# Common Drug Review

## *Clinical Review Report*

**October 2014**

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| **Drug** | Teriflunomide (Aubagio) (14 mg film-coated tablet) |
| **Indication** | Teriflunomide is indicated as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability |
| **Listing request** | For patients with relapsing forms of MS with similar listing criteria to interferons and glatiramer acetate on public drug formularies, which is aligned with the anticipated Aubagio Health Canada indication |
| **Manufacturer** | Genzyme Canada |

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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# ABBREVIATIONS

| | |
|---|---|
| **AE** | adverse event |
| **ALT** | alanine aminotransferase |
| **ARR** | annualized relapse rate |
| **CADTH** | Canadian Agency for Drugs and Technologies in Health |
| **CDR** | Common Drug Review |
| **CMSWG** | Canadian Multiple Sclerosis Working Group |
| **CNS** | central nervous system |
| **CI** | confidence interval |
| **DMT** | disease-modifying therapy |
| **EDSS** | Expanded Disability Status Scale |
| **EQ-5D** | European Quality of Life Scale |
| **FIS** | Fatigue Impact Scale |
| **GA** | glatiramer acetate |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **IM** | intramuscular |
| **INF** | interferon beta-1a |
| **ITT** | intention-to-treat |
| **IV** | intravenous |
| **LS** | least square |
| **MCID** | minimally clinically important difference |
| **MMRM** | mixed effect model with repeated measures |
| **MRI** | magnetic resonance imaging |
| **MS** | multiple sclerosis |
| **MSFC** | Multiple Sclerosis Functional Composite |
| **MSQOL-54** | Multiple Sclerosis Quality of Life-54 |
| **MTC** | mixed treatment comparison |
| **NA** | not applicable |
| **NR** | not reported |
| **NS** | not statistically significant |
| **PML** | progressive multifocal leukoencephalopathy |
| **PRMS** | progressive relapsing multiple sclerosis |
| **RCT** | randomized controlled trial |
| **RR** | relative risk |
| **RRMS** | relapsing-remitting multiple sclerosis |
| **SAE** | serious adverse event |
| **SC** | subcutaneous |
| **SD** | standard deviation |
| **SE** | standard error |
| **SF-36** | Short Form-36 |
| **SPMS** | secondary progressive multiple sclerosis |
| **TR** | teriflunomide |
| **TSQM** | Treatment Satisfaction Questionnaire for Medication |
| **WDAE** | withdrawal due to adverse event |

# EXECUTIVE SUMMARY

## Introduction

Multiple sclerosis (MS) is a central nervous system disorder characterized by progressive loss of myelin, the sheath that surrounds nerves, with subsequent impaired nerve conduction. This leads to disorders in movement, sensation, and cognition and results in significant disability. It is a slow progressing disorder that typically has an early onset (age late 20s/early 30s) and affects more females than males, and is also more common in Caucasians. Patients are most often diagnosed with the relapsing-remitting form of MS (RRMS). In addition to teriflunomide, therapies currently marketed for MS include several forms of interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, and alemtuzumab. Fingolimod, dimethyl fumarate, and teriflunomide are orally administered, while the other drugs must be injected, either subcutaneously, intramuscularly, or by intravenous infusion. Teriflunomide is administered at a dose of 14 mg once daily.

The indication under review is listed below:

| Indication under review |
| --- |
| As monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability |
| **Listing criteria requested by sponsor** |
| For the treatment of patients with relapsing multiple sclerosis to reduce the frequency of clinical exacerbations, to delay the accumulation of physical disability, and to decrease the number and volume of active brain lesions identified on magnetic resonance imaging scans |

The objective of this systematic review is to examine the beneficial and harmful effects of teriflunomide for the treatment of RRMS.

## Results and Interpretation

### Included Studies

Four randomized, multi-centre, parallel group, superiority trials met the inclusion criteria for this systematic review. TENERE (phase 3; N = 324) was an active control, investigator (but not patient)-blinded trial. TEMSO (phase 3; N = 1,088), TOWER (phase 3; N = 1,169), and Study 2001 (phase 2; N = 179) were double-blind, placebo-controlled trials. Included patients had MS with a relapsing course, were older than 18 years, and met the McDonald 2005 criteria or Poser criteria for MS. Two teriflunomide doses (7 mg or 14 mg) were compared with interferon beta-1a 44 mcg (TENERE) or to placebo (TEMSO, TOWER, and Study 2001). Only the results for the Health Canada–approved dose of teriflunomide (14 mg orally once daily) are included in this report.

In TENERE and in TOWER, patients were treated for a minimum of 48 weeks to a maximum of 118 weeks and 160 weeks, respectively. In TEMSO and in Study 2001, patients were treated for 108 weeks and 36 weeks, respectively. The primary efficacy end points were time to failure in TENERE, annualized relapse rate (ARR) in TOWER and TEMSO, and number of unique active lesions (combined T1 and T2) per magnetic resonance imaging (MRI) scan in Study 2001. In all trials, randomization was stratified by centre and baseline disability (Expanded Disability Status Scale [EDSS] ≤ 3.5 or EDSS > 3.5). Patients were offered long-term teriflunomide treatment in extension trials after Study 2001 or TOWER.

The majority of trial participants were women (range, 64% to 79%) and mean age ranged from 35 years to 40 years. Most patients had RRMS and were Caucasian. Baseline EDSS median score ranged from 1.5 to 2.5, with the majority of patients (> 75%) having an EDSS ≤ 3.5. Mean number of relapses in the past year ranged from 1.2 to 1.5.

Limitations of the available evidence include the open-label design of TENERE and the challenge of maintaining blinding in the placebo-controlled trials due to adverse events experienced by teriflunomide-treated patients (including gastrointestinal and alopecia). The high frequency of study withdrawal in all trials and the between-treatment imbalances in study withdrawals in TENERE and Study 2001 could potentially have biased the results of the between-treatment comparisons. [redacted]

**Efficacy**

Key outcomes identified a priori for this review by the Common Drug Review were relapse rate, disability, health-related quality of life (HRQoL), and fatigue.

Relapse rate was measured in all four trials; however, Study 2001 was designed to examine MRI outcomes and no statistical testing of relapse data was provided. In TOWER, the adjusted ARR was statistically significantly lower in the teriflunomide 14 mg group (0.32 [95% CI, 0.27 to 0.38]) compared with placebo (0.50 [95% CI, 0.43 to 0.58]); rate ratio 0.64 (95% CI, 0.51 to 0.79). Similarly in TEMSO, the adjusted ARR was statistically significantly lower in the teriflunomide 14 mg group (0.37 [95% CI, 0.31 to 0.44]) compared with placebo (0.54 [95% CI, 0.47 to 0.62]); rate ratio 0.69 [95% CI, 0.55 to 0.85]). In TENERE, there was no statistically significant difference in the adjusted ARR between the teriflunomide 14 mg group (0.26 [95% CI, 0.15 to 0.44]) and the interferon beta-1a group (0.22 [95% CI, 0.11 to 0.42]); rate ratio 1.2 (95% CI, 0.6 to 2.3). Unequal between-treatment study discontinuation may have biased the results of TENERE. In addition, it is important to note that TENERE was not designed to test equivalence or non-inferiority of teriflunomide compared with interferon beta-1a, and these cannot be inferred from the non-significant finding.

Various measures of disability were reported for the four included trials, including disability progression sustained for 12 weeks or 24 weeks, change from baseline in the EDSS, and Multiple Sclerosis Functional Composite (MSFC). Relapse effects may still be present at 12 weeks; hence, disability progression sustained for 24 weeks may be a better clinical measure of sustained disability progression. In TOWER and TEMSO, disability sustained for 24 weeks was not statistically significantly different between teriflunomide and placebo. In all four trials, mean changes from baseline in EDSS within groups were small and unlikely to represent clinically detectable differences. The MSFC, which measures leg function and ambulation, arm and hand function, and cognitive function, was employed in TEMSO and Study 2001. In Study 2001, no statistically significant differences in MSFC Z-scores were observed between teriflunomide 14 mg and placebo ($P$ = 0.89). In TEMSO, the statistical significance of between-treatment differences in MSFC Z-scores at week 24 and week 48 are unknown, as planned testing of this outcome fell below a non-significant parameter in the hierarchical chain to address multiplicity.

Generic HRQoL measures were employed in TOWER (Short Form-36 [SF-36]) and TEMSO (SF-36 and the European Quality of Life Scale [EQ-5D]); there appeared to be no notable between-treatment differences in these measures and $P$ values were not provided. Study 2001 employed a disease-specific measure of HRQoL, the Multiple Sclerosis Quality of Life-54 (MSQOL-54); no statistically significant differences between teriflunomide 14 mg and placebo were reported for the MSQOL-54 mental and physical health component scores.

Fatigue was measured in all trials using the Fatigue Impact Scale (FIS), a validated measure that evaluates the impact of fatigue on the lives of MS patients. No statistically significant difference was reported in FIS scores between teriflunomide and interferon beta-1a in TENERE, or between teriflunomide and placebo in Study 2001; the statistical significance of between-treatment differences in TOWER and TEMSO are uncertain, given that planned testing of this outcome fell below a non-significant parameter in the hierarchical chain to address multiplicity.

Subgroup results for treatment effects for ARR and disability progression were consistent across two subgroups: patients with or without prior use of disease-modifying treatments (DMTs) in the last two years, and patients with EDSS ≤ 3.5 or > 3.5.

Given the paucity of head-to-head trials of teriflunomide, the manufacturer provided a mixed treatment comparison (MTC), which reported no significant differences between teriflunomide and interferon beta-1a (subcutaneous and intramuscular), interferon beta-1b, or glatiramer acetate, whereas dimethyl fumarate, fingolimod, and natalizumab resulted in significantly lower ARRs. In addition, teriflunomide was not found to be significantly different compared with the other DMTs with respect to three-month sustained accumulated disability. The MTC was limited by the heterogeneity of the included trials and the limited direct evidence. Results from the manufacturer-provided MTC were relatively consistent with a recently published Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review for the outcomes of ARR and sustained disability; differences between the effect estimates for the outcome of sustained disability between the MTCs conducted by the manufacturer and CADTH may be related to differences in the included studies, differences in definition of the outcome, and the calculated measures of effect (relative risk versus hazard ratio). However, both the manufacturer and CADTH reports recommend caution in the interpretation of between-treatment differences suggested by the MTCs, given the lack of direct head-to-head evidence.

**Harms**

No deaths were reported in TENERE, TEMSO, and Study 2001. In TOWER, four deaths were reported: one death due to bacterial sepsis and another due to suicide in the teriflunomide 14 mg group; one death in the teriflunomide 7 mg group due to a road traffic accident; and a fourth death due to a respiratory tract infection in the placebo group.

The proportion of patients who experienced at least one adverse event was lower with teriflunomide 14 mg compared with interferon beta-1a, and slightly higher compared with placebo. Overall, the most common adverse events reported with teriflunomide included alopecia, diarrhea, and increased alanine aminotransferase (ALT). In TENERE, 5.5% of patients experienced a serious adverse event compared with 6.9% for the interferon beta-1a group. In the other three trials, patients with serious adverse events ranged from 11.9% to 15.9% with teriflunomide 14 mg and from 11.5% to 12.8% with placebo. Patients receiving interferon beta-1a were more likely to discontinue treatment due to adverse events compared with teriflunomide, whereas in the placebo-controlled trials, teriflunomide patients were more likely to discontinue treatment due to adverse events. No fetal malformations were reported in the trials. Of note, teriflunomide is an active metabolite of leflunomide (Arava), which was approved in 2000 for the treatment of rheumatoid arthritis. Teriflunomide may share some of the same known risks of leflunomide. A boxed warning regarding hepatotoxicity is included in the Health Canada–approved product monograph of teriflunomide.

In the manufacturer-submitted network meta-analysis, when compared with the other DMTs, teriflunomide was not associated with significant differences in treatment discontinuations due to adverse events. In both extension trials of Study 2001 and TEMSO, the majority of patients experienced adverse events; however, most were not serious and most did not lead to discontinuation.

### Pharmacoeconomic Summary

The manufacturer's submission relates to oral teriflunomide (Aubagio) 14 mg once daily for patients with relapsing forms of multiple sclerosis (MS) with an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 who are treatment naive, or those requiring a first switch to another therapy due to intolerance. The manufacturer's base-case analysis was based on the TEMSO trial population, in which 91.5% of subjects had relapsing-remitting multiple sclerosis (RRMS), and it was assumed that treatment would be discontinued when patients converted from RRMS to secondary progressive MS (SPMS).

A confidential price of $[redacted] per year was submitted.

### Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis based on a Markov model of disease progression, where patients progress through EDSS levels (1 to 9) and move from RRMS to SPMS, and death. The analysis was conducted over a 20-year time horizon using a cycle length of one year. Mortality can occur at any EDSS level and the rate is assumed to increase with EDSS level. The model also incorporated differential risks of relapses, costs, and utility values for each level. The analysis was conducted from the perspective of the health care payer. Data on the natural progression of MS were derived primarily from data from the London, Ontario, registry supplemented by data from the placebo arms of the TEMSO and TOWER trials. Data on relative effectiveness of all comparators in terms of disease progression, annualized relapse rates, and withdrawals were obtained through an unpublished mixed treatment comparison (MTC) restricted to studies published since 2000 with 80% of patients with RRMS.[1] Utility values and costs for each state were derived from Canadian data sources. The primary analysis compared teriflunomide with interferon beta-1a (Avonex), interferon beta-1a (Rebif), glatiramer acetate, and dimethyl fumarate. Comparison with best supportive care (no disease-modifying therapy) was also possible with the model, although not assessed in the manufacturer's base case.

### Results of Manufacturer's Analysis

In the manufacturer's base analysis, the following results were reported: teriflunomide is dominant over Rebif and Avonex; the incremental cost-utility ratio (ICUR) for teriflunomide versus glatiramer acetate is $33; dimethyl fumarate is more costly and associated with greater quality-adjusted life-years than teriflunomide.

### Interpretations and Key Limitations

There were a number of limitations within the model that required reanalysis:

- The MTC submitted by the manufacturer used studies published since 2000 and focused on treatment progression over a three-month period, which biased the results in favour of teriflunomide, especially compared with glatiramer acetate. Reanalysis employed estimates from the Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review on drug therapies for RRMS, where the MTC considered trials in which > 50% of the trial population had RRMS and looked at progression over a three- or six-month period.
- The utility values by EDSS state used by the manufacturer (Tappenden et al.) were much lower than those found in other studies. Alternative utility values were considered in reanalysis.

- The effectiveness of treatments was assumed to be maintained for a patient's lifetime. The duration of follow-up in the TEMSO clinical trial was 108 weeks. It would be reasonable to assume that benefit from treatment may wane beyond this time horizon. As of March 31, 2014, the manufacturer had not responded to the Common Drug Review (CDR) request to modify the model to allow treatment waning, so this issue could not be addressed in reanalysis.
- Analysis only included side effects for each therapy where the difference between active therapy and placebo was 4%. Considering the transient nature of most of the adverse events related to the RRMS treatments, CDR performed a reanalysis in which side effects were excluded.
- Health care costs by EDSS state and for relapse were purportedly derived from Karampampa et al. 2012; however, the methods of extrapolation were erroneous. Estimates for the cost of relapse and by EDSS state from the CADTH Therapeutic Review were considered in reanalysis.
- Mortality by EDSS state was derived from a 1992 study by Sadovnick et al., which reported mortality rates for three grouped EDSS categories: 0 to 3.5, 4 to 7, and 7.5 to 9. The manufacturer interpolated different mortality rates for each EDSS state. CDR reanalysis adopted the actual data from Sadovnick et al.
- Treatments were more cost-effective if they were associated with a higher withdrawal rate. Reanalysis assumed a constant withdrawal rate across all treatments.

### Results of Common Drug Review Analysis

CDR reanalysis concluded:

- Teriflunomide dominated Rebif and Avonex
- Teriflunomide was more effective than best supportive care: ICUR of $195,070
- Teriflunomide was more effective than glatiramer acetate: ICUR of $409,175
- Dimethyl fumarate was more effective than teriflunomide: ICUR of $10,130

CDR found several limitations with the manufacturer's economic analysis. A reanalysis addressing all of these limitations (except treatment waning over time) found that teriflunomide dominated Rebif and Avonex, but the ICUR for teriflunomide versus glatiramer acetate was $409,175.

### Conclusions

Based on the results of two phase 3 double-blind randomized controlled trials, teriflunomide 14 mg may reduce the annualized relapse rate (ARR) by approximately 30% to 35% compared with no treatment (placebo) over one to three years of treatment. However, the benefits of teriflunomide compared with no treatment in terms of reducing disability are less certain, given that disability sustained for 24 weeks was not statistically significantly different between teriflunomide and placebo in either trial. There were no differences in health-related quality of life or fatigue between teriflunomide and placebo. Direct head-to-head evidence for teriflunomide 14 mg, limited to one investigator-blinded randomized controlled trial, reported no statistically significant difference in ARR or time to failure (primary outcome) between teriflunomide 14 mg and interferon beta-1a 44 mcg; however, the trial was not designed to test equivalence or non-inferiority of teriflunomide, and thus this cannot be inferred.

A manufacturer-provided MTC reported no significant differences between teriflunomide 14 mg and any of interferon beta-1a (subcutaneous and intramuscular), interferon beta-1b, or glatiramer acetate with respect to the ARR. However, dimethyl fumarate, fingolimod, and natalizumab resulted in significantly lower ARRs compared with teriflunomide 14 mg. In addition, teriflunomide 14 mg was not found to be significantly different compared with the other disease-modifying treatments with respect to three-month sustained accumulated disability. However, the MTC was limited by the heterogeneity of the

included trials and, given the lack of direct evidence; caution is warranted in the interpretation of between-treatment differences suggested by the MTC.

The most common harms with teriflunomide were alopecia, diarrhea, and increased alanine aminotransferase. Serious safety concerns with teriflunomide include teratogenicity and hepatotoxicity.

**TABLE 1: SUMMARY OF RESULTS**

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| | TR 14 mg | INF 44 mcg | TR 14 mg | PL | TR 14 mg | PL | TR 14 mg | PL |
| N | 111 | 104 | 370 | 388 | 358 | 363 | 56 | 61 |
| **Relapses** | | | | | | | | |
| Adjusted ARR | 0.26 | 0.22 | 0.32 | 0.50 | 0.37 | 0.54 | NR | NR |
| 95% CI | 0.15 to 0.44 | 0.11 to 0.42 | 0.27 to 0.38 | 0.43 to 0.58 | 0.31 to 0.44 | 0.47 to 0.62 | NR | NR |
| Mean annual relapse rate (SD) | NR | NR | NR | NR | NR | NR | 0.55 (1.12) | 0.81 (1.22) |
| Rate ratio (95% CI) | 1.2 (0.6 to 2.3) | | 0.64 (0.51 to 0.79) | | 0.69 (0.55 to 0.85) | | NR | |
| **Time to Failure (Due to Relapse or Drug Discontinuation)** | | | | | | | | |
| HR (95% CI) | 0.86 (0.56 to 1.31) | | NR | NR | NR | NR | NR | NR |
| **Probability of Disability Progression Sustained for 24 Weeks** | | | | | | | | |
| At week 48 | NR | NR | 0.09 | 0.07 | 0.10 | 0.09 | NR | NR |
| 95% CI | NR | NR | 0.06 to 0.12 | 0.04 to 0.09 | 0.06 to 0.13 | 0.06 to 0.12 | NR | NR |
| At week 108 | NR | NR | 0.12 | 0.12 | 0.14 | 0.19 | NR | NR |
| 95% CI | NR | NR | 0.08 to 0.16 | 0.08 to 0.16 | 0.10 to 0.18 | 0.14 to 0.23 | NR | NR |
| **Time to Disability Progression** | | | | | | | | |
| HR (95% CI) | NR | | 0.84 (0.53 to 1.33) | | 0.75 (0.51 to 1.11) | | NR | |
| **MSFC Z-Scores** | | | | | | | | |
| N | NR | NR | NR | NR | 294 | 302 | 54 | 61 |
| Mean change from baseline (SE)[a] | NR | NR | NR | NR | –0.05 (0.05) | –0.20 (0.05) | –0.02 (0.04) | 0.004 (0.04) |
| **MSQOL-54, Overall Quality of Life Score** | | | | | | | | |
| N | NR | NR | NR | NR | NR | NR | 53 | 60 |
| Mean change from baseline (SD) | NR | NR | NR | NR | NR | NR | 2.36 (11.41) | –3.20 (12.40) |
| **FIS Total Score** | | | | | | | | |
| N | 83 | 65 | 275 | 297 | 297 | 307 | 53 | 60 |
| Mean change from baseline (SE)[b] | 4.10 (3.03) | 9.10 (3.21) | 1.92 (1.63) | 4.67 (1.58) | 4.96 (1.49) | 4.11 (1.48) | –1.49 (3.37) | 3.82 (3.45) |
| **Relapses Requiring Use of IV Corticosteroids** | | | | | | | | |
| AAR | NR | NR | 0.27 | 0.43 | 0.28 | 0.43 | NR | NR |

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| | TR 14 mg | INF 44 mcg | TR 14 mg | PL | TR 14 mg | PL | TR 14 mg | PL |
| **Harms, n (%)** | | | | | | | | |
| N (safety population) | 110 | 101 | 371 | 385 | 358 | 360 | 57 | 61 |
| Death | 0 | 0 | 2 (0.5) | 1 (0.3) | 0 | 0 | 0 | 0 |
| Serious AEs | 6 (5.5) | 7 (6.9) | 44 (11.9) | 47 (12.2) | 57 (15.9) | 46 (12.8) | 7 (12.3) | 7 (11.5) |
| WDAEs | 12 (10.9) | 22 (21.8) | 58 (15.6) | 24 (6.2) | 39 (10.9) | 29 (8.1) | 8 (14.0) | 4 (6.6) |
| **Notable Harms, n (%)** | | | | | | | | |
| Alopecia | 22 (20.0) | 1 (1.0) | 50 (13.5) | 17 (4.4) | 47 (13.1) | 12 (3.3) | 11 (19.3) | 6 (9.8) |
| Hepatotoxicity | NR | NR | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | NR | NR |
| Hypertension | 5 (4.5) | 4 (4.0) | 15 (4.0) | 8 (2.1) | 13 (3.6) | 6 (1.7) | 3 (5.3) | 1 (1.6) |
| Infection | 54 (49.1) | 47 (46.5) | 165 (44.5) | 197 (51.2) | 222 (62.0) | 209 (58.1) | 31 (54.4) | 24 (41.0) |
| Peripheral neuropathy | 5 (4.5) | 1 (1.0) | 4 (1.1) | 2 (0.5) | 3 (0.8) | 2 (0.6) | NR | NR |

AAR = adjusted annualized rate; AE = adverse event; ARR = annualized relapse rate; CI = confidence interval; FIS = Fatigue Impact Scale; HR = hazard ratio; INF = interferon beta-1a; IV = intravenous; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54; NR = not reported; PL = placebo; SD = standard deviation; SE = standard error; TR = teriflunomide; WDAE = withdrawal due to adverse events.
Source: Clinical Study Reports.[2-5]
[a]Outcome identified as important to the review (see Table 2 for review protocol): For TEMSO, least square mean reported at week 48; for Study 2001, adjusted mean reported at end point.
[b]Outcome identified as important to the review (see Table 2 for review protocol): For TENERE, TOWER, and TEMSO, least square mean reported at week 48; for Study 2001, adjusted mean reported at end point.

# 1. INTRODUCTION

## 1.1 Disease Prevalence and Incidence

Multiple sclerosis (MS) is a central nervous system (CNS) disorder characterized by progressive loss of myelin, the sheath that surrounds nerves.[6] Myelin facilitates the conduction of signals along nerves; thus, patients with MS gradually lose nerve conduction, manifesting clinically as disability that can be afferent (sensory; e.g., vision loss), efferent (motor; e.g., loss of ability to walk unassisted), or cognitive.[6] The exact cause of the CNS damage is unknown; however, inflammation and an inappropriate immune response likely play a key role in the pathogenesis.[7] MS affects up to three times as many women as men and typically has an age of onset between 20 and 50 years.[8] Patients are most often diagnosed with the relapsing-remitting form of MS (RRMS). Other types of MS include primary progressive MS and secondary progressive MS (SPMS).[7]

The prevalence of MS varies by geographic region.[7,9] Canada and the US (particularly the northern states) have above-average prevalence. In the US, overall the prevalence is approximately 0.1%.[7] The Multiple Sclerosis Society of Canada estimates that there are currently 100,000 patients with MS in Canada, which is one of the highest prevalence rates in the world.[10] There are many theories as to factors that may increase the risk of MS, including geography, genetics, and environment.[7,9]

## 1.2 Standards of Therapy

Relapses or acute flare-ups of the disease may be treated with systemic corticosteroids, depending on the severity of the attack and the level of functional impairment. The primary focus of MS management is preventing relapses and slowing progression of disability through the use of disease-modifying therapy (DMT; Table 2).[11,12]

According to recent treatment recommendations by the Canadian Multiple Sclerosis Working Group (CMSWG, 2013),[13] first-line drugs from RRMS are interferon beta or glatiramer acetate. For a number of years, these were the only DMTs available to treat for RRMS (interferon beta-1a [Rebif, Avonex], beta-1b [Betaseron, Extavia], and glatiramer acetate [Copaxone]). Although they have some tolerability issues (interferons: flu-like syndrome; glatiramer: injection-site reactions),[12] there have not been any major safety issues associated with these drugs in the 20 years since they became available.[13]

According to the CMSWG, patients with a poor response or intolerance to a first-line drugs may be switched to a different first line drugs.[13] Second line treatments include fingolimod and natalizumab, and according to CMSWG, RRMS patients with more active or progressive disease may benefit from early treatment with these two drugs.[13] Natalizumab, available since 2006, is a monoclonal antibody administered by intravenous infusion. Progressive multifocal leukoencephalopathy (PML) is a concern with natalizumab. Fingolimod, available since 2011, is an oral preparation; there are concerns of cardiovascular adverse events with this drugs.[12]

An oral route of administration may be preferable to patients as it may lessen the medication administration burden. Other orally administered therapies approved in Canada in 2013 include dimethyl fumarate and teriflunomide. Most recently, alemtuzumab, administered intravenously once a year, was approved by Health Canada (Notice of Compliance December 12, 2013).[14,15] The place in therapy of these recently marketed drugs was not reviewed by CMSWG.

Several drugs are in phase 3 clinical trials, including subcutaneous daclizumab 150 mg every two weeks, oral laquinimod 0.6 mg daily, and intravenous ocrelizumab 600 mg every 24 weeks.[12]

## 1.3 Drug

Teriflunomide is the primary active metabolite of leflunomide, a drug used in the treatment of rheumatoid arthritis.[16] The mechanism of action of teriflunomide is not completely understood. It acts primarily as an inhibitor of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in the novo synthesis of pyrimidines, thereby limiting the expansion of stimulated T cells and B cells and decreasing the migration of lymphocytes to the CNS.[17] Furthermore, it is thought that teriflunomide has other immunological effects independent of pyrimidine synthesis inhibition, such as the inhibition of protein tyrosine kinases and of cyclooxygenase-2.[16,17] Oral bioavailability is close to 100% and time to steady-state concentration is approximately three months.[16,17] Teriflunomide is excreted by the liver.[17] The median elimination half-life is 18 to 19 days after repeated oral doses.[16] Elimination from plasma is slow and can take up to two years.[17]

Teriflunomide is available as a 14 mg film-coated tablet administered orally once daily.[18] Notice of Compliance was granted by Health Canada on November 14, 2013.[19]

| Indication under review |
| --- |
| As monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability |
| **Listing criteria requested by sponsor** |
| For the treatment of patients with relapsing multiple sclerosis to reduce the frequency of clinical exacerbations, to delay the accumulation of physical disability, and to decrease the number and volume of active brain lesions identified on magnetic resonance imaging scans |

**TABLE 2: KEY CHARACTERISTICS OF DISEASE-MODIFYING TREATMENTS FOR MULTIPLE SCLEROSIS**

| | Mechanism of Action | Approved Indications | Route of Administration | Recommended Dose | Contraindications (According to PM) |
|---|---|---|---|---|---|
| **Alemtuzumab (Lemtrada)** | Binds to CD52 | RRMS | IV infusion | Initial treatment cycle: 12 mg/day for 5 consecutive days Second treatment cycle: 12 mg/day for 3 consecutive days administered 12 months after the initial treatment cycle | Contraindicated in patients who are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container; are infected with HIV; have active or latent TB, active severe infections, or active malignancies; are on antineoplastic or immunosuppressive therapies; have a history of PML |
| **Dimethyl fumarate (Tecfidera)** | Not completely understood; activates the Nrf2 pathway | RRMS | Oral capsule | 240 mg twice daily | Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container |
| **Fingolimod (Gilenya)** | Not known; likely reduces lymphocyte migration in the CNS | RRMS | Oral capsule | 0.5 mg/day | Contraindicated in patients who are hypersensitive to fingolimod; who are at risk for an opportunistic infection; are immunocompromised due to treatment or to disease; have hepatic insufficiency, active severe infections, or known active malignancies. Varicella zoster vaccination recommended |
| **Glatiramer acetate (Copaxone)** | Likely modifies the immune processes responsible for pathogenesis of MS | RRMS; single demyelinating event, accompanied by abnormal MRI scans and considered to | SC injection | 20 mg/day | Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol |

| | Mechanism of Action | Approved Indications | Route of Administration | Recommended Dose | Contraindications (According to PM) |
|---|---|---|---|---|---|
| | | be at risk of developing CDMS | | | |
| **Interferon beta-1a (Avonex; Rebif)** | Not completely understood; likely the upregulation of IL-10 | RRMS; SPMS with relapses; single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS | IM injection (Avonex)<br>SC injection (Rebif) | IM: 30 µg/week (increase up to 60 µg/week if needed)<br><br>SC: 22 µg or 44 µg<br>3 times/week | Contraindicated in patients with known hypersensitivity to natural or recombinant interferon; patients with liver disease; pregnant women |
| **Interferon beta-1b (Betaseron; Extavia)** | Not completely understood; likely mediated by binding to cell surface receptors | RRMS; SPMS; single demyelinating event accompanied by at least two clinically silent lesions typical of MS | SC injection (Betaseron, Extavia) | 0.25 mg every other day | Contraindicated in patients with known hypersensitivity to natural or recombinant interferon; patients with liver disease; pregnant women |
| **Natalizumab (Tysabri)** | Blocks interaction of α4β7 integrin with the mucosal address in cell adhesion molecule-1. Reduces formation or enlargement of MS lesions | RRMS | IV infusion | 300 mg every 4 weeks | Contraindicated in patients who have had PML; are at risk for PML; are hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; are immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies |
| **Teriflunomide (Aubagio)** | Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS | RRMS | Oral tablet | 14 mg once daily | Contraindicated in patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; pregnant women or women of child-bearing age who |

| | Mechanism of Action | Approved Indications | Route of Administration | Recommended Dose | Contraindications (According to PM) |
|---|---|---|---|---|---|
| | | | | | are not using contraception; immunodeficiency states such as AIDS; serious active infection; impaired bone marrow function or with significant anemia, leucopenia, neutropenia, or thrombocytopenia |

CDMS = clinically definite multiple sclerosis; CNS = central nervous system; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; PM = product monograph; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; TB = tuberculosis.
Source: eCPS,[20] Aubagio product monograph,[18] Lemtrada product monograph,[21] Coles[15]

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of oral teriflunomide 14 mg as monotherapy for the treatment of RRMS.

## 2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

**TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | Adults with RRMS |
| **Intervention** | Oral teriflunomide 14 mg once daily, used as monotherapy<br><br>Subgroups:<br>Treatment experience (naive/experienced)<br>Baseline EDSS score (EDSS ≤ 3.5 / EDSS > 3.5) |
| **Comparators** | • Interferon beta-1a (IM or SC)<br>• Interferon beta-1b<br>• Glatiramer acetate<br>• Natalizumab<br>• Fingolimod<br>• Dimethyl fumarate<br>• Alemtuzumab<br>• Placebo |
| **Outcomes** | **Key efficacy outcomes:**<br>• Relapse rate<br>• Disability (measured by a validated scale)<br>• HRQoL (measured by a validated scale)<br>• Fatigue<br><br>**Other efficacy outcomes:**<br>• Brain lesions on MRI (gadolinium-enhancing lesions, new or enlarging T2 lesions)<br>• Use of rescue medications<br>• Productivity (ability to attend work or school)<br>• Medication acceptance<br><br>**Harms outcomes:**<br>• Mortality<br>• Serious adverse events<br>• Adverse events<br>• Hospitalizations<br>• Withdrawals (including WDAE)<br>• Notable harms: hepatotoxicity, hypertension, infection, alopecia, peripheral neuropathy, teratogenicity |
| **Study Design** | Parallel group RCT |

EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; IM = intramuscular; MRI = magnetic resonance imaging; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946- ) with in-process records and daily updates via Ovid; Embase (1974- ) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Aubagio (teriflunomide) and multiple sclerosis.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on January 21, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 21, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

# 3. RESULTS

## 3.1 Findings from the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and are described in Section 3.2.

**FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**

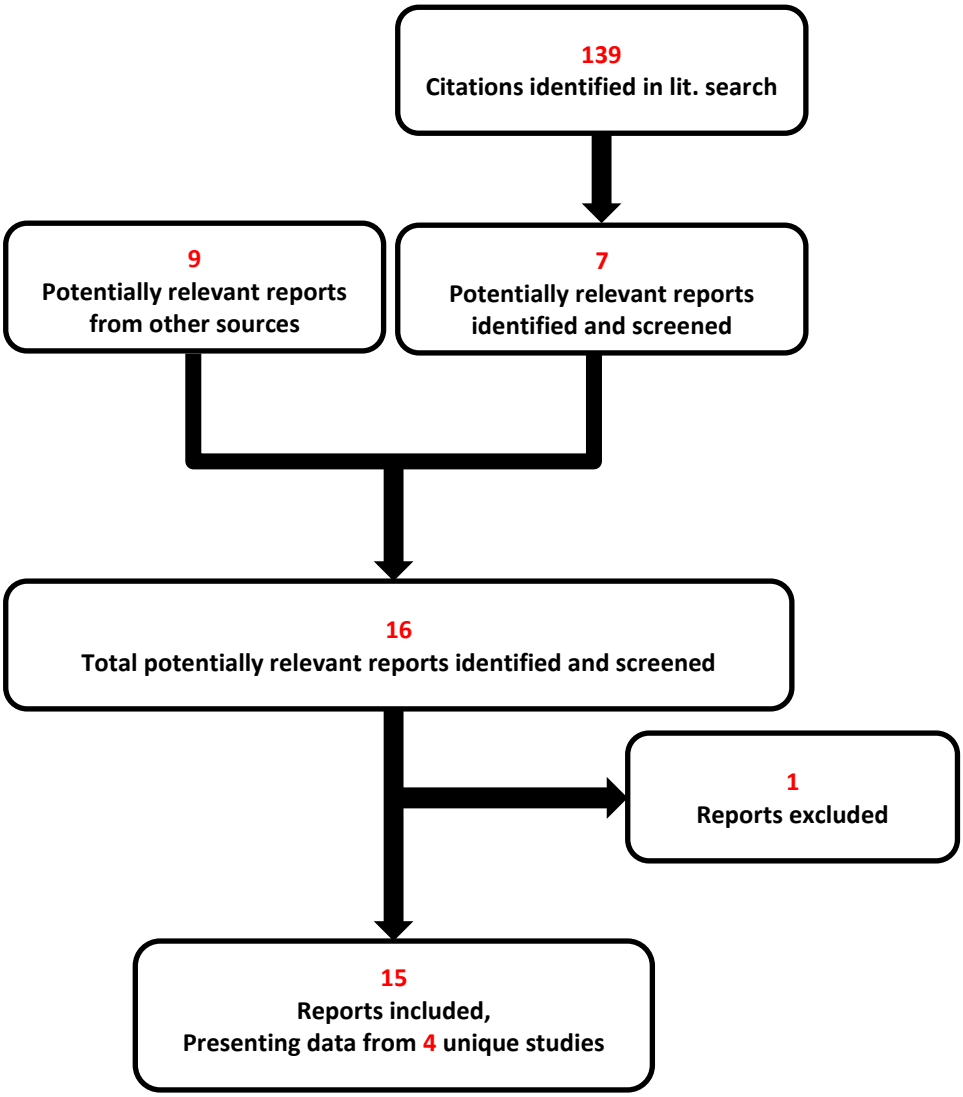

**TABLE 4: DETAILS OF INCLUDED STUDIES**

| | | TENERE (EFC10891) | TOWER (EFC10531) | TEMSO (EFC6049) | Study 2001 (HMR1726D) |
|---|---|---|---|---|---|
| DESIGNS AND POPULATIONS | **Study design** | Multi-centre RB RCT phase 3 | Multi-centre DB RCT phase 3 | Multi-centre DB RCT phase 3 | Multi-centre DB RCT phase 2 |
| | **Date first patient enrolled** | 16 April 2009 | 26 August 2008 | 24 September 2004 | 26 April 2001 |
| | **Date last patient enrolled** | 14 September 2011 | 17 April 2012 | 8 July 2010 | 17 March 2003 |
| | **Locations** | 53 centres: 13 countries (including Canada) | 189 centres: 26 countries (including Canada) | 126 centres: 21 countries (including Canada) | 16 centres; 2 countries (Canada and France) |
| | **Randomized (N)** | 324 | 1,169 | 1,088 | 179 |
| | **Inclusion criteria** | Patients > 18 years of age with relapsing MS, meeting 2005 McDonald criteria and EDSS ≤ 5.5; no recent or concomitant use of DMTs (never have used interferon beta-1a (Rebif) prior to randomization; no use of other interferons 3 months prior to randomization) | Patients 18 to 55 years of age with relapsing MS, meeting 2005 McDonald criteria and EDSS ≤ 5.5; at least 1 relapse in the year preceding the trial or at least 2 relapses over the 2 years preceding the trial; no recent or concomitant use of DMTs | | Patients 18 to 65 years of age with relapsing MS, meeting Poser Criteria and EDSS ≤ 6; at least 2 relapses in the 3 years preceding the trial with at least 1 relapse in the last year; no recent or concomitant use of DMTs |
| | **Exclusion criteria** | Patients with a relapse 30 days prior to randomization; anemia, leukopenia or thrombocytopenia; immunodeficiency or HIV; severe infection; history of TB, hepatitis, chronic pancreatic disease or pancreatitis; liver function impairment | Patients with a relapse 30 days prior to randomization; anemia, leukopenia or thrombocytopenia; immunodeficiency or HIV; severe infection; history of TB, hepatitis, chronic pancreatic disease or pancreatitis; liver function impairment | Patients with a relapse 60 days prior to randomization; anemia, leukopenia or thrombocytopenia; immunodeficiency or HIV; severe infection; history of TB, hepatitis, chronic pancreatic disease or pancreatitis; liver function impairment | Patients with anemia, leukopenia or thrombocytopenia; immunodeficiency or HIV; liver function impairment |

| | | TENERE (EFC10891) | TOWER (EFC10531) | TEMSO (EFC6049) | Study 2001 (HMR1726D) |
|---|---|---|---|---|---|
| DRUGS | **Intervention** | Teriflunomide 7 mg daily<br>Teriflunomide 14 mg daily<br>(Patients were blind to dose assignment) | Teriflunomide 7 mg daily<br>Teriflunomide 14 mg daily | | |
| | **Comparator** | Open-label interferon beta-1a 44 mcg SC 3 times per week; dose decreased to 22 mcg if AEs | Placebo | | |
| DURATION | **Phase:** | | | | |
| | Screening | Up to 4 weeks | Up to 4 weeks | Up to 4 weeks | 4 weeks |
| | Treatment | Minimum 48 weeks; maximum 118 weeks | Minimum 48 weeks; maximum 160 weeks | 108 weeks | 36 weeks |
| | Washout | 11 days | 11 days | 11 days | NR |
| OUTCOMES | **Primary end point** | Time to failure | ARR | ARR | Active lesions per MRI scan |
| | **Other end points** | • ARR<br>• TSQM<br>• FIS | • Time to relapse<br>• Time to disability progression<br>• Proportion of patients free of relapse<br>• Proportion of patients free of disability<br>Progression at 6 months, 1 year, and 2 years<br>• Change from baseline in EDSS<br>• FIS<br>• SF-36 | • Time to relapse<br>• Time to disability progression<br>• Proportion of patients free of relapse<br>• Proportion of patients free of disability<br>• Progression at 6 months, 1 year, and 2 years<br>• EDSS<br>• MRI outcomes<br>• FIS<br>• MSFC<br>• SF-36<br>• EQ-5D | • ARR<br>• Time to disability progression<br>• Time to relapse<br>• Other MRI outcomes<br>• Proportion of patients having progressed<br>• Proportion of patients with a relapse<br>• EDSS<br>• FIS<br>• MSFC<br>• MSQOL-54 |
| NOTES[a] | **Publications** | Vermersch et al.[22] | Confraveux et al.[23] | O'Connor et al.[24]<br>O'Connor et al.[25]<br>Miller et al.[26]<br>Wolinsky et al.[27] | O'Connor et al.[28] |

AE = adverse event; ARR = annualized relapse rate; DB = double-blind; DMTs = disease-modifying treatments; EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Scale; FIS = Fatigue Impact Scale; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54; NR = not reported; RB = rater-blinded; RCT = randomized controlled trial; SF-36 = Short Form-36; TB = tuberculosis; TSQM = Treatment Satisfaction Questionnaire for Medication.

[a]Eight additional reports were included: Clinical Study Reports,[2-5] Common Drug Review submission,[29] FDA Medical and Statistical Reports,[30,31] and Health Canada Reviewer's Report[32].

## 3.2 Included Studies

### 3.2.1 Description of Studies

Four randomized, multi-centre, parallel group, superiority trials met the inclusion criteria for this systematic review. The trials included patients with relapsing MS. TENERE (N = 324) was an active control, rater-blinded trial. TEMSO (N = 1,088), TOWER (N = 1,169), and Study 2001 (N = 179) were double-blind, placebo-controlled trials. Study 2001 was a phase 2 trial; TENERE, TOWER, and TEMSO were phase 3 trials. In TENERE, patients were randomized (1:1:1) to either one of two teriflunomide doses (7 mg or 14 mg) or to interferon beta-1a. In TOWER, TEMSO, and Study 2001, patients were randomized (1:1:1) to either one of two teriflunomide doses (7 mg or 14 mg) or placebo.

All four trials had a screening period of four weeks. In TENERE, patients were treated for a minimum of 48 weeks (provided a patient had not prematurely discontinued the trial) to a maximum of 118 weeks depending on time of enrolment. Similarly in TOWER, the treatment period was a minimum of 48 weeks (for the last patient enrolled) to a maximum of 160 weeks. In TEMSO and in Study 2001, patients were treated for 108 weeks and 36 weeks, respectively; at the end of trial, an offer was made to both placebo and teriflunomide patients to start or continue teriflunomide treatment in extension trials. For teriflunomide patients not entering a long-term extension trial, the treatment period was followed by a washout period.

### 3.2.2 Populations

#### a) Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they had MS with a relapsing course, were older than 18 years, and met the McDonald 2005 criteria (TENERE, TOWER, and TEMSO) or Poser criteria (Study 2001) for MS.

**Inclusion Criteria**

Inclusion criteria varied across trials in terms of history of relapse and EDSS scores, as outlined below:

- In TENERE, there were no specific criteria regarding the frequency of prior relapses; however, patients had to be relapse free for 30 days prior to randomization, with an EDSS ≤ 5.5 at screening.
- In TOWER and TEMSO, patients were included if they had experienced at least one relapse in the year preceding the trial or two relapses over the two years preceding the trial, and no relapse within 60 days (TEMSO) or 30 days (TOWER) prior to randomization. Patients were required to be clinically stable during the screening period and ambulatory (EDSS ≤ 5.5).
- In Study 2001, patients were included if they had experienced at least two relapses in the three years prior to screening and at least one relapse in the last year, and an EDSS ≤ 6.0.

**Exclusion Criteria (Related to Medication Use)**

Patients with prior or ongoing use of certain medications were excluded from entering the trial. The types and timing of medication varied across trials:

- TENERE
  - Prior use of subcutaneous interferon beta-1a
  - Prior or ongoing use of natalizumab, cladribine, mitoxantrone, or other immunosuppressants
  - Use of other interferons, glatiramer acetate, intravenous immunoglobulins, or cytokine therapy three months prior to randomization.
- TEMSO
  - Prior or ongoing use of cladribine, mitoxantrone, or other immunosuppressants
  - Use of other interferons, glatiramer acetate, or cytokine therapy four months prior to randomization.

- TOWER
  - Prior or ongoing use of natalizumab, cladribine, mitoxantrone, or other immunosuppressants
  - Prior or ongoing use of glatiramer acetate, intravenous immunoglobulins, or cytokine therapy three months prior to randomization.
- Study 2001
  - Prior treatment with interferon, gamma-globulin, glatiramer acetate, or other non-corticosteroid immunomodulatory therapies four months prior to randomization.

Due to concerns of teratogenicity with teriflunomide, women of child-bearing age and men were required to use contraception during the trial. Women were required to take pregnancy tests at regular intervals.

**b) Baseline Characteristics**

Across all trials, 64% to 79% of patients were women (Table 5). Mean age ranged from 35 years to 40 years. Most patients had RRMS and were Caucasian. In Study 2001, approximately 12% to 13% of patients had SPMS, compared with 0.8% in TOWER and 4.7% in TEMSO. Baseline EDSS median score ranged from 1.5 to 2.5. The majority of patients (> 75%) had EDSS ≤ 3.5. Based on the ranges of EDSS scores, all studies included some patients with an EDSS score of 0 at baseline. Mean number of relapses in the past year ranged from 1.2 to 1.5.

TENERE appears to have enrolled patients earlier in the disease process, as evidenced by lower median time since first MS symptoms, and lower mean EDSS. In addition, TENERE included patients with no history of relapse in the past two years.

Several differences were noted within trials:

- In TENERE, the interferon beta-1a group had a greater mean time since first MS symptoms (7.7 years) and a greater mean time since the most recent relapse (9.8 months) compared with the teriflunomide 14 mg group (6.6 years and 7.9 months, respectively). A total of 12% of patients in the teriflunomide 14 mg group had used a DMT within two years of screening, compared with the interferon beta-1a group (24%).
- In TOWER, mean time since first MS symptoms was 7.6 years for the placebo group, compared with 8.2 years for the teriflunomide 14 mg groups. Mean time since MS diagnosis was 4.9 years for the placebo groups, compared with 5.3 years for the teriflunomide 14 mg groups.
- In TEMSO, mean time since MS diagnosis was 5.1 years for the placebo groups, compared with 5.6 years for the teriflunomide 14 mg groups.
- In Study 2001, mean time since MS diagnosis was 4.4 years for the placebo groups, compared with 5.3 years for the teriflunomide 14 mg groups.

**TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS**

| | TENERE | | | TOWER | | | TEMSO | | | Study 2001 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **TR 7 mg** | **TR 14 mg** | **INF 44 mcg** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** |
| **N** | 109 | 111 | 104 | 408 | 372 | 389 | 366 | 359 | 363 | 61 | 57 | 61 |
| **Mean age, years (SD)** | 35.2 (9.2) | 36.8 (10.3) | 37.0 (10.6) | 37.4 (9.4) | 38.2 (9.4) | 38.1 (9.1) | 37.4 (9.0) | 37.8 (8.2) | 38.4 (9.0) | 40.1 (9.3) | 40.1 (9.1) | 39.2 (8.7) |
| **Female, n (%)** | 70 (64.2) | 78 (70.3) | 71 (68.3) | 300 (73.5) | 258 (69.4) | 273 (70.2) | 255 (69.7) | 255 (71.0) | 275 (75.8) | 46 (75.4) | 45 (78.9) | 41 (67.2) |
| **Race, n (%)** | | | | | | | | | | | | |
| **Caucasian** | 109 (100) | 111 (100) | 104 (100) | 329 (80.6) | 313 (84.1) | 318 (81.7) | 355 (97.3) | 347 (96.9) | 356 (98.3) | 56 (91.8) | 52 (91.2) | 59 (96.7) |
| **Black** | 0 | 0 | 0 | 8 (2.0) | 7 (1.9) | 7 (1.8) | 1 (0.3) | 1 (0.3) | 3 (0.8) | 1 (1.6) | 1 (1.8) | 0 |
| **Asian** | 0 | 0 | 0 | 60 (14.7) | 49 (13.2) | 60 (15.4) | 6 (1.6) | 8 (2.2) | 1 (0.3) | 2 (3.3) | 2 (3.5) | 0 |
| **Other** | 0 | 0 | 0 | 11 (2.7) | 3 (0.8) | 4 (1.0) | 3 (0.8) | 2 (0.6) | 2 (0.6) | 2 (3.3) | 2 (3.5) | 2 (3.3) |
| **RRMS, n (%)** | 109 (100) | 108 (97.3) | 104 (100) | 393 (96.3) | 366 (98.9) | 379 (97.4) | 333 (91.0) | 333 (92.8) | 329 (90.6) | 53 (88.3) | 49 (87.5) | 53 (86.9) |
| **SPMS, n (%)** | 0 | 1 (0.9) | 0 | 3 (0.7) | 2 (0.5) | 4 (1.0) | 17 (4.6) | 12 (3.3) | 22 (6.1) | 7 (11.7) | 7 (12.5) | 8 (13.1) |
| **PRMS, n (%)** | 0 | 2 (1.8) | 0 | 12 (2.9) | 2 (0.5) | 6 (1.5) | 16 (4.4) | 14 (3.9) | 12 (3.3) | 0 | 0 | 0 |
| **Mean time since diagnosis of MS, years (SD)** | 3.7 (5.2) | 3.7 (6.2) | 3.8 (5.7) | 5.3 (5.5) | 5.3 (5.9) | 4.9 (5.7) | 5.3 (5.4) | 5.6 (5.5) | 5.1 (5.6) | 6.0 (5.6) | 5.3 (6.2) | 4.4 (5.7) |
| **Mean time since first symptoms of MS, years (SD)** | 7.0 (6.9) | 6.6 (7.6) | 7.7 (7.6) | 8.2 (6.8) | 8.2 (6.7) | 7.6 (6.7) | 8.8 (6.8) | 8.7 (6.7) | 8.6 (7.1) | 10.4 (8.2) | 8.5 (7.2) | 8.6 (7.9) |
| **Median time since first symptoms of MS, years (min, max)** | 4.17 (0.1, 27.6) | 4.42 (0.3, 37.8) | 5.71 (0.3, 37.4) | 6.33 (0.1, 34.4) | 6.92 (0.2, 36.9) | 5.75 (0.2, 35.3) | 7.00 (0.3, 32.6) | 7.17 (0.4, 31.6) | 6.33 (0.3, 35.7) | 9.3 (0, 43) | 6.0 (1, 31) | 5.0 (1, 31) |

| | TENERE | | | TOWER | | | TEMSO | | | Study 2001 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mean time since most recent relapse, months (SD)** | 9.0 (14.0) | 7.9 (10.3) | 9.8 (10.7) | 5.2 (3.4) | 5.3 (3.3) | 5.3 (3.4) | 6.3 (3.3) | 6.5 (3.7) | 6.3 (3.6) | NR | NR | NR |
| **Median time since most recent relapse, months (min, max)** | 5.0 (1, 115) | 5.0 (1, 64) | 6.0 (1, 58) | 4.0 (1, 20) | 5.0 (1, 20) | 4.0 (1, 23) | 5.0 (1, 22) | 6.0 (2, 22) | 5.0 (0, 22) | NR | NR | NR |
| **Mean number of relapses in past year (SD)** | 1.3 (0.8) | 1.4 (0.8) | 1.2 (1.0) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.8) | 1.4 (0.7) | 1.3 (0.7) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.7) | 1.5 (0.7) |
| **Patients with relapses in past year, n (%)** | | | | | | | | | | | | |
| **0** | 13 (11.9) | 13 (11.7) | 22 (21.2) | 9 (2.2) | 5 (1.3) | 9 (2.3) | 9 (3.2) | 18 (6.6) | 10 (3.6) | NR | NR | NR |
| **1** | 60 (55.0) | 56 (50.5) | 47 (45.2) | 263 (64.5) | 240 (64.7) | 251 (64.7) | 174 (61.3) | 171 (62.9) | 163 (58.8) | NR | NR | NR |
| **2** | 29 (26.6) | 34 (30.6) | 28 (26.9) | 105 (25.7) | 99 (26.7) | 105 (27.1) | 88 (31.0) | 71 (26.1) | 86 (31.0) | NR | NR | NR |
| **≥ 3** | 7 (6.4) | 8 (7.2) | 7 (6.7) | 31 (7.6) | 27 (7.3) | 23 (5.9) | 13 (4.6) | 12 (4.4) | 18 (6.5) | NR | NR | NR |
| **Mean number of relapses in past 2 years (SD)** | 1.7 (0.9) | 1.7 (0.9) | 1.7 (1.1) | 2.1 (1.1) | 2.1 (1.2) | 2.1 (1.1) | 2.3 (1.2) | 2.2 (1.0) | 2.2 (1.0) | NR | NR | NR |
| **Patients with relapses in past 2 years, n (%)** | | | | | | | | | | | | |
| **0** | 7 (6.4) | 7 (6.3) | 11 (10.6) | 0 | NR | 0 | 0 | 0 | 0 | NR | NR | NR |
| **1** | 42 (38.5) | 41 (36.9) | 39 (37.5) | 137 (33.6) | 121 (32.7) | 129 (33.2) | 74 (20.2) | 71 (19.8) | 71 (19.6) | NR | NR | NR |
| **2** | 39 (35.8) | 41 (36.9) | 30 (28.8) | 148 (36.3) | 155 (41.9) | 162 (41.6) | 188 (51.4) | 192 (53.5) | 186 (51.2) | NR | NR | NR |

| | TENERE | | | TOWER | | | TEMSO | | | Study 2001 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **≥ 3** | 21 (19.3) | 22 (19.8) | 24 (23.1) | 123 (30.1) | 94 (25.4) | 98 (25.2) | 104 (28.4) | 96 (26.7) | 106 (29.2) | NR | NR | NR |
| **Mean number of relapses in past 3 years (SD)** | NR | NR | NR | NR | NR | NR | NR | NR | NR | 2.7 (0.9) | 2.8 (1.0) | 2.9 (1.2) |
| **Baseline EDSS score** | | | | | | | | | | | | |
| **Mean (SD)** | 2.0 (1.2) | 2.3 (1.4) | 2.0 (1.2) | 2.7 (1.4) | 2.7 (1.4) | 2.7 (1.4) | 2.7 (1.3) | 2.7 (1.2) | 2.7 (1.3) | NR | NR | NR |
| **Median (min, max)** | 1.5 (0, 5.5) | 2.0 (0, 5.5) | 2.0 (0, 5.5) | 2.5 (0, 5.5) | 2.5 (0, 6.5) | 2.5 (0, 5.5) | 2.5 (0, 6.0) | 2.5 (0, 5.5) | 2.5 (0, 6.0) | 2.5 (0, 6.0) | 2.0 (0, 6.5) | 2.5 (0, 6.0) |
| **DMT use in last 2 years, n (%)** | 23 (21.1) | 13 (11.7) | 25 (24.0) | 123 (30.1) | 126 (33.9) | 135 (34.7) | 102 (27.9) | 102 (28.4) | 90 (24.8) | NR | NR | NR |

DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; INF = interferon beta-1a; max = maximum; min = minimum; MS = multiple sclerosis; NR = not reported; PL = placebo; PRMS = progressive relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis; TR = teriflunomide.
Source: Clinical Study Reports.[2-5]

DMTs taken before randomization are outlined in Table 6. For TENERE, TOWER, and TEMSO, DMTs taken within two years prior to randomization were reported. For Study 2001, the table outlines medications taken by at least 10% of patients, which included corticosteroids and unknown or investigational drugs. Within each trial, the distribution of previous DMTs was balanced across treatment groups.

### 3.2.3 Interventions

In TENERE, patients were randomized 1:1:1 to receive teriflunomide 7 mg orally once daily, teriflunomide 14 mg orally once daily, or subcutaneous interferon beta-1a (Rebif) titrated to 44 mcg three times per week (8.8 mcg three times per week for the first two weeks, followed by 22 mcg three times per week for the next two weeks, and then 44 mcg three times per week thereafter). The interferon dose could be reduced to 22 mcg three times per week in case of intolerance. The trial was double-blind within the oral dose groups and teriflunomide was administered as identical white tablets. The trial was open label between the oral dosing and the injection arms.

TOWER, TEMSO, and Study 2001 were double-blind trials. Treatments were administered as identical white tablets of 7 mg teriflunomide, 14 mg teriflunomide, or matching placebo. Patients were randomized 1:1:1 to receive teriflunomide 7 mg orally once daily, teriflunomide 14 mg orally once daily, or placebo. In Study 2001, patients were required to take a loading dose of two tablets for the first seven days of treatment (i.e., the teriflunomide 14 mg group took two 14 mg tablets [28 mg] daily for the first seven days of treatment; the teriflunomide 7 mg group took two 7 mg tablets [14 mg] daily for the first seven days of treatment; and the placebo group took two placebo tablets for the first seven days of treatment).

For patients not entering a long-term extension trial, the treatment period was followed by an 11-day washout period with administration of cholestyramine or activated charcoal to accelerate the elimination of teriflunomide to levels < 0.02 µg/mL.

In all trials, randomization was stratified by centre and baseline disability (EDSS ≤ 3.5 or EDSS > 3.5).

### 3.2.4 Outcomes

Various outcomes were measured in the trials (Table 7).

**TABLE 6: DISEASE-MODIFYING TREATMENT USE PRIOR TO RANDOMIZATION**

| | TENERE[a] | | | TOWER[a] | | | TEMSO[a] | | | Study 2001[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **TR 7 mg** | **TR 14 mg** | **INF 44 mcg** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** |
| **N (%)** | 23 (21.1) | 13 (11.7) | 25 (24.0) | 123 (30.1) | 126 (33.9) | 135 (34.7) | 102 (27.9) | 102 (28.4) | 90 (24.8) | 51 (83.6) | 41 (71.9) | 50 (82.0) |
| Fingolimod | 0 | 0 | 0 | 2 (0.5) | 3 (0.8) | 1 (0.3) | NR | NR | NR | NR | NR | NR |
| Glatiramer acetate | 10 (9.2) | 7 (6.3) | 12 (11.5) | 47 (11.5) | 37 (9.9) | 52 (13.4) | 23 (6.3) | 43 (12.0) | 36 (9.9) | 6 (9.8) | 7 (12.3) | 5 (8.2) |
| Interferon beta | NA | NA | NA | 1 (0.2) | 1 (0.3) | 2 (0.5) | NR | NR | NR | 9 (14.8) | 7 (12.3) | 8 (13.1) |
| Interferon beta-1a IM | 6 (5.5) | 2 (1.8) | 5 (4.8) | 41 (10.0) | 28 (7.5) | 26 (6.7) | 24 (6.6) | 29 (8.1) | 23 (6.3) | NR | NR | NR |
| Interferon beta-1a SC | 0 | 0 | 0 | 30 (7.4) | 36 (9.7) | 34 (8.7) | 52 (14.2) | 37 (10.3) | 39 (10.7) | NR | NR | NR |
| Interferon beta-1a unspecified | 0 | 1 (0.9) | 1 (1.0) | 0 | 2 (0.5) | 3 (0.8) | 3 (0.8) | 3 (0.8) | 1 (0.3) | NR | NR | NR |
| Interferon beta-1b | 9 (8.3) | 5 (4.5) | 10 (9.6) | 27 (6.6) | 35 (9.4) | 38 (9.8) | 22 (6.0) | 27 (7.5) | 18 (5.0) | NR | NR | NR |
| Mitoxantrone | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NR | NR | NR |
| Natalizumab | 0 | 0 | 0 | 0 | 0 | 1 (0.3) | 0 | 0 | 0 | NR | NR | NR |

DMT = disease-modifying treatment; IM = intramuscular; INF = interferon beta-1a; NA = not applicable; NR = not reported; PL = placebo; SC = subcutaneous; TR = teriflunomide.
Source: Clinical Study Reports.[2-5]
[a]For TENERE, TOWER and TEMSO, DMT use is within 2 years prior to randomization.
[b]For Study 2001, medications taken by at least 10% of patients; includes corticosteroids and unknown or investigational drugs (not shown).

**TABLE 7: OUTCOMES MEASURED IN TRIALS**

| Outcome | TENERE | TOWER | TEMSO | STUDY 2001 |
|---|---|---|---|---|
| **Relapses** | | | | |
| ARR | √ | √ (Primary) | √ (Primary) | √ |
| Proportion of patients free of relapses | | √ | √ | |
| Time to relapse | | √ | √ | √ |
| **Disability progression** | | | | |
| Time to disability progression: | | | | |
| • No confirmation over time | | | | √ |
| • Confirmed for at least 12 weeks | | √ | √ | |
| • Confirmed for at least 24 weeks | | √ | √ | |
| Proportion of patients free of progression | | √ | √ | |
| **MRI outcomes** | | | | |
| Change from baseline in burden of disease | | | √ | √ |
| Number of unique active lesions per scan | | | √ | √ (Primary) |
| Number and volume of Gd-enhancing T1 lesions/scan | | | √ | √ |
| Volume of hypointense T1 lesions/scan | | | √ | |
| Volume of T2 lesions/scan | | | √ | |
| Change in baseline in atrophy and volume of white and grey matter | | | √ | √ (Atrophy only) |
| **Other** | | | | |
| Time to failure | √ (Primary) | | | |
| Change from baseline in: | | | | |
| • FIS | √ | √ | √ | √ |
| • MSFC | | | √ | √ |
| • SF-36 | | √ | √ | |
| • EQ-5D | | | √ | |
| • MSQOL-54 | | | | √ |
| • TSQM | √ | | | |

ARR = annualized relapse rate; EQ-5D = European Quality of Life Scale; FIS = Fatigue Impact Scale; Gd = gadolinium; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54; SF-36 = Short Form-36; TSQM = Treatment Satisfaction Questionnaire for Medication.
Source: Common Drug Review binder.[29]

The primary efficacy end point in TENERE was time to failure. In TOWER and TEMSO, the primary efficacy end point was annualized relapse rate (ARR). In Study 2001, the primary efficacy end point was the number of unique active lesions per magnetic resonance imaging (MRI) scan (includes combined T1 and T2 lesions).

Only the outcomes of interest identified in the protocol are described below. Also refer to APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

**a) Relapses**

**Relapse**

- The appearance of a new clinical sign or symptom or clinical worsening of a previous sign or symptom (stable for at least 30 days) that persisted for a minimum of 24 hours in the absence of fever. An independent evaluator had to document a 1-point increase in at least two functional symptom scores (FS) or a 2-point increase in at least one FS score (excluding bowel or bladder and cerebral) from the previous clinically stable assessment; or an increase of at least 0.5 points in EDSS score (unless EDSS = 0, then an increase of at least 1.0 point was required) from the previous clinically stable assessment (TENERE, TOWER, TEMSO).
- The appearance of a new symptom, reappearance or worsening of an old symptom attributable to MS. The change had to persist for at least 48 hours in the absence of fever and be preceded by stability or improvement for at least 30 days (Study 2001).

**Annualized relapse rate**

- The number of confirmed relapses that occurred during the study treatment period per patient-year of treatment (TENERE, TOWER, TEMSO).
- The number of relapses per patient-year (Study 2001).

**Time to failure**

- Time to first occurrence of relapse (see definition of relapse above) or permanent study treatment discontinuation for any cause, whichever occurred first (TENERE).

**b) Disability**

**Disability (disease) progression**

- *Sustained disease (disability) progression*: at least a 1-point increase on EDSS from baseline if baseline EDSS ≤ 5.5, or at least a 0.5-point increase from the baseline on EDSS if the baseline EDSS > 5.5 and was persistent for at least 12 weeks (TEMSO).
- *First sustained disease (disability) progression*: a persisting increase for at least 12 weeks of at least 1.0 point EDSS score from baseline visit (or at least 0.5 EDSS score for any patient whose baseline EDSS assessment was greater than 5.5) (TOWER).
- *Subsequent sustained disease (disability) progression*: persisting increases for at least 12 weeks of at least 1.0 EDSS score from the score of the last visit, requiring a new informed consent for sustained disease progression (at least 0.5 EDSS score for patients with EDSS assessment > 5 at the last visit) (TOWER).
- *EDSS progression*: at least a 1-point increase on EDSS from baseline if baseline EDSS ≤ 5.5, or at least a 0.5-point increase from the baseline on EDSS if the baseline EDSS > 5.5 with no confirmation of time (Study 2001).

**Time to disability progression**

- Time (days) from the date of randomization to the date of the first disability progression. Patients who had no disability progression on or before last during-treatment EDSS evaluation were censored at the date of the last during-treatment EDSS evaluation (TOWER, TEMSO; not defined in Study 2001).

**Expanded Disability Status Scale**

- Assessment of a patient's neurological functional impairment. It is based on the neurological testing of pyramidal (ability to walk), cerebellar (coordination), brain stem (including speech and swallowing), sensory (including touch and pain), bowel and bladder, visual, mental, and other functions attributed to MS.
- According to the clinical expert consulted for this review, a sustained change of 0.5 in EDSS is clinically relevant.

**Multiple Sclerosis Functional Composite**

- A three-part, standardized, quantitative MS assessment instrument that consists of measurements of three components: leg function and ambulation (timed 25-foot walk), arm and hand function (9-hole peg test), and cognitive function (paced auditory serial addition test) (TEMSO, Study 2001).
- A 20% change in scores on timed 25-foot walk and 9-hole peg test, and a 0.5 standard deviation (SD) change on paced auditory serial addition test are considered clinically meaningful; a clinically meaningful value for overall Multiple Sclerosis Functional Composite (MSFC) score has not been determined.

**Health-related Quality of Life**

**Short Form-36**

- The 36-item short form generic health survey measuring HRQoL. Two summary scores (physical health and mental health components), eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and reported health transition were measured (TOWER, TEMSO).
- No minimally clinically important differences (MCIDs) were found specific to MS.

**European Quality of Life Scale**

- A standardized, generic HRQoL questionnaire that consists of the European Quality of Life Scale (EQ-5D) descriptive system (comprises five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and the visual analogue scale, which rates a patient's perceived health on a vertical visual analogue scale (TEMSO).
- The MCID for EQ-5D ranges from 0.033 to 0.074 and it is uncertain as to whether this range is applicable to MS specifically.

**Multiple Sclerosis Quality of Life-54**

- A disease-specific, self-administered instrument that allows comparison of quality of life in MS with that in other diseases and in the general population and an assessment of health domains relevant to people with MS (54 questions relating to general health, physical health, emotional problems, bodily pain, health distress, cognitive function, sexual function, and general quality of life). There is no single overall score for Multiple Sclerosis Quality of Life-54 (MSQOL-54). Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (Study 2001). Scale scores range from 0 to 100 and a higher scale score indicates improved quality of life.

- No MCIDs for the summary scores were identified.

**Fatigue**

**Fatigue Impact Scale**

- A validated measure that evaluates the impact of fatigue on the lives of MS patients. It consists of a total score and three subscales: cognitive function (10 items), physical function (10 items), and psychosocial function (20 items). Each Fatigue Impact Scale (FIS) is ranked on a scale of 0 (no problem) to 4 (extreme problem). FIS total score ranges from 0 to 160 with a higher score indicating more severe fatigue levels. (TENERE, TOWER, Study 2001).
- The MCID of FIS total score ranges from 10 to 20 points.

**Magnetic Resonance Imaging Variables**

**Gadolinium-enhancing T1 lesion:**

- The total number of gadolinium (Gd)-enhancing T1-lesions that occurred during the study divided by the total number of scans during the study (Study 2001, TEMSO).

**New lesion**

- A count of all lesions that appeared on the current T2 scan but were not visible on any previous T2 scans (Study 2001).

**New enlarging T2 lesion**

- A count of all lesions that appeared enlarged on the current T2 scan but were stable on the previous T2 scan (Study 2001).

**Other**

**Treatment Satisfaction Questionnaire for Medication**

- A validated instrument that measures a patient's satisfaction with medication. It is composed of 14 questions on effectiveness (three items), side effects (five items), convenience (five items), and global satisfaction (one item). Score ranges from 1 to 100; a higher score represents greater satisfaction with the medication (TENERE).
- No MCID for Treatment Satisfaction Questionnaire for Medication (TSQM) was identified for MS patients.

Safety outcomes included adverse events, serious adverse events, withdrawal due to adverse events, vital signs, and laboratory data.

**Harms**

**Adverse event**

- Any untoward medical occurrence in a patient treated with a pharmaceutical product and the event did not necessarily have a causal relationship with the treatment (TENERE, TOWER).
- Any unfavourable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study — the adverse event may be a new illness, worsening of a concomitant illness, an effect of the study medication (including the comparator), or a combination of two or more of these factors (Study 2001; not defined in TEMSO).

**Serious adverse event**

- An event that at any dose resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or

incapacity, was a congenital anomaly or birth defect, or was a medically important event (TENERE, TOWER, TEMSO, and Study 2001).

### 3.2.5 Statistical Analysis

### a) Efficacy Criteria

**Sample Size for Included Trials**

- TENERE
  - Based on 100 randomized patients per treatment groups, the study had an 81% power to detect a difference between teriflunomide and interferon beta-1a on time to failure at a two-tailed significance level of alpha = 0.025 (to account for multiplicity). Hazard rates of 0.42 for teriflunomide and 0.74 for interferon beta-1a were assumed (based on 30% of patients relapsing at one year with teriflunomide and 46% with interferon beta-1a, with treatment discontinuation rate of 6% and 12% for teriflunomide and interferon beta-1a, respectively — ratios extrapolated with respect to the treatment duration and conditions of study).
- TOWER
  - Based on 370 randomized patients per treatment groups, the study had 94% power to detect a 25% relative reduction in ARR at a two-tailed significance level of alpha = 0.05 assuming an ARR of 0.74 in the placebo group and a dropout rate of 20% (considering a 1.5-year recruitment period and an average exposure of 1.75 years). Further, the study had 75% power to detect a 37% hazard ratio reduction in time to disability progression, assuming hazard rates of 0.11 for teriflunomide and 0.18 for placebo.
  - To address multiplicity, a step-down testing procedure was used and hypothesis rejected at the 5% level, in the following order: no treatment difference between teriflunomide 14 mg and placebo in ARR; no treatment difference between teriflunomide 7 mg and placebo in ARR; no treatment difference between teriflunomide 14 mg and placebo in disability progression; no treatment difference between teriflunomide 7 mg and placebo in disability progression. No other information was provided on how the statistical significance was determined for other outcomes.
- TEMSO
  - Based on 360 randomized patients per treatment groups, the study had 95% power to detect a 25% relative reduction in ARR at a two-tailed significance level of alpha = 0.05 assuming an ARR of 0.74 in the placebo group and a dropout rate of 20% (over two years). Further, the study had 80% power to detect a 37% hazard ratio reduction in time to disability progression, assuming hazard rates of 0.11 for teriflunomide and 0.18 for placebo.
  - Multiplicity was addressed in the same manner as described for the TOWER study (see above). For change from baseline in total score of FIS at week 108 and for total number of Gd-enhancing T1 lesions per MRI scan over the treatment period, if all hypothesis tests for ARR and disability progression were significant at a 5% level, a step-down testing procedure was applied within each dose at a 2.5% significance level. No other information was provided on how the statistical significance was determined for other outcomes.
- Study 2001
  - Based on 54 evaluable patients per treatment groups, the study had 90% power to detect an effect size of 0.32 at a two-tailed significance level of alpha = 0.05. Estimating a dropout rate of 10%, 60 patients were required to be randomized to each treatment groups.

**Statistical Tests for TENERE, TOWER, and TEMSO**

- Time to failure
  - Time to failure was analyzed using a log-rank test, with treatment group as the test variable, and region and baseline EDSS as stratum variables. An interaction test was conducted using time to failure as a response variable, and treatment group, baseline EDSS strata, and region as covariates. Kaplan–Meier method was used to estimate the rate of treatment failure at specified time intervals (weeks 24, 48, and 96).
- Relapses
  - Poisson regression model with robust error variance was used for the ARR analysis. The model used total confirmed relapses prior to discontinuation as the response variable, and treatment group, EDSS strata, and region as covariates. Log-transformed standardized treatment duration was included as an offset variable to account for differences in exposure.
- Disability
  - Log-rank test was used to analyze time to disability progression, with time to disability progression as the dependent variable, the treatment group as test variable, and region and baseline EDSS score as stratification factors. The hazard ratio estimates were determined using a Cox regression model with treatment group, region, and baseline EDSS as covariates. Kaplan–Meier estimates were used to determine the time to disability progression rate.
- Patient-reported outcomes
  - A mixed effect model with repeated measures (MMRM) was used to analyze changes in FIS, EDSS, SF-36 scores, MSFC, and TSQM scores.
- Magnetic resonance imaging variable (gadolinium-enhancing T1 lesions per scan)
  - Poisson regression model with robust error variance was use for the total number of Gd-enhancing T1 lesions. The model included the total number of Gd-enhancing T1 lesions as response variable, and treatment group, EDSS strata, region, and baseline number of Gd-enhancing T1 lesions as covariates. Log-transformed number of scans was included as an offset variable to account for the different number of scans performed among patients.
- Other
  - For categorical outcomes, patients with missing data were not included in calculations of percentages, unless otherwise specified.

**Statistical Tests for Study 2001**

The number of T2 lesions per treatment period and change from baseline assessments (e.g., EDSS and MSFC) were assessed using Analysis of Covariance (ANCOVA), with treatment, stratum, and centre as fixed-effects and baseline score as the covariate. Progression and relapse rates were tested with the Cochran-Mantel–Haenszel procedure, controlling for centre. Descriptive statistics were provided for annual relapse rates. Adjustments were made for multiple comparisons between treatment groups using Dunnett's test.

In Study 2001, missing date of the last intake of study medication and patients prematurely withdrawn were assumed to be identical to date of withdrawal.

**a) Analysis Populations**

**TENERE**

- *Intention-to-treat*: all randomized patients; patients analyzed in the treatment group to which they were randomized.
- *Safety*: all randomized patients exposed to the study medication regardless of the amount of medication administered.

**TOWER and TEMSO**

- *Intention-to-treat*: all randomized patients who had at least one dose of study treatment; patients analyzed in the treatment group to which they were randomized.
- *Per-protocol*: patients without a major efficacy-related protocol deviation.
- *Safety*: all randomized patients who had at least one dose or partial dose of study treatment; if a patient received a treatment different from that assigned by the randomization, the safety analyses were performed according to the treatment actually received.

**Study 2001**

- *Efficacy-evaluable*: all randomized patients for whom there was at least one on-treatment MRI assessment; patients analyzed in the treatment group to which they were randomized
- *Per-protocol*: all efficacy-evaluable patients, excluding patients with major protocol deviations
- *Safety*: all randomized patients who had at least one dose or partial dose of study treatment; if a patient received a treatment different from that assigned by the randomization, the safety analyses were performed according to the treatment actually received.

## 3.3 Patient Disposition

The disposition of patients is presented in Table 8.

TEMSO had an expected dropout rate of 20% to account for its two-year study duration. TOWER also had an expected 20% dropout rate, whereas TENERE had an expected dropout rate of 6% and 12% for teriflunomide and interferon beta-1a, respectively. Across the three phase 3 studies, the withdrawal rates were much higher than anticipated. Discontinuations ranged from 18.3% to 33.9% in individual treatment groups. Overall, the primary reason for discontinuation was adverse events. Noticeable between-treatment differences were observed in TENERE, where 28.8% of interferon beta-1a patients discontinued the study compared with 19.8% of teriflunomide 14 mg patients; these differences were reflected in the higher proportion of interferon patients who discontinued the study due to adverse events. In TOWER, withdrawals due to adverse events in the teriflunomide groups were twice that in the placebo group.

Study 2001 had assumed a 10% dropout rate. Overall dropout rate was 10.6%; most (~80%) were due to adverse events. A noticeable between-treatment difference in total study discontinuation was observed between placebo (6.6%) and teriflunomide 14 mg (21.1%); this difference was reflected in the higher proportion of teriflunomide patients who discontinued the study due to adverse events.

**TABLE 8: PATIENT DISPOSITION**

| | TENERE | | | TOWER | | | TEMSO | | | Study 2001 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TR 7 mg | TR 14 mg | INF 44 mcg | TR 7 mg | TR 14 mg | PL | TR 7 mg | TR 14 mg | PL | TR 7 mg | TR 14 mg | PL |
| **Screened, N** | 369 | | | 1493 | | | 1338 | | | 207 | | |
| **Randomized, N** | 109 | 111 | 104 | 408 | 372 | 389 | 366 | 359 | 363 | 61 | 57 | 61 |
| **Treated** | 109 | 111 | 101 | 407 | 370 | 388 | 365 | 358 | 363 | 61 | 57 | 61 |
| **Discontinued study, N (%)** | 20 (18.3) | 22 (19.8) | 30 (28.8) | 134 (32.8) | 126 (33.9) | 125 (32.1) | 91 (24.9) | 95 (26.5) | 104 (28.7) | 3 (4.9) | 12 (21.1) | 4 (6.6) |
| **Reasons, n (%)** | | | | | | | | | | | | |
| Adverse event | 9 (8.3) | 12 (10.8) | 22 (21.2) | 54 (13.2) | 58 (15.6) | 26 (6.7) | 37 (10.1) | 38 (10.6) | 29 (8.0) | 3 (4.9) | 8 (14.0) | 4 (6.6) |
| Lack of efficacy | 7 (6.4) | 4 (3.6) | 2 (1.9) | 30 (7.4) | 20 (5.4) | 37 (9.5) | 14 (3.8) | 17 (4.7) | 24 (6.6) | 0 | 2 (3.5) | 0 |
| Protocol violation | 0 | 0 | 1 (1.0) | 3 (0.7) | 4 (1.1) | 15 (3.9) | 2 (0.5) | 5 (1.4) | 3 (0.8) | 0 | 0 | 0 |
| Lost to follow-up | 1 (0.9) | 1 (0.9) | 0 | 4 (1.0) | 3 (0.8) | 6 (1.5) | 0 | 2 (0.6) | 4 (1.1) | 0 | 0 | 0 |
| Death[a] | 0 | 0 | 0 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Progressive disease | 0 | 0 | 0 | NR | NR | NR | 4 (1.1) | 2 (0.6) | 11 (3.0) | 0 | 0 | 0 |
| Patient's choice | 0 | 0 | 0 | NR | NR | NR | 32 (8.7) | 26 (7.2) | 33 (9.1) | 0 | 2 (3.5) | 0 |
| Other[b] | 3 (2.8) | 5 (4.5) | 5 (4.8) | 43 (10.5) | 41 (11.0) | 41 (10.5) | 2 (0.5) | 5 (1.4) | 0 | 0 | 0 | 0 |
| **ITT, N** | 109 | 111 | 104 | 407 | 370 | 388 | 365 | 358 | 363 | 61 | 57 | 61 |
| **Efficacy-evaluable** | NA | NA | NA | NA | NA | NA | NA | NA | NA | 60 | 56 | 61 |
| **PP, N** | NR | NR | NR | 400 | 352 | 381 | 356 | 350 | 353 | 51 | 43 | 53 |
| **Safety, N** | 110 | 110 | 101 | 409 | 371 | 385 | 368 | 358 | 360 | 61 | 57 | 61 |

INF = interferon beta-1a; ITT = intention-to-treat; NA = not applicable; NR = not reported; PL = placebo; PP = per-protocol; TR = teriflunomide.
Source: Clinical Study Reports[2-5] and O'Connor et al.[28]
[a]In the TOWER study, four patients died but were not included in the Clinical Study Report's Patient Disposition table.
[b]In the TEMSO study, the "other" category is not defined; in the TOWER study, the "other" category included patient's choice (e.g., wanting to get pregnant); in the TENERE study, the "other" category included patient's choice (e.g., refusing interferon treatment; wanting to get pregnant) and progression of disease.

**a) Major Protocol Deviations**

The major protocol deviations in the included trials were as follows:

- TENERE
  - In the teriflunomide 14 mg group, three patients (2.7%) had major protocol deviations, whereas six patients (5.8%) in the interferon beta-1a group had major protocol deviations. There was no protocol deviation reported in the teriflunomide 7 mg group.
- TOWER
  - In the teriflunomide 7 mg group, nine patients (2.2%) had major protocol deviations; in the teriflunomide 14 mg group, 20 patients (5.4%) had major protocol deviations; and in the placebo group, eight patients (2.1%) had major protocol deviations.
- TEMSO
  - In the teriflunomide 7 mg group, 10 patients (2.7%) had major protocol deviations; in the teriflunomide 14 mg group, nine patients (2.5%) had major protocol deviations, whereas 10 patients (2.8%) in the placebo group had a protocol deviation.
- Study 2001
  - A total of nine patients (15.9%), 13 patients (23.2%), and eight patients (13.1%) had major protocol deviations in the teriflunomide 7 mg, teriflunomide 14 mg, and the placebo groups, respectively. Reasons for deviations were equally distributed across the three groups. The most common deviation was the wrong application of Gd or the use of other drugs for the treatment of relapses that interfered with the interpretation of the MRI scans. A few patients did not meet the inclusion criteria for prior relapses or EDSS at baseline.

## 3.4 Exposure to Study Treatments

The exposure to study treatments is presented in Table 9. The mean duration of study treatment ranged from 230 to 249 days (33 to 36 weeks) in Study 2001; 405 to 457 days (58 to 65 weeks) in TENERE; 552 to 571 days (79 to 82 weeks) in TOWER; and 627 to 635 days (90 to 91 weeks) in TEMSO. The longest treatment exposure occurred in TEMSO with > 614 patient-years.

In TENERE, 76.4% and 71.3% of teriflunomide 14 mg patients and interferon beta-1a patients had treatment durations > 48 weeks, respectively. These percentages decreased to 35.5% and 31.5% for treatment durations > 72 weeks, respectively (data not shown).

In TOWER, 77.1% and 81.0% of teriflunomide 14 mg patients and placebo patients had treatment durations > 48 weeks, respectively. These percentages decreased to 62.0% and 57.9% for treatment durations > 72 weeks, respectively (data not shown).

## 3.5 Critical Appraisal

### 3.5.1 Internal Validity

**a) Study Design**

- TENERE study included an open-label (rater-blinded) interferon beta-1a group, while the teriflunomide groups were double-blinded. Because the trial was not completely double-blinded, between-treatment comparisons may be subject to bias, especially in the case of patient-reported outcomes.
- Unblinding occurred in TOWER and TEMSO when 41 (3.5%) and 40 (3.6%) randomization codes, respectively, were broken during trial due to medical or accidental reasons, or for regulatory purposes.

**TABLE 9: EXPOSURE TO TREATMENT**

| | TENERE | | | TOWER | | | TEMSO | | | Study 2001 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **TR 7 mg** | **TR 14 mg** | **INF 44 mcg** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** | **TR 7 mg** | **TR 14 mg** | **PL** |
| **N** | 110 | 110 | 101 | 409 | 371 | 385 | 368 | 358 | 360 | 60 | 56 | 61 |
| **Cumulative duration of treatment exposure** | | | | | | | | | | | | |
| Patient-years | 137.5 | 130.8 | 112.0 | 617.8 | 576.2 | 601.6 | 639.6 | 614.2 | 622.1 | NR | NR | NR |
| **Duration of study treatment (days)** | | | | | | | | | | | | |
| Mean (SD) | 457 (153) | 434 (181) | 405 (191) | 552 (280) | 567 (298) | 571 (275) | 635 (236) | 627 (242) | 631 (228) | 249 (30) | 230 (55) | 248 (27) |
| Median (min, max) | 466 (53, 804) | 450 (27, 755) | 421 (19, 800) | 556 (1, 1184) | 588 (1, 1214) | 581 (1, 1183) | 756 (6, 784 | 756 (1, 801) | 756 (17, 786) | 252 (39, 267) | 251 (29, 266) | 252 (99, 269) |

INF = interferon beta-1a; max = maximum; min = minimum; NR = not reported; PL = placebo; SD = standard deviation; TR = teriflunomide.
Source: Clinical Study Reports.[2-5]

**b) Population**

- In TENERE, there were differences between the teriflunomide 14 mg and the interferon beta-1a groups in terms of patients without relapses in the past year and in the past two years and previous use of MS medication in the last two years — with absolute values being lower in the teriflunomide 14 mg group, which could potentially indicate that this group had a different level of disease activity at baseline.
- In TEMSO, 7% to 9% of patients' reason for study discontinuation was reported as "patient's choice." The majority of patients in this category cited lack of efficacy and others discontinued due to the presence of adverse events. These patients should have been classified under the "lack of efficacy" or "adverse events" as reasons for discontinuation.
- A high percentage of study withdrawal was seen in the TOWER study (~33%) and in TEMSO (~27%); however, study discontinuations were balanced across treatment groups. In TENERE, close to 30% of interferon patients discontinued the study compared with ~20% in the teriflunomides. In Study 2001, 6.6% and 4.9% of placebo and teriflunomide 7 mg patients, respectively, discontinued the study, compared with 21.1% of patients in the teriflunomide 14 mg group. In general, adverse events accounted for the majority of the withdrawals, which were higher with teriflunomide. If there was a between-treatment difference in timing of study withdrawal, this may have biased the estimates of effect.

**c) Interventions**

- The presence of adverse events in teriflunomide patients may have interfered with the ability to maintain blinding.

### 3.5.2 External Validity

Patients were representative of RRMS patients, with the majority being females and the mean age between 35 years and 40 years.

Several generalizability issues were noted:

- The patients were included based on the 2005 revised McDonald criteria or the Poser criteria, whereas the 2010 revised McDonald criteria are used today for MS diagnosis. However, the clinical expert consulted for this review indicated that this would not affect the generalizability of the results.
- Across all trials, more than 80% of patients were Caucasian, which is typical of MS. The results may not be generalizable to non-Caucasian patients.
- The exclusion criteria were extensive and, as such, the results of the trial may not be applicable to MS patients with comorbid illnesses.
- Information on the lifetime use of DMTs was not collected in TENERE, TOWER, or TEMSO.
- Patients in the included studies had various levels of disease severity, as demonstrated in baseline EDSS scores (ranges from 0 to 5.5 or 0 to 6.0, depending on the trial). However, the majority of patients studied had not experienced considerable progression of MS, given that the median EDSS baseline score ranged from 1.5 to 2.5 across all trials and > 75% of patients had an EDSS score ≤ 3.5. In addition, enrolled patients may have been experiencing lower disease activity compared with those receiving treatment in clinical practice, given that the majority of patients (> 70%) had not received DMTs within two years prior to randomization despite a MS diagnosis > 3.5 years. Furthermore, patients in TENERE had the lowest mean EDSS at baseline and, thus, trial results may be more generalizable to patients with less severe disease. However, the clinical expert consulted for this review could not confirm that patients had low disease activity based on the baseline characteristics.

## 3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see Section 2.2 Table 3). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data.

As the approved Health Canada dose is 14 mg orally once daily, only this dose was considered in the CDR review.

None of the included trials were conducted strictly in RRMS patients. TEMSO and TOWER provided subgroup analyses for the primary end point by MS subtypes; however, the studies were not powered to examine subgroups. Furthermore, the number of patients with primary or secondary progressive MS included in the trials was so low that the results cannot be interpreted; hence, data by MS subtype are not presented in the CDR review.

ARR was the primary end point in TOWER and TEMSO studies. Time to failure (due to relapses or drug discontinuation) was the primary end point in TENERE. The primary end point in Study 2001 (number of unique active lesions per scan, which combined both T1 and T2 lesions) was not an outcome of interest for this review.

### 3.6.1 Relapses

#### a) TENERE

There was no statistically significant difference in the adjusted ARR between the teriflunomide 14 mg group (0.26 [95% CI, 0.15 to 0.44]) and the interferon beta-1a group (0.22 [95% CI, 0.11 to 0.42]); rate ratio 1.2 (95% CI, 0.6 to 2.3). In addition, there was not statistically significant between-treatment difference in the time to failure (the primary outcome in TENERE, composed of relapse and study discontinuation due to any cause); hazard ratio (HR) 0.86 (95% CI, 0.56 to 1.31).

#### b) TOWER

The adjusted ARR was statistically significantly lower in the teriflunomide 14 mg group (0.32 [95% CI, 0.27 to 0.38]) compared with placebo (0.50 [95% CI, 0.43 to 0.58]); rate ratio 0.64 (95% CI, 0.51 to 0.79). The result of the per-protocol population analysis was comparable to the result of the intention-to-treat (ITT) population analysis (data not shown).

#### c) TEMSO

The adjusted ARR was statistically significantly lower in the teriflunomide 14 mg group (0.37 [95% CI, 0.31 to 0.44]) compared with placebo (0.54 [95% CI, 0.47 to 0.62]); rate ratio 0.69 [95% CI, 0.55 to 0.85]). The result of the per-protocol population analysis was comparable to the result of the ITT population analysis (data not shown).

#### d) Study 2001

The mean annual relapse rate was 0.55 (SD 1.12) for the teriflunomide 14 mg group, and 0.81 (SD 1.21) for the placebo group (statistical significance not provided).

### 3.6.2 Disability

#### a) TENERE

Measure of disability was not a pre-specified outcome of interest for TENERE; however, the mean change from baseline in EDSS at week 48 was –0.05 (SD 0.61) for teriflunomide 14 mg and –0.13 (SD 0.73) for interferon beta-1a.

**b) TOWER**

- The percentage of patients with disability progression persisting for 12 weeks at week 48 was 8.0% and 14.0% in the teriflunomide 14 mg and placebo groups, respectively. Time to disability progression sustained for 12 weeks was statistically significantly less for placebo compared with teriflunomide 14 mg (HR 0.69 [95% CI, 0.47 to 1.00]). The result of the per-protocol population analysis was comparable to the result of the ITT population analysis (data not shown).
- The percentage of patients with disability progression persisting for 24 weeks at week 48 was 9.0% and 7.0% in the teriflunomide 14 mg and placebo groups, respectively. Time to disability progression sustained for 24 weeks was not statistically significantly different between placebo and teriflunomide 14 mg (HR 0.84 [95% CI, 0.53 to 1.33]).
- According to pre-specified multiplicity adjustment to control for type I error, a step-down procedure was applied. Because the result of 12-week sustained disability progression for teriflunomide 7 mg was not statistically superior to placebo (data not shown), no statistical significance could be claimed for all other end points.
- The least square (LS) mean change from baseline in EDSS at week 48 was –0.05 (standard error [SE] 0.05) for teriflunomide 14 mg and 0.09 (SE 0.05) for placebo.

**c) TEMSO**

- The percentage of patients with disability progression persisting for 12 weeks at week 108 was 20.0% and 27.0% in the teriflunomide 14 mg and placebo groups, respectively. Time to disability progression sustained for 12 weeks was statistically significantly less for placebo compared with teriflunomide 14 mg (HR 0.70 [95% CI, 0.51 to 0.97]). The result of the per-protocol population analysis was comparable to the result of the ITT population analysis (data not shown).
- The percentage of patients with disability progression persisting for 24 weeks at week 108 was 14.0% and 19.0% in the teriflunomide 14 mg and placebo groups, respectively. Time to sustained disability progression was not statistically significantly different between placebo and teriflunomide 14 mg (HR was 0.75 [95% CI, 0.51 to 1.11).
- According to pre-specified multiplicity adjustment to control for type I error, a step-down procedure was applied. Because the result of 12-week sustained disability progression for teriflunomide 7 mg was not statistically superior to placebo (data not shown), no statistical significance could be claimed for all other end points.
- Change from baseline in EDSS score at 48 weeks was similar for teriflunomide 14 mg (LS mean 0.14, SE 0.05) and placebo (LS mean 0.15, SE 0.05).
- At week 24, LS mean change from baseline in the MSFC Z-score was –0.05 (SE 0.02) for teriflunomide 14 mg and –0.12 (SE 0.02) for placebo. At week 48, LS mean change from baseline in the MSFC Z was –0.05 (SE 0.05) for teriflunomide 14 mg and –0.20 (SE 0.05) for placebo.

**d) Study 2001**

- With teriflunomide 14 mg, 4 patients (7.4%) had EDSS progression compared with 13 placebo patients (21.3%) at study end ($P = 0.04$).
- No statistically significant differences in changes from baseline in EDSS scores were observed between teriflunomide 14 mg (adjusted mean –0.11, SE 0.10) and placebo (adjusted mean 0.01, SE 0.91), $P = 0.52$.
- No statistically significant differences in MSFC Z-score were observed between teriflunomide 14 mg and placebo ($P = 0.89$).

### 3.6.3 Health-related Quality of Life

#### a) TENERE

**TENERE** did not measure quality of life.

**TOWER**

There appeared to be no notable between-treatment differences in SF-36 scores (data not shown); *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

**TEMSO**

- There appeared to be no notable between-treatment differences in SF-36 physical health summary score or in mental health summary score (data not shown); *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.
- There appeared to be no notable between-treatment differences in EQ-5D including index utility scores and visual analogue scale scores (data not shown); *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

**Study 2001**

- The mean change from baseline in mental health component score (from MSQOL-54) was 1.99 (SE 2.40) with teriflunomide 14 mg and –3.32 (SE 2.42) with placebo (*P* = 0.13).
- The mean change from baseline in physical health component score (from MSQOL-54) was 0.96 (SE 1.96) with teriflunomide 14 mg and –3.16 (SE 1.95) with placebo (*P* = 0.15).

### 3.6.4 Fatigue

#### a) TENERE and Study 2001

In TENERE and in Study 2001, there were no statistically significant between-treatment differences in change from baseline in FIS scores.

#### b) TOWER and TEMSO

There appeared to be no notable between-treatment differences in change from baseline in FIS scores; *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

### 3.6.5 Magnetic Resonance Imaging Outcomes

#### a) TENERE and TOWER

TENERE and TOWER did not assess MRI outcomes.

#### b) TEMSO

Patients treated with teriflunomide 14 mg had fewer Gd-enhancing T1 lesions per scan compared with placebo patients (0.26 lesions per scan for teriflunomide 14 mg versus 1.33 lesions per scan for placebo). *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

#### c) Study 2001

- The number of new T2 lesions for the treatment period was 0.42 (SE 0.19) for teriflunomide 14 mg and 1.07 (SE 0.19) for placebo (*P* = 0.008).
- There was no statistically significant difference in new, enlarging T2 lesions (*P* = 0.09).

### 3.6.6 Use of Rescue Medications and Hospitalization due to Relapses

**a) TENERE**

TENERE did not assess the use of rescue medications or hospitalizations due to relapses.

**b) TOWER**

- A total of 15.1% and 20.9% of teriflunomide 14 mg and placebo patients, respectively, were hospitalized due to MS relapse.
- Adjusted annualized rate (AARs), for relapses requiring IV corticosteroids, were 0.27 and 0.43 for teriflunomide 14 mg and placebo, respectively. *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

**c) TEMSO**

- A total of 9.2% and 19.6% of teriflunomide 14 mg and placebo patients, respectively, were hospitalized due to MS relapse.
- AARs, for relapses requiring IV corticosteroids, were 0.28 and 0.43 for teriflunomide 14 mg and placebo, respectively. *P* values are not provided as they fell below a non-significant parameter in the hierarchical chain to address multiplicity.

**d) Study 2001**

A total of 14.3% and 23.0% of teriflunomide 14 mg and placebo patients, respectively, used intravenous corticosteroids during an MS relapse.

### 3.6.7 Productivity

Productivity was not measured in any of the included trials.

### 3.6.8 Medication Acceptance

Medication acceptance was measured in TENERE only. Considering side effects, convenience, and global satisfaction, TSQM scores were statistically significantly in favour of teriflunomide 14 mg at week 48 compared with interferon beta-1a ($P < 0.0001$; $P < 0.0001$; and $P = 0.02$, respectively). There was no statistically significant between-treatment difference in patient satisfaction related to effectiveness between the two drugs ($P = 0.28$).

### 3.6.9 Subgroups

Based on TOWER and TEMSO, and compared with placebo, teriflunomide treatment effects for the outcomes of ARR and sustained disability progression were consistent across two subgroups: 1) patients with or without prior use of DMTs in the last two years; and 2) patients with EDSS ≤ 3.5 or > 3.5.

**TABLE 10: KEY EFFICACY OUTCOMES RESULTS**

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| | TR 14 mg | INF 44 mcg | TR 14 mg | PL | TR 14 mg | PL | TR 14 mg | PL |
| N | 111 | 104 | 370 | 388 | 358 | 363 | 56 | 61 |
| **Relapses** | | | | | | | | |
| Adjusted ARR | 0.26 | 0.22 | 0.32 | 0.50 | 0.37 | 0.54 | NR | NR |
| 95% CI | 0.15, 0.44 | 0.11, 0.42 | 0.27, 0.38 | 0.43, 0.58 | 0.31, 0.44 | 0.47, 0.62 | NR | NR |
| Mean ARR (SD) | NR | NR | NR | NR | NR | NR | 0.55 (1.12) | 0.81 (1.22) |
| RR (95% CI) | 1.2 (0.6 to 2.3) | | 0.64 (0.51 to 0.79) | | 0.69 (0.55 to 0.85) | | NR | |
| **Time to Failure (due to relapse or drug discontinuation)** | | | | | | | | |
| HR (95% CI) | 0.86 (0.56 to 1.31) | | NR | NR | NR | NR | NR | NR |
| **Disability Progression Sustained for 24 weeks** | | | | | | | | |
| At week 48 | NR | NR | 0.09 | 0.07 | 0.10 | 0.09 | NR | NR |
| 95% CI | NR | NR | 0.06 to 0.12 | 0.04 to 0.09 | 0.06 to 0.13 | 0.06 to 0.12 | NR | NR |
| At week 108 | NR | NR | 0.12 | 0.12 | 0.14 | 0.19 | NR | NR |
| 95% CI | NR | NR | 0.08 to 0.16 | 0.08 to 0.16 | 0.10 to 0.18 | 0.14 to 0.23 | NR | NR |
| **Time Disability Progression** | | | | | | | | |
| HR (95% CI) | NR | | 0.84 (0.53 to 1.33) | | 0.75 (0.51 to 1.11) | | NR | |
| **MSFC Z-Scores** | | | | | | | | |
| n | NR | NR | NR | NR | 294 | 302 | 54 | 61 |
| Mean change from baseline (SE)[a] | NR | NR | NR | NR | –0.05 (0.05) | –0.20 (0.05) | –0.02 (0.04) | 0.004 (0.04) |
| **MSQOL-54, Overall Quality of Life Score** | | | | | | | | |
| n | NR | NR | NR | NR | NR | NR | 53 | 60 |
| Mean change from baseline (SD) | NR | NR | NR | NR | NR | NR | 2.36 (11.41) | -3.20 (12.40) |
| **FIS Total Score** | | | | | | | | |
| n | 83 | 65 | 275 | 297 | 297 | 307 | 53 | 60 |
| Mean change from baseline (SE)[b] | 4.10 (3.03) | 9.10 (3.21) | 1.92 (1.63) | 4.67 (1.58) | 4.96 (1.49) | 4.11 (1.48) | –1.49 (3.37) | 3.82 (3.45) |
| **Relapses Requiring Use of IV Corticosteroids** | | | | | | | | |
| AAR | NR | NR | 0.27 | 0.43 | 0.28 | 0.43 | NR | NR |

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| | TR 14 mg | INF 44 mcg | TR 14 mg | PL | TR 14 mg | PL | TR 14 mg | PL |
| **Harms, n (%)** | | | | | | | | |
| N (safety population) | 110 | 101 | 371 | 385 | 358 | 360 | 57 | 61 |
| Death | 0 | 0 | 2 (0.5) | 1 (0.3) | 0 | 0 | 0 | 0 |
| Serious AEs | 6 (5.5) | 7 (6.9) | 44 (11.9) | 47 (12.2) | 57 (15.9) | 46 (12.8) | 7 (12.3) | 7 (11.5) |
| WDAEs | 12 (10.9) | 22 (21.8) | 58 (15.6) | 24 (6.2) | 39 (10.9) | 29 (8.1) | 8 (14.0) | 4 (6.6) |
| **Notable Harms, n (%)** | | | | | | | | |
| Alopecia | 22 (20.0) | 1 (1.0) | 50 (13.5) | 17 (4.4) | 47 (13.1) | 12 (3.3) | 11 (19.3) | 6 (9.8) |
| Hepatotoxicity | NR | NR | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | NR | NR |
| Hypertension | 5 (4.5) | 4 (4.0) | 15 (4.0) | 8 (2.1) | 13 (3.6) | 6 (1.7) | 3 (5.3) | 1 (1.6) |
| Infection | 54 (49.1) | 47 (46.5) | 165 (44.5) | 197 (51.2) | 222 (62.0) | 209 (58.1) | 31 (54.4) | 24 (41.0) |
| Peripheral neuropathy | 5 (4.5) | 1 (1.0) | 4 (1.1) | 2 (0.5) | 3 (0.8) | 2 (0.6) | NR | NR |

AAR = adjusted annualized rate; AE = adverse event; ARR = annualized relapse rate; CI = confidence interval; FIS = Fatigue Impact Scale; HR = hazard ratio; interferon beta-1a; IV = intravenous; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54; NR = not reported; PL = placebo; RR = rate ratio; SD = standard deviation; SE = standard error; TR = teriflunomide; WDAEs = withdrawal due to adverse events.
Source: Clinical Study Reports.[2-5]
[a]For TEMSO, least square mean reported at week 48; for Study 2001, adjusted mean reported at end point.
[b]For TENERE, TOWER, and TEMSO, least square mean reported at week 48; for Study 2001, adjusted mean reported at end point.

## 3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 11 for detailed harms data.

### 3.7.1 Adverse Events

In TENERE, 92.7% of patients in the teriflunomide 14 mg group experienced an adverse event compared with 96.0% of patients with interferon beta-1a. Common adverse event s with teriflunomide 14 mg included diarrhea (20.9% versus 7.9% for the interferon beta-1a group), nasopharyngitis (20.0%), and headache (15.5%). With interferon beta-1a, common adverse events included influenza-like illness (53.5%), headache (25.7%), and nasopharyngitis (17.8%).

In TOWER, 86.3% of patients in the teriflunomide 14 mg group experienced an adverse event compared with 83.1% of patients with placebo. In TEMSO, 90.8% of patients in the teriflunomide 14 mg group experienced an adverse event compared with 87.5% of patients with placebo. Compared with placebo, the proportion of patients experiencing diarrhea was higher in the teriflunomide 14 mg groups in both TOWER and TEMSO; 11.1% versus 7.3%, and 17.9% versus 8.9%, respectively. Other common adverse events included nasopharyngitis and headache for both teriflunomide 14 mg and placebo groups.

In Study 2001, every patient experienced an adverse event. Common adverse events included headaches and upper respiratory tract infections (> 20% each) in both treatment groups. Nasopharyngitis was also common in the teriflunomide 14 group (21.1% versus 16.4% with placebo) and fatigue was common in the placebo group (16.4% versus 12.3% in the teriflunomide group). Compared with placebo, the proportion of patients experiencing diarrhea was higher in the teriflunomide 14 mg group (12.3% versus 4.9% for placebo). Please see Section 3.7.5 for details of other common adverse events (alopecia, increased alanine aminotransferase (ALT), and infections or infestations).

### 3.7.2 Serious Adverse Events

In TENERE, 5.5% of patients experienced a serious adverse event compared with 6.9% for the interferon beta-1a group. In the other three trials, patients with serious adverse events ranged from 11.9% to 15.9% with teriflunomide 14 mg and from 11.5% to 12.8% with placebo. Across all trials, there were reports of increased alanine aminotransferase (10 patients), neutropenia (six patients), fractures (eight patients), and abnormal liver function tests (four patients) with teriflunomide 14 mg. Increased ALT and fractures were also reported with interferon beta-1a (one patient each) and placebo (14 patients and six patients, respectively).

### 3.7.3 Withdrawal due to Adverse Events

In TENERE, 21.8% of patients in the interferon beta-1a group withdrew compared with 10.9% of patients in the teriflunomide 14 mg group. In the other three trials, withdrawal due to adverse events was more common with teriflunomide 14 mg, ranging from 10.9% to 15.6% compared with 6.2% to 8.1% for the placebo group. The most common reasons for withdrawing from the teriflunomide 14 mg group included alopecia, increased ALT, and neutropenia. The most common reasons for withdrawing from the interferon beta-1a and placebo groups included ALT increased.

### 3.7.4 Mortality

No deaths were reported in TENERE, TEMSO, and Study 2001. In TOWER, there was one death due to bacterial sepsis and another due to suicide in the teriflunomide 14 mg group. In the placebo group, one death due to a respiratory tract infection was reported. There was also a fourth death in the teriflunomide 7 mg group due to a road traffic accident.

### 3.7.5 Notable Harms

#### a) Alopecia

Up to 20% of patients reported alopecia with teriflunomide 14 mg, compared with 1% interferon beta-1a and < 10% with placebo.

#### b) Increased ALT

With interferon beta-1a, 30.7% of patients reported increased ALT, compared with 10.0% of teriflunomide 14 mg patients. Increased ALT was more frequent with teriflunomide 14 mg (12.3% to 14.2%) compared with placebo (6.7% to 9.8%).

#### c) Hepatotoxicity

Across all trials, there were only three reports of hepatotoxicity: two in the placebo group and one in the teriflunomide 14 mg group.

#### d) Hypertension

Hypertension was more common with teriflunomide 14 mg, ranging from 3.6% to 5.3% compared with 1.6% to 2.1% with placebo, and similar to interferon beta-1a (4.0% versus 4.5% for teriflunomide).

#### e) Infection or infestation

All groups reported episodes of infection or infestation, ranging from 44.5% to 62.0% with teriflunomide, 46.5 % with interferon beta-1a, and 41.0% to 58.1% with placebo.

#### f) Peripheral neuropathy

There were 12 reports of peripheral neuropathy with teriflunomide 14 mg versus one with interferon beta-1a, and four with placebo.

#### g) Teratogenicity

There were no reports of fetal malformations.

**TABLE 11: HARMS**

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| | TR 14 mg | INF 44 mcg | TR 14 mg | PL | TR 14 mg | PL | TR 14 mg | PL |
| **N** | 110 | 101 | 371 | 385 | 358 | 360 | 57 | 61 |
| **AEs** | | | | | | | | |
| **Subjects with >0 AEs, n (%)** | 102 (92.7) | 97 (96.0) | 320 (86.3) | 320 (83.1) | 325 (90.8) | 315 (87.5) | 57 (100) | 61 (100) |
| **Most common AEs (≥10%)** | | | | | | | | |
| Back pain | 11 (10.0) | 7 (6.9) | 33 (8.9) | 33 (8.6) | 41 (11.5) | 47 (13.1) | 8 (14.0) | 4 (6.6) |
| Diarrhea | 23 (20.9) | 8 (7.9) | 41 (11.1) | 28 (7.3) | 64 (17.9) | 32 (8.9) | 7 (12.3) | 3 (4.9) |
| Fatigue | 6 (5.5) | 6 (5.9) | 38 (10.2) | 41 (10.6) | 52 (14.5) | 51 (14.2) | 7 (12.3) | 10 (16.4) |
| Headache | 17 (15.5) | 26 (25.7) | 46 (12.4) | 42 (10.9) | 67 (18.7) | 64 (17.8) | 12 (21.1) | 16 (26.2) |
| Influenza | 9 (8.2) | 4 (4.0) | 23 (6.2) | 21 (5.5) | 43 (12.0) | 36 (10.0) | 5 (8.8) | 3 (4.9) |
| Influenza-like illness | 3 (2.7) | 54 (53.5) | 8 (2.2) | 9 (2.3) | 8 (2.2) | 9 (2.5) | 3 (5.3) | 1 (1.6) |
| Insomnia | 1 (0.9) | 5 (5.0) | 14 (3.8) | 21 (5.5) | 15 (4.2) | 23 (6.4) | 5 (8.8) | 8 (13.1) |
| Nasopharyngitis | 22 (20.0) | 18 (17.8) | 44 (11.9) | 68 (17.7) | 93 (26.0) | 98 (27.2) | 12 (21.1) | 10 (16.4) |
| Nausea | 10 (9.1) | 4 (4.0) | 38 (10.2) | 34 (8.8) | 49 (13.7) | 26 (7.2) | 10 (17.5) | 3 (4.9) |
| Paresthesia | 11 (10.0) | 8 (7.9) | 22 (5.9) | 24 (6.2) | 35 (9.8) | 30 (8.3) | 8 (14.0) | 3 (4.9) |
| Pain in extremity | 7 (6.4) | 4 (4.0) | 2 5 (6.7) | 21 (5.5) | 33 (9.2) | 47 (13.1) | 6 (10.5) | 2 (3.3) |
| Sensory disturbance | 1 (0.9) | 0 | 5 (1.3) | 4 (1.0) | 6 (1.7) | 6 (1.7) | 8 (14.0) | 9 (14.8) |
| Upper RTI | 8 (7.3) | 8 (7.9) | 34 (9.2) | 44 (11.4) | 32 (8.9) | 25 (6.9) | 13 (22.8) | 13 (21.3) |
| UTI | 2 (1.8) | 4 (4.0) | 23 (6.2) | 37 (9.6) | 37 (10.3) | 3 5 (9.7) | 6 (10.5) | 5 (8.2) |

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| **SAEs** | | | | | | | | |
| **Subjects with >0 SAEs, n (%)** | 6 (5.5) | 7 (6.9) | 44 (11.9) | 47 (12.2) | 57 (15.9) | 46 (12.8) | 7 (12.3) | 7 (11.5) |
| **Most common SAEs (≥1%)** | | | | | | | | |
| ALT increased | 1 (0.9) | 1 (1.0) | 3 (0.8) | 6 (1.6) | 5 (1.4) | 5 (1.4) | 1 (1.8) | 3 (4.9) |
| Anal abscess | 0 | 1 (1.0) | NR | NR | NR | NR | NR | NR |
| Cervical polyp | 0 | 1 (1.0) | NR | NR | NR | NR | NR | NR |
| Cholecystitis | 0 | 1 (1.0) | 1 (0.3) | 3 (0.8) | 0 | 0 | NR | NR |
| Fracture | 0 | 1 (1.0) | 1 (0.3) | 3 (0.8) | 7 (2.0) | 3 (0.8) | NR | NR |
| Liver function tests abnormal | NR | NR | 1 (0.3) | 0 | NR | NR | 3 (5.3) | 3 (4.9) |
| Neutropenia | 1 (0.9) | 0 | 3 (0.8) | 0 | 1 (0.3) | 0 | 2 (3.5) | 1 (1.6) |
| Venous stasis | 0 | 1 (1.0) | NR | NR | NR | NR | NR | NR |
| Suicide attempt | NR | NR | 3 (0.8) | 0 | 0 | 1 (1.0) | 1 (1.8) | 0 |
| Uterine hemorrhage | NR | NR | 0 | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (1.6) |
| Vertebral disc disorder | 0 | 1 (1.0) | NR | NR | 1 (0.3) | 3 (0.8) | NR | NR |
| **WDAEs** | | | | | | | | |
| **WDAEs, n (%)** | 12 (10.9) | 22 (21.8) | 58 (15.6) | 24 (6.2) | 39 (10.9) | 29 (8.1) | 8 (14.0) | 4 (6.6) |
| **Most common reasons (≥2%)** | | | | | | | | |
| Alopecia | 3 (2.7) | 0 | 6 (1.6) | 1 (0.3) | 5 (1.4) | 0 | 1 (1.8) | 0 |
| ALT increased | 4 (3.6) | 9 (8.9) | 9 (2.4) | 6 (1.6) | 8 (2.2) | 8 (2.2) | 0 | 0 |
| AST increased | 0 | 1 (1.0) | 3 (0.8) | 2 (0.5) | NR | NR | 0 | 0 |
| GGT increased | NR | NR | 2 (0.5) | 0 | 0 | 0 | NR | NR |
| Insomnia | 0 | 2 (2.0) | NR | NR | 1 (0.3) | 0 | NR | NR |
| Liver function test abnormal | NR | NR | 1 (0.3) | 0 | NR | NR | 2 (3.5) | 3 (4.9) |
| Neutrophil count decreased | 0 | 1 (1.0) | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (1.8) | 0 |
| Neutropenia | 1 (0.9) | 0 | 8 (2.2) | 0 | NR | NR | NR | NR |
| Transaminases increased | 0 | 1 (1.0) | 3 (0.8) | 1 (0.3) | 2 (0.6) | 4 (1.1) | NR | NR |

| | TENERE | | TOWER | | TEMSO | | STUDY 2001 | |
|---|---|---|---|---|---|---|---|---|
| **Mortality** | | | | | | | | |
| Number of deaths, n (%) | 0 | 0 | 2 (0.5) | 1 (0.3) | 0 | 0 | 0 | 0 |
| **Notable Harms** | | | | | | | | |
| Alopecia | 22 (20.0) | 1 (1.0) | 50 (13.5) | 17 (4.4) | 47 (13.1) | 12 (3.3) | 11 (19.3) | 6 (9.8) |
| ALT increased | 11 (10.0) | 31 (30.7) | 52 (14.0) | 32 (8.3) | 51 (14.2) | 24 (6.7) | 7 (12.3) | 6 (9.8) |
| Hepatotoxicity | NR | NR | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | NR | NR |
| Hypertension | 5 (4.5) | 4 (4.0) | 15 (4.0) | 8 (2.1) | 13 (3.6) | 6 (1.7) | 3 (5.3) | 1 (1.6) |
| Infection or infestation | 54 (49.1) | 47 (46.5) | 165 (44.5) | 197 (51.2) | 222 (62.0) | 209 (58.1) | 31 (54.4) | 24 (41.0) |
| Peripheral neuropathy | 5 (4.5) | 1 (1.0) | 4 (1.1) | 2 (0.5) | 3 (0.8) | 2 (0.6) | NR | NR |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; interferon beta-1a; RTI = respiratory tract infection; SAE = serious adverse event; TR = teriflunomide; UTI = urinary tract infection; WDAE = withdrawal due to adverse events.
Source: Clinical Study Reports.[2-5]
Note: Outcomes identified as important to the review (see Table 2 for review protocol).

# 4. DISCUSSION

## 4.1 Summary of Available Evidence

Four randomized, multi-centre, parallel group, superiority trials met the inclusion criteria for this systematic review. TENERE (N = 324) was an active control investigator (but not patient)-blinded trial. TEMSO (N = 1,088), TOWER (N = 1,169) and Study 2001 (N = 179) were double-blind, placebo-controlled trials. Included patients had MS with a relapsing course, were older than 18 years, and met the McDonald 2005 criteria (TENERE, TOWER, and TEMSO) or Poser criteria (Study 2001) for MS. Two teriflunomide doses (7 mg or 14 mg) were compared with interferon beta-1a (TENERE) or with placebo (TOWER, TEMSO, and Study 2001). In TENERE and in TOWER, patients were treated for a minimum of 48 weeks to a maximum of 118 weeks and 160 weeks, respectively. In TEMSO and in Study 2001, patients were treated for 108 weeks and 36 weeks, respectively. The primary efficacy end points were time to failure in TENERE, ARR in TOWER and TEMSO, and number of unique active lesions per MRI scan (combined T1 and T2 lesions) in Study 2001. In all trials, randomization was stratified by centre and baseline disability (EDSS ≤ 3.5 or EDSS > 3.5).

The limitations of the available evidence included the open-label design of TENERE and the challenge of maintaining blinding in the placebo-controlled trials due to the occurrence of adverse events in the teriflunomide groups. The high frequency of study withdrawal in all trials and the between-treatment imbalances in study withdrawals in TENERE and Study 2001 could potentially have biased the results of the between-treatment comparisons. [redacted]

Health Canada has approved teriflunomide 14 mg orally once daily and only results for this dose were reported in the CDR review.

## 4.2 Interpretation of Results

### 4.2.1 Efficacy

Study 2001 was a relatively small phase 2 study designed to examine short-term effects of teriflunomide on MRI findings and thus provides limited evidence of the beneficial effect of teriflunomide for other outcomes of interest. Results of the other two placebo-controlled trials (TOWER and TEMSO) suggest that teriflunomide treatment results in a statistically significantly lower ARR compared with no treatment (placebo) over one to three years. While some between-treatment differences in baseline characteristics were observed in these trials (time since diagnosis or first symptoms), the clinical expert consulted for this review indicated that these differences were unlikely to bias the results. However, the high frequency of study withdrawal (approximately 30% over the duration of the study) may bias the estimate of treatment effect. This concern is mitigated somewhat, given that the percentage of patients discontinuing study participation was similar between teriflunomide and placebo groups in both studies. However, between-treatment differences in timing of study withdrawal may have biased the estimates of effect, although this effect is thought to be small. The observed 30% to 35% reduction in the ARR with teriflunomide compared with no treatment (placebo) was considered clinically important by the clinical expert consulted for this review. ARR is an outcome widely used in MS studies, and in clinical practice the frequency and intensity of relapses will dictate treatment choice. However, ARR has not been shown to correlate consistently with disability progression.

In the conduct of MS trials, the *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* by the European Medicines Agency recommends that sustained

disability progression be established by two consecutive examinations carried out at least six months apart.[33] This is also appropriate in clinical practice, as a recent clinical practice guideline by the CMSWG recommends that disability progression be confirmed at six months.[13] In TOWER and TEMSO, disability sustained for 24 weeks was not statistically significantly different between teriflunomide and placebo in either trial. The apparent lack of effect of teriflunomide on sustained disability progression may be related to the relatively short trial duration. Disability associated with MS accumulates over many years; therefore, the duration of TOWER and TEMSO studies may be inadequate to assess the potential impact of teriflunomide on long-term disability.

Direct head-to-head evidence for teriflunomide is limited to the TENERE study, which compared teriflunomide with interferon beta-1a (Rebif) in patient-naive to treatment with interferon beta-1a (Rebif). TENERE assessed a limited number of relevant outcomes. The primary outcome, time to failure, was defined as time to first relapse or treatment discontinuation due to any cause (including patients withdrawing due to adverse events), which does not give a clear picture of disease activity. While no statistically significant between-treatment differences were reported for the ARR or time to failure, study discontinuation was noticeably higher among interferon-treated patients, which may have biased the results of between-treatment comparisons. In addition, the higher-than-expected study discontinuation likely reduced the statistical power of between-treatment comparisons. It is important to note that TENERE was not designed to show equivalence or non-inferiority of teriflunomide to interferon beta-1a, and these cannot be inferred from the non-significant finding.

Given the paucity of head-to-head trials, the manufacturer submitted a mixed treatment comparison (MTC) comparing teriflunomide with other DMTs, which reported no significant differences between teriflunomide and interferon beta-1a (subcutaneous and intramuscular), interferon beta-1b, or glatiramer acetate with respect to the ARR, but indicated that dimethyl fumarate, fingolimod, and natalizumab resulted in significantly lower ARRs compared with teriflunomide. In addition, teriflunomide was not found to be significantly different compared with the other DMTs with respect to three-month sustained accumulated disability. These findings are solely dependent upon an indirect comparison; thus, there is less certainty regarding these results than if they had resulted from a well-conducted RCT. In addition, the MTC was limited by the inclusion of studies with high heterogeneity for patient characteristics, EDSS score at baseline, disease duration, disease severity, previous treatments, prior relapse rates, and duration of individual studies. Hence, additional head-to-head trials are needed to determine the comparative effectiveness of teriflunomide against other MS drugs, including the recently approved oral drugs.

Patient group input suggests that oral drugs are greatly preferred over injections and cites dislike of needles as a factor preventing patients from adhering to injectable MS therapies. According to the TSQM, an instrument not validated in MS patients and administered in TENERE, patient satisfaction related to convenience, side effects, and global satisfaction favoured teriflunomide over interferon beta-1a, although the open-label nature of this trial should be kept in mind in interpreting these findings. Given the indirect evidence suggesting that teriflunomide had similar activity to the interferons and glatiramer acetate, teriflunomide may be seen as an alternative to interferon and glatiramer acetate in patients who are unable or unwilling to use injectable preparations. Recent recommendations from the CMSWG did not make definite recommendations on the use of oral drugs such as teriflunomide because these drugs were still in development.[13] Similarly, CADTH recommendations for the use of DMTs for RRMS were silent with respect to teriflunomide's place in therapy because it had not been approved by Health Canada at the time the recommendations were made.[34]
Results for patient-reported outcomes such as quality of life and fatigue may be subject to bias to a greater extent than relapse or sustained progression of disability due to blinding issues. Specifically, in

TENERE, patients were aware of whether they were receiving teriflunomide or interferon beta-1a; however, no statistically significant between-treatment differences in fatigue were reported in TENERE. Despite the double-blind design of the placebo-controlled trials, potential unblinding related to adverse events (gastrointestinal or alopecia) may have biased the results. However, there were no differences between groups for the various patient-reported outcomes in these trials.

Finally, with respect to generalizability of the included trials, it was also unclear if patients were treatment experienced. Although < 25% of patients reported prior use of DMTs in the last two years, there was no information on lifetime treatment experience. Subgroup analyses showed that all patients stand to benefit from teriflunomide treatment irrespective of disability level (as measured with EDSS) and prior use of DMTs within two years.

### 4.2.2 Harms

The most common adverse events associated with teriflunomide in the trials included diarrhea, increased ALT, and alopecia. Serious adverse events included reports of increased ALT, neutropenia, fractures, and abnormal liver function tests. As teriflunomide has immunosuppressant properties, there is the potential for an increase in infections. However, this was not seen in the placebo-controlled trials and in TENERE.

Teriflunomide is an active metabolite of leflunomide (Arava), which was approved in 2000 for the treatment of rheumatoid arthritis. Teriflunomide may share some of the same known risks of leflunomide. Serious warnings for leflunomide include skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis), severe liver injury (including fatal liver failure), and interstitial lung disease. As such, a boxed warning on hepatotoxicity is included in teriflunomide's product monograph. In the extension trial of Study 2001, hepatic adverse events occurred in 45% of patients initially randomized to teriflunomide 14 mg and who continued in the 14 mg group in the extension phase, compared with 38.5% in patients initially randomized to placebo and who switched to teriflunomide 14 mg in the extension phase. In the TEMSO extension trial, hepatic adverse events occurred in 14.4% of patients initially randomized to teriflunomide 14 mg who continued on teriflunomide 14 mg in the extension phase, and 20.6% in patients initially randomized to placebo and who switched to teriflunomide 14 mg in the extension phase.

In TENERE, patients receiving interferon beta-1a were most likely to discontinue treatment due to adverse events compared with teriflunomide, whereas in the placebo-controlled trials, teriflunomide patients were most likely to discontinue treatment due to adverse events. In the manufacturer-submitted MTC, when compared with the other DMTs, teriflunomide was not associated with significant differences in treatment discontinuations due to adverse events. Compared with placebo, subcutaneous interferon beta-1a and dimethyl fumarate, but not teriflunomide, patients were more likely to discontinue treatment due to adverse events.

No fetal malformations were reported in the trials. Teriflunomide is considered teratogenic and is a concern because MS affects women of child-bearing age. Therefore, teriflunomide is contraindicated in pregnant women or women wishing to become pregnant. Teriflunomide is also found in human semen and men are also advised to discontinue teriflunomide should their partner wish to become pregnant. Given that teriflunomide is eliminated slowly from plasma, an accelerated elimination procedure using cholestyramine or activated charcoal is required when pregnancy is a consideration. Teratogenicity concerns may limit the use of teriflunomide in clinical practice. Teriflunomide's safety issues should be viewed in light of the fact that the various approved therapies for MS all have their own unique safety

and tolerability issues. For example, flu-like symptoms are an important tolerability issue for the interferons, and injection-site reactions are the most common issue with glatiramer acetate. Flushing and gastrointestinal adverse events have been associated with dimethyl fumarate. Furthermore, serious adverse events have been reported with fingolimod, most notably cardiac arrhythmias. Of the approved drugs for MS, natalizumab has the most serious safety issue associated with it (PML). Health Canada recommends that the use of fingolimod and natalizumab be reserved for the treatment of patients who have had an inadequate response or who are unable to tolerate other MS drugs.

# 5. CONCLUSIONS

Based on the results of two phase 3 double-blind RCTs, teriflunomide 14 mg may reduce the ARR by approximately 30% to 35% compared with no treatment (placebo) over one to three years of treatment. However, the benefits of teriflunomide compared with no treatment in terms of reducing disability are less certain, given that disability sustained for 24 weeks was not statistically significantly different between teriflunomide and placebo in either trial. There were no differences in HRQoL or fatigue between teriflunomide and placebo. Direct head-to-head evidence for teriflunomide 14 mg, limited to one investigator-blinded RCT, reported no statistically significant difference in ARR or time to failure (primary outcome) between teriflunomide 14 mg and interferon beta-1a 44 mcg; however, the trial was not designed to test equivalence or non-inferiority of teriflunomide, and thus this cannot be inferred.

A manufacturer-provided MTC reported no significant differences between teriflunomide 14 mg and any of interferon beta-1a (subcutaneous and intramuscular), interferon beta-1b, or glatiramer acetate with respect to the ARR. However, dimethyl fumarate, fingolimod, and natalizumab resulted in significantly lower ARRs compared with teriflunomide 14 mg. In addition, teriflunomide 14 mg was not found to be significantly different compared with the other DMTs with respect to three-month sustained accumulated disability. However, the MTC was limited by the heterogeneity of the included trials and, given the lack of direct evidence, caution is warranted in the interpretation of between-treatment differences suggested by the MTC.

The most common harms with teriflunomide were alopecia, diarrhea, and increased ALT. Serious safety concerns with teriflunomide include teratogenicity and hepatotoxicity.

# APPENDIX 1: LITERATURE SEARCH STRATEGY

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | January 21, 2014 |
| Alerts: | Weekly search updates until May 21, 2014 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Conference abstracts were excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj | Requires words are adjacent to each other (in any order) |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .pt | Publication type |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| 1 | (Aubagio* or teriflunomide* or A 1726 or A1726 or A 77-1726 or A 771726 or A771726 or Flucyamide or HMR 1726 or HMR1726 or SU 20 or SU20 or rs 61980 or rs61980 or "su 0020" or su0020).ti,ab,ot,sh,hw,rn,nm. |
| 2 | 163451-81-8.rn,nm. |
| 3 | 1 or 2 |
| 4 | exp Multiple sclerosis/ or (multiple sclerosis or disseminated sclerosis or insular sclerosis or ms or rrms or neurolog* or relapse rate* or relapse-remit*).ti,ab. |
| 5 | 3 and 4 |
| 6 | 5 use pmez |
| 7 | *Teriflunomide/ |
| 8 | (Aubagio* or teriflunomide* or A 1726 or A1726 or A 77-1726 or A 771726 or A771726 or Flucyamide or HMR 1726 or HMR1726 or SU 20 or SU20 or rs 61980 or rs61980 or "su 0020" or su0020).ti,ab. |
| 9 | 7 or 8 |
| 10 | Multiple sclerosis/ or (multiple sclerosis or disseminated sclerosis or insular sclerosis or ms or rrms or neurolog* or relapse rate* or relapse-remit*).ti,ab. |
| 11 | 9 and 10 |
| 12 | 11 use oemezd |
| 13 | 6 or 12 |
| 14 | conference abstract.pt. |
| 15 | 13 not 14 |
| 16 | remove duplicates from 15 |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (Clinicaltrials.gov and others) | Same keywords, limits used as per MEDLINE search. |

### Grey Literature

| | |
|---|---|
| Dates for Search: | January 2014 |
| Keywords: | Drug name, Indication |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the Canadian Agency for Drugs and Technologies in Health grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

# APPENDIX 2: PATIENT INPUT SUMMARY

*This section was summarized by Canadian Agency for Drugs and Technologies in Health (CADTH) staff based on the input provided by patient groups. It has not been systematically reviewed.*

**1. Brief Description of the Patient Group Supplying Input**

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports both MS research and services for people with MS and their families. Its mission is to be a leader in finding a cure for MS and enabling people affected by MS to enhance their quality of life. The MS Society has a membership of 20,500, is governed by a national board of volunteer members, and has an estimated 13,500 volunteers carrying out service programs, fundraising events, public awareness campaigns, and government relations activities.

In 2012, the MS Society received educational grants from Bayer; Biogen Idec; EMD Serono; Novartis; Pfizer; Genzyme; Allergan; and Teva Neuroscience. The contributions totalled less than 2% of the MS Society's overall revenue and are subject to strict policies that prevent any control or influence by the donor on MS Society decision-making. The MS Society declared no conflicts of interest in compiling this submission.

**2. Condition and Current Therapy Related Information**

Information for this submission was obtained from publicly available information about the impact of MS and from a MS Society survey (N = 1,345) conducted in English and French in February 2013 to gather data for patient input for the CADTH Therapeutic Review of MS Disease-Modifying Therapies. The majority of respondents were 41 to 60 years of age and included patients (91%) and caregivers (9%). The length of diagnosis varied from less than two years to more than 20 years. Respondents reported the following types of MS: possible MS (clinically isolated syndrome), relapsing-remitting (reported by 70% of respondents), secondary progressive, primary progressive, and "do not know." The survey was not population-based and cannot be interpreted as reflecting the views of all Canadians with MS or their caregivers.

MS is an unpredictable and often disabling disease that attacks the myelin, a protective coating of the central nervous system. Respondents reported varying degrees of the most common symptoms of MS (difficulty in walking, fatigue, difficulty with coordination of arms or legs, loss of vision, numbness or tingling, memory or attention problems, and pain), with 85% reporting fatigue. Respondents reported that multiple effects had an impact on their lives: fatigue (76.6%), difficulty in walking (51.6%), memory or attention problems (39.1%), bladder problems (37.6%), numbness or tingling (36.9%), and pain (35.8%). Heat intolerance and sensitivity were also reported. Almost 94% of respondents said MS had negatively affected their lives, including family relationships, "somewhat" (48.4%) to "a lot" (45.5%), and 6.5% said not at all. Further, 81% of respondents said their work lives had been affected from "somewhat" (25.6%) to "a lot" (55.4%). This is an important consideration, as employment affects many aspects of an individual's life, and in particular, their (and their family's) financial situation. Other aspects of day-to-day life that were much affected were recreational activities (48.3%), sleep (34.1%), and mobility (33.4%).

**Impact on Caregivers**

The care and assistance that many people with MS receive from spouses, other family members, and friends are key factors in maintaining quality of life and independence. Caregivers assist in both medical and non-medical tasks, with 52.6% administering medications all or some of the time. When asked if providing assistance had an impact on their own daily routines, 41.1% reported that it did all the time and 32.1%

reported that it did sometimes. Also, 62% of caregivers responded the current disease-modifying therapy (DMT) had negative effects on the person they care for at least some of the time.

**Experience with Current Therapies**

Eight drugs that reduce the frequency and severity of MS relapses are available in Canada. Some of the drugs have some data suggesting a slowing effect on the accumulation of disability over time. Respondents indicated that the most important symptoms to be controlled by DMTs are progression of disability (86.8%) and the number and/or severity of relapses (69.9%). None of the treatments are a cure and none prevent persistent symptoms such as fatigue or numbness. A number of drugs are available to help relieve MS symptoms such as spasticity, fatigue, and pain. No DMT has been approved to treat primary progressive MS. The lack of current therapies for progressive forms of MS was mentioned by numerous respondents as a concern.

In the survey, 62.6% of respondents were using a DMT: Copaxone (23.1%), Rebif (16.5%), Avonex (9.1%), Tysabri (5.6%), Betaseron (5.3%), Gilenya (3%), and Extavia (0.2%). Approximately 53% indicated that treatment reduced the frequency and severity of relapses, 40.9% said it appeared to slow the progression of disability, 25.7% said it allowed them to have a better quality of life, and 25.1% said they generally felt better. A respondent commented that, "I presume it's doing all the above [in helping them]. I certainly would rather be taking my DMT, and not find out what may have happened if I didn't."

Patients reported the following side effects in varying degrees from "somewhat" to "a lot," with injection-site reactions ranking first, followed by fatigue, sore muscles and joints, headache, depression, chills, spasticity, fever, rapid heartbeat, and breathlessness. Side effects not listed in the survey but reported by respondents included lipoatrophy, thyroid problems, liver toxicity, poor sleep, nausea, low white blood cell count, and bruising on the skin. Many were uncertain whether the side effects were caused by the drugs or were symptoms of MS. Most respondents (66.9%) said that side effects did not affect compliance with therapy. Fatigue and injection-site reactions were the most frequent reasons cited for non-compliance. Some respondents reported that they only use alternative therapies (e.g., diet, exercise, vitamins, acupuncture) to manage their disease.

The dislike of using a needle was second only to the high cost of MS therapies as factors preventing respondents from taking their current DMT at times. Other factors were anxiety regarding the use of needles, difficulty in using needles, rotation of sites, travel-related inconvenience, and concerns with insurance coverage. Some patients commented that current DMTs did not work and respondents did not see any benefit in taking them. Other comments included a mistrust of drug companies, neurologists, and the MS Society, as respondents felt they were biased toward pushing these medications.

**3. Related Information about the Drug Being Reviewed**

Most of the respondents to the MS Society survey had no experience with teriflunomide. This is not unexpected, as the only access patients have to this new treatment is through a drug trial. Many reported looking forward to having an improved quality of life with a drug that did not involve injections because of the pain and injection-site reactions, or infusions due to inconvenience and concern about serious side effects. Expectations for a new DMT included lower and/or limited side effects, greater affordability, greater convenience (e.g., no refrigeration), and improvement in everyday function. Some focus group participants commented that they hoped it would be available as a first line therapy, as it is an oral form and more tolerable than injections. Others noted that an oral drug would improve compliance, which can be a greater issue in a disease that can result in numbness and lack of coordination, which complicate self-injection.

## 4. Additional Information

The current MS therapies have provided people with a way of reducing relapses and possibly slowing the progression of disability. The potential choice of more MS drugs that have greater efficacy and an easier mode of administration is exciting for many people with MS.

Respondents noted the importance of having options of several therapies to match an individual's disease and life situation.

# APPENDIX 3: DETAILED OUTCOME DATA

## Relapses

**TABLE 12: RELAPSES, TENERE — INTENTION-TO-TREAT POPULATION**

| | TENERE | |
|---|---|---|
| **Confirmed MS relapses** | **TR 14 mg (N = 111)** | **Interferon (N = 104)** |
| Total number of relapses | 35 | 25 |
| Total number of patient-years followed | 132.2 | 112.1 |
| Unadjusted ARR[a] | 0.27 | 0.22 |
| Adjusted ARR (95% CI)[b] | 0.26 (0.15 to 0.44) | 0.22 (0.11 to 0.42) |
| Rate ratio (95% CI) | 1.2 (0.6 to 2.3) | |
| *P* value[c] | 0.59 | |
| **Relapses/patient, n (%)** | | |
| 0 | 85 (76.6) | 88 (84.6) |
| 1 | 18 (16.2) | 10 (9.6) |
| 2 | 7 (6.3) | 4 (3.8) |
| 3 | 1 (0.9) | 1 (1.0) |
| ≥4 | 0 | 1 (1.0) |

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; TR = teriflunomide.
Source: Clinical Study Report.[4]
[a]Total number of relapses that occurred during the treatment divided by the total number of patient-years treated in the study.
[b]Adjusted ARR derived from Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed treatment duration as an offset variable.
[c]Chi-square test from estimating the rate ratios.

**TABLE 13: TIME TO FAILURE, TENERE — INTENTION-TO-TREAT POPULATION**

| | TENERE | |
|---|---|---|
| **Time to Failure[a]** | **TR 14 mg (N = 111)** | **Interferon (N = 104)** |
| **Number of patients with outcome, n (%)** | 42 (37.8) | 44 (42.3) |
| • Relapse, n (%) | 26 (23.4) | 16 (15.4) |
| • Permanent treatment discontinuation, n (%) | 15 (13.5) | 25 (24.0) |
| • Other reason for failure, n (%) | 1 (0.9) | 3 (2.9) |
| **Kaplan–Meier estimates of probability of failure (95% CI) at:** | | |
| • 24 weeks | 0.24 (0.16 to 0.32) | 0.30 (0.21 to 0.39) |
| • 48 weeks | 0.33 (0.25 to 0.42) | 0.37 (0.27 to 0.46) |
| • 96 weeks | 0.41 (0.31 to 0.51) | 0.44 (0.34 to 0.54) |
| HR (95% CI)[b] | 0.86 (0.56, 1.31) | |
| *P* value[c] | 0.6 | |

CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; INF = interferon; TR = teriflunomide.
Source: Clinical Study Report.[4]
[a]Primary end point for TENERE trial. Time to failure = first occurrence of confirmed relapse, permanent study treatment discontinuation, or other reason for failure, whichever occurs first (includes patients who were never treated or received wrong treatment).
[b]Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.
[c]Derived using log-rank test with stratification of EDSS strata at baseline and region.

**TABLE 14: RELAPSES, TOWER, AND TEMSO — INTENTION-TO-TREAT POPULATION**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **Confirmed MS Relapses** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** |
| Total number of relapses | 227 | 335 | 177 | 296 |
| Total number of patient-years followed | 615.0 | 627.7 | 573.6 | 608.4 |
| Unadjusted ARR[a] | 0.37 | 0.53 | 0.31 | 0.49 |
| Adjusted ARR (95% CI)[b] | 0.37 (0.31 to 0.44) | 0.54 (0.47 to 0.62) | 0.32 (0.27 to 0.38) | 0.50 (0.43 to 0.58) |
| Rate ratio (95% CI) | 0.69 (0.55 to 0.85) | | 0.64 (0.51 to 0.79) | |
| *P* value[c] | 0.0005 | | 0.0001 | |
| Relapses/patient, n (%) | | | | |
| 0 | 217 (60.6) | 179 (49.3) | 248 (67.0) | 202 (52.1) |
| 1 | 86 (24.0) | 97 (26.7) | 79 (21.4) | 116 (29.9) |
| 2 | 33 (9.2) | 48 (13.2) | 36 (9.7) | 46 (11.9) |
| 3 | 16 (4.5) | 22 (6.1) | 4 (1.1) | 13 (3.4) |
| 4 | 4 (1.1) | 11 (3.0) | 2 (0.5) | 7 (1.8) |
| ≥5 | 2 (0.6) | 6 (1.7) | 1 (0.3) | 4 (1.0) |
| Patients with ≥1 relapse, n (%) | 141 (39.4) | 184 (50.7) | 122 (33.0) | 186(47.9) |
| Patients censored, n (%) | 217 (60.6) | 179 (49.3) | 248 (67.0) | 202 (52.1) |
| Absence of relapse during 48 weeks (95% CI)[d] | 0.68 (0.63 to 0.73) | 0.60 (0.55 to 0.65) | 0.76 (0.72 to 0.81) | 0.61 (0.56 to 0.66) |
| Absence of relapse during 108 weeks (95% CI)[d] | 0.57 (0.51 to 0.62) | 0.46 (0.40 to 0.51) | 0.57 (0.51 to 0.64) | 0.47 (0.41 to 0.53) |
| HR (95% CI)[e] | 0.72 (0.58 to 0.90) | | 0.63 (0.50 to 0.79) | |
| *P* value[f] | 0.003 | | <0.0001 | |

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MS = multiple sclerosis; TR = teriflunomide.

Source: Clinical Study Reports.[2,3]

[a]Total number of relapses that occurred during the treatment divided by the total number of patient-years treated in the study.

[b]Primary end point for TEMSO and TOWER. Adjusted ARR derived from Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed treatment duration as an offset variable.

[c]Chi-square test for estimating the rate ratios.

[d]Derived from Kaplan–Meier estimates.

[e]Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates (HR is for 108 weeks for TEMSO and 132 weeks for TOWER).

[f]Derived using log-rank test with stratification of EDSS strata at baseline and region.

**TABLE 15: RELAPSES, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **MS Relapses** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| N | 56 | 61 |
| **Patients with relapses during treatment period** | | |
| 0 relapse, n (%) | 43 (76.8) | 38 (62.3) |
| *P* value[a] | 0.10 | |
| At least one relapse, n (%) | 13 (23.2) | 23 (37.7) |
| **Annual relapse rate** [b] | | |
| Mean (SD) | 0.55 (1.12) | 0.81 (1.22) |
| Median (min, max) | 0 (0, 4.42) | 0 (0, 5.05) |

Max = maximum; min = minimum; MS = multiple sclerosis; SD = standard deviation; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Cochran–Mantel–Haenszel test controlling for centre.
[b]Annual relapse rate defined as number of relapses per patients × 365/days on treatment.

## Disability

**TABLE 16: SUSTAINED DISABILITY PROGRESSION, TEMSO AND TOWER — INTENTION-TO-TREAT POPULATION**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **Time to Disability Progression** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** |
| **Sustained for 12 weeks** | | | | |
| Patients with disability progression, n (%) | 62 (17.3) | 86 (23.7) | 44 (11.9) | 65 (16.8) |
| Patients censored, n (%) | 296 (82.7) | 277 (76.3) | 326 (88.1) | 323 (83.2) |
| | | | | |
| **Probability of disability progression at**[a] | | | | |
| 48 weeks | 0.11 (0.08 to 0.15) | 0.16 (0.12 to 0.20) | 0.08 (0.05 to 0.11) | 0.14 (0.11 to 0.18) |
| 108 weeks | 0.20 (0.16 to 0.25) | 0.27 (0.22, 0.32) | 0.16 (0.11 to 0.20) | 0.20 (0.15 to 0.24) |
| 132 weeks | NA | NA | 0.16 (0.11 to 0.20) | 0.21 (0.16 to 0.26) |
| | | | | |
| HR (95% CI)[b] | 0.70 (0.51 to 0.97) | | 0.69 (0.47 to 1.00) | |
| *P* value[c] | 0.03 | | 0.04 | |
| **Sustained for 24 weeks** | | | | |
| Patients with disability progression, n (%) | 43 (12.0) | 58 (16.0) | 33 (8.9) | 41 (10.6) |
| Patients censored, n (%) | 315 (88.0) | 305 (84.0) | 347 (89.4) | 337 (91.1) |
| **Probability of disability progression at**[a] | | | | |
| 48 weeks | 0.10 (0.06 to 0.13) | 0.09 (0.06 to 0.12) | 0.09 (0.06 to 0.12) | 0.07 (0.04 to 0.09) |
| 108 weeks | 0.14 (0.10 to 0.18) | 0.19 (0.14 to 0.23) | 0.12 (0.08 to 0.16) | 0.12 (0.08 to 0.16) |
| 132 weeks | NA | NA | 0.13 (0.09 to 0.18) | 0.12 (0.08 to 0.16) |
| HR (95% CI)[b] | 0.75 (0.51 to 1.11) | | 0.84 (0.53 to 1.33) | |
| *P* value[c] | 0.13 | | 0.45 | |

CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; NA = not applicable; TR = teriflunomide.
Source: Clinical Study Reports.[2,3]
[a]Kaplan–Meier estimates.
[b]HR derived using Cox proportional hazard model with treatment, EDSS strata at baseline, and region as covariates.
*P* value derived from log-rank test with stratification of EDSS strata at baseline and region.

**TABLE 17: SUSTAINED DISABILITY PROGRESSION, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **Progression[a] in EDSS** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| N | 54 | 61 |
| **Total number of patients with progression at end point (%)** | 4 (7.4) | 13 (21.3) |
| *P* value[b] | 0.04 | |
| **First progression before or at week 12** | | |
| n (%) | 2 (3.7) | 3 (4.9) |
| **First progression week 24** | | |
| n (%) | 1 (1.9) | 5 (8.2) |
| **First progression week 36** | | |
| n (%) | 1 (1.9) | 5 (8.2) |

EDSS = Expanded Disability Status Scale; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Progression defined as an increase in EDSS score by at least 1 in patients with baseline score ≤ 5.5 or by at least 0.5 in patients with baseline score > 5.
[b]Cochran–Mantel–Haenszel test controlling for centre.

**TABLE 18: EXPANDED DISABILITY STATUS SCALE, TENERE — INTENTION-TO-TREAT POPULATION**

| | TENERE | |
|---|---|---|
| **EDSS** | **TR 14 mg (N = 111)** | **Interferon (N = 104)** |
| **At week 48** | | |
| N | 92 | 74 |
| Mean (SD) | 2.2 (1.3) | 1.9 (1.1) |
| Median (min, max) | 2.0 (0, 5.5) | 1.5 (0, 6.0) |
| **Change from baseline** | | |
| Mean (SD) | –0.05 (0.61) | –0.13 (0.73) |
| Median (min, max) | 0 (–3.0, 2.0) | 0 (–3.0, 1.5) |

EDSS = Expanded Disability Status Scale; max = maximum; min = minimum; SD = standard deviation; TR = teriflunomide.
Source: Clinical Study Report.[4]

**TABLE 19: EXPANDED DISABILITY STATUS SCALE, TEMSO AND TOWER — INTENTION-TO-TREAT POPULATION, MIXED EFFECT MODEL WITH REPEATED MEASURES ANALYSIS**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **EDSS** | **TR 14 mg (N=358)** | **Placebo (N=363)** | **TR 14 mg (N=370)** | **Placebo (N=388)** |
| **At week 48** | | | | |
| N | 304 | 314 | 290 | 318 |
| Mean (SD) | 2.73 (1.33) | 2.68 (1.56) | 2.57 (1.4) | 2.66 (1.49) |
| Median (min, max) | 2.5 (0, 6.5) | 2.5 (0, 7.5) | 2.5 (0, 6.5) | 2.5 (0, 6.5) |
| **Change from baseline** | | | | |
| Mean (SD) | 0.06 (0.74) | 0.06 (0.91) | -0.09 (0.79) | 0.03 (0.88) |
| Median (min, max) | 0 (–3.0, 4.5) | 0 (–2.5, 4.0) | 0 (–4.0, 2.5) | 0 (–4.0, 3.0) |
| LS mean (SE) | 0.14 (0.05) | 0.15 (0.05) | –0.05 (0.05) | 0.09 (0.05) |
| *P* value | [a] | | [a] | |

EDSS = Expanded Disability Status Scale; LS = least square; MMRM = mixed effect model with repeated measures; SD = standard deviation; SE = standard error; TR = teriflunomide.
Source: Clinical Study Reports.[2,3]
MMRM analysis adjusted for EDSS strata at baseline, region and baseline value.
[a]*P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

**TABLE 20: EXPANDED DISABILITY STATUS SCALE, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **EDSS[a]** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| **End point** | | |
| N | 54 | 61 |
| Mean (SD) | 2.4 (1.8) | 2.5 (1.6) |
| Median (min, max) | 2.0 (0, 6.5) | 2.0 (0, 6.5) |
| **Change from baseline** | | |
| N | 54 | 61 |
| Mean (SD) | –0.10 (0.52) | 0.02 (0.68) |
| Median (min, max) | 0 (–1.5, 1.5) | 0 (–1.5, 2.0) |
| Adjusted mean (SE) | –0.11 (0.10) | 0.01 (0.09) |
| *P* value | 0.52 | |

EDSS = Expanded Disability Status Scale; max = maximum; min = minimum; SD = standard deviation; SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Analysis of variance (ANOVA); adjusted for multiple comparisons between treatment groups according to Dunnett.

**TABLE 21: MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE, TEMSO — INTENTION-TO-TREAT POPULATION, MIXED EFFECT MODEL WITH REPEATED MEASURES ANALYSIS**

| | TEMSO | |
|---|---|---|
| **MSFC Z-scores[a]** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** |
| **At week 24** | | |
| N | 314 | 327 |
| LS mean change from baseline (SE) | –0.05 (0.02) | –0.12 (0.02) |
| *P* value | [b] | |
| **At week 48** | | |
| N | 294 | 302 |
| LS mean change from baseline (SE) | –0.05 (0.05) | –0.20 (0.05) |
| *P* value | [b] | |

EDSS = Expanded Disability Status Scale; LS = least square; MMRM = mixed effect model with repeated measures; MSFC = Multiple Sclerosis Functional Composite; SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[2]
[a]MMRM analysis adjusted for EDSS strata at baseline, region and baseline value.
[b]*P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

**TABLE 22: MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **MSFC Z-score at End Point[a]** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| N | 54 | 61 |
| Adjusted mean change from baseline (SE) | –0.02 (0.04) | 0.004 (0.04) |
| *P* value | 0.89 | |

MSFC = Multiple Sclerosis Functional Composite; NS = not statistically significant, SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Analysis of covariance (ANCOVA); adjusted for multiple comparisons between treatment groups using Dunnett.

## Health-related Quality of Life Outcomes

**TABLE 23: MULTIPLE SCLEROSIS QUALITY OF LIFE-54, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **MSQOL-54 Scores at End Point[a]** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| **Mental health component score** | | |
| N | 53 | 60 |
| Adjusted mean change from baseline (SE) | 1.99 (2.40) | –3.32 (2.42) |
| *P* value | 0.13 | |
| **Physical health component score** | | |
| N | 49 | 58 |
| Adjusted mean change from baseline (SE) | 0.96 (1.96) | –3.16 (1.95) |
| *P* value | 0.15 | |
| **Overall quality of life** | | |
| N | 53 | 60 |
| Mean change from baseline (SD) | 2.36 (11.41) | –3.20 (12.40) |
| Median (min, max) | 0 (–26.7, 35.0) | –4.2(-36.7, 21.7) |

MSQOL-54 = Multiple Sclerosis Quality of Life-54; max = maximum; min = minimum; SD = standard deviation; SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Analysis of covariance (ANCOVA); adjusted for multiple comparisons between treatment groups using Dunnett.

## Fatigue

**TABLE 24: FATIGUE, TENERE — INTENTION-TO-TREAT POPULATION, MIXED EFFECT MODEL WITH REPEATED MEASURES ANALYSIS**

| | TENERE | |
|---|---|---|
| **FIS Scores at Week 48[a]** | **TR 14 mg (N = 111)** | **Interferon (N = 104)** |
| **FIS total score** | | |
| N | 83 | 65 |
| LS mean change from baseline (SE) | 4.10 (3.03) | 9.10 (3.21) |
| *P* value | 0.18 | |
| **FIS cognitive dimension score** | | |
| N | 83 | 65 |
| LS mean change from baseline (SE) | 0.87 (0.84) | 2.34 (0.89) |
| *P* value | 0.16 | |
| **FIS physical dimension score** | | |
| N | 83 | 65 |
| LS mean change from baseline (SE) | 1.19 (0.87) | 1.51 (0.92) |
| *P* value | 0.76 | |
| **FIS psychosocial dimension score** | | |
| N | 83 | 65 |
| LS mean change from baseline (SE) | 2.70 (1.53) | 5.52 (1.62) |
| *P* value | 0.14 | |

EDSS = Expanded Disability Status Scale; FIS = Fatigue Impact Scale; LS = least square; MMRM = mixed effect model with repeated measures; SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[4]
[a]MMRM analysis adjusted for EDSS strata at baseline, region, visit, treatment by visit interaction, baseline values, and baseline by visit interaction.

**TABLE 25: FATIGUE, TEMSO AND TOWER — INTENTION-TO-TREAT POPULATION, MIXED EFFECT MODEL WITH REPEATED MEASURES ANALYSIS**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **FIS Scores at Week 48[a]** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** |
| **FIS total score** | | | | |
| n | 297 | 307 | 275 | 297 |
| LS mean change from baseline (SE) | 4.96 (1.49) | 4.11 (1.48) | 1.92 (1.63) | 4.67 (1.58) |
| *P* value | [b] | | [b] | |
| **FIS cognitive dimension score** | | | | |
| N | 297 | 307 | 275 | 297 |
| LS mean change from baseline (SE) | 1.18 (0.40) | 0.86 (0.39) | 0.64 (0.45) | 1.40 (0.43) |
| *P* value | [b] | | [b] | |
| **FIS physical dimension score** | | | | |
| N | 296 | 307 | 275 | 297 |
| LS mean change from baseline (SE) | 1.05 (0.41) | 0.71 (0.41) | 0.09 (0.44) | 0.82 (0.43) |
| *P* value | [b] | | [b] | |
| **FIS psychosocial dimension score** | | | | |
| N | 297 | 307 | 275 | 297 |
| LS mean change from baseline (SE) | 2.91 (0.77) | 2.71 (0.76) | 1.28 (0.83) | 2.56 (0.80) |
| *P* value | [b] | | [b] | |

EDSS = Expanded Disability Status Scale; FIS=Fatigue Impact Scale; LS = least square; MMRM = mixed effect model with repeated measures; SE = standard error; TR = teriflunomide.
Source: Clinical Study Reports.[2,3]
[a]MMRM analysis adjusted for EDSS strata at baseline, region and baseline value.
[b]*P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

**TABLE 26: FATIGUE, STUDY 2001 EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **FIS Scores at End Point[a]** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| **FIS total score** | | |
| N | 53 | 60 |
| Adjusted mean change from baseline (SE) | –1.49 (3.37) | 3.82 (3.45) |
| *P* value | 0.33 | |
| **FIS cognitive dimension score** | | |
| N | 53 | 60 |
| Adjusted mean change from baseline (SE) | –0.60 (0.99) | 1.17 (1.00) |
| *P* value | 0.25 | |
| **FIS physical dimension score** | | |
| N | 53 | 60 |
| Adjusted mean change from baseline (SE) | –0.67 (0.98) | 0.11 (1.00) |
| *P* value | 0.74 | |
| **FIS psychosocial dimension score** | | |
| N | 53 | 60 |
| Adjusted mean change from baseline (SE) | –0.06 (1.70) | 2.87 (1.74) |
| *P* value | 0.27 | |

FIS = Fatigue Impact Scale; SE = standard error; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a]Analysis of Covariance (ANCOVA); adjusted for multiple comparisons between treatment groups using Dunnett.

## Magnetic Resonance Imaging Outcomes

**TABLE 27: MAGNETIC RESONANCE IMAGING OUTCOMES, TEMSO — INTENTION-TO-TREAT POPULATION**

| | TEMSO | |
|---|---|---|
| **MRI Outcomes** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** |
| **Gd-enhancing T1 lesions per scan post baseline** | | |
| Patients with ≥1 Gd-enhancing T1 lesions, n (%) | 122 (35.9) | 211 (61.0) |
| Adjusted Gd-enhancing T1 lesions per scan (95% CI)[a] | 0.26 (0.17 to 0.41) | 1.33 (1.06 to 1.67) |
| Relative risk (95% CI) | 0.20 (0.12 to 0.32) | |
| *P* value | [b] | |

CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging; TR = teriflunomide.
Source: Clinical Study Report.[2]
[a]Poisson model with total number of Gd-enhancing T1 lesions as response variable, treatment, EDSS strata at baseline, region, and baseline number of Gd-enhancing T1 lesions as covariates, and log-transformed number of scans as an offset variable.
[b]*P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

**TABLE 28: MAGNETIC RESONANCE IMAGING OUTCOMES, STUDY 2001 — EFFICACY-EVALUABLE POPULATION**

| | STUDY 2001 | |
|---|---|---|
| **MRI Outcomes** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| **Number of T2 lesions for the treatment period** | | |
| N | 56 | 61 |
| New, adjusted mean (SE) | 0.42 (0.19) | 1.07 (0.19) |
| *P* value [a] | 0.008 | |
| New enlarging, adjusted mean (SE) | 0.22 (0.06) | 0.37 (0.06) |
| *P* value [a] | 0.09 | |

MRI = magnetic resonance imaging; SE = standard deviation; TR = teriflunomide.
Source: Clinical Study Report.[5]
[a] *P* value for between-group difference using rank analysis of covariance.

## Other Outcomes

**TABLE 29: HOSPITALIZATION AND USE OF INTRAVENOUS CORTICOSTEROIDS, PLACEBO CONTROLLED TRIALS**

| | TEMSO | | TOWER | | STUDY 2001 | |
|---|---|---|---|---|---|---|
| **Outcome** [a] | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** | **TR 14 mg (N = 56)** | **Placebo (N = 61)** |
| **Patients hospitalized due to relapse** | | | | | | |
| n (%) | 33 (9.2) | 71 (19.6) | 56 (15.1) | 81 (20.9) | NR | NR |
| AAR [b] | 0.057 | 0.139 | 0.100 | 0.151 | NR | NR |
| RRR (%) | 59.0 | | 33.6 | | NR | |
| *P* value | [c] | | [c] | | [c] | |
| **Patients using corticosteroids due to relapse** | | | | | | |
| n (%) | NR | NR | NR | NR | 8 (14.3) | 14 (23.0) |
| AAR [b] | 0.28 | 0.43 | 0.27 | 0.43 | NR | NR |
| RRR (%) | 34.0 | | 35.7 | | NR | |
| *P* value | [c] | | [c] | | [c] | |

AAR = adjusted annualized rate; NR = not reported; RRR = relative risk reduction; TR = teriflunomide.
Source: Clinical Study Reports.[2,3,5]
[a] Intention-to-treat population for TEMSO and TOWER; Efficacy-Evaluable population for Study 2001.
[b] AAR were derived using a Poisson model.
[c] *P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

**TABLE 30: MEDICATION ACCEPTANCE, TENERE — INTENTION-TO-TREAT POPULATION, MIXED EFFECT MODEL WITH REPEATED MEASURES ANALYSIS**

| | TENERE | |
|---|---|---|
| **TSQM Scores at Week 48** | **TR 14 mg (N = 111)** | **Interferon (N = 104)** |
| **Effectiveness** | | |
| N | 84 | 69 |
| LS mean (SE) | 63.1 (2.7) | 59.3 (3.0) |
| *P* value | 0.28 | |
| **Side effects** | | |
| N | 84 | 69 |
| LS mean (SE) | 93.1 (2.3) | 71.4 (2.5) |
| *P* value | < 0.0001 | |
| **Convenience** | | |
| N | 85 | 70 |
| LS mean (SE) | 89.9 (2.0) | 61.9 (2.1) |
| *P* value | < 0.0001 | |
| **Global satisfaction** | | |
| N | 84 | 70 |
| LS mean change from baseline (SE) | 68.8 (2.8) | 61.0 (2.9) |
| *P* value | 0.02 | |

LS = least square; SE = standard error; TR = teriflunomide; TSQM = Treatment Satisfaction Questionnaire for Medication.
Source: Clinical Study Report.[4]

## Subgroups

**TABLE 31: ANNUALIZED RELAPSE RATE AND DISABILITY ACCORDING TO TREATMENT EXPERIENCE, TEMSO AND TOWER — INTENTION-TO-TREAT POPULATION**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **ARR and Disability** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** |
| **Prior use of DMT in last 2 years, n (%)** | | | | |
| Yes | 102 (28.5) | 90 (24.8) | 126 (34.1) | 135 (34.8) |
| No | 256 (71.5) | 273 (75.2) | 244 (65.9) | 253 (65.2) |
| **Adjusted ARR (95% CI)[a]** | | | | |
| DMT use, yes | 0.47 (0.33 to 0.66) | 0.78 (0.58 to 1.05) | 0.42 (0.32 to 0.55) | 0.54 (0.42 to 0.68) |
| DMT use, no | 0.31 (0.25 to 0.40) | 0.45 (0.38 to 0.54) | 0.26 (0.21 to 0.33) | 0.47 (0.38 to 0.57) |
| *P* value for interaction[b] | 0.53 | | 0.13 | |
| **Probability of disability progression sustained for 12 weeks at 108 weeks (95% CI)[c]** | | | | |
| DMT use, yes | 0.20 (0.12 to 0.29) | 0.36 (0.25 to 0.47) | 0.17 (0.09 to 0.25) | 0.25 (0.17 to 0.33) |
| DMT use, no | 0.20 (0.15 to 0.26) | 0.25 (0.19 to 0.30) | 0.15 (0.10 to 0.20) | 0.17 (0.12 to 0.22) |
| *P* value for interaction[d] | 0.15 | | 0.17 | |

ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; TR = teriflunomide.
Source: Clinical Study Reports.[2,3]
[a]Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline, and region as covariates, and log-transformed standardized study duration as an offset variable.
[b]Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline, region, prior MS drug use, and treatment by MS drug use interaction as covariates, and log-transformed standardized study duration as an offset variable.
[c]Derived from Kaplan–Meier estimates.
[d]Derived from Cox proportional hazard model with treatment, EDSS strata at baseline and region, prior MS drug use, and treatment by prior MS drug use as covariates.

**TABLE 32: ANNUALIZED RELAPSE RATE AND DISABILITY ACCORDING TO BASELINE EXPANDED DISABILITY STATUS SCALE SCORES, TEMSO AND TOWER — INTENTION-TO-TREAT POPULATION**

| | TEMSO | | TOWER | |
|---|---|---|---|---|
| **ARR and Disability** | **TR 14 mg (N = 358)** | **Placebo (N = 363)** | **TR 14 mg (N = 370)** | **Placebo (N = 388)** |
| **Adjusted ARR (95% CI)[a]** | | | | |
| EDSS ≤3.5 | 0.30 (0.25 to 0.37) | 0.50 (0.43 to 0.59) | 0.28 (0.23 to 0.35) | 0.45 (0.38 to 0.54) |
| EDSS >3.5 | 0.43 (0.31 to 0.60) | 0.47 (0.36 to 0.63) | 0.38 (0.29 to 0.51) | 0.58 (0.45 to 0.75) |
| *P* value for interaction[b] | 0.07 | | 0.74 | |
| **Probability of disability progression sustained for 12 weeks at 108 weeks (95% CI)[c]** | | | | |
| EDSS ≤3.5 | 0.22 (0.17 to 0.27) | 0.26 (0.20 to 0.31) | 0.17 (0.12 to 0.23) | 0.20 (0.15 to 0.26) |
| EDSS >3.5 | 0.14 (0.05 to 0.22) | 0.34 (0.22 to 0.46) | 0.12 (0.04 to 0.20) | 0.17 (0.09 to 0.26) |
| *P* value for interaction[d] | 0.07 | | 0.73 | |

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; TR = teriflunomide.

Source: Clinical Study Reports.[2,3]

[a]Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed standardized treatment duration as an offset variable.

[b]Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline, region, prior MS drug use and treatment by MS drug use interaction as covariates, and log-transformed standardized study duration as an offset variable.

[c]Derived from Kaplan–Meier estimates.

[d]Derived from Cox proportional hazard model with treatment, EDSS strata at baseline and region and treatment by EDSS strata at baseline interaction as covariates.

# APPENDIX 4: EXCLUDED STUDIES

| Reference | Reason for Exclusion |
|---|---|
| Confavreux C, Li DK, Freedman MS, Truffinet P, Benzerdjeb H, Wang D, et al. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler. 2012 Sep;18(9):1278-89. | Wrong study design |

# APPENDIX 5: VALIDITY OF OUTCOME MEASURES

***Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.***

**Objective**

To summarize the characteristics of the following outcome measures:

- Expanded Disability Status Scale (EDSS)
- European Quality of Life Scale (EQ-5D)
- Fatigue Impact Scale (FIS)
- Multiple Sclerosis Functional Composite (MSFC)
- Multiple Sclerosis Quality of Life-54 items (MSQOL-54)
- Short Form-36 (SF-36)
- Treatment Satisfaction Questionnaire for Medication (TSQM).

Information on validity, reliability, and minimally clinically important difference (MCID) is presented when available.

**Findings**

**Expanded Disability Status Scale**

EDSS is an ordinal scale used to measure disability in multiple sclerosis (MS). It relies on identification of eight functional systems (FS) (plus "other"). These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately on a scale of 0 (normal) to either 5 or 6.[35] The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates FS grades as well as the degree of functional disability and ambulation (Table 33). Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically biphasic, accumulating around 2 to 3 points, and 6 to 7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, including the fact that it has only modest intra-rater reliability, low reproducibility, poor assessment of upper limb and cognitive function, and it lacks linearity.[36-39] Other flaws include that it is an arbitrary scale with limited and discrete levels of disability, that it relies heavily on evaluation of motor function and ability to walk, and that it requires a subjective evaluation of disability using a parametric scale.

According to the clinical expert consulted for this review, a sustained change of 0.5 in EDSS is clinically relevant.

**TABLE 33: SCORING OF EXPANDED DISABILITY STATUS SCALE**

| | Normal neurological exam (all grade 0 in FS; cerebral grade 1 acceptable) |
|---|---|
| 1 | No disability, minimal signs in one FS (i.e., grade 1 excluding Cerebral grade 1) |
| 1.5 | No disability, minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1) |
| 2.0 | Minimal disability in one FS (one FS grade 2; other 0 or 1) |
| 2.5 | Minimal disability in two FS (two FS grade 2, others 0 or 1) |
| 3.0 | Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory |
| 3.5 | Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1) |
| 4.0 | Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 m |
| 4.5 | Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistances; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 m |
| 5.0 | Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0) |
| 5.5 | Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0) |
| 6.0 | Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 m with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+) |
| 6.5 | Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 m without resting. (Usual FS equivalents are combinations with more than two FS grade 3+) |
| 7.0 | Unable to walk beyond about 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone) |
| 7.5 | Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+) |
| 8.0 | Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems) |
| 8.5 | Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems) |
| 9.0 | Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+) |
| 9.5 | Totally helpless bed patient; unable to communicate effectively or eat or swallow. (Usual FS equivalents are combinations, almost all grade 4+) |
| 10.0 | Death due to MS |

FS = functional system; MS = multiple sclerosis.

**European Quality of Life Scale**

The EQ-5D is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[40,41] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[40,41] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system
- A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores lower than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale, although not specific for MS patients, have ranged from 0.033 to 0.074.[42]

*Validity*: No studies specifically validating EQ-5D in patients with MS were identified. As with any generic HRQoL instrument, there is the possibility that items important to patients with a specific disease may be missed by the EQ-5D, or that the instrument may lack sufficient sensitivity to detect clinically important changes. A recent Canadian study reported that the EQ-5D identified only four of 10 domains identified as important by patients with MS; the missed domains were fatigue, sports, social life, relationships, cognition, and balance. Furthermore, the instrument overestimated utility scores compared with a disease-specific measure.[43]

**Fatigue Impact Scale**

The FIS was developed to evaluate the impact of fatigue on the lives of people with MS.[44] It consists of a total score and three subscales to assess the impact of fatigue on cognitive function (10 items), physical function (10 items), and psychosocial function (20 items).[44] Each FIS is ranked on a scale of 0 (no problem) to 4 (extreme problem). FIS total score ranges from 0 to 160, with a higher score indicating more severe fatigue levels.[45] Psychometric properties and MCID in MS patients are provided below.

*Reliability*: FIS has good internal consistency reliability (Cronbach's alpha 0.97 for total score and > 0.92 for subscale items).[44] Intra-class coefficients of 0.76 and 0.81 (FIS total score) have been reported in one study.[46]

*Face validity:* A qualitative evaluation based on expert opinions (N = 30) does not support the face validity of FIS, as it is determined that all 40 items are not specific to fatigue impact.[44]

*Convergent validity (correlation with other scales)*: The correlation between FIS total score and three other instruments (the MS Impact Scale – physical (MSIS-29), the MS Walking Scale (MSWS-12), and the General Health Questionnaire [GHQ-30]) is modest (r = 0.72, r = 0.55, and r = 0.63, respectively) as determined in one study with 333 survey participants.[44]

*MCID*: The MCID of the total FIS score ranges from 10 to 20 points.[45]

**Multiple Sclerosis Functional Composite**

The MSFC is a measure of disability developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[47,48] Items were selected by analyzing longitudinal datasets from clinical trials and natural history studies to identify clinically relevant variables with good measurement properties. The MSFC assesses different clinical dimensions: arm (9-HPT = time to insert and remove nine pegs), leg (T25-FW = time to walk 25 feet) and cognition (PASAT3 = number of correct additions). The raw scores for each item are transformed into Z-scores in order to achieve a common metric, in standard deviation units. A Z-score represents the number of standard deviations a patient's test result is higher (Z > 0) or lower (Z < 0) than the average test result (Z = 0) of the reference population. The mean and standard deviation from test results at the baseline visit for all patients in each study was used as the reference population values to create the Z-scores for each component of the composite. The Z-score is calculated by subtracting the mean of the reference population from the test result and then dividing by the standard deviation of the reference population. For T25-FW and 9-HPT, a higher test result means the patient worsened from baseline. For PASAT3, a higher test result means that the patient improved from baseline. In order to ensure that all measures are in the same direction, a transformation is necessary. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[47] Psychometric properties and MCID in MS patients are provided below.

*Test-retest reliability*: Intra-class coefficients of 0.87 to 0.96 have been reported.[48]

*Construct validity*: MSFC scores were lower in more disabled patients (–0.4 in primary progressive MS, –0.3 in secondary progressive MS versus +0.42 in relapsing-remitting MS).[48]

*Convergent validity (correlation with EDSS)*: A study by Ozakbas et al. (N = 38) found a significant correlation between EDSS and MSFC.[36] In looking at individual components, the EDSS had the lowest correlation (r = 0.31) with the PASAT, and the authors suggested that this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25WT (r = 0.84) followed by 9-HPT (r = 0.51), which was only moderately correlated, again consistent with the observation of poor assessment of upper limb function by EDSS.[36]

*MCID*: A 20% change in scores on T25-FW and 9-HPT and a 0.5 SD change on PASAT3 are considered clinically meaningful; a clinically meaningful value for overall MSFC score has not been determined.[48]

**Short Form-36**

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS). The PCS and MCS and eight

dimensions are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 10 points in each dimension or 5 points in each component summary indicates a clinically meaningful improvement as determined at the discretion of the patient. An MCID for SF-36 was not identified for MS patients. Psychometric properties in MS patients are provided below.

*Reliability*: Internal consistency reliability was measured in one Dutch study (N = 187).[49] Cronbach's alpha ranged from 0.71 (bodily pain) to 0.93 (physical functioning). In another study (N = 149), Cronbach's alpha ranged from 0.77 to 0.94.[50]

Test-retest correlation coefficients varied from 0.46 to 0.87 in the Dutch study.[49] Coefficients were the lowest for the dimensions role–physical functioning (r = 0.48), social functioning (r = 0.50), and role–emotional functioning (r = 0.46). The physical functioning (r = 0.87) and vitality (r = 0.71) dimensions obtained the highest scores.[49]

*Construct validity*: SF-36 showed good construct validity for PCS and three dimensions: social functioning, physical functioning, and role–physical functioning, as it could differentiate between different levels of disease severity.[50]

*Convergent validity (correlation to EDSS)*: The relation between EDSS and SF-36 scales was examined using regression analyses in one study by Janssens et al. (2003).[51] Unadjusted analyses showed that EDSS was significantly related to all SF-36 physical and mental health scales. After adjustment for anxiety and depression, EDSS was significantly related only to the SF-36 physical functioning, role–physical functioning, and bodily pain scales, but not SF-36 mental health scales and the general health scale.[51] Another study[52] determined that low scores on the SF-36 mental health scale were correlated with increased (worsened) EDSS scores at one year (r = –0.29, *P* = 0.006). The results were not altered by adjusting for disease activity at baseline.[52]

**Multiple Sclerosis Quality of Life-54 items**

The MSQOL-54 is a self-reported disease-specific quality of life instrument developed in the US in 1995.[53,54] It is based on the SF-36 instrument, which was supplemented with 18 disease-specific dimensions measuring 1) anxiety provoked by the patient's health status (four items), sexual functioning (four items), satisfaction with sex life (one item), overall quality of life (two items), cognitive functioning (four items), energy (one item), pain (one item), and social functioning (one item). The instrument has Likert scales and multiple-choice items.[54] There is no single overall score for MSQOL-54. Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (scale scores range from 0 to 100 and a higher scale score indicates improved quality of life).[5] In addition, the multiple item scales of each of these scores can be analyzed individually to understand more clearly the changes on the composite scores. The physical health composite score is computed from the individual scores of the following scales: physical function, health perceptions, energy and fatigue, role limitations – physical, pain, sexual function, social function, and health distress. The mental health composite score is computed from the individual scores of the following scales: health distress, overall quality of life, emotional well-being, role limitations – emotional, and cognitive function.[5] No MCIDs were identified for the summary scores. Psychometric properties in MS patients are provided below.

*Reliability*: MSQOL-54 has good internal consistency reliability (Cronbach's alpha 0.75 to 0.96 scale items).[53] Intra-class coefficients ranged from 0.67 to 0.96.[53]

*Construct validity*: Statistically significant differences between patients with mild versus patients with moderate symptoms were found for physical function, health distress, and physical health composite. The role limitations due to emotional problems and the cognitive function scales were the least sensitive to group differences.[53]

**Treatment Satisfaction Questionnaire for Medication**

The TSQM is a generic instrument that measures patients' satisfaction with medication and can be used with diseases of any sort, according to the developers.[35] The questionnaire is self-administered and is intended for an adult population. TSQM consists of 14 items with a recall period of two to three weeks or since the last medication use. TSQM has four scales that address effectiveness (three items), side effects (five items), convenience (three items), and global satisfaction (three items). Using a continuous bipolar scale anchored by seven boxes with the words "Extremely Satisfied" and "Extremely Dissatisfied" at each end, item scores are transformed to a linear scale of 0 to 100 (with higher scores representing higher satisfaction in each scale).[35]

TSQM was developed by Atkinson et al. (2004).[35] The validation study assessed the questionnaire among 567 patients from eight diverse patient groups (arthritis, asthma, major depression, Type I diabetes, high cholesterol, hypertension, migraine, and psoriasis). Patients were recruited from a national longitudinal panel study of chronic illness and were randomized to complete the questionnaire using either visual analogue or Likert-type scaling methods. Statistical analyses supported the reliability and construct validity of TSQM scales. Two separate multi-step exploratory factor analyses were employed. Overall, the four scales possessed good psychometric properties, and the Likert-type scaling method was superior to the visual analogue scale method. Statistically significant differences in TSQM scores were found when factors such as level of illness severity, length and time on medication, and route of medication administration were assessed. No MCID for TSQM was identified for MS patients.

**Summary**

A summary of the characteristics of seven instruments employed in the teriflunomide trials included in the systematic review was provided: one measuring fatigue (using FIS), two measuring disability (with EDSS and MSFC), three measuring health-related quality of life (including EQ-5D, SF-36, and MSQOL-54), and one measuring treatment (medication) satisfaction (TSQM).

With respect to the reliability and validity of the instruments:

- FIS has good internal consistency reliability and test-retest reliability. It is moderately correlated to other MS scales.
- MSFC shows good construct validity but is only moderately correlated to EDSS.
- The reliability and validity of EQ-5D has not been determined in MS patients specifically. MSQOL-54 has good internal consistency reliability, test-retest reliability, and construct validity. SF-36 has good internal consistency reliability and test-retest reliability was low to high, depending on the dimension. Construct validity was good for physical-type dimensions.
- The reliability and validity of TSQM have not been determined in MS patients.

There is no MCID information for EDSS, EQ-5D, MSQOL-54, SF-36, and TSQM specific to MS. The MCID of FIS total score ranges from 10 to 20 points. A 20% change in scores on T25-FW and 9-HPT, and a 0.5 SD change on PASAT3 are considered clinically meaningful in MSFC; however, an MCID for overall MSFC score has not been determined.

# APPENDIX 6: SUMMARY OF EXTENSION STUDIES

**Objective**

The aim of this supplemental issue is to provide a brief summary of the Study 2001 extension and the TEMSO extension safety evaluation. Results from patients in the 7 mg teriflunomide group are not considered here.

**Study Characteristics**

**Study 2001 Extension**

Study 2001 extension was an extension of a 36-week randomized double-blind study in which patients with relapsing multiple sclerosis (MS) were randomized to placebo, 7 mg, or 14 mg teriflunomide daily.[32,55] Patients who completed the core study and who wished to continue to the open-label extension either stayed on their current treatment (if they had been randomized to teriflunomide) or were re-randomized from placebo to either teriflunomide 7 mg or teriflunomide 14 mg. Of the 179 patients who started Study 2001, 160 completed the trial and 147 participated in the extension trial, 66 of whom received 14 mg teriflunomide for the duration of the extension (21 patients re-randomized from placebo and 45 patients who received 14 mg teriflunomide for the core study). Outcomes were measured every 12 weeks in the extension and the publication available[55] reported outcomes up to week 372 following the start of the core study. Mean follow-up (from the start of the core study to the interim analysis of the extension) was 5.6 years (standard deviation [SD] 2.7 years). Baseline characteristics for patients who continued to the extension study were not reported. Further detail is presented in Table 34.

**TEMSO Extension**

TEMSO was a 108-week randomized, double-blind study in which patients with relapsing MS were randomized to placebo, 7 mg, or 14 mg teriflunomide daily. Patients who completed the core study (N = 798) were eligible to continue to the blinded extension study.[32] Patients who had been randomized to teriflunomide in the core study continued on teriflunomide (250 patients from the 14 mg group continued to receive 14 mg teriflunomide) and patients in the placebo group were re-randomized to either 7 mg or 14 mg teriflunomide (107 patients in the placebo to 14 mg group). The total duration of treatment for those who participated in the extension was 288 weeks. Mean follow-up was not available. Baseline characteristics for patients who continued on to the extension study were not reported. Further detail is presented in Table 34.

**TABLE 34: STUDY CHARACTERISTICS OF THE EXTENSION STUDIES**

| | Study 2001 Extension[32,55] | TEMSO Extension[32] |
|---|---|---|
| Study design; other study details | After original study completion, patients originally randomized to teriflunomide continued their assigned treatment; those in the placebo group were reallocated to teriflunomide, 7 mg[a] or 14 mg, according to a predefined randomization schedule. The extension was open label<br><br>Adverse events monitored every 12 weeks<br><br>Study duration (including core study and extension):<br>Mean: 5.6 years; SD 2.7 years<br>Median: 7.1 years; range 0.5 to 8.5 years<br><br>Outcomes are for week 372<br><br>Cumulative treatment exposure: 360.90 patient-years | After original study completion, patients originally randomized to teriflunomide continued their assigned treatment (blinded); those in the placebo group were reallocated to teriflunomide, 7 mg[a] or 14 mg. Post-treatment phase of 16 weeks planned for all patients discontinuing study drug, with a washout procedure to accelerate teriflunomide elimination<br><br>Total duration of treatment: 288 weeks<br><br>Cumulative treatment exposure: 760.47 patient-years<br><br>Only safety outcomes available |
| Number of patients randomized and completing original study | 179 (160; 7 mg = 57, PL = 58, 14 mg = 45) | NR in the report; 1,088 randomized and 798 completed TEMSO[24] |
| Number of patients in extension | 7 mg = 81 (24 re-randomized from placebo); 14 mg = 66 (21 re-randomized from placebo)[a] | Unclear in the report |
| Safety analysis (n) | 66 | 14 mg – 14 mg: 250<br>PL – 14 mg: 107 |
| ITT (n) | NR | NR |
| Patient characteristics | NR for extension | NR |

ITT = intention-to-treat; NR = not reported; PL = placebo; SD = standard deviation.
[a]Only the 14 mg dosing is considered in this report.

## Results

### Efficacy Outcomes

**Study 2001 Extension:** At the 372 week follow-up, the annualized relapse rate (ARR) for patients who were re-randomized from the placebo group to the teriflunomide 14 mg group was 0.213 (SD not reported) and for patients who received teriflunomide 14 mg from the start of the core study was 0.181 (SD not reported).[32,55] These were lower than in the core study, where the ARRs were 0.55 (SD 1.12) in the 14 mg group and 0.81 (SD 1.22) in the placebo group; however, it is not known if this is statistically significant. The number of patients with ≥ 1 relapse was 42.3% in patients who moved from placebo to teriflunomide 14 mg and 45.0% for those who received 14 mg teriflunomide from the start of the core study. This was higher than the rates in the core study (23.2% for the 14 mg group and 37.7% in the placebo group); however, this is expected, as the extension was significantly longer than the randomized controlled trial (RCT).

Mean change from baseline (from the core study to the extension analysis) in the Expanded Disability Status Scale (EDSS) in the extension study was 0.61 (SD 1.11) in the 14 mg to 14 mg group and –0.17 (SD 1.25) in the placebo to 14 mg group (*P* values not reported). In the primary study, the mean changes from baseline were –0.10 (SD 0.52) in the 14 mg group and 0.02 (SD 0.68) in the placebo group. Further detail and other efficacy outcomes are presented in Table 35.

**TEMSO Extension:** No efficacy outcomes were available for the TEMSO study.[32]

**TABLE 35: EFFICACY OUTCOMES REPORTED IN THE EXTENSION STUDIES**

| Efficacy Outcome | Study 2001 Extension[32,55] | | TEMSO Extension[32] |
|---|---|---|---|
| | 14 mg – 14 mg | PL – 14 mg | No efficacy outcomes available for the TEMSO extension |
| ARR | 0.181 | 0.213 | |
| Patients with ≥1 relapse, n | 18 (45.0%) | 11 (42.3%) | |
| Number of New T2 lesions, mean (SD) | 0.83 (1.76) | 0.33 (0.78) | |
| Number of Newly active T2 lesions, mean (SD) | 0.13 (0.45) | 0.33 (0.49) | |
| Number of Gd-enhancing T1 lesions, mean (SD) | 0.00 (0.00) | 1.7 (3.6) | |
| Disability progression | | | |
| EDSS mean at week 372, (SD) | 2.41 (1.55) | 1.58 (1.16) | |
| EDSS mean (SD) change from baseline | 0.61 (1.11) | –0.17 (1.25) | |

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; Gd = gadolinium; PL = placebo; SD = standard deviation.

**Safety Outcomes**

**Study 2001 Extension:** All of the patients in both the core study and extension study had at least one treatment emergent adverse event (TEAE); this led to discontinuation of treatment in approximately 20% of patients in both phases of the study.[32,55] The number of patients with treatment emergent serious adverse events (TESAEs) was higher in the extension study (28.8% of patients experienced a TESAE, 13.6% of whom discontinued due to the event) than in the primary study (approximately 12% of patients); however, with the much longer length of the extension, this is not a surprising result. The most common TEAEs in the extension study were nervous system adverse events (92.4%), infections (84.8%), and musculoskeletal or connective tissue adverse events (80.3%). Infections or infestations were also commonly experienced in the core study (47% of patients). Hepatic adverse events occurred in 45% of patients in the 14 mg to 14 mg group and 38.5% in the placebo to 14 mg group. Further detail regarding other safety outcomes is presented in Table 36.

**TEMSO Extension:** The majority of patients in the core TEMSO study and the extension experienced at least one TEAE.[32] More patients in the core study (14 mg: 90.9%; placebo: 87.5%) experienced events than in the extension (84% in the 14 mg to 14 mg group and 86% in the placebo to 14 mg group). Serious adverse events occurred in 12% of patients in the 14 mg group and 10.3% in the placebo to 14 mg group; this is fairly similar to the number of TESAEs in the core study, where approximately 12% of patients experienced one. Hepatic adverse events occurred in 14.4% of patients in the 14 mg to 14 mg group and 20.6% in the placebo to 14 mg group. Further detail regarding other safety outcomes is presented in Table 36.

**TABLE 36: HARM AND ADVERSE EVENT OUTCOMES IN THE EXTENSION STUDIES**

| Outcome | Study 2001 Extension[32,55] | | TEMSO Extension[32] | |
|---|---|---|---|---|
| | | | 14 mg – 14 mg | PL – 14 mg |
| Any TEAE | 66 (100%) | | 210 (84%) | 92 (86%) |
| Discontinuation due to TEAE | 13 (19.7%) | | 15 (6%) | 7 (6.5%) |
| Any treatment emergent SAE | 19 (28.8%) | | 30 (12%) | 11 (10.3%) |
| Discontinuation due to treatment emergent SAE | 9 (13.6%) | | NR | NR |
| Death | 1 patient | | 1 (0.4%)[a] | 0 |
| Infections | 56 (84.8%) | | NR | NR |
| GI AEs | 50 (75.8%) | | NR | NR |
| Nervous system AEs | 61 (92.4%) | | NR | NR |
| Skin and subcutaneous tissue AEs | 42 (63.6%) | | NR | NR |
| Musculoskeletal and connective tissue | 53 (80.3%) | | NR | NR |
| Psychiatric AEs | 34 (51.5%) | | NR | NR |
| General | 52 (78.8%) | | NR | NR |
| Renal and urinary | 23 (34.8%) | | NR | NR |
| Any hepatic TEAE | 18 (45%) | 10 (38.5%) | 36 (14.4%) | 22 (20.6%) |
| Hepatobiliary disorder | 2 (5%) | 0 | 0 | 2 (1.9%) |

AE = adverse event; GI = gastrointestinal; NR = not reported; PL = placebo; SAE = serious adverse event; TEAE = treatment emergent adverse event.
[a]TEAE leading to death.

**Summary**

During the extension phase of Study 2001 (during which all patients received teriflunomide), the ARR did not differ appreciably between patients who were originally randomized to placebo and those who had originally been randomized to teriflunomide 14 mg. In addition, ARRs were lower during the extension phase than during the double-blind comparative phase, for both groups, and the number of patients with at least one relapse was more than 40% in both patients who were in the placebo to teriflunomide 14 mg group and those who received 14 mg of teriflunomide from the start of the core study. This was higher than the rates in the core study (23.2% for the 14 mg group and 37.7% in the placebo group); however, this is expected, as the extension was significantly longer than the RCT. In both extension studies, the longest of which had a mean follow-up of 5.6 years, the majority of patients experienced adverse events, but most were not serious and most did not lead to discontinuation.

# APPENDIX 7: SUMMARY OF INDIRECT COMPARISON

**Objective**

The objective of this supplemental issue is to summarize and critically appraise the manufacturer-provided mixed treatment comparison (MTC)[1] comparing teriflunomide with other disease-modifying treatments (DMT) for the management of relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS). For this review, MTC is used interchangeably with network meta-analysis (NMA).

**Summary of Network Meta-analysis**

**Rationale**

The primary objective of the MTC and pairwise meta-analysis (MA) was to quantitatively examine the clinical efficacy and safety of teriflunomide compared with other DMTs for the management of RRMS and SPMS.

**Methods**

**Literature Search**

The literature search appeared to be comprehensive, comprising three databases and covering the period from January 1, 1980 to November 12, 2012.

**Intervention and Comparators**

The interventions to be included in the systematic review and/or MTC were not clearly stated. From an examination of the data extraction tables, it appeared that the manufacturer included both DMTs currently approved by Health Canada for the treatment of multiple sclerosis (MS) (teriflunomide, intramuscular [IM] interferon beta-1a, subcutaneous [SC] interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, natalizumab, and fingolimod), and DMTs not currently approved by Health Canada for MS (mitoxantrone, rituximab, and daclizumab). Alemtuzumab (a DMT currently approved by Health Canada for treatment of MS) was not included in the manufacturer-provided MTC. No rationale for the DMTs selected for inclusion was stated. The manufacturer's submission only provided MTC results for the Health Canada–approved DMTs, despite the inclusion of non-Health Canada–recommended DMTs in the MTC.

**Study Eligibility Criteria**

The study eligibility criteria for inclusion in the base-case MTC were:

- single- or double-blinded randomized placebo and randomized controlled trials (RCTs)
- patient recruitment from the year 2000 onward
- ≥ 80% of the study population with RRMS.

These eligibility criteria were chosen following a feasibility assessment to determine which trials should be included in the MTC analyses. The manufacturer stated that due to the changes in diagnostic criteria for RRMS (from the Poser to the McDonald criteria) that took place in approximately the year 2000, limiting inclusion to trials that began patient recruitment from the year 2000 and onward would reduce heterogeneity and increase comparability between trials. A quality assessment of individual trials included in the analyses was conducted and reported according to the National Institute for Health and Care Excellence (NICE) Criteria Assessment (NICE 2009) in the manufacturer's submission. However, it is unclear whether the inclusion for the MTC analyses applied any quality standard.

**Outcomes**

Direct meta-analyses and bayesian MTC analyses were conducted for five outcomes:

- annualized relapse rate (ARR); rate ratio (RR) calculated modelling the number of total events in each group as following a Poisson distribution
- proportion of relapse-free patients; odds ratio (OR) calculated for remaining relapse free
- three-month sustained accumulation of disability (SAD); hazard ratio (HR) calculated
- all-cause treatment discontinuation; OR calculated
- treatment discontinuation due to adverse events (DAE); OR calculated.

Results for ARR, three-month SAD, and all-cause treatment discontinuation from the MTC were used as inputs into the manufacturer's cost-utility analysis.

**Data Extraction and Analysis**

Data were extracted from published trials; however, unpublished data from three teriflunomide trials (TOWER, TEMSO, and TENERE) were also employed.

No graphical depictions of evidence networks were provided to demonstrate linkages between treatments based on the identified studies. These graphs are helpful to illustrate indirect comparisons or MTC as indicated by a closed loop. Data extraction tables for each outcome are provided for all trials, but it is not readily apparent which trials are included in the base-case or sensitivity analyses.

Both pairwise (frequentist) random effects meta-analyses and bayesian random effects MTC were conducted. Each treatment was compared to placebo followed by the comparison between teriflunomide and other DMTs. Random-effect bayesian MTC analyses compared all DMTs in a single model by applying a vague prior. No information was provided as to, for example, the assumptions associated with the specific model used for each outcome (Poisson regression or logistic regression), modelling diagnosis and model fit, etc. In response to a request from the Common Drug Review (CDR), the analysis results of the fixed model analysis were provided, as well as some information on deviance information criterion. It remains unclear how these models were finally selected.

As indicated in the manufacturer-provided report, it appeared there was significant potential for heterogeneity among the studies regarding patient baseline characteristics and study duration, including, for example, baseline relapse rate, Expanded Disability Status Scale (EDSS) score, disease duration, disease severity, previous treatments, and best supportive care. Sensitivity analyses were performed based on pre-specified subsets of the study population. The four sensitivity analyses included in the manufacturer's submission were all studies regardless of year and all relapsing MS population, all studies regardless of year with ≥ 80% RRMS, all studies recruiting from 2000 onward with 100% RRMS, and studies with at least one year of follow-up recruiting from 2000 onward and ≥ 80% RRMS. The sensitivity analyses were conducted to assess the impact of a significant change in disease diagnosis criteria from the Poser to the McDonald. The exclusion of earlier studies was expected to increase the comparability in terms of baseline relapse rate between studies. However, no assessment was conducted or reported regarding the impacts of other aspects of potential heterogeneities on the MTC. No assessment was available on whether the assumptions of similarity and consistency held for the analyses.

Critical appraisal of the included studies was performed by the investigators performing the MTC, using the NICE Quality Assessment of Trials tool. This includes the study design (randomization, concealment of allocation, blinding), execution (dropout rates), data analysis (intention-to-treat population), and

selective reporting of outcomes. However, although information was provided on the results of quality assessment, no information was provided as to whether this assessment had an impact on the study selection. Moreover, no information was available on the assessment of study heterogeneity (i.e., statistical testing) in the manufacturer's report. In principle, the possible impacts on the internal validity of the MTC analysis from the recognized heterogeneity among studies should be appropriately assessed. Subsequent to a request from CDR, the manufacturer provided results for both base-case and "all-years" sensitivity analyses for the outcomes three-month SAD, ARR, and discontinuation, adjusted for baseline ARR.

No rationale was provided for reporting ORs, rather than relative risks, for a number of dichotomous outcomes, and it is unclear how the HR was calculated for three-month SAD.

**Results**

**Study and Patient Characteristics:** In total, 52 primary trials were identified, 30 of which were included in the base-case analysis. In 21 of these trials, patient recruitment took place after 2000, and for the remaining nine trials, recruitment was assumed to be after 2000 on the basis of publication year. Twenty-five of the trials included in the base case used the McDonald criteria (year not specified) for MS diagnosis.

**Results of the Network Meta-analysis**

*ARRs:* The base-case MTC network for ARR was reported to include 28 trials.

***Disease-modifying Treatments versus Placebo:***

In both the pairwise MA and the MTC analyses, ARRs were significantly lower for all of the DMTs when compared with placebo. The RR for teriflunomide 14 mg resulting from the MTC base case (0.67; 95% credible interval (CrI), 0.57 to 0.77) was similar to that of GA and SC interferon beta-1a and interferon beta-1b. The greatest rate reduction relative to placebo was for natalizumab (RR: 0.31; CrI, 0.25 to 0.39). Table 37 contains further detail.

***Teriflunomide versus Other Disease-modifying Treatments:***

When compared with other DMTs, teriflunomide 14 mg showed no significant differences compared with SC IFN beta-1a 44mcg, IFN beta-1b 250 mcg, IFN beta-1a 30mcg, or glatiramer acetate. Dimethyl fumarate, fingolimod, and natalizumab resulted in significantly lower annualized relapse rates (higher ARR ratios) compared with teriflunomide. These results were consistent for both the base-case and sensitivity analyses. Table 38 contains further detail.

**Proportion of Relapse-Free Patients**

***Disease-modifying Treatments versus Placebo:***

When compared with placebo, only IM IFN beta-1a 30 mcg was not found to be significantly different with respect to the proportion of patients free from relapse in the MTC (1.39 CrI, 0.97 to 1.98). Pairwise MA was not performed for all comparisons. Table 39 contains further detail.

**TABLE 37: ANNUALIZED RELAPSE RATE RATIOS FOR DISEASE-MODIFYING TREATMENTS VERSUS PLACEBO IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Intervention | Analysis | Base Case | Sensitivity Analysis | | | |
|---|---|---|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations | All Years and ≥ 80% RRMS | Recruitment ≥ 2,000 and 100% RRMS | Recruitment ≥ 2,000, ≥ 80% RRMS and ≥ 1 Year Follow-up |
| **RR (95% CrI), versus placebo[a]** | | | | | | |
| Teriflunomide 14 mg | Pairwise MA | 0.66 (0.59 to 0.75) | 0.66 (0.59 to 0.75) | 0.66 (0.59 to 0.75) | 0.64 (0.57 to 0.73) | 0.66 (0.59 to 0.75) |
| | MTC | 0.67 (0.57 to 0.77) | 0.67 (0.59 to 0.76) | 0.67 (0.58 to 0.76) | 0.65 (0.56 to 0.76) | 0.67 (0.57 to 0.78) |
| IFN beta-1b 250 mcg | Pairwise MA | NA | 0.65 (0.59 to 0.72) | NA | NA | NA |
| | MTC | 0.68 (0.52 to 0.88) | 0.67 (0.61 to 0.73) | 0.68 (0.60 to 0.79) | 0.68 (0.51 to 0.91) | 0.69 (0.53 to 0.89) |
| IM IFN beta-1a 30 mcg | Pairwise MA | NA | 0.77 (0.68 to 0.87) | 0.77 (0.68 to 0.87) | NA | NA |
| | MTC | 0.78 (0.67 to 0.91) | 0.80 (0.72 to 0.89) | 0.79 (0.71 to 0.89) | 0.78 (0.67 to 0.91) | 0.78 (0.68 to 0.92) |
| SC IFN beta-1a 44 mcg | Pairwise MA | NA | NA | NA | NA | NA |
| | MTC | 0.62 (0.51 to 0.76) | 0.67 (0.59 to 0.75) | 0.65 (0.54 to 0.77) | 0.63 (0.51 to 0.78) | 0.64 (0.52 to 0.78) |
| GA 20 mg | Pairwise MA | NA | 0.71 (0.62 to 0.80) | 0.71 (0.62 to 0.80) | NA | NA |
| | MTC | 0.64 (0.53 to 0.76) | 0.66 (0.60 to 0.72) | 0.66 (0.59 to 0.74) | 0.64 (0.53 to 0.77) | 0.64 (0.54 to 0.76) |
| BG-12 240 mg b.i.d. | Pairwise MA | 0.51 (0.44 to 0.59) | 0.51 (0.44 to 0.59) | 0.51 (0.44 to 0.59) | 0.51 (0.44 to 0.59) | 0.51 (0.44 to 0.59) |
| | MTC | 0.50 (0.42 to 0.59) | 0.50 (0.43 to 0.59) | 0.50 (0.43 to 0.58) | 0.50 (0.42 to 0.59) | 0.50 (0.42 to 0.59) |
| Fingolimod 0.5 mg | Pairwise MA | 0.49 (0.42 to 0.56) | 0.49 (0.42 to 0.56) | 0.49 (0.42 to 0.56) | 0.48 (0.42 to 0.56) | 0.48 (0.42 to 0.56) |
| | MTC | 0.46 (0.40 to 0.54) | 0.46 (0.40 to 0.53) | 0.46 (0.40 to 0.53) | 0.46 (0.39 to 0.54) | 0.46 (0.39 to 0.54) |
| Natalizumab 300 mg | Pairwise MA | NA | NA | NA | NA | NA |
| | MTC | 0.31 (0.25 to 0.39) | 0.31 (0.26 to 0.38) | 0.31 (0.26 to 0.38) | 0.31 (0.25 to 0.39) | 0.32 (0.25 to 0.39) |

ARR = annualized relapse rate; BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis (direct evidence only); MTC = mixed treatment comparison (direct plus indirect evidence); NA = not applicable; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.

[a]All comparisons were statistically significant; RRs < 1 favour the active treatments.

**TABLE 38: ANNUALIZED RELAPSE RATE RATIOS FOR TERIFLUNOMIDE 14 MG VERSUS PLACEBO AND DISEASE-MODIFYING TREATMENTS IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analysis | | | |
|---|---|---|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations | All Years and ≥ 80% RRMS | Recruitment ≥ 2,000 and 100% RRMS | Recruitment ≥ 2,000, ≥ 80% RRMS and ≥1 Year Follow-up |
| **RR (95% CrI), teriflunomide 14 mg[a] versus** | | | | | | |
| Placebo | Pairwise MA | **0.66 (0.59 to 0.75)** | **0.66 (0.59 to 0.75)** | **0.66 (0.59 to 0.75)** | **0.64 (0.57 to 0.73)** | **0.66 (0.59 to 0.75)** |
| | MTC | **0.67 (0.57 to 0.77)** | **0.67 (0.59 to 0.76)** | **0.67 (0.58 to 0.76)** | **0.65 (0.56 to 0.76)** | **0.67 (0.57 to 0.78)** |
| IFN beta-1b 250 mcg | MTC | 0.98 (0.73 to 1.31) | 1.00 (0.85 to 1.17) | 0.97 (0.80 to 1.17) | 0.96 (0.70 to 1.32) | 0.97 (0.72 to 1.31) |
| IM IFN beta-1a 30 mcg | MTC | 0.86 (0.69 to 1.05) | **0.83 (0.70 to 0.98)** | 0.84 (0.71 to 1.00) | 0.83 (0.67 to 1.03) | 0.85 (0.68 to 1.04) |
| SC IFN beta-1a 44 mcg | MTC | 1.06 (0.84 to 1.35) | 0.99 (0.84 to 1.18) | 1.02 (0.82 to 1.26) | 1.02 (0.81 to 1.34) | 1.05 (0.83 to 1.34) |
| GA 20 mg | MTC | 1.05 (0.83 to 1.31) | 1.01 (0.87 to 1.20) | 1.01 (0.86 to 1.20) | 1.01 (0.81 to 1.29) | 1.04 (0.83 to 1.31) |
| BG-12 240 mg b.i.d. | MTC | **1.34 (1.06 to 1.68)** | **1.32 (1.09 to 1.63)** | **1.33 (1.08 to 1.63)** | **1.30 (1.03 to 1.66)** | **1.34 (1.06 to 1.70)** |
| Fingolimod 0.5 mg | MTC | **1.45 (1.17 to 1.80)** | **1.44 (1.20 to 1.73)** | **1.44 (1.19 to 1.76)** | **1.42 (1.14 to 1.79)** | **1.46 (1.16 to 1.82)** |
| Natalizumab 300 mg | MTC | **2.12 (1.63 to 2.75)** | **2.12 (1.71 to 2.65)** | **2.13 (1.69 to 2.66)** | **2.06 (1.58 to 2.72)** | **2.12 (1.61 to 2.78)** |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis; MTC = mixed treatment comparison (direct plus indirect evidence); RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.

[a]Bolding indicates that the result is statistically significant; RRs < 1 favour teriflunomide.

**TABLE 39: PROPORTION-FREE OF RELAPSE ODDS RATIOS FOR DISEASE-MODIFYING TREATMENTS VERSUS PLACEBO IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analysis |
|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations; All Years and ≥ 80% RRMS; Recruitment ≥ 2,000 and 100% RRMS; Recruitment ≥ 2,000, ≥80% RRMS and ≥1 Year Follow-up |
| **OR (95% CrI), versus placebo[a]** | | | |
| Teriflunomide 14 mg | Pairwise MA<br>MTC | **1.72 (1.40 to 2.10)**<br>**1.71 (1.28 to 2.30)** | Sensitivity Analyses Not Conducted |
| IFN beta-1b 250 mcg | Pairwise MA<br>MTC | **NA**<br>**1.78 (1.10 to 2.89)** | |
| IM IFN beta-1a 30 mcg | Pairwise MA<br>MTC | NA<br>1.39 (0.97 to 1.98) | |
| SC IFN beta-1a 44 mcg | Pairwise MA<br>MTC | NA<br>**2.39 (1.69 to 3.66)** | |
| GA 20 mg | Pairwise MA<br>MTC | NA<br>**1.94 (1.40 to 2.80)** | |
| BG12 240 mg b.i.d. | Pairwise MA<br>MTC | **1.99 (1.49 to 2.67)**<br>**2.07 (1.50 to 2.86)** | |
| Fingolimod 0.5 mg | Pairwise MA<br>MTC | **2.51 (2.05 to 3.08)**<br>**2.60 (1.96 to 3.43)** | |
| Natalizumab 300 mg | Pairwise MA<br>MTC | NA<br>**2.93 (1.85 to 4.67)** | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis (direct evidence only); MS = multiple sclerosis; MTC = mixed treatment comparison (direct plus indirect evidence); NA = not applicable; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.
[a]Bolding indicates that the result is statistically significant; ORs > 1 favour the active treatment.

### *Teriflunomide versus Other Disease-modifying Treatments*

The proportion of patients who were relapse free was not significantly different between teriflunomide and any of the interferons, glatiramer acetate, dimethyl fumarate, or natalizumab. The proportion of relapse-free patients was significantly lower for teriflunomide compared with fingolimod (OR: 0.66; CrI 0.45 to 0.99). No sensitivity analyses were performed. Further detail is presented in Table 40.

**TABLE 40: PROPORTION-FREE OF RELAPSE ODDS RATIOS FOR TERIFLUNOMIDE 14 MG VERSUS PLACEBO AND DISEASE-MODIFYING TREATMENTS IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analysis |
|---|---|---|---|
| | | Recruitment ≥2000 and ≥80% RRMS | All Years, All Relapsing MS Populations; All Years and ≥ 80% RRMS; Recruitment ≥ 2,000 and 100% RRMS; Recruitment ≥ 2,000, ≥ 80% RRMS and ≥ 1 Year Follow-up |
| **OR (95% CrI), teriflunomide 14 mg versus[a]** | | | |
| Placebo | Pairwise MA<br>MTC | **1.72 (1.40 to 2.10)**<br>**1.71 (1.28 to 2.30)** | Sensitivity Analyses Not Conducted |
| IFN beta-1b 250 mcg | MTC | 0.96 (0.56 to 1.67) | |
| IM IFN beta-1a 30 mcg | MTC | 1.24 (0.80 to 1.93) | |
| SC IFN beta-1a 44 mcg | MTC | 0.72 (0.45 to 1.07) | |
| GA 20 mg | MTC | 0.88 (0.57 to 1.35) | |
| BG-12 240 mg b.i.d. | MTC | 0.83 (0.54 to 1.28) | |
| BG-12 240 mg t.i.d. | MTC | 0.73 (0.49 to 1.14) | |
| Fingolimod 0.5 mg | MTC | **0.66 (0.45 to 0.99)** | |
| Natalizumab 300 mg | MTC | 0.58 (0.34 to 1.01) | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis (direct evidence only); MTC = mixed treatment comparison; MS = multiple sclerosis; OR = odds ratio; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; OR > 1 favour teriflunomide.

*Three-Month Sustained Accumulated Disability:* The base-case MTC network for three-month SAD was reported to include 15 trials.

***Disease-modifying Treatments versus Placebo***

Teriflunomide, dimethyl fumarate, fingolimod, and natalizumab were all found to be superior to placebo in both the base-case and all sensitivity analyses. Subcutaneous IFN beta-1a and glatiramer acetate were not superior in the base case, but were in one sensitivity analysis (all years, ≥ 80% RRMS, and all years, all relapsing MS populations, respectively). Further detail is presented in Table 41.

**TABLE 41: THREE-MONTH SUSTAINED ACCUMULATED DISABILITY HAZARD RATIOS FOR DISEASE-MODIFYING TREATMENTS VERSUS PLACEBO IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analyses | | | |
|---|---|---|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations | All Years and ≥ 80% RRMS | Recruitment ≥ 2,000 and 100% RRMS; | Recruitment ≥ 2,000, ≥ 80% RRMS and ≥ 1 Year Follow-up |
| **HR (95% CrI), versus placebo[a]** | | | | | | |
| Teriflunomide 14 mg | Pairwise MA<br>MTC | **0.69 (0.54 to 0.89)**<br>**0.71 (0.53 to 0.92)** | **0.69 (0.54 to 0.89)**<br>**0.71 (0.54 to 0.93)** | **0.69 (0.54 to 0.89)**<br>**0.69 (0.53 to 0.91)** | **0.70 (0.54 to 0.90)**<br>**0.71 (0.53 to 0.94)** | **0.69 (0.54 to 0.89)**<br>**0.71 (0.53 to 0.92)** |
| IFNbeta-1b 250 mcg | Pairwise MA<br>MTC | NA<br>1.21 (0.68 to 2.16) | **0.71 (0.58 to 0.87)**<br>0.79 (0.62 to 1.00) | NA<br>0.91 (0.62 to 1.29) | NA<br>1.22 (0.68 to 2.24) | NA<br>1.21 (0.68 to 2.16) |
| IM IFN beta-1a 30 mcg | Pairwise MA<br>MTC | NA<br>0.91 (0.61 to 1.33) | NA<br>0.94 (0.67 to 1.32) | NA<br>0.87 (0.62 to 1.22) | NA<br>0.93 (0.63 to 1.36) | NA<br>0.91 (0.61 to 1.33) |
| SC IFN beta-1a 44 mcg | Pairwise MA<br>MTC | NA<br>0.79 (0.51 to 1.24) | 0.82 (0.55 to 1.21)<br>0.84 (0.66 to 1.04) | NA<br>**0.71 (0.53 to 0.97)** | NA<br>0.81 (0.50 to 1.26) | NA<br>0.79 (0.51 to 1.24) |
| GA 20 mg | Pairwise MA<br>MTC | NA<br>0.93 (0.59 to 1.45) | 0.75 (0.40 to 1.40)<br>**0.72 (0.55 to 0.94)** | 0.75 (0.40 to 1.40)<br>0.77 (0.57 to 1.02) | NA<br>0.93 (0.57 to 1.46) | NA<br>0.93 (0.59 to 1.45) |
| BG-12 240 mg b.i.d. | Pairwise MA<br>MTC | **0.68 (0.52 to 0.89)**<br>**0.68 (0.51 to 0.93)** | **0.68 (0.52 to 0.89)**<br>**0.68 (0.51 to 0.94)** | **0.68 (0.52 to 0.89)**<br>**0.68 (0.51 to 0.93)** | **0.68 (0.52 to 0.89)**<br>**0.69 (0.50 to 0.93)** | **0.68 (0.52 to 0.89)**<br>**0.68 (0.51 to 0.93)** |
| Fingolimod 0.5 mg | Pairwise MA<br>MTC | **0.76 (0.61 to 0.94)**<br>**0.75 (0.58 to 0.96)** | **0.76 (0.61 to 0.94)**<br>**0.75 (0.59 to 0.97)** | **0.76 (0.61 to 0.94)**<br>**0.74 (0.57 to 0.94)** | **0.76 (0.61 to 0.94)**<br>**0.75 (0.58 to 0.97)** | **0.76 (0.61 to 0.94)**<br>**0.75 (0.58 to 0.96)** |
| Natalizumab 300 mg | Pairwise MA<br>MTC | NA<br>**0.58 (0.4 to 0.84)** | NA<br>**0.58 (0.40 to 0.83)** | NA<br>**0.58 (0.40 to 0.83)** | NA<br>**0.58 (0.40 to 0.84)** | NA<br>**0.58 (0.40 to 0.84)** |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; DAE = discontinuation due to adverse event; GA = glatiramer acetate; HR = hazard ratio; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis; MTC = mixed treatment comparison; NA = not applicable, analysis not conducted; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; HRs < 1 favour the active treatment.

### *Teriflunomide versus other Disease-modifying Treatments*

When compared with the other DMTs, teriflunomide was not found to be significantly different with respect to three-month sustained accumulated disability in either the base-case or sensitivity analyses. Further detail is presented in Table 42.

**TABLE 42: THREE-MONTH SUSTAINED ACCUMULATED DISABILITY HAZARD RATIOS FOR TERIFLUNOMIDE 14 MG VERSUS PLACEBO AND DISEASE-MODIFYING TREATMENTS IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analyses | | | |
|---|---|---|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations; | All Years and ≥ 80% RRMS | Recruitment ≥ 2,000 and 100% RRMS; | Recruitment ≥ 2,000, ≥ 80% RRMS and ≥ 1 Year Follow-up |
| **HR (95% CrI), teriflunomide 14 mg versus[a]** | | | | | | |
| Placebo | Pairwise MA MTC | **0.69 (0.54 to 0.89) 0.71 (0.53 to 0.92)** | **0.69 (0.54 to 0.89) 0.71 (0.54 to 0.93)** | **0.69 (0.54 to 0.89) 0.69 (0.53 to 0.91)** | **0.70 (0.54 to 0.90) 0.71 (0.53 to 0.94)** | **0.69 (0.54 to 0.89) 0.71 (0.53 to 0.92)** |
| IFNbeta-1b 250 mcg | MTC | 0.58 (0.30 to 1.12) | 0.90 (0.62 to 1.30) | 0.76 (0.49 to 1.22) | 0.58 (0.30 to 1.12) | 0.58 (0.30 to 1.12) |
| IM IFNbeta-1a 30 mcg | MTC | 0.77 (0.50 to 1.24) | 0.75 (0.49 to 1.16) | 0.79 (0.52 to 1.23) | 0.76 (0.48 to 1.22) | 0.77 (0.50 to 1.24) |
| SC IFNbeta-1a 44 mcg | MTC | 0.90 (0.54 to 1.45) | 0.84 (0.60 to 1.20) | 0.96 (0.66 to 1.42) | 0.87 (0.54 to 1.46) | 0.90 (0.54 to 1.45) |
| GA 20 mg | MTC | 0.76 (0.45 to 1.30) | 0.99 (0.66 to 1.46) | 0.90 (0.61 to 1.35) | 0.76 (0.44 to 1.35) | 0.76 (0.45 to 1.30) |
| BG-12 240 mg b.i.d. | MTC | 1.04 (0.68 to 1.53) | 1.03 (0.68 to 1.55) | 1.01 (0.68 to 1.50) | 1.03 (0.67 to 1.58) | 1.04 (0.68 to 1.53) |
| BG-12 240 mg t.i.d. | MTC | 1.02 (0.68 to 1.50) | 1.01 (0.68 to 1.51) | 0.99 (0.65 to 1.49) | 1.02 (0.67 to 1.55) | 1.02 (0.68 to 1.50) |
| Fingolimod 0.5 mg | MTC | 0.95 (0.64 to 1.35) | 0.94 (0.65 to 1.36) | 0.94 (0.66 to 1.35) | 0.94 (0.65 to 1.36) | 0.95 (0.64 to 1.35) |
| Natalizumab 300 mg | MTC | 1.22 (0.77 to 1.94) | 1.23 (0.77 to 1.94) | 1.20 (0.77 to 1.88) | 1.21 (0.77 to 1.95) | 1.22 (0.77 to 1.94) |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; HR = hazard ratio; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis; MTC = mixed treatment comparison; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; HRs < 1 favour teriflunomide.

*Total Discontinuation:* The base-case MTC network for total discontinuation was reported to include 25 trials.

***Disease-modifying Treatments versus Placebo***

Interferon beta-1b, glatiramer acetate, and the BG-12 twice daily were associated with significantly lower odds of discontinuing treatment for any reason compared with placebo while the remaining DMTs were not. Further detail is presented in Table 43.

**TABLE 43: TOTAL DISCONTINUATIONS ODDS RATIOS FOR DISEASE-MODIFYING TREATMENTS VERSUS PLACEBO IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analyses | |
|---|---|---|---|---|
| | | Recruitment ≥2000 and ≥80% RRMS | Recruitment ≥2000, ≥80% RRMS and ≥1 Year Follow-up | All Years, All Relapsing MS Populations; All Years and ≥80% RRMS; Recruitment ≥2000 and 100% RRMS |
| **OR (95% CrI), versus placebo[a]** | | | | |
| Teriflunomide 14 mg | Pairwise MA<br>MTC | 1.34 (0.56 to 3.17)<br>1.01 (0.80 to 1.31) | 0.99 (0.79 to 1.23)<br>0.96 (0.73 to 1.22) | Other sensitivity analyses not conducted |
| IFN beta-1b 250 mcg | Pairwise MA<br>MTC | NA<br>**0.48 (0.30 to 0.81)** | NA<br>**0.47 (0.29 to 0.76)** | |
| IM IFN beta-1a 30 mcg | Pairwise MA<br>MTC | NA<br>0.90 (0.58 to 1.37) | NA<br>0.87 (0.58 to 1.31) | |
| SC IFN beta-1a 44 mcg | Pairwise MA<br>MTC | NA<br>1.26 (0.85 to 1.85) | NA<br>1.21 (0.85 to 1.74) | |
| GA 20 mg | Pairwise MA<br>MTC | NA<br>**0.68 (0.50 to 0.94)** | NA<br>**0.66 (0.49 to 0.92)** | |
| BG-12 240 mg b.i.d. | Pairwise MA<br>MTC | **0.80 (0.64 to 0.99)**<br>0.83 (0.65 to 1.08) | **0.80 (0.64 to 0.99)**<br>0.83 (0.65 to 1.07) | |
| Fingolimod 0.5 mg | Pairwise MA<br>MTC | 0.85 (0.35 to 2.07)<br>0.70 (0.51 to 1.00) | NA<br>**0.65 (0.47 to 0.91)** | |
| Natalizumab 300 mg | Pairwise MA<br>MTC | NA<br>0.80 (0.52 to 1.26) | NA<br>0.81 (0.52 to 1.24) | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis; MTC = mixed treatment comparison; NA= not applicable, analysis not conducted; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.
[a]Bolding indicates that the result is statistically significant; ORs < 1 favour the active treatment.

***Teriflunomide versus Other Disease-modifying Treatments***

The proportion of patients discontinuing treatment was significantly higher for teriflunomide compared with interferon beta-1b 250 mcg (in both the base-case and the sensitivity analysis for recruitment ≥ 2,000, ≥ 80% RRMS and ≥ 1-year follow-up) and glatiramer acetate 20 mg (statistically significant in the base case only). Table 44 contains further detail.

**TABLE 44: TOTAL DISCONTINUATIONS ODDS RATIOS FOR TERIFLUNOMIDE 14 MG VERSUS PLACEBO AND DISEASE-MODIFYING TREATMENTS IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analyses | |
|---|---|---|---|---|
| | | Recruitment ≥2000 and ≥80% RRMS | Recruitment ≥2000, ≥80% RRMS and ≥1 Year Follow-up | All Years, All Relapsing MS Populations; All Years and ≥80% RRMS; Recruitment ≥2000 and 100% RRMS |
| **OR (95% CrI), teriflunomide 14 mg versus[a]** | | | | |
| Placebo | Pairwise MA<br>MTC | 1.34 (0.56 to 3.17)<br>1.01 (0.80 to 1.31) | 0.99 (0.79 to 1.23)<br>0.96 (0.73 to 1.22) | Other sensitivity analyses not conducted |
| IFN beta-1b 250 mcg | MTC | **2.10 (1.22 to 3.50)** | **2.06 (1.16 to 3.38)** | |
| IM IFN beta-1a 30 mcg | MTC | 1.13 (0.71 to 1.82) | 1.10 (0.69 to 1.73) | |
| SC IFN beta-1a 44 mcg | MTC | 0.80 (0.54 to 1.30) | 0.79 (0.79 to 1.15) | |
| GA 20 mg | MTC | **1.50 (1.02 to 2.23)** | 1.47 (0.99 to 2.10) | |
| BG-12 240 mg b.i.d. | MTC | 1.22 (0.86 to 1.73) | 1.16 (0.80 to 1.61) | |
| BG-12 240 mg t.i.d. | MTC | 1.24 (0.88 to 1.74) | 1.17 (0.81 to 1.64) | |
| Fingolimod 0.5 mg | MTC | 1.46 (0.96 to 2.12) | 1.48 (0.96 to 2.18) | |
| Natalizumab 300 mg | MTC | 1.27 (0.76 to 2.10) | 1.20 (0.72 to 1.93) | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; DAE = discontinuation due to adverse event; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis; MTC = mixed treatment comparison; NA = not applicable, analysis not conducted; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; ORs < 1 favour teriflunomide.

*Discontinuations due to Adverse Events*

***Disease-modifying Treatments versus Placebo***

Based on pairwise MA, teriflunomide and dimethyl fumarate were associated with significantly higher odds of discontinuation due to adverse events than placebo. Based on MTC, both subcutaneous interferon beta-1a 44 mcg and dimethyl fumarate were associated with higher odds of discontinuation due to adverse events. Further detail is presented in Table 45.

**TABLE 45: DISCONTINUATION DUE TO ADVERSE EVENT ODDS RATIOS FOR DISEASE-MODIFYING TREATMENTS VERSUS PLACEBO IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analysis |
|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations; All Years and ≥ 80% RRMS; Recruitment ≥ 2,000 and 100% RRMS; Recruitment ≥ 2,000, ≥80% RRMS and ≥1 Year Follow-up |
| **OR (95% CrI), versus placebo[a]** | | | |
| Teriflunomide 14 mg | Pairwise MA<br>MTC | **1.92 (1.37 to 2.70)**<br>1.70 (0.97 to 2.94) | Sensitivity Analyses Not Conducted |
| IFN beta-1b 250 mcg | Pairwise MA<br>MTC | NA<br>1.23 (0.30 to 5.30) | |
| IM IFN beta-1a 30 mcg | Pairwise MA<br>MTC | NA<br>1.11 (0.47 to 2.60) | |
| SC IFN beta-1a 44 mcg | Pairwise MA<br>MTC | NA<br>**2.45 (1.02 to 5.75)** | |
| GA 20 mg | Pairwise MA<br>MTC | NA<br>1.75 (0.72 to 4.28) | |
| BG-12 240 mg b.i.d. | Pairwise MA<br>MTC | **2.15 (1.47 to 3.15)**<br>**2.38 (1.25 to 4.69)** | |
| Fingolimod 0.5 mg | Pairwise MA<br>MTC | 1.04 (0.55 to 1.99)<br>1.12 (0.65 to 1.99) | |
| Natalizumab 300 mg | Pairwise MA<br>MTC | NA<br>1.53 (0.57 to 4.23) | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis (direct evidence only); MTC = mixed treatment comparison (direct plus indirect evidence); MS = multiple sclerosis; NA = not applicable, analysis not conducted; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; ORs < 1 favour the active treatment.

### *Teriflunomide versus Other Disease-modifying Treatments*

Overall, when compared with the other DMTs, teriflunomide was not associated with significant differences in treatment discontinuations due to adverse events. Only the base-case analysis was performed. Table 46 contains further detail.

**TABLE 46: DISCONTINUATION DUE TO ADVERSE EVENTS ODDS RATIOS FOR TERIFLUNOMIDE 14 MG VERSUS PLACEBO AND DISEASE-MODIFYING TREATMENTS IN PAIRWISE META-ANALYSIS AND MIXED TREATMENT COMPARISON ANALYSES**

| Comparator | Analysis | Base Case | Sensitivity Analysis |
|---|---|---|---|
| | | Recruitment ≥ 2,000 and ≥ 80% RRMS | All Years, All Relapsing MS Populations; All Years and ≥ 80% RRMS; Recruitment ≥ 2,000 and 100% RRMS; Recruitment ≥ 2000, ≥ 80% RRMS and ≥ 1 Year Follow-up |
| **OR (95% CrI), teriflunomide 14 mg versus [a]** | | | |
| Placebo | Pairwise MA<br>MTC | **1.92 (1.37 to 2.70)**<br>1.70 (0.97 to 2.94) | Sensitivity Analyses Not Conducted |
| IFN beta-1b 250 mcg | MTC | 1.39 (0.29 to 6.36) | |
| IM IFN beta-1a 30 mcg | MTC | 1.54 (0.60 to 3.87) | |
| SC IFN beta-1a 44 mcg | MTC | 0.69 (0.30 to 1.62) | |
| GA 20 mg | MTC | 0.98 (0.33 to 2.74) | |
| BG-12 240 mg b.i.d. | MTC | 0.72 (0.29 to 1.65) | |
| BG-12 240 mg t.i.d. | MTC | 0.55 (0.22 to 1.19) | |
| Fingolimod 0.5 mg | MTC | 1.51 (0.70 to 3.20) | |
| Natalizumab 300 mg | MTC | 1.11 (0.35 to 3.42) | |

BG-12 = dimethyl fumarate; b.i.d. = two times daily; CrI = credible interval; GA = glatiramer acetate; IFN beta-1a = interferon beta-1a; IFN beta-1b = interferon beta-1b; IM = intramuscular; MA = meta-analysis (direct evidence only); MTC = mixed treatment comparison (direct plus indirect evidence); NA = not applicable, analysis not conducted; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times per day.
[a]Bolding indicates that the result is statistically significant; ORs < 1 favour teriflunomide.

**Critical Appraisal of Network Meta-analysis**

Critical appraisal of the manufacturer-provided NMA by CDR was conducted based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) simplified checklist to assist decision-makers in evaluating a reported NMA.[56] A summary of the primary strengths and limitations is presented; full detail is presented in Table 47.

**Strengths and Limitations**

Bayesian random-effect model with vague prior is deemed an appropriate MTC framework for this analysis.

*Population*

Of note, there was significant potential for heterogeneity among the included studies in patient characteristics (age, gender, race), relapse rate, EDSS score at baseline, disease duration, disease severity, previous treatments (including DMTs), and best supportive care. The base-case criteria of including only studies with ≥ 80% of the study population with RRMS may still render a slightly mixed MS population.

*Trial Inclusion and Exclusion*

As previously stated, the primary method of diagnosing MS changed from the Poser to the McDonald criteria starting in approximately the year 2000. To control for this source of heterogeneity, the manufacturer elected to restrict its base-case analyses to trials that recruited patients after the year 2000. Many trials examining the DMTs — glatiramer acetate (6/12), natalizumab (2/3), teriflunomide

(1/4), interferon beta-1b (4/6), subcutaneous interferon beta-1a (6/8), and intramuscular interferon beta-1a (5/7) — were older and used Poser criteria or used Poser criteria despite being post 2000 (two glatiramer acetate studies, two interferon beta-1b studies, one teriflunomide study). Eliminating the older trials limits much of the body of evidence for some of the DMTs, and the fact that some trials that recruited patients after 2000 still used Poser criteria may call into question the usefulness of eliminating the trials based on the year 2000 as a means of controlling heterogeneity.

*Treatment Definition*
One of the strengths of the MTC is that treatments with different chemical structures, routes of administration, or dose were not combined into a single node. For example, interferon beta-1a subcutaneous, interferon beta-1a intramuscular, and interferon beta-1b were analyzed separately. However, it is unclear why specific interventions were or were not included in the MTC. As noted, a number of included drugs (mitoxantrone, rituximab, and daclizumab) are not approved by Health Canada for use in MS. The impact of the inclusion of these drugs is unclear.

*Presentation of the Data and Data Analyses*
Data extraction tables for all outcomes were presented; however, there is no table presenting specifically what studies or data were included in the base-case analysis or in the sensitivity analyses. There were no exclusions based on quality, nor were sensitivity analyses performed based on the quality of the included studies. It was unclear how the authors dealt with missing data. Network diagrams would assist in identifying the quantity of evidence available for the various analyses and facilitate exploration of the impact of including specific trials on results. Based on the number of trials included in base-case MTC networks, there was a lesser body of evidence for the outcome of three-month SAD (15 trials) compared with ARR (28 trials), or total discontinuation (25 trials).

As noted, the manufacturer elected to restrict its base-case analyses to trials that recruited patients after the year 2000, and in which ≥ 80% of the study population had RRMS. The manufacturer conducted a number of sensitivity analyses that varied criteria regarding year of recruitment and form (type) of MS. CDR considered the most appropriate analyses to be those that included all trials regardless of year and included all trials in which ≥ 80% of the study population had RRMS. This was considered most appropriate because inclusion of all trials allowed for the largest body of evidence. In addition, the manufacturer's sensitivity analyses that restricted to 100% RRMS patients was not consistently applied to all trials. Trials were excluded if they did not enroll 100% of RRMS patients, except for the teriflunomide trials, where the availability of patient-level data allowed for exclusion of data for only a proportion of trial participants.

Other than the above-described sensitivity analyses, the manufacturer's submission did not attempt to control for other sources of heterogeneity. Subsequent to a request by CDR, the manufacturer provided MTC results for all studies regardless of year and ≥ 80% RRMS with adjustment for baseline ARR. However, that meta-regression to adjust for covariates is of limited use when the number of trials is too small. Thus, CDR considered the unadjusted analysis to be more appropriate.

Finally, the included trials are predominantly placebo-controlled. Due to the paucity of direct head-to-head evidence, the authors of the manufacturer-provided MTC suggested that the results of between-treatment comparisons should be interpreted with caution.

**TABLE 47: SIMPLIFIED CHECKLIST TO ASSIST DECISION-MAKERS IN EVALUATING A REPORTED NETWORK META-ANALYSIS.[56]**

| Checklist Item | Comments |
|---|---|
| Are the rationale for the study and the study objectives stated clearly? | • Objective for review provided<br>• Rationale for the MTC not specifically provided |
| Does the methods section include the following?<br>• Description of eligibility criteria<br>• Information sources<br>• Search strategy<br>• Study selection process<br>• Data extraction (validity and quality assessment of individual studies) | • Eligibility criteria described<br>• Information sources described<br>• Search strategy described in general terms<br>• No clear description of interventions to be included, or rationale for inclusion<br>• Study selection process described<br>• Data extraction and quality assessment of individual studies conducted and provided |
| Are the outcome measures described? | • Outcome measures are described; however, the reason for the use of 3-month SAD is not provided and it is possible that 6-month data may be more appropriate |
| Is there a description of methods for analysis or synthesis of evidence? Do the methods described include the following?<br>• Description of analyses methods or models<br>• Handling of potential bias or inconsistency<br>• Analysis framework | • It is unclear which trials are included in the various analyses; network diagrams should have been provided<br>• No information provided regarding the assessment of heterogeneity, consistency and similarity assumptions, potential bias, and what methods were used or explored to control bias<br>• Random-effect MTC analyses were used to compare all DMTs under investigation within a single model. MTC analyses employed a vaguely informative normal prior with a uniform SD, the value of which was 1.0 for all outcomes. Fixed model analysis was not included in the initial report. Subsequent results from fixed model provided, along with a rationale for why random-effect model is more appropriate comparing to fixed model<br>• Convergence was confirmed through the use of three-chain BGR plots and inspection of the ratios of Monte Carlo error, the SDs of the posteriors; values of greater than 5% were strong signs of convergence issues<br>• RR for ARR (modelling the number of total events in each arm as following a Poisson distribution); OR for remaining relapse free; HR for three-month SAD; OR for total discontinuations; OR for DAEs. Rationale for choice of OR, rather than RR, for dichotomous outcomes is not stated, and it is unclear how the HR for 3-month SAD was calculated |
| Are sensitivity analyses presented? | • Sensitivity analyses are presented<br>• Difficult to determine precisely which studies were included in the sensitivity analyses<br>• Rationale for the analyses partially provided |
| Do the results include a summary of the studies included in the network of evidence?<br>• Individual study data?<br>• Network of studies? | • Description of results of study identification is provided<br>• Table of studies with information regarding study design and patient characteristics is included<br>• It was unclear which trials were included in the various analyses; no network diagrams were provided<br>• Some raw data from the included studies were provided |

| Checklist Item | Comments |
|---|---|
| | • Tables with critical appraisal of quality of individual studies were provided |
| Does the study describe an assessment of model fit? Are competing models being compared? | • Analyses were conducted assuming the treatment effect came from a random distribution of effects (random effects model). No information was provided on model fit and model selection was provided in the original report. This information was subsequently provided |
| Are the results of the evidence synthesis (ITC/MTC) presented clearly? | • Random effects model results for all outcomes are presented and discussed on an outcome-by-outcome basis. For each outcome, forest plots are presented in separate documents- each treatment was compared to placebo followed by the comparison between teriflunomide and other DMTs. 95% credible intervals presented |
| Sensitivity or scenario analyses findings | • Description of sensitivity analysis findings are presented |
| Does the discussion include the following?<br>• Description or summary of main findings<br>• Internal validity of analysis<br>• External validity<br>• Implications of results for target audience | • Summary of findings presented in discussion and in the executive summary<br>• No specific assessment of the internal validity of the findings other than the sensitivity analysis |

ARR = annualized relapse rate; BGR = Brooks–Gelman–Rubin; DAE = discontinuation due to adverse event; DMT = disease-modifying treatment; HR = hazard ratio; ITC = indirect treatment comparison; MTC = mixed treatment comparison; RR = rate ratio; SAD = sustained accumulation of disability; SD = standard deviation.

**Comparison with Canadian Agency for Drugs and Technologies in Health Therapeutic Review**

The recently published Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review included pairwise meta-analyses and MTC comparing available and emerging treatments for RRMS. The review included published data only and MTC was performed for two outcomes: ARR and sustained disability progression.[57] A comparative summary of the manufacturer-provided and CADTH MTCs is presented in Table 48.

**TABLE 48: SUMMARY OF MIXED TREATMENT COMPARISON CHARACTERISTICS AND METHODS**

| Component | CADTH Therapeutic Review[57] | Manufacturer MTC[1] |
|---|---|---|
| Inclusion Criteria | • Published RCTs<br>• Patients diagnosed with RRMS[a]<br>• Interventions: fingolimod, IM interferon beta-1a, SC interferon beta-1a, interferon beta-1b, natalizumab, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, and placebo | • Published RCTs, unpublished manufacturer-provided information<br>• Patients diagnosed with RRMS and SPMS<br>• Interventions: teriflunomide; IM interferon beta-1a, SC interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, natalizumab, fingolimod, daclizumab, mitoxantrone, rituximab, and placebo |
| Included Studies | • 27 studies<br>○ 14 with a placebo group<br>○ Alemtuzumab: 3 studies<br>○ Dimethyl fumarate: 2 studies<br>○ Fingolimod: 3 studies<br>○ Glatiramer acetate: 8 studies<br>○ SC interferon beta-1a: 9 studies | • 52 primary trials (30 RCTs included in the base-case analysis; 26 to 41 trials included in sensitivity analyses)<br>○ Dimethyl fumarate: 3 studies<br>○ Fingolimod: 5 studies<br>○ Glatiramer acetate: 11 studies<br>○ SC interferon beta-1a: 8 studies |

| Component | CADTH Therapeutic Review[57] | Manufacturer MTC[1] |
|---|---|---|
| | ○ IM interferon beta-1a: 9 studies<br>○ Interferon beta-1b: 5 studies<br>○ Natalizumab: 1 study<br>○ Teriflunomide: 2 studies<br>• 16,998 included patients<br>• Studies published between 1993 and 2013<br>• Follow-up from 16 weeks to 3.5 years | ○ IM interferon beta-1a: 8 studies<br>○ Interferon beta-1b: 8 studies<br>○ Natalizumab: 3 studies<br>○ Teriflunomide: 4 studies<br>○ Daclizumab (1 study, results not reported by manufacturer)<br>○ Interferon beta-1a 3a Oral (1 study, results not reported by manufacturer)<br>○ Mitoxantrone (2 studies, results not reported by manufacturer)<br>○ Rituximab (1 study, results not reported by manufacturer)<br>• Studies published between 1987 and 2012<br>• Follow-up from 6 to 36 months |
| Outcomes Examined | • ARR; rate ratio using the total number of relapses within a treatment group and total person-time of follow-up for that treatment group; Poisson outcome<br>• Sustained disability progression; risk ratio (dichotomous outcome); definitions for this outcome varied among studies based on how long the reduction in EDSS needed to be sustained (3 months or 6 months), 3- and 6- month outcomes were combined | • ARR; rate ratio calculated modelling the number of total events in each arm as following a Poisson distribution<br>• proportion of relapse-free patients; OR calculated for remaining relapse free<br>• 3-month SAD; HR calculated<br>• all-cause treatment discontinuation rate; OR calculated<br>• treatment DAE; OR calculated |
| Statistical Analyses | • Direct pairwise meta-analyses were performed for all outcomes, assessment consistency with MTC results when MTC was undertaken, and to obtain summary estimates for outcomes that were not analyzed by MTC<br>• Relapses were considered as count data and were summarized using a Poisson approach to obtain the relative ARR or rate ratio from the total number of relapses and patient-years.<br>• Bayesian MTCs were conducted for two outcomes: relapse and disability<br>• Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo methods. Prior distributions for overall effects of interest and study-specific effect estimates were assigned vague normal prior distributions centred at 0, with adequately large variances to allow the collected data to drive the calculation of pooled estimates. Model diagnostics including trace plots, autocorrelation plots, and the BGR statistic were assessed to ensure model convergence. Assessment of model fit for NMA comprised the assessment of | • Direct meta-analyses were pairwise (frequentist) random effects meta-analyses, and employed an empirical Bayes estimator of the random effects variance<br>• Random-effect MTC analyses were used to compare all DMTs under investigation within a single model. MTC analyses employed a vaguely informative normal prior with a uniform SD, the value of which was 1.0 for all outcomes<br>• Convergence was confirmed through the use of three-chain BGR plots and inspection of the ratios of Monte Carlo error, the SDs of the posteriors; values of greater than 5% were strong signs of convergence issues |

| Component | CADTH Therapeutic Review[57] | Manufacturer MTC[1] |
|---|---|---|
| | deviance information criterion and comparison of residual deviance to the number of unconstrained data points. Measures of effect were estimated according to the WinBUGS<br>• For comparative purposes, both fixed-effects and random effects NMAs were conducted | |

ARR = annualized relapse rate; BGR = Brooks–Gelman–Rubin; CADTH = Canadian Agency for Drugs and Technologies in Health; DAE = discontinuation due to adverse events; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IM = intramuscular; MRI = magnetic resonance imaging; MTC = mixed treatment comparison; NMA = network meta-analysis; OR = odds ratio; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SAD = sustained accumulation of disability; SC = subcutaneous; SD = standard deviation; SPMS = secondary progressive multiple sclerosis.
[a]RCTs having a mixed population (i.e., persons with primary progressive or secondary progressive MS; in addition, persons with RRMS) were included for completeness if the RRMS population was greater than 50% of the total population.

Differences between the CADTH Therapeutic Review and the manufacturer MTC include the different DMTs included, the number of trials examining teriflunomide, and the cut-off for the proportion of patients with RRMS in the base case. The manufacturer MTC included treatments (rituximab, mitoxantrone, and daclizumab) that have not been approved by Health Canada for the use in patients with MS; although these drugs were not included in the presentation of results, they were included in the network. The manufacturer MTC did not include alemtuzumab, in contrast to the CADTH Therapeutic Review. The CADTH Therapeutic Review included two trials examining teriflunomide, whereas the manufacturer MTC included four. While the manufacturer base-case MTC included trials with a cut-off of at least 80% of patients with RRMS, the CADTH Therapeutic Review had a cut-off of at least 50%. However, few trials in the CADTH Therapeutic Review included patients with forms other than RRMS: one study included patients with clinically isolated syndrome (19%), one study included patients with progressive relapsing MS (15%), one study included patients with SPMS (12%), and one study included patients with SPMS (5%) and progressive relapsing MS (3%). Thus, the patient population of the trials in the CADTH Therapeutic Review would be analogous to the manufacturer's analyses that include trials with ≥ 80% RRMS.

A further difference between the CADTH Therapeutic Review and manufacturer MTC was the definition of sustained disability progression, and the measure of effect reported for this outcome. The manufacturer MTC reported a hazard ratio for a three-month sustained accumulated disability; however, it is unclear how the hazard ratio was calculated. The CADTH Therapeutic Review reported a risk ratio for sustained disability progression, and combined either three- or six-month sustained progression, based upon what was reported in the publication.

*Results*

Results from the CADTH Therapeutic Review are compared with those from the manufacturer-provided MTC in Table 49. The results presented in the table are for the CADTH base-case analysis, and for the manufacturer's sensitivity analysis that included trials from all years and with ≥ 80% patients with RRMS, which was not adjusted for baseline ARR, as this analysis was judged to be the most appropriate by CDR.

In the CADTH Therapeutic Review, sensitivity analyses excluding older studies (before year 2000), studies of short duration (less than one year), or studies with a starting EDSS score of 0 to 3 and 1 to 3.5 did not affect the statistical significance or direction of the relative treatment differences. Sensitivity

analyses adjusting for various covariates (i.e., disease duration, mean relapses, baseline EDSS, or treatment duration) revealed no marked change in the magnitude and direction of the relative treatment effect from the results.

Similar to the manufacturer MTC, the CADTH Therapeutic Review found that teriflunomide 14 mg was not associated with statistically significant differences in ARR when compared with GA, beta-1a 44 mcg, or interferon betabeta-1b 250 mcg, and was associated with higher ARR when compared with dimethyl fumarate, fingolimod, and natalizumab. With respect to sustained disability progression, the CADTH Therapeutic Review found that teriflunomide 14 mg was associated with statistically significantly worse outcomes than natalizumab and alemtuzumab. The manufacturer-provided MTC found no significant differences between teriflunomide and any of the DMTs for which data were reported. The authors of both the CADTH Therapeutic Review and the manufacturer MTC suggest using caution when interpreting the results of between-treatment comparisons, due to the paucity of head-to-head evidence.

When compared with placebo, both the pairwise MA and the MTC results in both reports indicated that teriflunomide resulted in a significantly lower ARR. With respect to disability progression, both the manufacturer MA and MTC found teriflunomide to be superior to placebo (Table 49); whereas, only the CADTH MA, not MTC, found that teriflunomide was superior to placebo.

**TABLE 49: RESULTS OF REPORTS — TERIFLUNOMIDE VERSUS PLACEBO**

| Outcome | | CADTH Therapeutic Review (1993 to 2013, ≥ 50% RRMS) | Manufacturer MTC[b] (1987 to 2012, ≥ 80% RRMS) |
|---|---|---|---|
| ARR | Pairwise MA | RaR: **0.68 (0.51 to 0.84)**[a] | RaR: **0.66 (0.59 to 0.75)** |
| | MTC | RaR: **0.68 (0.56 to 0.83)** | RaR: **0.67 (0.58 to 0.76)** |
| Sustained Disability Progression[c] | Pairwise MA | RR: **0.74 (0.57 to 0.96)** | HR: **0.69 (0.54 to 0.89)** |
| | MTC | RR: 0.80 (0.50 to 1.15) | HR: **0.69 (0.53 to 0.91)** |

ARR = annualized relapse rate; CADTH = Canadian Agency for Drugs and Technologies in Health; HR = hazard ratio; MA = meta-analysis; MTC = mixed treatment comparison; RaR = rate ratio; RR = risk ratio; RRMS = relapsing-remitting multiple sclerosis.
[a]Bolding indicates a statistically significant difference; HR, RaR, and RR < 1 favour teriflunomide.
[b]Results presented are for the "All Years and ≥ 80% RRMS".
[c]In the CADTH Therapeutic Review, results for disability progression sustained for 3 or 6 months were combined, whereas in the manufacturer MTC, results for disability progression sustained for 3 months were used.

The effect sizes for ARR relative to placebo in the CADTH Therapeutic Review and in the manufacturer's MTC were very similar. With respect to sustained disability, the different approaches to the definition of the outcome, and the analysis of these data, including reporting of different effect measures (hazard ratio versus risk ratio) likely contributed to the differences observed.

**Summary**

The manufacturer undertook the MTC in order to quantitatively examine the clinical efficacy and safety of teriflunomide compared with other DMTs for the management of RRMS and SPMS. Several of the outcomes analyzed (ARR, three-month SAD, and all-cause treatment discontinuation) were used as inputs into the manufacturer's pharmacoeconomic analysis. The base-case analysis included trials that recruited patients from the year 2000 onward and with a ≥ 80% RRMS patient population. The manufacturer conducted a number of sensitivity analyses that varied criteria regarding year of recruitment and/or type (form) of MS, and performed an adjustment for baseline ARR. CDR considered

to be most appropriate the unadjusted analyses, which included all trials regardless of year and in which ≥ 80% of the study population had RRMS.

Based on this analysis, with respect to ARR, teriflunomide 14 mg showed no significant differences compared with subcutaneous interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, interferon beta-1a 30 mcg, or glatiramer acetate, but was associated with significantly higher ARRs compared with dimethyl fumarate, fingolimod, and natalizumab. Teriflunomide was not found to be significantly different from the other DMTs with respect to three-month sustained accumulated disability. Complete results for total discontinuation for all trials regardless of year and ≥ 80% RRMS were not provided.

Limitations of the manufacturer-provided MTC include the paucity of head-to-head trials, the lack of network diagrams or a specific list of studies that were included in the base-case and subsequent sensitivity analyses, lesser evidence for some outcomes (three-month SAD) compared with others (ARR and total discontinuation), and uncertainty regarding how hazard ratios were calculated for the outcome of sustained disability.

Results from the manufacturer-provided MTC for two outcomes (ARR and three-month SAD) were compared with those from a recent CADTH Therapeutic Review of DMTs in MS. The effect sizes for ARR, for teriflunomide relative to placebo, in the CADTH Therapeutic Review and in the manufacturer's MTC were very similar. Effect sizes for sustained disability, for teriflunomide 14 mg relative to placebo, varied by approximately 15% between the two reports. Differences in the specific trials included the different approaches to the definition of the outcome and the analysis of these data, including reporting of different effect measures (hazard ratio versus risk ratio), may have contributed to the difference observed.

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