**INTRODUCTION**

Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS 

In the TENERE (NCT00771881) study, teriflunomide 14 mg significantly reduced annualised relapse rate (ARR) and risk of disability progression compared with placebo. 

- Teriflunomide 7 mg significantly reduced ARR compared with placebo.
- For patients who had received other disease-modifying therapies (DMTs) prior to study entry, a minimum time interval between discontinuation of previous treatment and start of study treatment was required.
- Patients were excluded if they had ever received natalizumab, any investigational drug in the last 6 months, interferon-β or cyclosporine in the last 4 (TEMSO) or 2 (TOWER) months, glatiramer acetate, or intravenous immunoglobulins in the last 3 months.

In the phase 3 TENERE (NCT00833377) study, there was no difference between teriflunomide 14 mg and subcutaneous interferon beta-1a (INN, IFN-beta-1a) on either the primary endpoint of time to treatment failure (P=0.6), or the secondary endpoint of ARR (P=0.6).

The study was designed as a teriflunomide superiority study.

- In an open-label extension of TENERE, all patients, including those who were previously randomized to IFN-beta-1a, received teriflunomide 14 mg without an intervening washout interval.
- Patients who require a switch in treatment may potentially be considered suboptimal responders (due to safety/tolerability and/or efficacy reasons) and at higher risk of disease activity.
- Data from the pooled TEMSO/TOWER placebo-controlled studies, where a time interval between previous DMT use and study entry was required, together with data from patients switching directly from placebo to an uncontrolled TENERE extension, provide complementary information that could clarify treatment effects in patients switching to teriflunomide from other DMTs.

**RESULTS**

- **Baseline disease characteristics for the TEMSO/TOWER modified intent-to-treat population (N=2251) are shown in Figure 1.** Disease activity was no longer in the subgroup of patients who used 1 or 2 prior DMTs vs those who used ≥3 prior DMTs.

- Patients who had used 1 prior DMT in the 2 years before study entry had received ≥1 of the following DMTs: glatiramer acetate, IFN-beta-1a, fingolimod, or oral fingolimod.

- Of 241 patients who completed the TENERE study, 237 (98%) entered the extension (2 patients withdrawn due to consent violation) and treatment assignment was maintained in the TENERE extension are shown in Table 1 and were broadly similar across the 14-mg/14-mg, 7-mg/14-mg, and IFN-beta-1a/14-mg treatment groups.

**Annualized Relapse Rate**

- In the patients randomized to receive placebo in TEMSO/TOWER, within each subgroup defined by prior DMT use, adjusted ARRs were higher for patients who had used 2 or 1 prior DMT or in prior treatment-naïve patients. 

- Teriflunomide 14 mg consistently reduced ARR in all subgroups defined by prior DMT use (Figure 1), with no significant treatment-by-subgroup interactions in any subgroup defined by prior DMT use. 

- Adjusted ARRs were derived using the Poisson model, with the total number of confirmed relapses with onset between inclusion date and last-dose date as the response variable, Treatment Duration, Expanded Disability Status Scale, and region as covariates, and log-transformed treatment duration as a covariate.

**Disability Progression (Pooled TEMSO and TOWER Studies)**

- In the placebo arms of each subgroup defined by prior DMT use, there was a greater risk of disability progression in patients who had received 1 prior DMT compared with treatment-naïve patients. Although no statistically significant (possibly due to smaller sample size), the risk was also greater in patients who had used ≥2 prior DMTs (Figure 2).

- Teriflunomide 14 mg reduced the risk of disability progression in all subgroups defined by prior DMT use vs placebo (Figure 2), with significant treatment-by-subgroup interactions; reductions were significant in patients who had received 1 prior DMT (P=0.007) and P=0.0505 in patients who had received 2 prior DMTs.

**Safety**

- TEMSO and TOWER demonstrated a consistent and manageable safety profile for teriflunomide, similar for the 14-mg and 7-mg doses.

- The incidence and nature of adverse events in the TENERE extension were similar in all groups and consistent with those seen in TENERE.

**CONCLUSIONS**

- In the pooled TEMSO/TOWER dataset, teriflunomide 14 mg reduced ARR and disability progression across all subgroups defined by prior DMT use.

- In the TENERE extension study, ARR remained low in patients switching from sc IFN-beta-1a to teriflunomide 14 mg.

- Analyses of the pooled TEMSO studies and TENERE extension demonstrate efficacy for teriflunomide, regardless of pretrial therapy.

- Efficacy, supported by statistically significant results as well as numerical trends in this post hoc analysis with small subgroups of patients, and patient safety was observed in patients who were previously used and discontinued other DMTs (with or without a washout period) before commencing teriflunomide treatment.

**REFERENCES**


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**Disclosures**

Disclosures: The bodies of the authors of this work were covered by a patent for treatment of relapsing-remitting multiple sclerosis with teriflunomide (Genzyme/Sanofi). 

**Disclaimer**

Genzyme is approved in many countries, including the US and the European Union, for the approved indication. Please check local regulatory status and product labeling before prescribing. Continued passive exposure to teriflunomide may result in the development of sensitization.