ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 05/30/2014

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

Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis and Treated With Interferon-beta (TERACLES)

This study has been terminated.
(Sponsor decision to prematurely stop the study, not linked to any safety concern.)

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT01252355

Purpose

The primary objective was to demonstrate the effect of teriflunomide, in comparison to placebo, on frequency of Multiple Sclerosis (MS) relapses in patients with relapsing forms of MS who are treated with Interferon-beta (IFN-beta).

The secondary objectives were:

- Assess the effect of teriflunomide, in comparison to placebo, when added to IFN-beta on:
  - Disease activity as measured by brain Magnetic Resonance Imaging (MRI)
  - Disability progression
  - Burden of disease and disease progression as measured by brain MRI
- Evaluate the safety and tolerability of teriflunomide when added to IFN-beta therapy
- Assess the pharmacokinetics of teriflunomide in use in addition to baseline IFN-beta therapy
- Assess associations between variations in genes and clinical outcomes (safety and efficacy)
- Assess other measures of efficacy of teriflunomide such as fatigue and health-related quality of life
- Assess measures of health economics (hospitalization due to relapse, including the length of stay and any admission to intensive care unit)

Condition	Intervention	Phase
Multiple Sclerosis Relapse	Drug: Teriflunomide Drug: Placebo (for teriflunomide) Drug: Interferon-beta (IFN-beta)	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator, Outcomes Assessor), Randomized, Efficacy Study
Official Title: A Multi-center Double-blind Parallel-group Placebo-controlled Study of the Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis Who Are Treated With Interferon-beta

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Annualized Relapse Rate (ARR) (Poisson Regression Estimates) [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]

  ARR is the total number of confirmed relapses that occurred during the treatment period divided by the total number of patient-years treated. 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-beta dose stratum, and number of relapses in the year prior to randomization as covariates).

Secondary Outcome Measures:

- Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per Scan (Poisson Regression Estimates) [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]

  Number of Gd-enhancing T1-lesions per scan is the total number of Gd-enhancing T1-lesions that occurred during the treatment period divided by the total number of scans performed during the treatment period. 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-beta dose stratum and baseline number of Gd-enhancing T1-lesions as covariates).
- Time to 12-Week Sustained Disability Progression [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]

  The 12-week sustained disability progression was defined as an increase from baseline of at least 1-point in EDSS score (at least 0.5-point for participants with baseline EDSS score >5.5) that persisted for at least 12 weeks. Probability of disability progression was to be estimated using Kaplan-Meier method.
- Brain MRI Assessment: Volume of Gd-enhancing T1-lesions Per MRI Scan [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]

  Total volume of Gd-enhancing T1-lesions per scan is the sum of the volumes of Gd-enhancing T1-lesions observed during the treatment period divided by the total number of scans performed during the treatment period.
- Brain MRI Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]

  The total lesion volume (burden of disease) is the total volumes of hyperintense on T2 plus hypointense on T1 as measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data with factors for treatment, region, IFN-beta dose stratum, visit, treatment-by-visit interaction, cubic root transformed baseline burden of disease, and baseline-by-visit interaction.
- Time to Relapse: Kaplan-Meier Estimates of the Probability of no Relapse at Week 24, 48, and 72 [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]

Probability of no relapse at 24, 48 and 72 weeks was estimated using Kaplan-Meier method on the time to relapse defined as the time from randomization to first EDSS confirmed relapse. Participants free of confirmed relapse (no EDSS confirmed relapse observed on treatment) were censored at the date of the last study drug intake. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time <=t by any earlier computed probabilities to estimate the probability of being event-free for the amount of time t.

- Change From Baseline in Fatigue Impact Scale (FIS) Total Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  FIS is a participant-reported scale that qualifies the impact of fatigue on daily life in participants with MS.
- Change From Baseline in Short Form Generic Health Survey - 36 Items, Version 2 (SF-36v2) Summary Scores at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  SF-36 scale is a generic, self-administered, health-related quality-of-life (QOL) instrument.
- Resource Utilization When Relapse [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment] [Designated as safety issue: No]
  Resource utilization each time a participant experiences an MS relapse, specifically the number of hospitalizations, the number of over night spent in the hospital and number of intensive care admissions if hospitalized were to be reported.
- Overview of Adverse Events (AEs) [Time Frame: First study drug intake up to 28 days after last study drug intake, for up to 112 weeks] [Designated as safety issue: Yes]
  AEs are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.

Other Pre-specified Outcome Measures:

- Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [Time Frame: First study drug intake up to 28 days after last study drug intake, for up to 112 weeks] [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 or 10 Upper Limit of Normal (ULN); Aspartate Aminotransferase (AST) >3, 5 or 10 ULN; Alkaline Phosphatase >1.5 ULN; Total Bilirubin (TB) >1.5 ULN; and ALT >3 ULN and TB >2 ULN.

Enrollment: 534
Study Start Date: January 2011
Primary Completion Date: April 2013
Study Completion Date: April 2013

Arms	Assigned Interventions
Experimental: Teriflunomide 7 mg + IFN-beta Teriflunomide 7 milligram (mg) once a day concomitantly with IFN-beta therapy.	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726 Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is enrolled. Administration according to the package insert.
Experimental: Teriflunomide 14 mg + IFN-beta	Drug: Teriflunomide Film-coated tablet

Arms	Assigned Interventions
Teriflunomide 14 mg once a day concomitantly with IFN-beta therapy.	Oral administration Other Names: HMR1726 Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is enrolled. Administration according to the package insert.
Placebo Comparator: Placebo + IFN-beta Placebo (for teriflunomide) once a day concomitantly with IFN-beta therapy.	Drug: Placebo (for teriflunomide) Film-coated tablet Oral administration Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is enrolled. Administration according to the package insert.

Detailed Description:

The study period per patient was expected to be between 56 and 160 weeks depending on when the patient was randomized and this included the following:

- a screening period up to 4 weeks,
- a treatment period expected to be between 48 and 152 weeks,
- 4-week post rapid elimination follow-up period.

Patients were to continue on treatment until a fixed common end date which was approximately 48 weeks after randomization of the last patient.

For those patients who completed the treatment period, a long term extension study of approximately 1 year (including teriflunomide alone) was initially planned to be proposed.

Eligibility

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

Criteria

Inclusion criteria :

- Patient with relapsing forms of MS treated with IFN-beta
- Stable dose of IFN-beta (approved brand) for at least 6 months prior to randomization

- Disease activity in the 12 months prior to randomization and after first 3 months of IFN-beta treatment (defined by at least 1 relapse supported by EDSS or equivalent neurological examination, or, at least 1 brain or spinal cord MRI with at least one T1 gadolinium enhancing lesion)

Exclusion criteria:

- McDonald criteria for MS diagnosis not met at time of screening visit
- EDSS score greater than (>) 5.5 at randomization visit
- A relapse within 30 days prior randomization
- Persistent significant or severe infection
- Patients must not have used adrenocorticotrophic hormone or systemic corticosteroids for 2 weeks prior to randomization
- Prior or concomitant use of cytokine therapy (except baseline interferons), glatiramer acetate or intravenous immunoglobulins in the 3 months preceding randomization
- Liver function impairment or persisting elevations (confirmed by retest) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct bilirubin greater than 2 times the upper limit of normal range (ULN)
- Active hepatitis or hepatobiliary disease or known history of severe hepatitis
- Pregnant or breast-feeding women or those who were planning to become pregnant during the study
- Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia
- Human Immunodeficiency Virus (HIV) positive
- Known history of active tuberculosis not adequately treated
- Prior use within 2 years preceding randomization or concomitant use of cladribine and mitoxantrone
- Prior use within 6 months preceding randomization or concomitant use of natalizumab, or any other immunosuppressive agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate, or fingolimod

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:	Clinical Sciences & Operations	Sanofi

More Information

Responsible Party: Sanofi
Study ID Numbers: EFC6058
2010-023172-12 [EudraCT Number]
U1111-1115-2414 [UTN]
Health Authority: United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	The recruitment initiated in January 2011, was discontinued in December 2012 following the decision of the Sponsor to discontinue the study, the common treatment end date was defined as February 28th, 2013 (treatment duration between 24 and 108 weeks). A total of 846 participants were screened at 185 sites in 28 countries.
Pre-Assignment Details	Randomization was stratified by investigational site and Interferon-beta (IFN-beta) dose level (high/low). Assignment to groups was done centrally using an Interactive Voice Response System (IVRS) in a 1:1:1 ratio after confirmation of selection criteria. A total of 534 participants were randomized.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Overall Study

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Started	177 [1]	178 [1]	179 [1]
Treated	175	178	179 [2]
Completed	0	0	0
Not Completed	177	178	179
Adverse Event	9	17	22

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Lack of Efficacy	6	4	2
Lost to Follow-up	0	0	1
Poor Compliance to Protocol	1	1	1
Progressive Disease	2	0	0
Sponsor Early Termination of Study	149	149	146
Randomized but not Treated	2	0	0
Other Than Above	8	7	7

[1] Randomized.
[2] One participant received teriflunomide 7 mg.

Baseline Characteristics

Analysis Population Description
Randomized population: all randomized participants according to the treatment group to which they were assigned.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Baseline Measures

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta	Total
Number of Participants	177	178	179	534
Age, Continuous [units: years] Mean (Standard Deviation)	38.3 (8.9)	38.7 (9.5)	37.7 (9.2)	38.2 (9.2)
Gender, Male/Female [units: participants]				
Female	113	125	114	352
Male	64	53	65	182

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta	Total
Region of Enrollment [1] [units: participants]				
America	33	30	37	100
Western Europe	86	86	79	251
Eastern Europe	51	51	56	158
Asia, Africa and Australia	7	11	7	25
Time Since First Diagnosis of Multiple Sclerosis (MS) [units: years] Mean (Standard Deviation)	7.0 (5.6)	6.6 (5.6)	6.8 (5.9)	6.8 (5.7)
Number of MS Relapses [2] [units: MS relapses] Median (Full Range)				
Within the past year	1 (0 to 4)	1 (0 to 3)	1 (0 to 4)	1 (0 to 4)
Within the past 2 years	2 (0 to 6)	2 (0 to 8)	2 (0 to 8)	2 (0 to 8)
Time Since Most Recent MS Relapse Onset [units: months] Median (Full Range)	5.0 (1.0 to 75.0)	5.0 (1.0 to 36.0)	4.0 (1.0 to 174.0)	5.0 (1.0 to 174.0)
MS Subtype [units: participants]				
Relapsing Remitting	174	173	175	522
Secondary Progressive	2	3	4	9
Progressive Relapsing	1	2	0	3
Baseline Expanded Disability Status Scale (EDSS) Score [3] [units: units on a scale] Mean (Standard Deviation)	2.67 (1.25)	2.63 (1.37)	2.64 (1.18)	2.65 (1.26)
Dose Level of Interferon-beta (IFN-beta) Based on IVRS [units: participants]				
High dose	120	128	120	368

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta	Total
Low dose	57	50	59	166

[1] Due to the small sample size in some countries, the countries were pooled as follows:

- America: Argentina, Brazil, Canada, Chile, Columbia, The United States
- Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Spain, Sweden, The United Kingdom
- Eastern Europe = Estonia, Greece, Hungary, Lithuania, Russian Federation, Slovakia
- Asia, Africa and Australia = Australia, Republic of Korea, Tunisia

[2] The information was not available for one participant in the "Teriflunomide 14 mg + IFN-beta" group.

[3] EDSS is an ordinal scale in half-point increments that qualifies disability in participants 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	Annualized Relapse Rate (ARR) (Poisson Regression Estimates)
Measure Description	ARR is the total number of confirmed relapses that occurred during the treatment period divided by the total number of patient-years treated. 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-beta dose stratum, and number of relapses in the year prior to randomization as covariates).
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population: all randomized and treated participants. Participants were considered in the treatment group to which they were randomized regardless of the drug they actually received.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.

	Description
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	175	178	179
Annualized Relapse Rate (ARR) (Poisson Regression Estimates) [units: relapses per patient-year] Number (95% Confidence Interval)	0.298 (0.206 to 0.432)	0.242 (0.152 to 0.386)	0.238 (0.162 to 0.351)

2. Secondary Outcome Measure:

Measure Title	Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per Scan (Poisson Regression Estimates)
Measure Description	Number of Gd-enhancing T1-lesions per scan is the total number of Gd-enhancing T1-lesions that occurred during the treatment period divided by the total number of scans performed during the treatment period. 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-beta dose stratum and baseline number of Gd-enhancing T1-lesions as covariates).
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment
Safety Issue?	No

Analysis Population Description

ITT population as previously defined but including only participants who had post-baseline data.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	151	142	151
Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per Scan (Poisson Regression Estimates) [units: lesions per scan] Number (95% Confidence Interval)	0.542 (0.344 to 0.855)	0.257 (0.127 to 0.523)	0.158 (0.070 to 0.360)

3. Secondary Outcome Measure:

Measure Title	Time to 12-Week Sustained Disability Progression
Measure Description	The 12-week sustained disability progression was defined as an increase from baseline of at least 1-point in EDSS score (at least 0.5-point for participants with baseline EDSS score >5.5) that persisted for at least 12 weeks. Probability of disability progression was to be estimated using Kaplan-Meier method.
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment
Safety Issue?	No

Analysis Population Description

Data for this outcome was not analyzed because of insufficient data after early study termination.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	0	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

4. Secondary Outcome Measure:

Measure Title	Brain MRI Assessment: Volume of Gd-enhancing T1-lesions Per MRI Scan
Measure Description	Total volume of Gd-enhancing T1-lesions per scan is the sum of the volumes of Gd-enhancing T1-lesions observed during the treatment period divided by the total number of scans performed during the treatment period.
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment
Safety Issue?	No

Analysis Population Description

ITT population as previously defined but including only participants who had post-baseline data.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	151	142	151
Brain MRI Assessment: Volume of Gd-enhancing T1-lesions Per MRI Scan [units: milliliters per scan]	0.045	0.009	0.01

5. Secondary Outcome Measure:

Measure Title	Brain MRI Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) at Week 24
Measure Description	The total lesion volume (burden of disease) is the total volumes of hyperintense on T2 plus hypointense on T1 as measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data with factors for treatment, region, IFN-beta dose stratum, visit, treatment-by-visit interaction, cubic root transformed baseline burden of disease, and baseline-by-visit interaction.
Time Frame	Baseline, Week 24
Safety Issue?	No

Analysis Population Description

ITT population as previously defined but including only participants who had post-baseline data.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	142	132	141
Brain MRI Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) at Week 24 [units: milliliter] Least Squares Mean (Standard Error)	-0.008 (0.021)	-0.011 (0.021)	-0.044 (0.020)

6. Secondary Outcome Measure:

Measure Title	Time to Relapse: Kaplan-Meier Estimates of the Probability of no Relapse at Week 24, 48, and 72
Measure Description	Probability of no relapse at 24, 48 and 72 weeks was estimated using Kaplan-Meier method on the time to relapse defined as the time from randomization to first EDSS confirmed relapse. Participants free of confirmed relapse (no EDSS confirmed relapse observed on treatment) were censored at the date of the last study drug intake. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time <=t by any earlier computed probabilities to estimate the probability of being event-free for the amount of time t.
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment
Safety Issue?	No

Analysis Population Description

ITT population as previously defined.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.

	Description
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	175	178	179
Time to Relapse: Kaplan-Meier Estimates of the Probability of no Relapse at Week 24, 48, and 72 [units: percent probability of no relapse] Number (95% Confidence Interval)			
Percent probability of no relapse at Week 24	81.9 (75.8 to 88.0)	86.8 (81.4 to 92.1)	87.1 (81.8 to 92.3)
Percent probability of no relapse at Week 48	67.3 (58.8 to 75.8)	80.6 (73.3 to 87.8)	80.8 (73.9 to 87.7)
Percent probability of no relapse at Week 72	58.3 (45.4 to 71.2)	78.2 (69.8 to 86.6)	73.1 (62.2 to 83.9)

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in Fatigue Impact Scale (FIS) Total Score at Week 24
Measure Description	FIS is a participant-reported scale that qualifies the impact of fatigue on daily life in participants with MS.
Time Frame	Baseline, Week 24
Safety Issue?	No

Analysis Population Description

Data for this outcome was not analyzed because of insufficient data after early study termination.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	0	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

8. Secondary Outcome Measure:

Measure Title	Change From Baseline in Short Form Generic Health Survey - 36 Items, Version 2 (SF-36v2) Summary Scores at Week 24
Measure Description	SF-36 scale is a generic, self-administered, health-related quality-of-life (QOL) instrument.
Time Frame	Baseline, Week 24
Safety Issue?	No

Analysis Population Description

Data for this outcome was not analyzed because of insufficient data after early study termination.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	0	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

9. Secondary Outcome Measure:

Measure Title	Resource Utilization When Relapse
Measure Description	Resource utilization each time a participant experiences an MS relapse, specifically the number of hospitalizations, the number of over night spent in the hospital and number of intensive care admissions if hospitalized were to be reported.
Time Frame	Up to a maximum of 108 weeks depending on time of enrollment

Safety Issue?	No

Analysis Population Description

Data for this outcome was not analyzed because of insufficient data after early study termination.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	0	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

10. Secondary Outcome Measure:

Measure Title	Overview of Adverse Events (AEs)
Measure Description	AEs are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.
Time Frame	First study drug intake up to 28 days after last study drug intake, for up to 112 weeks
Safety Issue?	Yes

Analysis Population Description

Safety population: all randomized and treated participants. Participants were included in the treatment group according to the drug actually received.The participant randomized to Teriflunomide 14 mg group who received Teriflunomide 7 mg was analyzed in the Teriflunomide 7 mg group.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	175	179	178
Overview of Adverse Events (AEs) [units: participants]			
Any AE	119	140	140
Any Serious AE	8	13	14
Any AE Leading to Death	0	0	0
Any AE Leading to Study Drug Discontinuation	9	16	22

11. Other Pre-specified 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 or 10 Upper Limit of Normal (ULN); Aspartate Aminotransferase (AST) >3, 5 or 10 ULN; Alkaline Phosphatase >1.5 ULN; Total Bilirubin (TB) >1.5 ULN; and ALT >3 ULN and TB >2 ULN.
Time Frame	First study drug intake up to 28 days after last study drug intake, for up to 112 weeks
Safety Issue?	Yes

Analysis Population Description

Safety population as previously defined but including only participants who had post-baseline values.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Measured Values

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Number of Participants Analyzed	174	179	178

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [units: participants]			
ALT >3 ULN	6	9	9
ALT >5 ULN	1	6	5
ALT >10 ULN	1	3	2
AST >3 ULN	3	4	4
AST >5 ULN	2	3	3
AST >10 ULN	1	2	0
Alkaline Phosphatase >1.5 ULN	0	2	0
TB >1.5 ULN	2	0	2
ALT >3 ULN and TB >2 ULN	0	0	0

Reported Adverse Events

Time Frame	All AEs were collected regardless of seriousness or relationship to the drug, spanning from signature of the Informed Consent up to the last visit.
Additional Description	The analysis was performed on the safety population and included all AEs that developed or worsened from first study drug intake up to 28 days after last study drug intake, for up to 112 weeks. Participants were included in the treatment group according to the drug actually received.

Reporting Groups

	Description
Placebo + IFN-beta	Placebo (for teriflunomide) once daily concomitantly with IFN-beta.
Teriflunomide 7 mg + IFN-beta	Teriflunomide 7 mg once daily concomitantly with IFN-beta.
Teriflunomide 14 mg + IFN-beta	Teriflunomide 14 mg once daily concomitantly with IFN-beta.

Serious Adverse Events

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/175 (4.57%)	13/179 (7.26%)	14/178 (7.87%)
Blood and lymphatic system disorders			
Neutropenia [A] †	2/175 (1.14%)	0/179 (0%)	1/178 (0.56%)
Thrombocytopenia [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Cardiac disorders			
Myocardial infarction [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Supraventricular tachycardia [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Gastrointestinal disorders			
Diarrhoea [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Umbilical hernia [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
General disorders			
Chest pain [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Hepatobiliary disorders			
Cholelithiasis [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Drug-induced liver injury [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Hepatotoxicity [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Infections and infestations			
Cystitis [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Injury, poisoning and procedural complications			
Facial bones fracture [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Humerus fracture [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Overdose [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Thermal burn [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Investigations			
Alanine aminotransferase increased [A] †	0/175 (0%)	2/179 (1.12%)	2/178 (1.12%)
Aspartate aminotransferase increased [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Testicular seminoma (pure) [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Nervous system disorders			
Convulsion [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Loss of consciousness [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Multiple sclerosis [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Multiple sclerosis relapse [A] †	1/175 (0.57%)	2/179 (1.12%)	1/178 (0.56%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Pregnancy [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Psychiatric disorders			
Anxiety [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Depression [A] †	1/175 (0.57%)	0/179 (0%)	0/178 (0%)
Major depression [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)
Reproductive system and breast disorders			
Menorrhagia [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Ovarian cyst [A] †	0/175 (0%)	0/179 (0%)	1/178 (0.56%)
Vascular disorders			

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hypertension [A] †	0/175 (0%)	1/179 (0.56%)	0/178 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Other Adverse Events

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

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	85/175 (48.57%)	94/179 (52.51%)	104/178 (58.43%)
Blood and lymphatic system disorders			
Neutropenia [A] †	4/175 (2.29%)	8/179 (4.47%)	10/178 (5.62%)
Gastrointestinal disorders			
Diarrhoea [A] †	6/175 (3.43%)	16/179 (8.94%)	20/178 (11.24%)
Nausea [A] †	9/175 (5.14%)	18/179 (10.06%)	12/178 (6.74%)
General disorders			
Influenza like illness [A] †	8/175 (4.57%)	9/179 (5.03%)	4/178 (2.25%)
Infections and infestations			
Gastroenteritis [A] †	0/175 (0%)	1/179 (0.56%)	9/178 (5.06%)
Nasopharyngitis [A] †	20/175 (11.43%)	21/179 (11.73%)	20/178 (11.24%)
Upper respiratory tract infection [A] †	12/175 (6.86%)	9/179 (5.03%)	9/178 (5.06%)
Urinary tract infection [A] †	5/175 (2.86%)	10/179 (5.59%)	4/178 (2.25%)
Investigations			
Alanine aminotransferase increased [A] †	15/175 (8.57%)	16/179 (8.94%)	26/178 (14.61%)
Musculoskeletal and connective tissue disorders			
Back pain [A] †	9/175 (5.14%)	8/179 (4.47%)	7/178 (3.93%)

	Placebo + IFN-beta	Teriflunomide 7 mg + IFN-beta	Teriflunomide 14 mg + IFN-beta
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Nervous system disorders			
Dizziness [A] †	5/175 (2.86%)	8/179 (4.47%)	9/178 (5.06%)
Headache [A] †	14/175 (8%)	19/179 (10.61%)	22/178 (12.36%)
Skin and subcutaneous tissue disorders			
Alopecia [A] †	9/175 (5.14%)	11/179 (6.15%)	18/178 (10.11%)
Vascular disorders			
Hypertension [A] †	8/175 (4.57%)	7/179 (3.91%)	15/178 (8.43%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Limitations and Caveats

The early termination of study with reduced sample size and participant follow-up impacts the power and interpretability, and limits the ability to assess the overall benefit/risk of adjunctive therapy. Termination was not due to any safety concerns.

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.

If no publication has occurred within 12 months of the completion of the study, the Investigator shall have the right to publish/present independently the results of the study. The Investigator shall provide the Sponsor with a copy of any such presentation/publication for comment at least 30 days before any presentation/submission for publication. If requested by the Sponsor, any presentation/submission shall be delayed up to 90 days, to allow the Sponsor to preserve its proprietary rights.

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