



Clinical trial results:

An open label, two-arm, Phase 2a study to evaluate the effect of rilzabrutinib (PRN1008/SAR444671) on safety and disease activity in participants with IgG4-related disease

Summary

EudraCT number	2022-002959-18
Trial protocol	ES IT
Global end of trial date	15 October 2024

Results information

Result version number	v1 (current)
This version publication date	29 October 2025
First version publication date	29 October 2025

Trial information

Trial identification

Sponsor protocol code	ACT17125
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04520451
WHO universal trial number (UTN)	U1111-1260-3972

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	82 Avenue Raspail, Gentilly, France, 94250
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 October 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and the efficacy of daily oral administration of rilzabrutinib in participants with immunoglobulin G subclass 4 (IgG4)-related disease (IgG4-RD).

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	22 August 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	Canada: 10
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	27
EEA total number of subjects	4

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 centers in 5 countries. A total of 35 participants were screened between 22 August 2020 and 14 September 2020, of which 8 were screen failures.

Pre-assignment

Screening details:

27 participants were enrolled in the study, of which 13 were in Cohort A and 14 in Cohort B. In Cohort A, 10 participants were randomized to rilzabrutinib treatment group, and 3 participants to Control group. Participants in Cohort B received rilzabrutinib. Note: For Cohort B data collected for first 12 weeks is indicated as Main treatment period.

Period 1

Period 1 title	Induction Treatment Period (12 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Induction Treatment Period: Cohort A (Control)

Arm description:

Participants received glucocorticoid minimum starting dose of 20 milligram (mg)/day and the maximum dose of 40 mg/day prednisone equivalent orally for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent for 12 weeks.

Arm title	Induction Treatment Period: Cohort A (Rilzabrutinib)
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Arm description:

Participants received rilzabrutinib tablets 400 mg orally twice daily (BID) for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent a maximum of 4 weeks.

Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	SAR444671
Other name	PRN1008
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received rilzabrutinib tablets 400 mg BID for 12 weeks.

Arm title	Induction Treatment Period: Cohort B (Rilzabrutinib)
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Arm description:

Participants received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent a maximum of 4 weeks.

Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	SAR444671
Other name	PRN1008
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received rilzabrutinib tablets 400 mg BID for 12 weeks.

Number of subjects in period 1	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)
Started	3	10	14
Completed	3	9	10
Not completed	0	1	4
Adverse event, serious fatal	-	-	1
Adverse event, non-fatal	-	1	1
Unspecified	-	-	1
Protocol deviation	-	-	1

Period 2

Period 2 title	Crossover Treatment Period (12 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Crossover Treatment Period: Rilzabrutinib
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Arm description:

Participants in Cohort A who were randomized to the control (glucocorticoid) arm and were unable to be weaned off glucocorticoid by end of induction treatment period entered a 12-week open-label rilzabrutinib cross-over period, to receive rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	SAR444671
Other name	PRN1008
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received rilzabrutinib tablets 400 mg BID for 12 weeks.

Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent a maximum of 4 weeks.

Number of subjects in period 2^[1]	Crossover Treatment Period: Rilzabrutinib
Started	3
Completed	3

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: In Crossover treatment period, only participants from Control arm entered.

Period 3

Period 3 title	Maintenance Treatment Period (40 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Maintenance Treatment Period: Cohort A (Rilzabrutinib)
Arm description: Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks.	
Arm type	Experimental
Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	SAR444671
Other name	PRN1008
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered rilzabrutinib tablets 400 mg BID for 40 weeks.

Arm title	Maintenance Treatment Period: Cohort B (Rilzabrutinib)
Arm description: Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks.	
Arm type	Experimental
Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	SAR444671
Other name	PRN1008
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered rilzabrutinib tablets 400 mg BID for 40 weeks.

Number of subjects in period 3	Maintenance Treatment Period: Cohort A (Rilzabrutinib)	Maintenance Treatment Period: Cohort B (Rilzabrutinib)
Started	10	10
Completed	8	6
Not completed	2	4
Unspecified	2	4

Baseline characteristics

Reporting groups

Reporting group title	Induction Treatment Period: Cohort A (Control)
Reporting group description:	
Participants received glucocorticoid minimum starting dose of 20 milligram (mg)/day and the maximum dose of 40 mg/day prednisone equivalent orally for 12 weeks.	
Reporting group title	Induction Treatment Period: Cohort A (Rilzabrutinib)
Reporting group description:	
Participants received rilzabrutinib tablets 400 mg orally twice daily (BID) for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.	
Reporting group title	Induction Treatment Period: Cohort B (Rilzabrutinib)
Reporting group description:	
Participants received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.	

