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 1)

Summary

EudraCT number	2020-000637-41
Trial protocol	DE BG CZ FI SE AT DK LT PL IT RO
Global end of trial date	15 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	EFC16033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04410978
WHO universal trial number (UTN)	U1111-1238-1418

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	15 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of daily tolebrutinib compared to a daily dose of 14 milligrams (mg) teriflunomide (Aubagio) measured by the annualized adjudicated 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	30 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	Austria: 3
Country: Number of subjects enrolled	Belarus: 15
Country: Number of subjects enrolled	Bulgaria: 61
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	China: 118
Country: Number of subjects enrolled	Czechia: 70
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Estonia: 26
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	Mexico: 24
Country: Number of subjects enrolled	Poland: 81

Country: Number of subjects enrolled	Romania: 25
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Türkiye: 37
Country: Number of subjects enrolled	Ukraine: 132
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	974
EEA total number of subjects	417

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)	974
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1152 participants were screened from 30-Jun-2020 to 04-Aug-2022, of which 178 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 974 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 47 months.

Arm type	Active comparator
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 47 months.

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 47 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 48 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 48

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 48 months.

Number of subjects in period 1	Teriflunomide 14 mg	Tolebrutinib 60 mg
Started	488	486
Completed	415	409
Not completed	73	77
Consent withdrawn by subject	64	66
Poor compliance to protocol	2	4
Unspecified	6	7
Missing study status	1	-

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 47 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 48 months.	

Reporting group values	Teriflunomide 14 mg	Tolebrutinib 60 mg	Total
Number of subjects	488	486	974
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	36.6	36.8	
standard deviation	± 9.4	± 9.0	-
Sex: Female, Male Units: participants			
Female	325	334	659
Male	163	152	315
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	6	9
Asian	67	78	145
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	10	4	14
White	406	395	801
More than one race	1	1	2
Unknown or Not Reported	1	1	2

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 47 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 48 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	488	486		
Units: relapses per participant year				
number (confidence interval 95%)	0.122 (0.100 to 0.150)	0.130 (0.108 to 0.156)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.6691 [2]
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	1.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.808
upper limit	1.393

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	488	486		
Units: months				
median (full range (min-max))	17.97 (2.9 to 33.9)	15.38 (2.6 to 36.8)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4888 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	1.278

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	488	486		
Units: months				
median (full range (min-max))	17.96 (2.9 to 39.3)	14.93 (0.2 to 41.0)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.2991 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.582
upper limit	1.151

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 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	488	486		
Units: number of new and or enlarging T2lesions				
arithmetic mean (confidence interval 95%)	5.175 (4.447 to 6.024)	5.611 (4.826 to 6.524)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.4575
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	1.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.876
upper limit	1.342

Notes:

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

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	488	486		
Units: number of new Gd-enhancing T1 lesions				
arithmetic mean (confidence interval 95%)	0.285 (0.221 to 0.367)	0.530 (0.439 to 0.641)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0001
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.358
upper limit	2.548

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	396	393		
Units: score on a scale				
least squares mean (standard error)	0.329 (± 0.0318)	0.364 (± 0.0318)		

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	789
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.432
Method	MMRM
Parameter estimate	Least square (LS) mean difference
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.124

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	391	390		
Units: T-score				
least squares mean (standard error)	15.827 (± 0.7241)	17.700 (± 0.7236)		

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	781
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0675
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	1.873
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.135
upper limit	3.88

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	488	486		
Units: months				
median (full range (min-max))	12.04 (2.8 to 37.1)	11.82 (2.8 to 33.0)		

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	974
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.3594 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	1.245

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	346	351		
Units: percent change				
least squares mean (standard error)	-0.884 (± 0.0368)	-0.688 (± 0.0369)		

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	697
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0002
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.093
upper limit	0.298

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	400	399		
Units: score on a scale				
least squares mean (standard error)				
Physical health composite score (n=393, 394)	-2.468 (± 0.7014)	-0.460 (± 0.7021)		
Mental health composite score (n=400, 399)	-2.070 (± 0.8346)	-0.729 (± 0.8359)		

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 Treatment-emergent 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 Treatment-emergent Adverse Events of Special Interest (AESIs)

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the 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 the 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 the TE 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	488	486		
Units: participants				
TEAEs	423	407		
TESAEs	40	42		
TEAEs:permanent study intervention discontinuation	24	23		
TEAESIs	57	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Tolebrutinib and M2 Metabolite

End point title	Maximum Observed Plasma Concentration (Cmax) of Tolebrutinib and M2 Metabolite[14]

End point description:

Blood samples were collected at specified timepoints to assess Cmax of tolebrutinib and M2 metabolite using population pharmacokinetic (PK) model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

End point values	Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Tolebrutinib	12.0 (± 7.75)			
M2 Metabolite	28.3 (± 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Plasma Concentration (Tmax) of Tolebrutinib and M2 Metabolite

End point title	Time to Maximum Observed Plasma Concentration (Tmax) of Tolebrutinib and M2 Metabolite[15]

End point description:

Blood samples were collected at specified timepoints to assess Tmax of tolebrutinib and M2 metabolite using population PK model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

End point values	Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: hour (h)				
arithmetic mean (standard deviation)				
Tolebrutinib	1.28 (± 0.513)			
M2 Metabolite	1.40 (± 0.508)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve Over the Last 24-hours Dosing Interval (AUC0-24) of Tolebrutinib and M2 Metabolite

End point title	Area Under the Plasma Concentration-time Curve Over the Last 24-hours Dosing Interval (AUC0-24) of Tolebrutinib and M2 Metabolite[16]

End point description:

Blood samples were collected at specified timepoints to assess AUC0-24 of tolebrutinib and M2 metabolite using population PK model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

End point values	Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Tolebrutinib	30.5 (± 18.2)			
M2 Metabolite	76.7 (± 44.1)			

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	344	350		
Units: picogram/mL				
median (inter-quartile range (Q1-Q3))				
NfL (n=294, 296)	-1.665 (-6.100 to 0.830)	-0.325 (-3.505 to 2.220)		
Chi3L1 (n=344, 350)	1017.100 (-4494.850 to 7672.450)	1572.250 (-2582.000 to 6356.600)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cluster of Differentiation (CD)19+ B Cells at EOS

End point title	Change From Baseline in Cluster of Differentiation (CD)19+ B Cells at EOS

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in CD19+ B cells. 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.

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	95	100		
Units: cells/microliter				
median (inter-quartile range (Q1-Q3))	-45.000 (-81.000 to -5.000)	-60.500 (-97.500 to -28.500)		

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 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	263	266		
Units: gram/liter				
median (inter-quartile range (Q1-Q3))				
IgG (n=261, 266)	-0.660 (-1.460 to 0.150)	0.235 (-0.500 to 1.020)		
IgM (n=263, 263)	-0.150 (-0.330 to -0.030)	-0.340 (-0.520 to -0.190)		

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. 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 48 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 47 months.

Serious adverse events	Tolebrutinib 60 mg	Teriflunomide 14 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 486 (8.64%)	40 / 488 (8.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Ovarian Tumour			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Bone Neoplasm			

subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer Stage Ii			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Breast Carcinoma			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cancer			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Sarcoma			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	2 / 486 (0.41%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Varicose Vein			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			

subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	2 / 486 (0.41%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Haemorrhage			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual Bleeding			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (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			
Nasal Septum Deviation			
subjects affected / exposed	0 / 486 (0.00%)	2 / 488 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Thinking Abnormal			

subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
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 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Pressure Increased			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Meniscus Injury			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Injury			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Forearm Fracture			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns Second Degree			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella Fracture			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Fractures			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple Sclerosis Relapse			
subjects affected / exposed	3 / 486 (0.62%)	5 / 488 (1.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central Nervous System Lesion			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic Neuritis			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 486 (0.00%)	2 / 488 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status Epilepticus			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Impairment			
subjects affected / exposed	1 / 486 (0.21%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Field Defect			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision Blurred			

subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Epulis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Erosion			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Disorder			

subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food Poisoning			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Stone			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema Multiforme			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 486 (0.00%)	2 / 488 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 486 (0.21%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 486 (0.41%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	1 / 486 (0.21%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	4 / 486 (0.82%)	2 / 488 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic Sinusitis			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Tonsillitis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Chlamydial Infection			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-Oophoritis			

subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic Viral Infection			
subjects affected / exposed	0 / 486 (0.00%)	1 / 488 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis Infectious			
subjects affected / exposed	1 / 486 (0.21%)	0 / 488 (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	296 / 486 (60.91%)	321 / 488 (65.78%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	23 / 486 (4.73%)	40 / 488 (8.20%)	
occurrences (all)	26	43	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 486 (3.29%)	27 / 488 (5.53%)	
occurrences (all)	19	28	
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 486 (11.52%)	44 / 488 (9.02%)	
occurrences (all)	100	62	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 486 (2.88%)	58 / 488 (11.89%)	
occurrences (all)	22	93	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	22 / 486 (4.53%)	36 / 488 (7.38%)	
occurrences (all)	24	50	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 486 (7.41%)	73 / 488 (14.96%)	
occurrences (all)	36	75	
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 486 (2.26%)	27 / 488 (5.53%)	
occurrences (all)	11	27	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	31 / 486 (6.38%)	30 / 488 (6.15%)	
occurrences (all)	35	34	
Arthralgia			
subjects affected / exposed	18 / 486 (3.70%)	27 / 488 (5.53%)	
occurrences (all)	25	31	
Infections and infestations			
Covid-19			
subjects affected / exposed	117 / 486 (24.07%)	135 / 488 (27.66%)	
occurrences (all)	133	150	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	31 / 486 (6.38%)	34 / 488 (6.97%)	
occurrences (all)	54	48	
Urinary Tract Infection			
subjects affected / exposed	34 / 486 (7.00%)	27 / 488 (5.53%)	
occurrences (all)	45	32	
Upper Respiratory Tract Infection			
subjects affected / exposed	46 / 486 (9.47%)	46 / 488 (9.43%)	
occurrences (all)	69	65	
Nasopharyngitis			
subjects affected / exposed	59 / 486 (12.14%)	41 / 488 (8.40%)	
occurrences (all)	88	61	
Influenza			
subjects affected / exposed	19 / 486 (3.91%)	26 / 488 (5.33%)	
occurrences (all)	24	35	

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 to meet the regulatory requirement of a benefit/risk evaluation of the study in the context of the Coronavirus Disease 2019 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 respond to Japanese Health Authorities' requests.
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.
24 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" and update the country-specific requirements for Japan with additional guidelines in case of ALT increase >3 x upper limit of normal as per Health Authorities requests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported