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ORIGINAL RESEARCH ARTICLE

Integrated Safety Analysis of Ritlecitinib, an Oral JAK3/TEC Family Kinase Inhibitor, for the Treatment of Alopecia Areata from the ALLEGRO Clinical Trial Program

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Abstract

Background The ALLEGRO phase 2a and 2b/3 studies demonstrated that ritlecitinib, an oral JAK3/TEC family kinase inhibitor, is efficacious at doses of ≥ 30 mg in patients aged ≥ 12 years with alopecia areata (AA).

Objective The objective of this study was to evaluate the safety of ritlecitinib in an integrated analysis of four studies in AA.

Methods Two cohorts were analyzed: a placebo-controlled and an all-exposure cohort. Proportions and study size–adjusted incidence rates (IRs) of adverse events (AEs) of interest and laboratory abnormalities are reported.

Results In the placebo-controlled cohort ($n = 881$; median exposure: 169 days), the proportion of ritlecitinib-treated patients with AEs was 70.2–75.4% across doses versus 69.5% in the placebo group; serious AEs occurred in 0-3.2% versus 1.9% for the placebo. A total of 19 patients permanently discontinued due to AEs (5 while receiving the placebo). In the all-exposure cohort ($n = 1294$), median ritlecitinib exposure was 624 days [2091.7 total patient-years (PY)]. AEs were reported in 1094 patients (84.5%) and serious AEs in 57 (4.4%); 78 (6.0%) permanently discontinued due to AEs. The most common AEs were headache (17.7%; 11.9/100 PY), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test (15.5%; 9.8/100 PY), and nasopharyngitis (12.4%; 8.2/100 PY). There were two deaths (breast cancer and acute respiratory failure/cardiorespiratory arrest). Proportions (IRs) were < 0.1% (0.05/100 PY) for opportunistic infections, 1.5% (0.9/100 PY) for herpes zoster, 0.5% (0.3/100 PY) for malignancies (excluding nonmelanoma skin cancer), and 0.2% (0.1/100 PY) for major adverse cardiovascular events.

Conclusions Ritlecitinib is well tolerated with an acceptable safety profile up to 24 months in patients aged ≥ 12 years with AA (video abstract and graphical plain language summary available).

Trial Registries ClinicalTrials.gov: NCT02974868 (date of registration: 11/29/2016), NCT04517864 (08/18/2020), NCT03732807 (11/07/2018), and NCT04006457 (07/05/2019).

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1 Introduction

Alopecia areata (AA) is an autoimmune disease with an underlying immuno-inflammatory pathogenesis that is characterized by nonscarring hair loss ranging from small bald patches to complete loss of scalp, face, and/or body hair [1].

Previous presentation A portion of this work was presented as an oral presentation at the 2023 European Hair Research Society Meeting.

Extended author information available on the last page of the article

Key Points

This integrated analysis of data pooled from four clinical trials evaluated the safety of ritlecitinib, an oral JAK3/TEC family kinase inhibitor, in adults and adolescents with alopecia areata.

Most adverse events were mild and did not result in discontinuation of ritlecitinib; the most common adverse events included headache, SARS-CoV-2 test positive, and nasopharyngitis.

Ritlecitinib is well tolerated with an acceptable safety profile up to 24 months in patients aged ≥ 12 years with alopecia areata; ongoing studies will evaluate the safety of ritlecitinib in patients with alopecia areata who take it for up to 5 years.

AA has an unpredictable disease course and may result in chronic and extensive hair loss, with some patients progressing to alopecia totalis (complete loss of scalp and face hair) or alopecia universalis (complete loss of scalp, face, and body hair) [2, 3]. The global prevalence of AA has been estimated at approximately 2% [4], and patients with AA may experience psychological and psychosocial symptoms that can have a negative impact on quality of life [5–8].

Two therapies are currently approved for severe AA. These include baricitinib, an oral JAK1/2 inhibitor, approved for the treatment of adults with severe AA [9] and ritlecitinib, an oral, selective dual inhibitor of JAK3 and the TEC family of kinases, approved for the treatment of patients age ≥ 12 years with severe AA [10]. Given the often-chronic course of AA, the long-term safety of new treatments for AA is critical to understanding benefit–risk profiles and informing clinical decision making.

Based on safety findings from studies in rheumatoid arthritis (RA), regulatory agencies have issued precautions regarding increased risk of infection, malignancy, nonmelanoma skin cancer (NMSC), venous thromboembolism (VTE), major adverse cardiovascular events (MACE), increased lipid levels, and various changes in hematologic parameters with JAK inhibitors [11–16]. The safety profile of ritlecitinib may be distinct due to its mechanism of action (selective dual inhibition of JAK3 and TEC family kinases). Additionally, differences in underlying pathophysiology and associated comorbidities in the AA population versus other populations (such as RA) may impact the safety profile of drugs.

Here, we report an integrated safety analysis of ritlecitinib in patients aged ≥ 12 years with AA enrolled in the phase 2 and phase 3 studies of the ALLEGRO clinical program, including an ongoing, open-label, long-term study. The objective of this analysis was to assess the safety profile of ritlecitinib in AA, including evaluation of known safety events of interest for immunomodulators and JAK inhibitors. A graphical plain language summary is available (Electronic Supplementary Material 1).

2 Methods

2.1 Studies

This integrated safety analysis included data pooled from four studies: three randomized, placebo-controlled studies and an ongoing long-term, open-label, phase 3 study of ritlecitinib in AA from the ALLEGRO clinical development program: ALLEGRO phase 2a proof-of-concept study (NCT02974868; completed), ALLEGRO phase 2a safety study (NCT04517864; ongoing), pivotal ALLEGRO phase 2b/3 study (NCT03732807; completed), and long-term, open-label, phase 3 study (ALLEGRO-LT; NCT04006457; ongoing) (Table S1 in Electronic Supplementary Material 2). ALLEGRO-LT enrolled patients into two arms: (1) rollover patients who had received treatment in the ALLEGRO phase 2a proof-of-concept or phase 2b/3 study and (2) de novo patients who had not received treatment in either study. The data cutoff for this analysis was 30 May 2022.

Inclusion criteria for the ALLEGRO phase 2a safety study and phase 2b/3 study were described previously [10, 17]. Patients were aged ≥ 12 years (ALLEGRO-2b/3 and ALLEGRO-LT) or ≥ 18 years (ALLEGRO-2a and ALLEGRO-2a safety study), with ≥ 25% (ALLEGRO-2a safety study and de novo patients in ALLEGRO-LT) or ≥ 50% (ALLEGRO-2a and ALLEGRO-2b/3) scalp hair loss at baseline, including patients with alopecia totalis and alopecia universalis.

Patients with any previous use of a JAK inhibitor were excluded, except for rollover patients who had received ritlecitinib in ALLEGRO-2b/3. There were no specific exclusion criteria related to history or risk of VTE or MACE in any study. Detailed inclusion and exclusion criteria are outlined in Table S2.

2.2 Analysis Data Sets

Safety data were assessed in the placebo-controlled pool (Fig. 1A) and the all-exposure pool (Fig. 1B). The placebo-controlled pool included patients from the two phase 2a studies (ALLEGRO-2a and ALLEGRO-2a safety study) and ALLEGRO-2b/3 study, who received ritlecitinib or placebo up to week 24 during the placebo-controlled period of each study. This pool included patients who were randomized and received ritlecitinib 50 mg once daily (QD) with an initial 4-week 200-mg QD loading dose (200/50 mg) from all studies, 50 mg QD (without 200-mg loading dose) from ALLEGRO-2b/3 (50/50 mg), 200/30 mg QD from ALLEGRO-2b/3, 30 mg QD from ALLEGRO-2b/3, 10 mg QD from ALLEGRO-2b/3, or placebo QD from all studies. The ritlecitinib 200/50 mg and 50/50 mg groups from all studies were combined into an "all 50 mg" group, and the 200/30 mg and 30-mg groups from ALLEGRO-2b/3 were combined into an "all 30 mg" group. This data set was used to assess ritlecitinib safety relative to placebo, dose–response relationships for frequent adverse drug reactions, and laboratory changes during the first 24 weeks of therapy.

The all-exposure pool included all patients who received at least one dose of ritlecitinib in the ALLEGRO-2a, ALLEGRO-2a safety, ALLEGRO-2b/3, or ALLEGRO-LT study. This pool included two cohorts based on ritlecitinib dose: an "any ritlecitinib" group comprising patients who received any dose of ritlecitinib and a "ritlecitinib 50-mg" group,

including just the patients who received ritlecitinib 50 mg QD with or without an initial 200-mg QD loading dose in any of the four studies (Fig. 1B). In the all-exposure pool, for the any ritlecitinib group, day 1 of exposure was the first day of ritlecitinib exposure; patients randomized to ritlecitinib in parent studies continued to receive ritlecitinib in ALLEGRO-LT. For the ritlecitinib 50-mg group, day 1 of exposure was the first day of ritlecitinib 50-mg dose (or the 200-mg loading dose), as some patients received placebo or other ritlecitinib doses in ALLEGRO-2a or -2b/3 before switching to ritlecitinib 50 mg. This data set was used to ascertain incidence rates (IRs) for adverse events (AEs) of interest and examine events of low frequency and longer latency (such as malignancies and MACE) and for subgroup analysis. Both pools included evaluation of adolescents (aged 12–17 years) and adults (aged ≥ 18 years). All patients receiving ritlecitinib in the placebo-controlled pool were included in the all-exposure pool. Consequently, any event occurring in the ritlecitinib 50-mg group or with ritlecitinib treatment in the placebo-controlled pool was also counted in the any ritlecitinib group.

2.3 Adverse Event Collection and Safety Assessments

AEs for the placebo-controlled and all-exposure pools were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and MedDRA version 25.0, respectively, and were classified as mild (defined as: does not interfere with patient's usual function), moderate (defined as: interferes to some extent with patient's usual function), or severe (defined as: interferes significantly with patient's usual function), as judged by investigators. A severe AE was not necessarily a serious AE (SAE), as an SAE must have met a criterion of seriousness as defined in Table S3. AEs were summarized by MedDRA system organ class and/or preferred term. AEs of special interest categories were determined based on nonclinical and clinical experience with ritlecitinib and other immunomodulators, including JAK or TEC family kinase inhibitors. AEs of special interest were identified using standardized MedDRA queries or customized MedDRA queries; in many instances, identified events of interest were adjudicated. AEs other than SAEs were

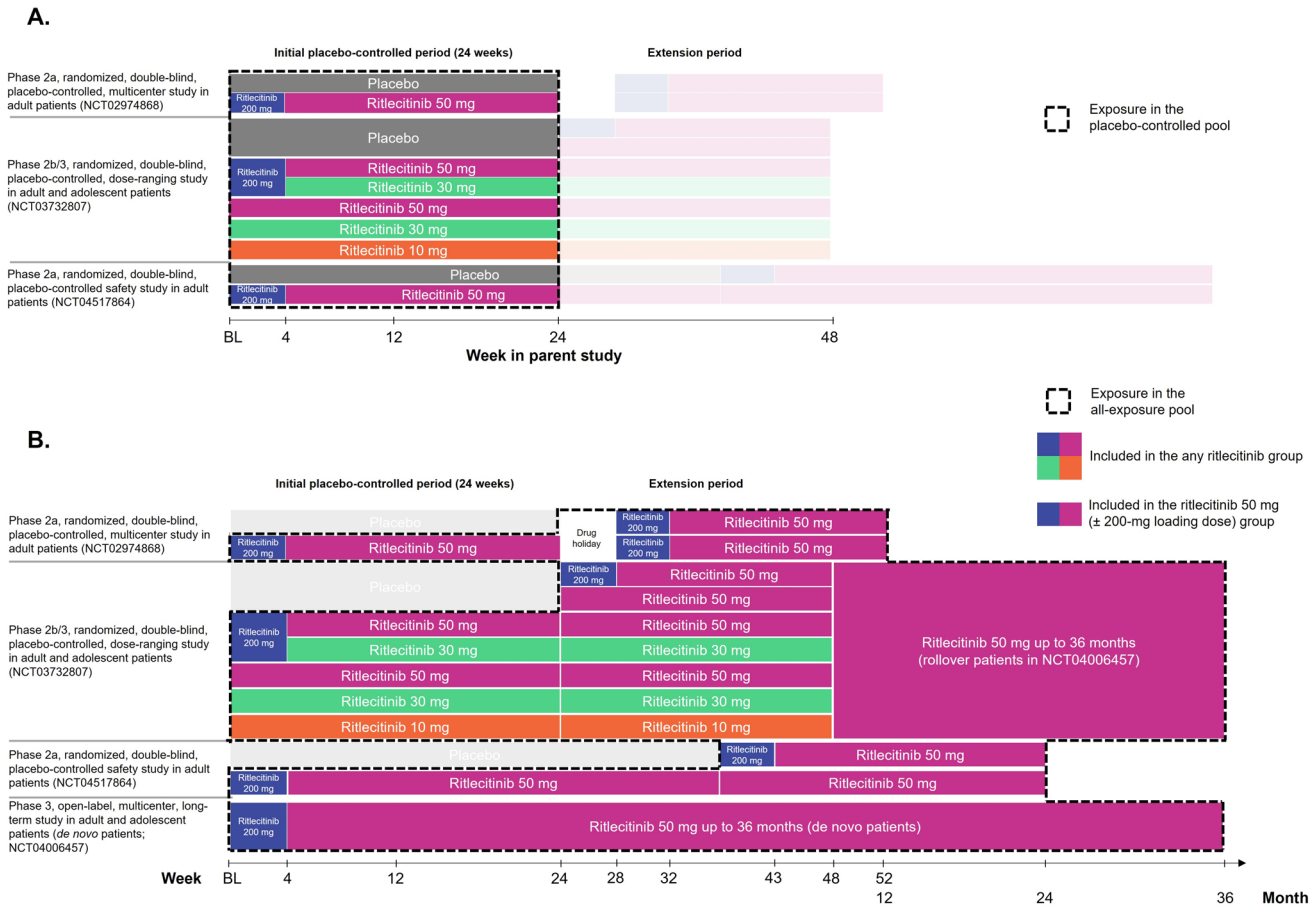

Fig. 1 Schematic of the **A** placebo-controlled pool and **B** the all-exposure pool. *BL* baseline

recorded from the day the patient entered the study through the last visit. SAEs were defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A [18]. SAEs were reported between the time a patient provided informed consent and 35 days after the last study dose or at any time after the last dose if the SAE was suspected to be related to treatment. Only treatment-emergent SAEs reported after the first dose of study treatment are presented in this safety summary.

2.4 Adjudication of Events

Adjudication committees (external experts, blinded to treatment and independent from the study sponsor) were established to obtain objective assessment of opportunistic infections, malignancies, cardiovascular (CV) and thromboembolic events, and neurological and audiological events.

2.5 Statistical Analyses

Statistical analyses were conducted on the safety analysis set, which included all patients who were randomized and received at least one dose of treatment in the respective studies. Continuous and categorical data were analyzed using descriptive statistics. For a specific event, study size–adjusted IR was defined as the crude IR weighted by the study size; the crude IR was defined as the number of patients with events during the risk period divided by the sum of the durations of exposure of all patients during the risk period. The risk period was defined as the period from day 1 to the last dose date plus 35 days, death date, or data cutoff date. Patient exposure was censored at the time of first event. Study size–adjusted IRs with 95% confidence intervals (CIs) computed using the mid-p gamma method are reported. Using the study size–adjusted IRs, a study with a larger study size (longer exposure time and larger sample size) would have a larger weight. Safety analyses were based on the observed data with no imputation of missing data.

3 Results

3.1 Patient Exposure and Demographics

The placebo-controlled pool included 881 patients: 215, 130, 345, 261, 62, and 213 patients in the ritlecitinib 200/50-mg, 50/50-mg, all 50-mg, all 30-mg, 10-mg, and placebo groups, respectively. The all-exposure pool comprised a total of 1294 patients (any ritlecitinib group), of which 1228 patients received ritlecitinib 50 mg with or without a 200-mg loading dose (ritlecitinib 50-mg group). Baseline characteristics for patients in the placebo-controlled pool and the all-exposure pool were comparable (Table 1) and were well matched between treatment groups in the placebo-controlled pool. Median age was 33.0 and 32.0 years in the placebo-controlled and all-exposure pools, respectively; 11.9% (n = 105) and 14.0% (n = 181) of patients were adolescents, respectively. The majority of patients were female and white; 22% of patients in each pool were Asian.

In the placebo-controlled pool, median [interquartile range (IQR)] exposure was 169 (167–173) days in each of the ritlecitinib and placebo groups. Total patient-years (PY) were 96.1, 58.3, 154.4, 114.7, 27.6, and 94.9 for the ritlecitinib 200/50-mg, 50/50-mg, all 50-mg, all 30-mg, 10-mg, and placebo groups, respectively. In total, 67 patients (7.6%) discontinued during the placebo-controlled period (Table S4). Among the 1294 patients in the all-exposure pool, median (IQR) exposure was 624 (407–792) days (2091.7 total PY); 1052 (81.3%) and 533 (41.2%) patients had ≥ 12 months and ≥ 24 months of cumulative ritlecitinib exposure, respectively (Table S5). Maximum duration of exposure was 1181 days (approximately 39 months). In the ritlecitinib 50-mg group, median (IQR) exposure was 547 (366–716) days (1813.7 total PY). At the time of data cutoff, 367 patients (28.4%) had discontinued in the all-exposure pool (Table S6).

3.2 Safety and Tolerability in the Placebo-Controlled Pool (up to 24 Weeks)

In the placebo-controlled pool, AEs occurred in 70.2%, 75.4%, 72.2%, 71.3%, and 69.4% of patients in the ritlecitinib 200/50-, 50/50-, all 50-, all 30-, and 10-mg groups, respectively, and in 69.5% of patients who received placebo (Table 2). Most treatment-emergent AEs (TEAEs) were mild to moderate in severity across treatment groups. There was no increase in overall number of TEAEs, SAEs, or severe AEs with increasing dose, and no individual SAE was reported for more than one patient in any treatment group during the placebo-controlled period. The number of temporary discontinuations due to AEs was higher in the ritlecitinib groups, occurring in 6.9–10.0% of patients compared with 3.8% of patients who received the placebo. The number of permanent discontinuations from the study or study drug due to AEs was similar across treatment groups and the placebo (1.5–3.2% for ritlecitinib groups versus 2.3% for placebo). Overall, the most common AEs (≥ 5% in any treatment group) were nasopharyngitis, upper respiratory tract infection, and headache (Table 2). The most frequent AEs (≥ 2% in any treatment group) that occurred more commonly in the ritlecitinib groups than the placebo, and in a dose-related fashion, were diarrhea, acne, urticaria, rash, and dizziness.

Table 1 Demographic and baseline characteristics in the placebo-controlled and all-exposure pools

	Placebo-controlled pool[a] (*n* = 881)	All-exposure pool[b] (*n* = 1294)	
		Ritlecitinib 50 mg ± 200-mg loading dose[c] (*n* = 1228)	Any ritlecitinib (*n* = 1294)
Age, mean (SD), years	34.2 (13.9)	33.8 (14.0)	33.8 (14.0)
Age group, *n* (%)			
12–17 years	105 (11.9)	172 (14.0)	181 (14.0)
≥ 18 years	776 (88.1)	1056 (86.0)	1113 (86.0)
≥ 65 years	22 (2.5)	24 (2.0)	27 (2.1)
Female, *n* (%)	560 (63.6)	780 (63.5)	822 (63.5)
Race, *n* (%)			
White	623 (70.7)	861 (70.1)	904 (69.9)
Black	41 (4.7)	52 (4.2)	55 (4.3)
Asian	194 (22.0)	270 (22.0)	287 (22.2)
Other	17 (1.9)	28 (2.3)	30 (2.3)
Not reported	6 (0.7)	17 (1.4)	18 (1.4)
Hispanic or Latino, *n* (%)	100 (11.4)	145 (11.8)	152 (11.7)
Duration of AA since diagnosis, years			
Mean (SD)	10.3 (10.6)	10.1 (10.5)	10.1 (10.4)
Median (IQR)	6.9 (2.7–13.7)	6.7 (2.6–13.5)	6.7 (2.7–13.5)
Duration of current AA episode, years			
Mean (SD)	3.5 (3.3)	3.3 (3.0)	3.3 (3.0)
Median (IQR)	2.5 (1.1–5.1)	2.3 (1.0–4.8)	2.3 (1.0–4.8)
Baseline SALT score[d]			
Mean (SD)	88.8 (17.4)	83.5 (22.7)	84.0 (22.3)
Median (IQR)	99.0 (82.2–100.0)	98.1 (69.6–100.0)	98.3 (70.5–100.0)
Type of AA, *n* (%)			
AT/AU[e]	391 (44.4)	502 (40.9)	533 (41.2)
Non-AT/AU	490 (55.6)	726 (59.1)	761 (58.8)

AA alopecia areata, *AT* alopecia totalis, *AU* alopecia universalis, *SALT* Severity of Alopecia Tool

[a]Placebo-controlled pool includes the placebo-controlled portion of studies ALLEGRO-2a (0–24 weeks), ALLEGRO-2b/3 (0–24 weeks), and the phase 2a safety study (0–24 weeks)

[b]All-exposure pool includes all patients who received ritlecitinib in ALLEGRO-2a, the phase 2a safety study, ALLEGRO-2b/3, and ALLEGRO-LT from the start of the first dose of ritlecitinib

[c]Patients received ritlecitinib 50 mg once daily (QD) with or without an initial 4-week 200-mg QD loading dose

[d]Baseline SALT scores for all patients including those with AT or AU, who had a SALT score of 100 at baseline

[e]Patients in the AT/AU group had a SALT score of 100 at baseline regardless of the category in the AA history case report form

3.3 Longer-Term Safety

The proportions of AEs, SAEs, and severe AEs across the all-exposure pool are presented in Table 3. In the any-ritlecitinib group, AEs were reported in 1094 patients (84.5%), SAEs in 57 (4.4%), and severe AEs in 83 (6.4%); 78 patients (6.0%) permanently discontinued due to AEs. The most common TEAEs in the any-ritlecitinib group were headache (17.7%), SARS-CoV-2 positive test (15.5%), nasopharyngitis (12.4%), acne (10.4%), and upper respiratory tract infection (10.2%). Except for events related to coronavirus disease 2019 (COVID-19, which predominantly occurred outside of the placebo-controlled periods), AEs were similar to those in the placebo-controlled pool. The incidence of AEs, SAEs, and severe AEs was consistent across the any-ritlecitinib and ritlecitinib 50-mg groups. Events in the infections and infestations system organ class were the most frequent SAEs (full listing of SAEs in Table S7); pregnancy (12 patients; 0.9%), headache, and urticaria (4 patients each; 0.3%) led to most of the permanent discontinuations. There were two deaths (0.2%) due to breast cancer and acute respiratory failure/cardiorespiratory arrest (described below).

Table 2 Overall safety summary and frequent treatment-emergent adverse events (all causalities) for the placebo-controlled pool

	Placebo (n = 213)	Ritlecitinib QD				
		10 mg (n = 62)	All 30 mg[a] (n = 261)	50/50 mg (n = 130)	200/50 mg (n = 215)	All 50 mg[b] (n = 345)
No. of patients evaluable for AEs	213	62	261	130	215	345
No. of AEs	370	113	513	243	404	647
Patients with AEs						
n (%)	148 (69.5)	43 (69.4)	186 (71.3)	98 (75.4)	151 (70.2)	249 (72.2)
IR (95% CI)	323.8 (272.1, 383.0)	250.5 (183.6, 334.3)	275.4 (237.9, 317.2)	310.2 (253.2, 376.3)	342.0 (286.6, 405.4)	353.3 (310.9, 399.9)
Patients with SAEs						
n (%)	4 (1.9)	2 (3.2)	1 (0.4)	0	4 (1.9)	4 (1.2)
IR (95% CI)	4.5 (1.3, 11.4)	5.8 (1.0, 19.0)	0.7 (0.0, 3.4)	0	5.3 (1.7, 12.9)	2.7 (0.9, 6.5)
Patients with severe AEs						
n (%)	5 (2.3)	2 (3.2)	10 (3.8)	2 (1.5)	4 (1.9)	6 (1.7)
IR (95% CI)	5.0 (1.7, 12.1)	5.9 (1.0, 19.3)	7.0 (3.6, 12.5)	2.7 (0.5, 9.0)	5.4 (1.7, 12.9)	4.1 (1.6, 8.4)
Discontinuations from study or study drug due to AEs[c]						
n (%)	5 (2.3)	2 (3.2)	4 (1.5)	2 (1.5)	6 (2.8)	8 (2.3)
IR (95% CI)	4.2 (1.4, 10.6)	5.8 (1.0, 19.1)	2.8 (0.9, 6.7)	2.7 (0.5, 9.0)	6.3 (2.4, 14.0)	5.0 (2.3, 9.6)
Most frequent AEs occurring in ≥ 5% of patients in any treatment group by PT						
Nasopharyngitis						
n (%)	15 (7.0)	6 (9.7)	34 (13.0)	13 (10.0)	21 (9.8)	34 (9.9)
IR (95% CI)	14.8 (8.2, 24.9)	18.5 (7.5, 38.4)	25.3 (17.8, 35.0)	19.0 (10.5, 31.6)	24.3 (15.0, 37.4)	23.2 (16.3, 32.1)
Upper respiratory tract infection						
n (%)	16 (7.5)	2 (3.2)	21 (8.0)	8 (6.2)	21 (9.8)	29 (8.4)
IR (95% CI)	17.1 (9.7, 28.2)	5.8 (1.0, 19.3)	15.1 (9.6, 22.6)	11.4 (5.3, 21.6)	25.5 (15.8, 39.2)	19.7 (13.4, 28.0)
Headache						
n (%)	17 (8.0)	11 (17.7)	30 (11.5)	12 (9.2)	20 (9.3)	32 (9.3)
IR (95% CI)	19.0 (11.1, 30.9)	35.9 (18.9, 62.4)	22.5 (15.5, 31.8)	17.3 (9.4, 29.5)	20.4 (12.3, 32.4)	21.3 (14.7, 29.8)
Diarrhea						
n (%)	8 (3.8)	0	10 (3.8)	12 (9.2)	14 (6.5)	26 (7.5)
IR (95% CI)	8.4 (3.7, 16.8)	0	7.0 (3.6, 12.5)	17.7 (9.6, 30.1)	14.3 (7.7, 24.6)	17.4 (11.6, 25.3)
Acne						
n (%)	10 (4.7)	3 (4.8)	14 (5.4)	8 (6.2)	12 (5.6)	20 (5.8)
IR (95% CI)	10.3 (5.0, 19.4)	8.9 (2.3, 24.2)	9.9 (5.6, 16.2)	11.2 (5.2, 21.3)	11.2 (5.7, 20.4)	12.7 (8.0, 19.4)
Folliculitis						
n (%)	4 (1.9)	2 (3.2)	11 (4.2)	4 (3.1)	12 (5.6)	16 (4.6)
IR (95% CI)	4.6 (1.4, 11.6)	5.7 (1.0, 18.9)	7.8 (4.1, 13.5)	5.5 (1.7, 13.2)	13.9 (7.3, 24.4)	10.4 (6.2, 16.6)
Nausea						
n (%)	15 (7.0)	3 (4.8)	12 (4.6)	3 (2.3)	12 (5.6)	15 (4.3)
IR (95% CI)	14.2 (7.8, 24.1)	8.9 (2.3, 24.2)	8.6 (4.7, 14.6)	4.2 (1.1, 11.3)	13.3 (6.9, 23.6)	9.7 (5.6, 15.7)
Urticaria						
n (%)	3 (1.4)	1 (1.6)	10 (3.8)	6 (4.6)	11 (5.1)	17 (4.9)
IR (95% CI)	4.0 (1.0, 11.0)	2.9 (0.1, 14.3)	7.0 (3.6, 12.6)	8.2 (3.3, 17.1)	13.5 (6.9, 24.1)	11.4 (6.8, 17.9)
Dizziness						
n (%)	3 (1.4)	1 (1.6)	10 (3.8)	3 (2.3)	11 (5.1)	14 (4.1)
IR (95% CI)	2.4 (0.5, 7.8)	2.9 (0.1, 14.2)	7.0 (3.6, 12.5)	4.2 (1.1, 11.3)	11.8 (5.9, 21.4)	9.0 (5.1, 14.8)