Reporting group values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)
Number of subjects	3	10	14
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	60.3	63.4	55.2
standard deviation	± 22.74	± 12.92	± 14.10
Sex: Female, Male			
Units: Participants			
Female	1	3	2
Male	2	7	12
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	1	7	5
More than one race	0	0	0
Other: Unknown or Not Reported	0	2	2

Reporting group values	Total		
Number of subjects	27		
Age categorical			
Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Participants			
Female	6		
Male	21		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	9		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	13		
More than one race	0		
Other: Unknown or Not Reported	4		

End points

End points reporting groups

Reporting group title	Induction Treatment Period: Cohort A (Control)
Reporting group description: Participants received glucocorticoid minimum starting dose of 20 milligram (mg)/day and the maximum dose of 40 mg/day prednisone equivalent orally for 12 weeks.	
Reporting group title	Induction Treatment Period: Cohort A (Rilzabrutinib)
Reporting group description: Participants received rilzabrutinib tablets 400 mg orally twice daily (BID) for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.	
Reporting group title	Induction Treatment Period: Cohort B (Rilzabrutinib)
Reporting group description: Participants received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.	
Reporting group title	Crossover Treatment Period: Rilzabrutinib
Reporting group description: Participants in Cohort A who were randomized to the control (glucocorticoid) arm and were unable to be weaned off glucocorticoid by end of induction treatment period entered a 12-week open-label rilzabrutinib cross-over period, to receive rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.	
Reporting group title	Maintenance Treatment Period: Cohort A (Rilzabrutinib)
Reporting group description: Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks.	
Reporting group title	Maintenance Treatment Period: Cohort B (Rilzabrutinib)
Reporting group description: Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks.	
Subject analysis set title	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)
Subject analysis set type	Per protocol
Subject analysis set description: Main TP included participants from Cohort A (12-week induction period and crossover TP), who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.	
Subject analysis set title	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)
Subject analysis set type	Per protocol
Subject analysis set description: Main TP included participants from Cohort B 12-week induction period, who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.	
Subject analysis set title	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)
Subject analysis set type	Per protocol
Subject analysis set description: Main TP included participants from Cohort A (12-week induction period and crossover TP), who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of	

rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Subject analysis set title	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Main TP included participants from Cohort B 12-week induction period, who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Subject analysis set title	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Main TP included participants from Cohort A (12-week induction period and crossover TP), who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Subject analysis set title	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Main TP included participants from Cohort A (12-week induction period and crossover TP), who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Subject analysis set title	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Main TP included participants from Cohort B 12-week induction period, who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Primary: Induction Treatment Period: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation and Possible Glucocorticoid-Related TEAEs

End point title	Induction Treatment Period: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation and Possible Glucocorticoid-Related TEAEs ^[1]
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End point description:

An AE was any untoward medical occurrence in a participant, temporally associated with use of study treatment, whether or not considered related. TEAEs were defined as AEs that developed, worsened or became serious during TE period (defined as time from first administration of study treatment [Day 1] to last administration of study treatment+7 days). SAE: 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 or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs leading to discontinuation of study treatment and possible glucocorticoid-related TEAEs are also reported. Safety population (Cohort A) and Rilzabrutinib-treated population (Cohort B) consisted of all participants who received at least 1 dose of study treatment.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 13 weeks)

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: No additional statistical analysis was prespecified for this endpoint.

End point values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	14	
Units: participants				
TEAEs	3	8	13	
TESAEs	0	1	1	
TEAEs leading to discontinuation	0	1	2	
Possible glucocorticoid-related TEAEs	2	1	9	

Statistical analyses

No statistical analyses for this end point

Primary: Main + Maintenance Treatment Period: Number of Participants With Treatment-Emergent Adverse Events, Treatment-Emergent Serious Adverse Events, TEAEs Leading to Discontinuation and Possible Glucocorticoid-Related TEAEs

End point title	Main + Maintenance Treatment Period: Number of Participants With Treatment-Emergent Adverse Events, Treatment-Emergent Serious Adverse Events, TEAEs Leading to Discontinuation and Possible Glucocorticoid-Related TEAEs ^[2]
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End point description:

TEAEs were defined as the AEs that developed, worsened or became serious during the treatment-emergent period (defined as time from first administration of study treatment [Day 1] to last administration of study treatment + 7 days). SAE: 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 or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs leading to discontinuation of study treatment and possible glucocorticoid-related TEAEs are also reported. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 53 weeks)

Notes:

[2] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Main+Maintenance Treatment Period: Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period: Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: participants				
TEAEs	10	13		
TESAEs	1	1		
TEAEs leading to discontinuation	2	3		
Possible glucocorticoid-related TEAEs	2	9		

Statistical analyses

No statistical analyses for this end point

Primary: Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities (PCSAs) for Vital Signs

End point title	Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities (PCSAs) for Vital Signs ^[3]
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End point description:

Vital signs assessments included systolic blood pressure (SBP), diastolic blood pressure (DSP), pulse rate (PR), and weight. Criteria for PCSA: pulse rate: ≤ 50 beats per minute (bpm) and decrease from baseline ≥ 20 bpm, ≥ 120 bpm and increase from baseline ≥ 20 bpm; SBP: ≤ 95 millimeters of mercury (mmHg) and decrease from baseline ≥ 20 mmHg, ≥ 160 mmHg and increase from baseline ≥ 20 mmHg, ≤ -20 mmHg; DBP: ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg, ≥ 110 mmHg and increase from baseline ≥ 10 mmHg, ≤ -10 mmHg; Weight: ≥ 5 percentage (%) increase from baseline, $\geq 5\%$ decrease from baseline. Safety population (Cohort A) and Rilzabrutinib-treated population (Cohort B) consisted of all participants who received at least 1 dose of study treatment.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 13 weeks)

Notes:

[3] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	14	
Units: participants				
PR: ≤ 50 bpm and decrease from baseline ≥ 20 bpm	0	0	0	
PR: ≥ 120 bpm and increase from baseline ≥ 20 bpm	0	0	0	
SBP: ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	0	0	0	
SBP: ≥ 160 mmHg and increase from baseline ≥ 20 mmHg	0	0	0	

SBP: <=-20 mmHg	0	0	0	
DBP: <=45 mmHg and decrease from baseline >=10 mmHg	0	0	0	
DBP: >=110mmHg and increase from baseline >=10 mmHg	0	0	0	
DBP: <=-10 mmHg	0	0	0	
Weight: >=5% increase from baseline	2	0	1	
Weight: >=5% decrease from baseline	0	2	1	

Statistical analyses

No statistical analyses for this end point

Primary: Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Vital Signs

End point title	Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Vital Signs ^[4]
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End point description:

Vital signs assessments included SBP, DSP, pulse rate, and weight. Criteria for PCSA: PR: <=50 bpm and decrease from baseline >=20 bpm, >=120 bpm and increase from baseline >=20 bpm; SBP: <=95 mmHg and decrease from baseline >=20 mmHg, >=160 mmHg and increase from baseline >=20 mmHg, <=-20 mmHg; DBP: <=45 mmHg and decrease from baseline >=10 mmHg, >=110 mmHg and increase from baseline >=10 mmHg, <=-10 mmHg; Weight: >=5% increase from baseline, >=5% decrease from baseline. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 53 weeks)

Notes:

[4] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: participants				
PR: <=50 bpm and decrease from baseline >=20 bpm	0	0		
PR: >=120 bpm and increase from baseline >=20 bpm	0	0		
SBP:<=95 mmHg and decrease from baseline >=20 mmHg	0	0		
SBP:>=160mmHg and increase from baseline >=20 mmHg	0	0		
SBP: <=-20 mmHg	0	0		
DBP:<=45 mmHg and decrease from baseline >=10 mmHg	0	0		

DBP: ≥ 110 mmHg and increase from baseline ≥ 10 mmHg	0	0		
DBP: ≤ -10 mmHg	0	0		
Weight: $\geq 5\%$ increase from baseline	2	1		
Weight: $\geq 5\%$ decrease from baseline	5	3		

Statistical analyses

No statistical analyses for this end point

Primary: Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Hematology and Coagulation Parameters

End point title	Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Hematology and Coagulation Parameters ^[5]
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End point description:

Criteria for PCSA: Leukocytes $< 3.0 \times 10^9$ per liter (/L) (Non-Black [NB]) or $< 2 \times 10^9$ /L (Black[B]), $\geq 16.0 \times 10^9$ /L; Lymphocytes $> 4.0 \times 10^9$ /L; Neutrophils $< 1.5 \times 10^9$ /L (NB) or $< 1.0 \times 10^9$ /L (B); Monocytes $> 0.7 \times 10^9$ /L; Basophils $> 0.1 \times 10^9$ /L; Eosinophils: $> 0.5 \times 10^9$ /L, > 1 upper limit of normal range (ULN) (if ULN ≥ 0.5 Giga/L); Hemoglobin (Hb): ≤ 115 grams per liter (g/L) (M); ≤ 95 g/L (F), ≥ 185 g/L (M); ≥ 165 g/L (F), decrease from baseline ≥ 20 g/L; Hematocrit: ≤ 0.37 volume per volume (v/v) (M); ≤ 0.32 v/v (F), ≥ 0.55 v/v (M); ≥ 0.5 v/v (F); Erythrocytes $\geq 6.0 \times 10^{12}$ /L; Platelets: $< 100 \times 10^9$ /L, $\geq 700 \times 10^9$ /L. Safety population (Cohort A) and Rilzabrutinib-treated population (Cohort B) consisted of all participants who received at least 1 dose of study treatment.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 13 weeks)

Notes:

[5] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	14	
Units: participants				
Leukocytes: $< 3.0 \times 10^9$ /L (NB) or $< 2.0 \times 10^9$ /L (B)	0	0	0	
Leukocytes: $\geq 16.0 \times 10^9$ /L	0	2	2	
Lymphocytes: $> 4.0 \times 10^9$ /L	1	1	3	
Neutrophils: $< 1.5 \times 10^9$ /L (NB) or $< 1.0 \times 10^9$ /L (B)	1	0	1	
Monocytes: $> 0.7 \times 10^9$ /L	2	6	8	
Basophils: $> 0.1 \times 10^9$ /L	3	2	5	
Eosinophils: $> 0.5 \times 10^9$ /L	2	5	5	
Eosinophils: > 1 ULN (if ULN ≥ 0.5 Giga/L)	0	0	0	
Hb: ≤ 115 g/L (M); ≤ 95 g/L (F)	0	0	1	
Hb: ≥ 185 g/L (M); ≥ 165 g/L (F)	0	0	0	

Hb: Decrease from baseline ≥ 20 g/L	0	0	3	
Hematocrit: ≤ 0.37 v/v (M); ≤ 0.32 v/v (F)	0	1	2	
Hematocrit: ≥ 0.55 v/v (M); ≥ 0.5 v/v (F)	1	0	0	
Erythrocytes: $\geq 6.0 \times 10^{12}/L$	0	0	1	
Platelets: $< 100 \times 10^9/L$	0	0	0	
Platelets: $\geq 700 \times 10^9/L$	0	0	0	
Coagulation parameter	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Hematology and Coagulation Parameters

End point title	Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Hematology and Coagulation Parameters ^[6]
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End point description:

Criteria for PCSA: Leukocytes $< 3.0 \times 10^9/L$ (NB) or $< 2 \times 10^9/L$ (B), $\geq 16.0 \times 10^9/L$; Lymphocytes $> 4.0 \times 10^9/L$; Neutrophils $< 1.5 \times 10^9/L$ (NB) or $< 1.0 \times 10^9/L$ (B); Monocytes $> 0.7 \times 10^9/L$; Basophils $> 0.1 \times 10^9/L$; Eosinophils: $> 0.5 \times 10^9/L$, > 1 ULN (if ULN ≥ 0.5 Giga/L); Hb: ≤ 115 g/L (M); ≤ 95 g/L (F), ≥ 185 g/L (M); ≥ 165 g/L (F), decrease from baseline ≥ 20 g/L; Hematocrit: ≤ 0.37 v/v (M); ≤ 0.32 v/v (F), ≥ 0.55 v/v (M); ≥ 0.5 v/v (F); Erythrocytes $\geq 6.0 \times 10^{12}/L$; Platelets: $< 100 \times 10^9/L$, $\geq 700 \times 10^9/L$. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 53 weeks)

Notes:

[6] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: participants				
Leukocytes: $< 3.0 \times 10^9/L$ (NB) or $< 2.0 \times 10^9/L$ (B)	0	0		
Leukocytes: $\geq 16.0 \times 10^9/L$	2	2		
Lymphocytes: $> 4.0 \times 10^9/L$	3	3		
Neutrophils: $< 1.5 \times 10^9/L$ (NB) or $< 1.0 \times 10^9/L$ (B)	0	1		
Monocytes: $> 0.7 \times 10^9/L$	7	10		
Basophils: $> 0.1 \times 10^9/L$	3	5		

Eosinophils: $>0.5 \times 10^9/L$	8	5		
Eosinophils: >1 ULN (if ULN ≥ 0.5 Giga/L)	0	0		
Hb: ≤ 115 g/L (M); ≤ 95 g/L (F)	0	1		
Hb: ≥ 185 g/L (M); ≥ 165 g/L (F)	0	0		
Hb: Decrease from baseline ≥ 20 g/L	1	3		
Hematocrit: ≤ 0.37 v/v (M); ≤ 0.32 v/v (F)	1	2		
Hematocrit: ≥ 0.55 v/v (M); ≥ 0.5 v/v (F)	0	0		
Erythrocytes: $\geq 6.0 \times 10^{12}/L$	1	1		
Platelets: $<100 \times 10^9/L$	1	0		
Platelets: $\geq 700 \times 10^9/L$	0	0		
Coagulation parameters	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Chemistry Parameters

End point title	Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Chemistry Parameters ^[7]
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End point description:

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST): >3 , >5 , >10 , and >20 ULN; Alkaline phosphatase (ALP) >1.5 ULN; Bilirubin: >1.5 and >2 ULN; Creatine kinase: >3 and >10 ULN; Creatinine clearance (CrC): <15 (end stage renal disease), ≥ 15 - <30 (severe decrease in glomerular filtration rate [GFR]), ≥ 30 - <60 (moderate decrease in GFR), ≥ 60 - <90 (mild decrease in GFR), ≥ 90 (normal GFR); Creatinine: ≥ 150 micromoles per liter (mcmol/L) (Adults), $\geq 30\%$ change from baseline, $\geq 100\%$ change from baseline; Urea nitrogen ≥ 17 millimoles per liter (mmol/L); Chloride: <80 and >115 mmol/L; Sodium: ≤ 129 and ≥ 160 mmol/L; Potassium: <3 and ≥ 5.5 mmol/L; Lipase ≥ 3 ULN; Amylase ≥ 3 ULN; Glucose: ≤ 3.9 mmol/L and $<$ lower limit of normal range (LLN), ≥ 7 mmol/L; Albumin ≤ 25 g/L. Safety population (Cohort A) and Rilzabrutinib-treated population (Cohort B) consisted of all participants who received at least 1 dose of study treatment.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 13 weeks)

Notes:

[7] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	14	
Units: participants				
ALT: >3 ULN	0	0	1	
ALT: >5 ULN	0	0	1	

ALT: >10 ULN	0	0	0
ALT: >20 ULN	0	0	0
AST: >3 ULN	0	0	1
AST: >5 ULN	0	0	1
AST: >10 ULN	0	0	0
AST: >20 ULN	0	0	0
ALP: >1.5 ULN	0	1	2
Bilirubin: >1.5 ULN	0	0	1
Bilirubin: >2 ULN	0	0	1
Creatine kinase: >3 ULN	0	0	0
Creatine kinase: >10 ULN	0	0	0
CrC: <15 (end stage renal disease)	0	0	0
CrC: >=15-<30 (severe decrease in GFR)	0	0	0
CrC: >=30-<60 (moderate decrease in GFR)	0	0	1
CrC: >=60-<90 (mild decrease in GFR)	0	0	0
CrC: >=90 (normal GFR)	0	0	0
Creatinine: >=150 mcmmol/L (Adults)	0	1	1
Creatinine: >=30% change from baseline	1	3	8
Creatinine: >=100% change from baseline	0	0	0
Urea nitrogen: >=17 mmol/L	0	0	0
Chloride: <80 mmol/L	1	0	0
Chloride: >115 mmol/L	0	0	0
Sodium: <=129 mmol/L	1	1	1
Sodium: >=160 mmol/L	0	0	0
Potassium: <3 mmol/L	1	0	0
Potassium: >=5.5 mmol/L	0	0	2
Lipase: >=3 ULN	0	1	1
Amylase: >=3 ULN	0	0	0
Glucose: <=3.9 mmol/L and <LLN	0	1	1
Glucose: >=7 mmol/L	1	6	6
Albumin: <=25 g/L	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Chemistry Parameters

End point title	Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Chemistry Parameters ^[8]
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End point description:

Criteria for PCSA: ALT and AST: >3 ULN, >5 ULN, >10 ULN, >20 ULN; ALP >1.5 ULN; Bilirubin: >1.5 ULN, >2 ULN; Creatine kinase: >3 ULN, >10 ULN; CrC: <15 (end stage renal disease), >=15-<30 (severe decrease in GFR), >=30-<60 (moderate decrease in GFR), >=60-<90 (mild decrease in GFR), >=90 (normal GFR); Creatinine: >=150 mcmmol/L (Adults), >=30% change from baseline, >=100% change from baseline; Urea nitrogen >=17 mmol/L; Chloride: <80 mmol/L, >115 mmol/L; Sodium: <=129 mmol/L, >=160 mmol/L; Potassium: <3 mmol/L, >=5.5 mmol/L; Lipase >=3 ULN; Amylase

>=3 ULN; Glucose: <=3.9 mmol/L and < LLN, >=7 mmol/L; Albumin <=25 g/L. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib.

End point type	Primary
End point timeframe:	
From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 53 weeks)	

Notes:

[8] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: participants				
ALT: >3 ULN	2	0		
ALT: >5 ULN	2	0		
ALT: >10 ULN	1	0		
ALT: >20 ULN	0	0		
AST: >3 ULN	2	0		
AST: >5 ULN	2	0		
AST: >10 ULN	1	0		
AST: >20 ULN	1	0		
ALP: >1.5 ULN	2	1		
Bilirubin: >1.5 ULN	2	0		
Bilirubin: >2 ULN	1	0		
Creatine kinase: >3 ULN	1	0		
Creatine kinase: >10 ULN	0	0		
CrC: <15 (end stage renal disease)	0	0		
CrC: >=15-<30 (severe decrease in GFR)	0	0		
CrC: >=30-<60 (moderate decrease in GFR)	1	2		
CrC: >=60-<90 (mild decrease in GFR)	0	1		
CrC: >=90 (normal GFR)	1	1		
Creatinine: >=150 mcml/L (Adults)	1	1		
Creatinine: >=30% change from baseline	13	5		
Creatinine: >=100% change from baseline	0	0		
Urea nitrogen: >=17 mmol/L	0	0		
Chloride: <80 mmol/L	1	1		
Chloride: >115 mmol/L	0	0		
Sodium: <=129 mmol/L	1	2		
Sodium: >=160 mmol/L	0	0		
Potassium: <3 mmol/L	0	1		
Potassium: >=5.5 mmol/L	2	2		
Lipase: >=3 ULN	2	1		
Amylase: >=3 ULN	0	0		
Glucose: <=3.9 mmol/L and <LLN	2	2		

Glucose: ≥ 7 mmol/L	7	7		
Albumin: ≤ 25 g/L	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Urinalysis

End point title	Induction Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Urinalysis ^[9]
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End point description:

PCSA criteria for urinalysis included: pH ≤ 4.6 and pH ≥ 8 . Safety population (Cohort A) and Rilzabrutinib-treated population (Cohort B) consisted of all participants who received at least 1 dose of study treatment.

End point type	Primary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 13 weeks)

Notes:

[9] - 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: No additional statistical analysis was prespecified for this endpoint.

End point values	Induction Treatment Period: Cohort A (Control)	Induction Treatment Period: Cohort A (Rilzabrutinib)	Induction Treatment Period: Cohort B (Rilzabrutinib)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	14	
Units: participants				
pH: ≤ 4.6	0	0	0	
pH: ≥ 8	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Urinalysis

End point title	Main + Maintenance Treatment Period: Number of Participants With Potentially Clinically Significant Abnormalities for Clinical Laboratory Tests: Urinalysis ^[10]
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End point description:

PCSA criteria for urinalysis included: pH ≤ 4.6 and pH ≥ 8 . Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib.

End point type	Primary			
End point timeframe:				
From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days (up to approximately 53 weeks)				
Notes:				
[10] - 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: No additional statistical analysis was prespecified for this endpoint.				
End point values	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)		
	Subject group type	Subject analysis set	Subject analysis set	
	Number of subjects analysed	14	13	
	Units: participants			
	pH: <=4.6	0	0	
pH: >=8	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Without Disease Flare Following the First Dose of Rilzabrutinib

End point title	Percentage of Participants Without Disease Flare Following the First Dose of Rilzabrutinib ^[11]			
End point description:				
Disease flare was defined as any of the following criteria: An increase in immunoglobulin G subclass 4-related disease (IgG4-RD) responder index (RI) >2 from the prior assessment; Initiation of rescue treatment following the first dose of rilzabrutinib until the end of treatment; Any end of study reason related to the disease under treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to control arm who crossed over and who received at least 1 dose of rilzabrutinib. It was pre-specified in Statistical Analysis Plan (SAP), efficacy analysis was planned only for Main+Maintenance period.				
End point type	Primary			
End point timeframe:				
Up to end of treatment (52 Weeks)				
Notes:				
[11] - 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: No additional statistical analysis was prespecified for this endpoint.				
End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: percentage of participants				
number (not applicable)	76.9	64.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Reduction From Baseline Immunoglobulin G Subclass 4-Related Disease Responder Index Activity Score by ≥ 2 Points Over Time

End point title	Percentage of Participants With Reduction From Baseline Immunoglobulin G Subclass 4-Related Disease Responder Index Activity Score by ≥ 2 Points Over Time
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End point description:

The IgG4-RD RI was designed to detect changes in disease activity in each affected organ system in a composite scoring system, assessed using computed tomography scan (CT scan). Physician assessed status by assigning a 0-3 score after organ/site as follows: 0=absence of active disease in that site. 1=improved but persistent activity in that site. 2=new or recurrent disease activity in that site while off treatment, or unchanged from previous visit. 3=worse or new despite treatment. Baseline= last observation recorded prior to first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned for Main+Maintenance period.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Weeks 12, 24, 36, 48, 52, and end of study (Week 56)

End point values	Main+Maintenance Treatment Period: Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period: Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: percentage of participants				
number (not applicable)				
Week 12 (n = 13,11)	69.2	100.0		
Week 24 (n = 10,5)	80.0	100.0		
Week 36 (n = 9,6)	66.7	100.0		
Week 48 (n = 7,6)	85.7	100.0		
Week 52 (n = 8,6)	87.5	100.0		
End of study (Week 56) (n = 8,12)	75.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Reduction From Baseline Immunoglobulin G4-Related Disease Responder Index Activity Score=0 Over Time

End point title	Percentage of Participants With Reduction From Baseline Immunoglobulin G4-Related Disease Responder Index Activity Score=0 Over Time
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End point description:

The IgG4-RD RI was designed to detect changes in disease activity in each affected organ system in a composite scoring system, assessed using CT scan. The physician assessed status by assigning a 0-3 score after the organ/site as follows: 0=absence of active disease in that site. 1=improved but persistent activity in that site. 2=new or recurrent disease activity in that site while off treatment, or unchanged from previous visit. 3=worse or new despite treatment. Baseline= last observation recorded prior to the first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Weeks 12, 24, 36, 48, 52, and End of study (Week 56)

End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: percentage of participants				
number (not applicable)				
Week 12 (n = 13,11)	7.7	0.0		
Week 24 (n = 10,5)	10.0	0.0		
Week 36 (n = 9,6)	11.1	0.0		
Week 48 (n = 7,6)	14.3	0.0		
Week 52 (n = 8,6)	12.5	16.7		
End of study (Week 56) (n = 8,12)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin G4-Related Disease Responder Index Over Time

End point title	Change From Baseline in Immunoglobulin G4-Related Disease Responder Index Over Time
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End point description:

The IgG4-RD RI was designed to detect changes in disease activity in each affected organ system in a composite scoring system, assessed using CT scans. At specified visits, the physician assessed the status by assigning a 0-3 score after the organ/site as follows: 0=absence of active disease in that site. 1=improved but persistent activity in that site. 2=new or recurrent disease activity in that site while off treatment, or unchanged from previous visit. 3=worse or new despite treatment. Baseline was defined as the last observation recorded prior to the first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Weeks 12, 24, 36, 48, 52, and end of study (Week 56)	

End point values	Main+Maintenance Treatment Period: Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period: Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n = 13, 11)	-5.31 (± 4.131)	-11.91 (± 5.467)		
Week 24 (n = 10, 5)	-6.90 (± 3.784)	-10.60 (± 1.817)		
Week 36 (n = 9,6)	-5.22 (± 5.357)	-14.33 (± 6.055)		
Week 48 (n = 7,6)	-7.29 (± 4.231)	-14.17 (± 5.707)		
Week 52 (n = 8,6)	-7.50 (± 3.928)	-15.00 (± 6.481)		
End of study (Week 56) (n = 8,12)	-5.50 (± 4.440)	-11.17 (± 5.132)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin G4-Related Disease Damage Over Time

End point title	Change From Baseline in Immunoglobulin G4-Related Disease Damage Over Time
End point description:	
<p>Damage was defined as the occurrence of permanent tissue injury or organ dysfunction that results from active or previously active IgG4-RD. Damage in this context does NOT refer to treatment-induced injury. Baseline was defined as the last observation recorded prior to the first dose of study treatment. The IgG4-RD RI was designed to detect changes in disease activity in each affected organ system in a composite scoring system, assessed using CT scans. At specified visits, the physician assessed the status by assigning a 0-3 score after the organ/site as follows: 0=absence of active disease in that site. 1=improved but persistent activity in that site. 2=new or recurrent disease activity in that site while off treatment, or unchanged from previous visit. 3=worse or new despite treatment. Rilzabrutinib-treated population. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.</p>	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Weeks 12, 24, 36, 48, 52, and end of study (Week 56)	

End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n = 13,11)	0.15 (± 0.899)	0.36 (± 0.505)		
Week 24 (n = 10,5)	0.00 (± 0.943)	0.20 (± 0.447)		
Week 36 (n = 9,6)	-0.22 (± 0.667)	0.33 (± 0.516)		
Week 48 (n = 7,6)	-0.71 (± 1.254)	0.33 (± 0.516)		
Week 52 (n = 8,6)	0.13 (± 1.126)	0.17 (± 0.408)		
End of study (Week 56) (n = 8,12)	0.00 (± 0.756)	0.25 (± 0.452)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Each Subclass of the Following Serological Markers: IgG4, IgG1, IgG, IgM, Complement C3 and C4 at Week 52

End point title	Change From Baseline of Each Subclass of the Following Serological Markers: IgG4, IgG1, IgG, IgM, Complement C3 and C4 at Week 52
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End point description:

Serum samples were collected at specified timepoints to assess the changes in serum concentrations of immunoglobulin G subclass 4 (IgG4), immunoglobulin G subclass 1 (IgG1), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3, and complement C4 serological parameters. Baseline was defined as the last observation recorded prior to the first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and end of treatment (Week 52)

End point values	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: milligram per deciliter				
arithmetic mean (standard deviation)				
IgG4 (n = 7, 7)	-114.757 (± 93.1197)	-223.671 (± 329.2337)		

IgG1 (n = 7, 7)	-130.414 (± 84.0370)	-74.957 (± 106.7538)		
IgG (n = 7, 7)	-150.857 (± 181.8859)	-405.286 (± 574.3781)		
IgM (n = 8, 8)	-12.750 (± 10.6335)	1.000 (± 49.5955)		
Complement C3 (n = 8, 8)	-5.250 (± 14.5283)	17.750 (± 23.7231)		
Complement C4 (n = 8, 8)	-0.875 (± 5.1669)	6.875 (± 6.3794)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Each Subclass of the Following Serological Marker: IgE at Week 52

End point title	Change From Baseline of Each Subclass of the Following Serological Marker: IgE at Week 52
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End point description:

Serum samples were collected at specified timepoints to assess the changes in serum concentrations of immunoglobulin E (IgE) serological parameter. Baseline was defined as the last observation recorded prior to the first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to Control arm who crossed over and who received at least 1 dose of rilzabrutinib. Only participants with data collected at specified timepoints are reported. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and end of treatment (Week 52)

End point values	Main+Maintenance Treatment Period: Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period: Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		
Units: International units per milliliter				
arithmetic mean (standard deviation)	297.529 (± 661.2851)	-49.025 (± 494.3543)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved a Reduction in Baseline Serum Immunoglobulin G Subclass 4 Level of 10% Over Time

End point title	Percentage of Participants who Achieved a Reduction in Baseline Serum Immunoglobulin G Subclass 4 Level of 10%
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End point description:

Serum samples were collected at specified timepoints to assess percentage of participants who achieved a reduction in baseline serum IgG4 level of 10% over time. Baseline was defined as the last observation recorded prior to the first dose of study treatment. Rilzabrutinib-treated population (Cohort B): all participants who received at least 1 dose of study treatment; (Cohort A): a subset of safety population consisted of only those participants randomized to the rilzabrutinib and to control arm who crossed over and who received at least 1 dose of rilzabrutinib. Here, 'n' = number of participants analyzed at specific time point. It was pre-specified in SAP, efficacy analysis was planned only for Main+Maintenance period.

End point type

Secondary

End point timeframe:

Baseline (Week 0) and Weeks 2, 4, 12, 24, 52, and end of study (Week 56)

End point values	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Main+Maintenance Treatment Period:Cohort B (Rilzabrutinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: percentage of participants				
number (not applicable)				
Week 2 (n = 9, 14)	77.8	35.7		
Week 4 (n = 13, 13)	61.5	53.8		
Week 12 (n = 12, 11)	50.0	63.6		
Week 24 (n = 10, 7)	60.0	85.7		
Week 52 (n = 8, 6)	75.0	83.3		
End of study (Week 56) (n = 12, 12)	33.3	75.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs collected from first dose of study treatment (Day 1) up to last dose +7 days (up to 13 [Induction TP] and 53 weeks [Main+Maintenance TP]). Death was assessed from signing of informed consent form (Week -4) to end of follow-up, approximately 216 weeks.

Adverse event reporting additional description:

Analysis was performed on safety population. It was pre-specified in SAP, separate safety analysis for main treatment period was not planned.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Main Treatment Period: Rilzabrutinib (Cohort B)
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Reporting group description:

Main TP included participants from Cohort B 12-week induction period, who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort B (rilzabrutinib) arm who completed the 12-week course of rilzabrutinib, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Reporting group title	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)
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Reporting group description:

Main TP included participants from Cohort A (12-week induction period and crossover TP), who received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks. Participants from Cohort A (rilzabrutinib) arm or those who completed the 12-week course of rilzabrutinib in crossover period, continued to receive rilzabrutinib tablets 400 mg orally BID for an additional 40 weeks in Maintenance TP.

Reporting group title	Induction Treatment Period: Cohort A (Rilzabrutinib)
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Reporting group description:

Participants received rilzabrutinib tablets 400 mg orally BID for 12 weeks, along with glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for a maximum of 4 weeks.

Reporting group title	Induction Treatment Period: Cohort A (Control)
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Reporting group description:

Participants received glucocorticoid minimum starting dose of 20 mg/day and the maximum dose of 40 mg/day prednisone equivalent orally for 12 weeks.

Serious adverse events	Main Treatment Period: Rilzabrutinib (Cohort B)	Main+Maintenance Treatment Period:Cohort A (All Rilzabrutinib)	Induction Treatment Period: Cohort A (Rilzabrutinib)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	1 / 10 (10.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			

Pneumonitis Aspiration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (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			
Campylobacter Infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Induction Treatment Period: Cohort A (Control)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pneumonitis Aspiration			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Campylobacter Infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Main Treatment Period: Rilzabrutinib (Cohort B)	Main+Maintenance Treatment Period: Cohort A (All Rilzabrutinib)	Induction Treatment Period: Cohort A (Rilzabrutinib)
Total subjects affected by non-serious adverse events subjects affected / exposed	13 / 14 (92.86%)	10 / 13 (76.92%)	8 / 10 (80.00%)
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Intermittent Claudication			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Chest Pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Allergic Sinusitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Oropharyngeal Pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Confusional State subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Investigations Blood Creatinine Increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Blood Glucose Increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Transaminases Increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Injury, poisoning and procedural complications Arthropod Sting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Alcohol Poisoning subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0

Arthropod Bite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Meniscus Injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Muscle Strain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Periorbital Haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin Laceration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 14 (14.29%)	3 / 13 (23.08%)	2 / 10 (20.00%)
occurrences (all)	2	3	2
Cognitive Disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ivth Nerve Paralysis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Increased Tendency To Bruise subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0
Eye disorders Eczema Eyelids subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Dry Eye subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Dacryoadenitis Acquired subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Eye Pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0
Ocular Hyperaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Lacrimation Increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Lacrimal Gland Enlargement subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Abdominal Distension subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Abdominal Pain Lower			

subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Abdominal Pain Upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	6 / 14 (42.86%)	5 / 13 (38.46%)	4 / 10 (40.00%)
occurrences (all)	10	5	4
Dry Mouth			
subjects affected / exposed	3 / 14 (21.43%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	3	1	1
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Glossodynia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Steatorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Parotid Gland Enlargement			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 13 (15.38%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Abdominal Pain			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 4	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hepatitis Cholestatic			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acute Febrile Neutrophilic Dermatositis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dermatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dermatitis Contact			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Lichen Planus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Night Sweats			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Rash			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 2	0 / 10 (0.00%) 0
Skin Mass			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Urticaria			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Renal and urinary disorders			
Renal Cyst			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Haematuria			
subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0
Urinary Retention			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	2 / 13 (15.38%) 5	2 / 10 (20.00%) 4
Flank Pain			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Muscle Spasms			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal Stiffness			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0
Neck Pain			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1
Infections and infestations			
Vulval Abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 14 (0.00%)	2 / 13 (15.38%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Sinusitis			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Respiratory Tract Infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Pneumonia Bacterial			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Covid-19			
subjects affected / exposed	2 / 14 (14.29%)	3 / 13 (23.08%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Malnutrition			

subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Induction Treatment Period: Cohort A (Control)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Intermittent Claudication			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Allergic Sinusitis			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Oropharyngeal Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Confusional State subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Investigations Blood Creatinine Increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Blood Glucose Increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Transaminases Increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Injury, poisoning and procedural complications Arthropod Sting subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Alcohol Poisoning subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Arthropod Bite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Meniscus Injury			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Muscle Strain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Periorbital Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Skin Laceration			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Cognitive Disorder			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Ivth Nerve Paralysis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Increased Tendency To Bruise			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			

Tinnitus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Eye disorders			
Eczema Eyelids subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dry Eye subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dacryoadenitis Acquired subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Eye Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Ocular Hyperaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Lacrimation Increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Lacrimal Gland Enlargement subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gastrointestinal disorders			
Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Abdominal Distension subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Abdominal Pain Lower subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Abdominal Pain Upper			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dry Mouth			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Glossodynia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Steatorrhoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Parotid Gland Enlargement			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			

Hypertransaminasaemia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hepatitis Cholestatic			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acute Febrile Neutrophilic Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dermatitis Contact			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Lichen Planus			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Night Sweats			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Rash			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Skin Mass subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Urticaria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Renal and urinary disorders Renal Cyst subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Haematuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Urinary Retention subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Flank Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Muscle Spasms subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Musculoskeletal Stiffness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Neck Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Infections and infestations			

Vulval Abscess			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Urinary Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Pneumonia Bacterial			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Laryngitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Covid-19			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2021	Removal of inclusion criteria and secondary efficacy endpoint. Addition of exclusion criteria. Improvement of operational feasibility in case of regional or national emergency such as coronavirus disease pandemic. Visit window updated to allow timely and complete Data Safety Monitoring Committee evaluations. Primary endpoint definition clarified. Exploratory objectives were added.
14 March 2022	Contents from of Clinical Study Protocol Version 3.1 (Canada only, 18 November 2020) were consolidated with Amended Clinical Study Protocol 05 (United States only, 15 April 2021) under a single global protocol. Additional changes were intended to clarify and simplify description of overall study design and plan. Safety information from the rilzabrutinib development program and include benefit-risk information to align with Investigator Brochure version 12 (14 June 2021) were updated, exclusion criteria and stopping rules for elevated liver transaminases were modified and added section on adverse events of special interest to align with Sanofi protocol standards. Change in shape and color of rilzabrutinib tablets described.
14 September 2022	Primary objective was changed to address a greater unmet medical need than induction of response. Background information was updated to align with the Investigator's Brochure Edition 13 (15 August 2022). The inclusion and exclusion criteria were updated to align with other rilzabrutinib clinical trial protocols. Study synopsis was simplified to conform to the Sanofi protocol template.
23 February 2023	The primary reason for this amendment was to incorporate feedback from health authorities as well as other clarifications deemed necessary by the Sponsor.
20 February 2024	The primary reasons for this amendment were to clarify temporal aspects of statistical considerations and include uveitis as an important potential risk.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported