Clinical trial results:
A Phase 3, randomized, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with nonrelapsing secondary progressive multiple sclerosis (HERCULES)

Summary

EudraCT number	2020-000647-30
Trial protocol	BG FR DE GB CZ NO FI DK BE LT AT GR NL PT PL HU IT RO
Global end of trial date	29 August 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	EFC16645

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04411641
WHO universal trial number (UTN)	U1111-1246-7768

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	27 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of tolebrutinib compared to placebo in delaying disability progression in non-relapsing secondary progressive multiple sclerosis.

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	24 September 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: 26
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bulgaria: 60
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	China: 24
Country: Number of subjects enrolled	Czechia: 40
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	France: 107
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 27
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Israel: 13

Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Russian Federation: 103
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Türkiye: 36
Country: Number of subjects enrolled	Ukraine: 63
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 111
Worldwide total number of subjects	1131
EEA total number of subjects	629

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)	1131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1131 participants were randomized in this study in a 2:1 ratio to receive either tolebrutinib or matching placebo in the double-blind (DB) period. Participants with 6-month confirmed disability progression (CDP) were given the option to receive open-label (OL) tolebrutinib.

Pre-assignment

Screening details:

This was an event-driven (6-month CDP) trial with a variable treatment duration (end-of-study [EOS] duration: up to approximately 47 months).

Period 1

Period 1 title	DB 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	DB: Placebo

Arm description:

Participants received placebo matched to tolebrutinib orally once daily up to approximately 47 months.

Arm type	Placebo
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 orally once daily up to approximately 47 months.

Arm title	DB: Tolebrutinib 60 mg

Arm description:

Participants received tolebrutinib 60 milligrams (mg) tablet orally once daily up to approximately 47 months.

Arm type	Experimental
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 once daily up to approximately 47 months.

Number of subjects in period 1	DB: Placebo	DB: Tolebrutinib 60 mg
Started	377	754
Completed	192	434
Not completed	185	320
Consent withdrawn by subject	67	122
Adverse event, non-fatal	13	29
Randomized and not treated	2	2
Unspecified	7	27
Poor compliance to protocol	1	5
Progressive disease	76	116
Lack of efficacy	19	19

Period 2

Period 2 title	OL
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OL: Placebo/Tolebrutinib 60 mg

Arm description:

Participants who received placebo in DB period and achieved 6-month CDP were given the option to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.

Arm type	Experimental
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 optionally administered as a tablet orally once daily in OL up to approximately 39 months to those participants who received placebo in DB period and achieved 6-month CDP.

Arm title	OL: Tolebrutinib 60 mg/Tolebrutinib 60 mg

Arm description:

Participants who received tolebrutinib 60 mg in DB period and achieved 6-month CDP were given the option to continue to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.

Arm type	Experimental
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 optionally administered as a tablet orally once daily in OL up to approximately 39 months to those participants who received tolebrutinib 60 mg in DB period and achieved 6-month CDP.

Number of subjects in period 2[1]	OL: Placebo/Tolebrutinib 60 mg	OL: Tolebrutinib 60 mg/Tolebrutinib 60 mg
Started	76	120
Completed	67	95
Not completed	9	25
Consent withdrawn by subject	6	17
Adverse event, non-fatal	1	-
Poor compliance to protocol	1	-
Unspecified	-	6
Progressive disease	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only eligible participants switched to OL.

Baseline characteristics

Reporting groups	
Reporting group title	DB: Placebo
Reporting group description:	
Participants received placebo matched to tolebrutinib orally once daily up to approximately 47 months.	
Reporting group title	DB: Tolebrutinib 60 mg
Reporting group description:	
Participants received tolebrutinib 60 milligrams (mg) tablet orally once daily up to approximately 47 months.	

Reporting group values	DB: Placebo	DB: Tolebrutinib 60 mg	Total
Number of subjects	377	754	1131
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	48.9	48.9	
standard deviation	± 8.0	± 8.0	-
Sex: Female, Male Units: participants			
Female	242	454	696
Male	135	300	435
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	19	36	55
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	6	10
White	348	703	1051
More than one race	0	1	1
Unknown or Not Reported	6	7	13

End points

End points reporting groups

Reporting group title	DB: Placebo
Reporting group description:	
Participants received placebo matched to tolebrutinib orally once daily up to approximately 47 months.	
Reporting group title	DB: Tolebrutinib 60 mg
Reporting group description:	
Participants received tolebrutinib 60 milligrams (mg) tablet orally once daily up to approximately 47 months.	
Reporting group title	OL: Placebo/Tolebrutinib 60 mg
Reporting group description:	
Participants who received placebo in DB period and achieved 6-month CDP were given the option to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.	
Reporting group title	OL: Tolebrutinib 60 mg/Tolebrutinib 60 mg
Reporting group description:	
Participants who received tolebrutinib 60 mg in DB period and achieved 6-month CDP were given the option to continue to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.	

Primary: Time to Onset of 6-Month Confirmed Disability Progression (CDP) as Assessed by Expanded Disability Status Scale (EDSS)

End point title	Time to Onset of 6-Month Confirmed Disability Progression (CDP) as Assessed by Expanded Disability Status Scale (EDSS)
End point description:	
The EDSS is a disability scale that assesses the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS ranges from 0 (normal) to 10 (death due to multiple sclerosis [MS]) (0.5 increments from 1-10; next increase after 0 is 1). Higher scores indicated increased disability. Time to onset of 6-month CDP was defined as the time from randomization to the onset of a sustained increase from baseline in EDSS score of >=1.0 point from the baseline EDSS score when the baseline score was <=5.0 or of >=0.5 points when the baseline EDSS score was >5.0 confirmed after a minimum 6-month interval. 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) up to approximately 47 months	

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: months				
median (full range (min-max))	11.97 (0.5 to 39.1)	12.04 (2.8 to 37.4)		

Statistical analyses

Statistical analysis title	Time to onset of 6-month CDP as assessed by EDSS

Statistical analysis description:

Derived using Cox proportional-hazards model with robust variance estimation.Covariates were treatment group,age at screening (>40,<=40 years),geographic region (United States [US], non-US),baseline EDSS score & baseline gadolinium (Gd)-enhancing T1 lesions (presence, absence).In this analysis, for participants who completed study with 3-month confirmation and continued to meet disability progression criteria throughout EOS, their 6-month CDP status was imputed via multiple imputation method.

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0026 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.693
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	0.88

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.

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

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

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

End point description:

The EDSS is a disability scale that assesses the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS ranges from 0 (normal) to 10 (death due to MS) (0.5 increments from 1-10; next increase after 0 is 1). Higher scores indicated increased disability. Time to onset of 3-month CDP was defined as the time from randomization to the onset of a sustained increase from baseline in EDSS score (of >=1.0 point from the baseline EDSS score when the baseline score is <=5.0, of >=0.5 points when the baseline EDSS score is >5.0) confirmed after a minimum 3-month interval. The confirmation of 3-month CDP followed the same criteria as that of 6-month CDP. 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) up to approximately 47 months

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: months				
median (full range (min-max))	11.96 (0.5 to 39.1)	12.04 (2.8 to 39.5)		

Statistical analyses

Statistical analysis title	Time to onset of 3-month CDP as assessed by EDSS

Statistical analysis description:

Derived using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence).

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0134 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.757
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.607
upper limit	0.944

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.
[4] - Threshold for significance at 2-sided 0.05 level.

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 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) up to approximately 47 months

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: number of T2 lesions				
arithmetic mean (confidence interval 95%)	2.948 (2.239 to 3.880)	1.835 (1.441 to 2.336)		

Statistical analyses

Statistical analysis title	New/enlarging T2-hyperintense lesions per year

Statistical analysis description:

Derived 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, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score, and baseline number of T2 lesions as covariates, and log transformed observation duration as the offset variable.

