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Improvements in Patient-Reported Outcomes With Teriflunomide: Week 24 Interim Results From the US Cohort of the Teri-PRO Phase 4 Study

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OBJECTIVES

- **To describe, for patients enrolled in US centers in the global Teri-PRO (Teriflunomide Patient-Reported Outcomes) study:**
  - **Interim treatment satisfaction results at Week 4**
  - **Interim patient-reported disability results at Week 24**

INTRODUCTION

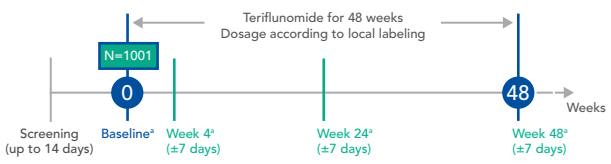
- Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS
  - Teriflunomide was approved in the US on September 12, 2012[1]
- In placebo-controlled clinical trials, teriflunomide demonstrated consistent efficacy on both clinical (relapse[2-4] and disability[2,3]) and magnetic resonance imaging[2,3] parameters in patients with relapsing forms of MS, and in those who experienced a first clinical episode suggestive of MS.[5] It also has a well-characterized and manageable safety and tolerability profile[2-6]
- Patient-reported outcomes can complement clinical evaluations and are applied to evaluate the experience and satisfaction of patients with their treatment; consequently, patient-reported outcome measures also provide insight into patients' health-related quality of life
- The phase 4 Teri-PRO study (NCT01895335) is evaluating efficacy, tolerability, and satisfaction with teriflunomide in clinical practice

METHODS

Study Design and Patients

- Teri-PRO is a prospective, global, single-arm open-label study (**Figure 1**)

Figure 1. Teri-PRO Study Design[7]



[a]Timing of efficacy and safety assessments. All patient screening and monitoring to be performed as per local labeling. Patients continuing treatment after Teri-PRO will have the opportunity to switch to commercially available teriflunomide.

- Patients were prescribed teriflunomide 7 mg or 14 mg once daily for 48 weeks according to local labeling; in the US, where the 7-mg dose is available, choice of dose was determined by the treating neurologist
- Teri-PRO enrollment is complete; patients with relapsing forms of MS aged ≥18 years (N=1001) were recruited across sites in the US, Canada, Europe, and Latin America
  - Keeping with the clinical practice setting, there were no disease activity eligibility criteria; full exclusion criteria have been presented previously[7]
- Patients were classified into the following groups based on previous use of disease-modifying therapy (DMT):
  - Patients with no DMT intake in the past 2 years
  - Patients with last DMT intake within 2 years of study entry:
    - Patients with last DMT intake 6–24 months before study entry
    - Patients with last DMT intake within 6 months of study entry

Study Outcomes

- The primary endpoint is global satisfaction with teriflunomide treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM, version 1.4),[8] at Week 48 (or end of treatment; EOT)
  - The TSQM consists of 14 questions assessing the effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) of medication over the previous 2–3 weeks or since last use
  - A higher TSQM score indicates greater treatment satisfaction
- Secondary endpoints reported here are:
  - Change in TSQM score from baseline to Week 4 in patients switching from another DMT
  - Patient-reported disability at baseline and Week 24, as measured by the Multiple Sclerosis Performance Scale (MSPS)[9]
    - The MSPS requires patients to indicate their level of disability during the past month on the following subscales: Mobility, Hand Function, Vision, Fatigue, Cognitive Symptoms, Bladder/Bowel, Sensory Symptoms, and Spasticity Symptoms
    - All subscales are scored on a scale of 0 (normal) to 5 (total disability), except Mobility, which is scored from 0 to 6
    - Subscale scores have been added together to give a total MSPS score; a higher score reflects greater disability
    - Three further questions pertaining to Pain, Depression, and Tremor and Coordination (also rated on a scale of 0 to 5) were added to the MSPS, but these were not included in calculating the MSPS summary score
  - Occurrence of adverse events (AEs)
    - AEs occurring between the first administration of teriflunomide and Week 24 (or EOT) are included and summarized using Medical Dictionary for Regulatory Activities[10] terminology

Timing of Assessments

- TSQM score is assessed at:
  - Week 4 and Week 48 (or EOT) in all patients
  - Baseline, Week 4, and Week 48 (or EOT) in patients switching from another DMT
- MSPS score is assessed at baseline, Week 24, and Week 48 (or EOT) in all patients

Effect Size

- Effect size (ES) for TSQM and MSPS was defined as the change from baseline divided by the standard deviation (SD) of the change. Clinical significance was defined as per the ES limits set out by Cohen[11]: <0.2, negligible; ≥0.2 to <0.5, small; ≥0.5 to ≤0.8, moderate; and >0.8, high
  - ES can be useful in evaluating whether statistically significant differences in groups over time are clinically meaningful and relevant to patients[11]

Analysis Population

- All patients who receive ≥1 dose of teriflunomide are included in the efficacy and safety analyses

CONCLUSIONS

- **Patients were recruited to Teri-PRO, during the first 18 months following US approval of teriflunomide, with a view to understanding the early experience of teriflunomide treatment in a routine clinical practice setting**
- **Interim results suggest that teriflunomide is associated with high levels of treatment satisfaction in all US patients**
  - **Patients switching to teriflunomide from other DMTs reported substantial increases in treatment satisfaction across all 4 TSQM domains after 4 weeks, with moderate to high effect sizes**
- **Patient-reported disability remained stable after 6 months of teriflunomide treatment**
- **The safety and tolerability profile of teriflunomide for US patients in the Teri-PRO study at Week 24, and the low rate of treatment discontinuation, was consistent with that seen in phase 2 and 3 studies**

RESULTS

- US patients were enrolled between June 21, 2013 and June 24, 2014, inclusive
- Of 545 US patients included in Teri-PRO, most received teriflunomide 14 mg (n=473, 86.8%). The rest received 7 mg (n=72, 13.2%)
  - At Week 24, 464 (85.1%) patients remained in the study
- Demographic and baseline disease characteristics are detailed in **Table 1**

Table 1. US Patients' Demographic and Baseline Disease Characteristics

Characteristic	N=545
Age, mean (SD), y	50.6 (10.5)
Female, n (%)	414 (76.0)
Race, n (%)	
Black	49 (9.0)
Caucasian/white	489 (89.7)
Other	7 (1.3)
Time since first symptom of MS, mean (SD), y	14.7 (9.8)
Time since most recent relapse onset, mo	
Median (min:max)	10.0 (0.0:372.2)[a]
Mean (SD)	32.1 (51.7)[a]
Number of relapses within past 2 years, n (%)	
0	196 (36.0)[b]
1	183 (33.6)[b]
2	77 (14.2)[b]
3	36 (6.6)[b]
≥4	52 (9.6)[b]
Baseline EDSS score, median (min:max)	3.5 (0.0:8.0)[c]
Previous DMT within past 2 years, n (%)	
No	160 (29.4)
Yes	385 (70.6)
Not within past 6 months	69 (12.7)
Within past 6 months	316 (58.0)

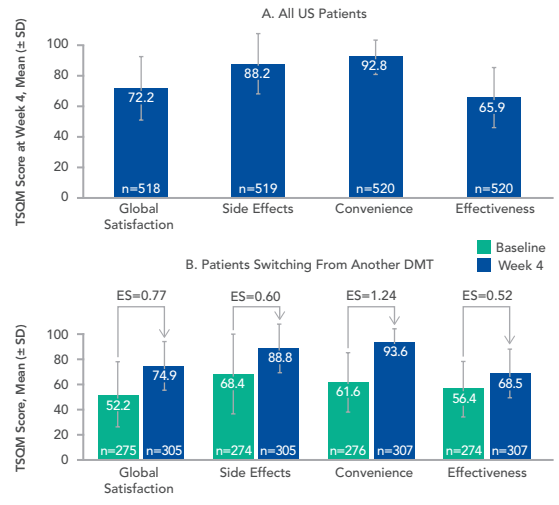
Efficacy population. [a]n=519; [b]n=544; [c]n=543.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; SD, standard deviation.

- The most recent prior therapies for patients who switched to teriflunomide within 6 months of discontinuing another DMT (n=316) were injectable DMTs (n=207), other oral DMTs (n=75), or infused therapy (n=34)
- The most frequent reason given by physicians for choosing treatment with teriflunomide was the convenience of oral therapy, followed by side effects/risk of side effects with previous DMT use

Treatment Satisfaction

- High mean treatment satisfaction scores with teriflunomide were seen for all patients at Week 4 (**Figure 2A**)
- Improvements from baseline to Week 4 in TSQM scores were seen across all TSQM domains in patients who had switched from another DMT within the last 6 months (**Figure 2B**); mean change (SD): Global Satisfaction, 22.7 (29.4); Side Effects, 21.8 (36.1); Convenience, 31.8 (25.6); Effectiveness, 12.8 (24.8)
  - High or moderate ESs were observed in all domains: Global Satisfaction (0.77), Side Effects (0.60), Convenience (1.24), and Effectiveness (0.52)

Figure 2. Treatment Satisfaction by TSQM Domain at Week 4 in All US Patients and Improvement in Treatment Satisfaction Relative to Baseline in US Patients Switching From Another DMT Within 6 Months

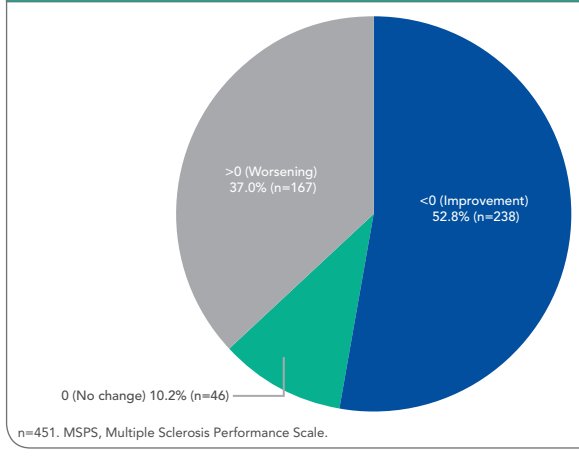


Patient numbers for ES were as follows: Global Satisfaction and Effectiveness, n=268; Side Effects, n=266; Convenience, n=270.
DMT, disease-modifying therapy; ES, effect size; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication (version 1.4).

Patient-Reported Disability

- At Week 24, mean (SD) MSPS total score was 14.1 (7.3), compared with 15.1 (7.0) at baseline
  - The ES for this change was negligible (-0.16), suggesting that patient-reported disability remained stable over this time
- Overall, 63.0% of patients reported either an improvement or no change in MSPS total score at Week 24 compared with baseline (**Figure 3**)

Figure 3. MSPS Total Score Change From Baseline to Week 24



n=451. MSPS, Multiple Sclerosis Performance Scale.

- A higher percentage of patients reported normal or minimal disability at Week 24 vs baseline for 7 out of the 8 subscales that formed part of the MSPS total score (**Table 2**)
- For each of the 3 additional MSPS questions, the proportion of patients reporting normal or minimal disability at Week 24 also increased compared with baseline (**Table 2**)

Table 2. MSPS Subscale Score Change From Baseline to Week 24

	Patients Reporting Normal/ Minimal Disability, %	
	Baseline	Week 24
MSPS Subscale		
Mobility	36.7[a]	43.6[b]
Hand Function	57.1[c]	58.8[d]
Vision	56.7[c]	60.4[d]
Fatigue	18.0[e]	24.9[f]
Cognitive Symptoms	41.3[c]	48.1[g]
Bladder/Bowel	56.6[h]	48.1[i]
Sensory Symptoms	49.3[j]	51.3[k]
Spasticity Symptoms	46.9[l]	55.8[e]
Additional MSPS Questions		
Pain	44.2[l]	47.8[e]
Depression	59.5[m]	67.8[f]
Tremor and Coordination	54.6[j]	59.7[d]

[a]n=528; [b]n=447; [c]n=538; [d]n=452; [e]n=540; [f]n=453; [g]n=451; [h]n=541; [i]n=455; [j]n=537; [k]n=454; [l]n=539; [m]n=536. MSPS, Multiple Sclerosis Performance Scale.

Safety

- At Week 24 or EOT, 400 patients (73.4%) reported AEs. AEs reported in ≥5% of patients are shown in **Table 3**
- A total of 44 patients (8.1%) experienced serious AEs
  - The most common serious AE was non-cardiac chest pain, reported by 3 patients (0.6%)
- A total of 50 patients (9.2%) discontinued treatment because of an AE
  - AEs leading to treatment discontinuation in ≥2 patients were diarrhea (n=11), events coded as alopecia (n=4), fatigue (n=3), urticaria, (n=2), nausea (n=2), vomiting (n=2), flu-like illness (n=2), and alanine aminotransferase increased (n=2)

Table 3. Summary of AEs Reported in ≥5% of Patients at Week 24, Presented by MedDRA-Preferred Term[10]

AE	Patients, n (%)
Alopecia	82 (15.0)
Diarrhea	76 (13.9)
Nausea	46 (8.4)
Urinary tract infection	28 (5.1)
Headache	27 (5.0)
Paresthesia	27 (5.0)

N=545.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

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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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