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Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With Multiple Sclerosis (TEMSO)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00134563

Purpose

The primary objective was to determine the effect of teriflunomide on the frequency of relapses in patients with relapsing multiple sclerosis (MS).

Secondary objectives were:

- to evaluate the effect of teriflunomide on the accumulation of disability as measured by Expanded Disability Status Scale [EDSS], the burden of disease as measured by Magnetic Resonance Imaging [MRI] and patient-reported fatigue;
- to evaluate the safety and tolerability of teriflunomide.

Condition	Intervention	Phase
Multiple Sclerosis	Drug: Teriflunomide Drug: Placebo (for teriflunomide)	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator, Outcomes Assessor), Randomized, Efficacy Study
Official Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Design Study to Evaluate the Efficacy and Safety of Teriflunomide in Reducing the Frequency of Relapses and Delaying the Accumulation of Physical Disability in Subjects With Multiple Sclerosis With Relapses

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Annualized Relapse Rate [ARR]: Poisson Regression Estimates [Time Frame: 108 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 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 baseline EDSS stratum as covariates).

Secondary Outcome Measures:

- Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints [Time Frame: 108 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. Probability of disability progression at 24, 48 and 108 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 (no disability progression observed on treatment) 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) and 108 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.
- Changes From Baseline in Fatigue Impact Scale [FIS] Total Score [Time Frame: baseline (before randomization) and 108 weeks] [Designated as safety issue: No]

  FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in patients with MS. It consists of 40 statements that measure fatigue in three areas; physical, cognitive, and social. FIS total score ranges from 0 (no problem) to 160 (extreme problem). Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on FIS total score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors).

Other Pre-specified Outcome Measures:

- Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates) [Time Frame: 108 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, baseline EDSS stratum and baseline number of Gd-enhancing T1-lesions as covariates).
- Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan [Time Frame: 108 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: 1088
Study Start Date: September 2004
Primary Completion Date: July 2010
Study Completion Date: July 2010

Arms	Assigned Interventions
Experimental: Teriflunomide 7 mg Teriflunomide 7 mg once daily for 108 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726
Experimental: Teriflunomide 14 mg Teriflunomide 14 mg once daily for 108 weeks	Drug: Teriflunomide Film-coated tablet Oral administration Other Names: HMR1726
Placebo Comparator: Placebo Placebo (for teriflunomide) once daily for 108 weeks	Drug: Placebo (for teriflunomide) Film-coated tablet Oral administration

Detailed Description:

The study period per participant was approximatively 128 weeks broken down as follows:

- Screening period up to 4 weeks,
- 108-week double-blind treatment period (approximatively 2 years)*,
- 16-week post-treatment elimination follow-up period.

'*' Participants successfully completing the week 108 visit were offered the opportunity to enter the optional long-term extension study LTS6050 - NCT00803049.

Eligibility

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

Criteria

Inclusion Criteria:

- Multiple sclerosis [MS] subject who was ambulatory (EDSS of ≤ 5.5)
- Exhibiting a relapsing clinical course, with or without progression (relapsing remitting, secondary progressive or progressive relapsing);
- Meeting McDonald's criteria for MS diagnosis;
- Experienced at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial;
- No relapse onset in the preceding 60 days prior to randomization;
- Clinically stable during the 30 days prior to randomization, without adrenocorticotrophic hormone [ACTH] or systemic steroid treatment.

Exclusion Criteria:

- Clinically relevant cardiovascular, hepatic, neurological, endocrine or other major systemic disease;
- Significantly impaired bone marrow function;
- 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;
- Any known condition or circumstance that would prevent in the investigator's opinion compliance or completion of the study;

Contacts and Locations

Locations

United States, New Jersey
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Bridgewater, New Jersey, United States, 08807
Austria
Sanofi-Aventis Austria
Vienna, Austria
Canada
sanofi-aventis, Canada
Laval, Canada
Chile
sanofi-aventis
Santiago de Chile, Chile
Czech Republic
sanofi-aventis administrative office
Praha, Czech Republic
Denmark
sanofi-aventis Denmark
Horsholm, Denmark
Estonia
sanofi-aventis administrative office
Tallinn, Estonia
Finland
sanofi-aventis Finland
Helsinki, Finland
France
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Paris, France
Germany
Sanofi-Aventis Deutschland GmbH
Berlin, Germany
Italy
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Milano, Italy
Netherlands
sanofi-aventis
Gouda, Netherlands
Norway
sanofi-aventis
Lysaker, Norway
Poland
sanofi-aventis Poland
Warszawa, Poland
Portugal
sanofi-aventis
Porto Salvo, Portugal
Russian Federation
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Investigators

Principal Investigator:	Paul O'Connor, MD	St. Michael's Hospital Toronto (Canada)

More Information

Results Publications:

O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, Truffinet P, Wang L, Miller A, Freedman MS; TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303. doi: 10.1056/NEJMoa1014656.

Responsible Party: Sanofi

Study ID Numbers:	EFC6049 2004-000555-42 [EudraCT Number] HMR1726D/3001 [HMR]
Health Authority:	Canada: Health Canada France: Ministry of Health Russia: Pharmacological Committee, Ministry of Health United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	The recruitment initiated in September 2004 was completed in February 2008. A total of 1338 patients were screened at 127 sites in 21 countries.
Pre-Assignment Details	Randomization was stratified by country and baseline disability (Expanded Disability Status Scale [EDSS] score ≤3.5 or >3.5). 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. 1088 participants were randomized.

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Overall Study

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Started	363 [1]	366 [1]	359 [1]
Treated	363 [2]	365	358 [3]
Completed	259 [4]	274 [4]	263 [4]
Not Completed	104	92	96
Not treated due to protocol violation	0	1	1

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Adverse Event	29	37	38
Lack of Efficacy	24	14	17
Protocol Violation	3	2	5
Lost to Follow-up	4	0	2
progressive disease	11	4	2
did not wish to continue	33	32	26
Reason other than above	0	2	5

[1] Randomized
[2] Two participants received doses of Teriflunomide 7 mg, one participant doses of Teriflunomide 14 mg
[3] one participant received doses of Teriflunomide 7 mg
[4] completed treatment period

Baseline Characteristics

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Baseline Measures

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Total
Number of Participants	363	365	358	1086
Age, Continuous [1] [units: years] Mean (Standard Deviation)	38.4 (9.0)	37.5 (9.0)	37.8 (8.2)	37.9 (8.8)
Gender, Male/Female [units: participants]				
Female	275	254	254	783
Male	88	111	104	303
Region of enrollment [2]				

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Total
[units: participants]				
America	82	83	80	245
Eastern Europe	114	116	108	338
Western Europe	167	166	170	503
Time since first diagnosis of multiple sclerosis (MS) [3] [units: Years] Mean (Standard Deviation)	5.13 (5.59)	5.29 (5.36)	5.59 (5.44)	5.33 (5.48)
Number of MS relapses [units: MS relapses] Median (Full Range)				
Within the past year	1 (0 to 6)	1 (0 to 6)	1 (0 to 4)	1 (0 to 6)
Within the past 2 years	2 (1 to 7)	2 (1 to 12)	2 (1 to 9)	2 (1 to 12)
Time since most recent MS relapse onset [units: months] Mean (Standard Deviation)	6.28 (3.62)	6.29 (3.29)	6.50 (3.71)	6.35 (3.54)
MS subtype [units: participants]				
Relapsing Remitting	329	332	332	993
Secondary Progressive	22	17	12	51
Progressive Relapsing	12	16	14	42
MS medication in the past 2 years [units: participants]				
Yes	90	102	102	294
No	273	263	256	792
Baseline EDSS total score [4] [units: participants]				
≤ 3.5	281	280	276	837
> 3.5	82	85	82	249

[1] Baseline characteristics of the population included in analyses

[2] America: Canada, Chile, and United States;

Eastern Europe: Czech Republic, Estonia, Poland, Russia and Ukraine;

Western Europe: Austria, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland, Turkey, and United Kingdom;

[3] The information was missing for one participant in the Teriflunomide 7 mg group.

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

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

Outcome Measures

1. Primary Outcome Measure:

Measure Title	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 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 baseline EDSS stratum as covariates).
Time Frame	108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	363	365	358
Annualized Relapse Rate [ARR]: Poisson Regression Estimates [units: relapses per year] Number (95% Confidence Interval)	0.539 (0.466 to 0.623)	0.370 (0.318 to 0.432)	0.369 (0.308 to 0.441)

Statistical Analysis 1 for Annualized Relapse Rate [ARR]: Poisson Regression Estimates

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 14 mg
	Comments	Null hypothesis: • H1: No difference between Teriflunomide 14 mg and placebo • H2: No difference between Teriflunomide 7 mg and placebo The study was sized to detect a 25% relative risk reduction with teriflunomide in the 2-year relapse rate at a significance level of 0.050 with a power ≥95% anticipating a potential 20% 2-year dropout rate.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0005
	Comments	Step down approach used to adjust for multiplicity: • H1 tested first • H2 tested only if the comparison H1 was statistically significant A priori threshold for statistical significance for both comparisons ≤0.05
	Method	Other [Regression, Poisson]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Relative risk reduction (%)]
	Estimated Value	31.5
	Estimation Comments	Relative risk reduction with Teriflunomide 14 mg compared to placebo

Statistical Analysis 2 for Annualized Relapse Rate [ARR]: Poisson Regression Estimates

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 7 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0002
	Comments	Step down approach used to adjust for multiplicity: • H1 tested first • H2 tested only if the comparison H1 was statistically significant A priori threshold for statistical significance for both comparisons ≤0.05
	Method	Other [Regression, Poisson]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Relative Risk Reduction (%)]
	Estimated Value	31.2
	Estimation Comments	Relative risk reduction with Teriflunomide 7 mg compared to placebo

2. 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	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 at 24, 48 and 108 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 (no disability progression observed on treatment) 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	108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	363	365	358
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	8.6 (5.7 to 11.6)	5.8 (3.3 to 8.3)	6.2 (3.6 to 8.8)
Probability of disability progression at 48 weeks	16.0 (12.1 to 20.0)	13.1 (9.4 to 16.7)	11.3 (7.9 to 14.8)
Probability of disability progression at 108 weeks	27.3 (22.3 to 32.3)	21.7 (17.1 to 26.3)	20.2 (15.6 to 24.7)

Statistical Analysis 1 for Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 14 mg
	Comments	Null hypothesis: • H1: No difference between Teriflunomide 14 mg and placebo • H2: No difference between Teriflunomide 7 mg and placebo The study was also sized to detect a 37% hazard rate reduction of an assumed disability progression hazard rate of 0.1783 in the placebo group and 0.1116 in the teriflunomide group by the end of 2 years with a power of 80% anticipating a potential 20% 2-year dropout rate.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0279
	Comments	Step down approach: • H1 tested only if both comparisons on the primary outcome measure were statistically significant • H2 tested only if the comparison H1 was statistically significant A priori threshold for statistical significance ≤0.05
	Method	Log Rank
	Comments	Two-sided Log-rank test stratified by region of enrollment and baseline EDSS stratum

Method of Estimation	Estimation Parameter	Other [Hazard ratio reduction (%)]
	Estimated Value	29.8
	Estimation Comments	Relative risk reduction with Teriflunomide 14 mg compared to placebo (estimated from a Cox proportional hazard model with treatment arm, region of enrollment and baseline EDSS stratum as covariates)

Statistical Analysis 2 for Time to 12-week Sustained Disability Progression: Kaplan-Meier Estimates of the Rate of Disability Progression at Timepoints

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 7 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0835
	Comments	Step down approach: • H1 tested only if both comparisons on the primary outcome measure were statistically significant • H2 tested only if the comparison H1 was statistically significant A priori threshold for statistical significance ≤0.05
	Method	Log Rank
	Comments	Two-sided Log-rank test stratified by region of enrollment and baseline EDSS stratum

Method of Estimation	Estimation Parameter	Other [Hazard ratio reduction (%)]
	Estimated Value	23.7

	Estimation Comments	Relative risk reduction with Teriflunomide 7 mg compared to placebo (estimated from a Cox proportional hazard model with treatment arm, region of enrollment and baseline EDSS stratum as covariates)

3. 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.
Time Frame	baseline (before randomization) and 108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	363	365	358
Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) [units: milliliters (mL)] Mean (Standard Deviation)			
Change in total lesion volume	2.208 (7.002)	1.308 (6.799)	0.723 (7.591)
- Change in T1-hypointense lesion component	0.533 (1.063)	0.499 (1.154)	0.331 (1.012)
- Change in T2-lesion component	1.674 (6.473)	0.810 (6.181)	0.392 (6.901)

Statistical Analysis 1 for Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease)

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 14 mg
	Comments	Mixed-effect model with repeated measures [MMRM] on cubic root transformed total lesion volume data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value (cubic root transformed) and baseline-by-visit interaction).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0003
	Comments	A priori threshold for statistical significance ≤0.05 No adjustment for multiple comparisons
	Method	t-test, 2 sided
	Comments	2-sided t-test on baseline adjusted least-square means

Statistical Analysis 2 for Cerebral Magnetic Resonance Imaging [MRI] Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease)

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 7 mg
	Comments	Mixed-effect model with repeated measures [MMRM] on cubic root transformed total lesion volume data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value (cubic root transformed) and baseline-by-visit interaction).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0317
	Comments	A priori threshold for statistical significance ≤0.05 No adjustment for multiple comparisons
	Method	t-test, 2 sided
	Comments	2-sided t-test on baseline adjusted least-square means

4. Secondary Outcome Measure:

Measure Title	Changes From Baseline in Fatigue Impact Scale [FIS] Total Score

Measure Description	FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in patients with MS. It consists of 40 statements that measure fatigue in three areas; physical, cognitive, and social. FIS total score ranges from 0 (no problem) to 160 (extreme problem). Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on FIS total score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors).
Time Frame	baseline (before randomization) and 108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	363	365	358
Changes From Baseline in Fatigue Impact Scale [FIS] Total Score [units: units on a scale] Least Squares Mean (Standard Error)	4.300 (1.670)	2.343 (1.641)	3.804 (1.670)

Statistical Analysis 1 for Changes From Baseline in Fatigue Impact Scale [FIS] Total Score

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 14 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8271
	Comments	A priori threshold for statistical significance ≤0.05 No adjustment for multiple comparisons
	Method	t-test, 2 sided
	Comments	2-sided t-test on baseline adjusted least-square means

Statistical Analysis 2 for Changes From Baseline in Fatigue Impact Scale [FIS] Total Score

Statistical Analysis Overview	Comparison Groups	Placebo, Teriflunomide 7 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3861
	Comments	A priori threshold for statistical significance ≤0.05 No adjustment for multiple comparisons
	Method	t-test, 2 sided
	Comments	2-sided t-test on baseline adjusted least-square means

5. Other Pre-specified 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, baseline EDSS stratum and baseline number of Gd-enhancing T1-lesions as covariates).
Time Frame	108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	346	350	340
Cerebral MRI Assessment: Number of Gd-enhancing T1-lesions Per Scan (Poisson Regression Estimates) [units: lesions per scan] Number (95% Confidence Interval)	1.331 (1.059 to 1.673)	0.570 (0.434 to 0.748)	0.261 (0.167 to 0.407)

6. Other Pre-specified 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	108 weeks
Safety Issue?	No

Analysis Population Description

All randomized and treated participants; Participants were included in the treatment group to which they were originally assigned (intent-to-treat analysis).

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Measured Values

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of Participants Analyzed	346	350	340

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Cerebral MRI Assessment: Volume of Gd-enhancing T1-lesions Per Scan [units: mililiters (mL)] Mean (Standard Deviation)	0.102 (0.329)	0.059 (0.247)	0.025 (0.079)

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 intake or up to first intake in the extension study, whichever came first (124 weeks max). Participants who received incorrect treatment were included considering the incorrect treatment.

Reporting Groups

	Description
Placebo	Placebo (for teriflunomide) once daily for 108 weeks
Teriflunomide 7 mg	Teriflunomide 7 mg once daily for 108 weeks
Teriflunomide 14 mg	Teriflunomide 14 mg once daily for 108 weeks

Serious Adverse Events

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	46/360 (12.78%)	52/368 (14.13%)	57/358 (15.92%)
Blood and lymphatic system disorders			
Anaemia [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Lymphadenitis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Neutropenia [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Cardiac disorders			

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Angina pectoris [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Myocardial infarction [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Ear and labyrinth disorders			
Hypoacusis [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Gastrointestinal disorders			
Abdominal pain lower [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Abdominal wall haematoma [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Anal fissure [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Aphthous stomatitis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Colitis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Colitis ulcerative [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Crohn's disease [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Diarrhoea [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Duodenal ulcer [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Inguinal hernia [A] *	0/360 (0%)	0/368 (0%)	4/358 (1.12%)
Intestinal functional disorder [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Nausea [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Pancreatitis [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Peritonitis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Toothache [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
General disorders			
Asthenia [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Hepatobiliary disorders			

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cholecystitis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Cholecystitis acute [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Cholecystitis chronic [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Cholelithiasis [A] *	1/360 (0.28%)	6/368 (1.63%)	0/358 (0%)
Hepatitis toxic [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Liver injury [A] *	1/360 (0.28%)	1/368 (0.27%)	0/358 (0%)
Infections and infestations			
Appendicitis [A] *	0/360 (0%)	2/368 (0.54%)	0/358 (0%)
Bacteraemia [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Cellulitis [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Cytomegalovirus hepatitis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Erysipelas [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Gastroenteritis [A] *	2/360 (0.56%)	0/368 (0%)	1/358 (0.28%)
Hepatitis C [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Herpes zoster [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Infected cyst [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Influenza [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Lung infection [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Pneumonia [A] *	0/360 (0%)	2/368 (0.54%)	0/358 (0%)
Pyelonephritis [A] *	0/360 (0%)	0/368 (0%)	3/358 (0.84%)
Renal abscess [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Urinary tract infection [A] *	1/360 (0.28%)	0/368 (0%)	1/358 (0.28%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Urinary tract infection enterococcal [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Injury, poisoning and procedural complications			
Ankle fracture [A] *	0/360 (0%)	0/368 (0%)	2/358 (0.56%)
Burns third degree [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Concussion [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Contrast media reaction [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Facial bones fracture [A] *	1/360 (0.28%)	0/368 (0%)	1/358 (0.28%)
Fall [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Femoral neck fracture [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Foot fracture [A] *	1/360 (0.28%)	1/368 (0.27%)	1/358 (0.28%)
Hand fracture [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Ligament injury [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Lower limb fracture [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Multiple drug overdose [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Muscle strain [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Post-traumatic pain [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Spinal compression fracture [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Tibia fracture [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Traumatic brain injury [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Investigations			
Alanine aminotransferase increased [A] *	5/360 (1.39%)	5/368 (1.36%)	5/358 (1.4%)
Hepatic enzyme increased [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Lipase increased [A] *	0/360 (0%)	2/368 (0.54%)	0/358 (0%)
Neutrophil count decreased [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Nuclear magnetic resonance imaging abdominal abnormal [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Transaminases increased [A] *	2/360 (0.56%)	1/368 (0.27%)	1/358 (0.28%)
Metabolism and nutrition disorders			
Dehydration [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Back pain [A] *	1/360 (0.28%)	0/368 (0%)	1/358 (0.28%)
Costochondritis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Intervertebral disc protrusion [A] *	3/360 (0.83%)	2/368 (0.54%)	1/358 (0.28%)
Osteochondrosis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Tendonitis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Breast cancer [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Cervix carcinoma stage 0 [A] *	1/360 (0.28%)	0/368 (0%)	1/358 (0.28%)
Meningioma [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Ovarian germ cell teratoma benign [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Thyroid adenoma [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Thyroid cancer [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Uterine leiomyoma [A] *	0/360 (0%)	1/368 (0.27%)	1/358 (0.28%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Nervous system disorders			
Cervical myelopathy [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Convulsion [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Facial nerve disorder [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Glossopharyngeal neuralgia [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Hypertonia [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Monoparesis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Multiple sclerosis [A] *	3/360 (0.83%)	0/368 (0%)	3/358 (0.84%)
Muscle spasticity [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Parkinsonism [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Status epilepticus [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Syncope [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Pregnancy, puerperium and perinatal conditions			
Abortion missed [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Abortion spontaneous [A] *	1/360 (0.28%)	0/368 (0%)	2/358 (0.56%)
Post abortion haemorrhage [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Psychiatric disorders			
Abnormal behaviour [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Conversion disorder [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Depression [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Major depression [A] *	0/360 (0%)	2/368 (0.54%)	0/358 (0%)
Mood altered [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Panic attack [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Psychosomatic disease [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Somatoform disorder [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Suicide attempt [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Renal and urinary disorders			
Renal colic [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Urethral stenosis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Reproductive system and breast disorders			
Benign prostatic hyperplasia [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Endometriosis [A] *	0/360 (0%)	2/368 (0.54%)	0/358 (0%)
Fallopian tube cyst [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Menorrhagia [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Metrorrhagia [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Ovarian cyst [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Uterine haemorrhage [A] *	0/360 (0%)	1/368 (0.27%)	1/358 (0.28%)
Uterine polyp [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Respiratory, thoracic and mediastinal disorders			
Haemothorax [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Pulmonary embolism [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Skin and subcutaneous tissue disorders			
Decubitus ulcer [A] *	1/360 (0.28%)	0/368 (0%)	0/358 (0%)
Eczema [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Skin necrosis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Surgical and medical procedures			
Meniscus operation [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Vascular disorders			
Circulatory collapse [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Orthostatic hypotension [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Thrombophlebitis [A] *	0/360 (0%)	0/368 (0%)	1/358 (0.28%)
Varicose vein [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)
Venous thrombosis [A] *	0/360 (0%)	1/368 (0.27%)	0/358 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

Other Adverse Events

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

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	259/360 (71.94%)	271/368 (73.64%)	265/358 (74.02%)
Gastrointestinal disorders			
Abdominal pain [A] *	24/360 (6.67%)	17/368 (4.62%)	21/358 (5.87%)
Abdominal pain upper [A] *	15/360 (4.17%)	19/368 (5.16%)	20/358 (5.59%)
Diarrhoea [A] *	32/360 (8.89%)	54/368 (14.67%)	64/358 (17.88%)
Nausea [A] *	26/360 (7.22%)	32/368 (8.7%)	49/358 (13.69%)
Vomiting [A] *	14/360 (3.89%)	15/368 (4.08%)	18/358 (5.03%)
General disorders			
Fatigue [A] *	51/360 (14.17%)	47/368 (12.77%)	52/358 (14.53%)
Infections and infestations			

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Bronchitis [A] *	22/360 (6.11%)	18/368 (4.89%)	29/358 (8.1%)
Gastroenteritis [A] *	15/360 (4.17%)	22/368 (5.98%)	20/358 (5.59%)
Influenza [A] *	35/360 (9.72%)	34/368 (9.24%)	43/358 (12.01%)
Nasopharyngitis [A] *	98/360 (27.22%)	94/368 (25.54%)	93/358 (25.98%)
Sinusitis [A] *	16/360 (4.44%)	15/368 (4.08%)	23/358 (6.42%)
Upper respiratory tract infection [A] *	25/360 (6.94%)	34/368 (9.24%)	32/358 (8.94%)
Urinary tract infection [A] *	35/360 (9.72%)	27/368 (7.34%)	36/358 (10.06%)
Investigations			
Alanine aminotransferase increased [A] *	21/360 (5.83%)	41/368 (11.14%)	47/358 (13.13%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	30/360 (8.33%)	30/368 (8.15%)	28/358 (7.82%)
Back pain [A] *	46/360 (12.78%)	39/368 (10.6%)	40/358 (11.17%)
Muscle spasms [A] *	22/360 (6.11%)	16/368 (4.35%)	13/358 (3.63%)
Muscular weakness [A] *	23/360 (6.39%)	15/368 (4.08%)	14/358 (3.91%)
Pain in extremity [A] *	47/360 (13.06%)	26/368 (7.07%)	33/358 (9.22%)
Nervous system disorders			
Dizziness [A] *	16/360 (4.44%)	22/368 (5.98%)	17/358 (4.75%)
Headache [A] *	64/360 (17.78%)	81/368 (22.01%)	67/358 (18.72%)
Hypoaesthesia [A] *	30/360 (8.33%)	18/368 (4.89%)	20/358 (5.59%)
Paraesthesia [A] *	30/360 (8.33%)	34/368 (9.24%)	35/358 (9.78%)
Psychiatric disorders			
Depression [A] *	27/360 (7.5%)	26/368 (7.07%)	33/358 (9.22%)
Insomnia [A] *	23/360 (6.39%)	20/368 (5.43%)	15/358 (4.19%)

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	16/360 (4.44%)	15/368 (4.08%)	19/358 (5.31%)
Skin and subcutaneous tissue disorders			
Alopecia [A] *	12/360 (3.33%)	38/368 (10.33%)	47/358 (13.13%)
Rash [A] *	15/360 (4.17%)	14/368 (3.8%)	19/358 (5.31%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

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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