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.011 [6]
Method	Chi-squared
Parameter estimate	Relative Risk
Point estimate	0.622
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.432
upper limit	0.897

Notes:

[5] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.

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

Secondary: Time to Onset of Sustained 20% Increase in the 9-hole peg Test (HPT) for at Least 3 Months

End point title	Time to Onset of Sustained 20% Increase in the 9-hole peg Test (HPT) for at Least 3 Months

End point description:

The 9-HPT is a brief, standardized, quantitative test of upper extremity function and the time to complete the 9-HPT is used to assess a participant’s manual dexterity and fine motor skills. A participant was asked to place the pegs into the holes and remove them with the dominant and non-dominant hand; two successful trials for each hand. The amount of time (in seconds) required to place and remove all nine pegs was recorded for each trial (ranging from 10 to 300 seconds). The mean time to test completion served for assessment of the participant’s hand dexterity. Higher value indicated worse outcome. An increase of >20% from the baseline in the 9-HPT was considered meaningful worsening; time to onset of sustained 20% increase for at least 3 months is presented. 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) up to approximately 47 months

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: months				
median (full range (min-max))	12.39 (2.5 to 33.3)	12.21 (2.8 to 39.2)		

Statistical analyses

Statistical analysis title	9-hole HPT

Statistical analysis description:

Derived using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence).

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.8428 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	1.286

Notes:

[7] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.
[8] - Threshold for significance at 2-sided 0.05 level.

Secondary: Time to Onset of Sustained 20% Increase in the Timed 25-foot Walk (T25-FW) for at Least 3 Months

End point title	Time to Onset of Sustained 20% Increase in the Timed 25-foot Walk (T25-FW) for at Least 3 Months

End point description:

The T25-FW test is a quantitative mobility and leg function performance test used to assess a participant’s walking ability. A participant was directed to one end of a clearly marked 25-foot course and instructed to walk 25 feet as quickly as safely possible for 2 trials. The amount of time (in seconds) to walk 25 feet was recorded (ranging from 2.2 to 180 seconds). The mean walk time was used for assessment of the participant’s walking ability. Higher value indicated worse outcome. An increase of >20% from the baseline in the T25-FW test was considered meaningful worsening; time to onset of sustained 20% increase for at least 3 months is presented. 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) up to approximately 47 months

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: months				
median (full range (min-max))	9.25 (2.5 to 36.3)	9.54 (2.8 to 39.3)		

Statistical analyses

Statistical analysis title	T25-FW

Statistical analysis description:

Derived using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence).

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.004
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.767
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.919

Notes:

[9] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.

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 is a disability scale that assesses the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS ranges from 0 (normal) to 10 (death due to MS) (0.5 increments from 1-10; next increase after 0 is 1). Higher scores indicated increased disability. CDI was defined as a >=1 point decrease in the EDSS score from baseline confirmed over 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) up to approximately 47 months

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	754		
Units: months				
median (full range (min-max))	12.04 (3.0 to 24.1)	11.89 (2.9 to 33.0)		

Statistical analyses

Statistical analysis title	Time to onset of 6-month CDI as assessed by EDSS

Statistical analysis description:

Derived using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence).

Comparison groups	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0206
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.102
upper limit	3.214

Notes:

[10] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.

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

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

End point description:

MRI of the brain was performed to evaluate percent change in brain volume which is considered as a marker of the central nervous system degenerative process. Least squares (LS) mean is presented. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Month 6 to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	451		
Units: percent change				
least squares mean (standard error)	-0.776 (± 0.0479)	-0.694 (± 0.0336)		

Statistical analyses

Statistical analysis title	Percent change in brain volume (EOS to Month 6)

Statistical analysis description:

Covariates in the mixed-effect model with repeated measures were treatment group, age at screening (>40, <=40 years), 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	DB: Placebo v DB: Tolebrutinib 60 mg
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.1646
Method	Mixed model repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.197

Notes:

[11] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the outcome measures are reported and continued when previous outcome measure was statistically significant at 2-sided 0.05. Primary and first 6 secondary endpoints are included in this procedure.

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

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

End point description:

The SDMT is used to assess processing speed, divided attention, visual scanning, tracking and motor speed. It involves 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) are recorded. A decrease of 4 points from baseline on the SDMT is considered meaningful worsening. The score was the number of correctly coded items from 0-110 in 90 seconds; higher scores indicated better outcome. LS mean is presented. Baseline was defined as the last available value prior to the first dose of study intervention. Analysis was performed on the ITT population. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	546		
Units: score on a scale				
least squares mean (standard error)	0.171 (± 0.0373)	0.136 (± 0.0264)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The CVLT-II is a verbal learning and memory test consisting of recall and recognition of a list of 16 words. The list was read by the examiner, participants listened to the list and reported as many of the items as possible. For each assessment, 5 trials were completed. Standardized scores were used for analysis. The maximum possible score was 80 and a minimum was 0. A higher score indicated better recall meaning improved cognitive function. LS mean is presented. 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 those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	531		
Units: score on a scale				
least squares mean (standard error)	13.448 (± 0.9571)	14.169 (± 0.6759)		

Statistical analyses

No statistical analyses for this end point

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 consists of 12 subscales & 2 single-item measures (satisfaction with sexual function [1 item] & change in health [1 item].12 subscales:a:physical health (10 items),b:health perceptions (5 items), c:energy (5 items),d:role limitation 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 calculated as weighted sum of 'a to h' subscales and 'i to l' subscales respectively.Each composite score transformed linearly to common 0 (worst) to 100 (best) score range;LS mean presented.Higher score=improved QoL.Baseline:last available value prior to first dose of study intervention. Analyzed on ITT population.Only those participants with data collected at specified timepoints are reported.n=number of participants for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	552		
Units: score on a scale				
least squares mean (standard error)				
Physical health composite score (n=262, 536)	-3.979 (± 0.8032)	-3.455 (± 0.5623)		
Mental health composite score (268, 552)	-4.648 (± 0.9964)	-3.944 (± 0.6959)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (AEs), Treatment-emergent Serious AEs, Treatment-emergent AEs 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 (AEs), Treatment-emergent Serious AEs, Treatment-emergent AEs 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 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 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 Investigator to the Sponsor was required. TEAEs were defined as AEs that developed, worsened or became serious during TE period. The safety population included all randomized participants exposed to study intervention, regardless of the

amount of exposure, analyzed according to the intervention actually received.

End point type	Secondary

End point timeframe:

From first dose of study intervention (Day 1) up to end of follow-up, up to approximately 47 months

End point values	DB: Placebo	OL: Placebo/Tolebrutinib 60 mg	DB: Tolebrutinib 60 mg	OL: Tolebrutinib 60 mg/Tolebrutinib 60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	375	76	752	120
Units: participants				
TEAEs	293	47	613	80
TESAEs	39	9	113	11
TEAEs:Permanent Study Intervention Discontinuation	11	1	29	0
TEAESIs	20	6	75	10

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[12]

End point description:

Blood samples were collected at specified timepoints to assess Tmax of tolebrutinib and M2 metabolite using a PopPK 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 those 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:

[12] - 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: Participants who received tolebrutinib are included in this endpoint.

End point values	DB: Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	669			
Units: hour (h)				
arithmetic mean (standard deviation)				
Tolebrutinib	1.42 (± 0.674)			
M2 Metabolite	1.52 (± 0.667)			

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[13]

End point description:

Blood samples were collected at specified timepoints to assess Cmax of tolebrutinib and M2 metabolite using a population pharmacokinetics (PopPK) 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 those 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:

[13] - 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: Participants who received tolebrutinib are included in this endpoint.

End point values	DB: Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	669			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Tolebrutinib	9.94 (± 6.18)			
M2 Metabolite	27.5 (± 17.3)			

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[14]

End point description:

Blood samples were collected at specified timepoints to assess AUC0-24 of tolebrutinib and M2 metabolite using a PopPK 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 those 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: Participants who received tolebrutinib are included in this endpoint.

End point values	DB: Tolebrutinib 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	669			
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Tolebrutinib	29.6 (± 17.8)			
M2 Metabolite	84.6 (± 53.7)			

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 study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only those participants with data collected at specified timepoints are reported. Here, n= number of participants for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	410		
Units: picogram/mL				
median (inter-quartile range (Q1-Q3))				
NfL (n=168, 403)	1.070 (-1.285 to 3.615)	1.900 (-0.370 to 4.470)		
Chi3L1 (n=171, 410)	5156.900 (-1555.700 to 12099.200)	3132.250 (-2822.100 to 13407.100)		

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 study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	58		
Units: cells/microliter				
median (inter-quartile range (Q1-Q3))	10.000 (-18.000 to 77.000)	-63.000 (-105.000 to -8.000)		

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 study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only those participants with data collected at specified timepoints are reported. Here, n= number of participants for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 47 months)

End point values	DB: Placebo	DB: Tolebrutinib 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	323		
Units: gram/liter				
median (inter-quartile range (Q1-Q3))				
IgG (n=149, 320)	0.350 (-0.280 to 1.310)	-0.085 (-0.845 to 0.665)		
IgM (n=142, 323)	0.050 (-0.080 to 0.150)	-0.240 (-0.450 to -0.120)		

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 end of follow-up, up to approximately 47 months

Adverse event reporting additional description:

Analysis was performed on safety population. All-cause mortality was performed on randomized population. This was an event-driven (6-month CDP) trial with a variable treatment duration, EOS: up to approximately 47 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	DB: Placebo

Reporting group description:

Participants received placebo matched to tolebrutinib orally once daily up to approximately 47 months.

Reporting group title	OL: Tolebrutinib 60 mg/tolebrutinib 60 mg

Reporting group description:

Participants who received tolebrutinib 60 mg in DB period and achieved 6-month CDP were given the option to continue to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.

Reporting group title	OL: Placebo/tolebrutinib 60 mg

Reporting group description:

Participants who received placebo in DB period and achieved 6-month CDP were given the option to receive OL tolebrutinib 60 mg tablet orally once daily up to approximately 39 months in the OL.

Reporting group title	DB: Tolebrutinib 60 mg

Reporting group description:

Participants received tolebrutinib 60 mg tablet orally once daily up to approximately 47 months.

Serious adverse events	DB: Placebo	OL: Tolebrutinib 60 mg/tolebrutinib 60 mg	OL: Placebo/tolebrutinib 60 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 375 (10.40%)	11 / 120 (9.17%)	9 / 76 (11.84%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm Of Thyroid Gland			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Myeloid Leukaemia			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer Stage 0, With Cancer In Situ			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial Adenocarcinoma			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Cancer Metastatic			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cell Carcinoma Stage I			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Assisted Suicide			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation Therapy			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rebound Effect			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acquired Hydrocele			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Murmur			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Vertebral Fracture			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Brain Contusion			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 375 (0.27%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural Haematoma			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula Fracture			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Dislocation			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Fracture			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb Injury			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-Traumatic Pain			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Laceration			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder Fracture			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull Fractured Base			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous Haematoma			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Haemothorax			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Liver Injury			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain Hypoxia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Hypotension			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Oedema			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Pseudo Relapse			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Spasticity			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-Traumatic Headache			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonian Gait			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restless Legs Syndrome			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary Progressive Multiple Sclerosis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal Neuralgia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo Cns Origin			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Acute Vestibular Syndrome			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo Positional			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Detachment			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual Field Defect			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Functional Gastrointestinal Disorder			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Haemorrhage			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Megacolon			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive Pancreatitis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Terminal Ileitis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-Induced Liver Injury			

subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder Polyp			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Failure			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondropathy			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscular Weakness			
subjects affected / exposed	1 / 375 (0.27%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck Pain			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain In Extremity			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Pyelonephritis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 Pneumonia			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Viral			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Bacterial			
subjects affected / exposed	2 / 375 (0.53%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Viral			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Pneumococcal			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 375 (0.80%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection Bacterial			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Chronic			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Infection			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 375 (0.00%)	1 / 120 (0.83%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella Zoster Pneumonia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	3 / 375 (0.80%)	0 / 120 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 375 (0.27%)	2 / 120 (1.67%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB: Tolebrutinib 60 mg		

Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 752 (15.03%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm Of Thyroid Gland			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Myeloid Leukaemia			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder Cancer Stage 0, With Cancer In Situ			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder Cancer			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial Adenocarcinoma			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Cancer Metastatic			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate Cancer			

subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Cell Carcinoma Stage I			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Assisted Suicide			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rehabilitation Therapy			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Malaise				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema Peripheral				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rebound Effect				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Cervical Dysplasia				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Benign Prostatic Hyperplasia				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acquired Hydrocele				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				

subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Murmur			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Craniocerebral Injury			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical Vertebral Fracture			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain Contusion			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	3 / 752 (0.40%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Extradural Haematoma			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral Neck Fracture			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus Fracture			
subjects affected / exposed	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip Fracture			

subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula Fracture				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional Overdose				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint Dislocation				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic Fracture				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar Vertebral Fracture				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Limb Injury				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post-Traumatic Pain				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius Fracture				

subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin Laceration				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road Traffic Accident				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shoulder Fracture				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib Fracture				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skull Fractured Base				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Compression Fracture				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous Haematoma				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna Fracture				

subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic Haemothorax				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic Liver Injury				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial Infarction				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Left Ventricular Dysfunction				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute Myocardial Infarction				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus Node Dysfunction				

subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain Hypoxia			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial Hypotension			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain Oedema			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss Of Consciousness			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar Radiculopathy			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Sclerosis Relapse			

subjects affected / exposed	8 / 752 (1.06%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Multiple Sclerosis				
subjects affected / exposed	3 / 752 (0.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Multiple Sclerosis Pseudo Relapse				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle Spasticity				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Optic Neuritis				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post-Traumatic Headache				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parkinsonian Gait				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				

subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Restless Legs Syndrome				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	3 / 752 (0.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subarachnoid Haemorrhage				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Secondary Progressive Multiple Sclerosis				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Trigeminal Neuralgia				
subjects affected / exposed	3 / 752 (0.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vertigo Cns Origin				

subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Acute Vestibular Syndrome			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo Positional			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal Detachment			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual Field Defect			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Lower			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Duodenal Ulcer Haemorrhage				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Functional Gastrointestinal Disorder				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric Ulcer Haemorrhage				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal Haemorrhage				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Megacolon				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive Pancreatitis				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Terminal Ileitis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Gastrointestinal Haemorrhage				

subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gallbladder Polyp			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Failure			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Colic			

subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chondropathy			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Neck Pain			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain In Extremity			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial Pyelonephritis			
subjects affected / exposed	1 / 752 (0.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Covid-19			
subjects affected / exposed	7 / 752 (0.93%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		

Covid-19 Pneumonia				
subjects affected / exposed	8 / 752 (1.06%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Viral				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis Bacterial				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	3 / 752 (0.40%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia Viral				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia Pneumococcal				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Bacterial				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 752 (0.66%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Acute				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection Bacterial				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				

subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	0 / 752 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Chronic				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound Infection				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral Upper Respiratory Tract Infection				
subjects affected / exposed	2 / 752 (0.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Varicella Zoster Pneumonia				
subjects affected / exposed	1 / 752 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	3 / 752 (0.40%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DB: Placebo	OL: Tolebrutinib 60 mg/tolebrutinib 60 mg	OL: Placebo/tolebrutinib 60 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 375 (48.53%)	41 / 120 (34.17%)	25 / 76 (32.89%)
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	19 / 375 (5.07%)	3 / 120 (2.50%)	0 / 76 (0.00%)
occurrences (all)	22	3	0
Fall			
subjects affected / exposed	40 / 375 (10.67%)	6 / 120 (5.00%)	4 / 76 (5.26%)
occurrences (all)	54	7	4
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 375 (7.20%)	4 / 120 (3.33%)	2 / 76 (2.63%)
occurrences (all)	31	4	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 375 (5.07%)	2 / 120 (1.67%)	0 / 76 (0.00%)
occurrences (all)	21	2	0
Back Pain			
subjects affected / exposed	24 / 375 (6.40%)	3 / 120 (2.50%)	1 / 76 (1.32%)
occurrences (all)	25	3	1
Infections and infestations			
Influenza			

subjects affected / exposed	13 / 375 (3.47%)	5 / 120 (4.17%)	2 / 76 (2.63%)
occurrences (all)	14	6	2
Covid-19			
subjects affected / exposed	85 / 375 (22.67%)	14 / 120 (11.67%)	4 / 76 (5.26%)
occurrences (all)	96	14	4
Nasopharyngitis			
subjects affected / exposed	26 / 375 (6.93%)	8 / 120 (6.67%)	2 / 76 (2.63%)
occurrences (all)	35	10	3
Urinary Tract Infection			
subjects affected / exposed	49 / 375 (13.07%)	12 / 120 (10.00%)	14 / 76 (18.42%)
occurrences (all)	81	19	22

Non-serious adverse events	DB: Tolebrutinib 60 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	368 / 752 (48.94%)		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	25 / 752 (3.32%)		
occurrences (all)	29		
Fall			
subjects affected / exposed	70 / 752 (9.31%)		
occurrences (all)	106		
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 752 (7.18%)		
occurrences (all)	79		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	49 / 752 (6.52%)		
occurrences (all)	55		
Back Pain			
subjects affected / exposed	47 / 752 (6.25%)		
occurrences (all)	56		
Infections and infestations			
Influenza			

subjects affected / exposed	41 / 752 (5.45%)		
occurrences (all)	60		
Covid-19			
subjects affected / exposed	185 / 752 (24.60%)		
occurrences (all)	225		
Nasopharyngitis			
subjects affected / exposed	70 / 752 (9.31%)		
occurrences (all)	94		
Urinary Tract Infection			
subjects affected / exposed	82 / 752 (10.90%)		
occurrences (all)	152		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2020	The overall rationale for this amended protocol consisted of regulatory requirements including addition of a relapse adjudication committee, change in stratification factor, removal of an endpoint and addition of a benefit-risk evaluation of the study in the context of the Coronavirus Disease 2019 pandemic.
03 November 2020	The overall rationale for this amended protocol was to respond to the feedback from Investigators with regard to the inclusion/exclusion criteria.
26 July 2021	The primary reason for this amendment was the availability of new information from drug-drug interaction studies.
21 December 2021	The primary reason for this amendment was to facilitate operational feasibility and reduce complexity, without compromising study integrity.
23 May 2022	The primary reason for this amended protocol was to update liver related exclusion criteria and monitor to mitigate risk of drug-induced liver injury (DILI).
13 September 2022	The rationale for this protocol amendment was to further reduce the risk of DILI by increasing the intensity of liver monitoring.
14 December 2022	The rationale for this protocol amendment was to clarify information about DILI and update the alanine aminotransferase (ALT) increase algorithm in relation to the risk of DILI.
28 September 2023	The rationale for this protocol amendment was to clarify the language and requirements for the use of OL tolebrutinib in participants who had achieved 6-month CDP and to update the testing requirements in the "increase in ALT algorithm" in accordance with the Council for International Organization of Medical Sciences working group on DILI consensus report.
20 November 2023	The rationale for this protocol amendment was to clarify the liver function monitoring requirements, update the testing requirements in the "increase in ALT algorithm", and update the concomitant medications that were prohibited during the conduct of the study as per health authority request.
20 December 2023	The rationale for this protocol amendment was to update the liver function test monitoring as per Health Authority request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported