Updated Integrated Safety Analysis of Ritlecitinib Over 72 Months In Patients With Alopecia Areata From the ALLEGRO Clinical Trial Program

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SYNOPSIS

- Alopecia areata (AA) is an autoimmune disease that is characterized by nonscarring hair loss of the scalp, face, and/or body[1]
- Ritlecitinib, an oral, selective dual inhibitor of JAK3/TEC family kinases, demonstrated efficacy and safety in patients ≥12 years of age with AA in the ALLEGRO phase 2b/3 study (NCT03732807) up to 48 weeks[2,3]
- Ritlecitinib had an acceptable safety profile in patients ≥12 years of age with AA in two ALLEGRO phase 2a studies, the ALLEGRO-2b/3 study, and the ALLEGRO-LT study (NCT04006457) up to 24 months[4]

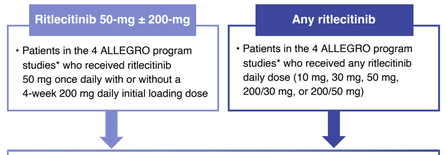
OBJECTIVE

- This updated integrated analysis of two phase 2a studies, the ALLEGRO phase 2b/3 study, and the ALLEGRO-LT phase 3 study investigated the long-term safety of ritlecitinib over 72 months in patients with AA

METHODS

Analysis populations

Figure 1. Analysis populations



AA, alopecia areata.
*The 4 ALLEGRO studies included a Phase 2a safety study (ALLEGRO-2a safety, NCT04517864; completed), a Phase 2a study (ALLEGRO-2a, NCT02974868; completed), a Phase 2b/3 study (ALLEGRO-2b/3, NCT03732807; completed), and an ongoing, long-term open-label Phase 3 study (ALLEGRO-LT, NCT04006457; ongoing). Data cutoff for the ongoing ALLEGRO LT was 25 June 2024.
†Patients in ALLEGRO-2a safety, ALLEGRO-2a, and ALLEGRO-2b/3 had ≥50% scalp hair loss; de novo patients in ALLEGRO-LT had ≥25% scalp hair loss.

Statistical analysis

- Safety data were integrated from the four phase 2 and phase 3 studies and summarized descriptively using counts and percentages for adverse events (AEs) and lab abnormalities in each cohort
  - Events were evaluated from the start of the patients' first dose of ritlecitinib
  - In the ritlecitinib 50-mg ± 200-mg group, events were evaluated from the time a patient started the 50 mg dose (or the 200 mg loading dose), as some patients received placebo or other ritlecitinib doses before switching to ritlecitinib 50 mg
- Study-size adjusted incidence rates of AEs were reported per 100 patient-years and are presented along with mid-p Gamma confidence intervals
- Data cutoff for the ongoing ALLEGRO-LT study was June 25, 2024

RESULTS

Baseline characteristics and patient disposition

- 1228 patients were included in the ritlecitinib 50-mg ± 200-mg group, and an additional 66 patients (1294) were included in the any ritlecitinib group (**Table 1**)

Table 1. Demographic and baseline characteristics

	Ritlecitinib 50-mg ± 200-mg (N=1228)*	Any ritlecitinib (N=1294)*
Age, mean (SD), years	33.8 (14.0)	33.8 (14.0)
Female, n (%)	780 (63.5)	822 (63.5)
Race, n (%)		
White	861 (70.1)	904 (69.9)
Asian	270 (22.0)	287 (22.2)
Black	52 (4.2)	55 (4.3)
Other	28 (2.3)	30 (2.3)
Weight, mean (SD), kg	70.9 (17.9)	70.9 (17.7)
AT/AU, n (%)†	503 (41.0)	534 (41.3)
AA disease duration, median (IQR), years	6.7 (2.6-13.5)	6.7 (2.7-13.5)

AT, alopecia totalis; AU, alopecia universalis.
*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.
†AT/AU was defined as a baseline SALT score of 100 (complete scalp hair loss).

- At the time of data cutoff for the ongoing ALLEGRO-LT study, 56.7% and 55.3% of patients in the ritlecitinib 50-mg ± 200-mg group and any ritlecitinib group, respectively, were either ongoing or had completed the study (**Table 2**)
  - The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients

Table 2. Patient disposition

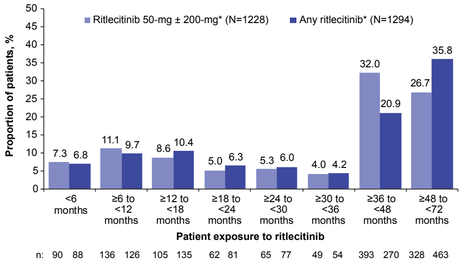
	Ritlecitinib 50-mg ± 200-mg (N=1228)*	Any ritlecitinib (N=1294)*
Ongoing at the data cutoff†	182 (14.8)	182 (14.1)
Completed	514 (41.9)	533 (41.2)
Completed the study	70 (5.7)	89 (6.9)
Removed from study per protocol as commercial drug became available	444 (36.2)	444 (34.3)
Discontinued	532 (43.3)	579 (44.7)
Adverse event‡	81 (6.6)	90 (7.0)
Other§	451 (36.7)	489 (37.8)

AE, adverse event; SAE, serious adverse event; SALT, Severity of Alopecia Tool.
*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.
†Data cutoff for the ongoing ALLEGRO-LT study was 25 June 2024.
‡Treatment discontinuation and participant withdrawal from the study were required in the study protocol for the following AEs: serious infections (defined as any infection requiring parenteral antimicrobial therapy or hospitalization for treatment or meeting other criteria that require the infection to be classified as a SAE), treatment-related SAEs, or other SAEs or severe AEs (at the discretion of the investigator or sponsor); clinically meaningful and treatment-emergent declines in hearing from baseline were discussed with the sponsor for possible withdrawal from study.
§Discontinued due to death, lack of efficacy, lost to follow-up, non-compliance with study drug, physician's decision, pregnancy, protocol deviation, study terminated by sponsor, withdrawal by subject, no longer meets eligibility criteria (i.e., adolescents who did not meet the protocol continuation criteria in ALLEGRO-LT [i.e., did not achieve a ≥50% improvement in SALT score at Month 3 from baseline in ALLEGRO 2b/3, or a SALT score of ≤20 at Month 6]), or other.

Exposure to study drug

- Median duration of exposure was 1197 days (range: 453-1371) in the 50-mg ± 200-mg group and 1204 days (range: 453-1444) in the any-ritlecitinib group. Total patient-years of exposure was 3261.5 and 3539.5 in the 50-mg ± 200-mg and any-ritlecitinib groups, respectively
- 68% and 67% of patients had ≥24 months of exposure to ritlecitinib, and 59% and 57% had ≥36 months of exposure in the 50-mg ± 200-mg and any-ritlecitinib groups, respectively (**Figure 2**)

Figure 2. Patient exposure to ritlecitinib



*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.

Adverse events overview

- 1070 (87.1%) and 1158 (89.5%) patients experienced AEs and 84 (6.8%) and 88 (6.8%) of patients experienced serious AEs (SAEs) in the 50-mg ± 200-mg and any-ritlecitinib groups, respectively (**Table 3**)
- There were 2 deaths (due to breast cancer and due to acute respiratory failure/cardiorespiratory arrest) in the ALLEGRO clinical trial program; both deaths were assessed by the investigator as unrelated to study treatment
- The cumulative safety data were similar to those previously reported,[4] and no new safety signals were identified (**Table 3**)

Table 3. Overview of AEs in the ritlecitinib 50-mg ± 200-mg and any ritlecitinib groups

	Ritlecitinib 50-mg ± 200-mg (N=1228)*		Any ritlecitinib (N=1294)*	
	n (%)	IR (95% CI)†	n (%)	IR (95% CI)†
AE	1070 (87.1)	148.08 (139.39-157.17)	1158 (89.5)	167.90 (158.43-177.79)
SAE	84 (6.8)	2.56 (2.05-3.16)	88 (6.8)	2.47 (1.99-3.03)
Death	2 (0.2)	0.06 (0.01-0.21)	2 (0.2)	0.05 (0.01-0.19)
Most frequent AEs‡				
SARS-CoV-2 test positive	242 (19.7)	8.40 (7.38-9.52)	250 (19.3)	7.97 (7.03-9.02)
Headache	231 (18.8)	7.97 (6.98-9.05)	272 (21.0)	8.89 (7.87-9.99)
Nasopharyngitis	175 (14.3)	5.81 (4.99-6.73)	212 (16.4)	6.69 (5.83-7.64)
Upper respiratory tract infection	167 (13.6)	5.49 (4.70-6.38)	194 (15.0)	5.90 (5.11-6.78)
Pyrexia	134 (10.9)	4.28 (3.59-5.06)	138 (10.7)	4.06 (3.42-4.79)
Cough	131 (10.7)	4.27 (3.58-5.06)	134 (10.4)	3.95 (3.32-4.67)
Acne	126 (10.3)	4.08 (3.41-4.85)	150 (11.6)	4.58 (3.89-5.37)
Oropharyngeal pain	119 (9.7)	3.82 (3.17-4.56)	125 (9.7)	3.66 (3.05-4.34)

AE, adverse event; CI, confidence interval; IR, incidence rate; PY, patient-years; SAE, serious adverse event.
*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.
†Study-size adjusted results per 100 PY and mid-p gamma intervals.
‡8 most frequent AEs in the any-ritlecitinib cohort, by preferred term

- Compared with the May 30, 2022 data cutoff,[4] there were:
  - Two new events of multi-dermatomal herpes zoster adjudicated as opportunistic infections
  - Three new events of malignancy excluding nonmelanoma skin cancer (2 adjudicated as cervical dysplasia and 1 as intraductal proliferative breast lesion)
  - Six new events of nonmelanoma skin cancer (5 adjudicated as basal cell carcinoma and 1 as squamous cell carcinoma)
  - Four additional participants with cardiovascular events (acute myocardial infarction [2 participants], myocardial infarction [1 participant], and cerebrovascular accident [1 participant]) adjudicated as major adverse cardiovascular events
- The incidence rates for AEs of special interest (**Table 4**) were similar to those previously reported,[4] with no change to the overall safety profile of ritlecitinib

Table 4. AEs of special interest

	Ritlecitinib 50-mg ± 200-mg (N=1228)*		Any ritlecitinib (N=1294)*	
	n (%)	IR (95% CI)†	n (%)	IR (95% CI)†
Serious infections‡	20 (1.6)	0.61 (0.38-0.93)	22 (1.7)	0.61 (0.38-0.91)
Opportunistic infections§	3 (0.2)	0.09 (0.02-0.26)	3 (0.2)	0.08 (0.02-0.23)
Herpes zoster	32 (2.6)	0.99 (0.68-1.38)	34 (2.6)	0.95 (0.67-1.32)
Malignances (excl. NMSC)¶	9 (0.7)	0.27 (0.12-0.5)	10 (0.8)	0.27 (0.13-0.49)
NMSC¶	9 (0.7)	0.26 (0.12-0.49)	9 (0.7)	0.25 (0.11-0.46)
MACE¶‖	7 (0.6)	0.20 (0.08-0.40)	7 (0.5)	0.19 (0.08-0.39)
VTE¶	1 (<0.1)	0.03 (0.00-0.16)	1 (<0.1)	0.03 (0.00-0.14)

CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, patient-years; VTE, venous thromboembolic event.
*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.
†Study-sized adjusted results per 100 PY and mid-p gamma intervals.
‡Serious infections were defined as any serious adverse event in the infections and infestations system organ class.
§Adjudicated safety events.
¶MACE was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Laboratory abnormalities

- Three participants had elevated creatine phosphokinase reported as treatment-emergent adverse events of rhabdomyolysis, considered by the investigator to be related to a recently started new exercise regimen or physical activity. All 3 events were mild and considered not related to the study intervention, the study intervention was not interrupted, and the events were resolved
- There were no clinically meaningful changes or safety signals identified when compared with those previously reported[4] (**Tables 5 and 6**)

Table 5. CTCAE Grade ≥2 hematological parameters

Parameter (CTCAE grade), n (%)		Ritlecitinib 50-mg ± 200-mg (N=1228)*	Any ritlecitinib (N=1294)*
Anemia (Hgb)	Grade 2: <10.0-8.0 g/dL	24 (2.0)	26 (2.0)
	Grade 3: <8.0 g/dL	1 (<0.1)	1 (<0.1)
Neutrophil count decreased	Grade 2: <1500-1000/mm³	66 (5.4)	80 (6.2)
	Grade 3: <1000-500/mm³	12 (1.0)	13 (1.0)
	Grade 4: <500/mm³	1 (<0.1)	1 (<0.1)
Lymphocyte count decreased	Grade 2: <800-500/mm³	272 (22.1)	282 (21.8)
	Grade 3: <500-200/mm³	40 (3.3)	42 (3.2)
	Grade 4: <200/mm³	2 (0.2)	2 (0.2)
Platelets†	Grade 2: <75.0-50.0 × 10³/mm³	1 (<0.1)	1 (<0.1)

CTCAE, Common Terminology Criteria for Adverse Events; Hgb, hemoglobin.
*The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.
†There were no cases of Grade 3 or higher decreases in platelets.

Table 6. Laboratory test abnormalities

n/N* (%)	Ritlecitinib 50-mg ± 200-mg (N=1223)†	Any ritlecitinib (N=1286)†
Aspartate aminotransferase >5x ULN	17/1221 (1.4)	19/1282 (1.5)
Alanine aminotransferase >5x ULN	10/1221 (0.8)	12/1282 (0.9)
Total bilirubin >2x ULN	12/1221 (1.0)	13/1282 (1.0)
CPK increased >10x ULN	38/1228 (3.1)	49/1294 (3.8)

CPK, creatine phosphokinase; ULN, upper limit of normal.
*N is defined as the total number of participants with at least one post-baseline observation of the given laboratory test for each treatment group.
†The analysis groups are not additive and are overlapping populations, with the any ritlecitinib group including all patients.

CONCLUSIONS

- Treatment with ritlecitinib in patients with AA was well tolerated over 72 months and up to 3539.5 patient-years of exposure, and safety was consistent with previously reported data.[4,5] There is no change to the general safety profile of ritlecitinib

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DISCLOSURES

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