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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor:	**Study Identifiers:**
Sanofi	UTN Number: U1111-1233-0136, NCT number: NCT04410965
Drug substance(s):	**Study code:**
Teriflunomide	BDR16019

Title of the study:

Evaluation of the relationship between ABCG2 mutation and teriflunomide exposure and safety in Chinese RMS patients treated with teriflunomide 14 mg once daily for 24 weeks

Study center(s):

18 centers in China

Study period:

Date first participant enrolled: 20 May 2020

Date last participant completed: 12 JUL 2021

Study Status: Completed

Phase of development: Phase 4

Objectives:

Primary: Evaluate the relationship between ABCG2 mutation (rs2231142) and teriflunomide exposure, during 24-week treatment with teriflunomide 14 mg.

Secondary: Characterize the safety (adverse events[AEs], such as alanine aminotransferase[ALT] enhancement, hair thinning, diarrhea, nausea, etc.) during 24-week treatment with teriflunomide.

Methodology:

This was a phase 4, non-controlled, interventional, non-randomized, same treatment in both groups, multi-center, 24-week study to evaluate the influence of genetic polymorphism of ABCG2/BCRP (rs2231142) on the pharmacokinetics of daily oral administration of teriflunomide 14 mg in Chinese participants with relapsing multiple sclerosis.

The study consisted of a screening period, within 28 days before the first dose of teriflunomide. After screening period, 80 participants were enrolled and genotyped for the rs2231142 mutation, 40 carriers and 40 non-carriers were included, respectively. During the 24 weeks, participants were treated with daily oral administration of 14 mg teriflunomide.

There were 8 visits at the investigational site during the trial:

Visit 1: Screening visit, start of screening period (days -28 to day1/ Visit 2)

Visit 2: Baseline visit (safety assessment), start of 24-week treatment period for 80 eligible participants: 40 participants with wild type sequence and 40 participants with variant genotypes for ABCG2 c.421C>A.

Visits 3~7: Safety assessment (laboratory tests) was performed at visit 3~7 (Week 4, Week 8, Week 12, Week 16 and Week 20). Pre-dose blood samples were collected within 1 h prior to administration for PK analysis at visit 4~7 (Week 8, Week 12, Week 16 and Week 20).

Visit 8: End of Treatment (EoT) visit, completion of the treatment period (Week 24), and collection blood samples for PK analysis and laboratory tests. Also record the subjects' willingness to initiate accelerated elimination procedure.

Number of subjects:

Planned: 80

Screened: 117

Treated: 82

Evaluated:

Efficacy/pharmacodynamics: N/A

Pharmacokinetics: 82

Safety: 82

Diagnosis and criteria for inclusion:

Inclusion Criteria:

- Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
- Participants (EDSS score ≤ 5.5) according to the diagnosis of the neurologist (using the 2017 Revised McDonald Diagnostic Criteria for MS) and upon treatment initiation with teriflunomide according to the approved product information (PI) in China.
- Participants will be genotyped for the rs2231142 mutation, enrolled 80 participants should include:

  a. 40 wildtype patients

  b. 40 patients with ABCG2 (rs2231142) mutation
- Male and/or female participants:

  a. Male participants: A male participant must agree to use contraception during the intervention period and undergo the accelerated eliminated procedure after the last dose of study intervention and refrain from donating sperm during this period. Effective contraception should be used until it is verified that plasma concentrations of teriflunomide are less than 0.02 mg/L (0.02 mcg/mL).

  b. Female participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

  - Not a woman of childbearing potential (WOCBP) .

    OR

  - A WOCBP who agrees to follow the contraceptive guidance during the intervention period and undergo the accelerated elimination procedure (if necessary) after the last dose of study intervention. Effective contraception should be used until it is verified that plasma concentrations of teriflunomide are less than 0.02 mg/L (0.02 mcg/mL).
- Participants who has signed written informed consent prior to entering the screening phase of the study.

Exclusion Criteria:

- Participant not willing /being able to complete the questionnaires and examination.
- Participants who have taken leflunomide within 2 years prior to screening.
- Pariticipant who have taken teriflunomide within 2 years prior to screening.
- Participants with severe hepatic impairment, including active hepatitis B/C diagnosed.
- Known history of active tuberculosis (TB) or latent TB infection not adequately treated, either diagnosed by standard medical practice or guidelines (including skin or blood test, or as appropriate per local practice), according to local labeling.
- Relapse within 30 days prior to enrollment.
- Participants who have any contraindications to AUBAGIO according to the local product insert leaflet.
- History of a hypersensitivity of teriflunomide, leflunomide, or any the inactive ingredients in Aubagio.
- Human immunodeficiency virus (HIV) positive patients.
- Participants treated with:

  a. glatiramer acetate, interferons, or dimethyl fumarate within 1 month prior to enrollment.

  b. fingolimod, or intravenous immunoglobulins within 3 months prior to enrollment.

  c. natalizumab, other immunosuppressant or immunomodulatory agents, such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate, within 24 weeks prior to enrollment.

  d. cladribine or mitoxantrone within 2 years prior to enrollment.

  e. adrenocorticotrophic hormone (ACTH) or systemic corticosteroids for 2 weeks prior to enrollment.
- Participant treated with BCRP inhibitors (such as cyclosporine, eltrombopag, gefitinib).
- Participant not suitable for participation, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.
- Any specific situation during study implementation/course that may rise ethics considerations.
- Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Study products

Investigational medicinal product(s): Teriflunomide

Formulation/Form & composition: 14 mg tablet is a pale blue to pastel blue, pentagonal film-coated tablet with the dose strength, “14” imprinted on one side and engraved with the corporate logo on the other side. Each tablet contains 14 mg of teriflunomide.

Route(s) of administration: Oral administration

Dose regimen: A single dose of 14 mg taken with or without food orally once daily.

Duration of treatment: 24 weeks

Duration of observation*:* 26 weeks

Criteria for evaluation:

Efficacy/pharmacodynamics: N/A

Safety: Characterize the safety (AEs, such as ALT enhancement, hair thinning, diarrhea, nausea, etc.) during 24-week treatment with teriflunomide.

Pharmacokinetics: PK exposure C_{max} and AUC_{tau} estimated by population pharmacokinetic (PopPK) analysis. (to explore whether and/or how ABCG2 mutation affects teriflunomide exposure).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Whole blood samples of approximately 3 mL were collected for measurement of plasma concentrations of teriflunomide at each time point as specified in the schedule of activities(SoA).Samples were used to evaluate the PK of Teriflunomide. Each plasma sample was divided into 2 aliquots (1 each for PK and a back-up). At least one additional blood sample was collected after cholestyramine or activated charcoal treatment in the follow-up period until the concentrations of teriflunomide were ≤0.02 μg/mL.Plasma concentrations of teriflunomide were measured using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods with lower limits of quantification (LLOQ) of 0.1 μg/mL primarily for samples collected during the treatment period and 0.01 μg/mL mainly for samples collected during follow-up period following the washout/rapid elimination procedure.

Statistical methods:

Analysis Populations:

- Screened population:All participants who signed the Informed Consent Form (ICF).
- Safety population:All enrolled participants who had been exposed to AUBAGIO®.
- Pharmacokinetic population:All enrolled and treated participants who had at least 1 PK sample data. Participants were analyzed according to their genotype.

Safety analyses:

All safety analyses were performed on the Safety Population. The safety analysis was based on the reported AEs and other safety information including clinical laboratory data and vital signs. The baseline value was defined as the last available value before the first intake of AUBAGIO®. The summary of safety results were presented using standard descriptive statistic. method.

Pharmacokinetic analyses:

All pharmacokinetic analyses were performed on the Pharmacokinetic Population.

Individual PK model parameters were determined using a Bayesian approach based on a prior population PK model established for teriflunomide in adult patients. The quality of the model was considered acceptable for simulation of the individual PK profiles of the patients and further determine their teriflunomide steady state exposures (C_{maxss} and $AUC_{0\text{-}24ss}$). Estimated steady state C_{maxss} and $AUC_{0\text{-}24ss}$ were summarized by mean, SD, geometric mean, median, minimum, and maximum for c, 421C>A carriers and non-carriers.

Teriflunomide plasma observed concentrations were summarized by mean, SD, geometric mean, coefficient of variation, median, minimum, and maximum at each visit where a PK sample was taken for teriflunomide-treated participants.

Summary Results

All 117 patients signing ICF entered the Screened population. A total of 82 patients screened successfully (42 in Variant Type group and 40 in Wild Type group) and all entered both the Safety Analysis (SA) population and the Pharmacokinetic (PK) population. Among the subjects who screened successfully, 78 (95.1%) subjects completed the study. 4 subjects did not complete the study treatments, 2 subjects from Variant Type group and 2 subjects from Wild Type group. In the Variant Type group, the median duration of study drug exposure is 167.0 days (min: 27 and max 170 days). In the Wild Type group, the median duration of study drug exposure is 167.0 days (min: 55 and max 168 days). All subjects' treatment compliance in both

groups is within 80%~120%.The overall treatment compliance of the two groups was consistent.

Population characteristics: The female and male subjects in the Variant Type group were 30 and 12 respectively, and in the Wild Type group, were 28 and 12. The mean (SD) of age is 33.7 (8.40) years in the Variant Type group and 31.4 (8.13) years in the Wild Type group. The mean (SD) of height is 163.8 (6.71) cm in the Variant Type group and 164.1 (7.55) cm in the Wild Type group. The mean (SD) of weight is 59.49 (10.230) kg in the Variant Type group and 58.47 (10.630) kg in the Wild Type group. The mean (SD) of BMI is 22.100 (3.100) kg/m2 in the Variant Type group and 21.709 (3.706) kg/m2 in the Wild Type group.

All 82 subjects in the Safety Analysis (SA) population had no drug abuse history and their tuberculosis test results were normal. 25 (30.5%) subjects had "Tea, Coffee or Caffeinated beverages Usage" history (12 subjects in Variant Type and 13 subjects in Wild Type group); 9 (11.0%) subjects with current tobacco use (2 subjects in Variant Type and 7 subjects in Wild Type group) and 5 (6.1%) subjects with former tobacco use (all from Variant Type group); 3 (3.7%) subjects with current alcohol use (1 subject in Variant Type and 2 subjects in Wild Type group). Among 5 female subjects who had FSH test to confirm menopause, 3 were menopausal (1 subject in Variant Type and 2 subjects in Wild Type group). For virology tests (Hepatitis B Surface Antigen, Hepatitis C Virus Antibody, and HIV Antibody), all SA patients had a normal or abnormal but not clinically significant result.

Efficay/pharmacodynamic results: N/A

Safety results: There were 72(87.8%) subjects experienced AEs during the study, 39 (92.9%) subjects in the Variant Type group and 33 (82.5%) subjects in the Wild Type group. In the Variant Type group, 29 (69.0%) subjects experienced treatment-related TEAEs; 3 (7.1%) subjects experienced CTCAE grade 3 or higher TEAEs; 4 (9.5%) subjects experienced serious TEAEs; no subjects experienced treatment-related serious TEAEs; 4 (9.5%) subjects experienced TEAEs of special interest (AESI); and 1 (2.4%) subject experienced TEAEs leading to permanent discontinuation of study drug. In the Wild Type group, 17 (42.5%) subjects experienced treatment-related TEAEs; 1 (2.5%) subject experienced CTCAE grade 3 or higher TEAEs; no subjects experienced serious TEAEs which are all treatment-related; no subjects experienced TEAEs of special interest (AESI) or TEAEs leading to permanent discontinuation of study drug.

The most frequently reported serious TEAEs by preferred terms of any grade in Variant Type group were "Multiple sclerosis relapse" (3 subjects, 7.1%) and "Multiple sclerosis" (1 subjects, 2.4%). The most frequently reported serious TEAEs by preferred terms of any grade in Wild Type group were "Multiple sclerosis relapse" (3 subjects, 7.1%) and "Angina pectoris" (1 subjects, 2.5%). Only 1 of the 82 (1.2%) subjects experienced TEAEs leading to discontinuation of study drug (PT: Drug-induced liver injury) , which was in Variant Type group and assessed by the investigator as possibly related to the study drug. There were no deaths reported during the study.

Pharmacokinetic results: The 82 subjects had at least one PK samples and were then included in PK evaluation. Individual model parameter estimates were obtained by Bayesian estimation from the population parameters. From those individual model parameters, individual steady state exposure parameters (area under the curve of concentration $AUC_{0\text{-}24SS}$, the maximal concentration C_{maxSS} and the concentration 24h after the last administration, C_{minSS}) were determined. Teriflunomide plasma trough concentrations have reached at least 80% of steady state conditions by Week 8. Overall, mean plasma trough concentrations were similar for the two groups showing the absence of difference between variant and wild type subjects.

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