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Effect of Teriflunomide in Subgroups Defined by Prior Treatment: Pooled Analysis of a Phase 2 Study and the Phase 3 TEMSO, TOWER and TENERE Studies

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OBJECTIVE

- **To investigate the efficacy and safety of teriflunomide in subgroups of patients with relapsing forms of MS, defined by prior treatment status, in a pooled *post-hoc* analysis of the Phase 2 study (NCT01487096) and the Phase 3 TEMSO (NCT00134563), TOWER (NCT00751881) and TENERE (NCT00883337) studies**

CONCLUSIONS

- **Teriflunomide 14 mg significantly reduced the risk of relapse compared with placebo irrespective of prior treatment status in this pooled analysis of a Phase 2 study and the Phase 3 TEMSO, TOWER and TENERE studies**
- **Although patients with prior DMT use had a higher level of baseline disease activity versus patients with no prior DMT use, teriflunomide demonstrated similar efficacy in these subgroups**
- **Most AEs were mild to moderate in severity and were generally similar across the three groups, though rates of diarrhoea were lower among patients who had not received a prior DMT**

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 forms of MS in a clinical trial programme, including a Phase 2 study[1] and the Phase 3 TEMSO[2], TOWER[3] and TENERE[4] studies
- Patients who received one or more previous disease-modifying therapies (DMTs) prior to study entry were eligible to participate
  - In the Phase 2 and TENERE studies, participants were not eligible to participate if they had received prior treatment with beta interferons
  - In all trials, patients were not eligible to enrol if they had received prior or concomitant treatment with cladribine, mitoxantrone, or other immunosuppressant agents
- Here, we evaluate the efficacy and safety of teriflunomide in subgroups of patients defined by prior treatment in a pooled *post-hoc* analysis of the Phase 2 study and the Phase 3 TEMSO, TOWER, and TENERE studies

METHODS

Phase 2, TEMSO and TOWER Study Designs and Patients

- Complete study designs, methods, and inclusion criteria for the Phase 2 study and the Phase 3 TEMSO and TOWER studies have been published previously[1-3]
- In the Phase 2 study, patients with relapsing MS (Expanded Disability Status Scale [EDSS] score ≤6, ≥2 relapses in the previous 3 years and ≥1 relapse during the preceding year) were randomised 1:1:1 to receive placebo, teriflunomide 7 mg, or teriflunomide 14 mg for up to 36 weeks
- In TEMSO and TOWER, patients with relapsing MS (EDSS score ≤5.5; ≥2 relapses in the previous 2 years or ≥1 relapse during the preceding year) were randomised 1:1:1 to receive placebo, teriflunomide 7 mg, or teriflunomide 14 mg for up to 108 weeks (TEMSO) or ≥48 weeks (TOWER)

TENERE Study Design and Patients

- The complete study design, methods and inclusion criteria for the TENERE study have been published previously[4]
- Patients with relapsing MS (EDSS score ≤5.5 at screening; relapse-free for 30 days prior to randomisation) were randomised 1:1:1 to receive teriflunomide 7 mg, teriflunomide 14 mg, or subcutaneous interferon (IFN) β-1a 44 µg for ≥48 weeks
- Patients who were randomised to IFN in the core period, but who entered the extension and were treated with teriflunomide 14 mg, were included in Group 2 (described below in **Table 1**) in the present analysis; their first 108 weeks on teriflunomide in the extension was considered their time on trial

Statistical Analysis

- Pooled data from patients from the intention to treat (ITT) study populations were included in these analyses
- Adjusted annualised relapse rates (ARRs) were compared between patients receiving placebo or teriflunomide (comparisons to the IFN arm were not conducted due to the relatively small sample size) according to the subgroups of prior MS treatment status outlined in **Table 1**
- Adjusted ARR was derived using Poisson regression

Table 1. Definitions of Prior MS Treatment Subgroups

Group	Definition
Group 1	Patients with no prior DMT
Group 2	Patients whose most recent prior DMT was discontinued within 6 months prior to randomisation
Group 3	Patients whose most recent prior DMT was discontinued 6 months to 2 years prior to randomisation

DMT, disease-modifying therapy.

- The response variable was the total number of confirmed relapses with an onset between randomisation date and last dose date
- Covariates included study, treatment and EDSS strata at baseline
- Log-transformed study duration was included as an offset variable
- Adverse events (AEs) were assessed among the safety population

RESULTS

Study Population

- There were 2643 patients in the pooled population, of whom 1883, 348 and 412 were in Groups 1, 2 and 3, respectively
- Demographics and baseline disease characteristics for the pooled study population are shown in **Table 2**
- Patients were predominantly white females and the mean age ranged from 37 to 39 years in the different groups. On average, disease duration was longer in patients in Groups 2 and 3 compared with Group 1

Table 2. Demographic and Baseline Characteristics (Safety Population[a])

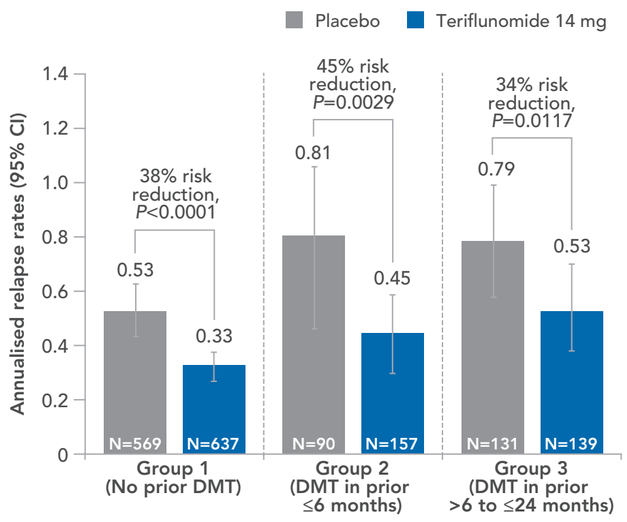
	Group 1 (No prior DMT)		Group 2 (DMT in prior ≤6 months)		Group 3 (DMT in prior >6 to ≤24 months)	
	Placebo (n=564)	Teriflunomide 14 mg (n=636)	Placebo (n=89)	Teriflunomide 14 mg (n=158)	Placebo (n=131)	Teriflunomide 14 mg (n=139)
Age, mean (SD), years	38.7 (9.0)	37.9 (9.3)	36.4 (9.5)	39.0 (9.6)	37.5 (8.6)	37.9 (8.4)
Female, n (%)	397 (70.4)	443 (69.7)	65 (73.0)	114 (72.2)	105 (80.2)	103 (74.1)
White, n (%)	497 (88.3)[b]	574 (90.3)	84 (94.4)	154 (97.5)	124 (94.7)	131 (94.9)[j]
Time since first diagnosis of MS, mean (SD), years	4.20 (5.60)	4.24 (5.52)[d]	5.85 (5.26)	6.18 (6.04)	6.83 (4.92)	8.00 (5.55)
Time since first symptoms of MS, mean (SD), years	7.57 (7.21)	7.39 (6.79)[e]	8.79 (7.02)	9.39 (7.19)	9.26 (5.63)	10.90 (6.87)
Number of relapses within past year, mean (SD)	1.40 (0.70)[c]	1.36 (0.68)[f]	1.49 (0.81)[g]	0.90 (0.88)[h]	1.42 (0.87)[i]	1.36 (0.81)[k]
Baseline EDSS score						
Mean (SD)	2.61 (1.38)	2.57 (1.33)	2.58 (1.37)	2.49 (1.38)	2.97 (1.32)	2.79 (1.37)
Median (min, max)	2.50 (0.0, 6.0)	2.50 (0.0, 6.5)	2.50 (0.0, 5.5)	2.00 (0.0, 6.5)	3.00 (0.0, 6.0)	2.50 (0.0, 6.0)

[a]The safety population included all patients who received at least one dose of the study drug; [b]n=563; [c]n=503; [d]n=635; [e]n=635; [f]n=579; [g]n=86; [h]n=151; [i]n=112; [j]n=138; [k]n=119; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Relapses

- Adjusted ARRs (95% confidence interval [CI]) were lower in patients treated with teriflunomide 14 mg compared with placebo, regardless of prior treatment status (**Figure 1**):
  - Group 1: 0.33 (0.28, 0.39) versus 0.53 (0.45, 0.62); relative risk (RR) 0.62, *P*<0.0001
  - Group 2: 0.45 (0.34, 0.60) versus 0.81 (0.57, 1.16); RR 0.55, *P*=0.0029
  - Group 3: 0.53 (0.40, 0.70) versus 0.79 (0.61, 1.03); RR 0.66, *P*=0.0117

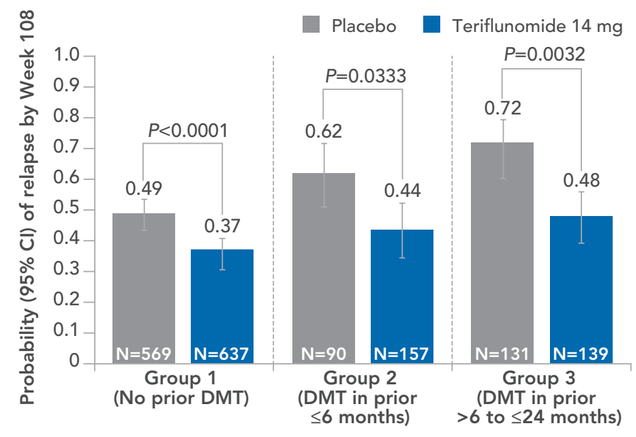
Figure 1. Annualised Relapse Rates in Patients Stratified by Prior Treatment Status



CI, confidence interval; DMT, disease-modifying therapy.

- Adjusted ARRs (95% CI) were lower in patients treated with teriflunomide 7 mg compared with placebo in Group 1 and Group 3, but not Group 2:
  - Group 1: 0.38 (0.33, 0.44) versus 0.53 (0.45, 0.62); RR 0.72, *P*=0.0001
  - Group 2: 0.68 (0.51, 0.92) versus 0.81 (0.57, 1.16); RR 0.84, *P*=0.4001
  - Group 3: 0.56 (0.44, 0.73) versus 0.79 (0.61, 1.03); RR 0.71, *P*=0.0284
- The probability (95% CI) of having had ≥1 relapse by Week 108 was significantly lower with teriflunomide 14 mg compared with placebo, regardless of prior treatment status (**Figure 2**):
  - Group 1: 0.37 (0.33, 0.42) versus 0.49 (0.45, 0.54), *P*<0.0001
  - Group 2: 0.44 (0.36, 0.53) versus 0.62 (0.51, 0.73), *P*=0.0333
  - Group 3: 0.48 (0.39, 0.58) versus 0.72 (0.63, 0.80), *P*=0.0032

Figure 2. Probability of Relapse by Week 108



Relapse probabilities are derived from Kaplan–Meier estimates.
CI, confidence interval; DMT, disease-modifying therapy.

- The probability (95% CI) of having had ≥1 relapse by Week 108 was lower with teriflunomide 7 mg compared with placebo in Group 1 and Group 3, but not Group 2
  - Group 1: 0.42 (0.38, 0.47) versus 0.49 (0.45, 0.54), *P* =0.0004
  - Group 2: 0.59 (0.47, 0.71) versus 0.62 (0.51, 0.73), *P*=0.5294
  - Group 3: 0.54 (0.45, 0.64) versus 0.72 (0.63, 0.80), *P*=0.0297

Safety

- The cumulative duration of exposure to teriflunomide 14 mg was 959.95, 311.11, and 211.33 patient years, for Groups 1, 2 and 3, respectively
- Rates of AEs, serious AEs (SAEs), and AEs leading to treatment discontinuation are shown in **Table 3**. Most AEs were mild to moderate in severity
- The most frequently reported AEs included diarrhoea, nasopharyngitis, upper respiratory tract infection, headache, nausea, hair thinning, fatigue and back pain
- In all three groups, rates of diarrhoea and hair thinning were higher among patients treated with teriflunomide 14 mg (ranging from 12.3% [Group 1] to 20.1% [Group 3] and 13.7% [Groups 1 and 3] to 13.9% [Group 2], respectively) than among patients treated with placebo (ranging from 5.9% [Group 1] to 15.3% [Group 3] and 3.7% [Group 1] to 6.1% [Group 3], respectively [data not shown])
- There were two deaths among patients with no prior DMT
  - These were due to suicide and bacterial sepsis
  - Both deaths occurred in patients treated with teriflunomide 14 mg in the TOWER trial. Neither death was adjudicated as being related to treatment

Table 3. Summary of AEs

	Group 1 (No prior DMT) Teriflunomide 14 mg (N=636)	Group 2 (DMT in prior ≤6 months) Teriflunomide 14 mg (N=158)	Group 3 (DMT in prior >6 to ≤24 months) Teriflunomide 14 mg (N=139)
Any AE, n (%)	559 (87.9)	142 (89.9)	129 (92.8)
Mild	181 (28.5)	24 (15.2)	27 (19.4)
Moderate	305 (48.0)	89 (56.3)	75 (54.0)
Severe	73 (11.5)	29 (18.4)	27 (19.4)
Any SAE, n (%)	76 (11.9)	25 (15.8)	21 (15.1)
Deaths, n (%)	2 (0.3)[a]	0	0
AE leading to treatment discontinuation, n (%)	74 (11.6)	24 (15.2)	20 (14.4)
AE preferred term, n (%)			
Diarrhoea	78 (12.3)	30 (19.0)	28 (20.1)
Nasopharyngitis	111 (17.5)	27 (17.1)	27 (19.4)
Upper respiratory tract infection	48 (7.5)	18 (11.4)	24 (17.3)
Headache	105 (16.5)	31 (19.6)	19 (13.7)
Nausea	66 (10.4)	19 (12.0)	19 (13.7)
Hair thinning (alopecia)	87 (13.7)	22 (13.9)	19 (13.7)
Back pain	64 (10.1)	15 (9.5)	17 (12.2)
Fatigue	63 (9.9)	22 (13.9)	16 (11.5)

AE, adverse event; DMT, disease-modifying therapy; SAE, serious adverse event.
[a]Deaths were due to suicide and bacterial sepsis.

References

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Acknowledgements and Disclosures

This poster was reviewed by Karyn Liu, PhD, Darren P Baker, PhD, and Jonathan Valenzano, PharmD, of Sanofi. Medical writing assistance for this poster was provided by David McMinn, PhD, for Onyx, Knutsford, UK, and was funded by Sanofi.

GC: Compensation for consulting services and/or speaking activities from Almirall, Biogen, Celgene, Excemed, Forward Pharma, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi and Teva; and fees for non-CME services from Almirall, Bayer, Biogen, Excemed, Genzyme, Merck Serono, Novartis, Receptos, Sanofi, SSIF and Teva. **MF:** Research/educational grant support from Bayer and Genzyme; honoraria/consulting fees from Bayer, Biogen, EMD Canada, Novartis, Sanofi and Teva; and member of company advisory boards/board of directors/other similar group for Bayer, Biogen, Chugai, Merck Serono, Novartis, Opexa Therapeutics, Sanofi and Teva. **JML:** Consulting fees from Almirall, Biogen, Merck Serono, Novartis, Sanofi and Teva. **PV:** Honoraria and consulting fees from Almirall, Bayer, Biogen, Celgene, Genzyme, Sanofi, GSK, Merck Serono, Novartis, Servier and Teva; and research support from Bayer, Biogen, Genzyme, Sanofi and Merck Serono. **BK:** Nothing to disclose. **AP:** Nothing to disclose. **KE:** Consulting fees from Biogen, Genzyme and EMD Serono; and research support from Biogen, Eli Lilly, Genentech, Sanofi, F Hoffmann-La Roche and Novartis. **RG:** Consulting fees from Bayer, Biogen, Elan, Genzyme, Roche and Teva; and grant/research support from Bayer, Biogen, Genzyme and Teva. **JO:** Speaker fees, advisory fees, travel and hospitality from Roche, Biogen, Novartis, Teva, Merck, MedDay, Allergan, Celgene and Genzyme; and research and departmental funds from Novartis, Biogen, Roche, Genzyme and Merck. **HK:** Employee of Sanofi with ownership interest. **JC:** Employee of Sanofi with ownership interest. **EP:** Employee of Sanofi with ownership interest. **PC:** Consulting fees from Accordant, Acorda, Bayer, Biogen, Celgene, Genentech, Roche, Genzyme, Sanofi, Novartis, Serono and Teva; and research support from Actelion, Alkermes, Genentech, Roche, MedDay, NINDS and Novartis.

Data included in this poster were presented at the 34th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS), 10-12 October 2018, Berlin, Germany.

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

Presented at the 26th Annual Meeting of the European Charcot Foundation (ECF), 15-17 November 2018, Baveno, Italy.
Funding provided by Sanofi.