Rilzabrutinib for patients with moderate-to-severe asthma with uncontrolled symptoms: a double-blind, placebo-controlled, phase 2 study

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Summary

Background Uncontrolled symptomatic asthma is a substantial challenge for patients despite optimised treatment. Bruton's tyrosine kinase (BTK) plays a key part in immune cell signalling involved in airway inflammation, and its inhibition might improve asthma control. We aimed to explore the effects of BTK inhibition by oral rilzabrutinib on asthma control as well as safety in participants with moderate-to-severe asthma with uncontrolled symptoms.

Methods This double-blind, placebo-controlled, phase 2 study, which was done at 48 centres across 13 countries, enrolled people aged 18–70 years with physician-diagnosed moderate-to-severe asthma for at least 12 months with uncontrolled symptoms on inhaled glucocorticoids plus a long-acting β_2-adrenergic agonist. In two staggered cohorts, participants were randomly assigned (1:1) to rilzabrutinib 800 mg per day orally or matching placebo (low-dose cohort), and rilzabrutinib 1200 mg per day or matching placebo (high-dose cohort), with background therapy gradually withdrawn by weeks 4–9 and resumed at week 12. The primary endpoint was the proportion of participants with a loss-of-asthma-control (LOAC) event during treatment and was assessed in the modified intention-to-treat population, which included all randomly assigned participants who received at least one dose of study drug. A key secondary endpoint was asthma control assessed by the 5-item Asthma Control Questionnaire in the modified intention-to-treat population. Safety was assessed in all randomly assigned participants who received at least one dose of study drug. The trial was registered on ClinicalTrials.gov, NCT05104892.

Findings 310 participants were screened for eligibility, with 196 (122 female and 74 male) randomly assigned in the low-dose cohort between Jan 6, 2022, and Feb 22, 2023 (32 to rilzabrutinib 800 mg per day and 32 to placebo) and randomly assigned in the high-dose cohort between Feb 23 and Nov 14, 2023 (64 to rilzabrutinib 1200 mg per day and 68 to placebo). Over 12 weeks, LOAC events occurred in 12 (38%) participants with rilzabrutinib 800 mg per day versus 16 (50%) with placebo (relative risk reduction 25%; absolute risk difference 12·3%; odds ratio 0·57 [95% CI 0·20–1·61], p=0·29); and 12 (19%) with 1200 mg per day versus 20 (29%) with placebo (relative risk reduction 36%; absolute risk difference 8·8%; 0·58 [0·25–1·35], p=0·21). Asthma control improvements were observed as early as week 2 with rilzabrutinib compared with placebo and sustained up to week 12 without background therapy (least-squares mean difference –0·59 [95% CI –1·07 to –0·10], p=0·018, for the 800 mg per day group; –0·54 [–0·86 to –0·21], p=0·0013, for the 1200 mg per day group). The most frequent adverse event with rilzabrutinib was diarrhoea. No increase in infections was observed with either dose of rilzabrutinib.

Interpretation BTK inhibition with rilzabrutinib was associated with a numerical decrease in LOAC events that was not statistically significant. However, continued meaningful asthma symptom improvements over 12 weeks were observed, despite background therapy withdrawal, potentially identifying a novel mechanism to treat uncontrolled symptomatic asthma.

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See Comment page 377

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Introduction

Asthma is a highly prevalent, chronic condition characterised by airway inflammation, airway hyperresponsiveness, and associated symptoms.[1] The condition affects 262 million individuals globally and is associated with reduced quality of life (QOL), exacerbations, and progressive disability due to persistent airflow limitation.[1–5] Poor control of symptoms despite optimal therapy is a major component of uncontrolled asthma, and control of symptoms is a key goal of asthma management.[1] Indeed, the proportion of uncontrolled asthma in the population of adults with asthma has been reported to range from 45% to 64% despite the use of inhaled corticosteroids and long-acting β_2-adrenergic agonists (LABAs).[5–7] Several biologic therapies are recommended as add-on treatments for individuals with severe uncontrolled asthma.[1,8] Although

Research in context

Evidence before this study

As one of the most prevalent chronic respiratory diseases, asthma affects millions globally. Despite adherence to standard-of-care treatment, a substantial number of patients with asthma have uncontrolled symptoms, leading to a significant disease burden and diminished quality of life. Approved biologics for patients with moderate-to-severe uncontrolled asthma primarily target type 2 inflammation. Although these therapies have shown significant benefit in improving lung function and reducing exacerbations in this population, they might have less effect on symptom control, and their effects are mainly seen in patients with evidence of type 2 inflammation. The optimal strategies for addressing the heterogeneity of asthma, particularly in patients with mixed inflammation who show only partial response to current targeted therapies, remain unclear. Our PubMed search on June 23, 2025, using the term "uncontrolled moderate-to-severe asthma" from Jan 1, 2020, onward, filtered for clinical trials published in English, identified 18 studies focused mainly on biological treatment. Although these studies confirm that the benefits of biologics have changed the landscape of asthma and how it is managed, there are still significant limitations with approved treatments, and there is an unmet need for oral treatments, treatments with a rapid onset, and treatments to address symptom control and varying inflammatory phenotypes in patients with asthma.

Added value of this study

This phase 2 study shows the potential of rilzabrutinib, a novel, oral, reversible Bruton's tyrosine kinase (BTK) inhibitor, as a therapeutic option for moderate-to-severe asthma with uncontrolled symptoms. In preclinical assessments, rilzabrutinib inhibited B cell receptor-mediated activation in B cells from whole blood, inhibited IgE-mediated degranulation in basophils and mast cells, and inhibited oxidative stress and adhesion molecules induced by IL-5 in isolated human eosinophils. Our findings show that rilzabrutinib 800 mg per day and 1200 mg per day led to a numerical but non-significant reduction in loss-of-asthma-control (LOAC) events, lowered asthma burden as measured by the 5-item Asthma Control Questionnaire (ACQ-5), and improved asthma-related quality of life in patients with moderate-to-severe asthma with uncontrolled symptoms. Notably, these improvements were observed across all biomarker and disease characteristic subgroups, suggesting a treatment effect in patients with type 2-low and type 2-high asthma. Moreover, rilzabrutinib was well tolerated over 12 weeks of treatment, with no evidence of cytopenia or an increase in infections.

Implications of all the available evidence

This study provides evidence that rilzabrutinib could be a new therapeutic avenue for individuals with moderate-to-severe asthma with uncontrolled symptoms, offering a potential solution to the suboptimal response to available therapies, particularly for patients with high symptom burden or non-type 2 inflammatory phenotypes. Larger and longer-term studies are required to further evaluate rilzabrutinib as a novel, first-in-class oral BTK inhibitor for uncontrolled symptomatic asthma.

biologics are effective in improving lung function and reducing exacerbations, not all are associated with clinically relevant improvement in asthma symptom control or are effective in a subgroup of patients with low biomarkers of type 2 airway inflammation. They are generally used for patients with severe asthma, who constitute a small proportion of the total population of patients with asthma.[9–11] Suboptimal response to available therapies could be explained by the complexity and heterogeneity of asthma pathophysiology, type of treatment, associated comorbidities, and varying inflammatory phenotypes in individuals with asthma. However, there is a need to identify novel treatment targets, especially in patients with high symptom burden, those with a non-type 2 inflammatory phenotype, and those who prefer not to take injectable treatments.[6,7,12–14]

See Online for appendix

Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase, plays a key part in signalling in immune cells involved in airway inflammation, including mast cells, B cells, basophils, eosinophils, and neutrophils.[15–18] Inhibition of BTK has been shown to reduce pathogenic IgE production, allergen-mediated or IgE-mediated bronchoconstriction, and inflammatory cell infiltration in both in vitro and in vivo models of asthma, allergy, and respiratory inflammation.[18–22] Rilzabrutinib (SAR444671), which is a novel, investigational, oral, reversible BTK inhibitor optimised for safety and efficacy by tailored covalency with non-covalent and covalent binding regions, enables binding with high potency and long residence time to BTK while also limiting binding to off-target kinases.[23] In preclinical assessments, rilzabrutinib inhibited B cell receptor-mediated activation in B cells from whole blood, inhibited IgE-mediated degranulation in basophils and mast cells, and inhibited oxidative stress and adhesion molecules induced by IL-5 and lipopolysaccharides in isolated human eosinophils (appendix p 28).[23,24] Therefore, rilzabrutinib has the potential to suppress inflammatory features, airway dysfunction, and associated symptoms in patients with type 2 and non-type 2 asthma. We report on the effects of BTK inhibition through oral rilzabrutinib on asthma control as well as safety in participants with moderate-to-severe asthma with uncontrolled symptoms.

Methods

Study design and participants

This double-blind, placebo-controlled, phase 2 study was done in 13 countries across 48 active centres that

screened at least one participant, 42 of which randomly assigned at least one participant (appendix pp 2–5). The rilzabrutinib dose regimens selected for this study were based on results from the BTK target occupancy of rilzabrutinib as well as clinical studies.[25,26] The initial study protocol included only one cohort evaluating the 800 mg per day dose versus placebo. The 800 mg per day dose is the approved regimen for immune thrombocytopenia, a mainly B cell-driven disease. Because the pathophysiology of asthma involves several immune cells, including mast cells, basophils, and eosinophils in addition to B cells, a higher dose was thought to be needed to ensure sufficient inhibition of immune cells other than B cells. Therefore, the 1200 mg per day dose regimen was added at a later timepoint as the second cohort. This trial comprised a 4-week screening period, a 12-week treatment period that included withdrawal of background controller therapy, and a 4-week follow-up period (appendix p 29).

Key inclusion criteria included age 18–70 years; BMI 17·5–40·0 kg/m²; physician-diagnosed asthma for at least 12 months based on the Global Initiative for Asthma guidelines (2019–21); current treatment with moderate-dose or high-dose inhaled glucocorticoids in combination with a LABA; at least one asthma exacerbation treated with glucocorticoids, hospitalisation, or emergency medical care in the previous 2 years; FEV_1 of 50% or higher of the predicted normal at baseline; and meeting reversibility criteria (≥12% and 200 mL increase in FEV_1 after treatment with a short-acting β_2-adrenergic agonist [SABA]). The full eligibility criteria are listed in the appendix (pp 6–16).

This study was conducted in accordance with the protocol (appendix pp 37–169), with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, and approved by institutional review boards and independent ethics committees at each study centre. Written informed consent was obtained from all participants before study initiation. The protocol amendments can be found in the appendix (pp 169–188). The trial was registered on ClinicalTrials.gov, NCT05104892.

Randomisation and masking

Eligible participants were stratified by IgE concentrations and by region at screening and were randomly assigned (1:1) to either oral rilzabrutinib or matching placebo in two staggered dose regimens added to a background therapy of medium-dose to high-dose inhaled glucocorticoids plus a LABA standardised at screening. The randomised intervention list was generated centrally by the sponsor, and randomisation and study treatment allocation were performed centrally by an interactive response technology, using block randomisation with a block size of four. The investigators, other staff members, and the participants remained masked during the study.

Procedures

The low-dose cohort received rilzabrutinib 800 mg per day administered orally as 400 mg twice daily or matching placebo. The high-dose cohort received rilzabrutinib 1200 mg per day administered orally as 400 mg three times daily or matching placebo.

Both dosing regimen cohorts were evaluated with the same double-blind approach and planned assessments. Efficacy endpoints were evaluated at on-site visits at baseline and at weeks 2, 4, 6, 8, 10, and 12. Safety was assessed continuously throughout the study. At week 4, the LABA background treatment (salmeterol) was withdrawn. The inhaled glucocorticoid background treatment (fluticasone) was then withdrawn in a stepwise dose reduction starting at week 6 and continuing at week 7, week 8, and, in those who were being tapered off high-dose inhaled glucocorticoids, week 9, provided that participants did not have a loss-of-asthma-control (LOAC) event. Therefore, there was no background therapy during week 8 (in those tapered from medium-dose inhaled glucocorticoids) or week 9 (in those tapered from high-dose inhaled glucocorticoids) to week 12. Participants who completed the 12-week treatment period resumed their pre-screening inhaled glucocorticoid–LABA therapy and entered the 4-week safety follow-up period. Participants who had a LOAC event permanently discontinued rilzabrutinib, resumed their pre-screening inhaled glucocorticoid–LABA therapy, and entered the 4-week safety follow-up period. Use of study treatment and background therapy was reported by patients daily via an e-diary.

Outcomes

The primary endpoint was the proportion of participants with a LOAC event during the treatment period, defined as any of the following: a 30% or higher reduction from baseline in morning peak expiratory flow on two consecutive days; six or more additional reliever puffs of salbutamol (also known as albuterol) or levosalbutamol (also known as levalbuterol) in a 24 h period compared with baseline on two consecutive days; an increase in inhaled glucocorticoids that was four times or more higher than the last prescribed inhaled glucocorticoid dose (or ≥50% of the prescribed inhaled glucocorticoid dose at visit 2 if background therapy withdrawal was completed); requiring use of systemic (oral or parenteral) glucocorticoid treatment; or requiring hospitalisation or an emergency room visit for asthma exacerbation.

Secondary endpoints were measures of lung function, asthma symptoms, asthma-related QOL, pharmacokinetics, and safety. Lung function was assessed as pre-bronchodilator FEV_1 change from baseline at end of treatment using Global Lung Function Initiative calculator. Asthma control was assessed by the 5-item Asthma Control Questionnaire (ACQ-5), which consists of five questions on asthma symptoms, with scores

For the **Global Lung Function Initiative calculator** see https://gli-calculator.ersnet.org/

ranging from 0 (well controlled) to 6 (extremely poorly controlled).[27] Asthma symptoms were assessed by the Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) questionnaires (scores range from 1 to 10, with lower scores signifying better control of daytime and nighttime asthma symptoms, respectively). Asthma-related QOL was assessed by the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]; scores range from 1 to 7, with higher scores signifying better QOL). A clinically meaningful response was defined as a change from baseline of –0·5 or lower for ACQ-5 and 0·5 or higher for AQLQ(S). Participants who had clinically meaningful responses were defined as ACQ-5 or AQLQ(S) responders (appendix p 17–19). Change in blood eosinophil counts per μL from baseline to the end of treatment was measured as a part of safety. Prespecified exploratory endpoints included change in fractional exhaled nitric oxide (FeNO), IgE, and IgG from baseline to the end of treatment and nasal brushings at baseline and the end of treatment for exploratory biomarker analysis using RNA sequencing (appendix pp 19–20). Other prespecified analyses included a subgroup analysis based on baseline patient demographics and disease characteristics to assess the homogeneity of the treatment effect on ACQ-5 score change from baseline. There was no adjudication planned for efficacy or safety outcomes.

