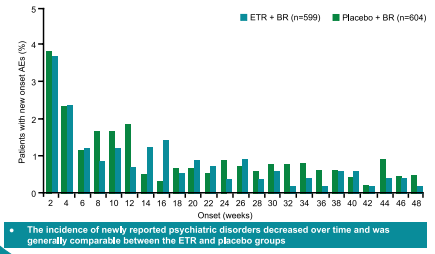
Psychiatric AEs over 48 weeks

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Psychiatric AEs*	**17**	**20†**
Insomnia	7	8
Depression	4	7
Anxiety	4	4
Sleep disorder	1	1
Libido decreased	1	1
Abnormal dreams	1	1
Nightmare	<1	<1
Panic attack	<1	0
Stress	<1	0
Grade 3 or 4 psychiatric AE	**<1**	**1**
Discontinuation due to psychiatric AE	**<1**	**<1**

*Most common psychiatric AEs are listed (reported in at least 0.3% patients in the ETR group); For psychiatric AEs, all reported events were included in the analysis; †p=0.2042; Fisher's exact test

- All psychiatric events were reported in ≤1% of ETR-treated patients, with the exception of insomnia, depression and anxiety

Psychiatric AEs: incidence of newly emerging AEs over 48 weeks



- The incidence of newly reported psychiatric disorders decreased over time and was generally comparable between the ETR and placebo groups

Conclusions

- Over 48 weeks, the incidence and severity of neuropsychiatric events of interest with ETR was comparable to placebo; events decreased over time
  - headache and insomnia were the most commonly reported nervous system and psychiatric events, respectively, and occurred at similar instances in both treatment groups.
- Incidences of grade 3 neuropsychiatric events of interest were low and similar between treatment groups.
- No grade 4 neuropsychiatric events of interest were reported with ETR.
- ETR was associated with low discontinuation rates and incidence of serious AEs.
- Although psychiatric history was associated with an increased frequency of neuropsychiatric events of interest, incidences were comparable between the ETR and placebo groups.

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DUET-1
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