50

Long-Term Efficacy and Safety of Teriflunomide: An Analysis of Pooled Clinical Trials

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OBJECTIVE

- **To report long-term (up to 12 years) efficacy and safety outcomes in a pooled analysis of teriflunomide 14 mg data from the Phase 2 (Core: NCT01487096, Extension: NCT00228163) study and Phase 3 TEMSO (Core: NCT00134563, Extension: NCT00803049), TOWER (NCT00751881), TOPIC (NCT00622700) and TENERE (NCT00883337) clinical trials and their extensions**

CONCLUSIONS

- **In this pooled analysis of patients receiving teriflunomide 14 mg over long-term follow-up, overall ARR (0.228) and yearly ARRs were low and stable (ranging from 0.321 in Year 1 to 0.080 in Year 12), and the yearly proportions of patients free from relapse were high and stable (ranging from 0.75 in Year 1 to 0.93 in Years 8 and 9)**
- **Disability status as measured by EDSS remained stable through Year 12 (2.57 at baseline and 2.27 at Year 12)**
- **No new safety signals were reported in these clinical trials; most AEs were mild to moderate in severity**
- **These data demonstrate the long-term efficacy and safety of teriflunomide**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of MS in over 80 countries, including the United States and those of the European Union. As of August 2018, over 93,000 patients were being treated with teriflunomide, with a total real-world exposure of approximately 186,000 patient-years as of December 2017
- The efficacy and safety of teriflunomide have been established in patients with relapsing MS (RMS) in one Phase 2[1] study and the Phase 3 TEMSO,[2] TOWER,[3] and TENERE[4] studies, and in patients with a first clinical episode suggestive of MS in the Phase 3 TOPIC[5] study
- In the Phase 2 trial, patients treated with teriflunomide 14 mg had fewer combined unique active lesions per magnetic resonance imaging (median: 0.3 vs 0.5, $P<0.01$) and lower mean annualised relapse rates (ARRs) compared with placebo (0.55 vs 0.81); significantly fewer patients receiving teriflunomide 14 mg versus placebo demonstrated disability increase (7.4% vs 21.3%; $P<0.04$)
- In TEMSO, TOPIC and TOWER, teriflunomide 14 mg was found to significantly reduce ARR by 31.5% ($P<0.001$), 31.9% ($P=0.0579$) and 36.3% ($P=0.0001$), respectively, compared with placebo. A lower percentage of patients experienced confirmed disability worsening (sustained for 12 weeks) with teriflunomide 14 mg compared with placebo in all three studies (TEMSO: 20.2% vs 27.3%; TOPIC 7% vs 10%; TOWER: 15.8% vs 19.7%) at 108 weeks
- In TENERE, patients treated with teriflunomide 14 mg had comparable ARRs to those receiving subcutaneous interferon β-1a 44 µg (IFN β-1a; 0.22 vs 0.26, $P=0.60$)
- In all five trials, the safety and tolerability profile of teriflunomide was acceptable. Common adverse events (AEs) associated with teriflunomide included headache, nausea, diarrhoea and hair thinning
- Here, we evaluate the long-term efficacy and safety of teriflunomide using pooled data from the Phase 2 study, and the Phase 3 TEMSO, TOPIC (safety data only), TOWER and TENERE core and extension studies

METHODS

Study Design and Methods

- The Phase 2 trial and Phase 3 TEMSO and TOWER trials were double-blind, placebo-controlled studies in which patients with RMS were randomised 1:1:1 to receive placebo, teriflunomide 7 mg, or teriflunomide 14 mg. The TOPIC study used the same design and randomisation ratio in patients with a first clinical episode suggestive of MS. Patients were treated for 36 weeks in the Phase 2 trial, 108 weeks in TEMSO and TOPIC, and ≥48 weeks in TOWER
- TENERE was a Phase 3, rater-blind study in which patients with RMS were randomised 1:1:1 to receive subcutaneous IFN β-1a 44 µg, teriflunomide 7 mg, or teriflunomide 14 mg. The study was completed 48 weeks after the last patient was randomised
- In the extension studies, patients initially treated with teriflunomide either continued their original dose (Phase 2, TEMSO, TOPIC) or received teriflunomide 14 mg regardless of their original dose (TOWER, TENERE). Patients who initially received placebo or IFN β-1a were reassigned 1:1 to teriflunomide 7 mg or 14 mg (Phase 2, TEMSO, TOPIC), or received teriflunomide 14 mg (TOWER, TENERE)
- In this analysis, efficacy and safety data were pooled from the Phase 2, TEMSO, TOPIC (safety data only), TOWER and TENERE core and extension studies for patients ever exposed to teriflunomide 14 mg
  - Outcome measures examined in the Phase 2 trial, TEMSO, TOWER and TENERE trials include ARR, percentage of patients free from relapse, Expanded Disability Status Scale (EDSS) scores, and AEs
  - Safety data (AE rates) also included data from TOPIC
  - While data were collected in patients for **up to 12.8 years**, data **through Year 12** are presented in this poster