Safety was assessed by monitoring treatment-emergent adverse events, clinical laboratory assessments, vital signs, electrocardiogram results, and physical examination findings. For safety analyses, adverse events were coded by using the Medical Dictionary for Regulatory Activities (version 26.1).

Statistical analysis

Sample size calculations were performed to ensure accuracy for the estimation of the difference between rilzabrutinib and placebo in the proportions of participants who had a LOAC event. The maximal width of the 95% CI of the difference between rilzabrutinib and placebo was calculated using the Wald method, and 96 participants per analysis group—with 20% in rilzabrutinib and 40% in placebo groups—expected to have a LOAC event provided a precision of 13% for the proportion difference between rilzabrutinib and placebo.

Efficacy analyses were performed in the modified intention-to-treat population, which was defined as all randomly assigned participants who received at least one dose of study drug. The primary analysis was performed using a logistic regression model with treatment, baseline IgE strata, region (Latin America *vs* rest of the world in the low-dose cohort and eastern Europe *vs* rest of the world in the high-dose cohort), and number of asthma exacerbation events within 2 years before screening as covariates. There were no missing data for the primary endpoint of LOAC.

For the secondary efficacy endpoints, which were assessed in the modified intention-to-treat population, the primary analysis for main continuous endpoints used an ANCOVA model with change from baseline to week 12 (end of treatment) as the response variable, and study intervention group, baseline value, and key baseline factors (including stratification factors) as covariates; the binary endpoints were analysed using a logistic regression model, with missing values imputed using a pattern-mixture model with multiple imputation approach (appendix p 200). For participants who experienced LOAC with rescue medications, discontinued due to lack of efficacy or adverse event related to asthma worsening, or started using oral glucocorticoids, the ACQ-5 scores collected after start of the events were set to missing. Missing data were imputed with last observation carried forward. After applying last observation carried forward, other missing values were multiply imputed 40 times. In each imputation, a responder is defined as a participant with change from baseline in ACQ-5 score at week 12 of –0·5 or lower. Estimates were derived from a logistic regression model with intervention, region, baseline IgE strata level, and baseline ACQ-5 score value as covariates in each imputation and then combined by Rubin's rule.

Safety variables, immunoglobulin concentrations, and serum-soluble and plasma-soluble biomarkers were summarised using descriptive statistics (appendix p 212). Safety was assessed in all randomly assigned participants who received at least one dose of study drug.

Analyses were conducted using SAS (version 9.4 or higher). There was no independent data monitoring committee for this study.

Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Participants were enrolled from Jan 6, 2022, to Feb 22, 2023, in the low-dose cohort, and from Feb 23 to Nov 14, 2023, in the high-dose cohort. 310 participants were screened for eligibility, with 196 randomly assigned in a staggered manner first to the low-dose cohort (32 to rilzabrutinib 800 mg per day and 32 to placebo) followed by the high-dose cohort (64 to rilzabrutinib 1200 mg per day and 68 to placebo; figure 1). The number of major protocol deviations was small and balanced across study treatment groups, with no apparent distribution pattern. Baseline demographics were generally balanced across the cohorts. The representativeness of this study population is shown in the appendix (p 22). More participants in the low-dose cohort were treated with high doses of inhaled glucocorticoids plus LABAs and had exacerbations in the previous year than in the high-dose cohort. Type 2 asthma was more prevalent in the low-dose cohort than in the high-dose cohort based

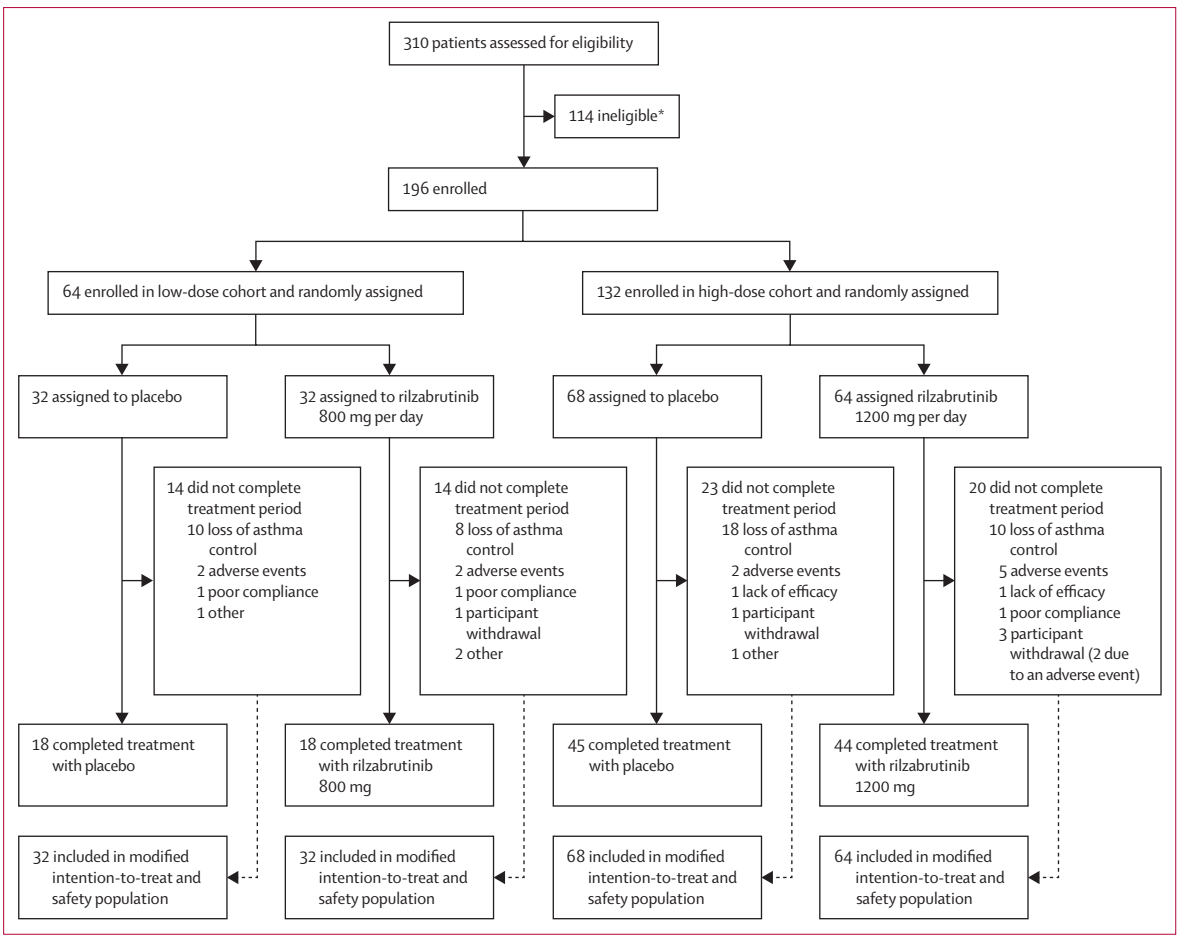

Figure 1: **Trial profile**
*The reasons for ineligibility were mainly related to the exclusion criterion of tuberculosis infection (26 [8%] of 310), inclusion criterion related to reversibility in FEV_1 (17 [5%]), and inclusion criterion related to pre-bronchodilator FEV_1 higher than 40% of the predicted normal at visit 1 (12 [4%]).

on blood eosinophil, IgE, and FeNO levels, as well as a history of atopic conditions (table 1). Despite the minor differences in disease characteristics, the asthma symptom burden, as measured by ACQ-5, was similar across cohorts.

For the primary endpoint, 12 (38%) of 32 participants in the rilzabrutinib 800 mg per day group and 16 (50%) of 32 in the placebo group had a LOAC event over 12 weeks of treatment (odds ratio [OR] 0·57 [95% CI 0·20–1·61]; p=0·29), with a relative risk reduction of 25% (absolute risk difference of 12·3%). The proportion of participants with a LOAC event over 12 weeks of treatment was 12 (19%) of 64 participants in the 1200 mg per day group and 20 (29%) of 68 in the placebo group (OR 0·58 [0·25–1·35]; p=0·21), with a relative risk reduction of 36% (absolute risk difference 8·8%; figure 2A; table 2). The number needed to treat was eight with 800 mg per day and 11 with 1200 mg per day. The reduction in LOAC events was mostly driven by a decrease in the proportion of participants requiring rescue medication (ie, six or more additional reliever puffs of a SABA compared with baseline on two consecutive days). The use of six or more additional reliever puffs was observed in two (6%) participants in the rilzabrutinib 800 mg per day group and four (13%) participants in the placebo group, and in no participants in the rilzabrutinib 1200 mg per day group and seven (10%) participants in the placebo group.

More participants on rilzabrutinib 800 mg per day and 1200 mg per day had a clinically meaningful response in mean ACQ-5 (minimal clinically important difference of ≤–0·5 for ACQ-5) than those in the respective placebo groups. Responder (ACQ-5 decrease of ≤0·5 from baseline) rates at week 12 were 66·1% for rilzabrutinib 800 mg per day and 35·9% for placebo (OR 5·18 [95% CI 1·48–18·15]; p=0·010), with a rate difference of 30·2%, and 59·8% for rilzabrutinib 1200 mg per day and 39·4% for placebo (2·38 [1·09–5·18]; p=0·030), with a rate difference of 20·4% (figure 2B; table 2). Improvement in ACQ-5 scores was observed with rilzabrutinib 800 mg per day compared with placebo as early as week 2 (least squares [LS] mean difference –0·54 [95% CI

	Low-dose cohort		High-dose cohort	
	Placebo (n=32)	Rilzabrutinib 800 mg per day (n=32)	Placebo (n=68)	Rilzabrutinib 1200 mg per day (n=64)
Age, years				
Mean (SD)	50·8 (12·3)	48·0 (13·4)	48·6 (13·7)	48·8 (13·3)
Median (IQR)	53·5 (42·0–61·0)	51·5 (38·5–70·0)	48·5 (40·0–61·0)	50·0 (39·5–62·0)
Sex				
Female	24 (75%)	18 (56%)	41 (60%)	39 (61%)
Male	8 (25%)	14 (44%)	27 (40%)	25 (39%)
Race				
American Indian or Alaska Native	1 (3%)	0	1 (1%)	0
Asian	2 (6%)	2 (6%)	2 (3%)	0
Black or African American	0	0	1 (1%)	0
White	29 (91%)	30 (94%)	64 (94%)	64 (100%)
Ethnicity				
Hispanic or Latino	21 (66%)	24 (75%)	16 (24%)	14 (22%)
Region				
Eastern Europe	4 (13%)	3 (9%)	45 (66%)	43 (67%)
Latin America	25 (78%)	25 (78%)	19 (28%)	19 (30%)
Western countries	1 (3%)	2 (6%)	2 (3%)	2 (3%)
Asia and Pacific region	2 (6%)	2 (6%)	2 (3%)	0
Age at onset of asthma, years	28·1 (16·6)	24·2 (16·4)	28·5 (18·0)	28·7 (16·5)
Duration of asthma, years	23·47 (13·87)	24·89 (14·90)	20·93 (14·00)	21·02 (13·28)
Asthma exacerbations within 2 years before screening				
Mean (SD)	2·3 (1·5)	1·9 (1·0)	1·3 (0·7)	1·5 (0·8)
Median (IQR)	2·0 (1·0–2·5)	2·0 (1·0–2·5)	1·0 (1·0–1·5)	1·0 (1·0–2·0)
Participants with ≥1 asthma exacerbation 1 year before screening	30 (94%)	30 (94%)	49 (72%)	41 (64%)
Inhaled glucocorticoid–LABA dose level				
High	29 (91%)	27 (84%)	33 (49%)	35 (55%)
Medium	3 (9%)	5 (16%)	35 (51%)	29 (45%)
Pre-bronchodilator FEV_1, L	2·16 (0·77)	2·11 (0·67)*	2·42 (0·90)†	2·50 (0·95)‡
Pre-bronchodilator FEV_1, % predicted	71·7% (12·7)	66·4% (10·4)*	76·0% (16·7)	75·7% (16·2)‡
FEV_1 reversibility, %	11·4% (13·2)	12·9% (9·7)	7·1% (8·2)	7·9% (10·1)
History of atopic medical conditions§	17 (53%)	20 (63%)	24 (35%)	21 (33%)
Blood eosinophil count¶, 10^9 cells per L	0·25 (2·26)	0·27 (2·39)	0·18 (2·42)	0·18 (2·17)
≥0·3×10^9 cells per L	13 (41%)	14 (44%)	19 (28%)	18 (28%)
FeNO¶, ppb	26·3 (2·2)*	29·1 (1·9)	18·8 (2·0)‖	18·0 (2·0)**
≥50 ppb	6 (19%)	5 (16%)	4 (6%)	4 (6%)
Total IgE¶, IU/mL	227·9 (4·4)	208·8 (4·1)	126·4 (5·1)	125·8 (7·3)
≥100 IU/mL	21 (66%)	24 (75%)	41 (60%)	41 (64%)
ACQ-5 score	2·19 (0·40)	2·04 (0·37)	2·18 (0·40)	2·24 (0·48)
AQLQ(S) score	4·67 (1·07)*	4·91 (1·04)	4·68 (0·83)†	4·96 (0·71)**
ADSD score				
Mean (SD)	2·40 (1·50)††	1·43 (1·31)‡‡	2·56 (1·81)‖	2·83 (1·88)§§
Median (IQR)	2·2 (1·5–3·1)††	1·04 (0·3–2·3)‡‡	2·3 (1·2–3·6)‖	2·7 (1·2–4·5)§§
ANSD score				
Mean (SD)	2·23 (1·51)††	1·45 (1·30)‡‡	2·55 (1·84)‖	2·80 (1·88)§§
Median (IQR)	2·14 (1·5–2·5)††	0·90 (0·3–2·4)‡‡	2·29 (1·0–3·7)‖	2·61 (1·3–4·5)§§

Data are mean (SD) or n (%) unless otherwise stated. The randomised population includes all participants from the screened population who were randomly assigned to an intervention, regardless of whether they received the intervention. ACQ-5=5-item Asthma Control Questionnaire. ADSD=Asthma Daytime Symptom Diary. ANSD=Asthma Nighttime Symptom Diary. AQLQ(S)=Asthma Quality of Life Questionnaire with Standardized Activities. FeNO=fractional exhaled nitric oxide. LABA=long-acting β_2-adrenergic agonist. NSAID=non-steroidal anti-inflammatory drug. ppb=parts per billion. *n=31. †n=67. ‡n=63. §A participant is considered to have an atopic medical condition if he or she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, hypersensitivity to aspirin or other NSAID, eosinophilic oesophagitis, food allergy, or hives. ¶Data are geometric mean (geometric SD). ‖n=64. **n=62. ††n=29. ‡‡n=28. §§n=60.

