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Teriflunomide Real-World Outcomes From the US Cohort of the Phase 4 Teri-PRO Study

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OBJECTIVE

- **To report patient-reported outcomes (PROs), effectiveness, safety, tolerability, and treatment satisfaction for patients enrolled in the phase 4 Teri-PRO study in the United States**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS in 70 countries, with more than 71,000 patients currently being treated with teriflunomide worldwide
- The global Teri-PRO study (NCT01895335) evaluated treatment satisfaction, disability, and quality of life (QoL) associated with teriflunomide treatment using validated PROs, as well as the effectiveness, safety, and tolerability of teriflunomide in routine clinical practice
  - High levels of treatment satisfaction were reported over the course of the 48-week study across the total study population[1]
- PROs can complement traditional outcome measures, enhancing understanding of the effects of the disease and treatment on health-related QoL, and providing insights on global satisfaction with therapy[2,3]
  - Patient perceptions of their treatment and overall satisfaction with the effect on their QoL may affect treatment adherence and, therefore, outcomes[2,4]

METHODS

Study Design

- Teri-PRO was a prospective, multicenter, single-arm, open-label study; the study design and inclusion criteria have been presented previously[5]
- Patients in the US cohort received once-daily teriflunomide 14 mg or 7 mg (US only), according to local labeling
  - "Treatment-naïve" patients in the context of this study are defined as those with no disease-modifying therapy (DMT) use within 2 years prior to study start
  - "Switchers" are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start

Study Outcomes

Treatment Satisfaction

- The primary outcome, global treatment satisfaction at Week 48, was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4)[6]
  - In treatment-naïve patients, TSQM scores were reported at Week 4 and Week 48, or end of treatment (EoT)
  - In switchers, TSQM scores were reported at baseline, Week 4, and Week 48, or EoT
- The TSQM has 14 items and generates 4 domain scores: Effectiveness, Side Effects, Convenience, and Global Satisfaction
  - A higher TSQM score indicates greater treatment satisfaction in a particular domain
- The TSQM has shown good measurement properties using traditional psychometric methods applied to data from both this study[7] and the TENERE (NCT00883337) phase 3 trial[8]
- Effect size (ES), potentially useful in evaluating whether differences in groups over time are clinically meaningful and relevant to patients, was defined as the mean 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[9]: <0.2, negligible; ≥0.2 to <0.5, small; ≥0.5 to ≤0.8, moderate; and >0.8, high

Disability

- Disability outcomes were measured using the Expanded Disability Status Scale, Patient-Determined Disease Steps (PDDS) scale,[10] and Multiple Sclerosis Performance Scale (MSPS)[11,12]
- The PDDS scale measures patient-reported disability, focusing mainly on ambulatory function, and is scored from 0 (normal) to 8 (bedridden)
- The MSPS requires patients to indicate their level of disability experienced during the past month
  - A total MSPS score (ranging from 0 to 41) is calculated as the sum of the scores on 8 individual subscales (Mobility, Hand Function, Vision, Fatigue, Cognitive Symptoms, Bladder/Bowel, Sensory Symptoms, and Spasticity Symptoms), with a higher score reflecting greater disability
- Disability was assessed at baseline and Week 48 (or EoT)

Quality of Life

- The Multiple Sclerosis International Quality of Life (MusiQoL)[13,14] scale consists of 31 questions, divided into 9 dimensions: Activities of Daily Living, Psychological Well-being, Symptoms, Relationships With Friends, Relationships With Family, Sentimental and Sexual Life, Coping, Rejection, and Relationship With Healthcare System
  - A total MusiQoL score is calculated as the mean of the dimension scores, with higher scores reflecting higher QoL
- QoL was assessed at baseline and Week 48 (or EoT)

Safety

- Adverse events (AEs) were reported at each study visit (baseline and Weeks 4, 24, and 48)

Statistical Analysis

- *P* values for change vs baseline were derived post hoc for TSQM, PDDS, MSPS, and MusiQoL scores, using an analysis of covariance model adjusted for baseline score and baseline EDSS score (categorized as ≤3.5 or >3.5). Post hoc analyses for TSQM scores were also performed for the switcher group based on prior DMT

RESULTS

- Of the 545 patients included in US sites in Teri-PRO, 160 (29.4%) were treatment-naïve and 316 (58.0%) were switchers
- Baseline demographics and disease characteristics are shown in **Table 1**
  - With the exception of time since first symptoms of MS and time since most recent relapse onset, characteristics were similar between both cohorts

Table 1. Baseline Demographics and Disease Characteristics

	Treatment-Naïve[a] (n=160)	Switchers[b] (n=316)
Age, mean (SD), y	50.5 (10.5)	51.1 (10.3)
Female, n (%)	116 (72.5)	245 (77.5)
Race, n (%)		
Black	14 (8.8)	27 (8.5)
Caucasian/white	145 (90.6)	284 (89.9)
Other	1 (0.6)	5 (1.6)
Time since first symptoms of MS, mean (SD), y	13.4 (10.7)	15.3 (9.7)
Number of relapses within past 2 years, mean (SD)	1.4 (1.7)[c]	1.3 (1.8)
Time since most recent relapse onset, mean (SD), mo	22.1 (37.1)[d]	37.8 (58.3)[e]
Reason for treating with teriflunomide, n (%)[f]		
Disease worsening[g]	15 (9.4)	65 (20.6)
Convenience (for oral daily intake)	131 (81.9)	147 (46.5)
Intolerance to administration mode	10 (6.3)	56 (17.7)
Side effects/risk of side effects	9 (5.6)	102 (32.3)
Other	13 (8.1)	17 (5.4)

[a]Treatment-naïve patients are defined as those with no DMT use within 2 years prior to study start; [b]switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start; [c]n=159; [d]n=149; [e]n=302; [f]more than 1 reason for teriflunomide treatment could be selected by the investigator; [g]as defined by the investigator. DMT, disease-modifying therapy; SD, standard deviation.

- The majority of switchers had previously received injectable DMTs (interferon B [IFN B] or glatiramer acetate [GA]), with some switching from other oral DMTs (dimethyl fumarate [DMF] or fingolimod) or infusible therapy (natalizumab) (**Table 2**)

Table 2. Last DMT Before First Teriflunomide Intake in US Switchers

US Cohort	n (%)
Interferon B	142 (44.9)
Glatiramer acetate	65 (20.6)
Dimethyl fumarate	51 (16.1)
Fingolimod	24 (7.6)
Natalizumab	34 (10.8)

DMT, disease-modifying therapy.

Treatment Satisfaction

- Treatment satisfaction in the US treatment-naïve cohort remained high over the study period across all TSQM domains (**Figure 1A**)
- In switchers, TSQM scores across all 4 domains significantly improved from baseline to Week 48 (**Figure 1B**). These improvements were observed as early as Week 4 (*P*<0.0001 in all domains)
  - At Week 48, a high ES value was observed in the Convenience domain (1.11)
- In patients switching from IFN B or DMF, scores in all 4 TSQM domains significantly improved at Week 48 compared with baseline (**Figures 2A** and **2C**). Improvements were observed as early as Week 4 (*P*<0.001 in all domains)
  - At Week 48, high ES values vs baseline were seen in the Convenience domain (1.56) for IFN B and high or moderate values were seen across all domains in patients who had previously received DMF (Global Satisfaction, 0.81; Effectiveness, 1.08; Side Effects, 0.77; and Convenience, 0.66)
- Improvements were also observed at Week 48 for patients switching from GA (significant in all domains except Effectiveness; **Figure 2B**) or fingolimod (significant in all domains except Side Effects; **Figure 2D**). Improvements were observed as early as Week 4 across all domains in patients switching from GA (*P*<0.001 in all domains) and in the domains of Effectiveness (*P*=0.0011), Side Effects (*P*=0.467), and Global Satisfaction (*P*=0.0005) in patients switching from fingolimod
  - At Week 48, high ES values vs baseline were seen in the Convenience domain (1.11) for GA and moderate values were observed in the domains of Global Satisfaction (0.58) and Convenience (0.58) in patients who had received fingolimod
- In patients switching from natalizumab, a significant increase was seen in the Convenience domain (**Figure 2E**). Improvements were observed as early as Week 4 in the domains of Global Satisfaction (*P*=0.0121), Effectiveness (*P*=0.0214), and Convenience (*P*<0.0001)
  - At Week 48, moderate ES values vs baseline were seen in the Convenience domain (0.77)

Disability

- EDSS, PDDS, and MSPS scores remained stable over the course of the study in both treatment-naïve patients and switchers (**Table 3**)
  - Patient-reported disability remained stable regardless of which prior DMT switchers had received

Quality of Life

- Mean (95% confidence interval) MusiQoL total scores also remained stable throughout the study for treatment-naïve patients (baseline: 64.8 [62.2, 67.3]; Week 48: 66.0 [62.9, 69.0]) and switchers (baseline: 64.8 [63.1, 66.4]; Week 48: 67.1 [65.4, 68.9])

Relapses Requiring Treatment

- Treatment-naïve patients had a lower mean treated relapse rate (0.11) than switchers (0.21)

Table 3. EDSS, PDDS, and MSPS Scores at Baseline and Week 48

	Treatment-Naïve[a]		Switchers[b]	
	Baseline	Week 48	Baseline	Week 48
EDSS score, mean (95% CI)	3.58 (3.28, 3.89)[c]	3.59 (3.22, 3.96)[d]	3.77 (3.55, 3.99)[e]	3.68 (3.44, 3.91)[f]
PDDS score, mean (95% CI)	2.88 (2.57, 3.20)[g]	2.91 (2.53, 3.29)[h]	2.73 (2.50, 2.96)[i]	2.64 (2.40, 2.89)[j]
MSPS overall score, mean (95% CI)	14.62 (13.53, 15.72)[k]	14.33 (13.01, 15.65)[l]	15.02 (14.23, 15.82)[m]	14.42 (13.56, 15.28)[n]

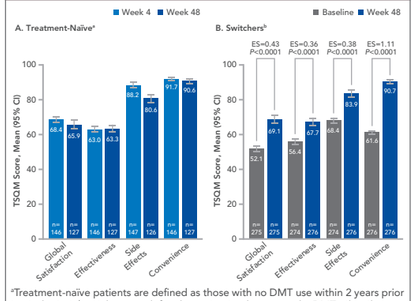
[a]Treatment-naïve patients are defined as those with no DMT use within 2 years prior to study start; [b]switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start; [c]n=157; [d]n=125; [e]n=313; [f]n=272; [g]n=155; [h]n=128; [i]n=309; [j]n=273; [k]n=157; [l]n=128; [m]n=311; [n]n=274. CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MSPS, Multiple Sclerosis Performance Scale; PDDS, Patient-Determined Disease Steps.

- Of 160 treatment-naïve patients and 316 switchers, 148 (92.5%) and 269 (85.1%), respectively, experienced no relapses requiring treatment during the study period

Safety

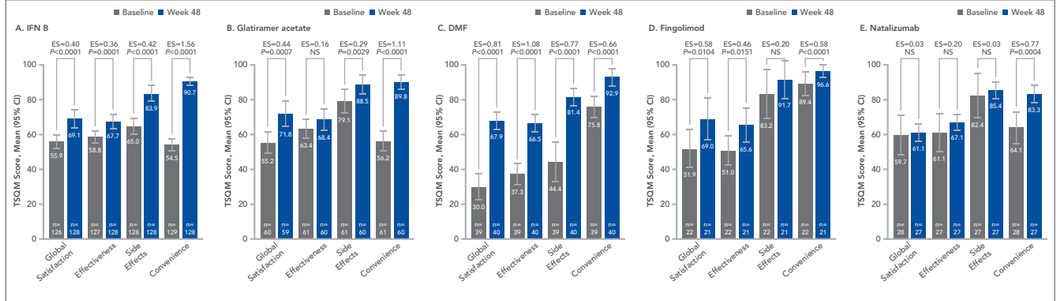
- AEs were reported in 126 (78.8%) treatment-naïve patients and 253 (80.1%) switchers, and were mostly of mild to moderate intensity
- Serious AEs were reported in 20 (12.5%) treatment-naïve patients and 42 (13.3%) switchers
- AEs leading to permanent treatment discontinuation were reported in 20 (12.5%) treatment-naïve patients and 34 (10.8%) switchers
- Three AEs leading to death were reported in US switchers: pneumonia, MS relapse, and myocardial infarction; no deaths were considered related to teriflunomide treatment

Figure 1. Treatment Satisfaction by TSQM Domain in the US Cohort



[a]Treatment-naïve patients are defined as those with no DMT use within 2 years prior to study start; [b]switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start. CI, confidence interval; ES, effect size; TSQM, Treatment Satisfaction Questionnaire for Medication.

Figure 2. Treatment Satisfaction at Baseline and Week 48 in Switchers[a] in the US Cohort According to Previous DMT



[a]Switchers are defined as patients who received a DMT other than teriflunomide within the 6 months prior to study start.
CI, confidence interval; DMF, dimethyl fumarate; DMT, disease-modifying treatment; ES, effect size; IFN, interferon; TSQM, Treatment Satisfaction Questionnaire for Medication.

CONCLUSIONS

- **These results support the use of teriflunomide 14 mg as an effective treatment in both treatment-naïve patients and patients switching from other DMTs**
- **In patients who switched from a prior DMT, improved treatment satisfaction, stable disability, and low relapse rates were observed over the course of the study**
- **High levels of treatment satisfaction may lead to improved adherence to therapy, thereby potentially improving overall outcomes**

References

1. Coyle et al. ePoster EP1484, ECTRIMS 2016.
2. Haase et al. *Ther Adv Neur Dis*. 2016;9:250.
3. Chua et al. *Mult Scler Relat Disord*. 2015;4:598.
4. Barbosa et al. *Patient Prefer Adherence*. 2012;6:39.
5. Coyle et al. Poster P078, ACTRIMS-ECTRIMS 2014.
6. Atkinson et al. *Health Qual Life Outcomes*. 2004;2:12.
7. Hobart et al. Poster P351, ECTRIMS 2016.
8. Vermersch et al. *Mult Scler*. 2017;23:604.
9. Cohen. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed, 1988: Ch8.
10. Hohol et al. *Neurology*. 1995;45:251.
11. Schwartz et al. *Neurology*. 1999;52:63.
12. Marrie et al. *Mult Scler*. 2007;13:1176.
13. Bandari et al. *Int J MS Care*. 2010;12:34.
14. Simeoni et al. *Mult Scler*. 2008;14:219.

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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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