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Long Term Safety of Teriflunomide When Added to Interferon-Beta or Glatiramer Acetate in Patients With Multiple Sclerosis

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00811395

Purpose

The primary objective was to evaluate the long-term safety and tolerability of teriflunomide when added to treatment with interferon-β [IFN-β] or glatiramer Acetate [GA] in patients with multiple sclerosis [MS] with relapses.

Secondary objectives were to evaluate the long-term effect on relapse rate, disability progression and Magnetic Resonance Imaging [MRI] parameters.

This study is the extension study of the PDY6045 (NCT00489489) and PDY6046 (NCT00475865) studies. Participants who successfully completed the initial study were offered to continue their treatment (same compound, same dose) for 24 additional weeks.

Condition	Intervention	Phase
Multiple Sclerosis	Drug: Teriflunomide Drug: Placebo (for teriflunomide) Drug: Interferon-β [IFN-β] Drug: Glatiramer Acetate [GA]	Phase 2

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

Official Title: Long-term Extension of the Multinational, Double-blind, Placebo Controlled Studies PDY6045 and PDY6046 to Document the Safety of Teriflunomide When Added to Treatment With Interferon-Beta or Glatiramer Acetate in Patients With Multiple Sclerosis With Relapses

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overview of Adverse Events [AE] [Time Frame: from first study drug intake in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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 Occurence [Time Frame: from first study drug intake in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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 in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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:

- Annualized Relapse Rate [ARR]: Poisson Regression Estimates [Time Frame: 48 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, two Poisson regression models with robust error variance were used (total number of confirmed relapses as response variable, log-transformed treatment duration as "offset" variable and: - Model 1 (IFN-β groups): treatment group, region of enrollment and IFN-β dose level as covariates - Model 2 (GA groups): treatment group and region of enrollment as covariates)
- Overview of 12-week Sustained Disability Progression [Time Frame: 48 weeks] [Designated as safety issue: No]
  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. If no disability progression was observed on or before last EDSS evaluation before study drug discontinuation, then the participant was considered as free of disability progression.
- Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints [Time Frame: 48 weeks] [Designated as safety issue: No]
  Probability of disability progression at 24 and 48 weeks was estimated using Kaplan-Meier method on the time to disability progression defined as the time from randomization to first EDSS increase. Participants free of disability progression were censored at the date of the last on-treatment EDSS evaluation. 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. Probability of event at time t is 1 minus the probability of being event-free for the amount of time t.
- Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) [Time Frame: baseline (before randomization in PDY6045 or PDY6046) and 48 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 two Mixed-effect models with repeated measures [MMRM] on cubic root transformed volume data: - Model 1 (IFN-β groups): 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; - Model 2 (GA groups): 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: 48 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, two Poisson regression models with robust error variance were used (total number of Gd-enhancing T1-lesions as response variable, log-transformed number of scans as "offset" variable and: - Model 1 (IFN-β groups): Treatment group, region of enrollment, IFN-β dose level and baseline number of Gd-enhancing T1-lesions as covariates - Model 2 (GA groups): Treatment group, region of enrollment and baseline number of Gd-enhancing T1-lesions as covariates)
- Cerebral MRI Assessment: Total Volume of Gd-enhancing T1-lesions Per Scan [Time Frame: 48 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.

Enrollment: 182
Study Start Date: October 2007
Primary Completion Date: April 2010
Study Completion Date: April 2010

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

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

Arms	Assigned Interventions
	Drug: Glatiramer Acetate [GA] Solution in prefilled syringe for subcutaneous injection Other Names: Copaxone®

Detailed Description:

The duration of the extension study per participants was 40 weeks broken down as follows:

- 24-week double-blind treatment period,
- 16-week post-treatment elimination follow-up period.

Eligibility

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

Criteria

Inclusion Criteria:

- PDY6045 or PDY6046 participant who:
  - completed the week 24 visit of either study PDY6045 or PDY6046,
  - was still meeting eligibility criteria for receiving treatment,
  - had agreed to continue stable dose of Interferon-β [IFN-β] or Glatiramer Acetate [GA] and consented to continue on treatment.

Exclusion Criteria:

- Any known condition or circumstance that would have prevented in the investigator's opinion, compliance or completion of the study

The above information is not intended to contain all considerations relevant to 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
Austria
sanofi-aventis administrative office
Wien, Austria
Canada

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Laval, Canada
Germany
sanofi-aventis administrative office
Berlin, Germany
Italy
sanofi-aventis administrative office
Milano, Italy
Spain
sanofi-aventis administrative office
Barcelona, Spain
United Kingdom
sanofi-aventis administrative office
Guildford, United Kingdom

Investigators

Study Director:	Clinical Sciences & Operations	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:	LTS6047 HMR1726D/2005 [HMR] 2007-003997-24 [EudraCT Number]
Health Authority:	Canada: Health Canada United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	107 and 110 participants who successfully completed 24-week visit in, respectively, PDY6045 and PDY6046 studies, were offered to continue their treatment in this extension study. After signature of the informed consent and confirmation of selection criteria, 86 and 96 participants entered the extension study.

Pre-Assignment Details	An Interactive Voice Response System was used to allocate kits containing the same treatment as in the initial study. Analysis included all participants randomized in the initial studies and all data collected from randomization according to intent-to-treat principal.

Reporting Groups

	Description
Placebo + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Initial Treatment (PDY6045 or PDY6046)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Started	41	37 [1]	38	40	42	41
Completed	38 [2]	33 [2]	36 [2]	38 [3]	37 [3]	35 [3]
Not Completed	3	4	2	2	5	6

[1] One participant received 7 mg instead of 14 mg as per randomization
[2] completed 24-week treatment (for more information see PDY6045/NCT00489489 record)
[3] completed 24-week treatment (for more information see PDY6046/NCT00475865 record)

Extension Treatment

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Started	31 [1]	28 [1]	27 [1]	37 [1]	30 [1]	29 [1]
Completed	29 [2]	22 [2]	24 [2]	34 [2]	30 [2]	27 [2]
Not Completed	2	6	3	3	0	2

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Adverse Event	1	2	2	2	0	1
Progressive disease	1	1	0	0	0	0
Participant did not wish to continue	0	3	0	1	0	1
Other than above	0	0	1	0	0	0

[1] continued initial treatment
[2] completed 48-week treatment

Baseline Characteristics

Reporting Groups

	Description
Placebo + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Baseline Measures

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA	Total
Number of Participants	41	37	38	40	42	41	239
Age, Customized [1] [units: participants]							
<38 years	17	9	15	11	12	13	77
>=38 years	24	28	23	29	30	28	162
Gender, Male/Female [units: participants]							
Female	31	25	25	31	33	33	178

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA	Total
Male	10	12	13	9	9	8	61
Region of Enrollment [2] [units: participants]							
Europe	28	25	24	22	22	22	143
North America	13	12	14	18	20	19	96

[1] Baseline characteristics before randomization in the initial study (PDY6045 or PDY6046)

[2] Europe: Austria, Germany, Italy, Spain and United Kingdom

North America: Canada and United States

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 in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	40	42	41
Overview of Adverse Events [AE] [units: participants]						
Any AE	35	35	33	39	40	38
- serious AE	2	4	1	6	5	2
- AE leading to death	0	0	0	0	0	0
- AE leading to study drug discontinuation	2	3	3	2	3	5

2. Primary Outcome Measure:

Measure Title	Overview of AE With Potential Risk of Occurence
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 in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	40	42	41
Overview of AE With Potential Risk of Occurence [units: participants]						
Any AE with potential risk of occurence	28	30	30	34	33	32
- Hepatic disorder AE	7	11	13	5	4	5
- Immune effects related AE	16	21	20	27	22	21
- Pancreatic disorder AE	8	5	11	6	6	11
- Malignancy AE	0	0	0	0	0	0
- Hair loss / hair thinning AE	1	3	4	1	5	7
- Pulmonary disorder AE	0	0	0	0	1	0
- Hypertension-related AE	1	4	6	0	2	2
- Peripheral neuropathy AE	5	3	4	4	5	10
- Psychiatric disorder AE	1	1	2	3	3	1
- Hypersensitivity AE	6	4	4	4	6	10

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 in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured last (64 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	40	42	41
Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities [PCSA] [units: participants]						
ALT >3 ULN	2	1	3	1	0	1
- ALT >5 ULN	1	0	1	1	0	1
- ALT >10 ULN	0	0	0	1	0	0

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
AST >3 ULN	1	0	1	1	0	0
- AST >5 ULN	1	0	0	0	0	0
Alkaline Phosphatase >1.5 ULN	1	0	0	0	0	0
TB >1.5 ULN	0	0	0	0	0	0
ALT >3 ULN and TB >2 ULN	0	0	0	0	0	0

4. 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, two Poisson regression models with robust error variance were used (total number of confirmed relapses as response variable, log-transformed treatment duration as "offset" variable and: • Model 1 (IFN-β groups): treatment group, region of enrollment and IFN-β dose level as covariates • Model 2 (GA groups): treatment group and region of enrollment as covariates)
Time Frame	48 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]

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

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	41	42	40
Annualized Relapse Rate [ARR]: Poisson Regression Estimates [units: relapses per year] Number (95% Confidence Interval)	0.343 (0.162 to 0.727)	0.231 (0.101 to 0.529)	0.144 (0.065 to 0.318)	0.420 (0.270 to 0.654)	0.262 (0.140 to 0.489)	0.497 (0.316 to 0.783)

5. Secondary Outcome Measure:

Measure Title	Overview of 12-week Sustained Disability Progression
Measure Description	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. If no disability progression was observed on or before last EDSS evaluation before study drug discontinuation, then the participant was considered as free of disability progression.
Time Frame	48 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]

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

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	41	42	40
Overview of 12-week Sustained Disability Progression [units: participants]						
Disability progression	0	3	2	4	1	4
Free of disability progression	40	33	36	37	41	36

6. Secondary Outcome Measure:

Measure Title	Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints
Measure Description	Probability of disability progression at 24 and 48 weeks was estimated using Kaplan-Meier method on the time to disability progression defined as the time from randomization to first EDSS increase. Participants free of disability progression were censored at the date of the last on-treatment EDSS evaluation. 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. Probability of event at time t is 1 minus the probability of being event-free for the amount of time t.
Time Frame	48 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]

	Description
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	41	42	40
Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints [units: percent probability] Number (95% Confidence Interval)						
Probability of disability progression at 24 weeks	0.0 (0.0 to 0.0)	3.0 (0.0 to 8.9)	2.7 (0.0 to 7.9)	2.5 (0.0 to 7.3)	0.0 (0.0 to 0.0)	5.6 (0.0 to 13.2)
Probability of disability progression at 48 weeks	0.0 (0.0 to 0.0)	11.1 (0.0 to 23.1)	6.4 (0.0 to 15.2)	10.6 (0.7 to 20.4)	3.3 (0.0 to 9.8)	12.8 (1.0 to 24.6)

7. 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 two Mixed-effect models with repeated measures [MMRM] on cubic root transformed volume data: • Model 1 (IFN-β groups): 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; • Model 2 (GA groups): 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 in PDY6045 or PDY6046) and 48 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	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)	-0.017 (0.028)	-0.011 (0.030)	-0.012 (0.029)	0.016 (0.036)	-0.010 (0.037)	-0.063 (0.039)

8. 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, two Poisson regression models with robust error variance were used (total number of Gd-enhancing T1-lesions as response variable, log-transformed number of scans as "offset" variable and: • Model 1 (IFN-β groups): Treatment group, region of enrollment, IFN-β dose level and baseline number of Gd-enhancing T1-lesions as covariates • Model 2 (GA groups): Treatment group, region of enrollment and baseline number of Gd-enhancing T1-lesions as covariates)
Time Frame	48 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	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)	0.521 (0.318 to 0.854)	0.080 (0.032 to 0.204)	0.090 (0.052 to 0.154)	0.333 (0.171 to 0.649)	0.120 (0.059 to 0.243)	0.178 (0.098 to 0.324)

9. Secondary Outcome Measure:

Measure Title	Cerebral MRI Assessment: Total 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	48 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]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for teriflunomide) once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with Glatiramer Acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with Glatiramer Acetate [GA]

Measured Values

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
Number of Participants Analyzed	41	37	38	41	42	40
Cerebral MRI Assessment: Total Volume of Gd-enhancing T1-lesions Per Scan [units: mililiters per scan]	0.068	0.019	0.020	0.052	0.031	0.014

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 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 in PDY6045/PDY6046 study up to 112 days after last intake in initial study or in the extension study, whichever occured first (64 weeks max).

Reporting Groups

	Description
Placebo + IFN-β	Placebo (for teriflunomide) once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 7 mg + IFN-β	Teriflunomide 7 mg once daily concomitantly with interferon-β [IFN-β]
Teriflunomide 14 mg + IFN-β	Teriflunomide 14 mg once daily concomitantly with interferon-β [IFN-β]
Placebo + GA	Placebo (for Teriflunomide) once daily concomitantly with glatiramer acetate [GA]
Teriflunomide 7 mg + GA	Teriflunomide 7 mg once daily concomitantly with glatiramer acetate [GA]
Teriflunomide 14 mg + GA	Teriflunomide 14 mg once daily concomitantly with glatiramer acetate [GA]

Serious Adverse Events

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	2/41 (4.88%)	4/37 (10.81%)	1/38 (2.63%)	6/40 (15%)	5/42 (11.9%)	2/41 (4.88%)
Ear and labyrinth disorders						
Vertigo [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Hepatobiliary disorders						
Cholecystitis [A] *	0/41 (0%)	0/37 (0%)	1/38 (2.63%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Infections and infestations						
Abscess [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Cystitis [A] *	0/41 (0%)	0/37 (0%)	1/38 (2.63%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Herpes zoster [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Lobar pneumonia [A] *	0/41 (0%)	0/37 (0%)	1/38 (2.63%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Mastoiditis [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Otitis media [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Injury, poisoning and procedural complications						
Ankle fracture [A] *	1/41 (2.44%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Facial bones fracture [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Fall [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Tendon rupture [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	1/41 (2.44%)
Investigations						
Alanine aminotransferase increased [A] *	1/41 (2.44%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	2/42 (4.76%)	0/41 (0%)
Hepatic enzyme increased [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Musculoskeletal and connective tissue disorders						
Musculoskeletal stiffness [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Pseudarthrosis [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Nervous system disorders						
Cerebral ischaemia [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Epilepsy [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Muscle spasticity [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Psychiatric disorders						
Suicidal ideation [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	1/41 (2.44%)
Suicide attempt [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Respiratory, thoracic and mediastinal disorders						
Interstitial lung disease [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Vascular disorders						
Deep vein thrombosis [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Hypertension [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (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	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	28/41 (68.29%)	33/37 (89.19%)	32/38 (84.21%)	34/40 (85%)	30/42 (71.43%)	34/41 (82.93%)
Ear and labyrinth disorders						
Vertigo [A] *	2/41 (4.88%)	0/37 (0%)	0/38 (0%)	3/40 (7.5%)	1/42 (2.38%)	0/41 (0%)
Gastrointestinal disorders						
Abdominal discomfort [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	3/42 (7.14%)	2/41 (4.88%)
Abdominal pain upper [A] *	3/41 (7.32%)	1/37 (2.7%)	3/38 (7.89%)	2/40 (5%)	1/42 (2.38%)	1/41 (2.44%)
Constipation [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	2/42 (4.76%)	4/41 (9.76%)
Diarrhoea [A] *	6/41 (14.63%)	4/37 (10.81%)	4/38 (10.53%)	2/40 (5%)	3/42 (7.14%)	8/41 (19.51%)
Nausea [A] *	3/41 (7.32%)	0/37 (0%)	5/38 (13.16%)	3/40 (7.5%)	5/42 (11.9%)	5/41 (12.2%)
Vomiting [A] *	2/41 (4.88%)	1/37 (2.7%)	4/38 (10.53%)	0/40 (0%)	0/42 (0%)	1/41 (2.44%)
General disorders						
Asthenia [A] *	1/41 (2.44%)	1/37 (2.7%)	3/38 (7.89%)	0/40 (0%)	0/42 (0%)	1/41 (2.44%)
Fatigue [A] *	4/41 (9.76%)	2/37 (5.41%)	5/38 (13.16%)	7/40 (17.5%)	4/42 (9.52%)	7/41 (17.07%)
Oedema peripheral [A] *	1/41 (2.44%)	0/37 (0%)	0/38 (0%)	3/40 (7.5%)	2/42 (4.76%)	2/41 (4.88%)
Infections and infestations						

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Bronchitis [A] *	0/41 (0%)	1/37 (2.7%)	2/38 (5.26%)	1/40 (2.5%)	3/42 (7.14%)	2/41 (4.88%)
Ear infection [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
Gastroenteritis [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	3/40 (7.5%)	0/42 (0%)	0/41 (0%)
Influenza [A] *	3/41 (7.32%)	1/37 (2.7%)	0/38 (0%)	1/40 (2.5%)	1/42 (2.38%)	2/41 (4.88%)
Nasopharyngitis [A] *	3/41 (7.32%)	3/37 (8.11%)	5/38 (13.16%)	6/40 (15%)	7/42 (16.67%)	4/41 (9.76%)
Respiratory tract infection [A] *	2/41 (4.88%)	2/37 (5.41%)	0/38 (0%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Respiratory tract infection viral [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	5/40 (12.5%)	2/42 (4.76%)	1/41 (2.44%)
Sinusitis [A] *	0/41 (0%)	1/37 (2.7%)	2/38 (5.26%)	0/40 (0%)	1/42 (2.38%)	4/41 (9.76%)
Upper respiratory tract infection [A] *	4/41 (9.76%)	2/37 (5.41%)	2/38 (5.26%)	6/40 (15%)	2/42 (4.76%)	4/41 (9.76%)
Urinary tract infection [A] *	7/41 (17.07%)	4/37 (10.81%)	1/38 (2.63%)	6/40 (15%)	5/42 (11.9%)	4/41 (9.76%)
Injury, poisoning and procedural complications						
Contusion [A] *	0/41 (0%)	1/37 (2.7%)	2/38 (5.26%)	1/40 (2.5%)	1/42 (2.38%)	2/41 (4.88%)
Procedural pain [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Investigations						
Alanine aminotransferase increased [A] *	6/41 (14.63%)	7/37 (18.92%)	12/38 (31.58%)	2/40 (5%)	3/42 (7.14%)	2/41 (4.88%)
Aspartate aminotransferase increased [A] *	1/41 (2.44%)	7/37 (18.92%)	4/38 (10.53%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Blood creatine phosphokinase increased [A] *	0/41 (0%)	3/37 (8.11%)	1/38 (2.63%)	1/40 (2.5%)	1/42 (2.38%)	0/41 (0%)
Blood pressure increased [A] *	0/41 (0%)	1/37 (2.7%)	3/38 (7.89%)	0/40 (0%)	0/42 (0%)	1/41 (2.44%)
Blood triglycerides increased [A] *	1/41 (2.44%)	1/37 (2.7%)	2/38 (5.26%)	1/40 (2.5%)	1/42 (2.38%)	0/41 (0%)
Lipase increased [A] *	0/41 (0%)	0/37 (0%)	2/38 (5.26%)	1/40 (2.5%)	0/42 (0%)	3/41 (7.32%)
Lymphocyte count decreased [A] *	1/41 (2.44%)	4/37 (10.81%)	5/38 (13.16%)	0/40 (0%)	0/42 (0%)	0/41 (0%)

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Neutrophil count decreased [A] *	1/41 (2.44%)	1/37 (2.7%)	4/38 (10.53%)	0/40 (0%)	1/42 (2.38%)	1/41 (2.44%)
Protein urine present [A] *	3/41 (7.32%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	0/41 (0%)
White blood cell count decreased [A] *	3/41 (7.32%)	3/37 (8.11%)	4/38 (10.53%)	0/40 (0%)	0/42 (0%)	1/41 (2.44%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A] *	2/41 (4.88%)	1/37 (2.7%)	2/38 (5.26%)	2/40 (5%)	1/42 (2.38%)	1/41 (2.44%)
Back pain [A] *	1/41 (2.44%)	2/37 (5.41%)	4/38 (10.53%)	2/40 (5%)	3/42 (7.14%)	1/41 (2.44%)
Pain in extremity [A] *	1/41 (2.44%)	1/37 (2.7%)	1/38 (2.63%)	4/40 (10%)	3/42 (7.14%)	2/41 (4.88%)
Nervous system disorders						
Carpal tunnel syndrome [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	3/41 (7.32%)
Dizziness [A] *	2/41 (4.88%)	0/37 (0%)	1/38 (2.63%)	3/40 (7.5%)	1/42 (2.38%)	1/41 (2.44%)
Headache [A] *	2/41 (4.88%)	2/37 (5.41%)	6/38 (15.79%)	7/40 (17.5%)	6/42 (14.29%)	7/41 (17.07%)
Hypoaesthesia [A] *	2/41 (4.88%)	0/37 (0%)	2/38 (5.26%)	2/40 (5%)	2/42 (4.76%)	2/41 (4.88%)
Muscle spasticity [A] *	0/41 (0%)	0/37 (0%)	0/38 (0%)	0/40 (0%)	4/42 (9.52%)	0/41 (0%)
Paraesthesia [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	0/40 (0%)	0/42 (0%)	3/41 (7.32%)
Sciatica [A] *	0/41 (0%)	2/37 (5.41%)	1/38 (2.63%)	2/40 (5%)	1/42 (2.38%)	1/41 (2.44%)
Psychiatric disorders						
Anxiety [A] *	1/41 (2.44%)	2/37 (5.41%)	1/38 (2.63%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Depression [A] *	1/41 (2.44%)	1/37 (2.7%)	1/38 (2.63%)	2/40 (5%)	5/42 (11.9%)	0/41 (0%)
Insomnia [A] *	1/41 (2.44%)	0/37 (0%)	3/38 (7.89%)	1/40 (2.5%)	1/42 (2.38%)	3/41 (7.32%)
Renal and urinary disorders						
Micturition urgency [A] *	0/41 (0%)	1/37 (2.7%)	0/38 (0%)	1/40 (2.5%)	3/42 (7.14%)	3/41 (7.32%)
Respiratory, thoracic and mediastinal disorders						

	Placebo + IFN-β	Teriflunomide 7 mg + IFN-β	Teriflunomide 14 mg + IFN-β	Placebo + GA	Teriflunomide 7 mg + GA	Teriflunomide 14 mg + GA
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Cough [A] *	3/41 (7.32%)	0/37 (0%)	2/38 (5.26%)	1/40 (2.5%)	0/42 (0%)	1/41 (2.44%)
Oropharyngeal pain [A] *	1/41 (2.44%)	2/37 (5.41%)	2/38 (5.26%)	1/40 (2.5%)	0/42 (0%)	0/41 (0%)
Skin and subcutaneous tissue disorders						
Alopecia [A] *	1/41 (2.44%)	3/37 (8.11%)	3/38 (7.89%)	1/40 (2.5%)	5/42 (11.9%)	7/41 (17.07%)
Dry skin [A] *	1/41 (2.44%)	0/37 (0%)	2/38 (5.26%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Pruritus [A] *	0/41 (0%)	2/37 (5.41%)	0/38 (0%)	1/40 (2.5%)	1/42 (2.38%)	1/41 (2.44%)
Rash [A] *	1/41 (2.44%)	0/37 (0%)	1/38 (2.63%)	1/40 (2.5%)	3/42 (7.14%)	6/41 (14.63%)
Urticaria [A] *	0/41 (0%)	2/37 (5.41%)	1/38 (2.63%)	0/40 (0%)	1/42 (2.38%)	0/41 (0%)
Vascular disorders						
Hypertension [A] *	1/41 (2.44%)	3/37 (8.11%)	4/38 (10.53%)	0/40 (0%)	1/42 (2.38%)	1/41 (2.44%)

* 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.

If no publication has occurred within 12 months after trial completion, the Investigator can publish the results. Prior to publication, the sponsor shall review the manuscript and can request changes, provided they do not jeopardize the accuracy and/or the scientific value of the publication. The approval is given in writing by the sponsor, not exceeding 90 days.

To protect by property right the sponsor can postpone the publication of any information, for a period not exceeding 18 months.

Results Point of Contact:

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