Table 1: **Baseline demographics and disease characteristics (randomly assigned population)**

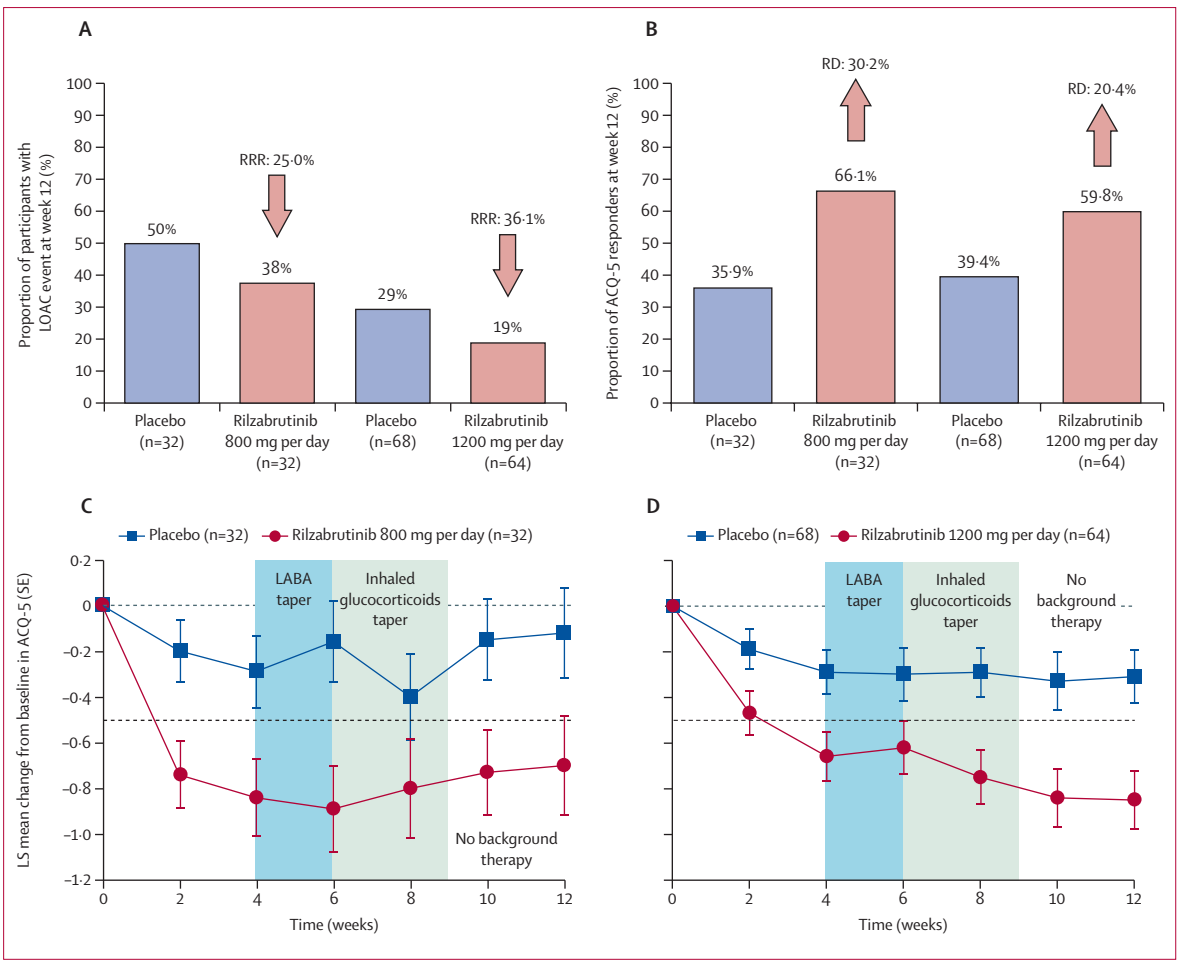

Figure 2: **LOAC events, ACQ-5 over time, and ACQ-5 responders (modified intention-to-treat population)**
(A) Proportion of participants with a LOAC event at week 12. (B) Proportion of ACQ-5 responders at week 12. (C) Change from baseline in ACQ-5 over 12 weeks of treatment with rilzabrutinib 800 mg per day. Data collected up to end-of-treatment visit were included. (D) Change from baseline in ACQ-5 over 12 weeks of treatment with rilzabrutinib 1200 mg per day. Dashed line represents a clinically meaningful response, which was defined as change from baseline in ACQ-5 score of ≤–0·5. The modified intention-to-treat population is defined as all randomly assigned participants who received at least one dose of investigational product analysed according to the treatment group allocated by randomisation. ACQ-5=5-item Asthma Control Questionnaire. LABA=long-acting β_2-adrenergic agonist. LOAC=loss of asthma control. LS=least squares. RD=rate difference. RRR=relative risk reduction.

–0·89 to –0·19]; p=0·0026), with a clinically meaningful difference at week 12 (–0·59 [–1·07 to –0·10]; p=0·018) without background therapy (figure 2C; table 2; appendix pp 23–24). Similarly, with rilzabrutinib 1200 mg per day compared with placebo, improvement in ACQ-5 scores was also observed as early as week 2 (LS mean difference –0·27 [95% CI –0·53 to –0·02]; p=0·033) and maintained at week 12 (–0·54 [–0·86 to –0·21]; p=0·0013) when inhaled glucocorticoids and LABAs had been withdrawn (figure 2D; table 2; appendix pp 23–24). Compared with placebo, rilzabrutinib (combined doses) was associated with improvement in ACQ-5 scores across all baseline demographic and characteristic subgroups analysed, including participants with low type 2 biomarkers (appendix pp 30–32).

Although not significant, there were numerical reductions in daytime symptoms at week 12 as assessed by ADSD with rilzabrutinib 800 mg per day compared with placebo (LS mean difference –0·39 [95% CI –1·03 to 0·26]; p=0·24) and with rilzabrutinib 1200 mg per day compared with placebo (–0·50 [–1·15 to 0·14]; p=0·13). There were also improvements in nighttime symptoms at week 12 as assessed by ANSD with rilzabrutinib 800 mg per day compared with placebo (LS mean difference –0·68 [95% CI –1·33 to –0·03]; p=0·039) and numerical improvements with rilzabrutinib 1200 mg per day that were not significant compared with placebo (–0·54 [–1·13 to 0·06]; p=0·076; table 2).

AQLQ(S) global scores improved from baseline for rilzabrutinib 800 mg per day compared with placebo (LS mean difference 0·84 [95% CI 0·34 to 1·34]; p=0·0010) and for rilzabrutinib 1200 mg per day compared with placebo (0·09 [–0·18 to 0·36]; p=0·49) as early as week 4, which was before withdrawal of background inhaled

	Low-dose cohort					High-dose cohort				
	Placebo (n=32)	Rilzabrutinib 800 mg per day (n=32)	OR or LS mean difference (95% CI)	Relative risk reduction or absolute risk difference	p value	Placebo (n=68)	Rilzabrutinib 1200 mg per day (n=64)	OR or LS mean difference (95% CI)	Relative risk reduction or absolute risk difference	p value
Primary endpoint										
Participants with LOAC event at week 12	16 (50%)	12 (38%)	OR 0·57 (0·20 to 1·61)*	Relative risk reduction 25·0%; absolute risk difference 12·3%	0·29*	20 (29%)	12 (19%)	OR 0·58 (0·25 to 1·35)*	Relative risk reduction 36·1%; absolute risk difference 8·8%	0·21*
Secondary endpoints										
LS mean change from baseline in pre-bronchodilator FEV_1 at week 12, L†	−0·08 (0·08)	−0·07 (0·08)	LS mean difference 0·01 (−0·17 to 0·19)†	..	0·95†	−0·04 (0·05)	−0·13 (0·05)	LS mean difference −0·09 (−0·21 to 0·03)†	..	0·15†
LS mean change from baseline in ACQ-5 score at week 12‡	−0·12 (0·20)	−0·70 (0·22)	LS mean difference −0·59 (−1·07 to −0·10)‡	..	0·018‡	−0·31 (0·12)	−0·85 (0·13)	LS mean difference −0·54 (−0·86 to −0·21)‡	..	0·0013‡
ACQ-5 responders at week 12§	11·5 (35·9%)	21·2 (66·1%)	OR 5·18 (1·48 to 18·15)§	Absolute risk difference 30·2%	0·01§	26·8 (39·4%)	38·3 (59·8%)	OR 2·38 (1·09 to 5·18)§	Absolute risk difference 20·4%	0·03§
LS mean change from baseline in AQLQ(S) score at week 12 (SE)¶	0·10 (0·18)	0·82 (0·20)	LS mean difference 0·72 (0·25 to 1·18)¶	..	0·0025¶	0·28 (0·12)	0·57 (0·12)	LS mean difference 0·29 (−0·01 to 0·60)¶	..	0·062¶
AQLQ(S) responders at week 12‖	10·6 (33·0%)	16·6 (51·7%)	OR 4·89 (1·19 to 20·17)‖	Absolute risk difference 18·7%	0·028‖	26·9 (39·6)	32·9 (51·4%)	OR 2·23 (1·02 to 4·89)‖	Absolute risk difference 11·8%	0·046‖
LS mean change from baseline in ADSD score at week 12**	0·12 (0·26)	−0·27 (0·27)	LS mean difference −0·39 (−1·03 to 0·26)**	..	0·24**	0·08 (0·25)	−0·43 (0·25)	LS mean difference −0·50 (−1·15 to 0·14)**	..	0·13**
LS mean change from baseline in ANSD score at week 12**	0·33 (0·26)	−0·35 (0·28)	LS mean difference −0·68 (−1·33 to −0·03)**	..	0·039**	0·06 (0·23)	−0·48 (0·23)	LS mean difference −0·54 (−1·13 to 0·06)**	..	0·076**

Data are LS mean (SE) or n (%) unless otherwise stated. The modified intention-to-treat population is defined as all randomly assigned participants who received at least one dose of investigational product analysed according to the treatment group allocated by randomisation. ACQ-5=5-item Asthma Control Questionnaire. ADSD=Asthma Daytime Symptom Diary. ANSD=Asthma Nighttime Symptom Diary. AQLQ(S)=Asthma Quality of Life Questionnaire with Standardized Activities. LOAC=loss of asthma control. LS=least squares. *Derived from logistic regression with study intervention group, baseline IgE strata level, region, and number of exacerbation events within 2 years before screening as covariates. †Derived from ANCOVA model with change from baseline value up to week 12 as the response variable, and study intervention group, baseline IgE strata level, region, and baseline pre-bronchodilator FEV_1 as covariates. ‡Derived from ANCOVA model with change from baseline at target week as the response variable, and study intervention group, baseline IgE strata level, region, and baseline ACQ-5 score as covariates. Data collected up to end-of-treatment visit were included. For participants who had LOAC with rescue medications, discontinuation due to lack of efficacy or adverse event related to asthma worsening, or started using oral glucocorticoids, the ACQ-5 scores collected after the start of the events were set to missing. §After applying last observation carried forward, other missing values were multiply imputed 40 times. In each imputation, a responder is defined as a participant with change from baseline in ACQ-5 score at week 12 of ≤−0·5. Estimates were derived from logistic regression model with intervention, region, baseline IgE strata level, and baseline ACQ-5 score value as covariates in each imputation and then combined by Rubin's rule. ¶Derived from ANCOVA model with change from baseline value up to week 12 as the response variable, and study intervention group, baseline IgE strata level, region, and baseline AQLQ(S) score as covariates. For participants who had LOAC with rescue medications, discontinuation due to lack of efficacy or adverse event related to asthma worsening, or started using oral glucocorticoids, the AQLQ(S) scores collected after the start of the events were set to missing. ‖After applying last observation carried forward, other missing values were multiply imputed 40 times. In each imputation, a responder is defined as a participant with change from baseline in AQLQ(S) score at week 12 ≥0·5. Estimates were derived from a logistic regression model with study intervention group, region, baseline IgE strata level, and baseline AQLQ(S) score value as covariates in each imputation and then combined by Rubin's rule. **Derived from ANCOVA model with change from baseline at target week as the response variable, and study intervention group, baseline IgE strata level, region, and baseline ANSD and ADSD scores as covariates. Data collected up to end-of-treatment visit were included. For participants who had LOAC with rescue medications, discontinuation due to lack of efficacy or adverse event related to asthma worsening, or started using oral glucocorticoids, the ANSD and ADSD scores collected after the start of the events were set to missing.

Table 2: **Primary and secondary outcomes (modified intention-to-treat population)**

glucocorticoids and LABAs. However, this did not reach significance for rilzabrutinib 1200 mg per day compared with placebo. After withdrawal of background therapy, improvements in AQLQ(S) global scores were sustained up to week 12 for rilzabrutinib 800 mg per day compared with placebo (LS mean difference 0·72 [95% CI 0·25 to 1·18]; p=0·0025) but remained non-significant for rilzabrutinib 1200 mg per day compared with placebo (0·29 [−0·01 to 0·60]; p=0·062). More participants on rilzabrutinib 800 mg per day and 1200 mg per day had a clinically meaningful response in mean AQLQ(S) than with placebo. Responder rates at week 12 were 51·7% for rilzabrutinib 800 mg per day and 33·0% for placebo (OR 4·89 [95% CI 1·19–20·17]; p=0·028), with a rate difference of 18·7%, and 51·4% for rilzabrutinib 1200 mg per day and 39·6% for placebo (2·23 [1·02–4·89]; p=0·046), with a rate difference of 11·8% (table 2; appendix pp 23–25).

	Low-dose cohort		High-dose cohort	
	Placebo (n=32)	Rilzabrutinib 800 mg per day (n=32)	Placebo (n=68)	Rilzabrutinib 1200 mg per day (n=64)
Treatment-emergent adverse events*†	20 (63%)	14 (44%)	18 (26%)	26 (41%)
Treatment-emergent adverse events >10% in any treatment group‡				
Nasopharyngitis	4 (13%)	0	1 (2%)	0
Headache	4 (13%)	0	1 (2%)	0
Diarrhoea	1 (3%)	3 (9%)	0	7 (11%)
Treatment-emergent adverse events by system organ class*				
Infections and infestations	12 (38%)	2 (6%)	9 (13%)	8 (13%)
Metabolism and nutrition disorders	0	0	1 (2%)	0
Nervous system disorders	4 (13%)	1 (3%)	2 (3%)	1 (2%)
Eye disorders	0	0	1 (2%)	1 (2%)
Vascular disorders	1 (3%)	0	0	0
Respiratory, thoracic, and mediastinal disorders	3 (9%)	3 (9%)	1 (2%)	7 (11%)
Gastrointestinal disorders	5 (16%)	4 (13%)	3 (4%)	13 (20%)
Skin and subcutaneous tissue disorders	0	1 (3%)	1 (2%)	1 (2%)
Musculoskeletal and connective tissue disorders	0	3 (9%)	0	1 (2%)
Renal and urinary disorders	0	0	1 (2%)	0
Investigations	0	2 (6%)	2 (3%)	0
Injury, poisoning, and procedural complications	0	2 (6%)	1 (2%)	0
Treatment-emergent serious adverse events*	0	2 (6%)	0	0
Treatment-emergent adverse events of special interest*§	2 (6%)	1 (3%)	4 (6%)	3 (5%)
Treatment-emergent adverse events leading to treatment discontinuation*	2 (6%)	4 (13%)	3 (4%)	7 (11%)
Eosinophil counts, 10^9 cells per L				
Baseline geometric mean (geometric SD)	0·25 (2·26)	0·27 (2·39)	0·18 (2·42)	0·18 (2·17)
Baseline median (IQR)	0·29 (0·16–0·42)	0·28 (0·14–0·50)	0·17 (0·10–0·32)	0·17 (0·10–0·33)
Week 12 geometric mean (geometric SD)	0·24 (2·29)	0·28 (2·36)	0·17 (2·54)	0·18 (2·25)
Week 12 median (IQR)	0·29 (0·14–0·39)	0·34 (0·13–0·46)	0·18 (0·10–0·30)	0·16 (0·13–0·30)
IgG counts, g/L				
Baseline geometric mean (geometric SD)	12·07 (1·23)	11·63 (1·27)	11·28 (1·24)	11·37 (1·25)
Baseline median (IQR)	12·21 (10·6–13·5)	11·65 (9·7–14·1)	10·99 (9·6–12·9)	11·39 (9·8–13·1)
Week 12 geometric mean (geometric SD)	12·16 (1·22)	11·28 (1·26)	10·91 (1·23)	11·08 (1·22)
Week 12 median (IQR)	12·53 (10·7–13·6)	11·20 (9·4–13·5)	10·55 (9·5–12·7)	11·25 (9·5–12·9)
Neutrophil counts, 10^9 cells per L¶				
Baseline geometric mean (geometric SD)	4·03 (1·42)	3·42 (1·49)	3·42 (1·60)	3·74 (1·45)
Baseline median (IQR)	3·66 (3·2–5·0)	3·52 (2·5–4·4)	3·62 (2·9–4·5)	3·61 (2·8–4·8)
Week 12 geometric mean (geometric SD)	3·80 (1·41)	3·72 (1·45)	3·55 (1·51)	3·80 (1·41)
Week 12 median (IQR)	3·48 (3·0–5·3)	3·98 (2·9–4·7)	3·34 (2·6–4·5)	3·89 (3·0–4·5)

Data are n (%) unless otherwise stated. The safety population is defined as all randomly assigned participants who took at least one dose of study intervention. *The analysis is focused on treatment-emergent adverse events that occurred within last study drug administration plus 7 days. †No treatment-emergent adverse events led to death in either treatment group. ‡Eight headache episodes occurred in four patients in the placebo group of the low-dose cohort, and four diarrhoea episodes occurred in three patients in the rilzabrutinib 800 mg per day group. §Treatment-emergent adverse events of special interest include any of the following: pregnancy, clinically significant alanine aminotransferase elevation, symptomatic overdose with study drug, severe or serious infection, opportunistic infection, tuberculosis or initiation of medications for suspected tuberculosis, active COVID-19 infection, major haemorrhagic events, serious adverse events of cytopenia, or atrial fibrillation. ¶Only participants who had that parameter assessed at baseline or post-baseline are included. Only on-treatment values are included.

***Table 3*: Safety summary (safety population)**

No difference was seen in the change from baseline to week 12 in pre-bronchodilator FEV_1 between rilzabrutinib and placebo (table 2). Additionally, no difference was seen in the change from baseline to week 12 in levels of FeNO, IgE, blood eosinophils, or IgG between rilzabrutinib and placebo (data not shown).

In an RNA sequencing analysis of nasal brushings, rilzabrutinib 1200 mg per day downregulated gene expression in BTK pathways associated with eosinophils, mast cells, basophils, and B cells, including high-affinity IgE receptor (FcεRI) signalling and major histocompatibility complex class I antigen

processing and presentation compared with placebo (appendix p 26). Importantly, there was also a downregulation of asthma-related pathways, including those associated with B-cell activating factor (BAFF), IL-33, granulocyte colony-stimulating factor (G-CSF), and IL-5 (appendix p 27). There was no significant signal observed with the rilzabrutinib 800 mg per day group.

Over 12 weeks, treatment-emergent adverse events occurred in 14 (44%) of 32 participants in the rilzabrutinib 800 mg per day group versus 20 (63%) of 32 participants in the placebo group, and in 26 (41%) of 64 participants in the rilzabrutinib 1200 mg per day group versus 18 (26%) of 68 participants in the placebo group. Infections were the most common treatment-emergent adverse events by system organ class, occurring at a higher incidence with placebo than with rilzabrutinib 800 mg per day (12 [38%] *vs* two [6%]) and placebo vs rilzabrutinib 1200 mg per day (nine [13%] *vs* eight [13%]). Treatment-emergent adverse events with an incidence of higher than 10% were nasopharyngitis and headache, occurring more frequently with placebo than with rilzabrutinib (five [5%] of 100 *vs* none of 96 for each of nasopharyngitis and headache), and diarrhoea, which occurred more frequently with rilzabrutinib than with placebo (ten [10%] of 96 on rilzabrutinib *vs* one [1%] of 100 with placebo). Diarrhoea events were mostly mild, occurred early on, and did not require corrective therapy. Two serious treatment-emergent adverse events, asthma as emergency room visits, occurred with rilzabrutinib 800 mg per day (table 3). No treatment-emergent adverse events of cytopenia, bleeding, or atrial fibrillation were observed, which have been reported with older-generation BTK inhibitors. There were no relevant median or geometric mean decreases from baseline to week 12 in eosinophil and neutrophil counts with rilzabrutinib (table 3; appendix pp 33–34).

Discussion

This exploratory study of rilzabrutinib, an oral BTK inhibitor, for the treatment of asthma showed that doses of 800 mg per day and 1200 mg per day were well tolerated and associated with improvements in asthma control compared with placebo over 12 weeks in participants with moderate-to-severe asthma with uncontrolled symptoms. Despite not reaching statistical significance, rilzabrutinib 800 mg per day and 1200 mg per day were associated with a numerical reduction in LOAC events over 12 weeks compared with placebo. The magnitude of this effect was smaller than what has been seen with biological agents in a similar patient population and study design in which LOAC was the prespecified primary endpoint.[28] Although sample size calculations for this study were based on the effects observed in a similar study,[28] several factors might have affected the observed outcome. These factors include a relatively small sample size (with only 64 participants in the low-dose cohort) and baseline disease characteristics (the high-dose cohort had no or few exacerbations in the past year and low type 2 inflammation). These disease characteristics are likely to have contributed to the lower LOAC rate observed in the high-dose cohort placebo group (29%) than in a study by Wechsler and colleagues (41%).[28] Larger and longer studies are needed to evaluate the effect of rilzabrutinib on LOAC and exacerbations of asthma.

Rilzabrutinib treatment was associated with a greater reduction in ACQ-5 scores over 12 weeks than previously seen with biological agents.[28] This effect was evident before background therapy withdrawal, suggesting an additive benefit beyond those mediated by inhaled glucocorticoids and LABAs. The effect was also observed across all biomarker and disease characteristic subgroups, which is consistent with a treatment effect in patients with type 2-low and type 2-high asthma. The trend for continued improvement in ACQ-5 scores despite background therapy withdrawal was seen with the high dose more than with the low dose, suggesting that the high dose has the potential for better asthma control. Additionally, numerical improvements in symptoms with rilzabrutinib 800 mg per day and 1200 mg per day were observed during both the day and the night, as substantiated by ADSD and ANSD scores. This striking effect of treatment on symptoms provides a potentially important insight into the mechanisms of persistent morbidity in patients uncontrolled on background inhaled therapy and in patients in whom type 2 inflammation is low.

These clinical findings were further supported by rilzabrutinib 1200 mg per day showing a downregulation of gene expression associated with BTK and specific asthma-related pathways in nasal brushings. These results provide evidence of BTK pathway engagement in the nasal epithelium, which can serve as a proxy for bronchial epithelium. By inhibiting a range of inflammatory activities in immune cells, including mast cells, basophils, and eosinophils,[23] rilzabrutinib might be targeting local inflammation and airway smooth muscle cells, potentially improving asthma symptom control, which was seen as early as week 2 in this study. The less specific tyrosine kinase inhibitor, imatinib, has been shown to reduce airway responsiveness in patients with asthma via a mechanism that might involve reduction in mast cell activation.[29] BTK is expressed by mast cells and is involved in mast cell activation;[16] therefore, a similar effect of rilzabrutinib is plausible. In addition, rilzabrutinib reduced disease activity in patients with moderate-to-severe chronic spontaneous urticaria while simultaneously decreasing MRGPRX2, an important mast cell receptor associated with disease activity.[30,31] In the current study, no improvements were observed in lung function, FeNO, IgE, blood eosinophils, or IgG at the end of 12 weeks with rilzabrutinib. It is difficult to predict the long-term effect of rilzabrutinib on these outcomes because of the short study duration, background therapy withdrawal, and enrolment of participants with milder impairment of lung

function at baseline. Further studies are required to assess the longer-term effect of BTK inhibition in asthma.

Although previous generations of BTK inhibitors have been associated with off-target adverse events, rilzabrutinib 800 mg per day and 1200 mg per day were generally safe and well tolerated over 12 weeks of treatment, with no evidence of cytopenia or an increase in infections. Mild diarrhoea was the most frequent treatment-emergent adverse event associated with rilzabrutinib. Data from a pharmacokinetic food effect study indicate a reduction in these events when rilzabrutinib is taken with food. Longer and larger studies are needed to better establish the safety profile. However, the reversible nature of the covalent interaction between rilzabrutinib and BTK is associated with increased selectivity against closely related kinases and might translate into reducing off-target adverse events.[32–34]

This phase 2 study was limited by the small sample size, withdrawal design, staggered cohorts, limited racial diversity, and short 12-week treatment duration. Taken together, these factors limit the generalisability of the results and the ability to evaluate sustained asthma control or demonstrate a dose-related effect on the primary and secondary outcomes. The study design with two staggered cohorts resulted in patients with different disease characteristics being enrolled in each cohort, preventing data pooling. However, several factors might increase our confidence in the importance and clinical relevance of the treatment effect observed. These include replication of the effect of rilzabrutinib in two different cohorts involving diverse type 2-high and type 2-low populations; the magnitude of the effect on symptoms; its consistency across various symptom questionnaires; the different profile of clinical effects compared with biologics; and the presence of an effect before background therapy withdrawal. Additional larger studies are needed to further investigate the efficacy of rilzabrutinib as a novel, first-in-class oral BTK inhibitor for the treatment of uncontrolled symptomatic asthma. These studies should address key outstanding questions, such as the sustained effect of rilzabrutinib on asthma control, reduction of severe exacerbation, and maintenance of lung function, as well as inform on the efficacy across different disease characteristics and biomarker subgroups. Such data would help to define the populations that are most likely to benefit from rilzabrutinib treatment. Notably, rilzabrutinib demonstrated efficacy in terms of secondary outcomes in both cohort 1 (type 2-predominant population with exacerbations) and cohort 2 (less type 2-driven disease, with 30% of patients having no exacerbations in the past year). This broad efficacy profile supports possible clinical trials in a more diverse population than those typically targeted by biologics.

Contributors

JFM, IDP, MEW, WB, TML, and RMM participated in advisory committees or as study investigators. TL, VM, BTS, JG, LM, and RM participated in the design of the study and provided study oversight. JFM and TL verified the underlying data. All authors participated in data acquisition or research execution, or both. TL performed all statistical analyses. All authors participated in the analysis or interpretation of the data, or both, and the drafting and critical review of the manuscript. All authors had full access to the data and provided final approval on all aspects of this publication.

Declaration of interests

JFM is a speaker, an adviser, or a clinical investigator for Sanofi, GSK, AstraZeneca, Insmed, Inmunotek, Teva, Novartis, and Noucor, and has received research grants from Sanofi, GSK, AstraZeneca, Insmed, Inmunotek, Teva, Novartis, and Noucor. IDP has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Aerocrine, Sanofi/Regeneron, Menarini, and GSK; payments for organising educational events from AstraZeneca, GSK, and Sanofi/Regeneron; honoraria for attending advisory panels from Sanofi/Regeneron, AstraZeneca, GSK, Merck, Circassia, Chiesi, and Areteia; and sponsorship to attend international scientific meetings from GSK, AstraZeneca, and Sanofi/Regeneron. MEW has received consulting, advisory, or speaking honoraria from Allakos, Amgen, Areteia Therapeutics, Arrowhead Pharmaceutical, AstraZeneca, Avalo Therapeutics, Celldex, Connect Biopharma, Eli Lilly, Equillium, GSK, Incyte, Kinaset, Kymera, Merck, MyBiometry, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, Recludix Pharma, Regeneron, Roche/Genentech, Sanofi/Genzyme, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Upstream Bio, Verona Pharma, and Zurabio. WB is a consultant for GSK, Sanofi, and Regeneron; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, as well as congress attendance support from GSK, Sanofi, and Regeneron; and receives royalties or licenses from GSK, Sanofi, and Regeneron. TML has served on scientific advisory boards for GSK, Sanofi-Genzyme, Novartis, Eli Lilly, and Regeneron. RMM has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, Berlin-Chemie, Novartis, Roche, and MSD, and payments for organising educational events from AstraZeneca, Chiesi, Berlin-Chemie, and Novartis; honoraria for attending advisory panels from AstraZeneca, Chiesi, Novartis, Roche, MSD, and Bristol Myers Squibb; and sponsorship to attend international scientific meetings from AstraZeneca, Chiesi, and Novartis. TL, VM, BTS, JG, LM, and RM are Sanofi employees and may hold stock or stock options in the company.

Data sharing

Qualified researchers can request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

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