Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Teriflunomide is an oral disease-modifying therapy approved for treatment of relapsing or relapsing–remitting multiple sclerosis. We aimed to provide further evidence for the safety and efficacy of teriflunomide in patients with relapsing multiple sclerosis.

Methods This international, randomised, double-blind, placebo-controlled, phase 3 study enrolled adults aged 18–55 years with relapsing multiple sclerosis, one or more relapse in the previous 12 months or two or more in the previous 24 months but no relapse in the previous 30 days, and an Expanded Disability Status Scale (EDSS) score of 5·5 points or less. Patients were recruited from 189 sites in 26 countries and randomly assigned (1:1:1) to once-daily placebo, teriflunomide 7 mg, or teriflunomide 14 mg via an interactive voice recognition system. Treatment duration was variable, ending 48 weeks after the last patient was included. The primary endpoint was annualised relapse rate (number of relapses per patient-year) and the key secondary endpoint was time to sustained accumulation of disability (an EDSS score increase of at least 1 EDSS point sustained for a minimum of 12 weeks), both analysed in the modified intention-to-treat population (all patients who received at least one dose of assigned study medication). This study is registered with ClinicalTrials.gov, number NCT00751881.

Findings Between Sept 17, 2008, and Feb 17, 2011, 1169 patients were randomly assigned to a treatment group, of whom 388, 407, and 370 patients received at least one dose of placebo, teriflunomide 7 mg, or teriflunomide 14 mg, respectively. By the end of the study, the annualised relapse rate was higher in patients assigned to placebo (0·50 [95% CI 0·43–0·58]) than in those assigned to teriflunomide 14 mg (0·32 [0·27–0·38]; p=0·0001) or teriflunomide 7 mg (0·39 [0·33–0·46]; p=0·0183). Compared with placebo, teriflunomide 14 mg reduced the risk of sustained accumulation of disability (hazard ratio [HR] 0·68 [95% CI 0·47–1·00]; log-rank p=0·0442); however, teriflunomide 7 mg had no effect on sustained accumulation of disability (HR 0·95 [0·68–1·35]; log-rank p=0·7620). The most common adverse events were alanine aminotransferase increases (32 [8%] of 385 patients in the placebo group *vs* 46 [11%] of 409 patients in the teriflunomide 7 mg group *vs* 52 [14%] of 371 patients in the teriflunomide 14 mg group), hair thinning (17 [4%] *vs* 42 [10%] *vs* 50 [13%]), and headache (42 [11%] *vs* 60 [15%] *vs* 46 [12%]). Incidence of serious adverse events was similar in all treatment groups (47 [12%] *vs* 52 [13%] *vs* 44 [12%]). Four deaths occurred, none of which was considered to be related to study drug (respiratory infection in the placebo group, traffic accident in the teriflunomide 7 mg group, and suicide and septicaemia due to Gram-negative infection complicated by disseminated intravascular coagulopathy in the teriflunomide 14 mg group).

Interpretation Teriflunomide 14 mg was associated with a lower relapse rate and less disability accumulation compared with placebo, with a similar safety and tolerability profile to that reported in previous studies. These results confirm the dose effect reported in previous trials and support the use of teriflunomide 14 mg in patients with relapsing multiple sclerosis.

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See Online for appendix

Introduction

Until recently, the first-line treatment options for relapsing forms of multiple sclerosis have been mainly injectable disease-modifying therapies such as the interferon betas and glatiramer acetate. However, oral drugs are needed that are appropriate for use as first-line treatments, to avoid injection-related adverse events and potentially to improve treatment acceptance and adherence, and to provide alternative options to patients with suboptimal response or intolerance to other agents. The availability of new treatments with distinct mechanisms of action will also provide opportunities to individualise therapy for each patient. Teriflunomide is an oral, once-daily, disease-modifying therapy approved in several countries (including the USA and the European Union) for treatment of relapsing multiple sclerosis or relapsing–remitting multiple sclerosis. Teriflunomide is the principal active metabolite of leflunomide, a drug approved for treatment of rheumatoid arthritis. Teriflunomide selectively and reversibly inhibits

dihydroorotate dehydrogenase, a key mitochondrial enzyme for de-novo pyrimidine synthesis required by rapidly dividing B and T lymphocytes. Through this cytostatic effect, teriflunomide has the potential to limit the immune responses that can contribute to multiple sclerosis disease activity.[1,2]

In the first phase 3, placebo-controlled trial—the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial[3]—teriflunomide 14 mg significantly reduced the annualised relapse rate (the number of confirmed relapses per patient-year) and the risk of disability progression sustained for at least 12 weeks. Teriflunomide 7 mg also significantly reduced the annualised relapse rate, but had no significant effect on disability progression. Superiority to placebo on several MRI endpoints was also shown, with evidence of a dose effect.[4] Moreover, extension studies showed that the effects of teriflunomide were maintained with long-term treatment (up to 8·5 years).[5,6] The safety profile of teriflunomide has been assessed in placebo-controlled clinical trials[3,7] and extension studies,[5,6] with diarrhoea, nausea, hair thinning (alopecia), and increased alanine aminotransferase concentrations being the most frequently reported adverse events.[3,7]

To add to the results reported in the TEMSO trial, we undertook the phase 3 Teriflunomide Oral in People With Relapsing Multiple Sclerosis (TOWER) trial to assess the safety and efficacy of teriflunomide in patients with relapsing multiple sclerosis.

Methods

Study design and participants

TOWER was a randomised, double-blind, placebo-controlled, phase 3 trial that recruited patients from 189 mainly hospital-based sites in 26 countries. Eligible patients were aged 18–55 years and had relapsing multiple sclerosis meeting 2005 McDonald criteria,[8] with or without underlying progression, an Expanded Disability Status Scale (EDSS)[9] score of 5·5 points or less, at least one relapse in the previous year or at least two relapses in the previous 2 years, and no relapse in the 30 days before randomisation. Patients were excluded if they had other relevant diseases, were pregnant, breastfeeding, or planned to conceive or father a child during the study. Patients were also excluded if they had previously or concomitantly received cytokine therapy, interferon beta, or glatiramer acetate within 3 months of randomisation, or had ever used natalizumab or other immunosuppressive agents. A full list of all exclusion and inclusion criteria is included in the appendix.

The protocol with amendments and statistical analysis plan were approved by independent ethics committees and institutional review boards, and all patients provided written informed consent before entry into the study.

The study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[10] and the Declaration of Helsinki.[11]

Randomisation and masking

Randomisation was done centrally, via an interactive voice recognition system that generated an allocation sequence using a permuted-block randomisation schedule with stratification according to study site and baseline EDSS score (≤3·5 or >3·5). The interactive voice recognition system was run by an independent company (ClinPhone, Perceptive Informatics, Nottingham, UK) and was maintained by them for the course of the study, under the responsibility of the study sponsor. After a screening phase (up to 4 weeks), investigators used the allocation sequence to randomly assign eligible patients in a 1:1:1 ratio to receive once-daily oral placebo, teriflunomide 7 mg, or teriflunomide 14 mg (identical in taste and appearance), until a fixed timepoint 48 weeks after the last patient had been randomly assigned. Patients, individuals administering the interventions, and those assessing the outcomes were masked to treatment assignment.

Procedures

A treating neurologist was responsible for assessment of patient eligibility, supervision of administration of study drug or placebo, recording of adverse events, and assessment of relapses. An examining neurologist, certified in the Neurostatus system for consistent EDSS assessment,[12] assigned EDSS scores at screening, randomisation, and every 12 weeks until the last treatment visit, and on any unscheduled visits for assessment of suspected relapse or disability worsening. Patients took their first dose of teriflunomide (Genzyme, a Sanofi company, Compiègne, France) or placebo either on the day of randomisation or the day after. Compliance was principally measured by counting tablets ([total number of drug tablets dispensed minus total number of drug tablets returned minus total number of drug tablets that the patient forgot to return], divided by treatment duration). Patients were asked to contact their treating investigator immediately upon suspected relapse and were to be examined within 7 days of symptom onset. Relapses were not to be reported as adverse events.

Patient safety was overseen by an independent data monitoring committee. Safety was assessed through adverse event reporting (upon occurrence), clinical laboratory tests (every 2 weeks until week 24, then every 6 weeks while still on treatment), vital signs (at weeks 2 and 6, then every 6 weeks until week 24, then every 12 weeks while still on treatment), abdominal ultrasonography (at week 24, then every 24 weeks), and electrocardiography (at baseline and end of treatment). Intensity of an adverse event was rated as mild (event that led to no modification of daily activities and/or did not require symptomatic treatment), moderate (hindered normal daily activities and/or required symptomatic treatment), or severe (prevented daily activities and required symptomatic treatment). A serious adverse event was defined as an event that resulted in death, was life-threatening, needed inpatient

hospital admission or prolonged an existing hospital stay, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was a medically important event.

Patients were required to discontinue treatment in the event of confirmed increases in alanine aminotransferase concentrations greater than three times the upper limit of normal, or decreases in neutrophil count below 1×10^9/L. Patients who discontinued study treatment underwent an 11 day accelerated elimination procedure, receiving activated charcoal (50 g every 6 h) or cholestyramine (8 g every 8 h).[13] Patients who completed the study on treatment were eligible to enrol in an ongoing open-label extension study, in which all patients receive teriflunomide 14 mg.

Outcomes

The primary endpoint was annualised relapse rate (number of relapses per patient-year). Relapse was defined as new or worsening clinical signs or symptoms lasting at least 24 h without fever. Protocol-defined relapses constituted an increase of either 1 point in at least two EDSS functional system scores, or 2 points in one EDSS functional system score (excluding bowel and bladder function, and cerebral function), or 0·5 points in total EDSS score from a previous clinically stable assessment.

The key secondary endpoint was time to 12 week sustained accumulation of disability, defined as an increase from baseline of at least 1 EDSS point (or ≥0·5 points when baseline EDSS score was >5·5 points) that persisted for at least 12 weeks. For clarification, a score of 5·5 points or more could occur in patients whose EDSS score deteriorated between screening and baseline. Other secondary endpoints were time to first relapse, proportion of patients free from relapses, proportion of patients free of accumulation of disability, and change from baseline in EDSS score at week 48, and change in Fatigue Impact Scale (FIS) and Short Form-36 (SF-36) scores at week 48 and last study visit. In view of the evidence provided by the TEMSO trial[3] and a phase 2 study,[7] no MRI endpoints were included in TOWER.

This study is registered with ClinicalTrials.gov, number NCT00751881.

Statistical analysis

We estimated that 370 patients randomly assigned to each treatment group would provide 94% power to detect a 25% relative risk reduction in annualised relapse rate at the two-tailed significance level of $\alpha=0\cdot05$, assuming an annualised relapse rate of 0·74 in the placebo group. We did efficacy analyses on the modified intention-to-treat population, consisting of all randomly assigned patients

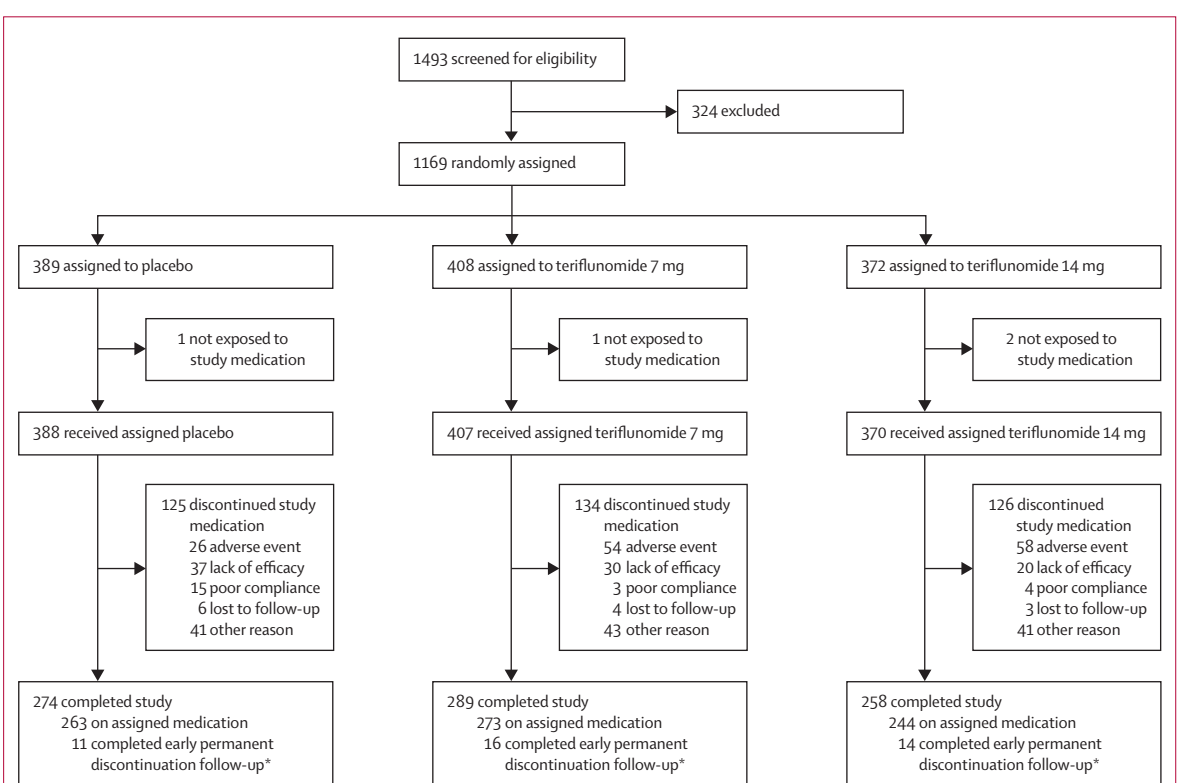

***Figure 1*: Trial profile**

*Patients who discontinued study treatment and participated in the early permanent treatment discontinuation follow-up completed study visits at the end of treatment, post-washout (4 weeks and 12 weeks after end of treatment), and about every 12 weeks until the planned end of treatment.

who received at least one dose of study drug or placebo. We did inferential analyses at the two-sided 5% significance level. The analysis of annualised relapse rate (protocol-defined relapses occurring between randomisation and last dose of study drug or placebo received) was based on a Poisson regression model with robust error variance including factors for treatment, baseline EDSS strata (≤3·5 or >3·5), and region. We used a log-rank test to analyse time to 12 week sustained accumulation of disability, with treatment group as test variable, and region and baseline EDSS score as stratification factors. We used a complementary Cox proportional hazards model with covariates for treatment, EDSS strata, and region for estimation of hazard ratios. We estimated the proportion of patients free from accumulation of disability at specific timepoints using the Kaplan–Meier method. We analysed change from baseline to week 48 in FIS and SF-36 scores by a mixed-effect model with repeated measures (MMRM), with change from baseline to last visit analysed using an ANCOVA model. For full details of statistical analyses for secondary endpoints see appendix. We did safety analyses in all patients who underwent randomisation and were exposed to study drug or placebo, classified according to the treatment that they received.

	Placebo (n=389)	Teriflunomide 7 mg (n=408)	Teriflunomide 14 mg (n=372)
Demographic characteristics			
Age, years	38·1 (9·1)	37·4 (9·4)	38·2 (9·4)
Women	273 (70%)	300 (74%)	258 (69%)
Race			
White	318 (82%)	329 (81%)	313 (84%)
Asian	60 (15%)	60 (15%)	49 (13%)
Black	7 (2%)	8 (2%)	7 (2%)
Other	4 (1%)	11 (3%)	3 (1%)
Region			
Western Europe and Tunisia	121 (31%)	127 (31%)	120 (32%)
Eastern Europe	117 (30%)	124 (30%)	116 (31%)
America	84 (22%)	92 (23%)	81 (22%)
Asia and Australia	67 (17%)	65 (16%)	55 (15%)
Clinical characteristics			
Time from first symptoms of MS, years*	7·64 (6·70)	8·18 (6·75)	8·18 (6·73)
Time since most recent relapse onset, months*	5·29 (3·41)	5·18 (3·41)	5·33 (3·32)
Relapses per patient			
Within previous year†	1·4 (0·8)	1·4 (0·7)	1·4 (0·7)
Within previous 2 years‡	2·1 (1·1)	2·1 (1·1)	2·1 (1·2)
MS subtype‡			
Relapsing–remitting	379 (97%)	393 (96%)	366 (99%)
Secondary progressive	4 (1%)	3 (1%)	2 (1%)
Progressive relapsing	6 (2%)	12 (3%)	2 (1%)
Use of MS medication in the previous 2 years	135 (35%)	123 (30%)	126 (34%)
Interferon beta-1a	59 (15%)	63 (15%)	64 (17%)
Glatiramer acetate	52 (13%)	47 (12%)	37 (10%)
Interferon beta-1b	38 (10%)	27 (7%)	35 (9%)
EDSS total score	2·69 (1·36)	2·71 (1·39)	2·71 (1·35)
FIS score	54·67 (37·89)	56·16 (38·20)	55·25 (38·26)

Data are mean (SD) or number (%). MS=multiple sclerosis. EDSS=Expanded Disability Status Scale. FIS=Fatigue Impact Scale. *Data are not available for one patient in the teriflunomide 14 mg group. †Data are not available for one patient in each of the placebo and teriflunomide 14 mg groups. ‡Data are not available for two patients in the teriflunomide 14 mg group.

***Table 1*: Baseline demographics and clinical characteristics in the randomly assigned population**

Role of the funding source

The sponsor of the study (Genzyme) developed the study protocol with guidance from a steering committee of multiple sclerosis experts. Data were obtained by the investigators and analysed by the sponsor. Interpretation of the data was done by the sponsor and the authors. All authors had full access to, and take responsibility for, the veracity of study data, were assisted in writing the manuscript by an independent medical writing agency (funded by the sponsor), and had final responsibility for the decision to submit for publication.

Results

Between Sept 17, 2008, and Feb 17, 2011, 1169 patients were randomly assigned to a treatment group, of whom 1165 (>99%) were exposed to study drug or placebo (modified intention-to-treat population). 821 (70%) of 1169 patients completed the study, with similar proportions of patients completing the study in each group (274 [70%] of 389 in the placebo group, 289 [71%] of 408 in the teriflunomide 7 mg group, and 258 [69%] of 372 in the teriflunomide 14 mg group; figure 1). 780 (67%) patients completed the study while still receiving study treatment. The median duration of study treatment was similar across all groups (581 days [IQR 392–756] in the placebo group *vs* 556 days [385–749] in the teriflunomide 7 mg group *vs* 588 days [351–765] in the teriflunomide 14 mg group). Median compliance to study drug intake, defined as the number of compliant administrations (ie, no more or less than one tablet daily) divided by the total number of administrations planned during the treatment period, was in excess of 99% in all groups (placebo, 99·7% [range 23–100]; teriflunomide 7 mg, 99·6% [39–100]; and teriflunomide 14 mg, 99·7% [23–100]). Baseline characteristics were generally well balanced between the study groups (table 1).

In the primary analysis, teriflunomide 7 mg and teriflunomide 14 mg significantly reduced the annualised relapse rate (adjusted rates of 0·50 [95% CI 0·43–0·58] for placebo *vs* 0·39 [0·33–0·46] for teriflunomide 7 mg *vs* 0·32 [0·27–0·38] for teriflunomide 14 mg), corresponding to relative rate reductions of 22·3% (95% CI 4·2–37·0; p=0·0183) in the teriflunomide 7 mg group and 36·3% (20·7–48·8; p=0·0001) in the teriflunomide 14 mg group versus placebo (table 2). In a secondary analysis, teriflunomide was associated with a significantly longer time to first relapse than was placebo (table 2). Compared with placebo, both doses of teriflunomide reduced the risk of relapse over the study period, by 30·2% (95% CI

13·2–43·8) for teriflunomide 7 mg (p=0·0016) and 36·9% (20·6–49·8) for teriflunomide 14 mg (p<0·0001).

In the key secondary analysis, a reduction in the risk of sustained accumulation of disability was observed with teriflunomide 14 mg compared with placebo (risk reduction 31·5% [95% CI –0·4 to 53·3]; log-rank p=0·0442; figure 2 and table 2). We noted no significant reduction with teriflunomide 7 mg (risk reduction 4·5% [95% CI –34·7 to 32·3]; p=0·7620). A larger proportion of patients was estimated to be free from accumulation of disability

	Placebo (n=388)	Teriflunomide 7 mg (n=407)	Teriflunomide 14 mg (n=370)
Annualised relapse rate (primary endpoint)			
Adjusted annualised relapse rate* (95% CI)	0·50 (0·43 to 0·58)	0·39 (0·33 to 0·46)	0·32 (0·27 to 0·38)
Relative risk (95% CI)	NA	0·78 (0·63 to 0·96)	0·64 (0·51 to 0·79)
Relative reduction versus placebo, % (95% CI)	NA	22·3% (4·2 to 37·0)	36·3% (20·7 to 48·8)
p value versus placebo	NA	0·0183	0·0001
Absolute reduction versus placebo (95% CI)	NA	–0·11 (–0·20 to –0·02)	–0·18 (–0·27 to –0·09)
p value versus placebo	NA	0·0189	0·0001
Time to sustained accumulation of disability (key secondary endpoint)			
HR versus placebo (95% CI)†	NA	0·95 (0·68 to 1·35)	0·68 (0·47 to 1·00)
p value versus placebo‡	NA	0·7620	0·0442
Other secondary endpoints			
Proportion free from protocol-defined relapse at 48 weeks, % (95% CI)§	60·6% (55·5 to 65·6)	71·9% (67·3 to 76·5)	76·3% (71·7 to 81·0)
Days to first relapse, 25% quartile (95% CI)	188 (142 to 249)	272 (201 to 354)	369 (282 to 485)
HR versus placebo (95% CI)†	NA	0·70 (0·56 to 0·87)	0·63 (0·50 to 0·79)
p value versus placebo‡	NA	0·0016	<0·0001
Proportion free from sustained accumulation of disability, % (95% CI)§			
24 weeks	92·0% (89·3 to 94·8)	94·7% (92·4 to 97·0)	97·3% (95·6 to 99·1)
48 weeks	85·8% (82·1 to 89·4)	87·9% (84·5 to 91·3)	92·2% (89·2 to 95·1)
108 weeks	80·3% (75·9 to 84·8)	78·9% (73·9 to 83·9)	84·2% (79·6 to 88·8)
Change in EDSS score from baseline to week 48			
Least square mean (SE), MMRM¶	0·09 (0·05)	0·04 (0·05)	–0·05 (0·05)
p value versus placebo	NA	0·4819	0·0429
Change in SF-36 physical health summary score from baseline to week 48			
Least square mean (SE), MMRM¶	–1·08 (0·41)	–0·40 (0·40)	–0·11 (0·42)
p value versus placebo	NA	0·2065	0·0817
Change in SF-36 physical health summary score from baseline to last visit			
Least square mean (SE), ANCOVA‖	–1·63 (0·44)	–0·91 (0·44)	–0·64 (0·44)
p value versus placebo	NA	0·1772	0·0687
Change in SF-36 mental health summary score from baseline to week 48			
Least square mean (SE), MMRM¶	–2·91 (0·59)	–2·03 (0·57)	–1·43 (0·61)
p value versus placebo	NA	0·2635	0·0702
Change in SF-36 mental health summary score from baseline to last visit			
Least square mean (SE), ANCOVA‖	–2·79 (0·59)	–1·70 (0·60)	–1·09 (0·59)
p value versus placebo	NA	0·1363	0·0224
Change in FIS score from baseline to week 48			
Least square mean (SE), MMRM¶	4·67 (1·58)	2·51 (1·53)	1·92 (1·63)
p value versus placebo	NA	0·3090	0·2083
Change in FIS score from baseline to last visit			
Least square mean (SE), ANCOVA‖	6·31 (1·67)	4·46 (1·66)	2·04 (1·68)
p value versus placebo	NA	0·3686	0·0429

NA=not applicable. HR=hazard ratio. EDSS=Expanded Disability Status Scale. SF-36=Short Form-36. MMRM=mixed-effect model with repeated measures. FIS=Fatigue Impact Scale. *Derived using a Poisson model with robust error variance: total number of confirmed relapses that occurred between randomisation and last dose was the response variable; treatment, EDSS strata at baseline, and region were covariates; and log-transformed treatment duration was an offset variable. †Derived using a Cox proportional hazard model with treatment, EDSS strata, and region as covariates. ‡Derived from a log-rank test, with treatment group as test variable, and region and baseline EDSS score as stratification factors. §Derived from Kaplan–Meier estimates. ¶MMRM analysis with factors for treatment, EDSS strata at baseline, region, and baseline value. ||ANCOVA with factors for EDSS strata at baseline, region, and baseline value.

***Table 2*: Clinical results in the modified intention-to-treat population**

after 48 weeks in the teriflunomide 14 mg group (92·2% [95% CI 89·2–95·1]) than in the placebo group (85·8% [82·1–89·4]). The median time to sustained accumulation of disability could not be estimated because less than half of the patients had an event. During the first 48 weeks of treatment, patients who received teriflunomide 14 mg had a small improvement in disability (least square mean change in EDSS score of –0·05 points [SE 0·05]) compared with the placebo group (least square mean change of +0·09 points [0·05]; p=0·0429); however, we observed no difference between the teriflunomide 7 mg group (least square mean change of +0·04 EDSS points [0·05]) and the placebo group (p=0·4819; table 2).

During 48 weeks of treatment, we observed no statistically significant decrease from baseline in SF-36 physical and mental health summary scores with teriflunomide 14 mg compared with placebo (MMRM analysis; table 2). Based on ANCOVA change from baseline to last visit, teriflunomide 14 mg showed a significant benefit when compared with placebo with regard to change in SF-36 mental health summary score but not with regard to SF-36 physical health summary score, and significant benefits were not recorded with teriflunomide 7 mg (table 2).

A greater increase in fatigue was reported with placebo compared with teriflunomide 14 mg using an ANCOVA, but we observed no significant differences between study groups when we analysed data from the first 48 weeks of treatment using the MMRM analysis or using either type of analysis for teriflunomide 7 mg (table 2).

Similar proportions of patients had adverse events across the study groups (83–86%; table 3; appendix), which were mostly mild to moderate in intensity (data not shown). The incidence of serious adverse events was also similar between treatments, at about 12% (table 3). More patients receiving teriflunomide discontinued treatment because of adverse events than did those receiving placebo (figure 1 and table 3), mainly because of the protocol-defined requirement to discontinue treatment in the event of increased alanine aminotransferase or decreased neutrophils. Four deaths were reported, none of which was considered to be related to study drug: one in the placebo group (respiratory infection), one in the teriflunomide 7 mg group (traffic accident), and two in the teriflunomide 14 mg group (suicide, and septicaemia due to Gram-negative infection complicated by disseminated intravascular coagulopathy; appendix).

Raised alanine aminotransferase concentrations (greater than one times the upper limit of normal range) occurred more frequently with teriflunomide treatment than with placebo, although more profound increases (greater than five times the upper limit of normal range) occurred at a similar frequency in all study groups (table 3). Four patients—two receiving placebo and two receiving teriflunomide 7 mg—met Hy's law criteria (alanine aminotransferase concentrations greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal); all had alternative explanations beyond study treatment. Study treatment was stopped in each of these patients (as per protocol requirement) and they subsequently recovered.

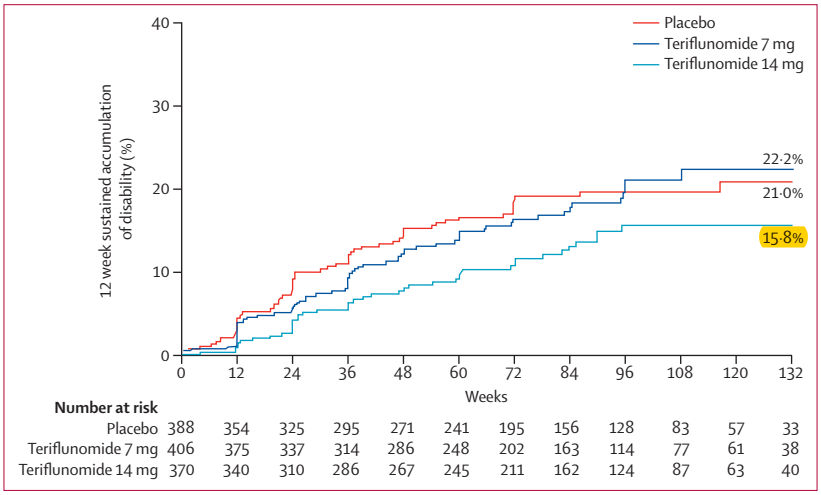

***Figure 2*: Sustained accumulation of disability in the modified intention-to-treat population**
Sustained accumulation of disability was defined as an increase of at least 1 point in Expanded Disability Status Scale (EDSS) score from baseline (or at least 0·5 points for patients with baseline EDSS score of >5·5 points) that persisted for at least 12 weeks.

	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
All adverse events	320 (83%)	344 (84%)	320 (86%)
Serious adverse event	47 (12%)	52 (13%)	44 (12%)
Event leading to permanent treatment discontinuation	24 (6%)	53 (13%)	58 (16%)
Death	1 (<1%)	1 (<1%)	2 (1%)
Common adverse events*			
ALT increased	32 (8%)	46 (11%)	52 (14%)
Hair thinning†	17 (4%)	42 (10%)	50 (13%)
Headache	42 (11%)	60 (15%)	46 (12%)
Nasopharyngitis	68 (18%)	49 (12%)	44 (12%)
Diarrhoea	28 (7%)	49 (12%)	41 (11%)
Fatigue	41 (11%)	35 (9%)	38 (10%)
Nausea	34 (9%)	34 (8%)	38 (10%)
Neutropenia	11 (3%)	29 (7%)	35 (9%)
Upper respiratory tract infection	44 (11%)	37 (9%)	34 (9%)
Back pain	33 (9%)	29 (7%)	33 (9%)
Urinary tract infection	37 (10%)	37 (9%)	23 (6%)
Infections			
Any event	197 (51%)	198 (48%)	165 (44%)
Serious infections	11 (3%)	14 (3%)	11 (3%)
Serious infections that occurred in ≥2 patients			
Urinary tract infection	2 (1%)	2 (<1%)	2 (1%)
Appendicitis	0	1 (<1%)	1 (<1%)
Pyelonephritis	1 (<1%)	0	1 (<1%)
Respiratory tract infection	1 (<1%)	1 (<1%)	0

(Table 3 continues on next page)

Neutrophil and lymphocyte counts declined from baseline in both teriflunomide groups. The mean reduction from baseline in either teriflunomide group was $0{\cdot}85\times10^9$/L or less (equivalent to <21% decrease in neutrophils) and the mean counts remained within normal limits (data not shown). The overall trend was for neutrophil counts to be reduced during the first 6 weeks, but some patients did have reduced counts later in the course of the study (data not shown). Five cases of serious neutropenia occurred (two in the teriflunomide 7 mg group and three in the teriflunomide 14 mg group), and another patient receiving teriflunomide 7 mg had a grade 4 reduction in neutrophil count. All patients were asymptomatic, without signs of fever or infection, and all recovered, either while continuing on study treatment, or after discontinuing (mandatory for neutrophil decreases below 1×10^9/L). One patient had immune-mediated thrombocytopenia in the teriflunomide 7 mg group, with platelet counts returning to normal after corticosteroid treatment, teriflunomide discontinuation, and rituximab therapy.

Infections and serious infections occurred at a similar frequency across treatment groups (table 3; appendix). Two opportunistic infections of note were identified: concomitant hepatitis C and cytomegalovirus infection (placebo), and intestinal tuberculosis (teriflunomide 14 mg). The patient with intestinal tuberculosis was given standard antituberculosis agents and recovered. No corrective treatments were given to the patient with hepatitis C and cytomegalovirus infection who received placebo study treatment, and at last report the patient was deemed to have not recovered. However, in both cases, the investigator considered the infection unrelated to study treatment.

18 pregnancies were reported in 14 female patients and four female partners of male patients. Of the 14 female patients, ten elected to have induced abortions and four pregnancies resulted in healthy babies (one in the placebo group, two in the teriflunomide 7 mg group, and one in the teriflunomide 14 mg group). Of the four pregnancies in partners of male patients, one woman elected to have an induced abortion and three pregnancies resulted in healthy babies (all in the teriflunomide 7 mg group).

Because of the known safety profiles of teriflunomide and leflunomide, and potential risks associated with immune interventions, some additional adverse events were monitored, including malignancy, hypertension, peripheral neuropathy, and hair thinning (table 3). A thyroid tumour coded as thyroid neoplasm was reported in a patient receiving teriflunomide 14 mg; the investigator regarded this event to be non-serious and the patient continued treatment. Hypertension was more frequent in the teriflunomide groups; two serious cases occurred in patients receiving teriflunomide 14 mg, both in patients with a history of hypertension, neither of whom discontinued teriflunomide treatment. One patient had an episode of high blood pressure (resolved during the course of the study) that was secondary to a course of intravenous methylprednisolone given for a relapse, and the other patient had several episodes of high blood pressure (not resolved) that led to hospital admission and modification of antihypertensive treatment, but continued receiving study treatment until the end of the study. Two further patients discontinued teriflunomide 7 mg because of hypertension with additional adverse events; both received corrective treatment for hypertension and recovered. Systolic blood

	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
(Continued from previous page)			
Hepatic laboratory data‡			
ALT >1×ULN	148 (39%)	205 (50%)	205 (55%)
ALT >3×ULN	22 (6%)	31 (8%)	29 (8%)
ALT >5×ULN	14 (4%)	10 (2%)	11 (3%)
ALT >10×ULN	5 (1%)	2 (<1%)	2 (1%)
ALT >20×ULN	2 (1%)	0	0
ALT >3×ULN and total bilirubin >2×ULN§	2 (1%)	2 (<1%)	0
AST >3×ULN	13 (3%)	9 (2%)	9 (2%)
GGT >2·5×ULN	14 (4%)	19 (5%)	15 (4%)
Haematological laboratory data‡			
Neutrophil counts			
<1·5×10⁹/L	26 (7%)	51 (13%)	62 (17%)
<0·5×10⁹/L	0	1 (<1%)	0
Lymphocyte counts			
<0·8×10⁹/L	28 (7%)	54 (13%)	48 (13%)
<0·5×10⁹/L	1 (<1%)	8 (2%)	11 (3%)
<0·2×10⁹/L	0	1 (<1%)	0
Additional adverse events of interest			
Hypertension¶	9 (2%)	22 (5%)	19 (5%)
Peripheral neuropathy‖	4 (1%)	9 (2%)	9 (2%)
Adverse events leading to permanent treatment discontinuation**			
ALT increased††	6 (2%)	12 (3%)	9 (2%)
Neutropenia‡‡	0	4 (1%)	8 (2%)
Hair thinning†	1 (<1%)	0	6 (2%)
AST increased	2 (1%)	5 (1%)	3 (1%)
Diarrhoea	1 (<1%)	4 (1%)	3 (1%)

The safety population is defined as all patients who underwent randomisation and were exposed to study medication, classified according to treatment actually received (some patients received a dose other than that assigned by randomisation). ALT=alanine aminotransferase. ULN=upper limit of normal. AST=aspartate aminotransferase. GGT=gamma-glutamyltransferase. *Events with a crude incidence rate of ≥8% in either teriflunomide group; adverse events are as reported by the treating neurologist. †Medical Dictionary for Regulatory Activities (MedDRA) preferred term is alopecia. ‡Placebo, n=384; teriflunomide 7 mg, n=407; teriflunomide 14 mg, n=370. §Possible alternative explanations included concomitant cortisone-pulse therapy and hepatitis C (placebo), and Gilbert's syndrome and alcoholic liver enzyme (teriflunomide 7 mg). ¶Standard MedDRA query for hypertension disorders (narrow). ||Confirmed by nerve conduction studies; additionally, suspected (but unconfirmed) peripheral neuropathy was reported in 11 (3%), nine (2%), and 12 (3%) patients in the placebo, 7 mg, and 14 mg groups, respectively. **That occurred in ≥1% of patients in any treatment group. ††Protocol required discontinuation in cases of confirmed ALT increase of >3×ULN. ‡‡Protocol required discontinuation in cases of confirmed neutrophil count below 1×10^9/L; a protocol ambiguity around the permitted lower level of neutrophils resulted in a further nine patients discontinuing teriflunomide treatment owing to neutrophil counts of 1–1·5×10⁹/L.

***Table* 3: Adverse events in the safety population**

pressure measurements of greater than 160 mm Hg occurred more often in the teriflunomide groups (16 [4%] of 404 patients in the 7 mg group and 13 [4%] of 367 patients in the 14 mg group) than in the placebo group (seven [2%] of 382 patients). Mean changes in systolic/diastolic blood pressure from baseline to study end were –0·22 (SD 12·22)/–0·09 (8·95) mm Hg in the placebo group, 2·55 (14·43)/1·74 (9·67) mm Hg in the teriflunomide 7 mg group, and 2·69 (12·23)/2·20 (10·20) mm Hg in the teriflunomide 14 mg group. Mean increases in blood pressure occurred early after treatment initiation and remained stable over time (data not shown). However, on an individual basis, blood pressure was well controlled in patients who had hypertension that was then treated with antihypertensive medication (data not shown). Cases of peripheral neuropathy confirmed by results of nerve conduction studies occurred more frequently in both teriflunomide groups, and were mild to moderate in intensity; two patients in the teriflunomide 7 mg group and three in the teriflunomide 14 mg group discontinued treatment as a result. Although hair thinning was more common with teriflunomide, occurring in 10% and 13% of patients taking teriflunomide 7 mg and 14 mg, respectively, most cases were mild to moderate, occurred during the first 6 months, and resolved on study treatment. Six (2%) patients in the teriflunomide 14 mg group and no patients in the teriflunomide 7 mg group discontinued treatment because of hair thinning.

Discussion

Once-daily oral teriflunomide 14 mg significantly reduced both annualised relapse rate and disability accumulation compared with placebo. Patients who received teriflunomide 7 mg had a significant, albeit smaller, reduction in annualised relapse rate, but without a significant effect on accumulation of disability. These observations are in accordance with the results of the phase 3, placebo-controlled TEMSO study of teriflunomide in relapsing multiple sclerosis.[3] Teriflunomide 14 mg has, therefore, shown significant benefits for both annualised relapse rate and accumulation of disability, as reflected by 12 week confirmed EDSS progression, consistently across two large phase 3 studies. The designs and populations of patients in the TEMSO and TOWER trials were sufficiently similar to allow data from the two studies to be pooled, with the integrated analysis confirming the significant effect of teriflunomide 14 mg on both annualised relapse rate and sustained accumulation of disability (table 4).[14] In a post-hoc analysis of the TEMSO trial, the efficacy of teriflunomide extended to relapses with neurological sequelae, and a dose-dependent reduction in frequency of relapses was noted.[15]

The most frequent adverse events associated with teriflunomide treatment in TOWER were increases in alanine aminotransferase concentrations, hair thinning, and headache, consistent with the known safety and tolerability profile of teriflunomide reported in previous

	TEMSO			TOWER			TEMSO and TOWER		
	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Baseline characteristics*, n	363	366	359	389	408	372	752	774	731
Age, years	38·4 (9·0)	37·4 (9·0)	37·8 (8·2)	38·1 (9·1)	37·4 (9·4)	38·2 (9·4)	38·2 (9·0)	37·4 (9·2)	38·0 (8·9)
Women	275 (76%)	255 (70%)	255 (71%)	273 (70%)	300 (74%)	258 (69%)	548 (73%)	555 (72%)	513 (70%)
Time from first symptom of MS, years	8·6 (7·1)	8·8 (6·8)	8·7 (6·7)	7·6 (6·7)	8·2 (6·8)	8·2 (6·7)	8·1 (6·9)	8·5 (6·8)	8·5 (6·7)
Relapses in previous 2 years	2·2 (1·0)	2·3 (1·2)	2·2 (1·0)	2·1 (1·1)	2·1 (1·1)	2·1 (1·2)	2·2 (1·1)	2·2 (1·1)	2·2 (1·1)
Baseline EDSS score	2·68 (1·34)	2·68 (1·34)	2·67 (1·24)	2·69 (1·36)	2·71 (1·39)	2·71 (1·35)	2·69 (1·35)	2·70 (1·37)	2·69 (1·30)
Duration of study treatment, days	756 (570·5–758)	756 (743·5–758)	756 (652–759)	581 (392–756)	556 (385–749)	588 (351–765)	724 (433–758)	718 (419–758)	749 (424–759)
Key efficacy outcomes†, n	363	365	358	388	407	370	751	772	728
Adjusted annualised relapse rate‡	0·539	0·370	0·369	0·501	0·389	0·319	0·534	0·390	0·354
Relative risk (95% CI)	NA	0·69 (0·56–0·84)	0·68 (0·55–0·85)	NA	0·78 (0·63–0·96)	0·64 (0·51–0·79)	NA	0·73 (0·63–0·84)	0·66 (0·57–0·77)
p value	NA	0·0002	0·0005	NA	0·0183	0·0001	NA	<0·0001	<0·0001
Proportion of patients with SAD§ at 108 weeks (95% CI)	27·3% (22·3–32·3)	21·7% (17·1–26·3)	20·2% (15·6–24·7)	19·7% (15·2–24·1)	21·1% (16·1–26·1)	15·8% (11·2–20·4)	24·0% (20·5–27·4)	21·3% (18·0–24·6)	17·9% (14·7–21·1)
HR (95% CI)	NA	0·76 (0·56–1·05)	0·70 (0·51–0·97)	NA	0·95 (0·68–1·35)	0·68 (0·47–1·00)	NA	0·85 (0·67–1·07)	0·70 (0·54–0·89)
p value	NA	0·0835	0·0279	NA	0·7620	0·0442	NA	0·1389	0·0029

Data are mean (SD), number (%), and median (IQR). TEMSO=Teriflunomide Multiple Sclerosis Oral trial.[3] TOWER=Teriflunomide Oral in People With Relapsing Multiple Sclerosis trial. MS=multiple sclerosis. EDSS=Expanded Disability Status Scale. SAD=sustained accumulation of disability. HR=hazard ratio. *In the randomly assigned population. †In the modified intention-to-treat population. ‡Primary efficacy endpoint. §Key secondary efficacy endpoint, defined as a persisting increase for at least 12 weeks of ≥1·0 point on the EDSS from baseline (or ≥0·5 points on the EDSS from baseline if baseline EDSS score was >5·5 points); derived from Kaplan-Meier estimates.

Table 4: **Baseline characteristics and key clinical efficacy outcomes in TEMSO, TOWER, and integrated analyses**

Panel: Research in context

Systematic review

We identified relevant references for this study by searching PubMed and recent published abstracts of relevant meetings with the terms "multiple sclerosis" AND "trial" AND "oral", without any language or date restrictions (accessed Nov 26, 2013). In view of the well established limitations related to comparison of outcomes data across clinical trials, we confined our discussion to a description of baseline characteristics of recent placebo-controlled trials that assessed three other oral disease-modifying therapies in relapsing multiple sclerosis. We identified six such studies—two for fingolimod,[19,20] two for dimethyl fumarate,[16,17] and two for laquinimod.[21,22] Our study population and the study population in our earlier phase 3 study (TEMSO)[3] had similar baseline disease characteristics. Differences in study populations might account for some of the differences observed in efficacy outcomes in comparison with other phase 3 studies. Generally, treatment discontinuation in our study was in line with that reported for patients assigned to dimethyl fumarate and laquinimod in other studies, and was driven by the protocol requirement to discontinue treatment in the event of increased alanine aminotransferase concentration or decreased neutrophils.

Interpretation

Results of our trial showed that oral, once-daily teriflunomide 14 mg was significantly more effective than placebo at reducing both the annualised relapse rate and the risk of 12 week confirmed accumulation of disability in patients with relapsing forms of multiple sclerosis. The 7 mg once-daily dose also significantly reduced the annualised relapse rate, but had no significant effect on disability progression. Teriflunomide has now been studied in three placebo-controlled trials—a phase 2 study (with a long-term extension),[6,7] and two large, placebo-controlled phase 3 trials (TEMSO[3] and TOWER)—which together show the consistent efficacy of teriflunomide and, along with the established safety and tolerability, confirm a favourable benefit–risk profile for both doses of teriflunomide. Although the adverse event profile is similar for both doses and the significance of the difference in efficacy between groups has not been tested statistically, teriflunomide 14 mg has shown consistently greater efficacy than 7 mg. These data support the use of teriflunomide as an initial therapy for patients with relapsing multiple sclerosis and as an option for patients who are unable to tolerate other disease-modifying therapies.

studies in relapsing multiple sclerosis[3,6] and from the extensive clinical experience with leflunomide in rheumatoid arthritis. Adverse events and serious adverse events occurred at a similar incidence across all treatment groups in the study, although permanent treatment discontinuations because of adverse events occurred more frequently with teriflunomide than with placebo. Treatment discontinuations in all groups were often related to increased alanine aminotransferase concentrations and neutropenia, and were driven by the protocol discontinuation requirements.

TOWER did not include any MRI endpoints, which might be regarded as a limitation of the study, although data from TEMSO and the phase 2 study clearly showed that teriflunomide had significant and dose-dependent benefits on MRI markers of both disease burden and activity.[3,7] An additional limitation is that about 30% of participants discontinued study treatment before study end. However, the rates of treatment discontinuation in TOWER were similar to those reported in other trials of oral disease-modifying therapies.[16,17]

Although injectable disease-modifying therapies have been the mainstay of treatment of relapsing multiple sclerosis for many years, they are not without limitations. Disease progression still occurs while on treatment and parenteral administration is associated with tolerability and patient adherence issues.[18] As a result, an effective oral treatment option with an adverse event profile that is compatible with use as a first-line treatment is needed. The safety and tolerability profile of teriflunomide, as characterised in this and previous studies (panel), was similar for both the 7 mg and 14 mg doses, including long-term treatment observations.[3,6] Considering the efficacy findings from TOWER and TEMSO, and the phase 2 and extension study, the benefit–risk ratio for patients with relapsing multiple sclerosis consistently seems more favourable at the 14 mg dose than at the 7 mg dose.[3,6,7]

Contributors

CC (until he passed away in September, 2013), PO'C, GC, MSF, AEM, TPO, JSW, and LK were members of the Teriflunomide Steering Committee and as such they contributed to the study design, data collection, data interpretation, writing, and critical review of the manuscript, and approved the final submission draft. LK coordinated the submission process. TB, J-LD, DD, and PT are employees of Sanofi and contributed to the study design, data analysis, data interpretation, writing, and critical review of the manuscript, and approved the final submission draft.

Conflicts of interest

CC received consulting fees (Biogen Dompé, Biogen Idec, Gemacbio, Genzyme, Hertie Foundation, Novartis, Sanofi-Aventis, Teva, UCB Pharma); lecture fees (Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Teva); research support (Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Teva Pharma); and fees for membership of company advisory boards (Biogen Idec, Genzyme, Novartis, Sanofi-Aventis, Teva, UCB). PO'C has received consulting fees or research support (Actelion, Bayer, Biogen Idec, BioMS, Cognosci, Daiichi Sankyo, EMD Serono, Genentech, Genmab, Novartis, Roche, Sanofi-Aventis, Teva). GC has received consulting fees (Actelion, Bayer Schering, Merck Serono, Novartis, Sanofi-Aventis, Teva Pharma) and speaker fees (Bayer Schering, Biogen Dompè, Merck Serono International, Novartis, Sanofi-Aventis, Serono Symposia International Foundation, Teva Pharma). MSF has received consulting fees or honoraria (Bayer HealthCare, Biogen Idec, EMD Canada, Novartis, Sanofi-Aventis, Teva Canada Innovation); research or educational grant support (Bayer Healthcare, Genzyme); and is a member of company advisory boards, board of directors, or other similar groups (Bayer Healthcare, Biogen Idec, Celgene, Merck Serono, Novartis, and Sanofi-Aventis). AEM has received research support (Acorda Therapeutics, Biogen Idec, Genentech, Genzyme, Novartis, Osmotica, Roche, Sanofi-Aventis, Teva) and consulting fees (Acorda Therapeutics, Biogen Idec, EMD Serono, GlaxoSmithKline, Merck

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