Clinical trial results:
A Phase 2, randomized, double-blind, placebo-controlled, multicenter proof-of-concept study evaluating efficacy and safety of rilzabrutinib in adult patients with moderate to severe atopic dermatitis who are inadequate responders or intolerant to topical corticosteroids

Summary

EudraCT number	2021-001704-15
Trial protocol	DE NL CZ
Global end of trial date	23 June 2023

Results information

Result version number	v1 (current)
This version publication date	04 July 2024
First version publication date	04 July 2024

Trial information

Trial identification

Sponsor protocol code	ACT17207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05018806
WHO universal trial number (UTN)	U1111-1261-7565

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	21 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of rilzabrutinib in participants with atopic dermatitis (AD).

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of 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 trail, 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	09 September 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	124
EEA total number of subjects	50

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)	119
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 31 centers in 7 countries. 61 participants in twice a day(BID) cohort and 106 participants in three times a day(TID) cohort were screened from 09 September 2021 to 24 February 2023, of which 16 in BID cohort and 27 in TID cohort were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 45 participants in BID cohort and 79 participants in TID cohort were randomized in a ratio of 3:2 to receive either rilzabrutinib or matching placebo on Day 1 in the BID and TID cohorts, respectively.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BID cohort: Placebo

Arm description:

Participants received placebo matched to rilzabrutinib orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).

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

Dosage and administration details:

Placebo matched to rilzabrutinib was available as tablets (modified-capsule shaped tablets/caplets) and was administered orally BID from Day 1 up to Week 16.

Arm title	BID cohort: Rilzabrutinib 400 mg BID

Arm description:

Participants received rilzabrutinib 400 milligrams (mg) orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).

Arm type	Experimental
Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	
Other name	SAR444671, PRN1008
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rilzabrutinib was supplied as 400 mg tablets (modified-capsule shaped tablets/caplets) and was administered orally BID from Day 1 up to Week 16.

Arm title	TID cohort: Placebo

Arm description:

Participants received placebo matched to rilzabrutinib orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).

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

Dosage and administration details:

Placebo matched to rilzabrutinib was available as tablets (modified-capsule shaped tablets/caplets) and was administered orally TID from Day 1 up to Week 16.

Arm title	TID cohort: Rilzabrutinib 400 mg TID

Arm description:

Participants received rilzabrutinib 400 mg orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).

Arm type	Experimental
Investigational medicinal product name	Rilzabrutinib
Investigational medicinal product code	
Other name	SAR444671, PRN1008
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rilzabrutinib was supplied as 400 mg tablets (modified-capsule shaped tablets/caplets) and was administered orally TID from Day 1 up to Week 16.

Number of subjects in period 1	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo
Started	18	27	31
Completed	14	23	26
Not completed	4	4	5
Consent withdrawn by subject	3	3	3
Adverse event: Not related to COVID-19	1	1	2

Number of subjects in period 1	TID cohort: Rilzabrutinib 400 mg TID
Started	48
Completed	31
Not completed	17
Consent withdrawn by subject	10
Adverse event: Not related to COVID-19	7

Baseline characteristics

Reporting groups	
Reporting group title	BID cohort: Placebo
Reporting group description:	
Participants received placebo matched to rilzabrutinib orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).	
Reporting group title	BID cohort: Rilzabrutinib 400 mg BID
Reporting group description:	
Participants received rilzabrutinib 400 milligrams (mg) orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).	
Reporting group title	TID cohort: Placebo
Reporting group description:	
Participants received placebo matched to rilzabrutinib orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).	
Reporting group title	TID cohort: Rilzabrutinib 400 mg TID
Reporting group description:	
Participants received rilzabrutinib 400 mg orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).	

Reporting group values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo
Number of subjects	18	27	31
Age categorical Units: Subjects			
Adults (18-64 years)	18	25	29
From 65-84 years	0	2	2
Age Continuous Units: Years			
arithmetic mean	33.9	38.3	33.1
standard deviation	± 13.0	± 16.1	± 12.4
Sex: Female, Male Units: Participants			
Female	10	15	15
Male	8	12	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	2
White	16	23	25
More than one race	0	1	0
Unknown or Not Reported	0	0	0

Reporting group values	TID cohort: Rilzabrutinib 400 mg TID	Total	
Number of subjects	48	124	

Age categorical Units: Subjects			
Adults (18-64 years)	47	119	
From 65-84 years	1	5	
Age Continuous Units: Years			
arithmetic mean	36.1		
standard deviation	± 14.1	-	
Sex: Female, Male Units: Participants			
Female	31	71	
Male	17	53	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	6	14	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	4	7	
White	38	102	
More than one race	0	1	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	BID cohort: Placebo
Reporting group description:	
Participants received placebo matched to rilzabrutinib orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).	
Reporting group title	BID cohort: Rilzabrutinib 400 mg BID
Reporting group description:	
Participants received rilzabrutinib 400 milligrams (mg) orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).	
Reporting group title	TID cohort: Placebo
Reporting group description:	
Participants received placebo matched to rilzabrutinib orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).	
Reporting group title	TID cohort: Rilzabrutinib 400 mg TID
Reporting group description:	
Participants received rilzabrutinib 400 mg orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).	

Primary: Percent Change From Baseline to Week 16 in Eczema Area and Severity Index (EASI) Score

End point title	Percent Change From Baseline to Week 16 in Eczema Area and Severity Index (EASI) Score
End point description:	
EASI index is validated investigator-administered scoring system to measure severity of clinical signs in atopic dermatitis(AD). Four AD disease characteristics(erythema, thickness[induration, papulation, edema],scratching[excoriation],and lichenification) were each assessed for severity by investigator or designee on scale of "0"(absent) through "3(severe).In addition, area of AD involvement were assessed as percentage by body area of head,trunk,upper limbs,and lower limbs,and converted to score of 0 to 6. 0: 0% of body surface area(BSA) involvement with AD;1:1-9%;2: 10-29%;2:30-49%;4: 50-69%;5: 70-89% and 6: 90-100%.Total score=0(minimum) to 72(maximum);higher scores=greater severity of AD.Baseline=Day 1 assessment value. Intent-to-treat(ITT) population:all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was received or not.Only those participants with data collected at specified timepoints are reported.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to Week 16	

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	24	29	37
Units: Percent change				
least squares mean (standard error)	-47.33 (± 9.77)	-53.57 (± 8.25)	-43.33 (± 6.99)	-47.21 (± 6.26)

Statistical analyses

Statistical analysis title	BID cohort:Placebo versus Rilzabrutinib 400 mg BID

Statistical analysis description:

Analysis was performed by using an analysis of covariance (ANCOVA) model with the baseline EASI score, intervention group, randomization stratification of screening Immunoglobulin E (IgE) levels (< or ≥300 units international per milliliter [UI/mL]) as covariates.

Comparison groups	BID cohort: Placebo v BID cohort: Rilzabrutinib 400 mg BID
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6246
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-6.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.26
upper limit	18.77

Statistical analysis title	TID cohort:Placebo versus Rilzabrutinib 400 mg TID

Statistical analysis description:

Analysis was performed by using an ANCOVA model with the baseline EASI score, intervention group, randomization stratification of screening IgE levels (< or ≥300UI/mL) as covariates.

Comparison groups	TID cohort: Placebo v TID cohort: Rilzabrutinib 400 mg TID
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.674
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.97
upper limit	14.21

Secondary: Percentage of Participants With Investigator's Global Assessment (IGA) of 0 or 1 At Week 16

End point title	Percentage of Participants With Investigator's Global Assessment (IGA) of 0 or 1 At Week 16

End point description:

IGA is a static 5-point measure of disease severity based on an overall assessment of the skin lesions on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease). Higher score indicated higher severity. ITT population included all randomized participants analyzed according to the intervention group allocated by randomization regardless of whether the intervention was received or not.

