P646

Stable Disability and Patient-Reported Performance Outcomes Over 48 Weeks of Teriflunomide Treatment: Results From the Phase 4 Teri-PRO Study

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OBJECTIVE

- **To describe disability and patient-reported performance outcomes for patients enrolled in the 48-week 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 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
- The consistent efficacy of teriflunomide on relapse and disability measures, and MRI parameters, has been demonstrated in placebo-controlled studies of patients with relapsing forms of MS,[1–3] and in those who experienced a first clinical episode suggestive of MS[4]
- Teriflunomide also has a manageable, well-characterized safety and tolerability profile,[1–5] confirmed over the longer term in extension studies[6–9]
- The phase 4 Teri-PRO study (NCT01895335) evaluated treatment satisfaction with teriflunomide using patient-reported outcomes, as well as efficacy, safety and tolerability, in routine clinical practice
- Patient-reported disability outcomes were key secondary endpoints evaluated in the Teri-PRO study
- Teri-PRO outcomes, including patient treatment satisfaction (primary outcome), quality of life, and safety and tolerability, are described in ePoster EP1484 (Coyle et al),[10] and posters P647 (Gold et al)[11] and P648 (Coyle 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, in addition to sites in Canada, Austria, Belgium, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, the United Kingdom, and Chile (rest of the world, RoW); patients in the US were treated with teriflunomide 7 or 14 mg (dose determined by the treating neurologist), while those in the RoW were treated with teriflunomide 14 mg, according to local labeling
- The full study design and eligibility criteria have been presented previously,[13] and are briefly described in ePoster EP1484[10] at this congress

Study Outcomes

Multiple Sclerosis Performance Scale

- Measuring patient-reported disability, the Multiple Sclerosis Performance Scale (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[14,15]
- A total MSPS score (ranging from 0 to 41) is calculated as the sum of the scores on the above individual subscales, with a higher score reflecting greater disability. In addition, patient responses were collected with respect to Pain, Depression, and Tremor and Coordination, but these were not included in the total MSPS score
  - All subscales are scored on a scale of 0 (normal) to 5 (total disability), except Mobility, which is scored from 0 to 6

Expanded Disability Status Scale and Patient-Determined Disease Steps

- The Patient-Determined Disease Steps (PDDS) scale measures patient-reported disability, focusing mainly on ambulatory function; it is measured on a scale of 0 (normal) to 8 (bedridden)[14–16]
- Physician-reported disability, measured by Expanded Disability Status Scale (EDSS) score, was also assessed
  - PDDS scores have been found to correlate strongly with EDSS scores[17,18]

Symbol Digit Modalities Test

- The Symbol Digit Modalities Test (SDMT) is a measure of cognitive impairment[19,20] and involves a simple substitution task; higher scores are indicative of better cognitive function
  - This test complements patient-reported data collected by the MSPS Cognitive Symptoms subscale

Timing of Assessments

- All endpoints were reported at baseline and Week 48. MSPS scores were also assessed at Week 24

Effect Size

- Effect size (ES), potentially useful in evaluating whether differences in groups over time are clinically meaningful and relevant to patients, 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[21]: <0.2, negligible; ≥0.2 to <0.5, small; ≥0.5 to ≤0.8, moderate; and >0.8, high

Analysis Population

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

RESULTS

- A total of 1001 patients were included in the Teri-PRO study and 1000 received treatment; most received teriflunomide 14 mg (n=928, 92.8%), with only a small number receiving teriflunomide 7 mg (n=72, 7.2%, US only)
- Demographics and baseline disease characteristics are summarized in **Table 1** for the whole cohort and by region
  - Patients in the US cohort were older, with a longer time since first MS symptoms, and a higher baseline EDSS score than that seen in the RoW cohort, reflecting how teriflunomide was used at launch in the US

CONCLUSIONS

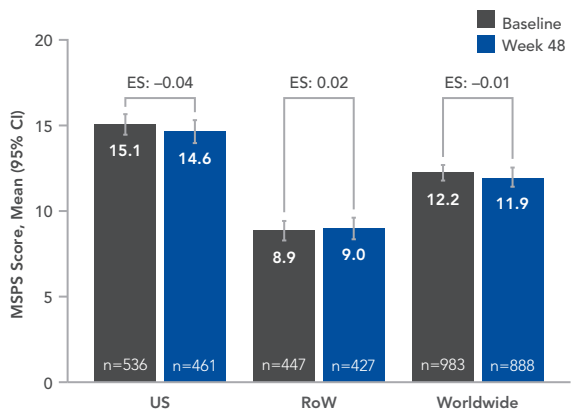
- **Patient-reported disability, as measured by the MSPS total score and PDDS, remained stable over the course of the Teri-PRO study, regardless of region and associated differences in baseline disability**
  - **Over the course of the study, there was a decrease in the total proportion of patients reporting severe or total disability in most of the MSPS subscales**
- **Patient-reported PDDS scale scores correlated strongly with EDSS scores**
- **Patients' cognitive function remained stable over the course of the study, as measured by both the Cognitive Symptoms MSPS subscale and the SDMT**
- **In combination with other Teri-PRO outcomes, including the primary outcome of patient treatment satisfaction, these disability and cognition results support the use of teriflunomide as a first-line therapy for relapsing-remitting MS**

Table 1. Demographics and Baseline Disease Characteristics

Characteristic	US (n=545)	RoW (n=455)	Worldwide (N=1000)
Age, mean (SD), y	50.6 (10.5)	42.9 (10.1)	47.1 (11.0)
Female, n (%)	413 (75.8)	343 (75.4)	756 (75.6)
Race, n (%)			
Asian/Oriental	0	3 (0.7)	3 (0.3)
Black	49 (9.0)	1 (0.2)	50 (5.0)
Caucasian/white	488 (89.5)	450 (98.9)	938 (93.8)
Other	8 (1.5)	1 (0.2)	9 (0.9)
Time since first symptoms of MS, mean (SD), y	14.7 (9.8)	11.3 (8.9)	13.2 (9.5)
Time since most recent relapse onset, mean (SD), mo	32.2 (51.6)[a]	30.1 (39.9)[b]	31.2 (46.5)[c]
Number of relapses within past 2 years, mean (SD)	1.3 (1.7)[d]	1.1 (1.1)	1.2 (1.5)[e]
Baseline EDSS score, mean (SD)	3.7 (1.9)[f]	2.2 (1.6)[g]	3.1 (2.0)[h]
Previous DMT within past 2 years, n (%)			
No	160 (29.4)	125 (27.5)	285 (28.5)
Yes	385 (70.6)	330 (72.5)	715 (71.5)
Previous DMT within past 6 months (switchers), n (%)	316 (58.0)	278 (61.1)	594 (59.4)

[a]n=519; [b]n=452; [c]n=971; [d]n=544; [e]n=999; [f]n=543; [g]n=453; [h]n=996.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; RoW, rest of the world; SD, standard deviation.

Figure 1. MSPS Total Scores at Baseline and Week 48 in All Patients and by Region



MSPS score was calculated from the sum of individual scores in 8 of the domains evaluated.
CI, confidence interval; ES, effect size; MSPS, Multiple Sclerosis Performance Scale; RoW, rest of the world.

Disability

Multiple Sclerosis Performance Scale

- At baseline, MSPS total score was higher for US patients compared with RoW patients, reflecting the higher baseline EDSS score in the US cohort (**Figure 1**)
- MSPS total scores remained stable (and with negligible ES values) in both regional groups, as well as in all patients, over the course of the 48-week study (**Figure 1**)
- In all patients, the proportion reporting no or minimal disability at Week 48 vs baseline was similar or had increased in 10 of the 11 MSPS subscales (**Figure 2**)
  - A small decrease was seen in the proportion of patients reporting no or minimal disability in the subscale relating to bladder or bowel symptoms
  - Over the course of the study, the proportion of patients with severe or total disability declined in several subscales

Expanded Disability Status Scale and Patient-Determined Disease Steps

- At baseline, EDSS scores were substantially higher in the US compared with the RoW cohort (**Table 2**). However, EDSS score distributions over the course of the study remained stable regardless of region (**Figure 3**)
- At baseline, patient-reported disability measured by PDDS was also higher in the US vs the RoW cohorts, and also remained stable from baseline to Week 48 regardless of region (**Table 2**)
- There were strong and significant correlations between PDDS scores and EDSS scores at both baseline and Week 48

Table 2. Evolution of EDSS and PDDS Scores and Correlations for US, RoW, and Worldwide Patient Cohorts[a]

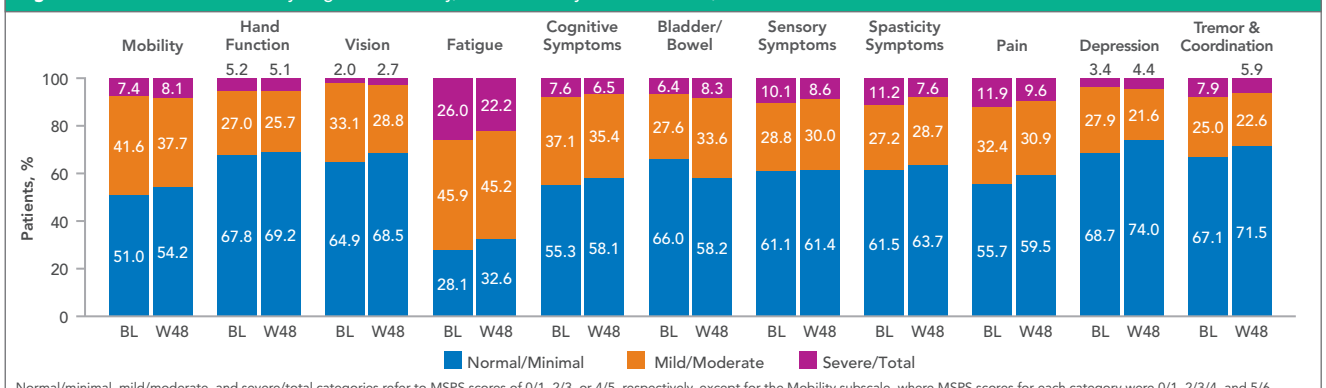
Characteristic	US (n=545)		RoW (n=455)		Worldwide (N=1000)	
	EDSS	PDDS	EDSS	PDDS	EDSS	PDDS
Baseline score, mean (SD)	3.7 (1.9)	2.8 (2.0)	2.2 (1.6)	1.6 (1.7)	3.1 (1.9)	2.3 (2.0)
PDDS–EDSS correlation, r_s	0.76 (P<0.0001)		0.67 (P<0.0001)		0.75 (P<0.0001)	
Week 48 score, mean (SD)	3.7 (2.0)	2.8 (2.1)	2.4 (1.7)	1.6 (1.7)	3.1 (2.0)	2.2 (2.0)
PDDS–EDSS correlation, r_s	0.74 (P<0.0001)		0.69 (P<0.0001)		0.73 (P<0.0001)	

[a]Based on available data. EDSS, Expanded Disability Status Scale; PDDS, Patient-Determined Disease Steps; RoW, rest of the world; r_s, Spearman's rank correlation coefficient; SD, standard deviation.

Cognition

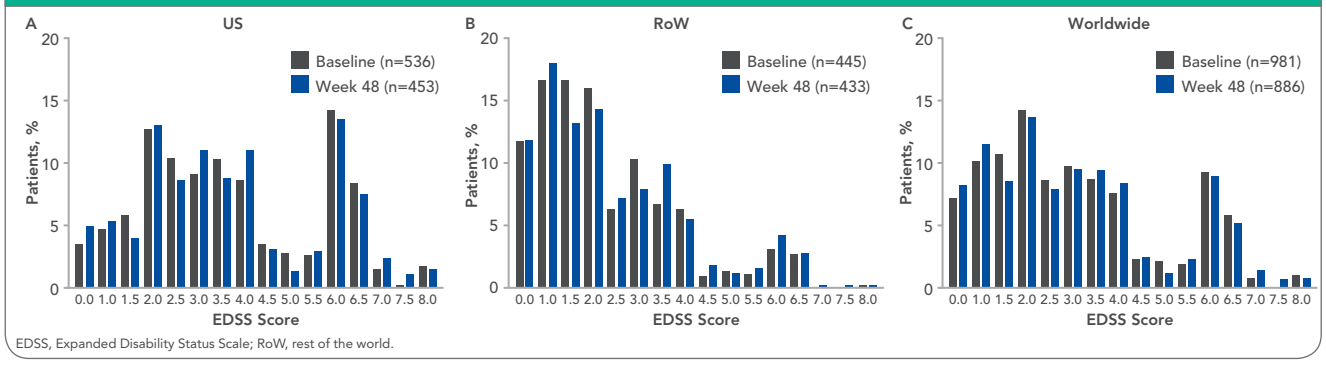
- Clinician-administered SDMT scores measuring cognition were high and similar at baseline and Week 48, with mean (standard deviation) values of 0.97 (0.05) and 0.98 (0.05), respectively
  - In the patient-reported MSPS Cognitive Symptoms subscale, more than half of patients reported no or minimal disability at both baseline and Week 48 (55.3% and 58.1% of patients, respectively, **Figure 2**)

Figure 2. Distribution of Patients by Degree of Disability, as Measured by MSPS Subscales, at Baseline and Week 48 in All Patients



Normal/minimal, mild/moderate, and severe/total categories refer to MSPS scores of 0/1, 2/3, or 4/5, respectively, except for the Mobility subscale, where MSPS scores for each category were 0/1, 2/3/4, and 5/6, respectively. BL, baseline; MSPS, Multiple Sclerosis Performance Scale; W48, Week 48.

Figure 3. Frequency Distribution of EDSS Scores at Baseline and Week 48 in (A) US, (B) RoW, and (C) All Patients



EDSS, Expanded Disability Status Scale; RoW, rest of the world.

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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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