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

Introduction

- TMC278 (rilpivirine) is an investigational NNRTI with potent in vitro anti-HIV activity1
- TMC278 has non-inferior efficacy to efavirenz (EFV) in treatment-naive, HIV-1-infected adults. The primary objectives of these trials was to demonstrate non-inferiority (12% margin) of TMC278 compared with EFV in confirmed response (real-world) analysis of the Phase II, double-blind trials, ECHO (TMC278–C3002) and THRIVE (TMC278–C3002A)2
- As NNRTIs have been associated with neurologic and psychiatric adverse events (AEs), the aim of the current preplanned Phase 4 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-naive, HIV-1-infected adults. The primary efficacy endpoint was confirmed response at Week 48. These trials included participants in Phase II, double-blind trials of TMC278 compared with EFV and other regimens
- Patients were randomized to receive TMC278 25 mg qd or EFV 600 mg qd, plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or investigator-selected TDF/FTC, abacavir/lamivudine (ABC/3TC) or abacavir/lamivudine/EFV (ABC/EFV)/TRUVADA (rilpivirine, tenofovir, emtricitabine)3

Study assessments and endpoints

- The safety 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 National Institutes of Health (NIH) Common TerminologyCriteria for Adverse Events (CTCAE)4
- Treatment comparisons (using Fisher’s Exact test) were performed for any neurocognitive or psychiatric adverse event (AE) associated with current NNRTIs, and any single preferred term (abnormal dreams/nightmares) were grouped with an incidence <1% in either group.

Results

Baseline characteristics

- Overall (treatment arms), no significant patient demographics and disease characteristics were similar between treatment groups (Table 1). Background regimens were balanced between treatment groups: TDF/FTC, ABC/3TC and ABC/EFV/TRUVADA

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 ≥3 AEs was observed in TMC278-treated patients than in EFV-treated patients (16% vs 23%, p = 0.008)
- AEs leading to permanent discontinuation also occurred less frequently with TMC278 (8% vs 14%, p = 0.006, post-first analysis)
- Most AEs were grade 1 or 2 in both treatment groups

The incidence of psychiatric AEs at the time of the Week 48 analysis

- The most frequent psychiatric AEs were depression, anxiety and insomnia
- Anxiety and depression were the most common psychiatric AEs leading to permanent discontinuation

The cumulative incidence of psychiatric AEs at the time of the Week 48 analysis

- The incidence of psychiatric AEs of interest at least possibly related to treatment was significantly lower with TMC278 than with EFV (40% vs 57%, respectively; p<0.0001) at Week 48
- The incidence of psychiatric AEs of interest was significantly lower with TMC278 than with EFV (40% vs 57%, respectively; p<0.0001)

Conclusion

- 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-naive, HIV-1-infected patients treated with TMC278 than with EFV
- Patients treated with TMC278 reported significantly fewer all cause and at least possibly treatment-related neurocognitive or psychiatric AEs of interest than those treated with EFV
- AEs generally emerged within the first 4 weeks of treatment and were less common with TMC278 than with EFV throughout
- Depression and abnormal dreams/nightmares in particular occurred significantly less frequently with TMC278 than EFV. No difference between treatment groups was observed for the incidence of anxiety

Acknowledgments and disclosures

- All authors are employees of Tibotec. No other financial disclosure is necessary
- At present, no relevant conflicts of interest exist for any of the authors
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References

2. Center C, et al. 18th International AIDS Conference, Toronto, Canada; 14-19 July 2013: Abstract TBLA08
3. Edition of the European Medicines Agency (EMA) database for the reporting of adverse events and serious adverse events, 2012 (12 December 2012)

Table 1. Patient demographics and baseline disease characteristics.

Table 2. Summary of neurocognitive AEs of interest at least possibly related to treatment reported in ≥2% of patients in each treatment group.

Table 3. Summary of psychiatric AEs of interest.

Table 4. Table of summary of psychiatric AEs of interest by grade and treatment group.

Table 5. Table of summary of psychiatric AEs of interest by grade and treatment group.

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

Figure 2. Incidence and prevalence of neurocognitive AEs of interest at least possibly related to treatment reported in ≥2% of patients in each treatment group.

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

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

Figure 5. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 6. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 7. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 8. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 9. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 10. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 11. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 12. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 13. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 14. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.

Figure 15. Incidence and prevalence of psychiatric AEs of interest over 48 weeks.