End point type	Secondary

End point timeframe:

Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Percentage of participants				
number (not applicable)	22.2	7.4	12.9	14.6

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving EASI-75 (Reduction of EASI Score By ≥75% From Baseline) At Week 16

End point title	Percentage of Participants Achieving EASI-75 (Reduction of EASI Score By ≥75% From Baseline) At Week 16

End point description:

The EASI index is validated investigator-administered scoring system used to measure severity of clinical signs in AD. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) were each assessed for severity by investigator or designee on scale of "0" (absent) through "3" (severe).In addition, area of AD involvement were assessed as percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to score of 0 to 6. 0: 0% of BSA involvement with AD; 1: 1-9%; 2: 10-29%; 2: 30-49%; 4: 50-69%; 5: 70-89% and 6: 90-100%. Total score=0 (minimum) to 72 (maximum); higher scores indicated greater severity of AD. Participants who achieved EASI-75 were defined as participants with reduction of EASI score by ≥75% from baseline. ITT population included all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was received or not.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Percentage of participants				
number (not applicable)	27.8	29.6	29.0	18.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Reduction of Weekly Average of Daily Peak Pruritus Numerical Rating Scale (PP-NRS) of ≥4 Points From Baseline at Week 16

End point title	Percentage Of Participants With Reduction of Weekly Average of Daily Peak Pruritus Numerical Rating Scale (PP-NRS) of ≥4 Points From Baseline at Week 16

End point description:

The PP-NRS is a simple assessment tool that participants used to report the intensity of their pruritus (itch) during a daily recall period. Participants were asked to rate their worst itch on a 0 (no itch) to 10 (worst itch imaginable) NRS by answering the following question: For itch intensity, "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". The total score on the scale ranged from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicated worse symptoms. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. ITT population included all randomized participants analyzed according to the intervention group allocated by randomization regardless of whether the intervention was received or not.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Percentage of participants				
number (not applicable)	11.1	18.5	12.9	20.8

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Weekly Average of Daily PP-NRS Reduction ≥4 From Baseline During The 16-Week Treatment Period

End point title	Number of Participants With Weekly Average of Daily PP-NRS Reduction ≥4 From Baseline During The 16-Week Treatment Period

End point description:

The PP-NRS is a simple assessment tool that participants used to report the intensity of their pruritus (itch) during a daily recall period. Participants were asked to rate their worst itch on a 0 (no itch) to 10 (worst itch imaginable) NRS by answering the following question: For itch intensity, "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', howwould you rate your itch at the worst moment during the previous 24 hours?". The total score on the scale ranged from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicated worse symptoms. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. ITT population included all randomized participants analyzed according to the intervention group allocated by randomization regardless of whether the intervention was received or not.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Participants	2	7	4	13

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving EASI-50/90 (Reduction of EASI Score by ≥50% or ≥90% From Baseline) at Week 16

End point title	Percentage of Participants Achieving EASI-50/90 (Reduction of EASI Score by ≥50% or ≥90% From Baseline) at Week 16

End point description:

EASI index is validated investigator-administered scoring system used to measure severity of clinical signs in AD. Four AD disease characteristics(erythema, thickness[induration, papulation, edema],scratching[excoriation], and lichenification)were each assessed for severity by investigator or designee on scale of "0" (absent) through "3" (severe).In addition, area of AD involvement were assessed as percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6.0: 0% of BSA involvement with AD;1: 1-9%;2: 10-29%;2: 30-49%;4: 50-69%;5: 70-89% and6: 90-100%. Total score=0 (minimum) to 72 (maximum);higher scores=greater severity of AD. Participants who achieved EASI-50/90 were defined as participants with reduction of EASI score by ≥50% or ≥90% from baseline respectively. ITT population included all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Percentage of participants				
number (not applicable)				
EASI-50	55.6	44.4	38.7	29.2
EASI-90	16.7	11.1	12.9	8.3

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline to Week 16 in EASI Score

End point title	Absolute Change From Baseline to Week 16 in EASI Score

End point description:

EASI index is validated investigator-administered scoring system used to measure severity of clinical signs in AD. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) were each assessed for severity by investigator or designee on scale of "0" (absent) through "3" (severe).In addition, area of AD involvement were assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to score of 0 to 6. 0: 0% of BSA involvement with AD; 1: 1-9%; 2: 10-29%; 2: 30-49%; 4: 50-69%; 5: 70-89% and 6: 90-100%. Total score=0 (minimum) to 72 (maximum); higher scores indicated greater severity of AD. Baseline=Day 1 assessment value. ITT population included all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was received or not. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	24	29	37
Units: Scores on a scale				
least squares mean (standard error)	-12.83 (± 2.31)	-14.00 (± 1.94)	-10.37 (± 2.48)	-11.34 (± 2.20)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 16 in Percent BSA of AD

End point title	Change From Baseline to Week 16 in Percent BSA of AD

End point description:

BSA affected by AD were assessed for each section of the body (the possible highest score for each region was: head and neck [10%], trunk including genitalia [30%], upper limbs [20%], lower limbs [40%]) and were reported as a percentage of all major body sections combined. Total score ranges from 0% to 100%. The higher score indicates a worse value and a lower score indicates a better value. Baseline was defined as the Day 1 assessment value. ITT population included all randomized participants analyzed according to the intervention group allocated by randomization regardless of whether the intervention was received or not. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	20	29	37
Units: Percent of body surface area				
least squares mean (standard error)	-10.45 (± 4.37)	-15.30 (± 3.61)	-7.35 (± 3.38)	-11.80 (± 3.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline to Week 16 in Weekly Average of Daily PP-NRS

End point title	Absolute Change From Baseline to Week 16 in Weekly Average of Daily PP-NRS

End point description:

The PP-NRS is a simple assessment tool that participants used to report the intensity of their pruritus (itch) during a daily recall period. Participants were asked to rate their worst itch on a 0 (no itch) to 10 (worst itch imaginable) NRS by answering the following question: For itch intensity, "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". The total score on the scale ranged from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicated worse symptoms. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. Baseline was defined as the Day 1 assessment value. ITT population=all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was received or not. Only those participants with data collected at specified timepoints are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	23	26	36
Units: Scores on a scale				
least squares mean (standard error)	-1.60 (± 0.66)	-3.11 (± 0.52)	-0.83 (± 0.51)	-2.07 (± 0.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 16 in Weekly Average of Daily PP-NRS

End point title	Percent Change From Baseline to Week 16 in Weekly Average of Daily PP-NRS

End point description:

The PP-NRS is a simple assessment tool that participants used to report the intensity of their pruritus (itch) during a daily recall period. Participants were asked to rate their worst itch on a 0 (no itch) to 10 (worst itch imaginable) NRS by answering the following question: For itch intensity, "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". The total score on the scale ranged from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicated worse symptoms. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. Baseline was defined as the Day 1 assessment value. ITT population=all randomized participants analyzed according to intervention group allocated by randomization regardless of whether intervention was received or not. Only those participants with data collected at specified timepoints are reported

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	23	26	36
Units: Percent change				
least squares mean (standard error)	-21.55 (± 8.37)	-43.53 (± 6.80)	-10.36 (± 7.19)	-30.13 (± 6.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving IGA*BSA-50/75/90 (Reduction of IGA*BSA by ≥50% or 75% or 90% From Baseline) At Week 16

End point title	Percentage of Participants Achieving IGA*BSA-50/75/90 (Reduction of IGA*BSA by ≥50% or 75% or 90% From Baseline) At Week 16

End point description:

IGA is a static 5-point measure of disease severity based on an overall assessment of the skin lesions on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease). Higher score indicated higher severity. Participants who achieved IGA*BSA-50-75-90 were defined as participants with reduction of IGA*BSA by ≥50% or 75% or 90% from baseline. ITT population included all randomized participants analyzed according to the intervention group allocated by randomization regardless of whether the intervention was received or not.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Week 16

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Percentage of participants				
number (not applicable)				
IGA*BSA-50	38.9	40.7	38.7	29.2
IGA*BSA-75	22.2	25.9	22.6	18.8
IGA*BSA-90	5.6	18.5	9.7	10.4

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), Adverse Events of Special Interest (AESIs) and Study intervention Discontinuation

End point title	Number Of Participants With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), Adverse Events of Special Interest (AESIs) and Study intervention Discontinuation

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. TEAEs were defined as AEs that developed, worsened or became serious during treatment-emergent period. SAE was any AE 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. An AESI was an AE (serious or nonserious) of scientific and medical concern specific to Sponsor’s product or program, for which ongoing monitoring and immediate notification by investigator to Sponsor was required. Safety population included all randomized participants who took at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to 16 weeks

End point values	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo	TID cohort: Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	27	31	48
Units: Participants				
TEAEs	10	15	19	38
TESAEs	0	0	1	1
AESI	3	0	2	0
TEAE leading to study intervention discontinuation	0	2	2	9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from Baseline (Day 1) to 16 weeks. All-cause mortality (Deaths) was collected throughout the study, approximately 97 weeks.

Adverse event reporting additional description:

Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	BID cohort: Placebo

Reporting group description:

Participants received placebo matched to rilzabrutinib orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).

Reporting group title	BID cohort: Rilzabrutinib 400 mg BID

Reporting group description:

Participants received rilzabrutinib 400 mg orally BID from Day 1 up to Week 16. Consecutive doses were ideally administered 12 hours apart (and not less than 8 hours apart).

Reporting group title	TID cohort: Placebo

Reporting group description:

Participants received placebo matched to rilzabrutinib orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).

Reporting group title	TID cohort: Rilzabrutinib 400 mg TID

Reporting group description:

Participants received rilzabrutinib 400 mg orally TID from Day 1 up to Week 16. Consecutive doses were ideally administered at least 6 hours apart (and not less than 4 hours apart).

Serious adverse events	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cutaneous T-Cell Lymphoma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (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			
Abscess Limb			

subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TID cohort: Rilzabrutinib 400 mg TID		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cutaneous T-Cell Lymphoma			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 48 (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: 0 %

Non-serious adverse events	BID cohort: Placebo	BID cohort: Rilzabrutinib 400 mg BID	TID cohort: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	15 / 27 (55.56%)	19 / 31 (61.29%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Influenza Like Illness			

subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstruation Delayed			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	2 / 27 (7.41%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Anxiety			

subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Weight Decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Transaminases Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Body Temperature Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Blood Pressure Increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Eyelid Injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Ligament Sprain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Limb Crushing Injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Stab Wound			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Coronary Artery Stenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Coronary Artery Disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Supraventricular Tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 18 (5.56%)	2 / 27 (7.41%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
Dysaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Tremor			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Spontaneous Haematoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Deficiency Anaemia			

subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Swelling Of Eyelid			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Conjunctivitis Allergic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Blepharitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal Distension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal Discomfort			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Lower			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	0 / 18 (0.00%)	4 / 27 (14.81%)	0 / 31 (0.00%)
occurrences (all)	0	7	0
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Frequent Bowel Movements			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	8 / 27 (29.63%)	1 / 31 (3.23%)
occurrences (all)	0	8	1
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Chronic Spontaneous Urticaria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	3 / 31 (9.68%)
occurrences (all)	1	0	3

Dermatitis Atopic			
subjects affected / exposed	3 / 18 (16.67%)	4 / 27 (14.81%)	9 / 31 (29.03%)
occurrences (all)	3	7	13
Hand Dermatitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Livedo Reticularis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Sensitive Skin			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Back Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Acute Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Covid-19			
subjects affected / exposed	2 / 18 (11.11%)	0 / 27 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
Eczema Impetiginous			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Pustule			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Eczema Infected			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Gastroenteritis Viral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Viral Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Influenza			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 27 (7.41%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Oral Herpes			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Pulpitis Dental			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Skin Bacterial Infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Rhinolaryngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Rash Pustular			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Staphylococcal Skin Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal Candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection Bacterial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Tinea Pedis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Systemic Viral Infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Food Aversion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 27 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 27 (3.70%)	0 / 31 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	TID cohort: Rilzabrutinib 400 mg TID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 48 (79.17%)		
Vascular disorders			
Hot Flush			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Influenza Like Illness			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menstruation Delayed			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Psychiatric disorders			
Stress			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Weight Decreased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Transaminases Increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Body Temperature Increased			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Blood Pressure Increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		

