Sponsor: Sanofi **Drug substance(s):** Teriflunomide	**Study Identifiers:** U1111-1205-3009; NCT03856619 **Study code:** TERIFL08918/ LPS15678
Title of the study: A single arm phase IV clinical trial to describe the Safety And efficacy of Aubagio® in patients with relapsing forms of multiple sclerosis (SAFE trial)	
Study centers: 15 Centers and 1 country	
Study period: Study Initiation date [date of first patient in (FPI)]: 27-Mar-2019 Study completion date [date of last patient out (LPO)]: 13 May 2022 Study Status: Completed	
Phase of development: Phase IV	
Objectives: **Primary:** To describe the safety of Aubagio® in patients with relapsing forms of multiple sclerosis **Secondary:** To describe the efficacy of Aubagio® in patients with relapsing forms of multiple sclerosis	
Methodology: This study was a multicentric, single arm, noncontrolled phase 4 clinical trial. This study was conducted only in India. This study was conducted as per the locally approved label. This is an outpatient study and consists of 7 on-site visits. The study comprises of screening visit (within 2 weeks of baseline visit), baseline visit, followed by clinic visits conducted at the end of 3 months (± 15 days), 6 months (± 20 days), 9 months (± 25 days), and 12 months (±30 days). Post treatment safety follow up visit was conducted 4 weeks (± 5 days) after the patient takes the last dose of teriflunomide. For post treatment safety follow up visit in case the patient was unable to visit the clinic, this visit was done telephonically. The visit schedule consists of the following visits: 1.Screening (Visit 1, D-14): Onsite visit This visit was conducted within 14 days prior to baseline visit (V2). Only patients who met the eligibility criteria was screened. 2.Baseline Visit (V2, D1): Onsite visit At Visit 2, the patient was asked to confirm that there have been no relevant changes in his physical condition since screening.	

3.Clinic visits (V3, V4, V5 and V6)

Study drug dispensation (V3, V4, V5): The patient received sufficient tablets to last until the next planned study medication administration visit of 3 months later, including a reserve to allow for unplanned postponement of the next visit as per the defined window period for the visit.

4.Post treatment safety follow up visit (V7- End of study)

Following the last dose of IMP either as scheduled or prematurely, a post-treatment follow-up visit is performed 4 weeks after the end of treatment visit. This visit was conducted as a phone call visit, or an on-site visit. In case of ongoing or new adverse event during the post-treatment period, it was recommended to have an onsite visit.

Additional, visits were scheduled whenever considered necessary by the investigator especially following a neurological event or suspected MS relapse. It was preferred that all study visits take place in the morning. Fasting conditions (overnight fast or minimum of 8 hours fast) were required at Visit 1. When a patient is discontinued from study medication and/or withdraws from the study prematurely, the investigator performed all assessments included for V6.

Number of participants:

Planned:	193 patients
Screened:	132 patients
Eligible:	126 patients
Treated:	116 patients
Evaluated:	
Full analysis set:	126 patients
Safety population:	116 patients
Per protocol population:	90 patients

Diagnosis and main criteria for inclusion:

Patients aged ⩾18 years of age before screening were eligible to enroll. A signed written informed consent was a must to participate. The patient with relapsing form of multiple sclerosis at time of screening visit was also an important inclusion criterion.

Study products

Investigational medicinal product: Teriflunomide (Aubagio®)

Teriflunomide is available as pale blue to pastel blue, pentagonal film-coated tablets.

Composition: Active ingredient: Teriflunomide 14 mg

Excipients: lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating for the 14 mg tablet is composed of hypromellose, titanium dioxide, talc, polyethylene glycol and indigo carmine aluminum lake.

Route of administration: Teriflunomide tablet was taken orally once a day as per approved labelling. It was advised to take it approximately at the same time every day to ensure compliance. Teriflunomide tablet may be taken with or without food. Patients were be encouraged to take their study medication at approximately the same time each day.

If any doses of study medication were missed, the patient resumed his or her current dosing regimen at the next scheduled dosing time with no attempt made to catch up on the missed doses (eg, missed Monday and Tuesday, restart on Wednesday with 1 dose).

Duration of study intervention: Up to 12 months

Post-treatment follow-up: Up to 4 weeks

Criteria for evaluation:

Primary:

•Incidence, duration, severity (mild/moderate/severe), and outcome of any adverse events (AEs), serious adverse events (SAEs) during the study duration

Secondary:

•Annualized relapse rate, defined as number of relapses per patient-year

•Clinical outcomes: Time to first relapse

•Proportion of patients who remain relapse free during the study duration and also at the end of 3 months, 6 months and 9 months

•Neurological impairment/disability will be compared at the end of 3 months, 6 months, 9 months and 12 months as compared to baseline using Expanded Disability Status Scale (EDSS)

•Proportion of patients free of disability progression (disability will be assessed using EDSS)

•Drug compliance (using patient diary)

•Patient diary will capture if any drug dose is missed and safety events (if any)

Statistical methods:

·General Conventions:

Level of significance for statistical tests was 0.05 two-sided. All analyses were done using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Safety endpoints was analyzed in a descriptive manner. Continuous data are reported using the following descriptive statistics:

1.Number of observations (n)

2.Mean and Standard deviation (SD)

3.Minimum (min) and Maximum (max)

4.Median

Categorical data are presented using frequency (n = number of patients; m = number of events) and percentage (%). Listings was provided for all data recorded in eCRF to study patient profiles. All listings are sorted by patient ID and date. Unscheduled visit data are listed and not included in summaries.

All p-values are displayed to four decimal places, with p-values less than 0.0001 presented as '0.9999'. Minimum and maximum values are reported in the units of collection with 3 decimals being maximum value; the mean, median and standard deviation are presented with 1 decimal place more than the units of collection. Percentages for categorical summaries are represented to 1 decimal place.

·Multiplicity Adjustment:

Since there is only one primary endpoint defined in the study as per the protocol, multiplicity adjustment was not required.

·Subgroup for Analysis:

All primary and secondary end point analyses were displayed by the following subgroup categories:

· IMP prior to V1: Patients took Teriflunomide before Visit 1 Patients who were exposed to Teriflunomide before they were enrolled into the study will be summarized under this group.

· IMP later than V1: Patient took teriflunomide only after Visit 1 Patients who were exposed to Teriflunomide only after they were enrolled into the study will be summarized under this group.

Summary Results:

・Demographic and other baseline characteristics:

The demographics and other baseline characteristics were analyzed for the patients belonging to the FAS population (N=126 patients). The population predominantly consists of female patients (n=90, 71.4%, N=126). Amongst 90 female patients, there were 61 (67.8%, N=126) patients with childbearing potential. The patients were of age ranging from 18 years to 65 years, height 143 cm to 190 cm and weight 35.3 kg to 127 kg.

The mean (SD) for the systolic blood pressure was 118.4 (12.10) mmHg, diastolic blood pressure 78.6 (7.56) mmHg, heart rate was 81.6 (10.71). An abnormality (any abnormality during physical examination) was observed in 8 patients (6.3%, N=126) for the physical examination result. As per investigators interpretation there were 9 patients (7.1%, N=126) who had abnormal Electrocardiogram result. The observed abnormalities were not clinically significant.

・Exposure:

In safety population (N=116 patients) who have taken at least one dose of the IMP, there were 18 patients (15.5%, N=116) who took Aubagio® before the baseline and the remaining 98 patients (84.5%, N=116) took the study drug after the baseline. About 41.4% (n=48, N=116) of the patients missed at least one dose of Aubagio® during the study treatment duration. No patients took overdose of the drug.

・Efficacy results:

The efficacy endpoints were analyzed for the per-protocol population (N=90). The Expanded Disability Status Scale (EDSS) was used for quantifying disability in MS patients and monitoring changes in the level of disability over time in study. The overall mean (SD) EDSS score was 2.71 (1.901) with median 2.00, at the end of 12 months the mean (SD) score was 2.45 (1.874) with no change in the median since baseline. The proportion of patients free of disability progression reduced from 76.6% (end of 3 months) to 68.9% at end of 12 months.

・Safety results:

There were 60 patients (57.1%, N=116) who reported about 169 events. Among those 169 events that were reported, there were 162 treatment emergent events reported by 58 patients (50.0%, N=116). The most reported events fall under the nervous system disorder class. There were 22 patients (19.0%, N=116) who reported events that were related to the study drug. The events reported by 10 patients (8.6%, N=116) were serious and amongst them 1 patient (0.9%, N=116) reported fatal event. About 8 patients (6.9%, N=116) discontinued from the study intervention and 7 patients (6.0%, N=116) discontinued from the study. There were 5 patients who reported events of special interest, which includes events due to increased ALT level.

・Pharmacokinetic results:

Not applicable

・Pharmacodynamic results:

Not applicable

・Other results:

Not applicable

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