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Phase II Study of Teriflunomide as Adjunctive Therapy to Interferon-beta in Subjects With Multiple Sclerosis

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00489489

Purpose

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

Secondary objectives were:

- to estimate the effects of the 2 doses of teriflunomide, compared to placebo, in combination with a stable dose of IFN-β 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 IFN-β.

Condition	Intervention	Phase
Multiple Sclerosis	Drug: Teriflunomide Drug: Placebo (for Teriflunomide) Drug: Interferon-β	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 Interferon-beta 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 of 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, IFN-β dose level, 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, IFN-β dose level 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, region of enrollment and IFN-β dose level 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: 118
Study Start Date: May 2007
Primary Completion Date: June 2009
Study Completion Date: June 2009

Arms	Assigned Interventions
Experimental: Teriflunomide 7 mg + IFN-β Teriflunomide 7 mg once daily concomitantly with Interferon-β (IFN-β) for 24 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726 Drug: Interferon-β Powder for reconstitution, of any licensed strength for either intramuscular or subcutaneous injection Other Names: Avonex® Rebif® Betaseron®
Experimental: Teriflunomide 14 mg + IFN-β Teriflunomide 14 mg once daily concomitantly with Interferon-β (IFN-β) for 24 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726 Drug: Interferon-β Powder for reconstitution, of any licensed strength for either intramuscular or subcutaneous injection Other Names: Avonex® Rebif® Betaseron®
Placebo Comparator: Placebo + IFN-β Placebo (for Teriflunomide) once daily concomitantly with Interferon-β (IFN-β) for 24 weeks	Drug: Placebo (for Teriflunomide) Film-coated tablet Oral administration Drug: Interferon-β Powder for reconstitution, of any licensed strength for either intramuscular or subcutaneous injection Other Names:

Arms	Assigned Interventions
	Avonex® Rebif® Betaseron®

Detailed Description:

The study period per 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 IFN-β 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

United States, New Jersey

sanofi-aventis administrative office

Bridgewater, New Jersey, United States, 08807

Canada

sanofi-aventis administrative office

Laval, Canada

Germany

sanofi-aventis administrative office

Berlin, Germany

Italy

sanofi-aventis administrative office

Milan, Italy

Spain

sanofi-aventis administrative office

Barcelona, Spain

Investigators

Study Director:	ICD	sanofi-aventis

More Information

Results Publications:

Freedman MS, Wolinsky JS, Wamil B, Confavreux C, Comi G, Kappos L, Olsson TP, Miller A, Benzerdjeb H, Li H, Simonson C, O'Connor PW; Teriflunomide Multiple Sclerosis Trial Group and the MRI Analysis Center. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. Neurology. 2012 Jun 5;78(23):1877-85. doi: 10.1212/WNL.0b013e318258f7d4. Epub 2012 May 23.

Responsible Party:	Sanofi
Study ID Numbers:	PDY6045 2006-003134-14 [EudraCT Number] HMR1726D-2003 [HMR]
Health Authority:	Canada: Health Canada Germany: Paul-Ehrlich-Institut Spain: Spanish Agency of Medicines United States: Food and Drug Administration

Participant Flow

Recruitment Details	The recruitment initiated in May 2007 was completed in August 2008. A total of 159 patients were screened at 29 sites in 5 countries.
Pre-Assignment Details	Randomization was stratified by country and dose level of interferon-β (high/low). 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. 118 participants were randomized.

Reporting Groups

	Description
Placebo + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Overall Study

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Started	41 [1]	37 [1]	40 [1]
Treated	41	36	39 [2]
Completed	38 [3]	32 [3]	37 [3]
Not Completed	3	5	3
Not treated due to protocol violation	0	1	1
Adverse Event	1	1	1
Protocol Violation	1	0	1
Progressive disease	0	1	0
Participant did not wish to continue	1	1	0
Other than above	0	1	0

[1] randomized
[2] One participant received teriflunomide 7 mg instead of teriflunomide 14 mg

[3] completed treatment period

Baseline Characteristics

Reporting Groups

	Description
Placebo + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Baseline Measures

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Total
Number of Participants	41	37	38	116
Age, Continuous [1] [units: years] Mean (Standard Deviation)	39.2 (9.0)	41.4 (6.8)	39.6 (8.1)	40.1 (8.0)
Gender, Male/Female [units: participants]				
Female	31	25	25	81
Male	10	12	13	35
Region of Enrollment [2] [units: participants]				
Europe	28	25	24	77
North America	13	12	14	39
Time since first diagnosis of Multiple Sclerosis (MS) [units: years] Mean (Standard Deviation)	8.78 (5.62)	8.35 (5.44)	7.97 (6.59)	8.38 (5.86)
Number of MS relapses [units: MS relapses] Median (Full Range)				
Within the past year	1 (0 to 4)	0 (0 to 3)	1 (0 to 3)	1 (0 to 4)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Total
Within the past 2 years	1 (0 to 5)	1 (0 to 5)	1 (0 to 4)	1 (0 to 5)
Time since most recent MS relapse onset [units: months] Mean (Standard Deviation)	27.68 (38.49)	28.97 (34.06)	24.71 (35.97)	27.12 (36.03)
MS subtype [units: participants]				
Relapsing Remitting	38	30	34	102
Secondary Progressive	2	2	3	7
Progressive Relapsing	1	5	1	7
Baseline Expanded Disability Status Scale (EDSS) score [3] [units: units on a scale] Mean (Standard Deviation)	2.61 (1.26)	2.41 (1.44)	2.46 (1.57)	2.50 (1.41)
Dose level of interferon-β [4] [units: participants]				
High dose	28	25	24	77
Low dose	13	12	14	39

[1] Baseline characteristics of the population included in the analyses: the 2 participants not treated were not included, and the participant who received teriflunomide 7 mg instead of teriflunomide 14 mg was included in the teriflunomide 7 mg group.

[2] Europe: Germany, Italy and Spain

North America: Canada and United States

[3] 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).

[4] 'High dose': Rebif® 44 µg 3 times per week subcutaneously and, Betaseron® 0.25 mg every other day subcutaneously

'Low dose': Rebif® 22 µg 3 times per week subcutaneously and, Avonex® 30 µg once a week intramuscularly

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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Overview of Adverse Events [AE] [units: participants]			
Any AE	35	33	32
- serious AE	1	2	0
- AE leading to death	0	0	0
- AE leading to study drug discontinuation	1	1	1

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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Overview of AE With Potential Risk of Occurrence [units: participants]			
Any AE with potential risk of occurence	24	25	26
- Hepatic disorder AE	5	8	11
- Pancreatic disorder AE	5	2	7
- Pulmonary disorder AE	0	0	0
- Immune effects related AE	13	18	19
- Hair loss / Hair thinning AE	0	3	3

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
- Hypertension-related AE	1	0	4
- Peripheral neuropathy AE	4	1	3
- Hypersensitivity AE	5	3	3
- Malignancy AE	0	0	0
- Psychiatric disorder AE	0	0	0

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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [units: participants]			
ALT >3 ULN	2	0	2
- ALT >5 ULN	1	0	1
AST >3 ULN	1	0	1
- AST >5 ULN	1	0	0
Alkaline Phosphatase >1.5 ULN	1	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 of 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, IFN-β dose level, 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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

	Description
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) [units: mililiters] Least Squares Mean (Standard Error)	-0.001 (0.030)	0.002 (0.032)	-0.028 (0.030)

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, IFN-β dose level 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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates) [units: lesions per scan] Number (95% Confidence Interval)	0.570 (0.350 to 0.929)	0.099 (0.041 to 0.241)	0.089 (0.050 to 0.159)

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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan [units: mililiters per scan]	0.068	0.022	0.024

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, region of enrollment and IFN-β dose level 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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β (IFN-β) for 24 weeks

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	41	37	38
Annualized Relapse Rate [ARR]: Poisson Regression Estimates [units: relapses per year] Number (95% Confidence Interval)	0.260 (0.108 to 0.625)	0.280 (0.101 to 0.774)	0.109 (0.031 to 0.388)

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 + IFN-β	Teriflunomide 7 mg once daily concomitantly with IFN-β for 24 weeks
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with IFN-β for 24 weeks

Measured Values

	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β
Number of Participants Analyzed	29	32
Pharmacokinetic [PK]: Teriflunomide Plasma Concentration [units: micrograms/mililiter (µg/mL)] Mean (Standard Deviation)	21.437 (16.034)	47.761 (25.413)

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 + IFN-β	Placebo (for teriflunomide) once daily concomitantly with IFN-β for 24 weeks
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with IFN-β for 24 weeks
Teriflunomide 14 mg + + IFN-β	Teriflunomide 14 mg once daily concomitantly with IFN-β for 24 weeks

Serious Adverse Events

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + + IFN-β
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	1/41 (2.44%)	2/37 (5.41%)	0/38 (0%)
Investigations			
Alanine aminotransferase increased [A] *	1/41 (2.44%)	0/37 (0%)	0/38 (0%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)
Vascular disorders			
Deep vein thrombosis [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (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 + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + + IFN-β
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	20/41 (48.78%)	28/37 (75.68%)	29/38 (76.32%)
Gastrointestinal disorders			
Diarrhoea [A] *	4/41 (9.76%)	3/37 (8.11%)	3/38 (7.89%)
Nausea [A] *	1/41 (2.44%)	0/37 (0%)	2/38 (5.26%)
Vomiting [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)
General disorders			
Fatigue [A] *	2/41 (4.88%)	1/37 (2.7%)	4/38 (10.53%)
Infections and infestations			
Nasopharyngitis [A] *	2/41 (4.88%)	3/37 (8.11%)	5/38 (13.16%)
Respiratory tract infection [A] *	2/41 (4.88%)	2/37 (5.41%)	0/38 (0%)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + + IFN-β
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Sinusitis [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)
Upper respiratory tract infection [A] *	4/41 (9.76%)	0/37 (0%)	2/38 (5.26%)
Urinary tract infection [A] *	4/41 (9.76%)	3/37 (8.11%)	1/38 (2.63%)
Injury, poisoning and procedural complications			
Contusion [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)
Investigations			
Alanine aminotransferase increased [A] *	5/41 (12.2%)	5/37 (13.51%)	11/38 (28.95%)
Aspartate aminotransferase increased [A] *	1/41 (2.44%)	4/37 (10.81%)	3/38 (7.89%)
Blood creatine phosphokinase increased [A] *	0/41 (0%)	2/37 (5.41%)	1/38 (2.63%)
Blood pressure increased [A] *	0/41 (0%)	0/37 (0%)	3/38 (7.89%)
Lipase increased [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)
Lymphocyte count decreased [A] *	1/41 (2.44%)	4/37 (10.81%)	3/38 (7.89%)
Neutrophil count decreased [A] *	1/41 (2.44%)	1/37 (2.7%)	4/38 (10.53%)
White blood cell count decreased [A] *	3/41 (7.32%)	3/37 (8.11%)	4/38 (10.53%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	0/41 (0%)	1/37 (2.7%)	2/38 (5.26%)
Back pain [A] *	0/41 (0%)	2/37 (5.41%)	3/38 (7.89%)
Nervous system disorders			
Headache [A] *	2/41 (4.88%)	2/37 (5.41%)	4/38 (10.53%)
Sciatica [A] *	0/41 (0%)	2/37 (5.41%)	1/38 (2.63%)
Psychiatric disorders			
Anxiety [A] *	0/41 (0%)	2/37 (5.41%)	1/38 (2.63%)
Insomnia [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + + IFN-β
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	3/41 (7.32%)	0/37 (0%)	2/38 (5.26%)
Oropharyngeal pain [A] *	1/41 (2.44%)	2/37 (5.41%)	2/38 (5.26%)
Skin and subcutaneous tissue disorders			
Alopecia [A] *	0/41 (0%)	3/37 (8.11%)	3/38 (7.89%)
Dry skin [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)
Pruritus [A] *	0/41 (0%)	2/37 (5.41%)	0/38 (0%)

* 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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