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Neurologic and psychiatric safety profile of TMC278 compared with efavirenz in treatment-naïve, HIV-1-infected patients: pooled analysis from the randomized, double-blind, Phase III ECHO and THRIVE trials at 48 weeks

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Introduction

- TMC278 (rilpivirine) is an investigational NNRTI with potent in-vitro anti-HIV-1 activity.[1]
- TMC278 had non-inferior efficacy to efavirenz (EFV) in treatment-naïve, HIV-1-infected adults in the Week 48 primary analysis of two Phase III, double-blind trials, ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725).[2]
- As NNRTIs have been associated with neurologic and psychiatric adverse events (AEs), the aim of the current preplanned Week 48 analysis was to evaluate these AEs using pooled data from the ECHO and THRIVE trials.

Methods

Study design

- ECHO and THRIVE are ongoing, international, Phase III, double-blind, double-dummy, randomized trials in treatment-naïve, HIV-1-infected adults. The primary objective of these trials was to demonstrate non-inferiority (12% margin) of TMC278 compared with EFV in confirmed response (viral load <50 copies/mL, ITT-TLOVR) at Week 48.
- Patients were randomized to receive TMC278 25 mg qd or EFV 600 mg qd, plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (ECHO) or investigator-selected TDF/FTC, zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC) (THRIVE).

Study assessments and endpoints

- The ITT population was used for all analyses, and all evaluations were performed on pooled safety data from the two trials when patients had either received at least 48 weeks of treatment or discontinued earlier. Safety analyses were performed using all available data, including those beyond Week 48.
- Reported AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of any reported AEs was graded using the Division of Acquired Immunodeficiency Syndrome (DAIDS) scale.[3]
- The safety and efficacy of the trial regimens were monitored throughout by an independent Data and Safety Monitoring Board (DSMB).
- Treatment comparisons (using Fisher's Exact test) were predefined for any neuropsychiatric, neurologic or psychiatric AE of interest (well-described AEs associated with current NNRTIs), and any single preferred terms (abnormal dreams/nightmares were grouped) with an incidence >10% in either group.

Results

Baseline characteristics

- Overall (N=1368), baseline patient demographics and disease characteristics were similar between treatment groups **(Table 1)**. Background regimens were balanced between treatment groups: TDF/FTC 80%; AZT/3TC 15% and ABC/3TC 5%.

Overall safety results

- The median duration of treatment was 56 weeks in both treatment groups.
- At the time of the Week 48 analysis, a significantly lower cumulative incidence of grade 2–4 AEs at least possibly related to treatment was reported by TMC278- than by EFV-treated patients (16% vs 31%; p<0.0001, predefined analysis).
- AEs leading to permanent discontinuation also occurred less frequently with TMC278 (3% vs 8%, respectively; p=0.0005, post-hoc analysis).
- The overall cumulative incidence of neuropsychiatric AEs (any cause) was significantly lower with TMC278 than with EFV (40% vs 57%, respectively; p<0.0001, predefined analysis).

Table 1. Patient demographics and baseline disease characteristics.

Parameter	TMC278 N=686	EFV N=682
Demographics		
Female, %	24.5	23.9
Median age, years (range)	36 (18–78)	36 (19–69)
Race, %		
Caucasian/White	61.4	60.1
Black/African-American	24.1	22.9
Asian	11.4	14.2
Other races/not allowed to ask	3.1	2.8
Disease characteristics		
Median log_{10} viral load, copies/mL (min–max)	5.0 (2–7)	5.0 (3–7)
Baseline viral load >100,000 copies/mL, %	46.4	51.6
Median CD4 cell count, cells/mm^3 (min–max)	249 (1–888)	260 (1–1137)
Prior history of neurologic or psychiatric illness, %	32.5	31.4

Cumulative incidence of neurologic AEs of interest at the time of the Week 48 analysis

- The most common (≥2% of patients) neurologic AEs of interest at least possibly related to treatment were dizziness, headache, somnolence and disturbance in attention **(Table 2)**.

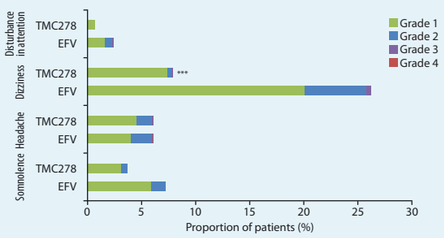
Table 2. Summary of neurologic AEs of interest.

Incidence, %	TMC278 N=686	EFV N=682	p value*
Any neurologic AE of interest (any cause)	**27**	**45**	<0.0001
Grade 1	24	36	ND
Grade 2	4	12	ND
Grade 3	0.3	1	ND
Grade 4	0.1	0.1	ND
Neurologic AE of interest by preferred term (any cause)†			
Headache	14	13	NS
Dizziness	10	28	<0.0001
Somnolence	4	7	ND
Disturbance in attention	1	2	ND
Any treatment-related neurologic AE of interest‡,§	**17**	**38**	<0.0001
Dizziness	8	26	<0.0001
Headache	6	6	ND
Somnolence	4	7	ND
Disturbance in attention	1	2	ND
Any SAE (any cause)	0.3	0.1	ND
Leading to permanent discontinuation (any cause)	0.1	1	ND
Neurologic AEs by history of neurologic or psychiatric illness (any cause), n/N (%)			
History of neurologic/psychiatric illness	77/223 (35)	105/214 (49)	ND
No history of neurologic/psychiatric illness	107/463 (23)	203/468 (43)	ND

*TMC278 versus EFV, Fisher's Exact test, predefined analysis; Reported in ≥5%† (except for disturbance in attention) or ≥2%‡ of patients in either group; §Judged by the investigator to be at least possibly related to treatment; NS = not significant; ND = not determined because not predefined

- Most neurologic AEs in both treatment groups were DAIDS grade 1 or 2 **(Figure 1)**.
- Two TMC278 patients (0.3%) reported serious AEs (SAEs): grade 4 alcohol poisoning and grade 3 dizziness. These events resolved, were judged to be not related to study medication by the investigator, and did not lead to permanent discontinuation. One EFV patient reported an SAE (0.1%): grade 4 headache considered possibly related to study medication, which led to temporary discontinuation.

Figure 1. Incidence by grade of neurologic AEs of interest at least possibly related to treatment reported in ≥2% of patients in either treatment group.



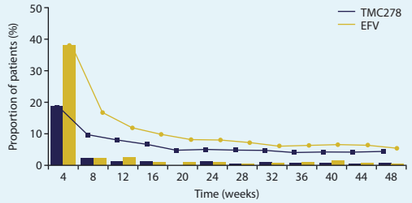
***p<0.0001 versus EFV, Fisher's Exact test, predefined analysis

- Permanent discontinuation of study medication occurred in one patient (0.1%) in the TMC278 group (grade 3 dizziness and headache) and five patients (1%) in the EFV group (grade 2 somnolence [two patients], grade 3 irritability, grade 2 dizziness and grade 2 headache, each in one patient).
- One fatal neurologic AE (cerebrovascular accident) occurred in the EFV group and was not considered to be related to study medication. There were no fatal neurologic AEs in the TMC278 group.
- Patients who had a history of neurologic or psychiatric illness, compared with those with no such history, reported more neurologic AEs **(Table 2)**.

Incidence and prevalence of neurologic AEs of interest over time

- Differences in incidence of AEs were most pronounced during the first 4 weeks of treatment. AE incidence decreased after 4–8 weeks and was stable to Week 48. Overall, neurologic AEs were less common with TMC278 than with EFV throughout **(Figure 2)**.

Figure 2. Incidence and prevalence of neurologic AEs of interest* over 48 weeks.



Incidence: bar chart; prevalence: line plot

Incidence = new AEs only (i.e., those with onset in the corresponding time period). AEs considered 'new' are those with no time-period overlaps (on the preferred term level)
Prevalence = AEs that cross different time periods and that are therefore counted in each of these periods
Percentages are calculated versus the number of patients in the treatment phase at that timepoint

*Well-described AEs associated with current NNRTIs

Cumulative incidence of psychiatric AEs of interest at the time of the Week 48 analysis

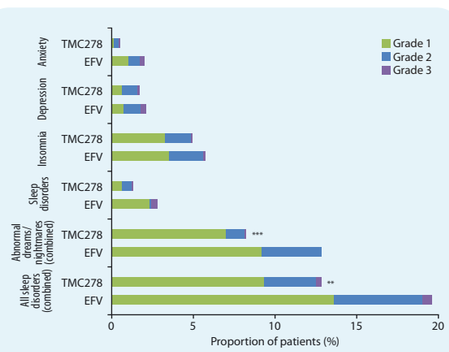
- The most common treatment-related psychiatric AEs of interest at least possibly related to treatment that occurred in ≥2% of patients in the TMC278 and EFV groups were abnormal dreams/nightmares, insomnia, depression, sleep disorder and anxiety **(Table 3)**.
- Most psychiatric AEs in both treatment groups were DAIDS grade 1 or 2 **(Figure 3)**.
- Ten patients in the TMC278 group (1%) and 15 in the EFV group (2%) permanently discontinued study medication (1%) because of psychiatric AEs of interest **(Table 3)**. These included three patients with SAEs in each group
  - TMC278: grade 4 suicide attempt, grade 3 suicide attempt, grade 2 depression
  - EFV group: grade 3 homicidal ideation, grade 3 depression, grade 3 acute psychosis.

Table 3. Summary of psychiatric AEs of interest.

Incidence, %	TMC278 N=686	EFV N=682	p value*
Any psychiatric AE of interest (any cause)	**24**	**29**	0.0321
Grade 1	16	22	ND
Grade 2	9	10	ND
Grade 3	1	2	ND
Grade 4	0.4	0.1	ND
Missing grade	0.1	0	ND
Psychiatric AE of interest by preferred term (any cause)†			
Abnormal dreams/nightmares	9	13	0.0093
Insomnia	8	8	ND
Depression	6	5	ND
Anxiety	2	5	ND
Sleep disorder	2	4	ND
Any treatment-related psychiatric AE of interest‡,§	**15**	**23**	0.0002
Abnormal dreams/nightmares	8	13	0.0061
Insomnia	5	6	ND
Depression	2	2	ND
Sleep disorder	1	3	ND
Anxiety	1	2	ND
Any SAE (any cause)	1	1	ND
Leading to permanent discontinuation (any cause)	1	2	ND
Psychiatric AEs by history of psychiatric illness (any cause), n/N (%)			
History of psychiatric illness	49/142 (35)	57/139 (41)	ND
No history of psychiatric illness	115/544 (21)	141/543 (26)	ND

*TMC278 versus EFV, Fisher's Exact test, predefined analysis; Reported in ≥5%† (except for sleep disorder) or ≥2%‡ of patients in either group; §Judged by the investigator to be at least possibly related to treatment

Figure 3. Incidence by grade of psychiatric AEs of interest at least possibly related to treatment in ≥2% of patients in either treatment group.



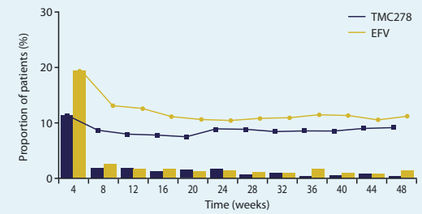
**p<0.001, ***p<0.0001 versus EFV, Fisher's Exact test, predefined analysis (abnormal dreams/nightmares), post-hoc analysis (all sleep disorders)

- There were no deaths resulting from psychiatric AEs.
- Patients with a history of psychiatric illness reported more psychiatric AEs than those with no such history **(Table 3)**.

Incidence and prevalence of psychiatric AEs of interest over time

- Psychiatric AEs of interest generally emerged within the first 4 weeks of treatment, and occurred at a lower rate in the TMC278 group than in the EFV group over 48 weeks **(Figure 4)**.

Figure 4. Incidence and prevalence of psychiatric AEs of interest* over 48 weeks.



Incidence: bar chart; prevalence: line plot

Incidence = new AEs only (i.e., those with onset in the corresponding time period). AEs considered 'new' are those with no time-period overlaps (on the preferred term level)
Prevalence = AEs that cross different time periods and that are therefore counted in each of these periods
Percentages are calculated versus the number of patients in the treatment phase at that timepoint

*Well-described AEs associated with current NNRTIs

Conclusions

- In the pooled ECHO and THRIVE trials, there was a significantly lower cumulative incidence of grade 2–4 treatment-related AEs and fewer discontinuations due to AEs in treatment-naïve, HIV-1-infected patients treated with TMC278 than with EFV.
- TMC278-treated patients reported significantly fewer all-cause and at least possibly treatment-related neurologic or psychiatric AEs of interest overall than EFV-treated patients
  - AEs generally emerged within the first 4 weeks of treatment and were less common with TMC278 than with EFV throughout.
- Dizziness and abnormal dreams/nightmares in particular occurred significantly less frequently with TMC278 than with EFV. No difference between treatment groups was observed for the incidence of depression.
- A once-daily single-tablet regimen of TMC278 and TDF/FTC is under development.

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