ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/05/2012

Grantor: CDER IND/IDE Number: 67,476 Serial Number:

Phase II Study of Teriflunomide as Adjunctive Therapy to Glatiramer Acetate in Subjects With Multiple Sclerosis

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00475865

Purpose

The primary objective was to estimate the tolerability and safety of 2 doses of Teriflunomide administered once daily for 24 weeks, compared to placebo, in patients with multiple sclerosis [MS] with relapses who were on a stable dose of Glatiramer Acetate [GA].

The secondary objectives were:

- to estimate the effect of the 2 doses of Teriflunomide, compared to placebo, in combination with a stable dose of GA on Magnetic Resonance Imaging [MRI] parameters, relapse rate and patient-reported fatigue;
- to perform pharmacokinetic analyses of the 2 doses of teriflunomide in combination with a stable dose of GA.

Condition	Intervention	Phase
Multiple Sclerosis	Drug: Teriflunomide Drug: Placebo (for teriflunomide) Drug: Glatiramer Acetate (GA)	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator, Outcomes Assessor), Randomized, Safety Study

Official Title: A Randomized, Multinational, Double-blind, Placebo-controlled, Parallel-group Design Pilot Study to Estimate the Tolerability, Safety, Pharmacokinetics, and Pharmacodynamic Effects of Teriflunomide for 24 Weeks When Added to Treatment With Glatiramer Acetate in Subjects With Multiple Sclerosis

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overview of Adverse Events (AE) [Time Frame: from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)] [Designated as safety issue: Yes]
  AE are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.
- Overview of AE With Potential Risk of Occurrence [Time Frame: from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)] [Designated as safety issue: Yes]
  AE with potential risk of occurrence were defined as follows: - Hepatic disorders; - Immune effects, mainly effects on bone marrow and infection; - Pancreatic disorders; - Malignancy; - Skin disorders, mainly hair loss and hair thinning; - Pulmonary disorders; - Hypertension; - Peripheral neuropathy; - Psychiatric disorders; - Hypersensitivity.
- Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [Time Frame: from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)] [Designated as safety issue: Yes]
  PCSA values are abnormal values considered medically important by the Sponsor according to predefined criteria based on literature review. Hepatic parameters thresholds were defined as follows: - Alanine Aminotransferase [ALT] >3, 5, 10 or 20 Upper Normal Limit [ULN]; - Aspartate aminotransferase [AST] >3, 5, 10 or 20 ULN; - Alkaline Phosphatase >1.5 ULN; - Total Bilirubin [TB] >1.5 or 2 ULN; - ALT >3 ULN and TB >2 ULN.

Secondary Outcome Measures:

- Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) [Time Frame: baseline (before randomization) and 24 weeks] [Designated as safety issue: No]
  Total lesion volume is the sum of the total volume of all T2-lesions and the total volume all T1-hypointense post-gadolinium lesions measured through T2/proton density scan analysis and gadolinium-enhanced T1 scan analysis. Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on cubic root transformed volume data (treatment group, region of enrollment, visit, treatment-by-visit interaction, baseline value (cubic root transformed), and baseline-by-visit interaction as factors).
- Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates) [Time Frame: 24 weeks] [Designated as safety issue: No]
  Number of Gd-enhancing T1-lesions per scan is obtained from the total number of Gd-enhancing T1-lesions observed during the study divided by the total number of scans performed during the study. To account for the different number of scans among participants, a Poisson regression model with robust error variance was used (total number of Gd-enhancing T1-lesions as response variable; log-transformed number of scans as "offset" variable; treatment group, region of enrollment and baseline number of Gd-enhancing T1-lesions as covariates).
- Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan [Time Frame: 24 weeks] [Designated as safety issue: No]
  Total volume of Gd-enhancing T1-lesions per scan is obtained from the sum of the volumes of Gd-enhancing T1-lesions observed during the study divided by the total number of scans performed during the study.
- Annualized Relapse Rate [ARR]: Poisson Regression Estimates [Time Frame: 24 weeks] [Designated as safety issue: No]
  ARR is obtained from the total number of confirmed relapses that occured during the treatment period divided by the sum of the treatment durations. Each episode of relapse - appearance, or worsening of a clinical symptom that was stable for at least 30 days, that persisted for a minimum of 24 hours in the absence of fever - was to be confirmed by an increase in Expanded Disability Status Scale [EDSS] score or Functional System scores. To account for the different treatment durations among participants, a Poisson regression model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group and region of enrollment as covariates).
- Pharmacokinetic [PK]: Teriflunomide Plasma Concentration [Time Frame: 24 weeks] [Designated as safety issue: No]
  Plasma concentrations of teriflunomide were measured using validated liquid chromatography-tandem mass spectrometry methods.

Enrollment: 123
Study Start Date: April 2007
Primary Completion Date: October 2009
Study Completion Date: October 2009

Arms	Assigned Interventions
Placebo Comparator: Placebo + GA Placebo (for teriflunomide) once daily concomitantly with glatiramer acetate (GA) for 24 weeks	Drug: Placebo (for teriflunomide) Film-coated tablet Oral administration Drug: Glatiramer Acetate (GA) Solution in prefilled syringe for subcutaneous injection Other Names: Copaxone®
Experimental: Teriflunomide 7 mg + GA Teriflunomide 7 mg once daily concomitantly with glatiramer acetate (GA) for 24 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726 Drug: Glatiramer Acetate (GA) Solution in prefilled syringe for subcutaneous injection Other Names: Copaxone®
Experimental: Teriflunomide 14 mg + GA Teriflunomide 14 mg once daily concomitantly with glatiramer acetate (GA) for 24 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726 Drug: Glatiramer Acetate (GA) Solution in prefilled syringe for subcutaneous injection Other Names: Copaxone®

Detailed Description:

The duration of the study period for a participant was approximatively 44 weeks broken down as follows:

- Screening period up to 4 weeks,
- 24-week double-blind treatment period*,

- 16-week post-treatment elimination follow-up period.

'*' Participants successfully completing the week 24 visit were offered the opportunity to enter the optional long-term extension study LTS6047 - NCT00811395.

Eligibility

Ages Eligible for Study: 18 Years to 55 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Definite MS diagnosis according to McDonald's criteria;
- Relapsing clinical course, with or without progression;
- Expanded Disability Status Scale [EDSS] less or equal to 5.5 (ambulatory);
- Stable dose of Glatiramer Acetate [GA] for at least 26 weeks prior to the screening visit;
- No onset of MS relapse in the preceding 60 days prior to randomization;
- Clinically stable for 4 weeks prior to randomization.

Exclusion Criteria:

- Other chronic disease of the immune system, liver function impairment or chronic pancreatic disease;
- Pregnant or nursing woman;
- Alcohol or drug abuse;
- Use of cladribine, Mitoxantrone, or other immunosuppressant agents such as Azathioprine, Cyclophosphamide, Cyclosporin, Methotrexate or Mycophenolate before enrollment;
- Human immunodeficiency virus [HIV] positive status;
- Any known condition or circumstance that would prevent in the investigator's opinion compliance or completion of the study.

The above information is not intended to contain all considerations relevant to a patient's potential participation in a clinical trial.

Contacts and Locations

Locations

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Investigators

Study Director:	ICD CSD	sanofi-aventis

More Information

Responsible Party:	Sanofi
Study ID Numbers:	PDY6046 2006-004893-29 [EudraCT Number] HMR1726D-2004 [HMR]
Health Authority:	Canada: Health Canada Germany: Paul-Ehrlich-Institut Austria: Federal Ministry for Health and Women United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	The recruitment initiated in April 2007 was completed in December 2008. A total of 148 patients were screened at 24 sites in 6 countries.
Pre-Assignment Details	Randomization was stratified by country. Assignment to groups was done centrally using an Interactive Voice Response System (IVRS] in a 1:1:1 ratio after confirmation of the selection criteria. 123 participants were randomized.

