Clinical trial results:
A Phase 3, randomized, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (GEMINI 2)

Summary

EudraCT number	2020-000644-55
Trial protocol	FR DE GB CZ LV SK BE NO GR NL PT HU HR IT EE
Global end of trial date	16 July 2024

Results information

Result version number	v1 (current)
This version publication date	06 July 2025
First version publication date	06 July 2025

Trial information

Trial identification

Sponsor protocol code	EFC16034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04410991
WHO universal trial number (UTN)	U1111-1238-1373

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	450 Water Street, Cambridge, Massachusetts, United States, 02141
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of daily tolebrutinib compared to a daily dose of 14 milligrams (mg) teriflunomide (Aubagio) measured by the annualized relapse rate (ARR) in participants with relapsing forms of multiple sclerosis (MS).

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 33
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 32
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 81
Country: Number of subjects enrolled	Croatia: 24
Country: Number of subjects enrolled	Czechia: 72
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	India: 26
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Latvia: 15

Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Russian Federation: 99
Country: Number of subjects enrolled	Serbia: 37
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Türkiye: 12
Country: Number of subjects enrolled	Ukraine: 112
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 105
Worldwide total number of subjects	899
EEA total number of subjects	304

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	899
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1093 participants were screened from 11-Jun-2020 to 08-Aug-2022, of which 194 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 899 participants were randomized in this study in a 1:1 ratio to either teriflunomide 14 mg or tolebrutinib 60 mg group. This was an event-driven (6-month confirmed disability worsening [CDW]) trial with a variable treatment duration (end-of-study [EOS] duration: up to approximately 48 months).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide 14 mg

Arm description:

Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 48 months.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to tolebrutinib was administered as a tablet orally QD up to approximately 48 months.

Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	
Other name	Aubagio
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide 14 mg was administered as a tablet orally QD up to approximately 48 months.

Arm title	Tolebrutinib 60 mg

Arm description:

Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 46 months.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to teriflunomide was administered as a tablet orally QD up to approximately 46

months.

Investigational medicinal product name	Tolebrutinib
Investigational medicinal product code	SAR442168
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tolebrutinib 60 mg was administered as a tablet orally QD up to approximately 46 months.

Number of subjects in period 1	Teriflunomide 14 mg	Tolebrutinib 60 mg
Started	452	447
Randomized and treated	451	447
Completed	378	384
Not completed	74	63
Consent withdrawn by subject	59	55
Poor compliance to protocol	5	4
Unspecified	10	4

Baseline characteristics

Reporting groups	
Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 48 months.	
Reporting group title	Tolebrutinib 60 mg
Reporting group description:	
Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 46 months.	

Reporting group values	Teriflunomide 14 mg	Tolebrutinib 60 mg	Total
Number of subjects	452	447	899
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	36.1	36.6	
standard deviation	± 9.3	± 9.3	-
Sex: Female, Male Units: participants			
Female	293	300	593
Male	159	147	306
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	19	23	42
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	11	7	18
White	417	411	828
More than one race	3	3	6
Unknown or Not Reported	2	3	5

End points

End points reporting groups

Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 48 months.	
Reporting group title	Tolebrutinib 60 mg
Reporting group description:	
Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 46 months.	

Primary: Annualized Relapse Rate as Assessed by Confirmed Protocol-defined Adjudicated Relapses

End point title	Annualized Relapse Rate as Assessed by Confirmed Protocol-defined Adjudicated Relapses
End point description:	
The MS relapse was defined as a monophasic, acute or subacute onset of new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms were attributable to MS, lasted for >=24 hours with or without recovery, present at normal body temperature, and preceded by >=30 days of clinical stability. The intent-to-treat (ITT) population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to approximately 48 months	

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: relapses per participant year				
number (confidence interval 95%)	0.109 (0.088 to 0.134)	0.108 (0.089 to 0.131)		

Statistical analyses

Statistical analysis title	Annualized Relapse Rate
Statistical analysis description:	
Analysis was performed using negative binomial model with number of adjudicated relapses onset between randomization date and EOS date as the response variable, treatment group, Gadolinium (Gd)-enhancing T1 lesions at baseline (presence, absence), expanded disability status scale (EDSS) strata (<4, >=4) and geographic region (United States [US], non-US) as covariates, and log transformed observation duration as the offset variable.	
Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.9758 [2]
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	0.996
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.754
upper limit	1.315

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error.

[2] - Threshold for significance at 2-sided 0.05 level.

Secondary: Time to Onset of 6-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

End point title	Time to Onset of 6-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. Time to onset of 6-month CDW was defined as the time from randomization to the onset of a confirmed, sustained increase from baseline in EDSS score (of >=1.5 points when the baseline score was 0, of >=1.0 point when the baseline score was 0.5 to <=5.5, of >=0.5 points when the baseline EDSS score was >5.5) over at least 6 months that was not attributable to another etiology. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: months				
median (full range (min-max))	12.14 (1.4 to 38.9)	15.12 (2.0 to 37.1)		

Statistical analyses

Statistical analysis title	Time to Onset of 6-Month CDW as Assessed by EDSS

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US).

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0114 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.891

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error.

[4] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Time to Onset of 3-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

End point title	Time to Onset of 3-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. Time to onset of 3-month CDW was defined as the time from randomization to the onset of a confirmed, sustained increase from baseline in EDSS score (of >=1.5 points when the baseline score was 0, of >=1.0 point when the baseline score was 0.5 to <=5.5, of >=0.5 points when the baseline EDSS score was >5.5) over at least 3 months that was not attributable to another etiology. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: months				
median (full range (min-max))	12.11 (1.4 to 39.1)	12.11 (2.0 to 42.1)		

Statistical analyses

Statistical analysis title	Time to Onset of 3-Month CDW as Assessed by EDSS

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US).

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0181 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.641
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.444
upper limit	0.925

Notes:

[5] - A hierarchical testing procedure was used to control the overall type I error.

[6] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Mean Number of new Gadolinium-Enhancing T1-Hyperintense Lesions per Scan

End point title	Mean Number of new Gadolinium-Enhancing T1-Hyperintense Lesions per Scan

End point description:

MRI of the brain was performed to identify number of new Gd-enhancing T1-hyperintense lesions defined as the sum of the individual number of new Gd- enhancing T1-hyperintense lesions starting from baseline up to and including the EOS visit. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: number of new Gd-enhancing T1 lesions				
arithmetic mean (confidence interval 95%)	0.217 (0.169 to 0.280)	0.460 (0.365 to 0.581)		

Statistical analyses

Statistical analysis title	Number of new Gd-Enhancing T1-Hyperintense Lesions

Statistical analysis description:

Analysis was performed using negative binomial model with the number of new Gd-enhancing T1-hyperintense lesions between randomization date and EOS date as the response variable, treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4) and geographic region (US, non-US) as covariates, and log transformed number of MRI scans as the offset variable.

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	2.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.502
upper limit	2.987

Notes:

[7] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Mean Number of new and/or Enlarging T2-Hyperintense Lesions per Year

End point title	Mean Number of new and/or Enlarging T2-Hyperintense Lesions per Year

End point description:

Magnetic resonance imaging (MRI) of the brain was performed to identify number of new and/or enlarging T2-hyperintense lesions defined as the sum of the individual number of new and/or enlarging T2 lesions starting from baseline up to and including the EOS visit. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: number of new and/or enlarging T2lesions				
arithmetic mean (confidence interval 95%)	4.369 (3.587 to 5.322)	5.092 (4.340 to 5.975)		

Statistical analyses

Statistical analysis title	Number of new/Enlarging T2-Hyperintense Lesions

Statistical analysis description:

Analysis was performed using negative binomial model with the number of new and/or enlarging T2-hyperintense lesions between randomization date and EOS date as the response variable, treatment group, baseline T2-hyperintense lesion count, EDSS strata (<4, >=4) and geographic region (US, non-US) as covariates, and log transformed observation duration as the offset variable.

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.2362
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	1.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.905
upper limit	1.502

Notes:

[8] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Cognitive Function as Assessed by the Symbol Digit Modalities Test (SDMT) at EOS

End point title	Change From Baseline in Cognitive Function as Assessed by the Symbol Digit Modalities Test (SDMT) at EOS

End point description:

The SDMT was used to assess processing speed, divided attention, visual scanning, tracking and motor speed. It involved a simple substitution task using a reference key. The number of correct substitutions and number of items completed within a 90 second interval (maximum 110 seconds) were recorded. A decrease of 4 points from baseline on the SDMT was considered meaningful worsening. The score was the number of correctly coded items from 0-110 in 90 seconds; higher scores indicating a better outcome. Baseline was defined as the last available value prior to the first dose of study intervention. Analysis was performed on the ITT population. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	366		
Units: score on a scale				
least squares mean (standard error)	0.428 (± 0.0373)	0.374 (± 0.0370)		

Statistical analyses

Statistical analysis title	Change From Baseline in Cognitive Function: SDMT

Statistical analysis description:

Covariates in the mixed-effect model with repeated measures (MMRM) were treatment group, EDSS strata (<4, >=4), geographic region (US, non-US), visit, treatment by visit interaction, baseline value, and baseline value-by-visit interaction.

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.31
Method	MMRM
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.156
upper limit	0.05

Notes:

[9] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Cognitive Function as Assessed by the California Verbal Learning Test Second Edition (CVLT-II) at EOS

End point title	Change From Baseline in Cognitive Function as Assessed by the California Verbal Learning Test Second Edition (CVLT-II) at EOS

End point description:

The CVLT-II was a verbal learning and memory test consisting of recall and recognition of a list of 16 words. For each assessment, 5 trials were completed. Total Correct Recall Trials 1–5 was scaled to a normalized T–score metric, which had a mean of 50 and standard deviation of 10, the maximum possible score was 80 and a minimum was 0. Higher values indicated improved cognitive function. Baseline was defined as the last available value prior to the first dose of study intervention. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	357		
Units: T-score				
least squares mean (standard error)	16.431 (± 0.6825)	15.819 (± 0.6740)		

Statistical analyses

Statistical analysis title	Change From Baseline in Cognitive Function:CVLT-II

Statistical analysis description:

Covariates in the MMRM were treatment group, EDSS strata (<4, >=4), geographic region (US, non-US), visit, treatment by visit interaction, baseline value, and baseline value-by-visit interaction.

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.5235
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.493
upper limit	1.269

Notes:

[10] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Time to Onset of 6-Month Confirmed Disability Improvement (CDI) as Assessed by Expanded Disability Status Scale

End point title	Time to Onset of 6-Month Confirmed Disability Improvement (CDI) as Assessed by Expanded Disability Status Scale

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. CDI was defined as a decrease of >=1 point from baseline in the EDSS score lasting at least 6 months. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	447		
Units: months				
median (full range (min-max))	12.05 (2.8 to 30.6)	9.04 (2.6 to 33.5)		

Statistical analyses

Statistical analysis title	Time to Onset of 6-Month CDI as Assessed by EDSS

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US).

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0079 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.652
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.145
upper limit	2.383

Notes:

[11] - A hierarchical testing procedure was used to control the overall type I error.

[12] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Percent Change in Brain Volume Loss at EOS Compared to Month 6

End point title	Percent Change in Brain Volume Loss at EOS Compared to Month 6

End point description:

MRI of the brain was performed at the specified timepoints to detect the changes in brain volume loss. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Month 6 to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	317		
Units: percent change				
least squares mean (standard error)	-0.740 (± 0.0394)	-0.696 (± 0.0387)		

Statistical analyses

Statistical analysis title	Percent Change in Brain Volume Loss

Statistical analysis description:

Covariates in the MMRM were treatment group, EDSS strata (<4, >=4), geographic region (US, non-US), visit, treatment by visit interaction, cube root transformed Month 6 brain volume, and cube root transformed Month 6 brain volume-by-visit interaction.

Comparison groups	Teriflunomide 14 mg v Tolebrutinib 60 mg

Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.4266
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	0.153

Notes:

[13] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Multiple Sclerosis Quality of Life 54 (MSQoL-54) Questionnaire Score at EOS

End point title	Change From Baseline in Multiple Sclerosis Quality of Life 54 (MSQoL-54) Questionnaire Score at EOS

End point description:

MSQoL-54 consisted of 12 subscales & 2 single-item measures(satisfaction with sexual function[1 item]; change in health[1 item]).12 subscales were:a:physical health(10 items), b:health perceptions(5 items), c:energy(5 items), d:role limit physical(4 items), e:sexual function(4 items), f:pain(3 items), g:social function(3 items), h:health distress(4 items), i:overall quality of life(2 items), j:emotional well-being(5 items), k:role limitations emotional(3 items) and l:cognitive function(4 items).Physical & mental health composite score were calculated as weighted sum of 'a to h' & 'i to l' subscales respectively. Each composite score was transformed linearly to common 0(worst) to 100(best) score range;higher score indicated improved QoL. Baseline=last available value prior to first dose of study intervention.Analysis was performed on ITT population.Only participants with data collected at specified timepoints are reported. n=number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	370		
Units: score on a scale				
least squares mean (standard error)				
Physical health composite score (n=353, 367)	-1.040 (± 0.7404)	-1.199 (± 0.7304)		
Mental health composite score (n=357, 370)	-1.657 (± 0.8709)	-1.390 (± 0.8581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events

(TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Permanent Study Intervention Discontinuation and Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Permanent Study Intervention Discontinuation and Adverse Events of Special Interest (AESIs)

End point description:

An AE was any untoward medical occurrence in participant or clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was an important medical event. An AESI was an AE (serious or nonserious) of scientific and medical concern specific to Sponsor's product or program for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required. TEAEs were defined as AEs that developed, worsened or became serious during treatment period. Safety population included all randomized participants exposed to study intervention, regardless of amount of exposure, analyzed according to intervention actually received.

End point type	Secondary

End point timeframe:

From first dose of study intervention (Day 1) up to the earliest of either 10 days post last dose, death or last contact; up to approximately 48 months

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	451	447		
Units: participants				
TEAEs	387	385		
TESAEs	37	49		
TEAEs:permanent study intervention discontinuation	17	19		
TEAESIs	40	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Neurofilament Light Chain (NfL) and Serum Chitinase-3 like protein-1 (Chi3L1) Levels at EOS

End point title	Change From Baseline in Plasma Neurofilament Light Chain (NfL) and Serum Chitinase-3 like protein-1 (Chi3L1) Levels at EOS

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in NfL and Chi3L1. Baseline was defined as the last available value prior to the first dose of study intervention. The safety population included all randomized participants exposed to the study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	319		
Units: picogram/milliliter				
median (inter-quartile range (Q1-Q3))				
NfL (n=301, 314)	-0.900 (-4.390 to 0.770)	-0.150 (-3.560 to 2.750)		
Chi3L1 (n=311, 319)	-281.100 (-6148.400 to 5647.000)	1462.500 (-4578.600 to 7002.700)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Immunoglobulin (Ig) Levels at EOS

End point title	Change From Baseline in Serum Immunoglobulin (Ig) Levels at EOS

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in IgG and IgM levels. Baseline was defined as the last available value prior to the first dose of study intervention. The safety population included all randomized participants exposed to the study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only participants with data collected at specified timepoints for the specified categories are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

End point values	Teriflunomide 14 mg	Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	287		
Units: gram per liter				
median (inter-quartile range (Q1-Q3))				
IgG	-0.590 (-1.330 to 0.230)	0.140 (-0.720 to 1.060)		
IgM	-0.160 (-0.320 to -0.020)	-0.320 (-0.530 to -0.150)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study intervention (Day 1) up to the earliest of either 10 days post last dose, death or last contact; up to approximately 48 months. Deaths were collected from baseline (Day 1) up to end of follow-up, approximately 48 months.

Adverse event reporting additional description:

Analysis was performed on the safety population. All-cause mortality was performed on the randomized population. This was an event-driven (6-month CDW) trial with a variable treatment duration (EOS duration: up to approximately 48 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Tolebrutinib 60 mg

Reporting group description:

Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 46 months.

Reporting group title	Teriflunomide 14 mg

Reporting group description:

Participants received teriflunomide 14 mg tablet orally QD along with a placebo matched to tolebrutinib orally QD up to approximately 48 months.

Serious adverse events	Tolebrutinib 60 mg	Teriflunomide 14 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 447 (10.96%)	37 / 451 (8.20%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oligodendroglioma			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal Proliferative Breast Lesion			

subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	1 / 447 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	2 / 447 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma Necrosis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral Ischaemia			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Systemic Inflammatory Response Syndrome			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Heavy Menstrual Bleeding			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenomyosis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal Uterine Bleeding			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	4 / 447 (0.89%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic Symptom Disorder			

subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Fatigue			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol Withdrawal Syndrome			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases Increased			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament Rupture			
subjects affected / exposed	1 / 447 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intentional Overdose			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun Shot Wound			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Craniocerebral Injury			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Sprain			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal Burn			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			

subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Guillain-Barre Syndrome			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			

subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing Multiple Sclerosis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing-Remitting Multiple Sclerosis			
subjects affected / exposed	2 / 447 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal Neuralgia			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric Haemorrhage			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Duodenal Ulcer			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis Acute			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Calculus Urethral			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Disorder			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 447 (0.22%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone Abscess			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 447 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Norovirus			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 447 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Pyelonephritis			
subjects affected / exposed	0 / 447 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue Fever			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	2 / 447 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			

subjects affected / exposed	2 / 447 (0.45%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 447 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 447 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 447 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tolebrutinib 60 mg	Teriflunomide 14 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 447 (62.42%)	313 / 451 (69.40%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	20 / 447 (4.47%)	23 / 451 (5.10%)	
occurrences (all)	23	28	
Vascular disorders			

Hypertension			
subjects affected / exposed	13 / 447 (2.91%)	34 / 451 (7.54%)	
occurrences (all)	14	35	
Nervous system disorders			
Headache			
subjects affected / exposed	61 / 447 (13.65%)	54 / 451 (11.97%)	
occurrences (all)	82	64	
Paraesthesia			
subjects affected / exposed	16 / 447 (3.58%)	25 / 451 (5.54%)	
occurrences (all)	16	30	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 447 (2.24%)	34 / 451 (7.54%)	
occurrences (all)	14	72	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 447 (6.71%)	21 / 451 (4.66%)	
occurrences (all)	30	22	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 447 (4.92%)	49 / 451 (10.86%)	
occurrences (all)	25	57	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	37 / 447 (8.28%)	73 / 451 (16.19%)	
occurrences (all)	39	74	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	24 / 447 (5.37%)	28 / 451 (6.21%)	
occurrences (all)	25	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 447 (5.15%)	17 / 451 (3.77%)	
occurrences (all)	35	21	
Back Pain			
subjects affected / exposed	27 / 447 (6.04%)	25 / 451 (5.54%)	
occurrences (all)	33	39	

Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 447 (4.25%)	24 / 451 (5.32%)	
occurrences (all)	28	26	
Urinary Tract Infection			
subjects affected / exposed	25 / 447 (5.59%)	30 / 451 (6.65%)	
occurrences (all)	35	43	
Covid-19			
subjects affected / exposed	106 / 447 (23.71%)	115 / 451 (25.50%)	
occurrences (all)	126	131	
Influenza			
subjects affected / exposed	27 / 447 (6.04%)	25 / 451 (5.54%)	
occurrences (all)	33	35	
Nasopharyngitis			
subjects affected / exposed	60 / 447 (13.42%)	64 / 451 (14.19%)	
occurrences (all)	102	97	
Upper Respiratory Tract Infection			
subjects affected / exposed	31 / 447 (6.94%)	36 / 451 (7.98%)	
occurrences (all)	43	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2020	The purpose of the amendment was to add exclusion criteria that were previously omitted and the regulatory requirement of a benefit-risk evaluation of the study in the context of the Coronavirus Disease 2019 (COVID-19) pandemic.
24 August 2020	The purpose of the amendment was to respond to European Health Authorities' requests.
28 September 2020	The purpose of the amendment was to update the protocol for COVID-19-related contingencies.
14 April 2021	The purpose of the amendment was to update the liver function test frequency in the European Union countries in accordance with the updated teriflunomide (Aubagio) summary of product characteristics. Alanine aminotransferase (ALT) exclusion criterion was also updated to align with the Aubagio label.
18 November 2021	The purpose of the amendment was to update the safety follow-up algorithms for ALT increase and thrombocytopenia and the platelet level threshold for definition of an AESI in order to harmonize them with the other studies in the Phase 3 program.
23 May 2022	The purpose of the amendment was to update liver related exclusion criteria and monitoring to mitigate risk of drug-induced liver injury (DILI).
13 September 2022	The purpose of the amendment was to further reduce the risk of DILI by increasing the intensity of liver monitoring.
12 December 2022	The purpose of the amendment was to clarify information about DILI and update the ALT increase algorithm in relation to the risk of DILI.
17 November 2023	The purpose of the amendment was to update the testing requirements in the "Increase in ALT algorithm" as per Health Authority request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported