Clinical trial results:
Long-term extension safety and efficacy study of SAR442168 in participants with relapsing multiple sclerosis

Summary

EudraCT number	2018-004731-76
Trial protocol	FR SK CZ EE ES NL
Global end of trial date	26 November 2024

Results information

Result version number	v2 (current)
This version publication date	23 November 2025
First version publication date	23 October 2025
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	LTS16004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03996291
WHO universal trial number (UTN)	U1111-1223-4256

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	13 December 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term safety and tolerability of tolebrutinib in participants with relapsing 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	23 September 2019
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	Canada: 4
Country: Number of subjects enrolled	Czechia: 31
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	125
EEA total number of subjects	48

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)	125
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This long-term study was conducted at 37 centers in 9 countries. Of the 129 participants who completed the parent study DRI15928 (2018-003927-12), 126 were screened in this study from 23-Sep-2019 to 10-Mar-2020 of which 1 failed screening due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 125 participants were treated in this study which consisted of 2 parts: Part A (double-blind) and Part B (open-label). Part A was a short transition period until the dose of tolebrutinib to be used in Phase 3 was determined. In Part B, all participants formed a single dose group (the selected Phase 3 dose).

Period 1

Period 1 title	Part A (double-blind period):39 weeks
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Tolebrutinib 5 mg

Arm description:

Participants who received tolebrutinib 5 milligrams (mg) orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

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 5 mg was administered orally once daily as specified in the protocol.

Arm title	Part A: Tolebrutinib 15 mg

Arm description:

Participants who received tolebrutinib 15 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

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 15 mg was administered orally once daily as specified in the protocol.

Arm title	Part A: Tolebrutinib 30 mg

Arm description:

Participants who received tolebrutinib 30 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

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 30 mg was administered orally once daily as specified in the protocol.

Arm title	Part A: Tolebrutinib 60 mg

Arm description:

Participants who received tolebrutinib 60 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

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 orally once daily as specified in the protocol.

Number of subjects in period 1	Part A: Tolebrutinib 5 mg	Part A: Tolebrutinib 15 mg	Part A: Tolebrutinib 30 mg
Started	31	31	32
Completed	30	31	32
Not completed	1	0	0
Unspecified	1	-	-

Number of subjects in period 1	Part A: Tolebrutinib 60 mg
Started	31
Completed	31
Not completed	0
Unspecified	-

Period 2

Period 2 title	Part B (open-label period):222 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Part B: Tolebrutinib 5/60 mg

Arm description:

Participants from Part A: tolebrutinib 5 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

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 orally once daily as specified in the protocol.

Arm title	Part B: Tolebrutinib 15/60 mg

Arm description:

Participants from Part A: tolebrutinib 15 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

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 orally once daily as specified in the protocol.

Arm title	Part B: Tolebrutinib 30/60 mg

Arm description:

Participants from Part A: tolebrutinib 30 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

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 orally once daily as specified in the protocol.

Arm title	Part B: Tolebrutinib 60/60 mg

Arm description:

Participants from Part A: tolebrutinib 60 mg arm who provided consent switched to Part B and continued to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

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 orally once daily as specified in the protocol.

Number of subjects in period 2	Part B: Tolebrutinib 5/60 mg	Part B: Tolebrutinib 15/60 mg	Part B: Tolebrutinib 30/60 mg
Started	30	31	32
Completed	20	23	20
Not completed	10	8	12
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	1
Unspecified	8	7	10
Poor compliance to protocol	-	1	1

Number of subjects in period 2	Part B: Tolebrutinib 60/60 mg
Started	31
Completed	26
Not completed	5
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Unspecified	5
Poor compliance to protocol	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Tolebrutinib 5 mg
Reporting group description:	
Participants who received tolebrutinib 5 milligrams (mg) orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 15 mg
Reporting group description:	
Participants who received tolebrutinib 15 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 30 mg
Reporting group description:	
Participants who received tolebrutinib 30 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 60 mg
Reporting group description:	
Participants who received tolebrutinib 60 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	

Reporting group values	Part A: Tolebrutinib 5 mg	Part A: Tolebrutinib 15 mg	Part A: Tolebrutinib 30 mg
Number of subjects	31	31	32
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	37.1	36.4	40.0
standard deviation	± 9.9	± 9.4	± 9.9
Sex: Female, Male Units: participants			
Female	23	20	20
Male	8	11	12
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	30	29	28
More than one race	0	1	0
Unknown or Not Reported	0	0	2

Reporting group values	Part A: Tolebrutinib 60 mg	Total	
Number of subjects	31	125	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	37.8		
standard deviation	± 9.0	-	
Sex: Female, Male Units: participants			
Female	23	86	
Male	8	39	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	6	
White	28	115	
More than one race	0	1	
Unknown or Not Reported	0	2	

End points

End points reporting groups

Reporting group title	Part A: Tolebrutinib 5 mg
Reporting group description:	
Participants who received tolebrutinib 5 milligrams (mg) orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 15 mg
Reporting group description:	
Participants who received tolebrutinib 15 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 30 mg
Reporting group description:	
Participants who received tolebrutinib 30 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part A: Tolebrutinib 60 mg
Reporting group description:	
Participants who received tolebrutinib 60 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.	
Reporting group title	Part B: Tolebrutinib 5/60 mg
Reporting group description:	
Participants from Part A: tolebrutinib 5 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.	
Reporting group title	Part B: Tolebrutinib 15/60 mg
Reporting group description:	
Participants from Part A: tolebrutinib 15 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.	
Reporting group title	Part B: Tolebrutinib 30/60 mg
Reporting group description:	
Participants from Part A: tolebrutinib 30 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.	
Reporting group title	Part B: Tolebrutinib 60/60 mg
Reporting group description:	
Participants from Part A: tolebrutinib 60 mg arm who provided consent switched to Part B and continued to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.	
Subject analysis set title	Tolebrutinib 5/60 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received tolebrutinib 5 mg in Part A and tolebrutinib 60 mg in Part B were included in this arm.	
Subject analysis set title	Tolebrutinib 15/60 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received tolebrutinib 15 mg in Part A and tolebrutinib 60 mg in Part B were included in this arm.	
Subject analysis set title	Tolebrutinib 30/60 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received tolebrutinib 30 mg in Part A and tolebrutinib 60 mg in Part B were included in this arm.	
Subject analysis set title	Tolebrutinib 60/60 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received tolebrutinib 60 mg in Part A and tolebrutinib 60 mg in Part B were included	

in this arm.

Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[1]

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug. An SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was an important medical event. TEAEs were defined as AEs that developed, worsened or became serious during the respective on-treatment periods. The safety population included all participants enrolled in this study and exposed to study drug, regardless of the amount of exposure.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to maximum exposure, 39 weeks in Part A and 222 weeks in Part B

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Part A: Tolebrutinib 5 mg	Part B: Tolebrutinib 5/60 mg	Part A: Tolebrutinib 15 mg	Part B: Tolebrutinib 15/60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	31	31
Units: participants				
TEAEs	17	26	17	29
TESAEs	0	5	2	3

End point values	Part A: Tolebrutinib 30 mg	Part B: Tolebrutinib 30/60 mg	Part A: Tolebrutinib 60 mg	Part B: Tolebrutinib 60/60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	31	31
Units: participants				
TEAEs	24	27	20	27
TESAEs	1	3	2	3

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of new Gadolinium (Gd)-enhancing T1-hyperintense Lesions at Week 240 Relative to Week 192

End point title	Mean Number of new Gadolinium (Gd)-enhancing T1-

	hyperintense Lesions at Week 240 Relative to Week 192

End point description:

Magnetic resonance imaging (MRI) of the brain was performed to identify number of new Gd-enhancing T1-hyperintense lesions. Central review was used to identify new Gd-enhancing T1-hyperintense lesions not present at the previous MRI. The modified intent-to-treat (mITT) population included all participants enrolled in this study who had at least 1 day of study drug exposure during study. As pre-specified in protocol and statistical analysis plan (SAP), the main objective of this study was to determine the long-term efficacy of selected Phase 3 dose (60 mg). Part A was a short transition period while picking phase 3 dose; no efficacy analysis was planned for this period alone. Hence, complete efficacy data is presented by LTS16004 dose groups of 5/60, 15/60, 30/60 and 60/60 mg. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Weeks 192 and 240

End point values	Tolebrutinib 5/60 mg	Tolebrutinib 15/60 mg	Tolebrutinib 30/60 mg	Tolebrutinib 60/60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	22	19	24
Units: number of new Gd-enhancing T1 lesions				
arithmetic mean (standard deviation)	0.24 (± 0.54)	0.36 (± 0.66)	0.32 (± 0.75)	0.13 (± 0.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of new or Enlarging T2 Lesions at Week 240 Relative to Week 192

End point title	Mean Number of new or Enlarging T2 Lesions at Week 240 Relative to Week 192

End point description:

MRI of the brain was performed to identify number of new or enlarging T2 lesions. Central review was used to identify new or enlarging T2 lesions not present at the previous MRI; the values were standardized to per month values by dividing by the number of months (4-week intervals) from the previous MRI to the current MRI. Analysis was performed on the mITT population. As pre-specified in protocol and SAP,main objective of this study was to determine long-term efficacy of selected Phase 3 dose (60 mg).Part A was a short transition period while picking phase 3 dose;no efficacy analysis was planned for this period alone. Hence, complete efficacy data is presented by LTS16004 dose groups of 5/60, 15/60, 30/60, and60/60 mg. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Weeks 192 and 240

End point values	Tolebrutinib 5/60 mg	Tolebrutinib 15/60 mg	Tolebrutinib 30/60 mg	Tolebrutinib 60/60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	23	21	26
Units: new or enlarging T2 lesions/month				
arithmetic mean (standard deviation)	0.32 (± 0.54)	0.37 (± 0.53)	0.15 (± 0.30)	0.24 (± 0.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Mean Number of Gd-enhancing T1-hyperintense Lesions at Week 240 Relative to Week 192

End point title	Total Mean Number of Gd-enhancing T1-hyperintense Lesions at Week 240 Relative to Week 192

End point description:

MRI of the brain was performed to identify number of Gd-enhancing T1-hyperintense lesions. Central review was used to identify Gd-enhancing T1-hyperintense lesions not present at the previous MRI. Analysis was performed on the mITT population. As pre-specified in protocol and SAP,main objective of this study was to determine long-term efficacy of selected Phase 3 dose (60 mg).Part A was a short transition period while picking phase 3 dose;no efficacy analysis was planned for this period alone. Hence, complete efficacy data is presented by LTS16004 dose groups of 5/60, 15/60, 30/60, and60/60 mg. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Weeks 192 and 240

End point values	Tolebrutinib 5/60 mg	Tolebrutinib 15/60 mg	Tolebrutinib 30/60 mg	Tolebrutinib 60/60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	22	19	24
Units: number of Gd-enhancing T1 lesions				
arithmetic mean (standard deviation)	0.24 (± 0.54)	0.36 (± 0.66)	0.37 (± 0.76)	0.13 (± 0.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR)

End point description:

Multiple sclerosis (MS) relapse was defined as acute, new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms were attributable to MS, lasted for >=24 hours with or without recovery, present at normal body temperature and preceded by >=30 days of clinical stability. ARR was the total number of relapses for participants by dose group divided by the sum of the standardized study duration for participants in the dose group. Analysis was performed on the mITT population. As pre-specified in protocol and SAP,main objective of

this study was to determine long-term efficacy of selected Phase 3 dose (60 mg).Part A was a short transition period while picking phase 3 dose;no efficacy analysis was planned for this period alone. Hence, complete efficacy data is presented by LTS16004 dose groups of 5/60, 15/60, 30/60, and60/60 mg.

End point type	Secondary

End point timeframe:

From Baseline (enrollment in LTS16004, Day 1) to Week 240

End point values	Tolebrutinib 5/60 mg	Tolebrutinib 15/60 mg	Tolebrutinib 30/60 mg	Tolebrutinib 60/60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	32	31
Units: relapses per participant year				
number (confidence interval 95%)	0.26 (0.15 to 0.46)	0.24 (0.14 to 0.42)	0.28 (0.18 to 0.43)	0.23 (0.13 to 0.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Expanded Disability Status Scale (EDSS) Score at Week 240

End point title	Change from Baseline in Expanded Disability Status Scale (EDSS) Score at Week 240

End point description:

The EDSS is 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. Baseline assessed for long-term tolebrutinib treatment by change from baseline: last non-missing value prior to the first administration of randomized study drug in DRI15928 study. Analysis performed on mITT population.As pre-specified in protocol and SAP,main objective of this study was to determine long-term efficacy of selected Phase 3 dose (60 mg).Part A was a short transition period while picking phase 3dose;no efficacy analysis was planned for this period alone; complete efficacy data is presented by LTS16004 dose groups of 5/60, 15/60, 30/60, and 60/60 mg. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of DRI15928) and Week 240

End point values	Tolebrutinib 5/60 mg	Tolebrutinib 15/60 mg	Tolebrutinib 30/60 mg	Tolebrutinib 60/60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	23	21	26
Units: score on a scale				
arithmetic mean (standard deviation)	-0.10 (± 0.96)	0.24 (± 0.95)	0.38 (± 0.69)	0.29 (± 0.70)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events: From first dose of study drug (Day 1) up to maximum exposure, 39 weeks in Part A and 222 weeks in Part B. Deaths: From signing informed consent form (Week -6) up to end of follow-up, approximately 62 months

Adverse event reporting additional description:

Analysis was performed on the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Part A: Tolebrutinib 5 mg

Reporting group description:

Participants who received tolebrutinib 5 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

Reporting group title	Part A: Tolebrutinib 30 mg

Reporting group description:

Participants who received tolebrutinib 30 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

Reporting group title	Part A: Tolebrutinib 15 mg

Reporting group description:

Participants who received tolebrutinib 15 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

Reporting group title	Part B: Tolebrutinib 30/60 mg

Reporting group description:

Participants from Part A: tolebrutinib 30 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

Reporting group title	Part B: Tolebrutinib 15/60 mg

Reporting group description:

Participants from Part A: tolebrutinib 15 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

Reporting group title	Part B: Tolebrutinib 5/60 mg

Reporting group description:

Participants from Part A: tolebrutinib 5 mg arm who provided consent switched to Part B to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

Reporting group title	Part B: Tolebrutinib 60/60 mg

Reporting group description:

Participants from Part A: tolebrutinib 60 mg arm who provided consent switched to Part B and continued to receive the selected Phase 3 dose of tolebrutinib 60 mg orally once daily until Month 60.

Reporting group title	Part A: Tolebrutinib 60 mg

Reporting group description:

Participants who received tolebrutinib 60 mg orally once daily in the parent study continued to receive the same dose until the dose of tolebrutinib to be used in Phase 3 was determined.

Serious adverse events	Part A: Tolebrutinib 5 mg	Part A: Tolebrutinib 30 mg	Part A: Tolebrutinib 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	2 / 31 (6.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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			
Ischaemic Stroke			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Reproductive system and breast disorders			

Uterine Polyp			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Ovarian Haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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 / 31 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burn Infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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 Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Infected Bite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Postoperative Wound Infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Pyelonephritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (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

Serious adverse events	Part B: Tolebrutinib 30/60 mg	Part B: Tolebrutinib 15/60 mg	Part B: Tolebrutinib 5/60 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	3 / 31 (9.68%)	5 / 30 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Investigations			
Haemoglobin Decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	0 / 30 (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
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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			
Ischaemic Stroke			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	0 / 30 (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
Migraine			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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
Ovarian Haemorrhage			

subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	0 / 30 (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
Covid-19			

subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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
Burn Infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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 Pneumonia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Bite			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	0 / 30 (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
Postoperative Wound Infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (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

Serious adverse events	Part B: Tolebrutinib 60/60 mg	Part A: Tolebrutinib 60 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 31 (9.68%)	2 / 31 (6.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn Infection			

subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Bite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: Tolebrutinib 5 mg	Part A: Tolebrutinib 30 mg	Part A: Tolebrutinib 15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)	15 / 32 (46.88%)	6 / 31 (19.35%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	2 / 31 (6.45%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Fatigue			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 31 (9.68%)	4 / 32 (12.50%)	1 / 31 (3.23%)
occurrences (all)	3	4	1
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Tension Headache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Petechiae			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Muscular Weakness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Pain In Extremity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	3 / 32 (9.38%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Cystitis Bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Covid-19			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	0	1	4
Urinary Tract Infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Obesity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: Tolebrutinib 30/60 mg	Part B: Tolebrutinib 15/60 mg	Part B: Tolebrutinib 5/60 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 32 (75.00%)	24 / 31 (77.42%)	24 / 30 (80.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 32 (12.50%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	4	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Influenza Like Illness			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences (all)	2	2	1
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	2	1
Contusion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	2 / 30 (6.67%)
occurrences (all)	2	2	4
Migraine			
subjects affected / exposed	2 / 32 (6.25%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	4	2	0
Tension Headache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 32 (0.00%)	3 / 31 (9.68%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	3 / 30 (10.00%)
occurrences (all)	1	1	3
Dyspepsia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Enteritis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Haemorrhoids			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

Nephrolithiasis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Muscular Weakness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	2
Back Pain			
subjects affected / exposed	1 / 32 (3.13%)	5 / 31 (16.13%)	6 / 30 (20.00%)
occurrences (all)	1	7	7
Pain In Extremity			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 32 (12.50%)	6 / 31 (19.35%)	5 / 30 (16.67%)
occurrences (all)	6	11	7
Influenza			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Cystitis Bacterial			
subjects affected / exposed	3 / 32 (9.38%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	7	0	1
Cystitis			
subjects affected / exposed	3 / 32 (9.38%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Covid-19			
subjects affected / exposed	7 / 32 (21.88%)	10 / 31 (32.26%)	10 / 30 (33.33%)
occurrences (all)	9	12	10
Sinusitis			

subjects affected / exposed	2 / 32 (6.25%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Pharyngitis			
subjects affected / exposed	2 / 32 (6.25%)	4 / 31 (12.90%)	1 / 30 (3.33%)
occurrences (all)	3	4	2
Tonsillitis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 32 (12.50%)	4 / 31 (12.90%)	1 / 30 (3.33%)
occurrences (all)	7	4	2
Urinary Tract Infection			
subjects affected / exposed	5 / 32 (15.63%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	6	3	0
Urinary Tract Infection Bacterial			
subjects affected / exposed	3 / 32 (9.38%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 32 (9.38%)	2 / 31 (6.45%)	3 / 30 (10.00%)
occurrences (all)	3	2	3
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Obesity			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	2 / 30 (6.67%)
occurrences (all)	0	1	2

Non-serious adverse events	Part B: Tolebrutinib 60/60 mg	Part A: Tolebrutinib 60 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 31 (80.65%)	16 / 31 (51.61%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	2	
Influenza Like Illness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Anxiety			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Contusion			

subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 31 (9.68%)	3 / 31 (9.68%)	
occurrences (all)	3	4	
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Tension Headache			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Carpal Tunnel Syndrome			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Enteritis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Petechiae			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Muscular Weakness			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Back Pain			
subjects affected / exposed	3 / 31 (9.68%)	2 / 31 (6.45%)	
occurrences (all)	3	3	
Pain In Extremity			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences (all)	1	3	
Arthralgia			

subjects affected / exposed	5 / 31 (16.13%)	1 / 31 (3.23%)	
occurrences (all)	5	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 31 (19.35%)	2 / 31 (6.45%)	
occurrences (all)	12	2	
Influenza			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Cystitis Bacterial			
subjects affected / exposed	5 / 31 (16.13%)	2 / 31 (6.45%)	
occurrences (all)	14	2	
Cystitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Covid-19			
subjects affected / exposed	14 / 31 (45.16%)	1 / 31 (3.23%)	
occurrences (all)	20	1	
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Tonsillitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Urinary Tract Infection			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	

Viral Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 31 (12.90%)	5 / 31 (16.13%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Obesity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2019	The protocol was primarily amended in response to comments from health authorities and ethics committees during the initial clinical trial application process. Furthermore, Sanofi Genzyme used that opportunity to update with new available information.
02 March 2020	It was based on the efficacy and safety findings from the DRI5928 trial which demonstrated that the dose of 60 mg taken with a meal was the most appropriate dose for further investigation. This was the recommended dose for Part B of this study (LTS16004). Furthermore, the Sponsor used this opportunity to update with new available information.
29 July 2021	The primary reason for this amendment was the availability of new information from drug-drug interaction studies.
23 May 2022	The primary driver for this amendment was to update the liver monitoring to mitigate risk of drug-induced liver injury (DILI) and to change the time between onsite visits to every 6 months after the Month 36 visit.
12 December 2022	The rationale for this protocol amendment was to clarify information about drug-induced liver injury and update the alanine aminotransferase (ALT) increase algorithm in relation to the risk of DILI.
19 June 2023	The rationale for this protocol amendment was to add the option for participants to continue to receive SAR442168 (tolebrutinib) in a separate clinical trial.
16 November 2023	The rationale for this protocol amendment was to update the testing requirements in the “Increase in ALT algorithm”, as per health authority request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported