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Teriflunomide Real-World Safety Profile: Results of the Phase 4 Teri-PRO Study

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OBJECTIVE

- **To report safety outcomes with teriflunomide in patients enrolled in the Teri-PRO 48-week (Teriflunomide Patient-Reported Outcomes) study**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS in 69 countries. Approximately 55,000 patients have been treated with teriflunomide as of April 2016, with total exposure to the 14-mg dose approaching 70,000 patient-years
- Teriflunomide has a well-characterized safety and tolerability profile, as demonstrated across phase 2 and 3 clinical studies,[1–5] and their extensions[6–9]
- The consistent efficacy of teriflunomide has been demonstrated in placebo-controlled studies of patients with relapsing forms of MS (RMS),[1–3] and in those who experienced a first clinical episode suggestive of MS[4]
- Safety and tolerability of teriflunomide treatment in routine clinical practice were key secondary outcomes of the phase 4 Teri-PRO study (NCT01895335)
  - Teri-PRO outcomes, including patient treatment satisfaction (primary outcome), patient-reported disability, and quality of life are described in ePoster EP1484 (Coyle et al),[10] poster P646 (Gold et al),[11] and poster P647 (Gold et al),[12] respectively, at this congress

METHODS

Study Design and Patients

- Teri-PRO was a prospective, global, multicenter, single-arm, open-label study
  - Patients with relapsing forms of MS were recruited from sites in the US, Canada, Europe, and Latin America; patients in the US were treated with teriflunomide 7 or 14 mg (dose determined by the treating neurologist), while those in the rest of the world were treated with teriflunomide 14 mg, according to local labeling
- The study design and full eligibility criteria have been presented previously,[13] and are briefly described in ePoster EP1484[10] at this congress

Study Endpoints and Timing of Assessments

- Adverse events (AEs) and vital signs were assessed at baseline, Week 4, Week 24, and Week 48 (or end of treatment; EOT)
  - AEs occurring between visits, including start date of the AE, were reported at the subsequent visit

Analysis Population

- All patients who received ≥1 dose of teriflunomide were included in the safety analysis

Statistical Analysis

- Descriptive analysis with frequency and percentage was used for reporting of summary of AEs. AEs related to hair thinning, diarrhea, and ALT increase were summarized by time of each occurrence of the respective AEs, presented at 4-weekly intervals

RESULTS

- Patient disposition is summarized in **Table 1**
  - A total of 1001 patients were included in the Teri-PRO study, of which 1000 were treated; most received teriflunomide 14 mg (n=928, 92.8%), with only a small number receiving teriflunomide 7 mg (n=72, 7.2%, US only)
  - The majority of patients (78.6%) completed the study treatment period
- AEs were reported in 82.3% (n=823) of patients; a summary of AEs is shown in **Table 2**
  - Most AEs were mild to moderate in severity
- Serious AEs (SAEs) were reported in 12.7% of patients; the only SAE occurring in ≥1% of patients was MS relapse (2.1%; **Table 2**)

CONCLUSIONS

- **In the Teri-PRO study, the real-world safety and tolerability profile of teriflunomide was consistent with that previously observed in the clinical development program**
  - **Most AEs were mild to moderate, with no unexpected AEs reported**
  - **AEs related to hair thinning, diarrhea, and ALT increases generally occurred during the first few months of treatment, and resolved or stabilized on treatment**
- **Adherence to treatment, key to the continued efficacy of MS therapy, was high, with most patients completing the study treatment period, and a low rate of teriflunomide treatment discontinuation due to AEs**

- AEs leading to treatment discontinuation were reported in 10.9% of patients; of these, only diarrhea and MS relapse led to discontinuation in >1% of patients (1.7% and 1.2% of patients, respectively, **Table 2**)
- Four AEs leading to death were reported: pneumonia, MS relapse, non-small cell lung cancer (Stage IV), and myocardial infarction
  - Three of the deaths occurred on treatment, while 1 (non-small cell lung cancer) occurred during the post-treatment period (>112 days after last administration)
  - No deaths were considered related to teriflunomide treatment
- Hair thinning, diarrhea, and alanine aminotransferase (ALT) increases were reported in 230 (23.0%), 173 (17.3%), and 63 (6.3%) patients, respectively
  - Most cases were mild to moderate, occurred in the first few months of treatment, and resolved or stabilized over the course of the study (**Figure 1**)
- The incidence of these AEs were similar in patients switching from another disease-modifying therapy within 6 months of study entry (n=594, 22.7%, 17.3%, and 6.6% for hair thinning, diarrhea, and ALT increase respectively), and also generally occurred over the first few months of treatment (**Figure 2**)

Table 1. Patient Disposition

Characteristic	Patients, n (%)
Treatment	
Teriflunomide 7 mg	72 (7.2)
Teriflunomide 14 mg	928 (92.8)
Completed study treatment period	786 (78.6)
Reason for discontinuation	
Adverse event	106 (10.6)
Lack of efficacy	53 (5.3)
Poor compliance	11 (1.1)
Other reason	44 (4.4)
Patients lost to follow-up	15 (1.5)

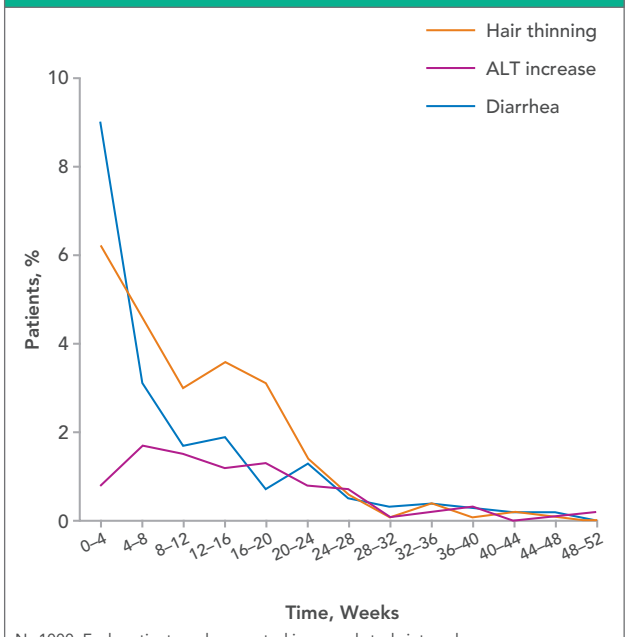
Safety population. N=1000.

Table 2. Summary of Adverse Events

	Patients, n (%)
AEs reported in ≥5% of patients[a]	
Hair thinning[b]	230 (23.0)
Diarrhea	173 (17.3)
Nausea	82 (8.2)
Headache	69 (6.9)
Urinary tract infection	67 (6.7)
ALT increase	63 (6.3)
Nasopharyngitis	54 (5.4)
Fatigue	52 (5.2)
SAEs reported in ≥0.5% of patients[a]	
MS relapse	21 (2.1)
Hypertension	6 (0.6)
ALT increase	6 (0.6)
Urinary tract infection	5 (0.5)
AEs leading to permanent treatment discontinuation in ≥0.5% of patients[a]	
Diarrhea	17 (1.7)
MS relapse	12 (1.2)
Hair thinning[b]	9 (0.9)
ALT increase	6 (0.6)

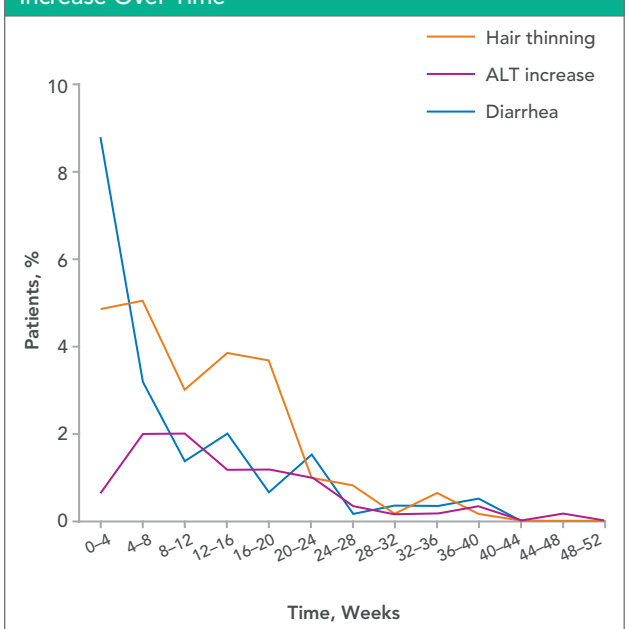
N=1000. [a]Listed by MedDRA-preferred term; [b]MedDRA-preferred term is alopecia. AE, adverse event; ALT, alanine aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities (Version 18.1); SAE, serious adverse event.

Figure 1. Proportions of Patients With Hair Thinning, Diarrhea, or ALT Increase Over Time



N=1000. Each patient can be counted in several study intervals.
AE, adverse event; ALT, alanine aminotransferase.

Figure 2. Proportions of Patients Switching to Teriflunomide From a Prior DMT Within 6 Months of Study Entry With Hair Thinning, Diarrhea, or ALT Increase Over Time



N=594. Each patient can be counted in several study intervals.
AE, adverse event; ALT, alanine aminotransferase; DMT, disease-modifying therapy.

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Teriflunomide is approved in many countries, including the US and the European Union, for the treatment of relapsing multiple sclerosis or relapsing-remitting multiple sclerosis. This material may contain information that is outside of the approved labeling in some countries.

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