Consistent Efficacy of Teriflunomide in Prespecified Subgroup Analyses From a Phase 3 Trial (TOPIC) in Patients With Early Multiple Sclerosis

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS
- The effect of teriflunomide has been assessed in 2 phase 3 clinical studies in patients with relapsing MS: TEMSO¹ (NCT00134563) and TOWER² (NCT00751881)
- Consistent and significant outcomes were observed for annualized relapse rate and disability progression in patients treated with teriflunomide 14 mg compared with placebo
- Teriflunomide 7 mg also significantly reduced annualized relapse rate in both TEMSO and TOWER
- Teriflunomide has shown a consistent and well-characterized safety profile that is similar for both the 14-mg and 7-mg doses
- TOPIC (NCT00622700) is a phase 3 study that evaluated the efficacy and safety
 of teriflunomide in patients with a first clinical episode suggestive of MS³
- The primary endpoint was relapse confirming clinically definite MS (CDMS)
- The key secondary endpoint was occurrence of a new clinical relapse or MRI lesion

OBJECTIVES

• To report primary efficacy outcomes and results of prespecified subgroup analyses of teriflunomide treatment effects in TOPIC

METHODS

Study Design and Patients

- Eligible patients were 18–55 years of age with a first acute or subacute neurological event consistent with demyelination (optic neuritis, spinal cord syndrome, brainstem/cerebellar syndromes) occurring within 90 days of randomization. An MRI scan demonstrating ≥2 T2 lesions of ≥3 mm in diameter, characteristic of MS (ie, ≥1 lesion periventricular in location or ovoid in shape), was also required
- A total of 614 patients were randomized (1:1:1) and treated with once-daily teriflunomide 14 mg, teriflunomide 7 mg, or placebo for up to 108 weeks
- The TOPIC study was stopped early following revisions to the MS diagnostic criteria in 2010⁴ that enabled earlier diagnosis, in some cases at first clinical event. Reevaluation of the power calculation based on updated information from the teriflunomide clinical program indicated that sufficient power to detect a reduction in risk of relapse had already been achieved
- MRI scans were performed at screening and at 12, 24, 48, 72, and 108 weeks, and were processed at a central MRI analysis center

Study Endpoints

- The primary endpoint was relapse confirming CDMS
- The key secondary endpoint was occurrence of a new clinical relapse or MRI lesion (gadolinium [Gd]-enhancing lesion or new T2 lesion), whichever occurred first

Subgroup Analyses

- The effect of teriflunomide on relapse indicating conversion to CDMS and on time to relapse or occurrence of a new MRI lesion was analyzed in subgroups defined by gender, age (< or ≥31 years), geographical region (Eastern Europe, Western Europe, the Americas, and Australia), baseline number of Gdenhancing lesions (0 or ≥1), total lesion volume (< or ≥5 mL), and monofocal/ multifocal status
- Consistency of treatment effects across subgroups was assessed using a Cox regression model utilizing a treatment-by-subgroup interaction test for each factor separately. The model included treatment, baseline monofocal/multifocal status, region, subgroup, and treatment-by-subgroup interaction as covariates

RESULTS

• Patient characteristics were well balanced across treatment groups (Table 1)

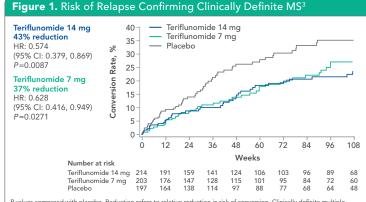
	Teriflunomide 14 mg (N=216)	Teriflunomide 7 mg (N=205)	Placebo (N=197)
Gender, %			
Female	71.3	63.4	68.5
Age, %			
<31 y	42.6	50.2	45.2
≥31 y	57.4	49.8	54.8
Region, %			
Eastern Europe	46.8	46.8	47.7
Western Europe	34.3	36.0	38.6
Americas and Australia	19.0	17.1	13.7
Gd-enhancing lesions, % ^{a,b}			
0	64.8	64.7	67.2
≥1	35.2	35.3	32.8
Total lesion volume, %°			
<5 mL	47.5	50.3	46.9
≥5 mL	52.5	49.7	53.1
Onset presentation, %			
Monofocal	59.7	59.5	57.9
Multifocal	40.3	40.5	42.1

*MRI values obtained within 14 days of systemic corticosteroid therapy were excluded from the analysis; "teriflunomide 14 mg, n=199; teriflunomide 7 mg, n=187; placebo, n=177; "teriflunomide 14 mg, n=200; teriflunomide 7 mg, n=187; placebo, n=177 Gd, gadolnium; SD, standard deviation.