Table 2 (continued)

	Placebo (n = 213)	Ritlecitinib QD				
		10 mg (n = 62)	All 30 mg[a] (n = 261)	50/50 mg (n = 130)	200/50 mg (n = 215)	All 50 mg[b] (n = 345)
Myalgia						
n (%)	3 (1.4)	5 (8.1)	6 (2.3)	1 (0.8)	5 (2.3)	6 (1.7)
IR (95% CI)	2.4 (0.5, 7.8)	15.3 (5.6, 33.8)	4.2 (1.7, 8.7)	1.4 (0.1, 6.7)	5.9 (2.1, 13.6)	3.9 (1.6, 8.1)

Study size-adjusted IRs are per 100 patient-years and are presented along with mid-p gamma CIs

AE adverse event, *CI* confidence interval, *IR* incidence rate, *PT* preferred term, *QD* once daily, *SAE* serious adverse event

[a]Ritlecitinib all 30 mg includes patients from ritlecitinib 200/30 mg and 30/30 mg groups combined

[b]Ritlecitinib all 50 mg includes patients from ritlecitinib 200/50 mg and 50/50 mg groups combined

[c]Patients with an AE record that indicated that the AE caused the patient to be discontinued from the study or study drug

3.4 Adverse Events of Special Interest

3.4.1 Infections

The proportions and IRs of serious infection in ritlecitinib groups were low across both the placebo-controlled and all-exposure pools. Serious infections occurred in 0.9% of patients in the 200/50-mg group, 0.6% in the all 50-mg group, 0.4% in the all 30-mg group, and none in the 50/50-mg and placebo groups. In the all-exposure pool, serious infections were reported in 12 patients (1.0%) in the ritlecitinib 50-mg group (IR: 0.66/100 PY [95% CI 0.35, 1.13]) and in 14 patients (1.1%) in the any ritlecitinib group (IR: 0.64/100 PY [95% CI 0.36, 1.06]) (Fig. 2). The most frequent serious infections (each occurring in ≤ 0.4% of patients in each group) included appendicitis, COVID-19, and COVID-19 pneumonia. Per protocol, all serious infections required discontinuation; however, all events resolved or were resolving, and none were fatal.

In the all-exposure pool, one patient (< 0.1%) in the 200/50-mg group experienced a TEAE of varicella zoster virus infection, which was adjudicated as an opportunistic infection (OI) of multidermatomal herpes zoster (HZ) [IR: 0.05/100 PY (95% CI 0.00, 0.23)]. The event was mild in severity and resolved without treatment interruption. There were no cases of active tuberculosis in any safety pool. With a single case of OI (multidermatomal HZ) across the entire pool of data, incidence rates of OIs were low across the placebo-controlled and all-exposure pools (Fig. 2).

In the placebo-controlled pool, HZ occurred more frequently in some ritlecitinib groups (50/50 mg, 1.5%; all 50 mg, 0.9%; all 30 mg, 0.8%) than in the placebo group, in which no events were reported. All were nonserious, mild, or moderate, and all resolved; there were no events with visceral involvement. In the all-exposure pool, the proportion of patients with HZ was 1.5% [0.99/100 PY (95% CI 0.60, 1.55)] in the ritlecitinib 50-mg group and 1.5% [0.92/100 PY (95% CI 0.57, 1.40)] in the any ritlecitinib group (Fig. 2); most events were localized, with only one event affecting multiple dermatomes (the OI described above). One patient (0.1%; 71-year-old woman; 50-mg group) who experienced HZ was permanently discontinued from the study; the event was deemed moderate and related to treatment, and the patient was recovering at the time of discontinuation. Across the program, the median time to onset for HZ events was 37.4 weeks, and most cases resolved in < 6 weeks (median 15.0 days). Events of herpes simplex were not dose dependent; a higher incidence was observed with placebo than ritlecitinib 50 mg (Fig. 2).

3.4.2 Dermatological Events

In the placebo-controlled pool, the proportions of patients with dermatological events of interest were similar across treatment groups. The most frequently reported dermatological AEs (> 2% in any treatment group) across all treatment groups were urticaria, folliculitis, acne, dermatitis atopic, dermatitis contact, pruritus, and rash. Events that occurred more commonly in patients in the all 50-mg group than placebo included urticaria (4.9% versus 1.4%), folliculitis (4.9% versus 1.9%), atopic dermatitis (2.3% versus 0.5%), and rash (3.2% versus 1.4%). The number of dermatological events of interest in the all-exposure pool was similar to that reported in the placebo-controlled pool. The most frequently reported dermatological events in the ritlecitinib 50-mg and any ritlecitinib groups included acne (9.0% and 10.4%, respectively), urticaria (6.0% and 6.8%), and folliculitis (5.1% and 6.3%); all events were nonserious and mild to moderate in severity, and few led to interruption or discontinuation of treatment. The majority (52.8%) of urticaria events occurred during the first 12 weeks of treatment (median time to onset: 10.1 weeks;

Table 3. Summary of treatment-emergent adverse events (all causalities) in the all-exposure pool

	Ritlecitinib 50 mg ± 200-mg loading dose[a] (*n* = 1228)		Any ritlecitinib (*n* = 1294)	
	n (%)	IR (95% CI)[b]	*n* (%)	IR (95% CI)[b]
No. of patients evaluable for AEs	1228		1294	
No. of AEs	4368		5234	
Patients with AEs	989 (80.5)	160.55 (150.77, 170.80)	1094 (84.5)	179.76 (169.33, 190.65)
Patients with SAEs	52 (4.2)	2.79 (2.10, 3.65)	57 (4.4)	2.64 (2.01, 3.40)
Patients with severe AEs	66 (5.4)	3.59 (2.79, 4.55)	83 (6.4)	3.91 (3.13, 4.83)
Deaths	2 (0.2)[c]	0.10 (0.01, 0.36)	2 (0.2)[c]	0.09 (0.01, 0.31)
Patients discontinued from study or study drug due to AEs[d]	68 (5.5)	3.63 (2.83, 4.58)	78 (6.0)	3.59 (2.84, 4.45)
Patients with temporary discontinuation due to AEs	259 (21.1)	15.78 (13.93, 17.81)	284 (21.9)	15.10 (13.42, 16.95)
AEs occurring in ≥ 5% of patients in any treatment group by PT				
Headache	186 (15.1)	10.72 (9.25, 12.36)	229 (17.7)	11.90 (10.43, 13.53)
SARS-CoV-2 positive test	192 (15.6)	10.68 (9.23, 12.29)	201 (15.5)	9.75 (8.47, 11.18)
Nasopharyngitis	117 (9.5)	6.57 (5.45, 7.86)	160 (12.4)	8.17 (6.97, 9.51)
Acne	111 (9.0)	6.17 (5.09, 7.42)	135 (10.4)	6.75 (5.68, 7.97)
Upper respiratory tract infection	104 (8.5)	5.91 (4.84, 7.14)	132 (10.2)	6.48 (5.44, 7.66)
Pyrexia	93 (7.6)	5.01 (4.06, 6.13)	98 (7.6)	4.64 (3.79, 5.64)
Cough	93 (7.6)	5.15 (4.17, 6.29)	96 (7.4)	4.54 (3.70, 5.53)
Fatigue	77 (6.3)	4.15 (3.29, 5.17)	91 (7.0)	4.33 (3.51, 5.30)
Urticaria	74 (6.0)	4.02 (3.17, 5.03)	88 (6.8)	4.25 (3.43, 5.22)
AEs of special interest[e]				
Serious infections	12 (1.0)	0.66 (0.35, 1.13)	14 (1.1)	0.64 (0.36, 1.06)
Opportunistic infections	1 (< 0.1)	0.05 (0.00, 0.25)	1 (< 0.1)	0.05 (0.00, 0.23)
Herpes zoster	18 (1.5)	0.99 (0.60, 1.55)	20 (1.5)	0.92 (0.57, 1.40)
Herpes simplex	25 (2.0)	1.31 (0.86, 1.91)	37 (2.9)	1.72 (1.22, 2.35)
Malignancies (excluding NMSC)	7 (0.6)	0.37 (0.16, 0.75)	7 (0.5)	0.32 (0.14, 0.64)
NMSC	3 (0.2)	0.15 (0.03, 0.43)	3 (0.2)	0.14 (0.03, 0.38)
Breast cancer[f]	4 (0.5)	0.39 (0.12, 0.97)	4 (0.5)	0.35 (0.10, 0.85)
MACE[g]	3 (0.2)	0.15 (0.03, 0.43)	3 (0.2)	0.14 (0.03, 0.38)
Thromboembolic events (PE)	1 (< 0.1)	0.06 (0.00, 0.29)	1 (< 0.1)	0.05 (0.00, 0.23)
Peripheral neuropathy	3 (0.2)	0.16 (0.03, 0.45)	4 (0.3)	0.18 (0.05, 0.45)
Paresthesia and dysesthesia	21 (1.7)	1.11 (0.69, 1.67)	26 (2.0)	1.20 (0.80, 1.75)
Sensorineural hearing loss[h]	12 (1.0)	0.67 (0.36, 1.16)	14 (1.1)	0.64 (0.36, 1.06)

AE adverse event, *IR* incidence rate, *MACE* major adverse cardiovascular event, *NMSC* nonmelanoma skin cancer, *PE* pulmonary embolism, *PT* preferred term, *PY* patient-years, *SAE* serious adverse event

[a]Patients received ritlecitinib 50 mg once daily (QD) with or without an initial 4-week 200-mg QD loading dose

[b]Study size–adjusted IRs per 100 PY and mid-p gamma CIs

[c]Two deaths were reported in the all-exposure pool: breast cancer (spindle cell carcinoma) and acute respiratory failure/cardiorespiratory arrest. Both events were determined by the investigator to be unrelated to the study treatment

[d]Patients with an AE record that indicated that the AE caused the patient to be discontinued from the study or study drug

[e]Opportunistic infections, malignancies, MACE, non-MACE, thromboembolic events, peripheral neuropathy, paresthesia and dysesthesia, and sensorineural hearing loss were adjudicated by independent clinical event committees

[f]Denominator and patient-years were adjusted to reflect the female patient population

[g]MACE was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. There was one event of percutaneous transluminal coronary angioplasty/percutaneous coronary intervention in the 50-mg group that was considered non-MACE

[h]Sensorineural hearing loss included Medical Dictionary of Regulatory Activities (MedDRA) PTs of deafness neurosensory, deafness unilateral, and hypoacusis. PT terms defined by MedDRA do not necessarily indicate that patients developed deafness

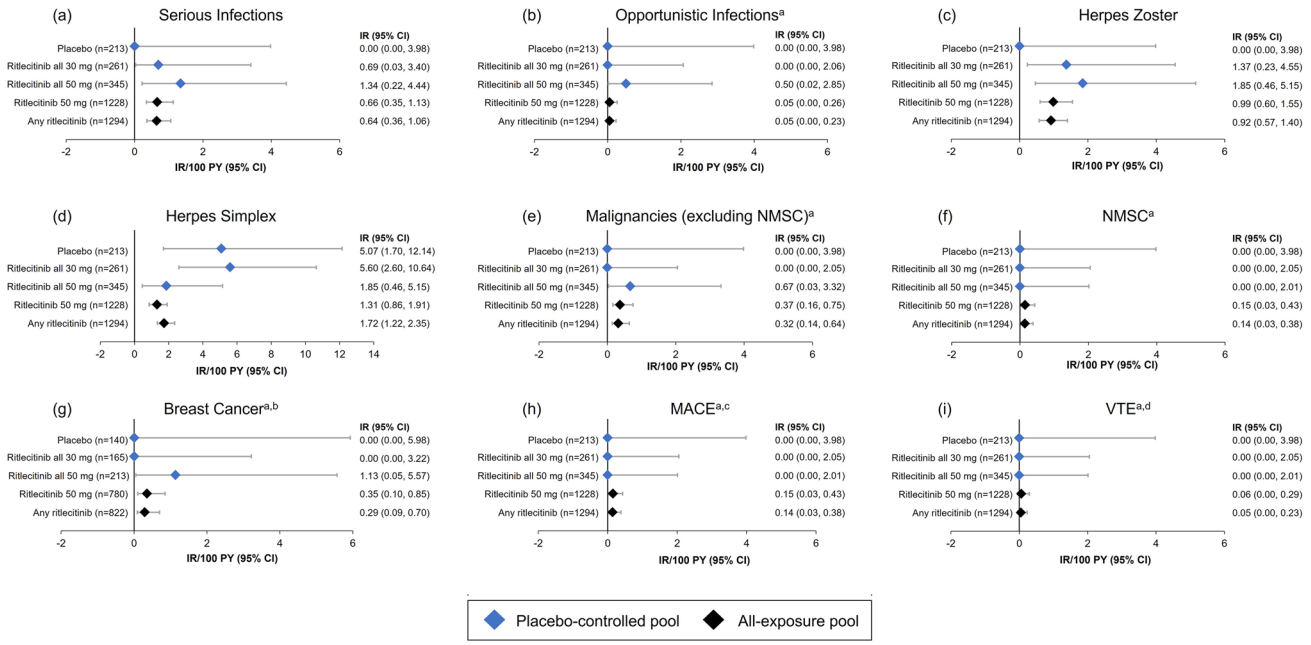

Fig. 2 IRs per 100 PY for adverse events of special interest (**a**–**i**). IRs are exposure adjusted and expressed as the number of patients with events per 100 PY. *IR* incidence rate, *MACE* major adverse cardiovascular events, *NMSC* nonmelanoma skin cancer, *PY* patient-years, *VTE* venous thromboembolic events. Study size-adjusted IRs are per 100 PY and are shown with mid-p gamma CIs. Ritlecitinib all 30 mg includes patients who received ritlecitinib 30 mg QD with or without an initial 4-week 200-mg QD loading dose. Ritlecitinib all 50 mg and ritlecitinib 50 mg includes patients who received ritlecitinib 50 mg QD with or without an initial 4-week 200-mg QD loading dose from the placebo-controlled and all-exposure pools, respectively. [a]Adjudicated safety events. [b]IRs shown for breast cancer in female patients. [c]MACE was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [d]VTE was defined as events of deep vein thrombosis and pulmonary embolism

Table S8); four patients (0.3%) permanently discontinued from the study due to urticaria.

3.4.3 Malignancies

Seven events were adjudicated as malignancies (excluding NMSC) in the all-exposure pool [0.32/100 PY (95% CI 0.14, 0.64)]; all events were reported in the ritlecitinib 50-mg group, and 2 (both breast cancers) occurred during the placebo-controlled period (Fig. 2, Table 3). Breast cancer occurred in four female patients [0.5%, IR: 0.29/100 PY (95% CI 0.09, 0.70)], for whom one event was fatal. The SAEs of breast cancer occurred in a 64-year-old woman (50-mg group), a 66-year-old woman (50-mg group), a 58-year-old woman (50-mg group), and a 46-year-old woman (200/50-mg group); clinical details for all SAEs of breast cancer are provided in Table S9. For the four events of breast cancer, the time to onset of the event ranged from 68 to 299 days (median 156 days) after starting ritlecitinib. All four patients had identified risk factors, including supplemental estrogen therapy, family history of breast cancer, or nulliparity in two patients, current smoker or a history of smoking in three patients, and alcohol consumption in all four patients.

There was one event each of testicular cancer (21-year-old man, 50-mg group; recovered/resolved) and papillary thyroid cancer (26-year-old man, 50-mg group; ongoing at the time of discontinuation); one adjudicated event of malignant melanoma (50-year-old woman, 50-mg group; ongoing at the time of discontinuation) was reported (Table S9).

There were three patients (0.2%) with adjudicated NMSC reported in the all-exposure pool [0.14/100 PY (95% CI 0.03, 0.38)], all of which occurred in the ritlecitinib 50-mg group [0.15/100 PY (95% CI 0.03, 0.43)]; these included two patients (0.2%) with basal cell carcinoma and one patient (0.1%) with Bowen disease (Table 3).

3.4.4 Cardiovascular Safety

In the ritlecitinib 50-mg group of the all-exposure pool, three patients (0.2%) with SAEs adjudicated as MACE were reported [0.15/100 PY (95% CI 0.03, 0.43)] (Fig. 2). These included one event of myocardial infarction in a 49-year-old man (200/50-mg group), who was a current smoker with a history of hyperlipemia and diabetes. The patient underwent percutaneous transluminal coronary angioplasty/percutaneous coronary intervention the following day; treatment was

discontinued and not resumed. The other events included one retinal artery occlusion in a 48-year-old woman (200/50-mg group) with a history of congenital carotid artery defect, patent foramen ovale, and migraine. This patient also experienced a non-SAE of antiphospholipid syndrome and was discontinued from the study. One sudden CV death (acute respiratory failure and cardiorespiratory arrest) occurred in a 51-year-old woman (50-mg group) with a history of asthma, anxiety, and smoking; ongoing concomitant medication was salbutamol for asthma (additional clinical details are provided in Table S10).

One patient (54-year-old woman) in the ritlecitinib 50-mg group of the all-exposure pool experienced a pulmonary embolism (PE) that met adjudication criteria for a VTE [0.06/100 PY (95% CI 0.00, 0.29)]. This patient had potential risk factors, including a recent positive SARS-CoV-2 test and a medical history of morbid obesity, sleep apnea, hypertension, hyperlipidemia, and monoclonal gammopathy of undetermined significance (Table S10). No AEs met the adjudication criteria for deep vein thrombosis.

3.4.5 Neuroaudiological Events

In the all-exposure pool, the most frequently reported adjudicated events of interest term was paresthesia and dysesthesia. In the ritlecitinib 50-mg group, 21 patients (1.7%) experienced TEAEs meeting criteria for adjudicated term paresthesia and dysesthesia [1.11/100 PY (95% CI 0.69, 1.67)] and three patients (0.2%) experienced TEAEs meeting criteria for adjudicated peripheral neuropathy [0.16/100 PY (95% CI 0.03, 0.45)]. In the any ritlecitinib group, 26 [2.0%; IR: 1.20/100 PY (95% CI 0.80, 1.75)] and four [0.3%; IR: 0.18/100 PY (95% CI 0.05, 0.45)] patients had adjudicated paresthesia and dysesthesia and peripheral neuropathy, respectively (Table 3).

In this analysis, TEAEs adjudicated by the external committee to meet criteria for an audiological event of interest reflect both the outcomes of protocol-specified audiological testing (even in the absence of spontaneously reported TEAEs related to hearing loss) and spontaneously reported TEAEs related to hearing loss. In the all-exposure pool, there were 12 patients [1.0%; 0.67/100 PY (95% CI 0.36, 1.16)] with TEAEs adjudicated to meet criteria for sensorineural hearing loss in the ritlecitinib 50-mg group and 14 patients [1.1%; 0.64/100 PY (95% CI 0.36, 1.06)] in the any ritlecitinib group; these events were all identified through protocol-specified audiological testing (Table 3), and no events were adjudicated as central hearing loss.

3.5 Laboratory Assessments

Overall, ritlecitinib was associated with small short-term changes in hematological parameters that remained stable during long-term treatment. Median platelet levels decreased to week 4 and remained stable at a lower level through month 36 (Fig. 3). In the all-exposure pool, no patients had platelet counts considered Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 or met protocol-specified discontinuation criteria ($< 75 \times 10^3/mm^3$). TEAEs of thrombocytopenia and platelet count decrease were reported in four (0.3%) and seven (0.5%) patients, respectively; one patient (0.1%) was permanently discontinued from the study due to a non-serious AE of thrombocytopenia (platelets $83 \times 10^3/mm^3$).

There was a slight decrease from baseline in median hemoglobin (Hgb) levels over the first 4 weeks, and then levels subsequently returned toward baseline and remained stable through month 36 (Fig. 3). In the all-exposure pool, TEAEs of anemia were reported for 17 patients (1.3%), and Hgb decrease was reported for 11 patients (0.9%). In the ritlecitinib 50-mg group, one patient (< 0.1%) met discontinuation criteria for change in Hgb (confirmed < 9.0 g/dL or decrease of > 30% from baseline) and one patient (< 0.1%) had Hgb levels considered CTCAE grade 3 (< 8.0 g/dL), leading to temporary treatment discontinuation (Table S11).

Absolute neutrophil count remained stable through month 36 (Fig. 3). In the ritlecitinib 50-mg group, nine patients (0.7%) had absolute neutrophil count decreases considered CTCAE grade 3 (< 1000 to $500/mm^3$); no patients had a decrease considered grade 4 ($< 500/mm^3$; Table S11). No patients met protocol-specified discontinuation criteria for neutrophils (confirmed $< 750/mm^3$). TEAEs of neutrophil count decrease, neutropenia, and abnormal neutrophil count were reported in five (0.4%), three (0.2%), and one (0.1%) patient, respectively, in the 50-mg group. Overall, two patients (0.2%) discontinued due to neutropenia, including one (0.1%) in the 50-mg group.

There was a decrease in median absolute lymphocyte count (ALC) from baseline to week 4 with ritlecitinib; ALC levels remained stable at a lower level through month 36 (Fig. 3). In the ritlecitinib 50-mg group, 25 patients (2.0%) had lymphocyte count decreases considered CTCAE grade 3 ($< 500–200/mm^3$), and one patient (< 0.1%) had grade 4 lymphocyte count decrease ($< 200/mm^3$; Table S11). One patient (<0.1%) met discontinuation criteria for lymphocytes (confirmed by two sequential tests ALC $< 500/mm^3$).

Treatment with ritlecitinib was associated with concurrent small increases in median total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol from baseline to week 4 that did not progress over time and remained stable through month 36 (Fig. 3). Hyperlipidemia and hypertriglyceridemia were reported in two patients (0.2%) each in the ritlecitinib 50-mg group of the all-exposure pool; none led to discontinuation of study or study drug.

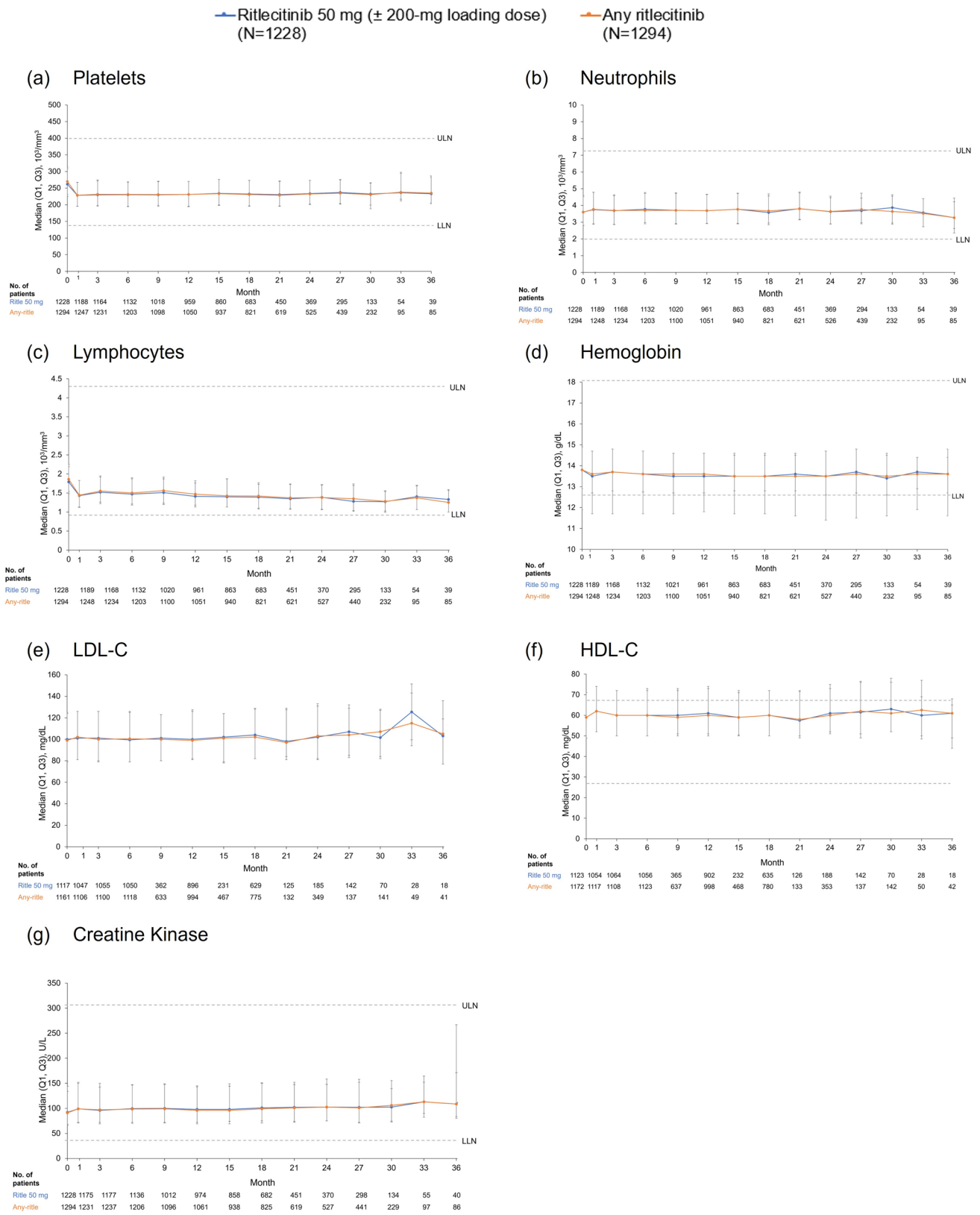

Fig. 3 Select laboratory parameters over time. *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LLN* lower limit of normal, *ULN* upper limit of normal

In the placebo-controlled and the all-exposure pool, there was no meaningful change over time in median alanine aminotransferase or aspartate aminotransferase levels. The proportion of patients with alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal (ULN) was similar in the ritlecitinib 50-mg and any ritlecitinib groups (Table S11). In the ritlecitinib 50-mg group, TEAEs of liver function test increase and abnormal liver function test were reported in four (0.3%) and two (0.2%) patients, respectively; none led to permanent discontinuation from the study or study drug. No AEs were adjudicated as Hy's law or drug-induced liver injury.

There were changes in serum creatinine or creatine kinase (CK) levels over time with ritlecitinib through month 36 (Fig. 3). In the ritlecitinib 50-mg group, 65 patients (5.3%) had CK increases considered CTCAE grade 3 or 4 (greater than five times ULN; Table S11); TEAEs of blood creatine phosphokinase increase were reported in 40 patients (3.3%). In total, three patients (0.2%) permanently discontinued due to blood creatine phosphokinase increases; one patient (< 0.1%) met discontinuation criteria for CK (two sequential tests greater than ten times ULN). No events of rhabdomyolysis were reported, and no AEs, including myalgia, were found to be associated with increases in CK.

4 Discussion

This is the first report of an integrated safety analysis for ritlecitinib, an oral selective dual JAK3/TEC family kinase inhibitor, in patients age ≥ 12 years with AA. Data pooled from four trials of the ALLEGRO clinical trial program, consisting of 1294 patients with AA (representing 2092 PY of exposure), were consistent with the known safety profile of ritlecitinib. The overall pattern of reported all-causality TEAEs was consistent between the placebo-controlled and all exposure pools and demonstrated no new safety signals emerging with longer exposure. Across the ALLEGRO program, the most frequently reported AEs were headache, nasopharyngitis, and upper respiratory tract infection. Most AEs were mild and infrequently required interruption or permanent discontinuation of ritlecitinib treatment.

The pooled data reported here represent the first assessment of the potential impact of selective JAK3/TEC family kinase inhibition on adverse events of special interest that may occur at a lower frequency or have a longer latency in patients with AA. Serious and opportunistic infections and viral reactivation are associated with immunomodulators, including JAK inhibitors, and have been reported with baricitinib (JAK1/2), upadacitinib (JAK1/2), tofacitinib (JAK1/3), abrocitinib (JAK1), and filgotinib (JAK1) [11–14, 19]. An increased risk of infection has also been reported with TEC family kinase inhibitors, including the BTK inhibitor ibrutinib [20–22]. Therefore, it was deemed important to determine if ritlecitinib treatment resulted in an increase in the number of infections in the AA population. The IRs of serious infections were low across the ALLEGRO program; in this analysis, the IR was 0.66/100 PY in the ritlecitinib 50-mg group. In a real-world US claims-based study, the IR for serious infections was 1.85/100 PY (95% CI 1.65, 2.08) in patients with AA [23].

A dose-related increase in HZ infections was observed with ritlecitinib, which is consistent with previous reports for other immunomodulators, including JAK inhibitors [11, 13]. In the ritlecitinib 50-mg group of the all exposure pool of this analysis, the IR for HZ was 0.99/100 PY (95% CI 0.60, 1.55); in the US-based cohort study in patients with AA, the IR was 0.78/100 PY (95% CI 0.65, 0.93) [23]. Rates were lower in the all-exposure pool than in the placebo-controlled pool, suggesting no increased risk with longer ritlecitinib treatment. As expected, there was a trend toward increasing IR/100 PY with increasing age in adults. Most events were found to resolve within 6 weeks (median 15 days). The IR is lower than the reported IRs for HZ in patients with AA treated with the JAK1/2 inhibitor baricitinib (IR: 1.8/100 PY) [24] and in patients with atopic dermatitis (AD) treated with the JAK1/2 inhibitor upadacitinib [IRs: 3.8/100 PY (15 mg), 6.7/100 PY (30 mg)] [15] or the JAK1 inhibitor abrocitinib [IRs: 2.0/100 PY (100 mg), 4.3/100 PY (200 mg)] [14]. However, future investigations are warranted to elucidate the specific contributions of the underlying disease versus JAK inhibitor therapy in influencing HZ.

JAK inhibitors have been associated with dermatological adverse reactions including acne, folliculitis, rash, and/or urticaria [25–27], all of which occurred at higher rates with ritlecitinib 50 mg than placebo in the placebo-controlled pool of the ALLEGRO studies. All events of acne, urticaria, and folliculitis were mild to moderate in severity. Acne has been reported as a common or very common adverse drug reaction for all JAK inhibitors approved for dermatological conditions [25–30]. While no clear mechanism of action is known for this, it has been suggested that JAK inhibitors may be associated with skin dysbiosis, including microbial colonization of *Demodex folliculorum*. Induction of acne lesions through inhibition of immune signaling by JAK inhibitors has also been suggested. However, overexpression of JAK1 and JAK3 has also been reported in acne vulgaris lesions suggesting a complex interplay of immune modulation and the potential that acne represents a paradoxical reaction to JAK inhibition [29, 31]. For the other dermatological adverse reactions associated with JAK inhibitors, there is no clear understanding of the pathogenic mechanisms that drive or exacerbate these events during JAK inhibitor treatment.

In the ALLEGRO program, all adjudicated malignancies occurred in patients receiving ritlecitinib ≥ 50 mg, representing the largest pool of patients in this analysis (1813.7

PY for patients receiving 50 mg ± 200 mg loading dose of total 2091.7 PY). The seven reported malignancies are among the more commonly reported malignancies in the general population, and five of the patients had additional risk factors for their reported malignancies. Across the ritlecitinib program, there were four cases of breast cancer; the IR for breast cancer in female patients receiving any dose of ritlecitinib was 0.29/100 PY (95% CI 0.09, 0.70) while the background IR from the AA cohort in a US-based cohort study was 0.46/100 PY (95% CI 0.33, 0.63) [23]. The IR for malignancy (excluding NMSC) in the ritlecitinib 50-mg group in this integrated analysis was 0.37/100 PY and the IR reported for the AA cohort in US-based cohort study was 1.25/100 PY (95% CI 1.08, 1.45) [23]. Generally, AA is not known to be associated with an increased risk of cancer. Other integrated safety analyses of immunomodulatory agents have reported IRs for malignancies (excluding NMSC) in patient populations with similar demographics, including baricitinib in AD (IR: 0.22/100 PY) [32] and AA (IR: 0.2/100 PY) [24], lebrikizumab in AD (IR: 0.5/100 PY) [33], and upadacitinib in AD (IR range 0.1–0.5/100 PY) [34]. However, given the low number of events, additional long-term data are needed to further assess this risk.

Following the results of the post authorization ORAL surveillance trial of tofacitinib in RA [35], it was recognized that JAK inhibitors may increase the risk of thrombosis, MACE, malignancy, and mortality in high-risk patient populations [36, 37]. However, it is not clear that the same risks should be assumed with regard to ritlecitinib in AA. Ritlecitinib is a selective dual inhibitor of JAK3 and TEC family kinases and offers a distinct mechanism of action. Furthermore, patients with AA generally have fewer comorbidities (versus patients with RA), and events of serious infections, HZ, MACE, VTE, and malignancies have been reported to occur less frequently in patients with dermatological disorders than with rheumatological diseases [38, 39].

Three adjudicated MACE and one VTE (PE) were reported in this analysis. Overall, the IRs for MACE and VTE in the ALLEGRO clinical program were 0.14/100 PY and 0.06/100 PY, respectively; the IRs (95% CI) in the US-based cohort study for MACE and VTE were 1.6/100 PY (1.41, 1.82) and 0.43/100 PY (0.33, 0.54), respectively [23]. Notably, patients with CV risk factors were not specifically excluded from the ALLEGRO studies, and all patients with CV events had at least one CV risk factor. Other integrated safety analyses have reported similar IRs for VTE in AA and AD, including baricitinib in AD (IR: 0.09/100 PY) [32] and AA (IR: 0.1/100 PY) [24], abrocitinib in AD (IR: 0.3/100 PY) [33], and upadacitinib in AD (IRs: 0.3/100 PY [15 mg], 0.2/100 PY [30 mg]) [34]. The relationship between thromboembolic and CV events and increased lipid levels observed with some JAK inhibitors is not well understood [40]. Notably, no clinically meaningful changes in lipid levels were observed over the course of ritlecitinib treatment. While the data presented here are reassuring, additional long-term data are needed to assess the VTE risk with selective JAK3/TEC inhibition in AA.

The four JAK isoforms have complex interactions with the development and function of hematopoietic cells, and selectivity in JAK inhibition may affect the pattern of changes in laboratory values. Additionally, TEC family kinases are involved in signal transduction from antigen receptors on B cells, T cells, and platelets, and changes in hematologic parameters have been reported with TEC family kinase inhibitors [41–43]. Ritlecitinib was associated with early dose-dependent decreases in lymphocyte counts; levels partially recovered toward baseline and remained stable throughout treatment. Early decreases in platelet counts that remained stable and above the lower limit of normal throughout treatment were also observed with ritlecitinib. A small decrease in platelet counts was also reported with abrocitinib (JAK1 inhibitor) in AD [14], whereas an increase in platelet count was observed with baricitinib (JAK1/2 inhibitor) in AA [24], reinforcing the differential impact of drugs in this class of medicine on hematologic laboratory parameters.

In nonclinical, chronic toxicology studies in dogs, reversible axonal dystrophy (swelling of axons without inflammation, degeneration, or gliosis) was observed in the central nervous system (cerebellum) with ritlecitinib at exposures ≥ 7.4 times the approved human dose (50 mg), as well as in the central nervous system (superior olivary nucleus, spinal cord, and lateral lemniscus) and peripheral nervous system (branches of the vagus nerve and/or Auerbach's and Meissner's plexuses) at exposures ≥ 14 times the approved human dose of 50 mg [data on file]. At 33 times the approved human dose, axonal dystrophy caused reversible hearing loss and waveform deficits in brainstem auditory evoked potential (BAEP) testing, a standard measure used to assess the auditory pathway in the brainstem. No auditory threshold deficits were noted at 6 months after the end of dosing. Because of these nonclinical results, additional diligence, including standard and specialized neurological and audiological safety evaluations and event adjudication, was conducted proactively across the ALLEGRO program. Clinical data presented in this report, including evaluation of events adjudicated as potential neurological or audiological events of interest, did not demonstrate evidence of neurotoxicity with ritlecitinib treatment. Neurological events of interest did not demonstrate a pattern or features of acute or chronic, cumulative injury to axons in the central nervous system or peripheral nervous system, such as immediate or dose-dependent onset of symptoms, that worsened over time and became unrelenting. The majority of AEs associated with neurological events of interest, such as dysesthesia, hyperesthesia, hypoesthesia, and paresthesia, are commonly

reported in the general population, were mild in severity, were considered unrelated to study treatment by the investigator, and resolved without change to study treatment. Of note, a phase 2a, placebo-controlled clinical safety study was conducted to specifically assess potential neurological/neuroaudiological effects of ritlecitinib in adults with AA through assessments of BAEP and intraepidermal axon histology. Results of the phase 2a study further confirmed the clinical safety of ritlecitinib, with no notable effects on nerve fiber counts or swelling of intraepidermal axons or integrity of the auditory pathway in the human brainstem, as assessed by BAEP (data on file, submitted for publication). Altogether, it provides evidence that the axonal dystrophy finding in dogs is not clinically relevant in humans.

5 Conclusions

This is the first report of integrated safety from multiple trials in AA of the oral, selective dual JAK3/TEC family kinase inhibitor, ritlecitinib. Ritlecitinib is well tolerated and has a safety profile appropriate for chronic clinical use. The ALLEGRO-LT long-term phase 3 study is ongoing; data from longer follow-up will provide further information on the long-term safety profile of ritlecitinib in AA.

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Declarations

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Conflict of interest Brett King: AbbVie, AltruBio, Almirall, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Myers Squibb, Concert Pharmaceuticals, Equillium, Horizon Therapeutics, Eli Lilly, Incyte, Janssen Pharmaceuticals, LEO Pharma, Otsuka/Visterra, Pfizer, Regeneron, Sanofi Genzyme, TWi Biotechnology, and Viela Bio. He has served on speaker bureaus for Pfizer. Jennifer Soung: speaker for Regeneron/Sanofi and Ortho Dermatologics; speaker and investigator for Amgen, AbbVie, and Pfizer; speaker, investigator, and advisor for Eli Lilly; investigator and advisor for LEO Pharma; investigator, speaker, and consultant for Novartis; investigator for UCB, Janssen, Kyowa Kirin, KoBio Labs, and Castel Biosciences; investigator and consultant for Dermavant; speaker and consultant for Bristol Myers Squibb, speaker, investigator and consultant for Arcutis. Christos Tziotzios: speaker for LEO Pharma; principal and chief investigator for Pfizer; consultant for Pfizer. Lidia Rudnicka: speaker for AbbVie, L'Oreal, LEO Pharma, Novartis, Pierre Fabre, and Pfizer; advisory board member for LEO Pharma, Janssen, L'Oreal, Novartis, Pfizer, Sanofi, and UCB. Pascal Joly: consultant for Amgen, Argenx, AstraZeneca, Innovaderm, Principia Biopharma, Roche, Sanofi-Regeneron Pharmaceuticals, Thermo Fisher Scientific, Novartis, Pfizer, Lilly, AbbVie, and Janssen Cilag. Melinda Gooderham: investigator, speaker, and/or advisor for AbbVie, Amgen, Akros, AnaptysBio, Arcutis, Bausch Health, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck, Moonlake, Nimbus, Novartis, Pfizer, Regeneron, Reistone, Roche, Sanofi Genzyme, Sun Pharma, and UCB. Rodney Sinclair: professional services to Aerotech, AbbVie, AstraZeneca, Akesobio, Amgen, Arcutis, Arena, Ascend, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Coherus Biosciences, Connect, Cutanea, Demira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MedImmune, Merck, MSD, Novartis, Oncobiologics, Pfizer, Regeneron, Reistone, Roche, Samson Clinical, Sanofi, Sun Pharma, and UCB. Natasha A. Mesinkovska: professional services to AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Concert Pharmaceuticals, Eli Lilly, La Roche Posay, and Pfizer. Carle Paul: consulting fees and/or grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, GSK, Janssen Cilag, LEO Pharma, Eli Lilly, Novartis, Pierre Fabre, Pfizer, Sanofi, and UCB Pharma. Yankun Gong, Helen Tran, Robert Wolk, Samuel H. Zwillich, and Alexandre Lejeune are employees of, and hold stock or stock options in, Pfizer. Susan D. Anway was an employee of Pfizer at the time of the study and holds stock or stock options in Pfizer.

Data availability Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Ethics approval Ethics approval was obtained for individual studies included in this integrated safety analysis. The study was performed in accordance with the ethical standards as provided in the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all participants of the individual studies included in this integrated safety analysis.

Patient consent to publish Patients signed informed consent regarding publishing their data.

Code availability Not applicable.

Author contributions All authors contributed to the concept and design of the study, to data analysis and interpretation, to critical revision of the publication, and all authors read and approved the final manuscript.

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