



Clinical trial results:

A randomized, double-blind, placebo-controlled, parallel-group, 12-week Proof-of-Concept study to assess the efficacy, safety, and tolerability of rilzabrutinib in participants with moderate-to-severe asthma who are not well controlled on inhaled corticosteroid plus long-acting 2 adrenergic agonist therapy

Summary

EudraCT number	2021-002490-26
Trial protocol	ES PL HU BG
Global end of trial date	28 February 2024

Results information

Result version number	v1 (current)
This version publication date	15 March 2025
First version publication date	15 March 2025

Trial information

Trial identification

Sponsor protocol code	ACT17208
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05104892
WHO universal trial number (UTN)	U1111-1262-2956

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	13 May 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of rilzabrutinib compared to placebo on reducing the incidence of "loss of asthma control" (LOAC) events.

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 law governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 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	Argentina: 58
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 26
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Türkiye: 2
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	196
EEA total number of subjects	97

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)	170
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 48 centers in 13 countries. A total of 310 participants were screened between 12 December 2021 and 14 November 2023, of which 114 were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 196 participants were randomized. Randomization was stratified by immunoglobulin E levels [(IgE) <100 international units per milliliter (IU/mL) or ≥100 IU/mL] and region. Assignment to arms was done centrally using interactive response technology (IRT) in 1:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo BID

Arm description:

Participants were administered placebo orally twice daily (BID) on Day 1 for 12 weeks, added to background therapy of inhaled corticosteroids/long-acting beta 2-adrenergic agonist (ICS/LABA) fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

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:

Participants were administered placebo orally BID, with or without food starting on Day 1.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puffs via MDI at a stable dose until Week 4.

Investigational medicinal product name	Fluticasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via dry powder inhaler (DPI) or 2 puff via metered dose inhaler (MDI) up to Week 9 and gradually withdrawn from Week 6.

Arm title	Rilzabrutinib 400 mg BID
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Arm description:

Participants were administered rilzabrutinib 400 milligram (mg) orally BID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

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

Dosage and administration details:

Participants were administered rilzabrutinib orally BID, with or without food starting on Day 1.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puffs via MDI at a stable dose until Week 4.

Investigational medicinal product name	Fluticasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puff via MDI up to Week 9 and gradually withdrawn from Week 6.

Arm title	Placebo TID
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Arm description:

Participants were administered placebo orally three times a day (TID) on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

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:

Participants were administered placebo orally TID, with or without food starting on Day 1.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puffs via MDI at a stable dose until Week 4.

Investigational medicinal product name	Fluticasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder

Routes of administration	Inhalation use
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Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puff via MDI up to Week 9 and gradually withdrawn from Week 6.

Arm title	Rilzabrutinib 400 mg TID
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Arm description:

Participants were administered rilzabrutinib 400 mg orally TID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

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

Dosage and administration details:

Participants were administered rilzabrutinib orally TID, with or without food starting on Day 1.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puffs via MDI at a stable dose until Week 4.

Investigational medicinal product name	Fluticasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered 1 puff via DPI or 2 puff via MDI up to Week 9 and gradually withdrawn from Week 6.

Number of subjects in period 1	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID
Started	32	32	68
Completed	31	30	67
Not completed	1	2	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	-
Poor compliance to protocol	1	-	-
Sponsor decision	-	1	-

Number of subjects in period 1	Rilzabrutinib 400 mg TID
Started	64

Completed	60
Not completed	4
Consent withdrawn by subject	4
Adverse event, non-fatal	-
Poor compliance to protocol	-
Sponsor decision	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo BID
Reporting group description: Participants were administered placebo orally twice daily (BID) on Day 1 for 12 weeks, added to background therapy of inhaled corticosteroids/long-acting beta 2-adrenergic agonist (ICS/LABA) fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Rilzabrutinib 400 mg BID
Reporting group description: Participants were administered rilzabrutinib 400 milligram (mg) orally BID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Placebo TID
Reporting group description: Participants were administered placebo orally three times a day (TID) on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Rilzabrutinib 400 mg TID
Reporting group description: Participants were administered rilzabrutinib 400 mg orally TID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	

Reporting group values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID
Number of subjects	32	32	68
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	50.8 ± 12.3	48.0 ± 13.4	48.6 ± 13.7
Sex: Female, Male Units: participants			
Female	24	18	41
Male	8	14	27
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	2	2	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	29	30	64
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Rilzabrutinib 400 mg TID	Total	
Number of subjects	64	196	
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	48.8 ± 13.3	-	
Sex: Female, Male Units: participants			
Female	39	122	
Male	25	74	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	2	
Asian	0	6	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	1	
White	64	187	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Placebo BID
Reporting group description: Participants were administered placebo orally twice daily (BID) on Day 1 for 12 weeks, added to background therapy of inhaled corticosteroids/long-acting beta 2-adrenergic agonist (ICS/LABA) fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Rilzabrutinib 400 mg BID
Reporting group description: Participants were administered rilzabrutinib 400 milligram (mg) orally BID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Placebo TID
Reporting group description: Participants were administered placebo orally three times a day (TID) on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	
Reporting group title	Rilzabrutinib 400 mg TID
Reporting group description: Participants were administered rilzabrutinib 400 mg orally TID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.	

Primary: Percentage of Participants With an Loss of Asthma Control (LOAC) Event

End point title	Percentage of Participants With an Loss of Asthma Control (LOAC) Event
End point description: An LOAC event was a deterioration of asthma defined as any of the following: A 30% or greater reduction from baseline in morning peak expiratory flow (PEF) on 2 consecutive days. >= 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in 24 hours (compared to baseline) on 2 consecutive days. Increase in inhaled corticosteroid (ICS) >= 4 times the last prescribed ICS dose. Required use of systemic (oral and/or parenteral) steroid treatment. Required hospitalization or emergency room visit for asthma exacerbation. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The modified intent-to-treat (mITT) included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe: Up to Week 12	

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	68	64
Units: percentage of participants				
number (not applicable)	50.0	37.5	29.4	18.8

Statistical analyses

Statistical analysis title	Placebo BID versus rilzabrutinib BID
Statistical analysis description:	
Derived from logistic regression with study treatment group, baseline IgE strata level, region (Latin America versus Rest of the world in BID cohort), and number of exacerbation events within 2 years prior to screening.	
Comparison groups	Placebo BID v Rilzabrutinib 400 mg BID
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.288
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.202
upper limit	1.608

Statistical analysis title	Placebo TID versus rilzabrutinib TID
Statistical analysis description:	
Derived from logistic regression with study intervention group, baseline IgE strata level, region (Eastern Europe versus Rest of the world in TID cohort), and number of exacerbation events within 2 years prior to screening.	
Comparison groups	Placebo TID v Rilzabrutinib 400 mg TID
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2083
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.584
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.253
upper limit	1.349

Secondary: Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in one Second (FEV1) at Week 12

End point title	Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in one Second (FEV1) at Week 12
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration. Spirometry was performed in the morning. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization. Only participants with data collected at Baseline and Week 12 are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	54	48
Units: liters				
arithmetic mean (standard deviation)	-0.06 (± 0.22)	-0.04 (± 0.39)	-0.06 (± 0.31)	-0.15 (± 0.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in one Second at Week 12

End point title	Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in one Second at Week 12
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the ATS/ERS guidelines. The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. After the measurement of pre-bronchodilator FEV1, participants received 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol. Post-bronchodilator FEV1 referred to the spirometry performed within 30 minutes after administration of bronchodilator. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization. Only participants with data collected at Baseline and Week 12 are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	55	43
Units: liters				
arithmetic mean (standard deviation)	-0.08 (± 0.28)	-0.01 (± 0.27)	-0.04 (± 0.32)	-0.10 (± 0.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pre-Bronchodilator and Post-Bronchodilator Forced Expiratory Volume in one Second Over Time

End point title	Change From Baseline in Pre-Bronchodilator and Post-Bronchodilator Forced Expiratory Volume in one Second Over Time
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the ATS/ERS guidelines. The FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed in morning. After the measurement of pre-bronchodilator FEV1, participants received 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol. Post-bronchodilator FEV1 referred to the spirometry performed within 30 minutes after administration of bronchodilator. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. mITT included all randomized participants who received at least 1 dose of study treatment analyzed. Only n=number of participants with data collected at specified times for specified categories are reported. 9999 indicates no participants evaluated at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Weeks 2, 4, 6, 8, and 10

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	29	63	55
Units: Liter				
arithmetic mean (standard deviation)				
Week 2: Pre-bronchodilator FEV1,(n = 29,26,63,55)	0.07 (± 0.29)	0.08 (± 0.29)	0.01 (± 0.20)	-0.04 (± 0.25)
Week 4: Pre-bronchodilator FEV1,(n = 26,26,55,51)	0.08 (± 0.28)	0.07 (± 0.24)	-0.04 (± 0.30)	0.02 (± 0.22)
Week 6: Pre-bronchodilator FEV1,(n = 29,24,57,53)	0.05 (± 0.32)	0.09 (± 0.38)	-0.08 (± 0.24)	-0.07 (± 0.34)
Week 8: Pre-bronchodilator FEV1,(n = 27,23,55,44)	0.02 (± 0.26)	0.04 (± 0.41)	-0.11 (± 0.22)	-0.12 (± 0.40)
Week 10: Pre-bronchodilator FEV1,(n = 27,20,53,50)	0.00 (± 0.28)	0.13 (± 0.33)	-0.10 (± 0.28)	-0.10 (± 0.27)

Week 2: Post-bronchodilator FEV1,(n = 0,0,49,45)	9999 (± 9999)	9999 (± 9999)	0.03 (± 0.18)	-0.07 (± 0.26)
Week 4: Post-bronchodilator FEV1,(n = 29,28,55,55)	0.03 (± 0.25)	-0.01 (± 0.25)	-0.05 (± 0.24)	-0.05 (± 0.20)
Week 6: Post-bronchodilator FEV1,(n = 29,29,59,50)	0.04 (± 0.30)	0.03 (± 0.26)	-0.06 (± 0.23)	-0.06 (± 0.19)
Week 8: Post-bronchodilator FEV1,(n = 28,26,53,46)	0.02 (± 0.23)	0.01 (± 0.31)	-0.07 (± 0.25)	-0.08 (± 0.21)
Week 10: Post-bronchodilator FEV1,(n=27,27,53,50)	0.03 (± 0.22)	0.10 (± 0.31)	-0.06 (± 0.25)	-0.09 (± 0.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Percent Predicted Forced Expiratory Volume in one Second at Week 12 (Pre-Bronchodilator and Post-Bronchodilator)

End point title	Change from Baseline in the Percent Predicted Forced Expiratory Volume in one Second at Week 12 (Pre-Bronchodilator and Post-Bronchodilator)
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the ATS/ERS guidelines. The FEV1 was the volume of air exhaled from the lungs in first second of a forced expiration as measured by spirometer. Spirometry was performed in the morning. After the measurement of pre-bronchodilator FEV1, participants received 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol. Post-bronchodilator FEV1 referred to spirometry performed within 30 minutes after administration of bronchodilator. Percent predicted FEV1 for pre and post bronchodilator is reported. The baseline is defined as the available value on the latest date up to randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	59	48
Units: percentage of predicted FEV1				
arithmetic mean (standard deviation)				
Week 12: Pre-bronchodilator, (n = 26,25,58,48)	-1.54 (± 7.40)	-2.80 (± 12.34)	-1.93 (± 10.31)	-3.35 (± 7.93)
Week 12: Post-bronchodilator, (n = 27,26,59,46)	-1.48 (± 8.38)	-0.77 (± 8.58)	-1.66 (± 9.89)	-3.87 (± 7.30)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Forced Vital Capacity (FVC) Over Time

End point title	Change From Baseline in the Forced Vital Capacity (FVC) Over Time
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the ATS/ERS guidelines. FVC measures the total volume of air that a participant can breathe out forcefully from a full breath, blowing all of it out. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization. Only participants with data collected at specified times are reported. Here, n=number of participants with data collected for each specified category.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 2, 4, 6, 8, 10, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	24	63	55
Units: liters				
arithmetic mean (standard deviation)				
Week 2 (n = 26,22,63,53)	0.05 (± 0.35)	0.12 (± 0.32)	0.03 (± 0.29)	-0.03 (± 0.29)
Week 4 (n = 26, 23,55,51)	0.05 (± 0.26)	0.06 (± 0.32)	-0.03 (± 0.35)	0.01 (± 0.21)
Week 6 (n = 25,23,58,49)	0.03 (± 0.31)	0.05 (± 0.33)	-0.06 (± 0.34)	-0.02 (± 0.35)
Week 8 (n = 27,20,55,44)	-0.03 (± 0.31)	0.02 (± 0.35)	-0.09 (± 0.27)	-0.11 (± 0.43)
Week 10 (n = 25,18,52,46)	0.02 (± 0.33)	0.07 (± 0.38)	-0.07 (± 0.33)	-0.09 (± 0.28)
Week 12 (n = 26,24,54,46)	-0.05 (± 0.26)	-0.10 (± 0.41)	-0.07 (± 0.34)	-0.12 (± 0.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Peak Expiratory Flow (PEF) Over Time

End point title	Change From Baseline in the Peak Expiratory Flow (PEF) Over Time
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End point description:

PEF is defined as participant's maximum speed of expiration as measured with electronic PEF meter. AM PEF was performed within 15 minutes after arising and PM PEF was performed in the evening. Baseline AM PEF is the mean AM measurement recorded for the 7 days prior to the first dose of study treatment, and baseline PM PEF is the mean PM measurement recorded for the 7 days prior to the first dose of study treatment. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT population. Only participants with data collected at specified times are reported. Here, n=number of participants with data collected for each specified category.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	68	63
Units: liter/minute				
arithmetic mean (standard deviation)				
Week 1, AM PEF (n = 32,32,68,63)	7.90 (± 29.78)	6.64 (± 29.81)	13.99 (± 35.33)	9.54 (± 41.80)
Week 2, AM PEF (n = 32,31,68,62)	4.42 (± 42.51)	5.05 (± 28.77)	18.37 (± 41.12)	12.61 (± 44.75)
Week 3, AM PEF (n = 31,31,68,61)	7.15 (± 51.14)	9.41 (± 27.61)	19.34 (± 47.74)	14.58 (± 49.67)
Week 4, AM PEF (n = 31,31,68,59)	7.68 (± 55.67)	13.03 (± 34.65)	21.78 (± 49.65)	13.87 (± 52.88)
Week 5, AM PEF (n = 30,31,68,59)	-5.67 (± 41.75)	5.74 (± 48.44)	14.70 (± 59.89)	9.11 (± 66.16)
Week 6, AM PEF (n = 30,31,67,58)	-10.29 (± 43.37)	-0.20 (± 45.61)	18.75 (± 66.05)	7.17 (± 70.72)
Week 7, AM PEF (n = 31,31,65,56)	-1.87 (± 42.62)	3.07 (± 38.33)	11.45 (± 66.84)	6.02 (± 76.11)
Week 8, AM PEF (n = 30,31,63,56)	-2.67 (± 42.98)	2.83 (± 43.91)	17.09 (± 63.60)	6.78 (± 78.57)
Week 9, AM PEF (n = 30,29,62,57)	-7.14 (± 39.18)	9.56 (± 52.59)	12.88 (± 64.87)	5.73 (± 80.84)
Week 10, AM PEF (n = 30,30,61,55)	-14.43 (± 46.89)	0.06 (± 40.14)	8.83 (± 63.87)	1.55 (± 82.02)
Week 11, AM PEF (n = 30,28,61,54)	-16.21 (± 39.93)	-3.10 (± 45.47)	5.77 (± 71.21)	4.32 (± 76.30)
Week 12, AM PEF (n = 28,27,60,50)	-15.01 (± 35.56)	-3.61 (± 44.25)	3.28 (± 74.37)	5.78 (± 77.70)
Week 1, PM PEF (n = 32,32,67,62)	10.54 (± 29.06)	-1.29 (± 27.56)	14.26 (± 34.42)	5.61 (± 44.88)
Week 2, PM PEF (n = 32,31,67,62)	4.41 (± 43.26)	-2.18 (± 34.63)	21.29 (± 42.63)	1.77 (± 50.34)
Week 3, PM PEF (n = 31,31,67,61)	12.95 (± 44.39)	-2.20 (± 32.42)	21.31 (± 44.56)	4.28 (± 50.30)
Week 4, PM PEF (n = 31,31,67,58)	6.82 (± 47.17)	1.34 (± 34.76)	21.77 (± 49.32)	7.46 (± 52.72)
Week 5, PM PEF (n = 30,31,67,57)	-10.77 (± 33.50)	-14.75 (± 41.57)	12.93 (± 55.72)	-0.64 (± 65.65)
Week 6, PM PEF (n = 30,31,66,57)	-8.31 (± 32.81)	-14.24 (± 53.62)	12.68 (± 60.20)	2.43 (± 73.08)
Week 7, PM PEF (n = 30,31,64,55)	-5.19 (± 33.45)	-13.33 (± 39.83)	13.07 (± 64.55)	4.97 (± 81.71)
Week 8, PM PEF (n = 30,30,63,55)	-5.64 (± 35.97)	-7.66 (± 41.46)	15.53 (± 59.67)	3.66 (± 78.98)
Week 9, PM PEF (n = 30,30,62,55)	-3.45 (± 35.09)	-5.87 (± 57.20)	12.61 (± 59.34)	2.68 (± 83.50)
Week 10, PM PEF (n = 30,30,61,54)	-16.01 (± 39.97)	-7.35 (± 51.10)	11.88 (± 60.74)	4.97 (± 83.30)
Week 11, PM PEF (n = 30,28,61,53)	-13.09 (± 31.44)	-12.40 (± 56.11)	1.28 (± 67.54)	-0.47 (± 83.71)
Week 12, PM PEF (n = 28,26,58,49)	-14.31 (± 34.08)	-16.94 (± 48.16)	-5.10 (± 71.12)	3.43 (± 87.98)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Flow [(FEV) 25-75%] Over Time

End point title	Change From Baseline in Forced Expiratory Flow [(FEV) 25-75%] Over Time
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End point description:

Spirometry is a standard test to measure the participant's lung function. It was performed in accordance with the ATS/ERS guidelines. FEF is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEF 25-75% was defined as the FEF at 25% to 75% of FVC, where FVC was defined as the total volume of air that a participant can breathe out forcefully from a full breath, blowing all of it out. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization. Only participants with data collected at specified times are reported. Here, n=number of participants with data collected for each specified category.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 2, 4, 6, 8, 10, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	29	65	29
Units: Liter/second				
arithmetic mean (standard deviation)				
Week 2 (n = 30,29,65,59)	0.11 (± 0.39)	0.01 (± 0.34)	0.02 (± 0.38)	-0.06 (± 0.35)
Week 4 (n = 28,27,60,55)	0.08 (± 0.38)	0.09 (± 0.33)	-0.03 (± 0.45)	0.03 (± 0.42)
Week 6 (n = 29,28,61,55)	0.10 (± 0.41)	0.05 (± 0.49)	-0.11 (± 0.39)	-0.08 (± 0.49)
Week 8 (n = 27,26,59,48)	0.03 (± 0.37)	0.07 (± 0.44)	-0.14 (± 0.41)	-0.15 (± 0.50)
Week 10 (n = 27,21,56,52)	0.02 (± 0.36)	0.11 (± 0.39)	-0.15 (± 0.49)	-0.13 (± 0.49)
Week 12 (n = 26,25,58,48)	-0.03 (± 0.22)	0.01 (± 0.38)	-0.13 (± 0.49)	-0.23 (± 0.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5) Score

End point title	Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5) Score
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End point description:

The ACQ-5 is a questionnaire that measured the adequacy of asthma control and any changes in asthma control that occurred spontaneously or as a result of treatment. The ACQ-5 has 5 questions on the asthma symptoms experienced by participants during the past week and to respond on a 7-point scale for each question (0 = no impairment, 6 = maximum impairment). The ACQ-5 score is the mean of the 5 questions and total score ranged from 0 (totally controlled) to 6 (severely uncontrolled), a high score indicates low asthma control. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT population. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 2, 4, 6, 8, 10, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	31	63	61
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2, (n = 30,30,63,61)	-0.25 (± 0.78)	-0.74 (± 0.62)	-0.17 (± 0.62)	-0.37 (± 0.79)
Week 4, (n = 30,31,62,59)	-0.40 (± 0.96)	-0.94 (± 0.64)	-0.23 (± 0.79)	-0.57 (± 0.77)
Week 6, (n = 28,30,60,57)	-0.26 (± 0.99)	-0.97 (± 0.74)	-0.38 (± 0.75)	-0.57 (± 0.83)
Week 8, (n = 30,28,63,52)	-0.56 (± 1.04)	-0.91 (± 0.80)	-0.19 (± 0.94)	-0.72 (± 0.73)
Week 10, (n = 28,27,55,56)	-0.42 (± 1.11)	-0.92 (± 0.89)	-0.33 (± 0.90)	-0.75 (± 0.81)
Week 12, (n = 28,28,60,49)	-0.34 (± 1.02)	-0.89 (± 0.93)	-0.22 (± 1.03)	-0.82 (± 0.72)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Self-Administered Score

End point title	Change From Baseline in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Self-Administered Score
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End point description:

The AQLQ (S) was a self-administered participant reported outcome (PRO) to measure the functional impairments in adult and adolescent participants. The instrument comprised of 32 items each rated on a 7-point Likert scales from 1 to 7. The AQLQ (S) has 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), and environmental stimuli (4 items). The score of each domain was the mean of response to each of the questions in that domain. The overall global score was calculated as the average of the 32 questions and ranges from 1 (total impairment) to 7 (no impairment). Higher scores indicate better quality of life. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT population. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 4, 8, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	31	65	60
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4, (n = 29,31,65,60)	-0.03 (± 1.35)	0.73 (± 0.93)	0.19 (± 0.72)	0.19 (± 0.89)
Week 8, (n = 30,31,65,58)	0.22 (± 1.06)	0.90 (± 0.85)	0.30 (± 0.86)	0.29 (± 0.74)
Week 12, (n = 29,29,62,53)	0.29 (± 1.15)	0.84 (± 0.99)	0.26 (± 0.90)	0.46 (± 0.86)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Daytime Symptom Diary (ADSD) Score

End point title	Change From Baseline in Asthma Daytime Symptom Diary (ADSD) Score
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End point description:

ADSD assesses asthma severity based on participant self-report of asthma core symptoms, i.e., difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough. Participants were asked to complete ADSD every night before they go to bed, thinking about their asthma symptoms today, from when they got up this morning until now. ADSD is composed of 6 items rated using an 11-point numeric pain scale (NRS) that ranges from 0 = None to 10 = as bad as you can imagine. Total score was calculated by averaging all 6 items and the score ranged from 0 to 10. Higher scores indicated worse outcomes. The baseline is defined as available value on latest date up to randomization date or first double-blind study treatment date whichever occurs earlier. mITT population. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	64	59
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1, (n = 29,28,64,59)	-0.11 (± 0.71)	-0.18 (± 0.60)	-0.08 (± 0.58)	-0.25 (± 0.85)
Week 2, (n = 29,28,63,59)	-0.30 (± 0.84)	-0.25 (± 0.81)	-0.21 (± 0.95)	-0.31 (± 0.93)
Week 3, (n = 28,28,63,58)	-0.28 (± 0.90)	-0.36 (± 0.80)	-0.20 (± 1.09)	-0.38 (± 0.95)
Week 4, (n = 28,28,63,57)	-0.25 (± 0.98)	-0.37 (± 0.77)	-0.24 (± 1.03)	-0.40 (± 0.96)
Week 5, (n = 27,28,63,56)	-0.34 (± 0.84)	-0.26 (± 0.81)	-0.30 (± 1.11)	-0.47 (± 1.31)
Week 6, (n = 27,28,62,56)	-0.42 (± 0.84)	-0.30 (± 0.90)	-0.26 (± 1.18)	-0.53 (± 1.30)
Week 7, (n = 27,28,60,55)	-0.56 (± 0.94)	-0.33 (± 0.98)	-0.31 (± 1.26)	-0.40 (± 1.68)
Week 8, (n = 27,28,60,55)	-0.58 (± 0.89)	-0.24 (± 0.99)	-0.25 (± 1.34)	-0.41 (± 1.64)
Week 9, (n = 27,27,58,54)	-0.43 (± 0.89)	-0.35 (± 1.15)	-0.17 (± 1.45)	-0.40 (± 1.67)

Week 10, (n = 27,27,57,53)	-0.13 (± 1.31)	-0.38 (± 1.12)	-0.20 (± 1.50)	-0.49 (± 1.72)
Week 11, (n = 27,26,57,51)	-0.04 (± 1.28)	-0.33 (± 1.14)	-0.12 (± 1.61)	-0.52 (± 1.79)
Week 12, (n = 26,24,54,48)	0.02 (± 1.25)	-0.24 (± 1.15)	-0.02 (± 1.82)	-0.63 (± 1.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Night Time Symptom Diary (ANSD) Score

End point title	Change From Baseline in Asthma Night Time Symptom Diary (ANSD) Score
End point description:	
ANSD is a PRO measure designed to measure asthma symptoms in adult and adolescent participants diagnosed with mild to severe asthma. ANSD assesses asthma severity based on participant self-report of asthma core symptoms, i.e., difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough. Participants were asked to complete ANSD when getting up, thinking about their asthma symptoms last night from when they went to bed until now. ANSD is composed of 6 items rated using an 11-point NRS that ranges from 0 (None) to 10 (as bad as you can imagine). Total score was calculated by averaging all 6 items and therefore the score ranged from 0 to 10. Higher scores indicated worse outcomes. The baseline is defined as available value on latest date up to randomization date or first double-blind study treatment date whichever occurs earlier. The mITT population. Only n=number of participants with data collected at specified times for specified categories are reported.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12	

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	64	61
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1, (n = 29,28,64,61)	-0.10 (± 0.63)	-0.26 (± 0.55)	-0.17 (± 0.59)	-0.36 (± 0.86)
Week 2, (n = 29,28,64,61)	-0.28 (± 0.70)	-0.35 (± 0.73)	-0.22 (± 0.95)	-0.35 (± 0.93)
Week 3, (n = 28,28,63,61)	-0.18 (± 0.79)	-0.44 (± 0.73)	-0.22 (± 1.01)	-0.43 (± 0.95)
Week 4, (n = 28,28,64,59)	-0.27 (± 0.91)	-0.46 (± 0.79)	-0.29 (± 1.01)	-0.52 (± 1.01)
Week 5, (n = 27,28,63,59)	-0.32 (± 0.72)	-0.31 (± 0.75)	-0.33 (± 1.08)	-0.50 (± 1.28)
Week 6, (n = 27,28,63,59)	-0.36 (± 0.79)	-0.43 (± 0.82)	-0.25 (± 1.14)	-0.47 (± 1.29)
Week 7, (n = 28,28,60,57)	-0.47 (± 0.84)	-0.35 (± 0.94)	-0.30 (± 1.28)	-0.47 (± 1.57)
Week 8, (n = 27,28,59,57)	-0.53 (± 0.80)	-0.27 (± 0.94)	-0.28 (± 1.30)	-0.45 (± 1.46)
Week 9, (n = 27,27,58,57)	-0.35 (± 0.98)	-0.37 (± 1.10)	-0.18 (± 1.40)	-0.48 (± 1.46)
Week 10, (n = 27,27,58,56)	-0.02 (± 1.41)	-0.40 (± 1.07)	-0.22 (± 1.43)	-0.55 (± 1.56)
Week 11, (n = 27,26,57,53)	0.07 (± 1.41)	-0.32 (± 1.10)	-0.07 (± 1.59)	-0.62 (± 1.69)
Week 12, (n = 26,25,57,50)	0.14 (± 1.40)	-0.42 (± 1.13)	0.00 (± 1.71)	-0.68 (± 1.74)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Rilzabrutinib Over Time

End point title	Plasma Concentrations of Rilzabrutinib Over Time ^[1]
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End point description:

Plasma samples were obtained and analyzed at specified timepoints for pharmacokinetic (PK) characterization of rilzabrutinib. PK population included all randomized and treated participants with at least 1 post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Pre-dose Day 1, Weeks 2, 4, 8 and 12; 2 hour post-dose Day 1, Weeks 4, and 8

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only PK population included all randomized and treated participants treated with Rilzabrutinib with at least 1 post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Only n=number of participants with data collected at specified times for specified categories are reported.

End point values	Rilzabrutinib 400 mg BID	Rilzabrutinib 400 mg TID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	63		
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Pre-dose: Day 1, (n = 30,63)	0.07 (± 0.39)	0.05 (± 0.43)		
Post-dose: 2-hour, Day 1, (n = 28,61)	147.06 (± 127.52)	140.78 (± 128.23)		
Pre-dose: Week 2, (n = 29,61)	26.09 (± 75.62)	45.15 (± 104.23)		
Pre-dose: Week 4, (n = 27,58)	8.03 (± 23.74)	23.19 (± 58.40)		
Post-dose: 2-hour, Week 4, (n = 23,58)	215.50 (± 203.33)	197.25 (± 206.39)		
Pre-dose: Week 8, (n = 23,47)	16.01 (± 46.49)	17.31 (± 45.96)		
Post-dose: 2-hour, Week 8, (n = 22,45)	162.14 (± 148.20)	181.16 (± 176.80)		
Pre-dose: Week 12, (n = 7,23)	14.06 (± 11.64)	16.55 (± 48.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)
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End point description:

Adverse event (AE): any untoward medical occurrence in participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. TEAEs: AEs that developed or worsened or became serious during treatment-emergent period, defined as time from first administration of study treatment (on 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. Safety population included all randomized participants who took at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

From first dose of study treatment (Day 1) up to last dose of study treatment + 7 days, approximately 91 days

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	68	64
Units: participants				
TEAEs	20	14	18	26
TESAEs	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Numbers of Inhalations/day of Albuterol or Levalbuterol for Symptom Relief

End point title	Change From Baseline in Numbers of Inhalations/day of Albuterol or Levalbuterol for Symptom Relief
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End point description:

The number of albuterol or levalbuterol inhalations were recorded daily by the participants in the electronic diary. A diary day is defined as the period beginning with an evening diary and ending with the following day's morning Diary. A diary day was not included in the calculation if an evening or morning diary is missing. The reliever medication baseline value was the average number of puffs taken in the most recent 7 diary days before next visit. The baseline is defined as the available value on the latest date up to the randomization date or the first double-blind study treatment date whichever occurs earlier. The mITT included all randomized participants who received at least 1 dose of study treatment analyzed according to the treatment group allocated by randomization. Only n=number of participants with data collected at specified times for specified categories are reported.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

End point values	Placebo BID	Rilzabrutinib 400 mg BID	Placebo TID	Rilzabrutinib 400 mg TID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	67	62
Units: inhalation per day				
arithmetic mean (standard deviation)				
Week 1, (n = 32,32,67,62)	-0.50 (± 1.03)	-0.41 (± 1.03)	-0.16 (± 1.45)	-0.22 (± 0.68)
Week 2, (n = 32,31,67,62)	-0.61 (± 1.34)	-0.68 (± 1.24)	-0.24 (± 1.38)	-0.26 (± 0.89)
Week 3, (n = 31,31,67,60)	-0.24 (± 1.98)	-0.83 (± 1.48)	-0.26 (± 1.42)	-0.10 (± 0.92)
Week 4, (n = 31,30,67,58)	-0.28 (± 2.14)	-0.81 (± 1.41)	-0.26 (± 1.46)	-0.18 (± 1.00)
Week 5, (n = 30,31,67,57)	-0.39 (± 1.97)	-0.51 (± 1.14)	-0.26 (± 1.49)	-0.11 (± 1.11)
Week 6, (n = 30,31,66,57)	-0.15 (± 1.94)	-0.61 (± 1.44)	-0.26 (± 1.49)	-0.18 (± 1.36)
Week 7, (n = 30,31,64,56)	-0.63 (± 2.16)	-0.00 (± 3.35)	-0.01 (± 0.99)	0.32 (± 3.61)
Week 8, (n = 30,30,62,56)	-0.68 (± 2.34)	-0.01 (± 3.76)	0.05 (± 1.40)	0.21 (± 3.60)
Week 9, (n = 30,29,61,55)	-0.57 (± 2.40)	-0.07 (± 3.96)	0.07 (± 1.40)	0.08 (± 3.66)
Week 10, (n = 29,29,61,54)	-0.25 (± 2.97)	-0.23 (± 3.88)	0.13 (± 1.48)	0.06 (± 3.74)
Week 11, (n = 30,27,60,53)	0.09 (± 3.30)	-0.10 (± 3.99)	0.47 (± 2.00)	0.09 (± 3.76)
Week 12, (n = 28,26,56,49)	0.16 (± 3.31)	0.26 (± 3.85)	1.48 (± 5.47)	0.16 (± 3.92)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and all-cause mortality (death) were collected from first dose of study drug (Day 1) up to last dose of study treatment + 7 days, approximately 91 days.

Adverse event reporting additional description:

Analysis was performed on safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Placebo BID
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Reporting group description:

Participants were administered placebo orally BID on Day 1 for 12 weeks, added to background therapy of ICS/LABA fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

Reporting group title	Placebo TID
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Reporting group description:

Participants were administered placebo orally TID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

Reporting group title	Rilzabrutinib 400mg TID
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Reporting group description:

Participants were administered rilzabrutinib 400 mg orally TID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

Reporting group title	Rilzabrutinib 400mg BID
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Reporting group description:

Participants were administered rilzabrutinib 400 mg orally BID on Day 1 for 12 weeks added to background therapy of ICS/LABA, fluticasone/salmeterol combination therapy at stable dose for 4 weeks. Salmeterol was withdrawn at Week 4; fluticasone was administered up to Week 9 and gradually withdrawn from Week 6.

Serious adverse events	Placebo BID	Placebo TID	Rilzabrutinib 400mg TID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 68 (0.00%)	0 / 64 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 32 (0.00%)	0 / 68 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rilzabrutinib 400mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo BID	Placebo TID	Rilzabrutinib 400mg TID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 32 (37.50%)	4 / 68 (5.88%)	12 / 64 (18.75%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 32 (12.50%)	1 / 68 (1.47%)	0 / 64 (0.00%)
occurrences (all)	8	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 68 (0.00%)	7 / 64 (10.94%)
occurrences (all)	1	0	7
Respiratory, thoracic and mediastinal disorders			
Rhinitis Allergic			
subjects affected / exposed	3 / 32 (9.38%)	0 / 68 (0.00%)	3 / 64 (4.69%)
occurrences (all)	3	0	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 32 (12.50%)	1 / 68 (1.47%)	0 / 64 (0.00%)
occurrences (all)	4	1	0

Covid-19 subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	2 / 68 (2.94%) 2	3 / 64 (4.69%) 3
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Non-serious adverse events	Rilzabrutinib 400mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Rhinitis Allergic			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Covid-19			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2022	This amendment was to evaluate the efficacy and safety of 2 different dose of regimens of rilzabrutinib, the current dose of 400 mg BID and an additional higher regimen of 400 mg TID in two staggered double-blind cohorts for a total number of 192 participants split. There were some editorial changes for better clarification and consistency.
13 September 2022	To update exclusion and inclusion criteria. Other minor clarifications and corrections deemed necessary by the Sponsor were also implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported