MEDIA BACKGROUNDER

Teriflunomide: A novel oral drug being investigated for the treatment of Multiple Sclerosis (MS)

1. Background

Teriflunomide is a new oral disease-modifying therapy (DMT), discovered by sanofi and developed specifically for the treatment of patients with various relapsing forms of MS.

Teriflunomide, $\text{C}_{12}\text{H}_9\text{F}_3\text{N}_2\text{O}_2$

Teriflunomide is a new chemical entity being studied in a far-reaching and ambitious clinical program which will include approximately 4,995 patients in 36 countries.

2. Clinical development program with teriflunomide in monotherapy

The first randomized double-blind placebo-controlled Phase II proof of concept (POC) study with teriflunomide in monotherapy was published in 2006 in Neurology\(^1\). The duration was nine months. This study demonstrated that the median number of combined unique active magnetic resonance imaging lesions was reduced significantly compared to placebo for both doses of teriflunomide (7 mg and 14 mg) with a favorable safety profile.

At the end of the nine months treatment period, patients were offered the opportunity to enter a long-term extension study. All patients originally on placebo were switched to either teriflunomide 7 mg or 14 mg. Results from over six years, as well as over eight years, have previously been presented at the European and for Treatment and Research in Multiple Sclerosis (ECTRIMS) congress, and this year results of a nine-year follow up study is being presented at the joint congress of the European and American Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS), taking place 19-22 October 2011,
Amsterdam, The Netherlands. Teriflunomide was well tolerated over the nine-year study period, with a safety profile that was consistent with that reported during the 36 weeks of double-blind treatment in the Phase II study.

Following the positive Phase II trial results, an extensive Phase III clinical program with teriflunomide in monotherapy was launched. The Phase III clinical program encompasses a broad range of disease stages from clinically isolated syndrome (CIS) to relapsing forms of MS.

This clinical program includes TEMSO with overall results recently been published online in the NEJM ECTRIMS 2009, TOWER3 and TENERE4, an extension of the TEMSO trial and one study in CIS patients, TOPIC5. These studies are being carried out in more than 30 countries and involve over 3,000 patients. TEMSO was the first in this series of Phase III trials to disclose data in 2010, during the ECTRIMS congress.

3.1 TEMSO trial

TEMSO (TEriflunomide Multiple Sclerosis Oral) was a Phase III multi-centre, multinational, randomized, placebo-controlled, double-blind, and parallel group study in ambulatory patients with relapsing multiple sclerosis (RMS). Patients were randomly assigned to one of the three treatment groups to receive a once-daily oral dose of placebo, teriflunomide 7 mg or teriflunomide 14 mg for 108 weeks. The primary objective was to determine the efficacy of teriflunomide compared with placebo in reducing the annualized relapse rate. The secondary objectives were to determine the effects of teriflunomide compared with placebo on the accumulation of disability and magnetic resonance imaging (MRI) variables.

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TEMSO Phase III study design
Phase III study involved 1,088 patients over a period of two years. These patients were randomized in 21 countries worldwide: Austria; Canada; Chile; Czech Republic; Denmark; Estonia; Finland; France; Germany; Italy; Netherlands; Norway; Poland; Portugal; Russian Federation; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; United States.

An extension of the Phase III trial, involving 742 patients on the long-term randomised double-blind study, showed that both doses of teriflunomide were well tolerated with up to four years of follow-up demonstrating a favorable safety profile.

Results were consistent with the core two-year TEMSO study and will be presented at ECTRIMS 2011.

2.2 TOWER trial

TOWER is an international (26 countries), multi-centre, double-blind, parallel-group, placebo-controlled study designed to assess the efficacy and safety of teriflunomide in 1,168 patients with RMS. The TOWER study was designed to further support the benefit/risk profile demonstrated from the TEMSO results. As for TEMSO, the primary objective is to evaluate the effect of teriflunomide (7 mg & 14mg) on annualized relapse rates vs. placebo. The efficacy on delaying the accumulation of disability, fatigue and health-related quality of life, as well as safety, will also be evaluated as secondary endpoints.

The average duration of the study period per patient is expected to be approximately two years, depending on when the patient is randomized. The completion date is estimated to be February 2012.
2.3 TENERE trial

TENERE is an international, multi-centre, randomized, parallel-group, single-blind study comparing the effectiveness and safety of teriflunomide versus IFNβ in 324 patients with relapsing multiple sclerosis.

The objective is to make a head to head comparison of the effectiveness and safety of two doses (7 mg or 14 mg oral once daily) of teriflunomide in comparison to IFNβ 1a (44µg, SC, three times per week) in RMS patients over one year of treatment. The primary endpoint is the “time of failure”, defined as the first occurrence of relapse or permanent study treatment discontinuation for any cause whichever comes first.

TENERE Phase III study design

Time to failure is an effectiveness endpoint that mimics what occurs in real life situations. The duration of treatment for the last patient in the trial is one year. The end of primary data collection has occurred for this study.

2.4 TOPIC trial

TOPIC is an international (19 countries), multi-centre, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two years of treatment with teriflunomide once daily 7 mg and 14 mg vs. placebo in 780 patients with a first clinical episode suggestive of MS. The primary objective of this study is to demonstrate the efficacy of teriflunomide in reducing time to conversion to clinically definite MS in patients presenting with their first clinical episode consistent with MS.
TOPIC Phase III study design

The TOPIC study in CIS is expected to take longer to recruit than other Phase III trials regarding the low number of CIS patients, with estimated completion at the end of 2015.

3. Clinical development program with teriflunomide in adjunct therapy

Two separate Phase II randomized, multinational, double-blind, placebo controlled parallel-group design pilot studies to assess the safety and efficacy of teriflunomide for 24 weeks in adjunct therapy were completed. It consisted of two placebo-controlled, double-blind, parallel-group studies, in patients with relapsing MS on stable treatment with either IFNβ (PDY6045) or glatiramer acetate (PDY6046). Patients were treated with placebo, 7 mg or 14 mg teriflunomide in addition to the stable dose of IFNβ or glatiramer acetate. The duration of treatment was 24 weeks; upon completion the patients were offered the option to stay on the same therapy and participate in a 24 week extension study.

Results of these phase II trials, presented at ACTRIMS 2010\(^6\), indicated that teriflunomide has an acceptable safety profile with promising efficacy as an adjunct therapy. Teriflunomide is the first oral DMT to have completed phase II trials in adjunctive therapy.

Due to these encouraging results observed in the initial phase II studies with teriflunomide, particularly with the robust results observed in adjunct to IFNβ, a phase III adjunctive therapy study (TERACLES) has been initiated\(^7\) comparing teriflunomide when added to a stable background of IFNβ to IFNβ plus placebo (this study is currently recruiting in 18 countries).

References:


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4. A Multi-center, Randomized, Parallel-group, Rater-blinded Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis. [TENERE]; Date of Access October 8, 2011
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5. Phase III Study With Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis [TOPIC] (Estimated study completion: November 2015) (Currently recruiting patients). Date of Access October 8, 2011
http://clinicaltrials.gov/ct2/show/NCT00622700?term=TOPIC&rank=1


7. Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis and treated with Interferon Beta [TERACLES] (Currently recruiting patients). Date of Access October 8, 2011
http://clinicaltrials.gov/ct2/show/NCT01252355?term=TERACLES&rank=1