Statistical Analysis

- Efficacy-related analyses were conducted using the combined modified intent-to-treat populations from the Phase 2 study and the Phase 3 TEMSO, TOWER and TENERE core and extension studies (i.e. all patients who were randomised and who received at least one dose of study drug)
- Unadjusted ARR was defined as the total number of confirmed relapses that occurred during the treatment period divided by the total number of patient-years followed during that period
- To assess potentially higher relapse activity in patients who discontinued early, we calculated ARR and proportion relapse-free in the last year of follow-up. Last year of follow-up was calculated for each patient as the last 365 days during which the patient participated in the study, regardless of whether they completed the study or discontinued early
- ARR, proportion of relapse-free patients, and EDSS scores were plotted to determine trends over time
- Analyses of AEs were conducted using the safety population (i.e. patients were analysed according to the dose of treatment they received, rather than the group to which they were randomised) of the Phase 2, TEMSO, TOPIC, TOWER and TENERE trials

RESULTS

Patient Demographics

- A total of **1978 patients** treated with teriflunomide 14 mg were included in the pooled analyses. Demographic and baseline disease characteristics are presented in **Table 1** for patients who ever received teriflunomide 14 mg in the core and extension studies
- 64.8% and 66.1% of patients completed the core studies (in the placebo and teriflunomide 14 mg groups, respectively), and the majority of these patients entered the extension (placebo: 60.4%, teriflunomide 14 mg: 62.3%). The overall completion rate in the extension was 69.3%
- The cumulative treatment exposure for the core plus extension studies for teriflunomide 14 mg was **6555.4 patient-years**. The median (minimum, maximum) duration of treatment was **153.2 (0.1, 668.9) weeks**

Table 1. Demographics and Baseline Characteristics of Patients in the Pooled Phase 2, TEMSO, TOPIC, TOWER and TENERE Core and Extension Studies

	Teriflunomide 14 mg (N=1978)
Age, mean (SD), years	37.9 (9.2)
Female, n (%)	1409 (71.2)
White, n (%)	1809 (91.5)
Time from diagnosis of MS, mean (SD), years[a]	5.8 (5.6)
Time from first symptoms of MS, mean (SD), years[a]	8.9 (6.9)
MS sub-type, n (%)	
Relapsing-remitting	1632 (82.6)
Progressive-relapsing	33 (1.7)
Secondary progressive	29 (1.5)
Clinically Isolated Syndrome[b] (CIS)	282 (14.3)
Number of relapses within past year, mean (SD)	0.9 (0.8)
Baseline EDSS score, mean (SD)	2.5 (1.4)

[a]TEMSO, TOWER, TENERE and Phase 2 study patients. [b]Only TOPIC study patients have CIS.
EDSS, Expanded Disability Status Scale; SD, standard deviation.

