

Original Research

A phase 2 trial of rilzabrutinib in IgG4-related disease

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ABSTRACT

Objectives: The objective of the article is to assess the efficacy and safety of rilzabrutinib, an oral, reversible inhibitor of Bruton's tyrosine kinase, in participants with IgG4-related disease.

Methods: This Phase 2a (NCT04520451) open-label, 52-week study enrolled 2 cohorts of participants with IgG4-related disease: Cohort A (participants who had failed or were intolerant to rituximab) and Cohort B (participants enrolled agnostic to rituximab history). Participants received rilzabrutinib plus a 2-to-4-week glucocorticoid (GC) taper followed by rilzabrutinib alone for up to 52 weeks. Primary endpoints were the proportion of participants without disease flare following first rilzabrutinib dose until the end of treatment and safety.

Results: This study included 27 participants (Cohort A: 13; Cohort B: 14). At the end of treatment, 70.4% (19/27) of participants were flare-free and off GCs/immunosuppressants. Disease activity (mean [SD]), measured by IgG4-related disease Responder Index, decreased by 8.3 (5.8) at week 12 in both cohorts and by 10.7 (6.3) in participants who completed 52 weeks of rilzabrutinib (14/17). Serious treatment-emergent adverse events (TEAEs) occurred in 2 participants, 1 resulting in death, but both events were judged unrelated to the study drug. The most frequent TEAEs were diarrhoea, 40.7% (11/27); coronavirus disease 2019, 18.5% (5/27); and dizziness, 18.5% (5/27).

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Jeeha Choi was with Sanofi at the time of this study.

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Conclusions: Rilzabrutinib had an acceptable safety profile in patients with IgG4-related disease who had failed/ intolerant to rituximab and who were rituximab-naïve. Most participants discontinued GCs successfully without disease flares and exhibited sustained disease activity reduction. Further investigation of this potential alternative to B-cell–depleting therapies is needed in larger, long-term, placebo-controlled trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- IgG4-related disease is a chronic inflammatory condition characterised by B-cell–driven inflammation. Glucocorticoids (GCs) are currently the first-line therapy in IgG4-related disease. However, GCs are associated with short- and long-term toxicity and failure to control the disease during or after GC tapers, leading to the potential for permanent organ damage. Although B-cell–depleting agents are effective, persistent depletion of B cells is a concern. The development of safe GC-sparing options that do not deplete B cells is an important unmet need in IgG4-related disease.

WHAT DOES THIS STUDY ADDS?

- This Phase 2a study is the first clinical trial to evaluate rilzabrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, in people with IgG4-related disease.
- The majority (70%) of participants remained flare-free and off GCs/immunosuppressants at the end of treatment with rilzabrutinib.
- Rilzabrutinib was associated with clinically meaningful and sustained reductions in disease activity with promising results observed in both rituximab-experienced and rituximab-naïve participants.
- Rilzabrutinib was generally well tolerated with an acceptable safety profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

- These data suggest that BTK inhibition with rilzabrutinib has potential as an oral, GC-sparing, non-B-cell–depleting treatment option for IgG4-related disease.
- Efficacy and safety of rilzabrutinib will be further evaluated in larger Phase 3 trials in patients with IgG4-related disease.

INTRODUCTION

IgG4-related disease is a chronic inflammatory condition characterised by tissue infiltration of IgG4-positive plasma cells, immune system activation, tissue fibrosis, and organ dysfunction [1,2]. It is a rare, multiorgan disease, with an estimated prevalence of 5.3 per 100,000 persons in the United States as of 2019 [3,4]. The diagnosis of IgG4-related disease is made by correlating clinical, serological, radiological, and histopathological findings. The American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) has developed and endorsed the IgG4-related disease classification criteria, which are widely used in clinical research studies of the disease [5]. Glucocorticoids (GCs), currently the first-line treatment across most of the world, are efficacious for the induction of remission in active IgG4-related disease. However, disease flares resulting in chronic damage and organ dysfunction are common when GC doses are tapered or discontinued, and GC treatment seldom results in long-term, treatment-free remissions [6]. Moreover, since IgG4-related disease patients are generally middle-aged or older and frequently have comorbidities such as hypertension, glucose intolerance, and obesity, GC treatment is a poor option beyond the short term. Additionally, the substantial

pancreatic injury that often results from IgG4-related disease further complicates the use of GCs in IgG4-related disease [7], underscoring the need for GC-sparing therapies.

B cells play a key role in the pathophysiology of IgG4-related disease. It has been hypothesised that the activation of B cells by follicular helper T cells and the activation of CD4+ cytotoxic T cells in turn by B cells drive the inflammatory and fibrotic manifestations of IgG4-related disease [2,8,9]. Therefore, targeting B cells presents a promising therapeutic option. This hypothesis is supported by the reported efficacy of B-cell depletion in patients with IgG4-related disease. As an example, B-cell–depleting anti-CD20 monoclonal antibodies (rituximab) have been demonstrated to be efficacious in disease control and limiting patients' GC exposure in an open-label study [10,11]. In addition, inebilizumab, an IgG1κ monoclonal antibody targeting CD19+ B cells, was recently approved by the US Food and Drug Administration (FDA) for the treatment of IgG4-related disease [12] based on results of a Phase 3 randomised controlled trial [13]. In that trial, inebilizumab lowered the risk of IgG4-related disease flares and improved the likelihood of achieving a flare-free complete remission at 1 year [13]. However, the persistent depletion of B cells leads to reduced responsiveness to vaccinations, an increased risk of poor outcomes in coronavirus disease (COVID), and an increased risk of infections overall [13–15]. Therefore, novel GC-sparing therapies that modulate B-cell activation without leading to the long-term depletion of those cells represent an important unmet need in IgG4-related disease [16].

Bruton's tyrosine kinase (BTK), a Tec family tyrosine kinase, plays a central role in immune pathways. BTK is expressed in B cells and other haematopoietic cells (eg, macrophages, mast cells, and platelets), but not in T cells. BTK, a key mediator of B-cell receptor signalling, plays an essential role in the maturation, activation, function, and differentiation of B cells and their subsequent production of antibodies. BTK also regulates antibody signalling through the FcγR (Fc-gamma receptor) and FcεR (Fc-epsilon receptor) pathways [17–19]. Given the crucial role played by B cells in the pathophysiology of IgG4-related disease and the central function of BTK in mediating diverse immune pathways, BTK inhibition is a potential therapeutic strategy in IgG4-related disease [16,20].

Rilzabrutinib is an oral, reversible, covalent BTK inhibitor in clinical development for a wide range of immune-mediated diseases such as immune thrombocytopenia (ITP), warm autoimmune haemolytic anaemia, atopic dermatitis, chronic spontaneous urticaria, and pemphigus [17,21–27]. Rilzabrutinib was approved by the FDA in 2025 for ITP [28] and has shown clinically meaningful efficacy and acceptable safety profiles across immune-mediated diseases [23–27]. Inhibition of BTK by rilzabrutinib induces anti-inflammatory effects without causing B-cell depletion or cell death [17,22]. This facilitates the targeting of key immune pathways involved in IgG4-related disease [29] while preserving immune function, unlike B-cell–depleting therapies. The covalent and reversible binding pattern of rilzabrutinib aids in specific target engagement with limited off-target residence time, followed by rapid clearance, reducing the likelihood of off-target effects [17,24]. This Phase

2a, multicentre, open-label, 2-arm, 52-week study was conducted to evaluate the safety and efficacy of daily oral administration of rilzabrutinib in participants with IgG4-related disease.

METHODS

Trial design and oversight

This Phase 2a, open-label, 2-arm, multicentre, international study (NCT04520451) was conducted at 9 sites across 5 countries [30]. Investigators were selected based on their expertise and experience in diagnosing and treating patients with IgG4-related disease. The trial was conducted in full conformance with the Good Clinical Practice (GCP) guidelines outlined in the International Council for Harmonisation Tripartite Guideline GCP E6 and the principles of the Declaration of Helsinki [31]. Written informed consent was obtained from all participants before the initiation of study procedures, according to the regulatory and legal requirements of the participating country. All protocols and amendments were approved by the Institutional Review Board/Institutional Ethics Committee. The study was monitored by an independent data safety committee. No patients or public representatives were involved in the design, conduct, reporting, or dissemination of this study.

Participants

The trial enrolled adult participants (aged ≥ 18 years) who had a clinical diagnosis of IgG4-related disease based on the 2019 ACR/EULAR classification criteria and had an IgG4-related disease Responder Index (RI) of ≥ 2 at screening, with active IgG4-related disease manifestations in at least one organ system, excluding lymph nodes. Participants with retroperitoneal fibrosis, sclerosing mesenteritis, fibrosing mediastinitis, or other overwhelmingly fibrotic expressions of IgG4-related disease as their sole disease manifestations were excluded, as were those requiring > 40 g; 40 mg/d of prednisone. Key eligibility criteria are summarised in [Supplementary Table S1](#).

The trial enrolled 2 cohorts of participants. Cohort A included participants from the US with active IgG4-related disease who were refractory to or unable to tolerate rituximab. Cohort B included participants from Canada, France, Italy, and Spain with active IgG4-related disease. Unlike Cohort A, which specifically enrolled participants refractory or intolerant to rituximab, Cohort B enrolment was not restricted by prior rituximab exposure.

Treatment

In Cohort A, participants were randomly assigned to either an open-label oral rilzabrutinib 400 mg BID (twice daily) plus a 2-to-4-week GC taper, or to a 12-week GC monotherapy taper in a 3:1 ratio. Participants randomised to the 12-week GC taper were eligible to cross over to rilzabrutinib 400 mg BID with a 2-to-4-week GC taper if they met eligibility criteria. Participants in Cohort B were treated with oral rilzabrutinib 400 mg BID concurrently with a 2-to-4-week GC taper. Both cohorts included a 4-week screening period and a follow-up visit 4 weeks after discontinuing the last dose of rilzabrutinib ([Supplementary Fig S1](#)). Prednisone doses ranging from 20 to 40 mg/d were permitted prior to the first dose of rilzabrutinib. Rescue treatment for disease flares was at the discretion of the investigator.

Endpoints

The primary safety endpoints were the nature, frequency, and severity of adverse events (AEs), including serious AEs, AEs leading to discontinuation, and possible GC-related adverse effects. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) was used for the grading of AEs.

The primary efficacy endpoint was the proportion of participants who were without disease flare following the first dose of rilzabrutinib until the end of treatment, which was any time up to 52 weeks in which treatment was discontinued for any reason other than an IgG4-related disease flare. Disease flare was defined as an increase in the total RI activity score of > 2 or the initiation of rescue treatment to treat recurrent disease. The initial protocol stated the primary endpoint as the proportion of participants achieving complete remission (IgG4-related disease RI = 0 at week 12). This was amended later to address a greater unmet medical need than the induction of response ([Supplementary Appendix](#)). The RI total activity score (the sum of individual nonurgent organ/site activity scores plus the sum of each urgent organ/site activity score multiplied by 2) was employed as a measure of disease activity [32]. Because a reduction in RI total activity score by ≥ 2 points was part of the efficacy outcome in an open-label rituximab study by Carruthers et al [11] and reflects clinically important change within an organ system, this value was considered appropriate for this study. To facilitate RI scoring, whole-body computed tomography was required during screening, at week 12, and at the end of treatment to capture asymptomatic occult disease activity.

The secondary efficacy endpoints included the proportion of participants with a reduction in the baseline IgG4-related disease RI activity score by ≥ 2 points; the proportion of participants achieving an IgG4-related disease RI activity score of 0; the change from baseline in the IgG4-related disease RI activity score; the change from baseline in IgG4-related disease damage (as recorded on the damage section of the IgG4-related disease RI); the level and change from baseline in serum IgG4 and IgG concentrations; and the proportion of participants achieving a reduction in serum IgG4 level of 10%.

Statistical analysis

A sample size of 25 participants was considered adequate for assessing safety and providing a reasonable estimation to investigate the treatment effect of rilzabrutinib. The intent-to-treat population and safety populations included all participants who received at least 1 dose of the investigational product. Because some participants were treated initially with GC, the rilzabrutinib-treated population—all participants who received at least 1 dose of rilzabrutinib, including those assigned initially to the 12-week GC taper—was used for efficacy analyses. Analyses were performed separately for Cohort A and Cohort B as well as combined for the Pooled Cohort. The primary and secondary efficacy endpoints were analysed according to the prespecified statistical analysis plan, based on observed data up to the end of treatment, without any imputation. Data from participants who discontinued for reasons other than flare were included up to the point of discontinuation (ie, end of treatment). To complement these analyses, post-hoc exploratory analyses were conducted with the imputation of missing data using last observation carried forward (LOCF) to enhance interpretability of the findings. The proportion of participants meeting the primary endpoint, along with corresponding Wilson score and 95% CI, was summarised. Descriptive statistics were used for all

Table 1
Demographics (ITT population) and disease characteristics at baseline

	Cohort A (N = 13)	Cohort B (N = 14)	Pooled (N = 27)
Age, median (Q1, Q3)	66.0 (52, 75)	57.5 (47, 62)	60.0 (47, 72)
Male sex, n (%)	9 (69.2)	12 (85.7)	21 (77.8)
Weight (kg at baseline), mean (SD)	81.42 (16.19)	81.19 (13.76)	81.30 (14.68)
BMI ^a (kg/m ²), mean (SD)	28.31 (5.80)	26.89 (3.20)	27.57 (4.60)
Race, n (%)			
White	8 (61.5)	5 (35.7)	13 (48.1)
African American	1 (7.7)	0 (0.0)	1 (3.7)
Asian	2 (15.4)	7 (50.0)	9 (33.3)
Other	2 (15.4)	2 (14.3)	4 (14.8)
Ethnicity, n (%)			
Hispanic or Latino	2 (15.4)	0 (0.0)	2 (7.4)
Non-Hispanic or Latino	11 (84.6)	14 (100.0)	25 (92.6)
Disease characteristics, mean (SD)			
Duration since first symptom (y)	5.5 (1.8)	5.1 (2.5)	5.2 (2.2)
Duration of disease (y)	5.8 (2.5)	2.7 (1.8)	4.1 (2.6)
No. of participants treated with rituximab, n (%)	13 (100)	2 (14.3)	15 (55.6)
IgG4 symptom distress index score at Baseline	49.2 (33.8)	38.2 (18.0)	43.7 (27.1)
IgG4-related disease RI: total activity score at baseline	9.1 (5.3)	15.9 (7.0)	12.6 (7.0)
Prior rituximab experience			
Flared on therapy	9 (69.2)	1 (7.1)	10 (37.0)
Unable to taper prednisone	1 (7.7)	0 (0.0)	1 (3.7)
Adverse reaction	3 (23.1)	0 (0.0)	3 (11.1)
Remission	0 (0.0)	1 (7.1)	1 (3.7)
Serum IgG4 level (mg/dL)	503.6 (496.2)	349.8 (289.6)	423.8 (402.1)
Normal range ^b n (%)	3/13 (23.1)	3/14 (21.4)	6/27 (22.2)
>ULN and ≤ 2 × ULN ^b n (%)	0	2/14 (14.3)	2/27 (7.4)
> 2 × ULN and ≤ 5 × ULN ^b n (%)	6/13 (46.2)	5/14 (35.7)	11/27 (40.7)
> 5 × ULN ^b n (%)	4/13 (30.8)	4/14 (28.6)	8/27 (29.6)
Total IgG level (mg/dL)	1553.3 (796.5)	1457.2 (523.8)	1503.5 (657.5)
IgE (IU/mL)	649.7 (965.5)	484.3 (533.4)	563.7 (759.4)
C3 (mg/dL)	108.6 (19.1)	126.5 (29.9)	117.9 (26.4)
C4 (mg/dL)	19.5 (11.4)	25.9 (10.6)	22.9 (11.3)
Number of organs involved n (%)			
2 or 3	4 (30.8)	7 (50.0)	11 (40.7)
4 or 5	6 (46.2)	3 (21.4)	9 (33.3)
≥ 6	3 (23.1)	4 (28.6)	7 (25.9)
Frequencies of organ or tissue involvement			
Salivary glands	9 (69.2)	13 (92.9)	22 (81.5)
Orbits and lacrimal glands	9 (69.2)	9 (64.3)	18 (66.7)
Lymph nodes	7 (53.8)	9 (64.3)	16 (59.3)
ENT	5 (38.5)	5 (35.7)	10 (37.0)
Lungs	5 (38.5)	5 (35.7)	10 (37.0)
Pancreas	5 (38.5)	4 (28.6)	9 (33.3)
Bile duct	4 (30.8)	3 (21.4)	7 (25.9)
Kidney	3 (23.1)	1 (7.1)	4 (14.8)
Skin	1 (7.7)	2 (14.3)	3 (11.1)
Sclerosis/mass formation	2 (15.4)	1 (7.1)	3 (11.1)
Central nervous system	1 (7.7)	1 (7.1)	2 (7.4)
Pituitary gland	0 (0.0)	2 (14.3)	2 (7.4)
Heart/Pericardium	2 (15.4)	0 (0.0)	2 (7.4)
Liver	1 (7.7)	1 (7.1)	2 (7.4)
Thyroid	1 (7.7)	0 (0.0)	1 (3.7)
Retroperitoneum	1 (7.7)	0 (0.0)	1 (3.7)
Mediastinum	0 (0.0)	1 (7.1)	1 (3.7)
Other IgG4-related disease manifestations	1 (7.7)	0 (0.0)	1 (3.7)

BMI, body mass index; C3, complement 3; C4, complement 4; ENT, ear, nose, and throat (otolaryngology); IgE, immunoglobulin E; ITT, intent-to-treat; RI, Responder Index; ULN, upper limit of normal.

^a BMI = (Weight (kg) at baseline)/(Height (m) at baseline).

^b Results from the post-hoc analysis; Baseline was the last measurement reported prior to the first dose of the study intervention.

observed data and change from baseline data. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA v27.0). Any AEs that occurred, worsened, or became serious during the period up to the first dose of the study intervention were listed as pretreatment AEs. In contrast, AEs that occurred >7 days after the last dose of rilzabrutinib were listed as post-treatment AEs. All statistical tests were conducted at the 0.05 significance level using 2-tailed tests and reporting the *P*-values. The corresponding 2-sided 95% CIs were provided for statistical tests, if applicable.

RESULTS

Participants

The study was conducted between August 20, 2020, and October 15, 2024. A total of 35 participants were screened, of whom 27 fulfilled the eligibility criteria and were enrolled. Thirteen participants were included in Cohort A (rilzabrutinib arm, *n* = 10; control arm, *n* = 3) and 14 in Cohort B ([Supplementary Fig S1 and Table 1](#)). All 27 participants received at least 1 dose of

rilzabrutinib, including the 3 participants in Cohort A who were randomised to initial treatment with GC monotherapy. Overall, 14 participants completed the 52-week rilzabrutinib treatment and 13 participants discontinued. The reasons for discontinuation included disease flares ($n = 8$), AEs (3), noncompliance (1), and death (1) (Supplementary Fig S2).

Most of the study participants were male (78%), and the median age at baseline was 60 years, with the youngest being 47. The majority of participants were White. Demographic and disease characteristics reflected some variation between the cohorts. A higher percentage of the participants in Cohort B were Asian, and participants in that cohort had shorter disease duration, higher disease activity score, and lower mean serum IgG4/IgE levels compared with those in Cohort A. The mean period of time since appearance of the first disease symptom was similar between the cohorts (5.2 years) (Table 1). Of the 13 participants in Cohort A, all of whom were rituximab-experienced, 9 had flared after receiving rituximab, 1 was unable to taper off GC after rituximab, and 3 had AEs on rituximab. In Cohort B, among the 2 rituximab-experienced participants, 1 participant had flared after rituximab, and 1 had achieved remission after rituximab but no longer had access to that medication.

Efficacy

Considering both cohorts, 19 of 27 (70.4%) (95% CI: 0.515, 0.841) participants were without disease flare and off GCs or

immunosuppressants at the end of treatment with rilzabrutinib. The proportion of participants in Cohorts A and B who were free of disease flares were 76.9% (95% CI: 0.497, 0.918) and 64.3% (95% CI: 0.388, 0.837), respectively, at the end of treatment with rilzabrutinib (Fig 1A and Table 2). Excluding participants who discontinued for reasons other than flare ($n = 5$) (Supplementary Fig S2), 14/22 (63.6%) (95% CI: 0.430, 0.803) were without disease flare. A prespecified supportive analysis in rilzabrutinib-treated participants who experienced a flare ($n = 8$) showed that the median number of days to first disease flare was 123.5 for pooled population (Fig 1B): 238 days in Cohort A and 115 days in Cohort B (Supplementary Fig S3).

After excluding the 8 participants who flared and the 5 participants who discontinued for reasons other than flare, 13 of the 14 (92.9%; 95% CI: 0.69, 0.99) participants who completed the 52-week study experienced a reduction of ≥ 2 points from their baseline IgG4-related disease RI score. Among the 14 participants who completed week 52, the mean (SD) IgG4-related disease RI reduction was 10.7 (6.3) points with a greater reduction in Cohort B (-15.0 [6.5]) than in Cohort A (-7.5 [3.9]) (Table 2). Reduction in RI total activity score was evident at week 12 with the mean (SD) decline of -8.3 (5.8) and continued to remain low at each subsequent visit (Fig 2). Post-hoc analysis using LOCF imputation indicated that 79.2% (19/24) of participants with both a baseline and post-treatment value experienced a reduction of >2 points from their baseline IgG4-related disease RI score. The overall mean change (SD) was -8.21 (6.86), and a numerically greater

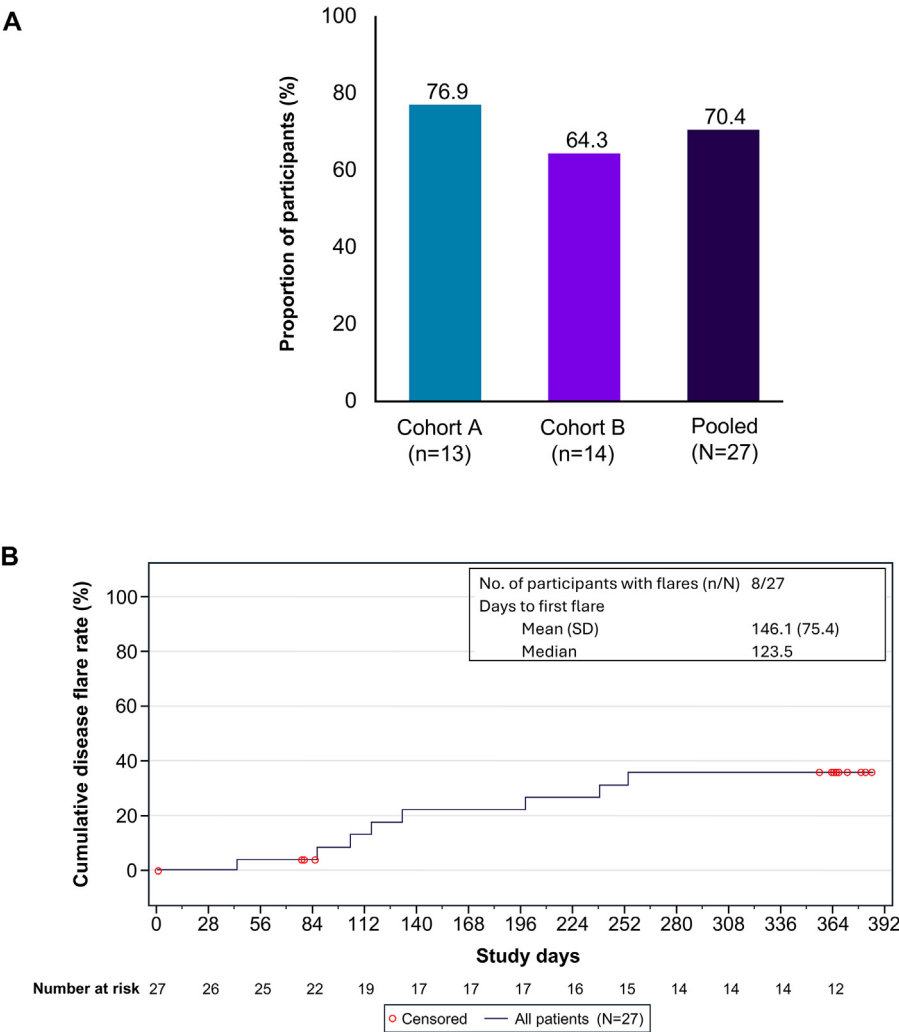


Figure 1. (A) Proportion of participants without IgG4-related disease, disease flare at the end of treatment* (primary efficacy endpoint) and (B) Kaplan-Meier plot illustrating the time to first disease flare (days) for the pooled population. *Disease flare was defined as (i) an increase in IgG4-related disease RI > 2 from the prior assessment between first and last dose of rilzabrutinib or (ii) initiation of rescue therapy between first and last dose of rilzabrutinib or (iii) any end-of-study early termination reason related to the disease under treatment. Participants who did not experience a flare during this period were considered censored at the time of their last rilzabrutinib dose. Days are based on the days from the first dose of rilzabrutinib. The RI is a holistic measure of IgG4-related disease for disease activity which has been validated in a multinational, multispecialty study. It allows an Investigator to characterise disease activity and damage for each individual anatomic domain. For each organ/site, an activity score is assigned: 0 (normal or resolved), 1 (improved but still present), 2 (new or recurrent activity off treatment or unchanged from the previous visit), or 3 (worsened or new disease manifestation despite treatment). RI, Responder Index.

Table 2
Summary of results for the primary and secondary efficacy endpoints (prespecified analysis)

	Cohort A (N = 13)	Cohort B (N = 14)	Pooled (N = 27)
Primary endpoint			
Participants without disease flare ^a and off GCs from the first dose of rilzabrutinib until the end of treatment, % (n/N)	76.9 (10/13)	64.3 (9/14)	70.4 (19/27)
95% CI	0.50, 0.92	0.39, 0.84	0.52, 0.84
Secondary endpoints			
Disease activity at week 52	N = 6	N = 8	N = 14
IgG4-related disease RI score, mean (SD)	3.1 (3.68)	1.7 (1.51)	2.5 (2.95)
Change from baseline in IgG4-related disease RI, mean (SD)	-7.50 (3.93)	-15.00 (6.48)	-10.71 (6.27)
95% CI	-10.78, -4.22	-21.80, -8.20	-14.33, -7.09
Participants with reduction from baseline IgG4-related disease RI ≥ 2, % (n/N)	87.5 (7/8)	100.0 (6/6)	92.9 (13/14)
95% CI	0.53, 0.98	0.61, 1.00	0.69, 0.99
Participants with IgG4-related disease RI = 0, % (n/N)	12.5 (1/8)	16.7 (1/6)	14.3 (2/14)
95% CI	0.02, 0.47	0.03, 0.57	0.04, 0.40
Biomarkers			
Percentage change from baseline in IgG levels at week 52, mean (SD), (n/N)	-31.97 (32.49), (7/13)	-43.23 (26.26), (7/14)	-37.60 (28.96), (14/27)
Participants with reduction in IgG level ≥ 10% at week 52, % (n/N)	75.0 (6/8)	75.0 (6/8)	78.6 (11/14)
95% CI	41, 93	44, 97	52, 92
Percentage change from baseline in IgG levels at week 52, mean (SD), (n/N)	-14.73 (20.20), (7/13)	-10.57 (13.06), (7/14)	-12.65 (16.45), (14/27)

GC, glucocorticoids; RI, Responder Index.
^a A disease was flare defined as (i) increase in IgG4-related disease RI > 2 from the prior assessment between the first and last dose of rilzabrutinib or (ii) initiation of rescue therapy between first and last dose of rilzabrutinib or (iii) any end-of-study early termination reason related to the disease under treatment. Change in RI ≥ 2 is clinically meaningful.

improvement was observed in Cohort B compared with Cohort A (Supplementary Table S2 and Supplementary Fig S4). An IgG4-related disease RI score of 0 was achieved by 2 participants in the pooled population at the end of 52 weeks (Table 2).
The median GC starting dose in Cohort A was equivalent to 20 mg/d of prednisone and 30 mg/d in Cohort B. All rilzabrutinib-treated participants completed the GC taper by week 8 (Supplementary Table S3). None of the 3 participants who started the study on GC monotherapy was able to successfully withdraw from GCs before initiating rilzabrutinib treatment.

Safety

Overall, 23/27 (85.2%) of participants reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs observed in the rilzabrutinib-treated population were diarrhoea (11/27;40.7%), COVID-19 (5/27; 18.5%), dizziness (5/27; 18.5%), dry mouth (4/27; 14.8%), nausea (4/27; 14.8%), haematuria (3/27; 11.1%), and arthralgia (3/27; 11.1%). All of these AEs, summarised in Table 3 and Supplementary Table S4, were mild to moderate in severity.

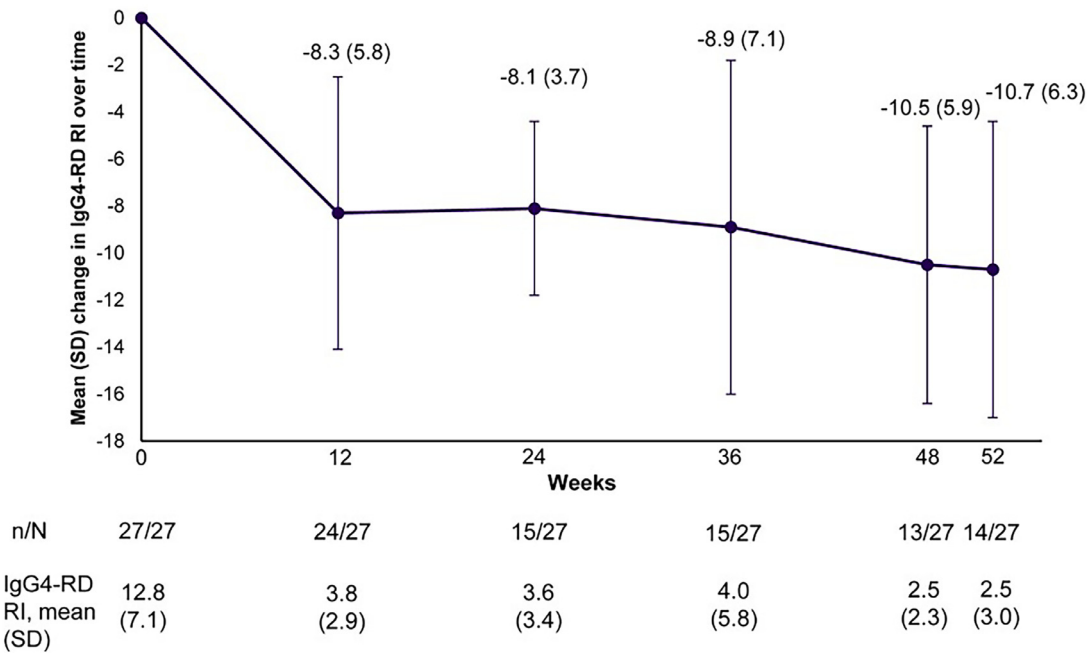


Figure 2. Change in IgG4-related disease RI over time in pooled population. The rilzabrutinib-treated population included participants randomised to the rilzabrutinib arm and control arm participants who crossed over and received at least 1 dose of rilzabrutinib. The main + maintenance treatment period included all data collected from participants who were on rilzabrutinib treatment and received at least 1 dose of rilzabrutinib. IgG4-RD, IgG4-related disease; RI, Responder Index.

Table 3
Summary of adverse events and the most common adverse events reported during the study ($\geq 10\%$)

Summary of adverse events n (%)	Cohort A (N = 13)	Cohort B (N = 14)	Pooled (N = 27)
Participants with at least 1 TEAE	10 (76.9)	13 (92.9)	23 (85.2)
Participants with at least 1 serious TEAE	1 (7.7)	1 (7.1)	2 (7.4)
<i>Campylobacter</i> infection	1 (7.7)	0 (0.0)	1 (3.7)
Acute kidney injury	0 (0.0)	1 (7.1)	1 (3.7)
Pneumonitis aspiration	0 (0.0)	1 (7.1)	1 (3.7)
Participants with TEAE leading to death ^a	0 (0.0)	1 (7.1)	1 (3.7)
Participants with TEAE leading to permanent study intervention discontinuation ^b	2 (15.4)	3 (21.4)	5 (18.5)
Participants with treatment-emergent AEs ^c	4 (30.8)	3 (21.4)	7 (25.9)
Severe infections	1 (7.1)	0 (0.0)	1 (3.7)
SARS-CoV-2 infection	3 (23.1)	2 (14.3)	5 (18.5)
Increase in ALT level ^d ($> 3 \times$ ULN)	0 (0.0)	1 (7.1)	1 (3.7)
Adverse events in $\geq 10\%$ of participants ^e			
Diarrhoea	5 (38.5)	6 (42.9)	11 (40.7)
Dry mouth	1 (7.7)	3 (21.4)	4 (14.8)
Nausea	2 (15.4)	2 (14.3)	4 (14.8)
COVID-19	3 (23.1)	2 (14.3)	5 (18.5)
Dizziness	3 (23.1)	2 (14.3)	5 (18.5)
Haematuria	1 (7.7)	2 (14.3)	3 (11.1)
Arthralgia	2 (15.4)	1 (7.1)	3 (11.1)

AESI, adverse event of special interest; ALT, alanine transaminase; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

^a Caused by pneumonitis aspiration (pneumonitis caused by aspiration of food or vomit) and found to be not related to the study drug by the investigator.

^b Diarrhoea (n = 2), pruritus (n = 1) with hepatitis cholestatic (n = 1) and dacryoadenitis (n = 1) were counted as discontinuations due to disease flare in the overall disposition.

^c Pregnancy, symptomatic overdose, increase in ALT ($> 3 \times$ ULN), severe infections, tuberculosis, SARS-CoV-2 infection, major haemorrhagic events, severe or serious cytopenia, and atrial fibrillation uveitis were included under AESI events.

^d Related to disease flare and consistent with prior liver involvement before treatment initiation.

^e Adverse events that occurred during the main + maintenance treatment period in at least 10% participants in the pooled cohort were coded using the MedDRA 27.0; Percentages are based on the number of participants in the rilzabrutinib-treated population.

Two participants experienced serious TEAEs. One participant had a *Campylobacter* infection, but this was demonstrated to have been present at the baseline visit (with the diarrhoea initially attributed incorrectly to pancreatic exocrine insufficiency). The other participant had a long-standing history of chronic kidney disease and experienced acute kidney injury (AKI) and, while hospitalised, developed an aspiration pneumonitis resulting in death. Neither of these serious TEAEs was considered to have been related to the study drug by investigators (Table 3).

Severe acute respiratory syndrome coronavirus 2 infection, the most common AE of special interest, occurred in 18.5% (5/27) of participants. An increase in alanine aminotransferase (ALT) levels exceeding 3 times the upper limit of normal (ULN) was reported for 1 participant (1/27; 3.7%). That event, assessed as being unrelated to the study drug, was attributed to a disease flare. The ALT levels subsequently normalised with GC treatment. A severe infection (*Campylobacter*) was observed in 1 participant (1/27; 3.7%) in Cohort A, which was also classified as a

serious TEAE. That infection, as noted, was present at the time of the baseline visit.

Biomarkers

At baseline, the pooled population mean (SD) serum IgG4 level was 423.8 (402.1) mg/dL, with 30% (8/27) of the participants exceeding $5 \times$ ULN. Cohort A had higher baseline levels (503.6 [496.2] mg/dL) than Cohort B (349.8 [289.6] mg/dL), although the proportion of participants $> 5 \times$ ULN was similar between the 2 cohorts (Table 1). Reductions in serum IgG4 levels were evident as early as week 2, and the serum IgG4 values for the group as a whole continued to decline even after the completion of GC tapering and throughout treatment with rilzabrutinib (Fig 3A). Among participants who completed 52 weeks of rilzabrutinib, the IgG4 levels had declined by 32.0 (32.5)% to a mean (SD) value of 234.5 (297.7) mg/dL in Cohort A and by 43.2 (26.2)% to 145.7 (123.4) mg/dL in Cohort B. In comparison, total IgG levels had a smaller change of -14.7 (20.2)% to a mean (SD) value of 1279.1 (459.7) mg/dL in Cohort A and -10.6 (13.1)% to 1181.9 (216.5) mg/dL in Cohort B (Table 2 and Fig 3).

DISCUSSION

Reduction in the risk of flares and the preservation of organ function while minimising the need for GC therapy are crucial goals of IgG4-related disease management [6]. This Phase 2a, open-label study showed that following a short GC taper, a substantial proportion of participants (70.4%) remained flare-free and off GCs while receiving rilzabrutinib. Treatment with rilzabrutinib was associated with a clinically meaningful decline in disease activity as reflected by the RI total activity score, along with a decline in the mean serum IgG4 concentration. BTK inhibition with rilzabrutinib was the likely cause of this clinical and serological improvement because the reductions in disease activity and IgG4 levels persisted long after completion of the GC taper. Only 2 participants achieved an RI total activity score of 0, which represents a normal or resolved status for all involved organs/sites. This low number is not surprising, given that the RI assigns a score of 2 to any involved organ/site, and these scores generally remain unchanged unless improvement can be confirmed through physical examination (of the major salivary glands or orbits) or follow-up imaging [33].

Although the expectation was that participants who had been unable to maintain disease control while treated with rituximab would be less responsive to rilzabrutinib, the results of this study suggest that prior rituximab experience did not influence the overall treatment outcomes. The participants in Cohort A (all of whom were rituximab-experienced) tended to have lower baseline activity scores than participants in Cohort B, perhaps because of their previous B-cell-depleting therapies and a higher likelihood of diagnosing their disease flares, leading to entry more quickly [11,33]. Nevertheless, the RI total activity scores declined substantially in both cohorts.

Rilzabrutinib was generally well tolerated. Most AEs were self-limited and of mild severity. In this study, no BTK inhibitor-reported AEs (such as atrial fibrillation, cytopenia, or haemorrhagic events) were observed [34,35]. The majority of commonly reported AEs, such as diarrhoea, dizziness, nausea, and dry mouth, were of mild (Grade 1) or moderate (Grade 2) severity. All AEs resulting in treatment discontinuations (for 5 participants including 2 AEs also considered as evidence of disease flare) were nonserious. In addition, no instances of hepatic

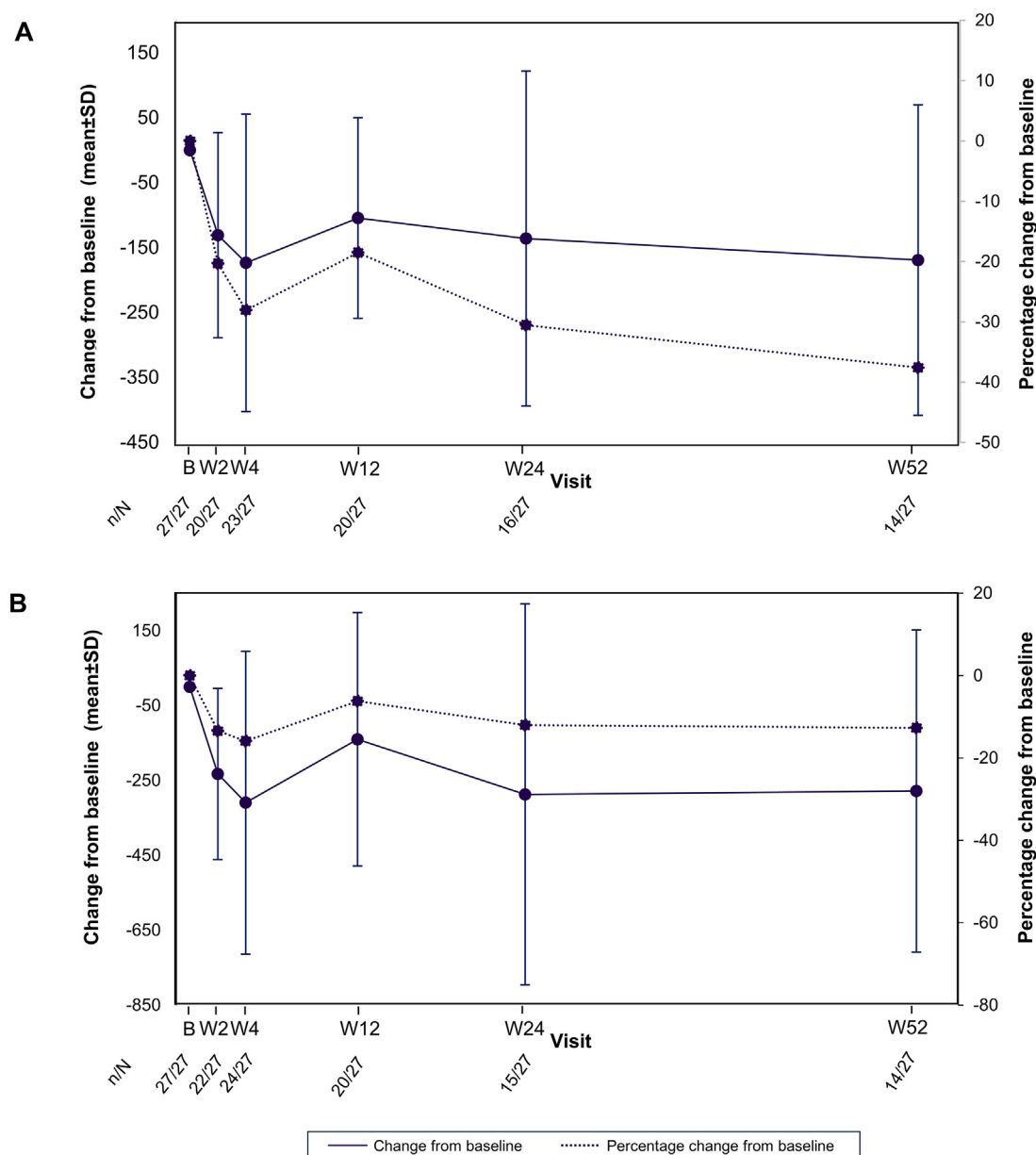


Figure 3. Change from baseline over time in levels of serological markers (A) IgG4 and (B) IgG. Baseline was the last observation recorded prior to the first dose of the study drug. The rilzabrutinib-treated population included participants randomised to the rilzabrutinib arm and control arm participants who crossed over and received at least one dose of rilzabrutinib. B, baseline; W, week.

dysfunction meeting Hy's law criteria were reported during the study, and only 1 serious infection was observed, highlighting the overall tolerability of rilzabrutinib. This favourable safety profile may reflect rilzabrutinib's selective BTK inhibition [26].

Given the potential of IgG4-related disease to affect multiple organs, it is not surprising that several of the AEs observed during the trial (trochlear nerve palsy, cholestatic hepatitis, ALT elevation, and acquired dacryoadenitis) were manifestations of IgG4-related disease flares. The severe *Campylobacter* infection and the reported death of a participant due to aspiration pneumonitis were considered to be unrelated to the study drug by the investigator. In the participant with AKI, although pre-existing chronic kidney disease leading to AKI may have contributed to overall clinical vulnerability, aspiration pneumonitis was identified as the cause of death. The overall safety profile was consistent with the findings of previous studies of rilzabrutinib [21,24], and no new AEs were identified [26]. Across clinical studies of rilzabrutinib in other immune-mediated diseases,

some of the most frequently reported TEAEs included diarrhoea, nausea, and headache, which were predominantly mild (grade 1/2) in severity; notably, rilzabrutinib was not associated with AEs characteristic of early-generation BTK inhibitors, including cardiac arrhythmias, hepatotoxicity, cytopenia, and bleeding complications [25–27,36,37]. Although no head-to-head trials have compared safety across therapies for IgG4-related disease, rilzabrutinib is orally administered and inherently without a risk for infusion-related reactions associated with rituximab and inebilizumab. Furthermore, by inhibiting BTK without depleting B cells, rilzabrutinib potentially has a lower risk of serious or severe infection than reported with B-cell depletion [13,38].

Several aspects of this study are novel. To our knowledge, this is the only study that examined up to 1 year of BTK inhibition in patients with IgG4-related disease and the only proof-of-concept study that included approximately equal numbers of participants who were rituximab-experienced on one hand and naïve to B-cell depletion on the other.

The open-label design, small sample size, and absence of a placebo control present important limitations to the generalizability of the study findings. In addition, independent adjudication of the IgG4-related disease diagnosis and disease flares was not conducted for this study; however, all investigators were experts in the disease and experienced in conducting clinical trials.

We note that the prespecified primary efficacy outcome did not consider the participants who discontinued treatment early for reasons other than disease flare in the numerator, resulting in potential inflation of efficacy results. However, if the 5 participants who discontinued treatment for reasons other than flare were included as failures, the flare-free rate would decline to only 64% (14/22).

BTK regulates multiple immune signalling pathways and is expressed in a number of immune cell types in addition to B cells (eg, monocytes, macrophages, and basophils). Notably, BTK expression in macrophages regulates their activation and contributes to M2 polarisation, driving fibrotic tissue remodelling in IgG4-related disease [39–41]. Thus, in comparison to B-cell-targeted therapies, targeting BTK signalling pathways may enable broader modulation of the immunological pathways that are hypothesised to be involved in IgG4-related disease while avoiding the limitations of B-cell depletion [42]. These observations suggest that rilzabrutinib might lead to effective disease control without broader immune suppression, potentially reducing the risk of infections and the high frequency of vaccine unresponsiveness observed in patients who have undergone B-cell depletion [43]. This hypothesis requires validation in larger trials.

The expression of BTK in a number of cell types beyond B cells may also have practical implications for managing atopic manifestations, such as bronchial asthma and atopic dermatitis, which are relatively common in IgG4-related disease and are not consistently controlled by B-cell depletion alone [6,44]. The relevance of BTK inhibition in immune cell types other than B cells, including any potential effects on macrophage-driven fibrotic processes, in IgG4-related disease warrants further investigation.

The biological activity of rilzabrutinib is supported by observed changes in disease-relevant biomarkers. It has been reported that serum IgG4 levels are increased in ~70% of patients with IgG4-related disease [45]. Furthermore, changes in serum IgG4 concentrations perform reasonably well as a biomarker: elevated levels generally reflect worsening of disease, and declining levels correspond to treatment responses [11,13,31]. In this study, rilzabrutinib treatment resulted in marked reductions in IgG4, which continued to decline in both cohorts long after GC treatment had been discontinued.

In conclusion, the data from this Phase 2 trial suggest that rilzabrutinib treatment resulted in clinically meaningful improvements in disease activity, deserving further evaluation of its potential efficacy and safety in patients with IgG4-related disease.

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Competing interests

JHS reports consulting for Sanofi, Amgen, Bristol-Myers Squibb, Hoffmann-La Roche, Horizon Pharma, IgG4ward! Foundation, Novartis Pharma, Q32 Bio, Sobi. Inc, and Zenas; grants from National Institutes of Health/National Institute of Allergy and Infectious Diseases; is an executive chairman of IgG4ward! Foundation; and Chairman and on Scientific Advisory Board of Steritas. MC reports consulting for Sanofi, AbbVie, Amgen, Janssen, Pfizer, Uniion Chimique Belge (UCB), Roche and Zenas Biopharma. MCB reports consulting for Sanofi, Amgen, Zenas Biopharma, Eli Lilly, Gilead, Neurocrine, and argenx. AM was in Amgen (Adviser or Reviewer Panel Member, Consultant, Speaker/Honorary (Includes Speakers, Bureau, Symposia, and Expert Witness)), AstraZeneca (Adviser or Review Panel Member), GlaxoSmithKline (GSK) (Adviser or Review Panel Member), Janssen (Adviser or Review Panel Member), and Zenas (Adviser or Review Panel Member). RS reports consulting for GlaxoSmithKline, Boehringer Ingelheim, Regeneron, AbbVie, Sanofi, Chemocentryx, Novartis, Galderma, Vera, Chemomab, and Bristol-Myers Squibb (BMS); Roche-Genentech, AstraZeneca, GlaxoSmithKline, Kadmon, Boehringer Ingelheim, Chemocentryx, Corbus, Formation Biologics, Novartis, Inflarx, and Principia (research grants); GlaxoSmithKline, AbbVie, Sanofi, Chemocentryx, Novartis, Galderma, and BMS (honoraria). DG reports consulting for Amgen (Adviser or Reviewer Panel member), Revelo Biotherapeutics. FMV reports consulting for Sanofi,

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Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

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Not commissioned; externally peer reviewed.

Data availability statement

Qualified researchers may request access to patient-level data and related documents (including, eg, 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 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>.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ard.2026.05.017.

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