Appendix e-1

Supplementary methods

Inclusion criteria for TEMSO: Patients with relapsing forms of MS (RMS) meeting 2001 McDonald diagnostic criteria[e1] and aged 18–55 years, with an Expanded Disability Status Scale (EDSS) score of ≤5.5 at screening, and ≥2 relapses in the previous 2 years or ≥1 relapse in the preceding year, were eligible to enter TEMSO.

Assessment of disability progression and MRI measures of disease: EDSS scores were assessed every 24 weeks and at unscheduled relapse/disability progression visits. If an EDSS score increase was identified, EDSS was assessed after 12 weeks and 24 weeks to confirm disability progression. MRI was performed annually until a January 2012 protocol amendment that eliminated MRI scans for study purposes. MRI scans were evaluated for total number and volume of Gd-enhancing T1 lesions, T2 lesion volume, T1-hypointense lesion volume, and total lesion volume (sum of T2-hyperintense and T1-hypointense lesion volumes without double-counting).

Efficacy analysis:

Twelve-week and 24-week confirmed disability progression was analyzed using time-to-event methods. Annualized relapse rate (ARR) over core and extension periods were estimated based on a Poisson regression model with robust variance estimation including factors for treatment, baseline EDSS strata (≤3.5 or >3.5), and region. ARR by treatment year was calculated as the ratio of total number of relapses observed to follow-up time during the corresponding year. Efficacy outcomes are presented for time points with ≥30 patients in all treatment groups, and MRI outcomes are presented up to week 252 to include the results of 5 annual scans (before MRI scans ceased per the 2012 protocol amendment).

Study sites: The study was carried out at 126 active sites (ie, sites that recruited at least 1 patient) in 21 countries: 4 in Austria, 12 in Canada, 5 in Chile, 1 in Czech Republic, 3 in Denmark, 2 in Estonia, 5 in Finland, 14 in France, 11 in Germany, 9 in Italy, 4 in The

Netherlands, 3 in Norway, 9 in Poland, 3 in Portugal, 10 in Russia, 2 in Sweden, 1 in Switzerland, 6 in Turkey, 9 in Ukraine, 9 in the United Kingdom, and 4 in the United States.

Randomization: In the core study, patients were centrally randomized via an interactive voice response system (IVRS) in a 1:1:1 ratio (blocked randomization [block size: 6] within strata) to 1 of 3 treatment groups (placebo, teriflunomide 7 mg, or teriflunomide 14 mg daily). Randomization was stratified based on center and by EDSS score (≤3.5 or >3.5). Study medication was dispensed by treatment kits with preprinted 5-digit medication kit numbers randomly assigned by the IVRS. Every 12 weeks during the study, the investigational site was to contact the IVRS to allocate a new medication kit number to a patient that corresponded to the treatment designated by the randomization number; each patient received a total of 9 medication kits.

In the extension study, patients continued to receive the same teriflunomide double-blind treatment, except for patients who were previously randomized in the placebo group and who were blindly randomized in a 1:1 ratio to either the 7 mg/day or 14 mg/day teriflunomide treatment arm. At extension Visit 1, the investigator called the IVRS to dispense the treatment for the extension study protocol. Every 12 weeks during the study, the investigational site was to contact the IVRS to allocate a new medication kit number to a patient that corresponded to the treatment designated by the randomization number.

Blinding: The study medication teriflunomide (7 mg and 14 mg) was supplied as identical white to slightly yellow film-coated biconvex tablets sealed in child-resistant blister packs. Treatment codes were maintained by the IVRS and no code-breaking material was provided to the site.

Supplementary results

Recruitment dates: Recruitment for the core TEMSO study took place from 24 September 2004 to 13 March 2008,[3] and patients were eligible for inclusion in the extension after completing 108 weeks of treatment in the core TEMSO study.

Patients who discontinued teriflunomide following hematological disorders: Three patients discontinued for neutrophil count decrease (7-mg/7-mg group, n = 1; placebo/7-mg group, n = 2) and 1 patient discontinued for neutropenia (placebo/14-mg group). Additionally, there was a discontinuation for leukopenia (placebo/14-mg group) and a discontinuation for white blood cell count decrease (14-mg/14-mg group).

Reference
e1.   McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of neurology 2001;50:121-127.