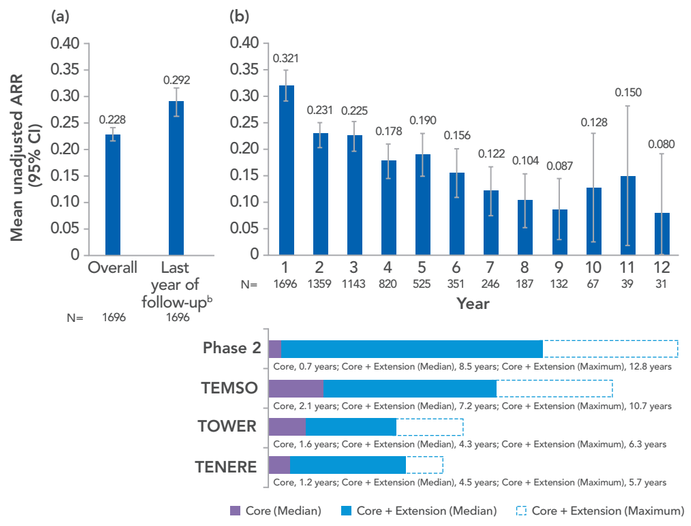
Relapses

- The overall ARR with teriflunomide 14 mg was 0.228 (**Figure 1a**). ARRs generally decreased over time (**Figure 1b**)
- The yearly ARR ranged from 0.321 in Year 1 to 0.080 in Year 12
- The overall proportion of patients remaining free from relapse during the course of the core and extension studies was 0.41 (0.36, 0.45) (**Figure 2a**)
- The proportion of patients remaining free from relapse during the last year of follow-up was 0.80 (0.77, 0.81) (**Figure 2a**)
- The yearly proportion (95% confidence interval) of patients remaining free from relapse ranged from 0.75 (0.73, 0.77) in Year 1 to 0.93 (0.88, 0.96) in Years 8 and 9 (0.87, 0.97) (**Figure 2b**)

EDSS Score

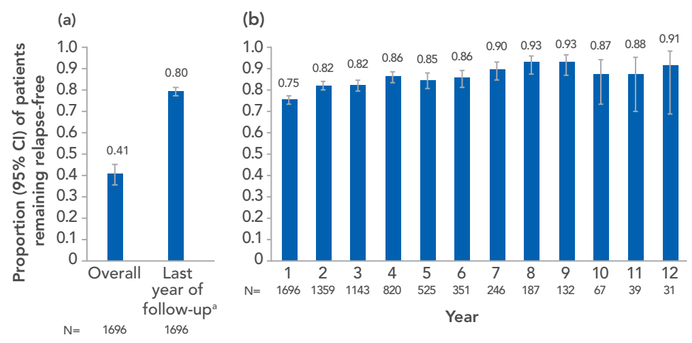
- Mean EDSS scores were 2.57 at baseline and 2.27 at Year 12 (**Figure 3a**)
- Mean EDSS scores in the individual core and extension studies are shown in **Figure 3b**
- Mean EDSS change from baseline was 0.08 at Year 1 and 0.68 at Year 12 (**Figure 3c**)

Figure 1. Mean ARR in the Phase 2, TEMSO, TOWER and TENERE Pooled Core and Extension Studies (a) Overall and in the Last Year of Follow Up, and (b) in Each Year[a]



[a]Lower part of figure displays median duration of exposure to teriflunomide 14 mg in the core study and median and maximum duration in the core plus extension studies. The planned extension durations varied across the studies: Phase 2, up to when teriflunomide was to be commercially available in the country where the patient resided; TEMSO, 192 weeks; TOWER, duration dependent on local availability of teriflunomide; and TENERE, a maximum of 106 weeks.
[b]The last year of follow-up was calculated for each patient as the last 365 days during which the patient participated in the study, regardless of whether they completed the study or discontinued early.
ARR, annualised relapse rate; CI, confidence interval.

Figure 2. Proportion of Patients Remaining Relapse-Free in the Phase 2, TEMSO, TOWER and TENERE Pooled Core and Extension Studies (a) Overall and in the Last Year of Follow-Up, and (b) in Each Year



[a]The last year of follow-up was calculated for each patient as the last 365 days during which the patient participated in the study, regardless of whether they completed the study or discontinued early.
ARR, annualised relapse rate; CI, confidence interval.

Safety

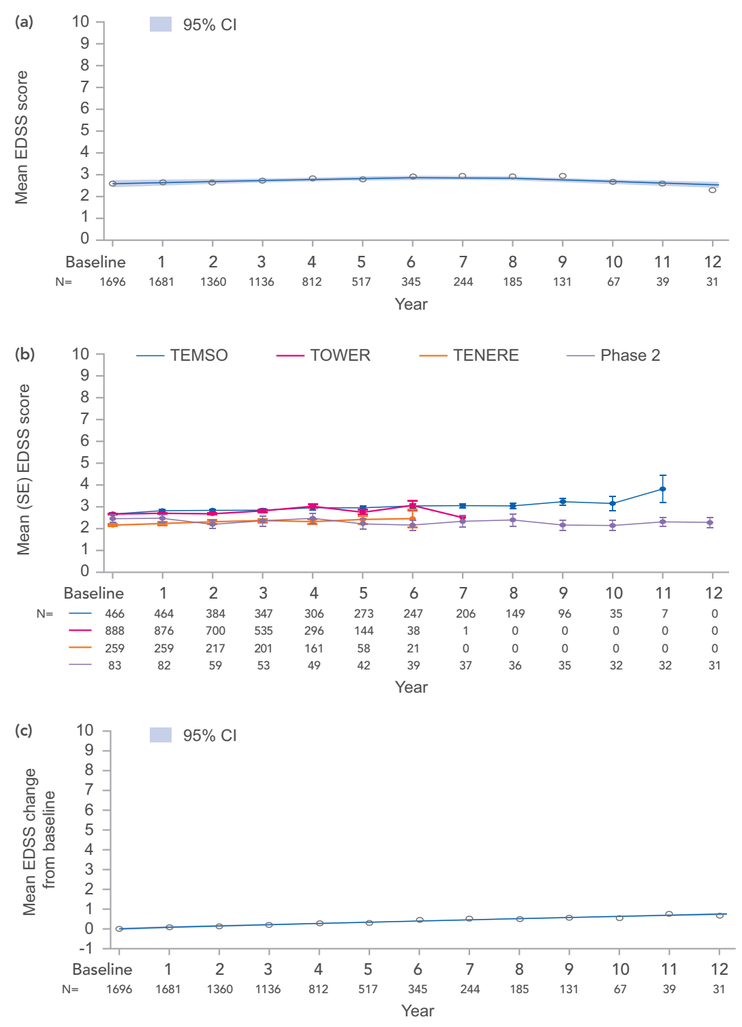
- Overall, 89.0% (1760/1978) of patients receiving teriflunomide 14 mg reported ≥1 AE; most AEs were mild to moderate in nature (**Table 2**)
- 18.5% (365/1978) of patients experienced serious AEs and 13.9% (274/1978) experienced AEs leading to permanent treatment discontinuation (**Table 2**)
- Over the 12-year period, there were 10 deaths among patients receiving teriflunomide 14 mg
  - Three of the deaths (due to pulmonary tuberculosis, suicide, and haematemesis), all occurring during the TOWER extension, were reported by investigators as related to teriflunomide treatment. The death due to haematemesis was later updated by the investigator as not associated with teriflunomide treatment. The remaining seven deaths (due to tachycardia, acute cardiac failure, gastrointestinal haemorrhage, suicide, septicemia, and sepsis) were not deemed to be related to treatment
  - The safety findings in the teriflunomide 7 mg arm were generally similar to that of teriflunomide 14 mg (data not shown)

Table 2. Summary of AEs

n (%)	Teriflunomide 14 mg N=1978
AEs	1760 (89.0)
Mild	442 (22.3)
Moderate	997 (50.4)
Severe	321 (16.2)
Serious AEs	365 (18.5)
ALT increased	30 (1.5)
Hepatic enzyme increased	12 (0.6)
Suicide attempt	11 (0.6)
Deaths	10 (0.5)
AE leading to permanent treatment discontinuation	274 (13.9)
AEs reported in ≥10% of patients[a]	
Nasopharyngitis	451 (22.8)
Headache	341 (17.2)
Diarrhoea	316 (16.0)
ALT increased	294 (14.9)
Hair thinning[b]	265 (13.4)
Back pain	254 (12.8)
Upper respiratory tract infection	229 (11.6)
Urinary tract infection	227 (11.5)
Influenza	222 (11.2)
Fatigue	220 (11.1)
Nausea	204 (10.3)
Arthralgia	160 (8.1)

[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)

Figure 3. Mean EDSS Scores in the Phase 2, TEMSO, TOWER and TENERE Core and Extension Studies (a) in Each Year, (b) for Individual Studies, and (c) Change from Baseline



Extension baseline was considered for the patients switched to teriflunomide 14 mg from placebo, teriflunomide 7 mg, or interferon β-1a 44 µg. Last non-missing post-baseline visit within each year was considered as the corresponding year. Graph line represents a Loess smoothing curve, with smooth=1. Shaded area represents 95% CI.
CI, confidence interval; EDSS, Expanded Disability Status Scale; SE, standard error.

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

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