Injury, poisoning and procedural complications			
Eyelid Injury			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Ligament Sprain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Limb Crushing Injury			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Stab Wound			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Cardiac disorders			
Coronary Artery Stenosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Coronary Artery Disease			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Supraventricular Tachycardia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Dysaesthesia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Blood and lymphatic system disorders			
Spontaneous Haematoma			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Deficiency Anaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Eye disorders			
Swelling Of Eyelid			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Conjunctivitis Allergic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Blepharitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Abdominal Distension			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Abdominal Discomfort			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Abdominal Pain Lower			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Frequent Bowel Movements			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	15 / 48 (31.25%)		
occurrences (all)	16		
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Abdominal Pain Upper			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Chronic Spontaneous Urticaria			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Alopecia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Acne			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Dermatitis Atopic			
subjects affected / exposed	15 / 48 (31.25%)		
occurrences (all)	15		
Hand Dermatitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Livedo Reticularis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Sensitive Skin			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Arthropathy			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Back Pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Bursitis			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Covid-19			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Eczema Impetiginous			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Pustule			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Eczema Infected			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastroenteritis Viral			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Gastrointestinal Viral Infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Impetigo				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Laryngitis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	3 / 48 (6.25%)			
occurrences (all)	3			
Oral Herpes				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Pulpitis Dental				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Cystitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Skin Bacterial Infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Rhinolaryngitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Rash Pustular				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			

Staphylococcal Skin Infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Vulvovaginal Candidiasis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Urinary Tract Infection Bacterial subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Upper Respiratory Tract Infection Bacterial subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Tinea Pedis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Systemic Viral Infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Food Aversion subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2021	To incorporate feedback from health authorities as well as other clarifications and corrections deemed necessary by the Sponsor. Correction and clarification were done in the schedule of activities and inclusion criteria. Consistency was provided in Pregnancy section. In addition, other minor editorial changes (e.g., grammatical and minor typographical error corrections) were implemented throughout the protocol.
03 January 2022	The main reason was to evaluate the efficacy and safety of two dose regimen of rilzabrutinib, the current dose regimen of 400 mg BID and an additional higher regimen of 400 mg TID in two staggered double-blind cohorts for a total number of 120 participants split as follows: The total number of participants in the BID cohort was reduced from 70 to 50 (n=30 rilzabrutinib / 20 matching placebo); The total number of participants in the TID cohort is 70 (n=42 rilzabrutinib / 28 matching placebo). Bruton's tyrosine kinase (BTK) appeared as an attractive drug target in AD by inhibiting the dysregulated signaling and activation of the pathogenic cells B-cells, mast cells and basophils implicated in skin inflammation suggesting the presence of both Type 1 and Type 2 inflammation as per the Gell and Coombs classification (Type 1 being an immediate hypersensitivity mediated by IgE and Type 2b being mediated by IgG autoantibody). The basophil histamine release assay (BHRA) had been used in assessing endotypes of chronic spontaneous urticaria. Those with BHRA- results were classified as Type 1 (immediate hypersensitivity mediated by IgE) while those with BHRA+ results were classified as Type 2b (mediated by IgG autoantibody). This endotype classification system had been demonstrated to contribute to clinical responses to BTK inhibitors. BHRA had not been studied extensively in AD. Thus, determining the BHRA status at baseline and end of study would provide epidemiology of BHRA classification in AD and assess if a given endotype had a better response to BTK inhibitor or not. In addition, clarifications and corrections had been made based on feedback from study sites. In addition, other minor editorial changes were implemented throughout the protocol. Administrative changes in the cover page were done. Clarification was provided in schedule of activities, study intervention(s) and concomitant therapy, eligibility criteria. Template language update was made.
24 August 2022	Inclusion and exclusion criteria were updated. In addition, clarifications and corrections deemed necessary by Sponsor were implemented. Administrative change to comply with Sanofi standard format was added. Clarification and accuracy in synopsis, schema, overall design, population for analysis, schedule of activities, study intervention compliance, concomitant therapy was provided. Updated information with the current investigator brochure. Changes were made for clarification in Clinical Safety laboratory assessments, AESI and exploratory endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported