Teriflunomide in multiple sclerosis: an update

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Practice points

Dosage & administration

- Teriflunomide is a once-daily oral immunomodulator approved in the European Union (14 mg) for the treatment of relapsing-remitting multiple sclerosis (MS) and in the USA (7 and 14 mg) for the treatment of relapsing forms of MS.

Mechanism of action: immunomodulation

- Teriflunomide reversibly inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme necessary for *de novo* pyrimidine synthesis.
- Dihydroorotate dehydrogenase inhibition limits the available pyrimidine pool for T- and B-cell proliferation, thereby decreasing the number of activated T and B cells available to cross the blood–brain barrier and enter the central nervous system.
- Immune responses are preserved during treatment with teriflunomide.

Pharmacodynamics, pharmacokinetics & metabolism

- Oral bioavailability of teriflunomide is approximately 100%.
- Pharmacokinetic characteristics of teriflunomide do not vary significantly with food intake, mild-to-moderate hepatic impairment, renal impairment, gender or age.
- Teriflunomide binds extensively to plasma protein (>99%).
- Two accelerated elimination procedures have been shown to rapidly lower the plasma concentration of teriflunomide by >98% over 11 days.

Drug interactions

- Exposure to drugs metabolized by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, OAT3, BCRP and OATP1B1/B3 transporters may be increased by teriflunomide.
- Ethinylestradiol and levonorgestrel exposure may be increased by teriflunomide.
- Exposure to drugs metabolized by CYP1A2 may be decreased by teriflunomide.
- Peak international normalized ratio in patients treated with warfarin may be decreased by teriflunomide.
- In patients receiving teriflunomide, rosuvastatin dosages should not exceed 10 mg once daily or should be reduced by 50%, in accordance with local guidelines.
- Cholestyramine or activated charcoal should not be used in patients treated with teriflunomide unless an accelerated elimination of teriflunomide is desired.
- Patients should be monitored and the doses of concomitant drugs adjusted accordingly.

Clinical efficacy

- Annualized relapse rates were significantly better with teriflunomide compared with placebo in two pivotal trials (TEMPO and TOWER).

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Practice points (cont.)

Clinical efficacy (cont.)

- Expanded Disability Status Scale scores were significantly improved with teriflunomide 14 mg versus placebo in two Phase III trials (TEMPO and TOPIC).
- Teriflunomide significantly reduced brain volume loss compared with placebo after 12 and 24 months in TEMPO when evaluated using standardized analysis of brain atrophy using the Structural Image Evaluation Using Normalization of Atrophy method.
- The efficacy of teriflunomide in patients with relapsing-remitting MS is also supported by supplementary measures such as predictions of disease outcomes with modified Rio score, number needed to treat and no evidence of disease activity.
- Efficacy of up to 9 and 5.5 years of teriflunomide treatment have been demonstrated in extensions of the TEMPO and TOWER trials, respectively.
- Significantly fewer patients receiving teriflunomide converted to clinically definite MS compared with those receiving placebo in a randomized, double-blind, placebo-controlled Phase III clinical trial of the efficacy of teriflunomide in patients with a first clinical episode suggestive of MS (TOPIC).
- Rate of relapse or treatment discontinuation was not significantly better with teriflunomide than with IFNB-1a in patients with relapsing forms of MS (TENERE).

Safety & tolerability

- Teriflunomide has a well-characterized, manageable safety and tolerability profile that is consistent across studies and established with up to 12 years of exposure.

Teriflunomide, a once-daily, oral disease-modifying therapy, has demonstrated efficacy in patients with relapsing forms of multiple sclerosis (MS) and patients with a first clinical episode suggestive of MS. As the only disease-modifying therapy with positive disability results in two Phase III trials, teriflunomide significantly slowed disability in patients with relapsing forms of MS. We highlight data from the Phase II study and the TEMPO, TOWER, TOPIC and TENERE teriflunomide studies. TEMPO MRI outcomes have been supported with Structural Image Evaluation Using Normalization of Atrophy analyses. We present data from long-term extensions of the Phase II study, TEMPO and TOWER, as well as results from patients who switched from other disease-modifying therapies to teriflunomide, patient-reported outcomes and supplementary measures of response.

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KEYWORDS

- clinical trials
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- drug development
- multiple sclerosis
- teriflunomide

Multiple sclerosis (MS), an autoimmune demyelinating disease, is one of the most common neurological diseases and the leading cause of nontrauma-related disability in young adults [1]. In approximately 85% of cases, the disease follows a relapsing–remitting course in which patients have episodes of relapse usually followed by improvements, with an overall tendency toward worsening disability and reduced cognitive function [1]. Relapsing–remitting MS (RRMS) often transitions to a phase called secondary progressive MS, in which symptoms gradually worsen or accumulate [2]. Approximately 10% of patients have a progressive disease course from the time of disease

onset, known as primary progressive MS [1]. All forms of MS share the characteristic of a faster rate of brain atrophy relative to normal controls, which occurs even at the earliest stages of the disease [3].

In clinical trials, efficacy of MS treatments is typically assessed using annualized relapse rate (ARR) and disability worsening, although there is no direct link between relapses and long-term disability worsening [4,5]. Supplementary measures such as number needed to treat (NNT) [6], no evidence of disease activity (NEDA) [5], modified Rio (mRio) scoring [7] and patient-reported outcomes [8], may help to provide a more complete picture of treatment effects. MRI

assessments of disease activity, such as lesion numbers and volume, and brain atrophy, are also key indicators of MS disease activity, particularly as evidence supporting the association between brain atrophy and long-term disability has accumulated [9].

Overview of currently available disease-modifying therapies

• Injectable disease-modifying therapies

Injectable agents – interferons (IFNs) and glatiramer acetate (GA) – were the first disease-modifying therapies (DMTs) available for MS treatment. These therapies have been shown to reduce relapse frequency and MRI lesion development in patients with RRMS [10–13] and in patients with early MS [14–16], and the IFNs have also been shown to reduce the risk of disability in patients with RRMS. Although these agents are widely used, tolerability remains a concern; IFNs are associated with injection site reactions, flu-like symptoms and liver dysfunction, whereas GA is also associated with injection site reactions and transient systemic postinjection reactions [17].

In 2014, a pegylated form of IFN-beta (IFNB)-1a was approved. Pegylation increases the half-life, reducing dosing frequency thereby potentially improving overall tolerability [18]. A high-dose (40 mg) formulation of GA, dosed three-times weekly instead of daily to improve convenience and adherence, was also approved in the USA in 2014 and in Europe in 2015 [19,20].

• Oral DMTs

Three oral DMTs – fingolimod (GILENYA®, Novartis Pharmaceuticals Corp, NJ, USA), teriflunomide (AUBAGIO®, Sanofi Genzyme, MA, USA) and dimethyl fumarate (DMF; TECFIDERA®, Biogen Inc, MA, USA) – have been approved for treatment of RRMS. Fingolimod, the first oral therapy to be approved, is an oral sphingosine-1-phosphate receptor modulator that binds with high affinity to sphingosine-1-phosphate receptor and prevents lymphocyte egress from lymph nodes, thereby reducing auto-aggressive lymphocyte infiltration into the CNS [21]. In FREEDOMS (NCT00289978), once-daily fingolimod 0.5 mg decreased ARR by 54% versus placebo ($p < 0.001$) [22]. The proportion of patients with disability worsening confirmed for 12 weeks was lower with fingolimod (17.7%, $p = 0.03$) than placebo (24.1%). Patients treated with fingolimod also had significantly

fewer gadolinium (Gd)-enhancing lesions, fewer new/enlarged T_2 lesions and smaller increases in T_2 lesion volume than those in the placebo group (all $p < 0.001$) [22]. In FREEDOMS II (NCT00355134), a second placebo-controlled Phase III trial, a similar relative reduction in ARR versus placebo was observed (48% reduction vs placebo) [23]. However, no significant effects of fingolimod on disability worsening were reported in FREEDOMS II [23]. When fingolimod treatment is initiated, patients should be closely monitored for cardiovascular events, such as bradyarrhythmia and atrioventricular block [24]. Patients should also be monitored for macular edema because of the increased risk associated with the treatment. Fingolimod may also increase the risk of infections. In the postmarketing setting, serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including one fatal event, have been reported with fingolimod treatment. At the time of publication, there had been five postmarketing reports of progressive multifocal leukoencephalopathy (PML) in patients receiving fingolimod who had not previously received natalizumab (NTZ) [25–28].

DMF is an oral DMT administered twice-daily to treat RRMS. Although its mechanism of action in MS is not fully understood, DMF is known to activate the nuclear factor (erythroid-derived 2)-like 1 pathway, which is involved in the oxidative stress response [29]. In two Phase III clinical trials (CONFIRM [NCT00451451] and DEFINE [NCT00420212]), twice-daily DMF 240 mg reduced ARRs by 44 and 53% versus placebo, respectively ($p < 0.001$ for both) [30,31]. In DEFINE, twice-daily DMF reduced the risk of disability worsening by 38% versus placebo ($p = 0.005$) [31]; however, reductions in disability worsening with DMF were not significant in CONFIRM [30]. DMF reduced the numbers of Gd-enhancing lesions and new/enlarging T_2 lesions versus placebo in both trials ($p < 0.001$) [30,31]. Adverse events (AEs) commonly associated with DMF were flushing and gastrointestinal events; these typically dissipated after the first month of treatment [30,31]. In clinical trials, DMF treatment was associated with persistent lymphopenia in some patients, although persistent lymphopenia in DMF recipients was not associated with increased rates of infections or serious infections (vs placebo) [32]. Four patients treated with DMF in the postmarketing setting have now been reported to have

developed PML, not always in the context of prolonged lymphopenia [33].

• Monoclonal antibody therapies

NTZ (TYSABRI®, Biogen Idec Inc, MA, USA) was the first monoclonal antibody approved for MS treatment. NTZ targets very-late antigen 4,3 $\alpha_4\beta_1$ -integrin, CD49d/CD29 (VLA4) adhesion molecule, which plays a major role in the regulation of immune cell recruitment to sites of inflammation. Blockade of VLA4 prevents lymphocytes from crossing the blood–brain barrier and entering the CNS [34,35]. NTZ is administered intravenously (iv.) once every 4 weeks and is most often used in patients with highly active MS (frequent clinical relapses and/or MRI activity despite use of other DMTs). In AFFIRM (NCT00027300), a pivotal, randomized, double-blind Phase III trial, patients treated with NTZ for 2 years had a significantly reduced cumulative probability of disability worsening versus those who received placebo (17 vs 29%, respectively; $p < 0.001$) [36]. ARR was lower in patients treated with NTZ versus placebo at 2 years (0.23 vs 0.73, respectively; $p < 0.001$) [36]. Although NTZ is generally well tolerated, it is associated with an increased incidence of PML, a serious and potentially fatal brain infection caused by activation of the John Cunningham virus [37]. As of 7 September 2016, 682 cases of PML had been confirmed in patients with MS who had received NTZ [34].

Alemtuzumab (LEMTRADA®, Sanofi Genzyme, MA, USA), the second monoclonal antibody approved for use in patients with MS, targets CD52 and depletes circulating T and B cells [38]. Within weeks of the initial depletion, lymphocytes begin to repopulate, which is thought to play a role in the therapeutic effect of alemtuzumab by rebalancing the dysfunctional immune system in MS [39]. Although the shift in the T-cell population might mediate the therapeutic effects of alemtuzumab, it has been proposed that the more rapid repopulation of B cells relative to T cells might contribute to the autoimmune AEs associated with alemtuzumab [40]. Alemtuzumab has a unique dosing regimen, administered via intravenous infusion on 5 consecutive days at baseline and on 3 consecutive days 12 months later. Alemtuzumab has been shown to reduce relapse rates and MRI disease activity versus IFNB-1a in treatment-naïve patients and in patients who had relapsed on prior therapy [41,42]. In CARE-MS I (NCT00530348),

a 2-year, pivotal, randomized Phase III trial in patients with active RRMS who were treatment-naïve, alemtuzumab significantly reduced the ARR compared with patients receiving IFNB-1a (0.18 vs 0.39, respectively, $p < 0.0001$) [41]. In CARE-MS II (NCT00548405) alemtuzumab was evaluated in patients with active RRMS who relapsed on prior therapy. Similar to CARE-MS I, alemtuzumab treatment reduced ARR compared with IFNB-1a treatment (0.26 vs 0.52, respectively; $p < 0.0001$) and was also associated with significant reductions in 6-month confirmed disability worsening [42]. In both studies, alemtuzumab also demonstrated improvements in MRI outcomes, with greater proportions of patients free of Gd-enhancing lesions, new/enlarging T₂ lesions and new T₁ hypointense lesions after up to 4 years [43,44]. In addition, alemtuzumab-treated patients demonstrated a reduced rate of brain atrophy, as determined by median yearly percentage change in brain parenchymal fraction over 2 years [41,42]. Close safety monitoring is needed for patients treated with alemtuzumab because of concerns that include infusion-associated reactions and autoimmune events (such as thyroid disease, and, less frequently, immune thrombocytopenia and rare cases of antglomerular basement membrane disease) [38].

Daclizumab (ZINBRYTA™, Biogen, MA, USA/AbbVie, IL, USA), the most recently approved treatment for adults with relapsing forms of MS, is a monoclonal antibody directed against CD25, the α subunit of the IL-2 receptor [45]. In the Phase II SELECT trial (NCT00390221), 1 year of daclizumab 150 mg once-monthly led to significant reduction in ARR compared with placebo (0.21 vs 0.46, respectively; $p < 0.0001$) and 52-week confirmed disability worsening (6 vs 13%; $p = 0.021$). Serious AEs, excluding MS relapse, occurred in 6 and 7% of patients in the placebo and daclizumab 150 mg groups, respectively [46]. In DECIDE (NCT01064401), a Phase II, double-blind, active-controlled trial, treatment with daclizumab for up to 96 weeks significantly improved ARR compared with IFNB-1a (0.22 vs 0.39, respectively; $p < 0.001$). Numbers of new or newly enlarged T₂ hyperintense lesions were significantly reduced with daclizumab versus IFNB-1a (4.3 vs 9.4; $p < 0.001$). Disability worsening confirmed for 12 weeks did not differ significantly between the treatment groups [47]. Serious AEs, excluding MS relapse, occurred in

15% of patients in the daclizumab group and 10% of patients in the IFNB-1a group [47].

Introduction to teriflunomide

Teriflunomide is a once-daily oral DMT, first approved in the USA in 2012, for the treatment of patients with relapsing forms of MS [48], and then subsequently for RRMS in other countries [49]. In core clinical trials and long-term extensions, teriflunomide treatment led to significant and consistent benefits on a range of clinical, MRI and disability markers of disease activity in several patient populations [50–53]. In addition, teriflunomide has a well characterized and manageable safety and tolerability profile over a long time period [50–56].

• Chemistry

Teriflunomide is the principal active metabolite of leflunomide (ARAVA®, Sanofi, NJ, USA), an immunomodulator approved in 1998 to treat rheumatoid arthritis [57]. Teriflunomide, (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl)-amide, is formulated as film-coated tablets for oral administration [48]. Where available, teriflunomide is marketed only as a 14 mg dose, except in the USA, where the 7 mg dose is also available [48,49].

• Proposed mechanism of action

An overabundance of activated T and B cells in the CNS is thought to mediate the inflammatory damage that occurs in patients with MS [58]. Teriflunomide reversibly inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme necessary for the *de novo* pyrimidine synthesis required to support the rapid expansion that occurs in antigen-activated lymphocytes [58]. Inhibiting *de novo* pyrimidine synthesis limits the available pyrimidine pool for T- and B-cell proliferation, thereby decreasing the number of activated T and B cells available to cross the blood–brain barrier and enter the CNS [59].

Unlike activated lymphocytes, resting lymphocytes do not require *de novo* pyrimidine synthesis to self-renew [58]. Consequently, the pyrimidine requirements for homeostatic lymphocyte proliferation can be met by the salvage pathway, which is unaffected by teriflunomide. The presence of this other pathway ensures that teriflunomide selectively inhibits proliferation of activated lymphocytes without interrupting normal homeostatic proliferation of resting lymphocytes (Figure 1) [58].

Further insight into the mechanism of action of teriflunomide came from Teri-DYNAMIC, a nonrandomized, open-label Phase III study to evaluate the effects of teriflunomide on lymphocytes in patients with RRMS [60]. Adaptive immune cell subsets, CD4⁺ T-cell function and changes in absolute number and clonal diversity of CD4⁺ T-cell receptors were compared in 39 patients with RRMS who received teriflunomide 14 mg for 24 weeks and 19 untreated healthy participants. In patients with MS, teriflunomide lowered lymphocyte counts, increased CD4⁺/CD8⁺ T-cell ratios, and resulted in increased regulatory T-cell counts and reduced Th1 counts. Teriflunomide also significantly reduced clonal diversity of CD4⁺ T cells. This selective effect on different CD4⁺ T-cell subsets suggests a shift in T-cell populations from pro-inflammatory to regulatory. However, T cells from patients treated with teriflunomide still mounted appropriate proliferative and cytokine responses, consistent with an immunomodulatory rather than immunosuppressive mechanism of action in MS [60].

• Pharmacodynamics, pharmacokinetics & metabolism

Key pharmacokinetic characteristics of teriflunomide are shown in Table 1. Systemic exposure to teriflunomide increases in a dose-proportional manner after oral administration over a dose range of 7 to 14 mg [49]. Pharmacokinetic characteristics do not vary significantly with food intake, mild-to-moderate hepatic impairment, renal impairment, gender or age [49].

Clinical efficacy

Clinical efficacy of teriflunomide has been evaluated extensively in Phase II and Phase III clinical trials in patients with relapsing forms of MS [50–52] and those who have experienced a first clinical episode suggestive of MS [53].

• Phase II study

The Phase II proof-of-concept study evaluated the efficacy and safety of teriflunomide in patients with relapsing forms of MS (NCT01487096) [50]. In this randomized, double-blind, placebo-controlled trial, 179 patients with MS were randomized (1:1:1) to receive placebo, teriflunomide 7 mg or teriflunomide 14 mg for 36 weeks. Results of the core Phase II study have been previously published [50]. Patients completing the core Phase II study were eligible to participate

Figure 1. Proposed mechanism of action for teriflunomide [58].
B: B cell; DHODH: Dihydroorotate dehydrogenase; T: T cell.

in an open-label extension in which all patients receiving teriflunomide continued their original dose, and patients who received placebo were rerandomized to either teriflunomide 7 or 14 mg. After up to 12 years of teriflunomide exposure, a greater percentage of patients were relapse-free in the teriflunomide 14 mg group (51.5%) than in the teriflunomide 7 mg group (39.5%) [62]. In both groups, relapse rates and Expanded Disability Status Scale (EDSS) scores remained stable and low throughout the follow-up.

• Phase III clinical trials

TEMSO

TEMSO, a randomized, double-blind, placebo-controlled Phase III trial, was the first clinical trial designed to evaluate the effects of teriflunomide on the relapse and disability outcomes of patients with relapsing forms of MS (NCT00134563) [51]. A total of 1088 patients were randomized (1:1:1) to receive placebo, teriflunomide 7 mg, or teriflunomide 14 mg for 108 weeks, 1086 of whom were treated. Key efficacy outcomes from the TEMSO core study are summarized in **Table 2**. ARR and 12-week confirmed disability outcomes are shown in **Figure 2**. Prespecified subgroup analyses of TEMSO showed that the benefits of teriflunomide on ARR and disability confirmed for

12 weeks were consistent across the subgroups of gender, age, geographic region, baseline EDSS strata, relapse history, MS subtype, prior DMT use and MRI parameters (number of Gd-enhancing lesions, total lesion volume) [63].

In a blinded independent analysis of MRIs in TEMSO, the median annualized percentage change in brain volume from baseline to week 48 was calculated using the validated Structural Image Evaluation Using Normalization of Atrophy (SIENA) method [65]. By SIENA, brain volume loss was lower for both teriflunomide groups versus placebo at month 12 (reductions of 34.4% with teriflunomide 7 mg, $p = 0.0011$, and 36.9% with teriflunomide 14 mg, $p = 0.0001$) and month 24 (reductions of 27.6% with teriflunomide 7 mg, $p = 0.0019$, and 30.6% with teriflunomide 14 mg, $p = 0.0001$) [65]. These results are not unexpected, given the strong association between brain volume loss and disability worsening, and the positive and consistent effects of teriflunomide on disability worsening observed in TEMSO.

In *post hoc* analyses of TEMSO, teriflunomide decreased incidence on several measures of severe relapse outcomes [66]. Teriflunomide 14 mg significantly reduced ARRs with sequelae (defined as EDSS/Functional Score increase at 30 days post relapse) by 36% ($p = 0.0011$),

relapse leading to hospitalization by 59% ($p < 0.0001$), relapse requiring iv. corticosteroids by 34% ($p = 0.0003$) and relapse with sequelae (as determined by the investigator) by 53% ($p < 0.0001$). Teriflunomide 7 mg significantly reduced ARR with sequelae (defined by EDSS/Functional Score), relapse leading to hospitalization and relapse requiring iv. corticosteroids [66].

Patients completing TEMSO were eligible to enter the TEMSO extension [55]. Patients who received teriflunomide in the core trial continued this treatment, and those who received placebo were rerandomized (1:1) to teriflunomide 7 or 14 mg. After ≤ 9 years of teriflunomide treatment, ARRs were further improved compared with the core study: 0.198 and 0.215 for patients continuing teriflunomide 7 and 14 mg and 0.225 and 0.177 for patients switching to teriflunomide 7 or 14 mg, respectively. Risk of sustained disability remained low and EDSS scores were stable across all groups [55].

TOWER

TOWER was a randomized, double-blind, placebo-controlled Phase III trial designed to evaluate the effects of teriflunomide on relapse and disability outcomes in patients with relapsing forms of MS (NCT00751881) [52]. A total of 1169 patients were randomized (1:1:1) to receive

placebo or teriflunomide 7 or 14 mg for a variable duration, with the study ending 48 weeks after the last patient was randomized. MRI outcomes were not evaluated in this trial [52]. Key efficacy outcomes are summarized in **Table 2**. ARR and disability worsening confirmed for 12 weeks are shown in **Figure 3**.

Patients completing TOWER were eligible to enter a long-term extension in which all patients received teriflunomide 14 mg [67]. At the data cut-off (31 July, 2014), patients had received teriflunomide for ≤ 5.5 years. At the end of the core study, patients who ultimately entered the extension ($n = 750$) had ARRs of 0.305 (core/extension treatment: 7/14 mg) and 0.257 (14/14 mg). At the end of extension year (EY) 1 and EY2, relapse rates were further decreased in both treatment groups (0.295 and 0.188, 7/14 mg and 0.260 and 0.193, 14/14 mg EY1 and EY2, respectively). Changes in EDSS from baseline (start of core study) through week 96 of the extension were small and comparable between groups [67]. The risk of disability worsening confirmed for 12 weeks was reduced by 27.6% in patients who received teriflunomide 14 mg continuously (early treatment) compared with those who switched to teriflunomide 14 mg in the extension (delayed treatment; $p = 0.0473$), providing evidence of the importance of early intervention with teriflunomide in relapsing forms of MS [68].

Table 1. Pharmacokinetic characteristics of teriflunomide.

Parameter	Characteristics	Ref.
Absorption	C_{max} (single oral dose): mean (SD): – 7 mg: 1.06 (0.22) $\mu\text{g/ml}$ – 14 mg: 2.25 (0.47) $\mu\text{g/ml}$ Rapid absorption. Median time to reach maximum plasma concentrations: 1–2 h post-dose following repeated oral administration Approximately 100% oral bioavailability	[61]
Distribution	Mainly distributed in the plasma Extensively bound to plasma protein (>99%) Volume of distribution: ~ 11 l after a single iv. administration	[61]
Metabolism	Teriflunomide is moderately metabolized and the only component detected in plasma Primary biotransformation pathway of teriflunomide is hydrolysis: – Oxidation is a minor pathway	[48]
Elimination	Median half-life: Approximately 19 days in patients with MS Eliminated mainly through direct biliary excretion of unchanged drug as well as renal excretion of metabolites Two accelerated elimination procedures have been shown to rapidly lower the plasma concentration of teriflunomide by >98% over 11 days: – 8 g cholestyramine every 8 h for 11 days. If 8 g is poorly tolerated, 4 g cholestyramine every 8 h may be used – 50 g activated charcoal powder every 12 h for 11 days	[48,49]

C_{max} : Maximum serum concentration; iv.: Intravenous; MS: Multiple sclerosis; SD: Standard deviation.

Table 2. Summary of key end points of Phase III clinical trials of teriflunomide.

	TEMSO (study duration: 108 weeks) [51]			TOWER (study duration: variable; 48 weeks after the last patient randomized) [52]			TOPIC (study duration: ≤108 weeks) [53]			TENERE (study duration: variable; 48 weeks after last patient randomized) [64]		
	Placebo	Teriflunomide		Placebo	Teriflunomide		Placebo	Teriflunomide		sc. IFNB-1a 44 µg [†]	Teriflunomide	
		7 mg	14 mg		7 mg	14 mg		7 mg	14 mg		7 mg	14 mg
Patient number entering study, n	363	365	358	388	407	370	197	203	214	104	109	111
Clinical end points												
ARR	0.54	0.37	0.37	0.50	0.39	0.32	0.284	0.190	0.194	0.22	0.41	0.26
Relative risk reduction (vs control), %	–	31.2	31.5	–	22.3	36.3	–	33.1	31.9	–	–19	–4
p-value	–	<0.001	<0.001	–	0.018	0.0001	–	0.054	0.058	–	0.03	0.59
Proportion of patients relapse-free [‡] , %	45.6	53.7	56.5	60.6	71.9	76.3	–	–	–	84.6	57.8	76.6
p-value (vs control)	–	0.01	0.003	–	0.002	<0.001	–	–	–	–	–	–
Patients with relapse indicating CDMS [§] , %	–	–	–	–	–	–	28	19	18	–	–	–
Risk reduction (vs placebo), %	–	–	–	–	–	–	–	37.2	42.6	–	–	–
p-value	–	–	–	–	–	–	–	0.027	0.009	–	–	–
Time to relapse or new Gd-enhancing or T ₂ lesions, %	–	–	–	–	–	–	76	62	64	–	–	–
Risk reduction (vs placebo), %	–	–	–	–	–	–	–	31.4	34.9	–	–	–
p-value	–	–	–	–	–	–	–	0.002	0.0003	–	–	–
Relapse or treatment discontinuation [¶] , %	–	–	–	–	–	–	–	–	–	42.3	48.6	37.8
HR	–	–	–	–	–	–	–	–	–	–	1.12	0.86
p-value (vs control)	–	–	–	–	–	–	–	–	–	–	0.52	0.60
Disability end points												
Proportion of patients with sustained disability worsening confirmed for 12 weeks [‡] , %	27.3	21.7	20.2	19.7	21.1	15.8	10 ^{††}	10 ^{††}	7 ^{††}	–	–	–
Risk reduction (vs placebo), %	–	23.7	29.8	–	4.5	31.5	–	2.2	29.9	–	–	–
p-value (vs placebo)	–	0.08	0.03	–	0.762	0.044	–	0.995	0.424	–	–	–
Mean change in EDSS score from baseline	–	–	–	0.09	0.04	–0.05	–0.056	–0.250	–0.265	–	–	–
p-value (vs placebo)	–	–	–	–	0.482	0.043	–	0.033	0.044	–	–	–
Mean change in FIS score from baseline ^{‡‡}	4.3	2.3	3.8	4.67	2.51	1.92	–3.535	–2.730	–4.487	9.10	0.97	4.10
p-value (vs control)	–	0.39	0.83	–	0.309	0.208	–	0.997	0.849	–	0.03	0.18

[†]Dosing was titrated from 8.8 mg for the first 2 weeks to 22 mg for the next 2 weeks, and 44 mg until study completion. If dose was not tolerated, dose was reduced to 22 mg.

[‡]In TEMSO, defined as free from protocol-defined relapse at 48 weeks.

[§]Defined as a new neurological abnormality separated by ≥30 days from a preceding clinical event, present for ≥24 h in the absence of fever or known infection.

[¶]This includes three patients in the interferon group that were not treated and one patient in the 14 mg group who received 7 mg.

^{‡‡}Values in TOWER are those after 108 weeks of treatment.

^{†††}Patients presenting with a first episode suggestive of MS do not have prolonged disease.

^{‡‡‡}Higher FIS scores indicate greater adverse impact on fatigue.

ARR: Annualized relapse rate; CDMS: Clinically definite multiple sclerosis; FIS: Fatigue Impact Scale; Gd: Gadolinium; HR: Hazard ratio; IFNB: Interferon beta; MS: Multiple sclerosis; NS: Not significant; UAL: Unique active lesion; sc.: Subcutaneous.

Table 2. Summary of key end points of Phase III clinical trials of teriflunomide (cont.).

	TEMSO (study duration: 108 weeks) [51]			TOWER (study duration: variable; 48 weeks after the last patient randomized) [52]			TOPIC (study duration: ≤108 weeks) [53]			TENERE (study duration: variable; 48 weeks after last patient randomized) [64]		
	Placebo	Teriflunomide		Placebo	Teriflunomide		Placebo	Teriflunomide		sc. IFNB-1a	Teriflunomide	
		7 mg	14 mg		7 mg	14 mg		7 mg	14 mg		44 µg [†]	7 mg
MRI end points												
Mean change in total lesion volume from baseline, ml	2.21	1.31	0.72	–	–	–	0.044	0.023	-0.028	–	–	–
Relative reduction (vs placebo), %	–	39.4	67.4	–	–	–	–	–	–	–	–	–
p-value	–	0.03	<0.001	–	–	–	–	0.779	0.037	–	–	–
Number of Gd-enhancing T ₁ lesions per scan	1.33	0.57	0.26	–	–	–	0.953	0.749	0.395	–	–	–
Relative risk	–	0.43	0.20	–	–	–	–	0.786	0.415	–	–	–
p-value (vs placebo)	–	<0.001	<0.001	–	–	–	–	0.444	0.001	–	–	–
Number of UALs per scan	2.46	1.29	0.75	–	–	–	–	–	–	–	–	–
Relative risk	–	0.52	0.31	–	–	–	–	–	–	–	–	–
p-value (vs placebo)	–	<0.001	<0.001	–	–	–	–	–	–	–	–	–

[†]Dosing was titrated from 8.8 mg for the first 2 weeks to 22 mg for the next 2 weeks, and 44 mg until study completion. If dose was not tolerated, dose was reduced to 22 mg.

[‡]In TEMSO, defined as free from protocol-defined relapse at 48 weeks.

[§]Defined as a new neurological abnormality separated by ≥30 days from a preceding clinical event, present for ≥24 h in the absence of fever or known infection.

[¶]This includes three patients in the interferon group that were not treated and one patient in the 14 mg group who received 7 mg.

^{||}Values in TOWER are those after 108 weeks of treatment.

^{|||}Patients presenting with a first episode suggestive of MS do not have prolonged disease.

^{||||}Higher FIS scores indicate greater adverse impact on fatigue.

ARR: Annualized relapse rate; CDMS: Clinically definite multiple sclerosis; FIS: Fatigue Impact Scale; Gd: Gadolinium; HR: Hazard ratio; IFNB: Interferon beta; MS: Multiple sclerosis; NS: Not significant; UAL: Unique active lesion; sc.: Subcutaneous.

TOPIC

TOPIC, a randomized, double-blind, placebo-controlled Phase III trial, was designed to evaluate the efficacy of teriflunomide in patients with a first clinical episode suggestive of MS, defined as a new neurological event consistent with demyelination, starting within 90 days of randomization, and with ≥2 T₂ MRI lesions ≥3 mm in diameter (NCT00622700) [53]. A total of 618 patients were randomized (1:1:1) to receive placebo or teriflunomide 7 or 14 mg for 108 weeks. Baseline demographics and disease characteristics were well balanced across treatment groups. Upon entering the trial, the average patient ages were 32.0, 31.6 and 32.8 years in the placebo, teriflunomide 7 and 14 mg groups, respectively; the average time since the initial neurological event was 1.88, 1.89 and 1.80 months, respectively. Patients presenting with a first episode suggestive of MS do not have prolonged disease. Bearing this point in mind facilitates interpretation of the efficacy outcomes summarized for TOPIC in **Table 2** [53]. The sponsor of TOPIC filed to stop the trial on 10 August 2012, because revisions to the MS diagnostic criteria in 2010 facilitated

earlier diagnoses [69]. Re-evaluation of the power calculation based on available information from the teriflunomide clinical program indicated that the study was still sufficiently powered to detect reduced relapse risk. The TOPIC study demonstrated that teriflunomide was superior to placebo in reducing the risk of relapse indicating clinically definite MS (primary end point), with significant reductions of 37.2% (hazard ratio [HR]: 0.628 [95% CI: 0.416–0.949]; p = 0.027) and 42.6% (HR: 0.574 [0.379–0.869]; p = 0.009) compared with placebo for the 7 and 14 mg doses, respectively [53]. Patients completing the 108-week core study, as well as those who had received ≥24 weeks of treatment and had experienced a relapse that defined clinically definite MS, were eligible to enroll in the TOPIC extension [53]. Patients who had received teriflunomide in the core study continued active treatment, and patients who had received placebo were randomized (1:1) to teriflunomide 7 or 14 mg [53].

TENERE

TENERE was a randomized, rater-blinded Phase III study that compared the efficacy,

Figure 2. Annualized relapse rate (A) and disability worsening (B) in TEMSO. Modified intent-to-treat population.
 HR: Hazard ratio.
 Data taken from [51].

safety and tolerability of teriflunomide with subcutaneous (sc.) IFNB-1a in patients with MS (NCT00883337) [64]. A total of 324 patients were randomized (1:1:1) to receive SC IFNB-1a 44 µg three-times per week or oral teriflunomide 7 or 14 mg once daily. Treatment duration was variable, and like TOWER, ended 48 weeks after the last patient was randomized. Key results are summarized in Table 2. In addition, patients in both teriflunomide groups

reported significantly greater satisfaction in the Treatment Satisfaction Questionnaire for Medication (TSQM) domains of Side Effects, Convenience and Global Satisfaction. MRI outcomes were not assessed in TENERE [64].
 Participants in the TENERE extension transitioned directly from core study treatment to teriflunomide 14 mg [70]. This direct transition, without a drug-free period, allowed an assessment of the effects of switching from

sc. IFNB-1a to teriflunomide. Of the 237 patients who entered the TENERE extension, 59 switched from IFNB-1a (sc. IFN/14 mg), 90 switched from teriflunomide 7 mg (7/14 mg) and 88 continued to receive teriflunomide 14 mg (14/14 mg). In all groups, relapse rates were low (0.239, sc. IFN/14 mg; 0.223, 7/14 mg; and 0.181, 14/14 mg); intergroup differences were not significant. Type and rates of AEs were consistent with previous studies,

and there were no new or unexpected AE signals with the switch from sc. IFNB-1a to teriflunomide [70].

• Vaccination studies

As discussed previously, teriflunomide prevents proliferation of activated lymphocytes by reversibly inhibiting dihydroorotate dehydrogenase [58]. Given this, the effects of teriflunomide on the immune response to vaccines were investigated

Figure 3. Annualized relapse rate (A) and disability worsening (B) in TOWER. Modified intent-to-treat population.

HR: Hazard ratio.

Data taken from [52].

in two studies [71,72]. In TERIVA, the immune responses to a recall antigen (influenza vaccine) were measured in patients with relapsing forms of MS, on a stable dose of IFNB, teriflunomide 7 or 14 mg [71]. Overall, teriflunomide did not adversely affect the ability of patients to successfully mount an immune response to the vaccine. In the second vaccination study, healthy subjects receiving teriflunomide were able to mount an effective response to a neoantigen challenge (rabies vaccine) [72]. Together, these studies demonstrate that immune responses are preserved during teriflunomide treatment, providing further supportive evidence for a selective immunomodulatory mechanism of action for teriflunomide.

• Supplementary measures of efficacy Number needed to treat

Obtaining measures of comparative efficacy between different treatment options is important to help inform clinical decisions in the absence of head-to-head comparative studies [6]. NNT is a parameter designed to facilitate cross-trial comparisons by expressing treatment efficacies as the number of patients that need to be treated with a given therapy to prevent one occurrence of a given event [73]. NNT, which is derived from absolute risk reduction, has become a useful tool for comparing clinical outcomes in a range of disease areas, including MS [73,74]. A lower NNT reflects a greater benefit of therapeutic intervention [6].

The NNT approach has been used to compare relapse rates of patients with MS who received teriflunomide with those treated with DMF [75]. In DEFINE [31] and CONFIRM [30], twice-daily DMF showed a greater relative risk reduction (53 and 44% vs placebo, respectively) than teriflunomide 14 mg in TEMSO [51] and TOWER [52] (31.5 and 36.3%, respectively). However, the NNT to prevent one relapse was comparable between DMF (5.3 in DEFINE and 5.6 in CONFIRM) and teriflunomide 14 mg (5.9 in TEMSO and 5.6 in TOWER) [75]. Furthermore, NNT to prevent a relapse leading to hospitalization was significantly reduced versus placebo in both TEMSO and TOWER, but not in DEFINE or CONFIRM; corresponding NNTs were 12.5 (TEMSO) and 20 (TOWER), and 50 in both DEFINE and CONFIRM. NNTs to prevent disability worsening were 13.8, 17.4, 10.8 and 30.2 for TEMSO, TOWER, DEFINE and CONFIRM, respectively [75].

No evidence of disease activity

NEDA is a composite measure of efficacy that includes clinical (no confirmed clinical relapse; no disability worsening confirmed for 12 weeks) and MRI outcomes (no Gd-enhancing T₁ lesions and no new/enlarging T₂ lesions) [76].

NEDA has been assessed in *post hoc* analyses of TEMSO core and extension studies [76–78]. From baseline to the end of the 2-year core study, NEDA was achieved by significantly more patients in the teriflunomide 14 mg group than in the placebo group (22.9 vs 14.3%; odds ratio [OR] 1.78; *p* = 0.0031); more patients reached NEDA in the 7 mg group than placebo, but this was not significant (18.4 vs 14.3%, respectively) [76]. To ensure that residual disease activity was not an influencing factor in NEDA assessments and that the full therapeutic effect of teriflunomide had been attained, achievement of NEDA from month 6 to year 2 was also evaluated [77]. During this period, NEDA achievement was greater with teriflunomide 14 mg (28.1%; OR: 2.34; *p* < 0.0001) or 7 mg (21.5%; OR: 1.64; *p* = 0.0180) than placebo (14.3%) [77].

mRio score

The mRio system was developed to predict future disability worsening based on MRI and relapse criteria. The number of relapses and occurrence of new T₂ lesions (6-monthly MRI scans) were evaluated during the first year of treatment. After 1 year of treatment, patients were classified using the mRio score for risk of disease worsening/treatment response according to relapse status (0 to ≥2 relapses) and the occurrence of active T₂ lesions (≤ or >5 lesions over 1 year). Patients with scores of 0, 1 or 2–3, were categorized as having a low, intermediate or high risk of treatment response, respectively [79]. In a *post hoc* analysis of TEMSO, patients treated with teriflunomide (7 and 14 mg groups combined) with a computable mRio score at the end of year 1 were classified based on their mRio scores as 0, 63.4% (*n* = 350); 1, 25.9% (*n* = 143); and 2 or 3, 10.7% (*n* = 59), compared with 48.8% (*n* = 139), 32.6% (*n* = 93), and 18.6% (*n* = 53) of patients who received placebo, respectively. Over 384 weeks (>7 years) from study initiation, the risk of disability worsening confirmed for 12 weeks in teriflunomide patients in the score 0 (treatment responder) category was significantly reduced compared with patients in the score 2 or 3 (nonresponder) category (HR: 2.055;

$p < 0.05$). These data demonstrate that relapses and MRI lesions in the first 1.5 years of treatment can be predictive of subsequent disability worsening [79].

• Real-world experience

Teri-PRO

Teri-PRO is a prospective, nonrandomized, open-label, global Phase IV study in which patients with relapsing forms of MS received teriflunomide per local labeling [80]. Enrollment is complete, with 1001 patients enrolled across sites in the USA, Canada, Europe and Latin America. The primary end point was global patient satisfaction with teriflunomide treatment, measured by TSQM (version 1.4). Patient-reported disability, measured with the MS Performance Scale, was a secondary end point. In the USA, a total of 545 patients were included, of which 13.2 and 86.8% received teriflunomide 7 or 14 mg, respectively. In interim results, at week 4 these patients had a mean TSQM Global Satisfaction score of 72.2 (0–100; higher scores indicate greater satisfaction). For patients who had switched to teriflunomide from a different DMT, the mean TSQM Global score was 74.9, a 22.7-point improvement from teriflunomide initiation (baseline). At week 24 ($n = 442$), mean MS Performance Scale score was 14.1, a decrease of 0.7 points from baseline, indicating stable levels of patient-reported disability. At week 24 or end of treatment, 73.4% of US patients reported AEs, and a total of 9.2% of patients discontinued treatment because of an AE. The safety and tolerability profile of teriflunomide for US patients in the Teri-PRO study at week 24, as well as the low rate of treatment discontinuation, was consistent with that seen in Phase II and III studies [80].

An interim analysis of study results from patients enrolled in Canada, Europe and Latin America demonstrated similar results. At week 4, the mean TSQM Global Satisfaction score for all patients ($n = 233$) was 73.9. The mean TSQM improvement from baseline to week 4 was 22.4 in patients switching from another DMT ($n = 115$) [81].

• Switching to teriflunomide from other DMTs

Patients who require a switch to an alternative DMT may be suboptimal responders and have a potential risk for more rapid disease worsening. In addition to observations in ‘switcher’ populations of Teri-PRO, further insight has been gleaned from analyses of the TEMSO and TOWER studies,

which required transitional interval of 3 and 4 months, respectively, between a prior treatment and teriflunomide, and the TENERE extension, which allowed a direct transition from IFNB-1a to teriflunomide [82]. In a *post hoc* analysis of pooled data from TEMSO and TOWER, teriflunomide 14 mg consistently reduced ARR in all prior DMT subgroups compared with placebo, with no significant treatment-by-subgroup interactions. Teriflunomide safety was also consistent across these subgroups [82]. The TENERE extension (discussed above) also yielded information about the efficacy and safety of switching from IFNB to teriflunomide 14 mg [70]; relapse rates were low in all treatment groups (0.239, SC IFN/14 mg; 0.223, 7/14 mg; and 0.181, 14/14 mg), and inter-group differences were not significant. No new or unexpected safety events were associated with switching from IFNB-1a to teriflunomide [70].

The effect of switching from NTZ to teriflunomide 14 mg within 4 weeks of the final NTZ dose is currently being investigated in a prospective study [82]. In a 6-month interim analysis, EDSS scores for 13 of 15 patients remained stable or showed an improvement. The two remaining patients experienced new Gd-enhancing lesions. There was no incidence of PML [82].

Safety & tolerability

• Pooled teriflunomide studies

Teriflunomide has a well-characterized, manageable safety and tolerability profile that is consistent across studies; safety data from individual studies have been previously reported [50–54]. To gain further insight into the safety and tolerability profile of teriflunomide, results from the teriflunomide clinical trial database have been pooled and analyzed [83]. Safety data were divided into two pools to compare the safety outcomes associated with long-term teriflunomide treatment (Pool 2) with safety outcomes observed in placebo-controlled core studies (Pool 1) [83]. Pool 1 consisted of data from placebo-controlled, double-blind core studies: Phase II, TEMSO, TOWER and TOPIC [83]. A total of 3044 patients were included in Pool 1, with a cumulative treatment duration of >1500 patient-years in each treatment group (placebo, teriflunomide 7 mg, and 14 mg). Pool 2 included data from Pool 1 core studies and long-term extension data from the Phase II and TEMSO studies. All patients in Pool 2 had been exposed to teriflunomide. Pool 2 was used to include long-term safety available at the time to determine whether

there was any change in the safety profile with long-term exposure to teriflunomide. The 2338 patients in Pool 2 had a maximum exposure of 12.1 years and a cumulative treatment duration of >3304 patient-years per treatment group [83]. Pooled safety data are shown in **Tables 3 & 4**. The nature of AEs reported in Pool 2 was similar to that of AEs observed in Pool 1, and no new or unexpected events were associated with long-term teriflunomide exposure across a wide spectrum of disease, from patients presenting with a first event to those with secondary progressive disease with relapses [83].

• Treatment discontinuations due to AEs

The majority of events in both pools was of mild-to-moderate intensity, was self-limiting and infrequently resulted in discontinuation of therapy. The most common reason for treatment discontinuation in all treatment groups was alanine aminotransferase (ALT) elevation, reflecting the protocol requirement to discontinue treatment on confirmation of ALT $>3\times$ the upper limit of normal. Teriflunomide safety and tolerability in the pooled data were consistent with results from individual studies, with no new or unexpected safety signals identified in these pooled analyses [83].

• AEs of special interest

The incidence of AEs of special interest for Pool 1 is shown in **Table 3**.

Patients treated with teriflunomide had a higher incidence of hepatic events, mainly owing to reversible ALT increases $\leq 3\times$ the upper limit of normal [76]. Longer term exposure (Pool 2) did not appear to increase clinically relevant hepatic events. Onset of hepatic events usually occurred during the first 6 months, events were mainly mild to moderate in nature and the majority of patients recovered [83].

In Pool 1, lymphopenia and neutropenia occurred more frequently in patients treated with teriflunomide and were generally observed during the first 6 weeks or 3 months of treatment, respectively, followed by stabilization with continued treatment. Actual mean decreases for both neutrophils and lymphocytes were generally no more than 15%, with mean counts remaining in the normal range [83]. One case of serious thrombocytopenia, potentially related to an immune-mediated mechanism, was considered to have had a possible causal relationship with teriflunomide. Similar results were observed in Pool 2, in which the proportion of patients with

neutropenia was 4.3 and 6.3%, and lymphopenia was 0.5 and 0.8%, for teriflunomide 7 and 14 mg, respectively [83].

Infections and serious infections occurred at similar rates in all Pool 1 treatment groups and there was no relationship between neutrophil count decrease and the occurrence of infections. Serious opportunistic infections occurred in two placebo patients (acute herpes zoster and hepatitis C with cytomegalovirus infection), one teriflunomide 7 mg patient (pulmonary tuberculosis) and two teriflunomide 14 mg patients (gastrointestinal tuberculosis and hepatitis with cytomegalovirus infection) [83]. Both patients with tuberculosis recovered following treatment with antituberculosis agents. Opportunistic infections led to treatment discontinuation in three patients in the 7 mg group and two patients in the 14 mg group. In Pool 2, one additional serious opportunistic oral herpes infection was reported in the teriflunomide 7 mg group; the patient recovered [83].

Malignancies did not occur at a higher rate in patients receiving teriflunomide in Pool 1 [83]. Thyroid cancer ($n = 1$), cervical carcinoma stage 0 ($n = 1$) and breast cancer ($n = 2$) were reported in the placebo group, and one patient in the teriflunomide 14 mg group was diagnosed with cervical carcinoma stage 0. In Pool 2, all malignancies were solid tumors, with no unusual pattern, and no cases of lymphoproliferative or hematological malignancies were observed [83].

In Pool 1, hypertension occurred more frequently with teriflunomide and the risk was greater in patients with pre-existing hypertension [83]. In Pool 2, hypertension was reported in 8.5 and 9.2% of patients treated with teriflunomide 7 and 14 mg, respectively. Most patients were successfully managed with the introduction of, or modification of existing, antihypertensive treatment [83].

In Pool 1, a small number of cases of peripheral neuropathy confirmed by nerve conduction studies occurred, leading to discontinuation of three patients in the teriflunomide 7 mg group and five patients in the 14 mg group [83].

No pulmonary disorders that could be attributed to interstitial lung disease were observed in Pool 1 [83]. One potential case, unlikely to be related to teriflunomide, was identified on day 1 of the extension study in a patient in the 14 mg group of Pool 2 who had a severe cold and history of tobacco use [83].

Pancreatic disorders occurred at similar rates in the three groups in Pool 1. Most disorders were asymptomatic, and enzyme increases were

Table 3. Overview of safety outcomes in Pool 1 (placebo-controlled, double-blind core studies): Phase II, TEMSO, TOWER and TOPIC.

Patients with adverse events	Placebo (n = 997), n (%)	Teriflunomide 7 mg (n = 1045), n (%)	Teriflunomide 14 mg (n = 1002), n (%)
All adverse events	853 (85.6)	895 (85.6)	885 (88.3)
Serious adverse event	119 (11.9)	125 (12.0)	133 (13.3)
Event leading to permanent treatment discontinuation	75 (7.5)	117 (11.2)	125 (12.5)
Deaths	2 (0.2)	1 (<0.1)	2 (0.2)
Intensity [‡] :			
– Mild	285 (33.4)	294 (32.8)	281 (31.8)
– Moderate	448 (52.5)	480 (53.6)	477 (53.9)
– Severe	120 (14.4)	121 (13.5)	127 (14.4)
Common adverse events[‡]			
Headache	150 (15.0)	186 (17.8)	157 (15.7)
ALT increase	98 (9.8)	136 (13.0)	150 (15.0)
Diarrhea	75 (7.5)	137 (13.1)	136 (13.6)
Hair thinning [§]	50 (5.0)	102 (9.8)	135 (13.5)
Nausea	72 (7.2)	84 (8.0)	107 (10.7)
Common adverse events leading to treatment discontinuation[¶]			
ALT increase	23 (2.3)	34 (3.3)	26 (2.6)
Hair thinning [§]	1 (0.1)	2 (0.2)	13 (1.3)
Pregnancy	3 (0.3)	6 (0.6)	8 (0.8)
Neutropenia	0	6 (0.6)	8 (0.8)
Transaminases increase	6 (0.6)	5 (0.5)	5 (0.5)
Hepatic enzyme increase	5 (0.5)	2 (0.2)	5 (0.5)
Diarrhea	1 (0.1)	5 (0.5)	4 (0.4)
AST increase	2 (0.2)	6 (0.6)	3 (0.3)
Abdominal pain upper	0	5 (0.5)	1 (<0.1)
Adverse events of special interest			
Hepatic disorders	152 (15.2)	207 (19.8)	215 (21.5)
Hematological measures:			
– Neutropenia	19 (1.9)	44 (4.2)	59 (5.9)
– Lymphopenia	2 (0.2)	4 (0.4)	5 (0.5)
Infections:	532 (53.4)	553 (52.9)	528 (52.7)
– Serious infections	22 (2.2)	23 (2.2)	27 (2.7)
Malignancies	4 (0.4)	0	1 (<0.1)
Hypertension	27 (2.7)	47 (4.5)	53 (5.3)
Peripheral neuropathy confirmed by NCS	4 (0.4)	13 (1.4)	17 (1.9)
Pancreatic disorders	28 (2.8)	27 (2.6)	27 (2.7)
Hair thinning [¶]	51 (5.1)	105 (10.0)	139 (13.9)
Gastrointestinal events:			
– Nausea	72 (7.2)	84 (8.0)	107 (10.7)
– Diarrhea	76 (7.6)	138 (13.2)	136 (13.6)

[‡]Mild: no modification of daily activities and/or does not require symptomatic treatment; Moderate: hinders normal daily activities and/or requires symptomatic treatment; Severe: prevents daily activities and requires symptomatic treatment. Calculated as percentage of patients with adverse events.

[§]Events with a crude incidence rate of ≥10% in either teriflunomide group, and ≥2% greater than placebo, listed in descending order for the teriflunomide 14 mg group.

[¶]MedDRA-preferred term: alopecia.

[¶]Events occurring in ≥5 patients in either teriflunomide group, listed in descending order for the teriflunomide 14 mg group.

[¶]Including related terms such as decreased hair density or hair loss.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities; NCS: Nerve conduction studies.

Data taken from [83].

Table 4. Overview of safety outcomes in Pool 2 (all patients treated with teriflunomide): Pool 1 plus Phase II and TEMSO long-term extensions.

Patients with adverse events [‡]	Teriflunomide 7 mg (n = 1204), n (%)	Teriflunomide 14 mg (n = 1134), n (%)
All adverse events	1056 (87.7)	1020 (89.9)
Serious adverse event	246 (20.4)	219 (19.3)
Event leading to permanent treatment discontinuation	184 (15.3)	172 (15.2)
Death	4 (0.3)	4 (0.4)
Intensity [‡] :		
– Mild	270 (22.4)	252 (22.2)
– Moderate	559 (46.4)	558 (49.2)
– Severe	227 (18.9)	210 (18.5)
Common adverse events[§]		
Nasopharyngitis	278 (23.1)	272 (24.0)
Headache	256 (21.3)	215 (19.0)
ALT increased	205 (17.0)	211 (18.6)
Diarrhea	189 (15.7)	192 (16.9)
Fatigue	177 (14.7)	170 (15.0)
Hair thinning [¶]	127 (10.5)	166 (14.6)
Back pain	150 (12.5)	157 (13.8)
Influenza	136 (11.3)	149 (13.1)
Upper respiratory tract infection	153 (12.7)	145 (12.8)
Nausea	120 (10.0)	142 (12.5)
Urinary tract infection	136 (11.3)	130 (11.5)
Paresthesia	115 (9.6)	129 (11.4)
Pain in extremity	128 (10.6)	123 (10.8)
Arthralgia	138 (11.5)	103 (9.1)

[‡]Includes patients initially randomized to placebo in core studies.

[‡]Mild: no modification of daily activities and/or does not require symptomatic treatment; Moderate: hinders normal daily activities and/or requires symptomatic treatment; Severe: prevents daily activities and requires symptomatic treatment.

[§]Events with a crude incidence rate of ≥10% in either teriflunomide group; listed in descending order in the teriflunomide 14 mg group.

[¶]MedDRA-preferred term: alopecia.

ALT: Alanine aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities.

Data taken from [83].

reversible. Serious pancreatitis was reported in two patients receiving placebo and one patient receiving teriflunomide 7 mg [83].

In Pool 1, teriflunomide groups had a higher incidence of gastrointestinal events. Most cases were mild to moderate in intensity and rarely led to discontinuation; most patients recovered during the observation period [83]. In Pool 2, nausea was reported by 10.0 and 12.5% of patients in the 7 and 14 mg groups; 15.7 and 16.9% reported diarrhea, respectively [83].

In Pool 1, hair thinning occurred more frequently in patients receiving teriflunomide; no events were classified as serious [83]. Hair thinning led to treatment discontinuation in 0.1, 0.2 and 1.3% of patients in the placebo and teriflunomide 7 and 14 mg groups, respectively. Hair thinning typically occurred during the first 6 months of teriflunomide treatment; no

complete hair loss was reported and most cases resolved without treatment discontinuation. In Pool 2, hair thinning was similar, occurring in 11 and 15.3% of patients in the teriflunomide 7 and 14 mg groups, respectively [83]. An evaluation of hair thinning in real-world clinical practice is discussed in further detail below [84].

• **Hair thinning**

Hair thinning may be a particular concern for a number of patients. Hair thinning associated with teriflunomide is characteristic of telogen effluvium, a common cause of reversible hair loss due to premature transition of follicles to the resting phase. This mechanism is distinct from the rapid and complete hair loss of anagen effluvium, typically observed following chemotherapy, when hair growth in the active anagen phase is interrupted [85]. Across all clinical trials, hair thinning

was reported in 10.0 and 13.9% of patients in teriflunomide 7 and 14 mg groups, respectively, versus 5.1% with placebo [83]. At nine MS treatment centers in the USA, patients with RRMS who reported hair thinning to healthcare professionals during teriflunomide treatment were eligible to enroll in the hair thinning photo project [84]. In this project, hair thinning was evaluated using patient and physician questionnaires administered at the onset and follow-up, and a standardized series of photographs of hair thinning was taken [84]. In all, 38 patients completed their participation, most of whom were female, white and with no prior history of hair loss [86]. For these 38 patients the mean duration between teriflunomide initiation and onset of hair thinning was 77 days, and physicians classified all but one case as mild (63%) or moderate (34%). The mean patient-perceived severity score was 5.1/10. At follow-up, 79% of patients reported either complete or near-complete resolution or marked improvement of hair thinning; only one patient described minimal improvement (hair thinning was rated as mild by the healthcare provider and 2/10 by the patient at both visits) [86].

• Pregnancy

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting teriflunomide. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment or prior to the completion of an accelerated elimination procedure after teriflunomide treatment [48]. However, to date, no pregnancy safety concerns have been identified in the teriflunomide clinical development program. Furthermore, prospective studies of leflunomide conducted by the Organization of Teratology Information Specialists and 2.4 million patient-years of leflunomide post-marketing surveillance have also not shown any teratogenic signal in humans [87]. Nevertheless, pregnancy must be excluded before teriflunomide treatment, and patients must use reliable contraception during and after treatment. An accelerated elimination procedure (to reduce plasma concentrations of teriflunomide to <0.02 µg/ml) is recommended for women who have taken teriflunomide and wish to become pregnant and for those who become pregnant

during treatment despite the contraindication [48]. In Denmark, pregnancy guidelines for women taking teriflunomide have been recently modified to be somewhat less conservative, recommending teriflunomide as a first-line first-choice therapy for women with MS who do not wish to become pregnant within the coming year [88].

A total of 83 pregnancies were reported in the teriflunomide clinical trial program, despite requirements for reliable use of contraception [89]. The outcomes of these pregnancies are shown in **Table 5**. No structural or functional abnormalities were noted at birth for babies born to patients exposed to teriflunomide and the spontaneous abortion rate in teriflunomide-exposed women was 18.6%, within the range for the general population. None of the induced abortions were due to defects or malformations [89,90].

Because teriflunomide-pregnancy exposure data are limited, two pregnancy registries have been established to collect additional prospective data. In the USA, the Organization of Teratology Information Specialists is maintaining a teriflunomide pregnancy registry [91] and an International Teriflunomide Pregnancy Exposure Registry has been established to monitor pregnancy outcomes in 17 additional countries [92]. This latter registry aims to recruit a total of 196 pregnant women exposed to teriflunomide to achieve 104 live births. Enrollment began in 2015 and will continue through December 2019. Pregnancy outcomes of study participants will be compared with those reported by the population-based European Surveillance of Congenital Anomalies.

Regulatory affairs

As of February 2016, teriflunomide has been approved in 63 countries. In the USA, both the 7 and 14 mg doses of teriflunomide have been approved for the treatment of relapsing forms of MS. In other countries, only the 14 mg dose has been approved. In the European Union, the approved indication is for treatment of adult patients with RRMS.

Conclusion

Teriflunomide treatment has had consistent effects on multiple markers of disease activity in patients with relapsing forms of MS or those with a first clinical episode suggestive of MS. In multiple clinical trials, patients with MS have shown improvements in disease measures, including ARR, disability worsening and MRI outcomes. These

Table 5. Outcomes of pregnancies in female patients and partners of male patients in the teriflunomide clinical trial program.

Pregnancy outcome	Placebo (n)	Teriflunomide (n)	IFNB (n)
Female patients			
Live birth	2	26	2
Induced abortion	8	29	0
Spontaneous abortion	1	13	0
Ongoing pregnancy	0	1 [†]	0
Unknown	0	1	0
Total	11	70	2
Female partners of male patients			
Live birth	2	16	–
Induced abortion	1	2	–
Spontaneous abortion	0	1	–
Total	3	19	–

[†]Following data cut-off, the ongoing pregnancy resulted in the delivery of a baby boy at 39 weeks of pregnancy.
 IFNB: Interferon beta.
 Data taken from [89].

improvements in ARR and disability worsening have been maintained in long-term extensions of the pivotal Phase III trials TEMSO and TOWER. Teriflunomide is the only currently approved oral DMT with positive disability results in two Phase III trials. In TEMSO, the positive and significant MRI outcomes observed with teriflunomide have been supported by a standardized analysis of brain atrophy using the SIENA method, which showed significantly reduced brain volume loss after 12 and 24 months of teriflunomide versus placebo. These positive efficacy outcomes are supported by results from analyses of supplementary outcomes such as predictions of disease outcomes with mRio score, NNT and NEDA assessments. In addition, teriflunomide has a well-characterized and favorable long-term safety profile that has been established with up to 12 years of exposure. Together, efficacy and safety data from clinical trials and real-world

outcomes support the use of teriflunomide in the treatment of patients with relapsing forms of MS.

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