Reporting Groups

	Description
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA] for 24 weeks

	Description
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA] for 24 weeks

Overall Study

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Started	41 [1]	42 [1]	40 [1]
Treated	41 [2]	42	40
Completed	39	37 [2]	34 [2]
Not Completed	2	5	6
Adverse Event	0	3	4
Lack of Efficacy	1	0	0
Progressive disease	0	1	2
Participant did not wish to continue	1	0	0
Other than above	0	1	0

[1] randomized
[2] completed treatment period

Baseline Characteristics

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Baseline Measures

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA	Total
Number of Participants	41	42	40	123
Age, Continuous [units: years]	41.8 (8.5)	42.1 (7.8)	40.3 (7.5)	41.4 (7.9)

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA	Total
Mean (Standard Deviation)				
Gender, Male/Female [units: participants]				
Female	32	33	32	97
Male	9	9	8	26
Region of Enrollment [1] [units: participants]				
Europe	23	22	21	66
North America	18	20	19	57
Time since first diagnosis of Multiple Sclerosis [MS] [units: years] Mean (Standard Deviation)	7.61 (6.04)	8.82 (5.85)	7.60 (6.03)	8.02 (5.95)
Number of MS relapses [units: MS relapses] Median (Full Range)				
Within the past year	1 (0 to 3)	1 (0 to 3)	1 (0 to 4)	1 (0 to 4)
Within the past 2 years	1 (0 to 5)	1 (0 to 7)	1 (0 to 6)	1 (0 to 7)
Time since most recent MS relapse onset [units: months] Mean (Standard Deviation)	24.90 (34.84)	21.52 (30.48)	23.88 (31.53)	23.41 (32.09)
MS subtype [units: participants]				
Relapsing Remitting	39	40	37	116
Secondary Progressive	2	2	3	7
Progressive Relapsing	0	0	0	0
Baseline Expanded Disability Status Scale [EDSS] score [2] [units: units on a scale] Mean (Standard Deviation)	2.54 (1.11)	2.43 (1.23)	2.60 (1.28)	2.52 (1.20)

[1] Europe: Austria, Germany, Italy and United Kingdom

North America: Canada and United States

[2] EDSS is an ordinal scale in half-point increments that qualifies disability in patients with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation.

EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overview of Adverse Events (AE]
Measure Description	AE are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.
Time Frame	from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)
Safety Issue?	Yes

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Overview of Adverse Events (AE) [units: participants]			
Any AE	32	35	35
- serious AE	3	3	1
- AE leading to death	0	0	0
- AE leading to study drug discontinuation	0	3	4

2. Primary Outcome Measure:

Measure Title	Overview of AE With Potential Risk of Occurrence
Measure Description	AE with potential risk of occurrence were defined as follows: • Hepatic disorders; • Immune effects, mainly effects on bone marrow and infection; • Pancreatic disorders; • Malignancy; • Skin disorders, mainly hair loss and hair thinning; • Pulmonary disorders; • Hypertension; • Peripheral neuropathy; • Psychiatric disorders; • Hypersensitivity.
Time Frame	from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)
Safety Issue?	Yes

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Overview of AE With Potential Risk of Occurrence [units: participants]			
Any AE with potential risk of occurence	24	28	28
- Hepatic disorder AE	4	2	5
- Pancreatic disorder AE	6	5	6

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
- Pulmonary disorder AE	0	1	0
- Immune effects related AE	18	18	15
- Hair loss / Hair thinning AE	1	5	7
- Hypertension-related AE	0	1	0
- Peripheral neuropathy AE	2	1	5
- Hypersensitivity AE	3	3	8
- Malignancy AE	0	0	0
- Psychiatric disorder AE	1	3	1

3. Primary Outcome Measure:

Measure Title	Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA)
Measure Description	PCSA values are abnormal values considered medically important by the Sponsor according to predefined criteria based on literature review. Hepatic parameters thresholds were defined as follows: • Alanine Aminotransferase [ALT] >3, 5, 10 or 20 Upper Normal Limit [ULN]; • Aspartate aminotransferase [AST] >3, 5, 10 or 20 ULN; • Alkaline Phosphatase >1.5 ULN; • Total Bilirubin [TB] >1.5 or 2 ULN; • ALT >3 ULN and TB >2 ULN.
Time Frame	from first study drug intake up to 112 days after last intake or up to the first intake in the extension study LTS6047, whichever occured first (40 weeks max)
Safety Issue?	Yes

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

	Description
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [units: participants]			
ALT >3 ULN	1	0	1
- ALT >5 ULN	1	0	1
- ALT >10 ULN	1	0	0
AST >3 ULN	1	0	0
- AST >5 ULN	1	0	0
Alkaline Phosphatase >1.5 ULN	0	0	0
TB >1.5 ULN	0	0	0
ALT >3 ULN and TB >2 ULN	0	0	0

4. Secondary Outcome Measure:

Measure Title	Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease)
Measure Description	Total lesion volume is the sum of the total volume of all T2-lesions and the total volume all T1-hypointense post-gadolinium lesions measured through T2/proton density scan analysis and gadolinium-enhanced T1 scan analysis. Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on cubic root transformed volume data (treatment group, region of enrollment, visit, treatment-by-visit interaction, baseline value (cubic root transformed), and baseline-by-visit interaction as factors).
Time Frame	baseline (before randomization) and 24 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) [units: mililiters (mL)] Least Squares Mean (Standard Error)	-0.006 (0.036)	-0.030 (0.036)	-0.036 (0.037)

5. Secondary Outcome Measure:

Measure Title	Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates)
Measure Description	Number of Gd-enhancing T1-lesions per scan is obtained from the total number of Gd-enhancing T1-lesions observed during the study divided by the total number of scans performed during the study. To account for the different number of scans among participants, a Poisson regression model with robust error variance was used (total number of Gd-enhancing T1-lesions as response variable; log-transformed number of scans as "offset" variable; treatment group, region of enrollment and baseline number of Gd-enhancing T1-lesions as covariates).
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates) [units: lesions per scan] Number (95% Confidence Interval)	0.367 (0.183 to 0.736)	0.109 (0.054 to 0.220)	0.171 (0.093 to 0.313)

6. Secondary Outcome Measure:

Measure Title	Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan
Measure Description	Total volume of Gd-enhancing T1-lesions per scan is obtained from the sum of the volumes of Gd-enhancing T1-lesions observed during the study divided by the total number of scans performed during the study.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan [units: mililiters per scan]	0.063	0.028	0.017

7. Secondary Outcome Measure:

Measure Title	Annualized Relapse Rate [ARR]: Poisson Regression Estimates
Measure Description	ARR is obtained from the total number of confirmed relapses that occured during the treatment period divided by the sum of the treatment durations. Each episode of relapse - appearance, or worsening of a clinical symptom that was stable for at least 30 days, that persisted for a minimum of 24 hours in the absence of fever - was to be confirmed by an increase in Expanded Disability Status Scale [EDSS] score or Functional System scores. To account for the different treatment durations among participants, a Poisson regression model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group and region of enrollment as covariates).
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	42	40
Annualized Relapse Rate [ARR]: Poisson Regression Estimates [units: relapses per year] Number (95% Confidence Interval)	0.475 (0.260 to 0.867)	0.311 (0.151 to 0.642)	0.647 (0.379 to 1.103)

8. Secondary Outcome Measure:

Measure Title	Pharmacokinetic [PK]: Teriflunomide Plasma Concentration
Measure Description	Plasma concentrations of teriflunomide were measured using validated liquid chromatography-tandem mass spectrometry methods.

Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants who had at least one PK sample. Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Measured Values

	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	37	33
Pharmacokinetic [PK]: Teriflunomide Plasma Concentration [units: micrograms/mililiter (µg/mL)] Mean (Standard Deviation)	23.443 (10.917)	46.992 (32.154)

Reported Adverse Events

Time Frame	All Adverse Events (AE) were collected regardless of seriousness or relationship to the drug, spanning from signature of the Informed Consent Form up to the last visit.
Additional Description	The analysis was performed on the exposed population and included all AE that developed or worsened from first study drug intake up to 112 days after last study drug intake or up to the first study drug intake in the extension study LTS6047, whichever occured first (40 weeks max)

Reporting Groups

	Description
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA] for 24 weeks

Serious Adverse Events

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	3/41 (7.32%)	3/42 (7.14%)	1/40 (2.5%)
Infections and infestations			
Abscess [A] *	1/41 (2.44%)	0/42 (0%)	0/40 (0%)
Injury, poisoning and procedural complications			
Facial bones fracture [A] *	1/41 (2.44%)	0/42 (0%)	0/40 (0%)
Investigations			
Alanine aminotransferase increased [A] *	0/41 (0%)	1/42 (2.38%)	0/40 (0%)
Hepatic enzyme increased [A] *	1/41 (2.44%)	0/42 (0%)	0/40 (0%)
Nervous system disorders			
Cerebral ischaemia [A] *	1/41 (2.44%)	0/42 (0%)	0/40 (0%)
Epilepsy [A] *	0/41 (0%)	1/42 (2.38%)	0/40 (0%)
Psychiatric disorders			
Suicidal ideation [A] *	0/41 (0%)	0/42 (0%)	1/40 (2.5%)
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease [A] *	0/41 (0%)	1/42 (2.38%)	0/40 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	20/41 (48.78%)	20/42 (47.62%)	25/40 (62.5%)
Gastrointestinal disorders			
Constipation [A] *	0/41 (0%)	0/42 (0%)	4/40 (10%)

	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Diarrhoea [A] *	0/41 (0%)	3/42 (7.14%)	8/40 (20%)
Nausea [A] *	2/41 (4.88%)	4/42 (9.52%)	3/40 (7.5%)
General disorders			
Fatigue [A] *	6/41 (14.63%)	3/42 (7.14%)	7/40 (17.5%)
Infections and infestations			
Gastroenteritis [A] *	3/41 (7.32%)	0/42 (0%)	0/40 (0%)
Nasopharyngitis [A] *	3/41 (7.32%)	6/42 (14.29%)	4/40 (10%)
Upper respiratory tract infection [A] *	4/41 (9.76%)	1/42 (2.38%)	2/40 (5%)
Urinary tract infection [A] *	3/41 (7.32%)	4/42 (9.52%)	2/40 (5%)
Nervous system disorders			
Dizziness [A] *	3/41 (7.32%)	1/42 (2.38%)	0/40 (0%)
Headache [A] *	5/41 (12.2%)	6/42 (14.29%)	6/40 (15%)
Paraesthesia [A] *	0/41 (0%)	0/42 (0%)	3/40 (7.5%)
Skin and subcutaneous tissue disorders			
Alopecia [A] *	1/41 (2.44%)	5/42 (11.9%)	7/40 (17.5%)
Rash [A] *	0/41 (0%)	1/42 (2.38%)	5/40 (12.5%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:
Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The investigator can publish only the results of the work performed pursuant to this protocol. Prior to publication, the investigator provides the sponsor with the manuscript for review and comment at least 45 days in advance of its submission for publication.

The sponsor can require the investigator to withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as sponsor deems appropriate to establish and preserve its proprietary rights.

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