IP058

Teriflunomide for Relapsing-Remitting Multiple Sclerosis: A Multicentre, Non-Interventional, Prospective Study in Germany (TAURUS-MS I)

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OBJECTIVE

- **To assess the effectiveness, treatment satisfaction, and safety of teriflunomide in real-world clinical practice in Germany**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of multiple sclerosis (MS) in over 80 countries, including the United States and countries of the European Union. As of January 2019, over 96,800 patients were being treated with teriflunomide, with a total real-world exposure of approximately 237,400 patient-years as of September 2018. In Germany, approximately 13,800 patients were being treated with teriflunomide (as of May 2019).[1]
- Teriflunomide has demonstrated efficacy and safety in placebo-controlled Phase 3 studies (TEMSO[2] [NCT00134563] and TOWER[3] [NCT00751881]) in patients with relapsing forms of MS, and in patients with a first clinical episode suggestive of MS (TOPIC[4] [NCT00622700])
- TAURUS-MS I is a 2-year, non-interventional, prospective observational study conducted in Germany in patients with relapsing-remitting MS (RRMS) receiving teriflunomide 14 mg once daily[5]
- Here we present effectiveness, treatment satisfaction and safety findings from TAURUS-MS I

METHODS

Study Design

- TAURUS-MS I was conducted between January 2014 and April 2017 at clinics of 307 neurologists in Germany
- Patients were eligible to take part if they met the following criteria: aged ≥18 years, were already receiving teriflunomide 14 mg once daily as determined by the attending physician (independently of the decision to participate in the study), had a diagnosis of RRMS, were able to complete the study questionnaires, provided informed consent, and had no contraindications according to the Summary of Product Characteristics
- Data were recorded during routine clinic visits scheduled at baseline (approximately 4 weeks after initiation of teriflunomide treatment), month 3, month 6 and at 6-month intervals thereafter until month 24
- Recorded parameters included:
  - Patient demographics
  - Effectiveness (relapses and Expanded Disability Status Scale)
  - Fatigue Severity Scale
  - Treatment Satisfaction [Treatment Satisfaction Questionnaire For Medication (TSQM-9)]
  - Safety

Statistical Analyses

- For differences in relapse rates, TSQM-9 scores, and alanine aminotransferase (ALT) level changes from baseline, respectively, paired t-tests were used, and only patients with data at both timepoints were analysed
- For effectiveness and treatment satisfaction analyses, the patient population was stratified by prior treatment status:
  - treatment-naïve: patients with no prior disease modifying therapy (DMT) documented
  - patients recently treated with another DMT ("switchers"): patients whose most recent prior DMT was discontinued within 6 months before treatment initiation with teriflunomide
  - among switchers: recently treated with interferon (IFN)ß products or glatiramer acetate ("switchers from injectables")
- Demographic data were reported descriptively

RESULTS

Study Population

- A total of 1,128 patients were included in the per protocol set (PPS), and 1,139 patients were included in the safety analysis set (SAS)
- Patients in the PPS were predominantly female (67.5%) and had a mean (SE) age of 44.9 (0.3) years **(Table 1)**
- Three-quarters (848/1,128, 75.2%) of patients had previously received MS-specific immune therapy, and 24.8% (280/1,128) were treatment-naïve
- 593 patients had received a prior DMT, which was discontinued within 6 months before treatment initiation with teriflunomide, and were therefore classified as switchers
- The switcher subgroup consisted mostly of switchers from injectables (372/593, 62.7%)
- Main reasons for termination of prior DMT of patients with previous MS therapy documented were adverse reactions (500/848, 59.0%), insufficient efficacy (205/848, 24.2%), a desire to switch to an oral DMT (137/848, 16.2%), and a desire for treatment break (88/848, 10.4%)
- The most common reasons for teriflunomide treatment discontinuation in the TAURUS-MS I study were adverse events (AE) (40.1%), insufficient efficacy (22.7%), and patient request (11.6%)

CONCLUSIONS

- **In the real-world TAURUS-MS I study, teriflunomide was associated with reduced relapse rates after 12 months in patients with RRMS, independent of their prior treatment status**
- **Patients who recently switched to teriflunomide from another DMT have mainly been treated with injectables and showed significant improvements in treatment satisfaction as measured by changes of TSQM-9 scores**
- **Teriflunomide was generally well tolerated and the AE profile in the real-world setting was consistent with that observed in clinical trials**
  - **The mean ALT value curves peaked after approx. 3 months followed by an overall reduction to baseline values within the observation period**
  - **Incidence of hair thinning was lower than reported previously**
- **These findings supplement the effectiveness and safety data of teriflunomide in the real-world setting**

Table 1. Baseline Demographics and Patient Characteristics

	TAURUS-MS I (n=1,128)
Age in years, mean (SE)	44.9 (0.3)[a]
Sex, female, n (%)	761 (67.5)
Time (years) since MS diagnosis, mean (SE)	8.9 (0.2)[b]
Baseline EDSS, mean (SE)	2.3 (0.1)[c]
Relapses in 24 months prior to baseline, mean (SE)	1.0 (0.0)[d]
Number of T2 lesions, mean (SE)	10.3 (0.4)[e]
Number of Gd+ lesions, mean (SE)	0.5 (0.1)[f]
Previous MS therapy documented, n (%)	848 (75.2)
IFNβ-1a IM	257 (22.8)
IFNβ-1a SC	268 (23.8)
IFNβ-1b SC	222 (19.7)
Glatiramer acetate	303 (26.9)
Oral azathioprine	51 (4.5)
Immunoglobulin IV	13 (1.2)
Other	154 (13.7)
No previous MS therapy documented, n (%)	280 (24.8)

a: n=1126; b: n=1075; c: n=947; d: n=1117; e: n=514; f: n=681;
Gd+: gadolinium-enhancing; IFN: interferon; IM: intramuscular; IV: intravenous; SC: subcutaneous; SE: standard error.

Effectiveness

- A total of 754 patients had data available on the number of MS relapses at both baseline and following 12 months of teriflunomide treatment
- The mean (SD) relapse rate per year was significantly lower after 12 months of treatment with teriflunomide 14 mg once daily [0.24 (0.53)] compared with 12 months pre-baseline [0.59 (0.76)]
- For the subgroups treatment-naïve and switchers, data on number of relapses at both timepoints was available for 198 and 406 patients, respectively
- The mean (SD) relapse rate of treatment-naïve patients in the pre-baseline period was 0.82 (0.73), which was significantly decreased in the corresponding period after teriflunomide initiation 0.25 (0.55) **(Figure 1)**
- In patients switching from previous DMT (switchers), the mean relapse rate (SD) significantly decreased from pre-baseline 0.48 (0.76) to 0.22 (0.50) after teriflunomide initiation **(Figure 1)**

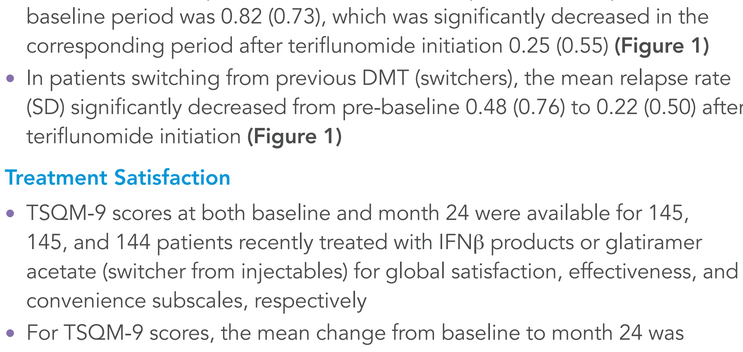
Treatment Satisfaction

- TSQM-9 scores at both baseline and month 24 were available for 145, 145, and 144 patients recently treated with IFNβ products or glatiramer acetate (switcher from injectables) for global satisfaction, effectiveness, and convenience subscales, respectively
- For TSQM-9 scores, the mean change from baseline to month 24 was analysed, and significant improvements in all subscales could be shown **(Figure 2)**
- Mean (SE) TSQM-9 scores increased significantly for the global satisfaction [15.90 (2.11), p<0.001], effectiveness [7.11 (2.37), p=0.003], and convenience [17.25 (2.26), p<0,001] subscales **(Figure 2)**

Safety

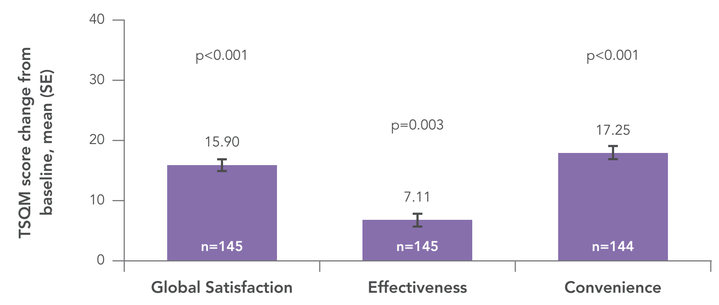
- Teriflunomide was generally well tolerated. AEs were experienced by 35.8% of patients, and serious AEs were experienced by 13.0% of patients **(Table 2)**
- The most common AEs were diarrhoea (4.8%), MS relapse (4.2%), and hair thinning (3.3%)
- There was one death (0.1%) due to fatal bronchopulmonary aspergillosis during the observation period
- It has been shown before that serum ALT levels in general are influenced by various factors, including gender[6]
- Mean ALT levels were therefore plotted by gender over time **(Figure 3)**

Figure 1. Mean Relapse Rates after 12 Months versus Baseline in Patients Stratified by Prior Treatment Status



a: Includes period of 12 months prior to teriflunomide treatment initiation.

Figure 2. Mean (SE) Change from Baseline in TSQM Global Satisfaction, Effectiveness, and Convenience Scores after 24 Months among „Switchers from Injectables"



SE: standard error; TSQM: Treatment Satisfaction Questionnaire for Medication.

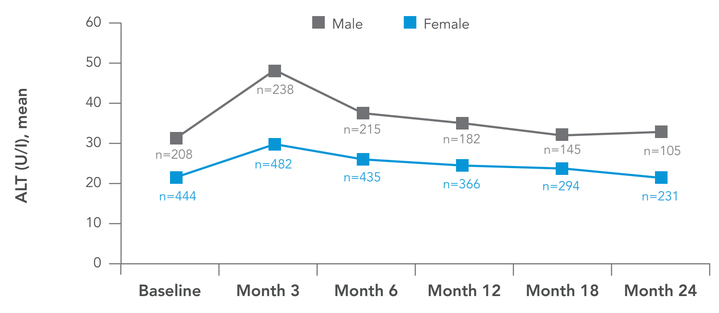
- The time curve of mean ALT values of female patients was generally below the curve of male patients, and in both time courses ALT levels peaked approx. 3 months after teriflunomide initiation **(Figure 3)**
- Mean ALT value change from baseline was analysed for male and female patients respectively, with available data on both visits **(Table 3)**
- Mean ALT levels increased significantly after 3 and 6 months compared to baseline for male and female patients, respectively, and also after 18 months for female patients **(Table 3)**

Table 2. Adverse Events

n (%)	TAURUS-MS I (n=1,139)
Any AE	408 (35.8)
Any serious AE	148 (13.0)
Most common AEs (MedDRA preferred term)	
Diarrhoea	55 (4.8)
MS relapse	48 (4.2)
Hair thinning (alopecia)	38 (3.3)
Viral upper respiratory tract infection	31 (2.7)
Influenza	22 (1.9)
Drug ineffective	19 (1.7)
Urinary tract infection	18 (1.6)
Bronchitis	17 (1.5)
Hypertension	16 (1.4)
Influenza-like illness	16 (1.4)
Nausea	15 (1.3)

MedDRA: Medical Dictionary for Regulatory Activities; AE: adverse event.

Figure 3. Mean Serum ALT (U/l) Levels by Gender over Time of Study



In case of several measurements, the worst value was chosen; only patients with no liver dysfunction were included; ALT: alanine aminotransferase; U/l: units per liter.

Table 3. Mean ALT (U/l) Value Change from Baseline* by Gender

Male	n	mean change (95% CI)	p
After 3 Months	178	8.75 (6.43, 11.10)	<0.001
After 6 Months	147	8.14 (5.11, 11.17)	<0.001
After 12 Months	127	3.77 (-0.19, 7.72)	0.062
After 18 Months	103	0.81 (-2.97, 4.60)	0.671
After 24 Months	68	-0.59 (-5.85, 4.66)	0.823
Female	**n**	**mean change (95% CI)**	**p**
After 3 Months	364	9.14 (5.87, 12.41)	<0.001
After 6 Months	307	3.70 (2.04, 5.35)	<0.001
After 12 Months	257	1.45 (-0.33, 3.23)	0.111
After 18 Months	204	2.46 (0.07, 4.84)	0.044
After 24 Months	155	-1.01 (-3.50, 1.49)	0.426

In case of several measurements, the worst value was chosen; only patients with no liver dysfunction were included; ALT: alanine transaminase; U/l: units per liter; *only patients with data on both visits were analysed

SE: standard error; SD: standard deviation

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* Audio comment in cooperation between Dr. Kallmann and Sanofi-Aventis Deutschland GmbH

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