Main Outcomes

New Clinical Relapses

- Both doses of teriflunomide reduced the risk of a new clinical relapse
- confirming CDMS compared with placebo (**Figure 1**)
- Teriflunomide 14 mg significantly reduced the risk of a new clinical relapse by 43% (P=0.0087)
- Teriflunomide 7 mg significantly reduced the risk of a new clinical relapse by 37% (P=0.0271)

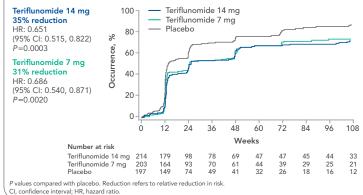


P values compared with placebo. Reduction refers to relative reduction in risk of conversion. Clinically definite multiple sclerosis defined by a new neurological abnormality separated by \geq 30 days from previous event with increase in \geq 1 functional system component or in Expanded Disability Status Scale score, and confirmed by the treating neurologist within 7 days. CI, confidence interval; HR, hazard ratio.

New Clinical Relapse or MRI Lesion

- Both doses of teriflunomide reduced the risk of a new clinical relapse or MRI lesion compared with placebo (Figure 2)
- Teriflunomide 14 mg significantly reduced the risk of a new clinical relapse or MRI lesion by 35% (P=0.0003)
- Teriflunomide 7 mg significantly reduced the risk of a new clinical relapse or MRI lesion by 31% (P=0.0020)

Figure 2. Risk of Relapse or MRI lesion³



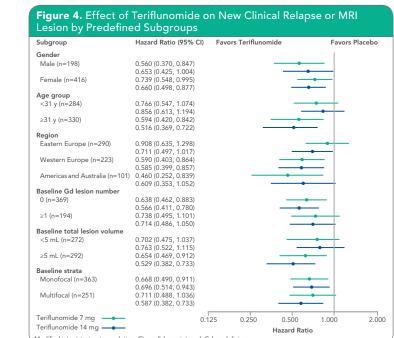
Subgroup Analyses New Clinical Relapse

• The efficacy of treatment on new clinical relapse was consistent across all predefined subgroups whether stratified according to demographic features (gender, age) or baseline disease characteristics (number of Gd-enhancing lesions, total lesion volume, monofocal/multifocal status), except for the Eastern European region in the teriflunomide 7-mg group (*P* value for interaction=0.0047), in which very few relapses were reported overall (Figure 3)

Gender Male (n=198) 0.536 (0.271, 1.059) 0.466 (0.216, 1.003) Female (n=416) 0.679 (0.404, 1.143) 0.632 (0.384, 1.042) Age group <31 y (n=284) 0.571 (0.329, 0.992) 0.633 (0.300, 1.116) ≥31 y (n=230) 0.657 (0.351, 1.230) 0.479 (0.269, 0.918) Region Eastern Europe (n=290) 1.659 (0.799, 3.446) 0.933 (0.419, 2.077) Western Europe (n=223) 0.479 (0.252, 0.815) Americas and Australia (n=101) 0.200 (0.054, 0.733) 0.549 (0.222, 1.359) 0.549 (0.275, 1.225) ≥1 (n=194) 0.732 (0.387, 1.383) 0.577 (0.268, 1.037) 0.557 (0.268, 1.037) Baseline total lesion volume - <5 mL (n=272) 0.633 (0.297, 1.221) 0.563 (0.297, 1.221) - 0.556 (0.255, 1.137) - Baseline strata 0.501 (0.286, 0.878) Monofocal (n=363) 0.632 (0.373, 1.068) 0.501 (0.272, 1.281) -	Subgroup	Hazard Ratio (95% Cl	Favors Teriflu	inomide	Fav	ors Plac	ebo
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New Clinical Relapse or MRI Lesion

 The treatment effect was also observed across all subgroups defined by gender, age, geographical region, number of Gd-enhancing lesions, total lesion volume, and monofocal/multifocal status for new clinical relapse or occurrence of a new MRI lesion, with no significant treatment by subgroup interaction (Figure 4)



Modified intent-to-treat population. CI, confidence interval; Gd, gadolinium.

CONCLUSIONS

- Both doses of teriflunomide had a consistently positive effect on time to new relapse and time to new relapse or occurrence of a new MRI lesion across patient subgroups defined by gender, age, baseline MRI variables, and monofocal/multifocal status
- These results were obtained despite premature termination of the study; therefore, the results may underestimate the true outcome
- Together with the results of TEMSO and TOWER, these findings support the consistent efficacy of teriflunomide across a broad range of patients and disease activity

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Disclosures

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Disclaimer

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.



DX23