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Clinical and Safety Outcomes From Patients Treated With Teriflunomide in the Phase 4 Teri-PRO Study

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OBJECTIVE

- **To report clinical and safety outcomes for patients in the phase 4 Teri-PRO (Teriflunomide Patient-Reported Outcomes) study**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS in 70 countries, and approximately 71,000 patients are currently being treated with teriflunomide worldwide
- The phase 4 Teri-PRO study (NCT01895335) primarily evaluated patient-reported treatment satisfaction, disability, and quality of life with teriflunomide using patient-reported outcomes (PROs). The effectiveness, safety, and tolerability of teriflunomide in routine clinical practice were also assessed
  - High levels of treatment satisfaction with teriflunomide were observed over the course of the study[1]
- PROs in patients switching to teriflunomide from another disease-modifying therapy (DMT) and in treatment-naïve patients are described in posters P3-363 (Coyle et al)[2] and P3-348 (Gold et al),[3] respectively, at this congress

METHODS

Study Design and Patients

- Teri-PRO was a prospective, global, multicenter, single-arm, open-label study
  - Patients were treated with teriflunomide 14 mg or 7 mg (US only) according to local labeling
  - The full study design and eligibility criteria have been presented previously[4]
- "Switchers" are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start

Study Outcomes

Clinical Outcomes

- Expanded Disability Status Scale (EDSS) scores were measured at baseline and Week 48
- Annualized treated relapse rate and number of patients with ≥1 treated relapse were also assessed
  - Annualized treated relapse rate was calculated as the total number of treated relapses that occurred during the treatment period divided by the total number of treated patient-years in the study
  - A treated relapse was defined as a relapse treated by systemic corticosteroid treatment or by another DMT during the study period

Safety and Tolerability Outcomes

- 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

Statistical Analysis

- All patients who received ≥1 dose of teriflunomide were included in the analysis
- In a post hoc analysis, *P* values for post-baseline change were assessed using an analysis of covariance model of change from baseline with values adjusted for baseline EDSS score. Analysis based on prior DMT in switcher patients was also performed post hoc

CONCLUSIONS

- **In the Teri-PRO study, real-world effectiveness and safety of teriflunomide were consistent with the results of the clinical development program**
  - **Disability (as measured by EDSS scoring) remained stable over the course of the study. In patients switching to teriflunomide from another DMT, EDSS remained stable regardless of prior DMT**
  - **Annualized treated relapse rates were low across the course of the study**
  - **Most AEs were mild to moderate in nature with no unexpected AEs reported**
- **In combination with other Teri-PRO outcomes, these observations support the use of teriflunomide as an effective treatment in patients with relapsing forms of MS, including in those patients switching from other DMTs**

RESULTS

- Of the overall Teri-PRO cohort (N=1000), 594 patients were switchers (defined as having received another DMT within 6 months prior to study start)
  - The majority of patients received teriflunomide 14 mg (total cohort: n=928, 92.8%; switchers: n=556, 93.6%)
- Baseline demographics and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Total Cohort[a] (N=1000)	Switchers[b] (n=594)
Age, mean (SD), y	47.1 (11.0)	47.5 (11.0)
Female, n (%)	756 (75.6)	454 (76.4)
Race, n (%)		
Asian/oriental	3 (0.3)	2 (0.3)
Black	50 (5.0)	27 (4.5)
Caucasian/white	938 (93.8)	560 (94.3)
Other	9 (0.9)	5 (0.8)
Time since first symptoms of MS, mean (SD), y	13.2 (9.5)	13.8 (9.3)
Number of relapses in the past 2 years, mean (SD)	1.2 (1.5)[c]	1.2 (1.5)
Time since most recent relapse onset, mean (SD), mo	31.2 (46.5)[d]	37.8 (51.5)[e]
Baseline EDSS score, mean (SD)	3.1 (2.0)[f]	3.1 (2.0)[g]
Reason for treating with teriflunomide, n (%)[h]		
Disease worsening with previous DMT[i]	143 (14.3)	107 (18.0)
Convenience (for oral daily intake)	572 (57.2)	269 (45.3)
Intolerance to administration mode of previous DMT	215 (21.5)	154 (25.9)
Side effects/risk of side effects with previous DMT	271 (27.1)	215 (36.2)
Other	46 (4.6)	18 (3.0)

[a]Includes patients who have not previously received a DMT; [b]switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start; [c]n=999; [d]n=971; [e]n=578; [f]n=996; [g]n=592; [h]more than 1 reason for treating with teriflunomide could be selected; [i]worsening as defined by investigator. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Clinical Outcomes

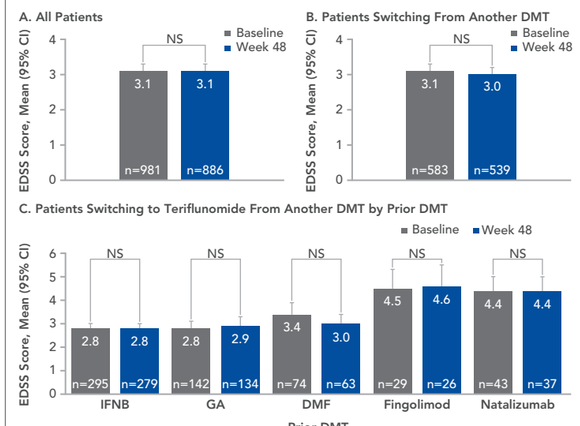
Disability

- EDSS scores remained stable over the entire study period for patients in both the total and switcher cohorts (**Figure 1A** and **B**)
- In the switcher cohort, EDSS scores remained stable regardless of prior DMT received (**Figure 1C**)
  - Baseline EDSS scores were higher in patients switching from natalizumab or fingolimod, but remained stable after 48 weeks of teriflunomide treatment

Relapses Requiring Treatment

- Most patients did not experience a relapse requiring treatment during the study period (all patients: 858 [85.8%]; switchers: 501 [84.3%])
- A higher mean number of relapses in the 2 years prior to study start were observed for patients previously receiving dimethyl fumarate (DMF) and fingolimod compared with other DMTs (**Table 2**)
- Annualized treated relapse rate remained low throughout the study period (all patients: 0.200; switchers: 0.216)
  - Annualized treated relapse rate was higher in patients who had previously received DMF, fingolimod, or natalizumab compared with patients who had previously received platform injectable therapies (**Table 2**)
  - The proportion of patients experiencing a treated relapse was higher in patients who had previously received DMF or fingolimod compared with platform injectable therapies or natalizumab (**Table 2**)

Figure 1. EDSS Scores at Baseline and Week 48



P values were assessed using an ANCOVA model of change from baseline with values adjusted for baseline EDSS score. ANCOVA, analysis of covariance; CI, confidence interval; DMF, dimethyl fumarate; DMT disease-modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFN, interferon; NS, not significant.

Table 2. Treated Relapses and Annualized Treated Relapse Rate in Patients Switching to Teriflunomide From Another DMT

Prior DMT	n	Number of Relapses in the Previous 2 Years (mean)	Patients With ≥1 Treated Relapse, n (%)	Annualized Treated Relapse Rate (95% CI)[a]
IFNB	301	1.0	47 (15.6)	0.199 (0.144, 0.253)
GA	145	1.2	19 (13.1)	0.183 (0.108, 0.258)
DMF	74	1.7	15 (20.3)	0.295 (0.155, 0.435)
Fingolimod	29	1.5	6 (20.7)	0.302 (0.078, 0.526)
Natalizumab	45	1.1	6 (13.3)	0.271 (0.103, 0.439)

[a]Total number of relapses that occurred during the treatment period divided by the total number of treated patient-years in the study. CI, confidence interval; DMF, dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; IFN, interferon.

Safety

- The safety profile of teriflunomide was similar in the total population and switcher cohort
  - AEs were reported in 823 (82.3%) and 481 (81.0%) patients in the total population and the switcher cohort, respectively
- Most AEs were mild to moderate in severity
  - Serious AEs were reported in 127 (12.7%) and 72 (12.1%) patients in the total population and the switcher cohort, respectively
  - AEs leading to treatment discontinuation were reported in 109 (10.9%) and 56 (9.4%) patients in the total population and the switcher cohort, respectively
  - A summary of AEs is shown in **Table 3**
- Four AEs leading to death were reported, of which 3 were in the switcher cohort: 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
- The real-world safety profile of teriflunomide was consistent with that seen in the clinical development program

Table 3. Summary of Adverse Events

	All Patients (N=1000)	Switchers[a] (n=594)
AEs reported in ≥5% of patients[b,c]		
Hair thinning[d]	230 (23.0)	135 (22.7)
Diarrhea	173 (17.3)	103 (17.3)
Nausea	82 (8.2)	48 (8.1)
Headache	69 (6.9)	36 (6.1)
Urinary tract infection	67 (6.7)	49 (8.2)
ALT increase	63 (6.3)	39 (6.6)
Nasopharyngitis	54 (5.4)	34 (5.7)
Fatigue	52 (5.2)	27 (4.5)
Serious AEs reported in ≥0.5% of patients[b,c]		
MS relapse	21 (2.1)	11 (1.9)
Hypertension	6 (0.6)	5 (0.8)
ALT increase	6 (0.6)	1 (0.2)
Urinary tract infection	5 (0.5)	0
AEs leading to permanent treatment discontinuation in ≥0.5% of patients[b,c]		
Diarrhea	17 (1.7)	9 (1.5)
MS relapse	12 (1.2)	5 (0.8)
Hair thinning[d]	9 (0.9)	5 (0.8)
ALT increase	6 (0.6)	2 (0.3)

Safety population. [a]Switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start; [b]in the All Patients cohort; [c]listed by MedDRA-preferred term; [d]MedDRA-preferred term is alopecia. AE, adverse event; ALT, alanine aminotransferase; DMT, disease-modifying therapy; MedDRA, Medical Dictionary for Regulatory Activities (Version 18.1).

References

1. Coyle et al. ePoster EP1484, ECTRIMS 2016.
2. Coyle et al. Poster P3-363, AAN 2017.
3. Gold et al. Poster P3-348, AAN 2017.
4. Coyle et al. Poster P078, ACTRIMS-ECTRIMS 2014.

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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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