Integrated Safety Analysis of Ritlecitinib for the Treatment of Alopecia Areata (AA) From the Phase 2 and Phase 3 ALLEGRO Clinical Trial Program

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BACKGROUND & OBJECTIVE

- AA is an autoimmune disease with an underlying immunoinflammatory pathogenesis characterized by nonscarring hair loss ranging from small bald patches to complete loss of scalp, face, and body hair[1]
- In the ALLEGRO phase 2b/3 study, ritlecitinib, an oral JAK3/TEC family kinase inhibitor, demonstrated efficacy and safety up to 48 weeks in patients aged ≥12 years with AA[2]
- Here we present an integrated safety analysis of ritlecitinib in patients with AA from 4 studies from the ALLEGRO clinical trial program

ANALYSIS POPULATIONS

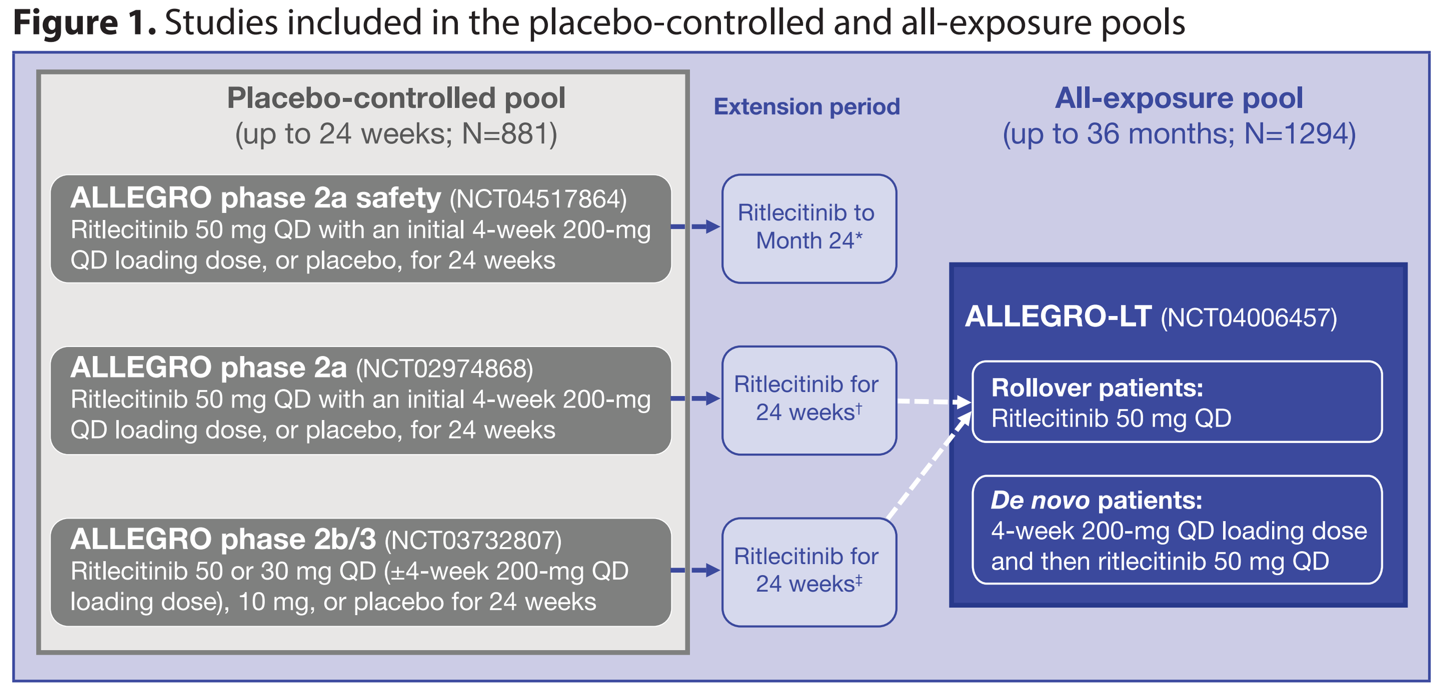
Two pools were analyzed:

- A **placebo-controlled pool** (up to 24 weeks)
- An **all-exposure pool:** patients who received ≥1 ritlecitinib dose (up to 36 months)
  - Data were analyzed for those exposed to any ritlecitinib dose (10 mg, 30 mg, 50 mg, 200/30 mg, or 200/50 mg) and for patients who only received ritlecitinib 50 mg (±200-mg loading dose)

Key eligibility criteria included:

- Male or female aged ≥12 years
- Diagnosis of AA with ≥25% or ≥50% scalp hair loss
- Current AA episode duration of 6 months to 10 years
- No concomitant treatments for AA allowed

Figure 1. Studies included in the placebo-controlled and all-exposure pools



*In the ALLEGRO phase 2a safety study, the placebo-controlled period continued to Month 9. At Month 9, patients entered an active therapy extension; placebo groups switched to 200/50 mg and the 50-mg group continued 50 mg until Month 24. †In the ALLEGRO phase 2a study, following a 4-week washout period after Week 24, patients could continue treatment in a 24-week single-blind extension in which placebo and active nonresponders received 200/50 mg. After another 4-week washout period, nonresponders could enter into a 24-week, cross-over, open label extension period. ‡In ALLEGRO-2b/3, after Week 24, ritlecitinib groups continued their 50-, 30-, or 10-mg maintenance doses for another 24 weeks, and patients initially assigned to placebo switched to ritlecitinib 200/50 mg or 50 mg daily for 24 weeks. Eligible patients who completed ALLEGRO-2a or -2b/3 could roll over into ALLEGRO-LT. Data cutoff for ALLEGRO-LT and the phase 2a safety study: May 30, 2022.

STATISTICAL METHODS

- Safety data were integrated from the 4 phase 2/3 studies and were summarized descriptively using counts and percentages for adverse events (AEs) and lab abnormalities in each pool
  - In the all-exposure pool, safety events were evaluated:
    - Any-ritlecitinib group: from the start of the patients' first dose of ritlecitinib (any ritlecitinib dose: 10 mg, 30 mg, 50 mg, 200/30 mg, or 200/50 mg)
    - Ritlecitinib 50-mg group: 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
- Incidence rates (IRs) are reported
  - Study-size–adjusted IRs were reported per 100 patient-years (PY) and are presented with mid-p gamma CIs

RESULTS

- This analysis includes data from a total of 1294 patients, representing 2091.7 total patient-years of exposure to any dose of ritlecitinib
- Median ritlecitinib exposure was 624 days; 69% of patients had ≥18 months of ritlecitinib exposure at the time of data cut off
- Baseline characteristics were generally similar and well balanced between groups in the placebo-controlled pool

Table 1. Duration of treatment and patient exposure

	All-Exposure Pool (N=1294)	
Duration of exposure	Ritlecitinib 50 mg* (n=1228)	Any ritlecitinib (n=1294)
Median (range), days	547 (1-1181)	624 (1-1181)
Mean (SD), days	540 (245)	590 (266)
Total patient-years	1813.7	2091.7

QD, once daily.
*Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose.

Table 2. Baseline characteristics

	Placebo-Controlled Pool (N=881)				All-Exposure Pool (N=1294)	
	Placebo (n=213)	Ritle 10 mg (n=62)	Ritle 30 mg* (n=261)	Ritle 50 mg† (n=345)	Ritle 50 mg† (n=1228)	Any-ritlecitinib (n=1294)
Age, mean (SD), years	35.0 (14.0)	34.6 (13.9)	33.7 (14.3)	34.1 (13.6)	33.8 (14.0)	33.8 (14.0)
Female, n (%)	140 (65.7)	42 (67.7)	165 (63.2)	213 (61.7)	780 (63.5)	822 (63.5)
Race, n (%)						
White	167 (78.4)	41 (66.1)	181 (69.3)	234 (67.8)	861 (70.1)	904 (69.9)
Asian	33 (15.5)	17 (27.4)	62 (23.8)	82 (23.8)	270 (22.0)	287 (22.2)
Black	8 (3.8)	2 (3.2)	9 (3.4)	22 (6.4)	52 (4.2)	55 (4.3)
Other	4 (1.9)	1 (1.6)	8 (3.1)	4 (1.2)	28 (2.3)	30 (2.3)
Weight, mean (SD), kg	73.2 (22.2)	68.8 (17.8)	70.4 (16.9)	72.3 (17.9)	71.1 (18.2)	71.1 (18.0)
AT/AU, n (%)‡	92 (43.2)	29 (46.8)	121 (46.4)	149 (43.2)	502 (40.9)	533 (41.2)
AA disease duration, median (IQR), years	7.2 (2.4-14.0)	7.2 (3.1-17.2)	6.8 (2.9-13.7)	6.9 (2.8-13.0)	6.7 (2.6-13.5)	6.7 (2.7-13.5)

*Patients received ritlecitinib 30 mg QD ± an initial 4-week 200-mg QD loading dose. †Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose. ‡AT/AU was defined as a baseline SALT score of 100 (complete scalp hair loss).

- AEs were generally mild, self-limiting, and seldom required dose interruption or permanent discontinuation of treatment
- In the all-exposure pool, most SAEs were in the Infections and Infestations SOC (n=14 [1.1%])
- There were 2 deaths; 1 patient died of breast cancer (spindle cell carcinoma) and 1 of acute respiratory failure/cardiorespiratory arrest; both events were assessed by the investigator as unrelated to study treatment

Table 3. Overview of AEs

	Placebo-Controlled Pool (N=881)				All-Exposure Pool (N=1294)	
n (%) **IR** (95% CI)*	Placebo (n=213)	Ritle 10 mg (n=62)	Ritle 30 mg† (n=261)	Ritle 50 mg‡ (n=345)	Ritle 50 mg‡ (n=1228)	Any-ritlecitinib (n=1294)
AEs	148 (69.5) **324** (272-383)	43 (69.4) **251** (184-334)	186 (71.3) **275** (238-317)	249 (72.2) **353** (311-400)	989 (80.5) **161** (151-171)	1094 (84.5) **180** (169-191)
SAEs	4 (1.9) **4.5** (1.3-11.4)	2 (3.2) **5.8** (1.0-19.0)	1 (0.4) **0.7** (0.0-3.4)	4 (1.2) **2.7** (0.9-6.5)	52 (4.2) **2.8** (2.1-3.7)	57 (4.4) **2.6** (2.0-3.4)
Severe AEs	5 (2.3) **5.0** (1.7-12.1)	2 (3.2) **5.9** (1.0-19.3)	10 (3.8) **7.0** (3.6-12.5)	6 (1.7) **4.1** (1.6-8.4)	66 (5.4) **3.6** (2.8-4.6)	83 (6.4) **3.9** (3.1-4.8)
Discontinuations due to AEs	5 (2.3) **4.2** (1.4-10.6)	2 (3.2) **5.8** (1.0-19.0)	4 (1.5) **2.8** (0.9-6.7)	8 (2.3) **5.0** (2.3-9.6)	68 (5.5) **3.6** (2.8-4.6)	78 (6.0) **3.6** (2.8-4.5)
Death	0	0	0	0	2 (0.2) **0.1** (0.0-0.4)	2 (0.2) **0.1** (0.0-0.3)

*Study-size–adjusted IRs are per 100 PY and are presented with mid-p gamma CIs. †Patients received ritlecitinib 30 mg QD ± an initial 4-week 200-mg QD loading dose. ‡Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose.

Table 4. Common TEAEs

	Placebo-Controlled Pool (N=881)				All-Exposure Pool (N=1294)	
n (%) **IR** (95% CI)*	Placebo (n=213)	Ritle 10 mg (n=62)	Ritle 30 mg† (n=261)	Ritle 50 mg‡ (n=345)	Ritle 50 mg‡ (n=1228)	Any-ritlecitinib (n=1294)
Headache	17 (8.0) **19.0** (11.1-30.9)	11 (17.7) **35.9** (18.9-62.4)	30 (11.5) **22.5** (15.5-31.8)	32 (9.3) **21.3** (4.7-29.8)	186 (15.1) **10.7** (9.3-12.4)	229 (17.7) **11.9** (10.4-13.5)
SARS-CoV-2 test positive	1 (0.5) **1.3** (0.1-6.6)	0	4 (1.5) **2.8** (0.9-6.7)	4 (1.2) **2.7** (0.9-6.5)	192 (15.6) **10.7** (9.2-12.3)	201 (15.5) **9.8** (8.5-11.2)
Nasopharyngitis	15 (7.0) **14.8** (8.2-24.9)	6 (9.7) **18.5** (7.5-38.4)	34 (13.0) **25.3** (17.8-35.0)	34 (9.9) **23.2** (16.3-32.1)	117 (9.5) **6.6** (5.5-7.9)	160 (12.4) **8.2** (7.0-9.5)
Acne	10 (4.7) **10.3** (5.0-19.4)	3 (4.8) **8.9** (2.3-24.2)	14 (5.4) **9.9** (5.6-16.2)	20 (5.8) **12.7** (8.0-19.4)	111 (9.0) **6.2** (5.1-7.4)	135 (10.4) **6.8** (5.7-8.0)
Upper respiratory tract infection	16 (7.5) **17.1** (9.7-28.2)	2 (3.2) **5.8** (1.0-19.3)	21 (8.0) **15.1** (9.6-22.6)	29 (8.4) **19.7** (13.4-28.0)	104 (8.5) **5.9** (4.8-7.1)	132 (10.2) **6.5** (5.4-7.7)
Pyrexia	0	1 (1.6) **2.9** (0.1-14.3)	3 (1.1) **2.1** (0.5-5.6)	8 (2.3) **5.3** (2.4-10.0)	93 (7.6) **5.0** (4.1-6.1)	98 (7.6) **4.6** (3.8-5.6)
Cough	2 (0.9) **2.7** (0.4-8.8)	0	3 (1.1) **2.1** (0.5-5.6)	6 (1.7) **4.1** (1.6-8.5)	93 (7.6) **5.2** (4.2-6.3)	96 (7.4) **4.5** (3.7-5.5)
Fatigue	5 (2.3) **4.3** (1.4-10.7)	2 (3.2) **5.9** (1.0-19.5)	12 (4.6) **8.5** (4.6-14.4)	5 (1.4) **3.4** (1.2-7.5)	77 (6.3) **4.2** (3.3-5.2)	91 (7.0) **4.3** (3.5-5.3)

Most frequent AEs in the any-ritlecitinib pool, >5% by preferred term.
*Study-size–adjusted IRs are per 100 PY and are presented with mid-p gamma CIs. †Patients received ritlecitinib 30 mg QD ± an initial 4-week 200-mg QD loading dose. ‡Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose.

- One event of multi-dermatomal herpes zoster was adjudicated as an opportunistic infection
- There were 4 events adjudicated as breast cancer and 1 event each of testis cancer, papillary thyroid cancer, and malignant melanoma
- One event of pulmonary embolism was adjudicated as a VTE

Table 5. AEs of special interest

	Placebo-Controlled Pool (N=881)				All-Exposure Pool (N=1294)	
n (%) **IR** (95% CI)*	Placebo (n=213)	Ritle 10 mg (n=62)	Ritle 30 mg‡ (n=261)	Ritle 50 mg§ (n=345)	Ritle 50 mg§ (n=1228)	Any-ritlecitinib (n=1294)
Serious infections	0	0	1 (0.4) **0.7** (0.0-3.4)	2 (0.6) **1.3** (0.2-4.4)	12 (1.0) **0.7** (0.4-1.1)	14 (1.1) **0.6** (0.4-1.1)
Opportunistic infections†	0	0	0	1 (0.3) **0.5** (0.0-2.9)	1 (<0.1) **0.1** (0.0-0.3)	1 (<0.1) **0.1** (0.0-0.2)
Herpes zoster	0	0	2 (0.8) **1.4** (0.2-4.6	3 (0.9) **1.9** (0.5-5.2)	18 (1.5) **1.0** (0.6-1.6)	20 (1.5) **0.9** (0.6-1.4)
Herpes simplex	5 (2.3) **5.1** (1.7-12.1)	1 (1.6) **2.9** (0.1-14.2)	8 (3.1) **5.6** (2.6-10.6	3 (0.9) **1.9** (0.5-5.2)	25 (2.0) **1.3** (0.9-1.9)	37 (2.9) **1.7** (1.2-2.4)
Malignancies (excl NMSC)†	0	0	0	1 (0.3) **0.7** (0.0-3.3)	7 (0.6) **0.4** (0.2-0.8)	7 (0.5)¶ **0.3** (0.1-0.6)
NMSC†	0	0	0	0	3 (0.2) **0.2** (0.0-0.4)	3 (0.2) **0.1** (0.0-0.4)
MACE†	0	0	0	0	3 (0.2) **0.2** (0.0-0.4)	3 (0.2) **0.1** (0.0-0.4)
VTE†	0	0	0	0	1 (<0.1) **0.1** (0.0-0.3)	1 (<0.1) **0.1** (0.0-0.2)

*Study-size–adjusted IRs are per 100 PY and are presented with mid-p gamma CIs. †Adjudicated safety events. ‡Patients received ritlecitinib 30 mg QD ± an initial 4-week 200-mg QD loading dose. §Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose. ¶One event of malignant melanoma was reported after the 30-day reporting period.

- Discontinuations due to changes in hematologic and laboratory parameters were infrequent
- 3 (0.2%) patients discontinued due to increased CPK levels; no events of rhabdomyolysis were reported
- There were no meaningful changes in median AST or ALT levels; no potential cases of drug-induced liver injury or Hy's law were reported

Table 6. Changes in hematologic and laboratory parameters

Parameter (CTCAE grade), n (%)		Placebo-Controlled Pool (N=881)				All-Exposure Pool (N=1294)	
		Placebo (n=213)	Ritle 10 mg (n=62)	Ritle 30 mg* (n=261)	Ritle 50 mg† (n=345)	Ritle 50 mg† (n=1228)	Any-ritlecitinib (n=1294)
Anemia (Hgb)	Grade 2: <10.0-8.0 g/dL	2 (0.9)	1 (1.6)	1 (0.4)	0	11 (0.9)	13 (1.0)
	Grade 3: <8.0 g/dL	0	0	0	0	1 (<0.1)‡	1 (<0.1)‡
Neutrophil count decreased	Grade 2: <1500-1000/mm³	6 (2.8)	3 (4.8)	12 (4.7)	6 (1.7)	51 (4.2)	66 (5.1)
	Grade 3: <1000-500/mm³	0	0	0	0	9 (0.7)	10 (0.8)
Lymphocyte count decreased	Grade 2: <800-500/mm³	5 (2.4)	2 (3.2)	16 (6.2)	22 (6.4)	201 (16.4)	212 (16.5)
	Grade 3: <500-200/mm³	0	0	2 (0.8)	4 (1.2)	25 (2.0)	27 (2.1)
	Grade 4: <200/mm³	0	0	0	1 (0.3)§	1 (<0.1)§	1 (<0.1)§
CPK increased	Grade 2 (>2.5-5× ULN)	3 (1.4)	1 (1.6)	4 (1.6)	9 (2.6)	64 (5.2)	70 (5.5)
	Grade 3 (>5-10× ULN)	1 (0.5)	1 (1.6)	3 (1.2)	11 (3.2)	37 (3.0)	37 (2.9)
	Grade 4 (>10× ULN)	1 (0.5)	1 (1.6)	4 (1.6)	5 (1.5)	28 (2.3)	39 (3.0)
AST >3× ULN		0	1 (1.6)	2 (0.8)	2 (0.6)	23 (1.9)	30 (2.3)
ALT >3× ULN		0	1 (1.6)	3 (1.2)	3 (0.9)	28 (2.3)	32 (2.5)
HDL cholesterol (mg/dL) <0.8× LLN		0	0	1 (0.4)	3 (1.0)	5 (0.4)	7 (0.6)
LDL cholesterol (mg/dL) >1.2× ULN		0	1 (1.6)	1 (0.4)	2 (0.7)	16 (1.4)	19 (1.6)
Triglycerides (mg/dL) >1.3× ULN		8 (4.6)	4 (6.6)	13 (5.1)	11 (3.6)	83 (7.2)	99 (8.2)

n based on number of patients with single, unconfirmed values meeting each CTCAE grade criterion during study treatment or lag time (35 days). There were no cases of Grade ≥2 decreases in platelets (<75,000/mm³) *Patients received ritlecitinib 30 mg QD ± an initial 4-week 200-mg QD loading dose. †Patients received ritlecitinib 50 mg QD ± an initial 4-week 200-mg QD loading dose. ‡This patient had a baseline Hgb of 12.7 g/dL. On Day 265, an NSAE of anemia (moderate) was reported due to Hgb of 7.8 g/dL, and study drug was temporarily interrupted. Hgb levels returned to within normal range (11.9 g/dL), and the patient later withdrew for private reasons. §This patient did not meet the per-protocol lymphocyte criteria for discontinuation (<500/mm³) as the result was not confirmed upon retest.

CONCLUSIONS

- This integrated safety analysis of 4 trials of ritlecitinib in 1294 patients aged ≥12 years with AA, reflecting 2092 patient-years of exposure (median: 1.7 years), revealed no new safety signals and was consistent with the known safety profile of ritlecitinib
- The most frequently reported AEs were headache, SARS-CoV-2 test positive, nasopharyngitis, acne, and upper respiratory tract infection
  - Most AEs were mild in severity and did not require dose interruption or permanent treatment discontinuation; 6% of patients (78/1294) discontinued due to AEs
- Long-term changes in laboratory parameters were generally minimal, and levels remained stable through the course of treatment
- Longer follow-up is needed to assess the risk of rare events, such as malignancies and cardiovascular events
- Data from across the ALLEGRO program suggest that the long-term safety profile of ritlecitinib is favorable and supports its use for the long-term treatment of AA

REFERENCES

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ABBREVIATIONS

AA, alopecia areata; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, alopecia totalis; AU, alopecia universalis; CI, confidence interval; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; HDL, high-density lipoprotein; Hgb, hemoglobin; IQR, interquartile range IR, incidence rate; LDL, low-density lipoprotein; LLN, lower limit of normal; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; NSAE, nonserious adverse event; PY, patient-years; QD, once daily; Ritle, ritlecitinib; SALT, Severity of Alopecia Tool; SAE, serious AE; SOC, system organ class; TEAE, treatment-emergent AE; ULN, upper limit of normal; VTE, venous thromboembolic event.

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