SUPPLEMENTAL MATERIALS

Updated integrated safety analysis of ritlecitinib up to ~5 years in patients with alopecia areata from the ALLEGRO clinical trial program

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Table S1. Death narratives

Age, years	Race	Sex	SAE(s) with fatal outcome, Preferred Term	Dose	Event start day	Event end day	Medical history	Event outcome	Causality assessment
64	Asian	Female	Breast cancer (spindle cell carcinoma)	200/50 mg	ALLEGRO-LT Day 90	ALLEGRO-LT Day 353	- Atopic dermatitis - Hypertension - Cystitis - History of alcohol use - Nonsmoker - No hormone replacement therapy - No family history of breast cancer - Oral contraceptive pills for >10 years - Menopause at age 51 years	Fatal	Not related to the study intervention (per investigator and per sponsor)
51	White	Female	Acute respiratory failure and cardio-respiratory arrest	ALLEGRO-2b/3, Days 1 to 337: 10 mg ALLEGRO-LT, Days 1 to 233: 50 mg	ALLEGRO-LT Day 234	ALLEGRO-LT Day 234	- Asthma - Prior smoker - Acute bronchitis Study Day 84 (considered mild by Investigator), resolved on Study Day 93 - Worsening asthma on Study Day 155	Fatal	Not related to the study intervention (per investigator and per sponsor)

SAE, serious adverse event.

Table S2. Details of patients with serious adverse events of adjudicated malignancy (excluding NMSC)

Baseline Age, years	Race	Sex	Preferred Term	Dose at time of onset	Event start day	Event end day	Risk factors	Event outcome	Causality assessment
64	Asian	Female	Breast cancer (spindle cell carcinoma)	50 mg	90	353	- History of alcohol use	Fatal	Not related (per investigator and per sponsor)
66	White	Female	Breast cancer	50 mg	124	-	- Current smoker - Mild alcohol use - Sedentary lifestyle - Estrogen hormone therapy for 5 years - Family history of breast cancer	Ongoing	Related to study intervention (per investigator and per sponsor)
58	White	Female	Breast cancer	50 mg	195	566	- History of smoking and alcohol use	Recovered/ resolved	Related to study intervention (per investigator) Not related to study intervention (per sponsor)
46	White	Female	Invasive lobular breast carcinoma	50 mg	68	-	- History of smoking and alcohol use	Ongoing	Not related (per investigator and per sponsor)
21	Multiracial	Male	Testicular cancer	50 mg	217	223	None	Recovered/ resolved	Related to the study intervention (per investigator) Not related (per sponsor)
26	White	Male	Papillary thyroid cancer	50 mg	116	-	None	Not recovered/ not resolved	Not related (per investigator and per sponsor)
50	White	Female	Malignant melanoma	50 mg	314	-	- Fair skinned with blond hair/ blue eyes	Ongoing	Related to the study intervention

Baseline Age, years	Race	Sex	Preferred Term	Dose at time of onset	Event start day	Event end day	Risk factors	Event outcome	Causality assessment
							- Current smoker - Previous sunburn - Left shin atypical squamoproliferative lesion		(per investigator and per sponsor)
New events adjudicated as malignancy excluding NMSC since the previous data cut (King et al. 2024)									
29	White	Female	Cervical dysplasia	30 mg	ALLEGRO-2b/3 Day 263	ALLEGRO-LT Day 348	-	Recovered/ Resolved	Not related (per investigator)
28	White	Female	Cervical dysplasia	50 mg	Day 544	Day 572	-	Recovered/ Resolved	Not related (per investigator)
50s	-	Female	Intraductal proliferative breast lesion	50 mg	Day 466	Day 566	-	Ongoing at the time of study withdrawal	Related to study intervention (per investigator)

NMSC, nonmelanoma skin cancer.

Table S3. Details of patients with serious adverse events adjudicated as major adverse cardiovascular events or venous thromboembolism

Age	Race	Sex	Preferred Term	Dose at time of onset	Event start day	Event end day	Risk factors	Event outcome	Causality assessment
51	White	Female	Acute respiratory failure, cardiorespiratory failure	50 mg	234	234	Asthma; prior history of smoking; AE of acute bronchitis (Day 84; resolved)	Fatal	Not related (per investigator and per sponsor)
49	Unknown	Male	Acute myocardial infarction	50 mg	384	-	Smoker; hyperlipidemia; diabetes	Ongoing	Not related (per investigator and per sponsor)
48	White	Female	Retinal artery occlusion	50 mg	442	445	Congenital arterial malformation (pulsating lesion right carotid congenital anomaly); family history of atrial septal defect	Recovered / resolved with sequalae	Not related (per investigator and per sponsor)
54	White	Female	Pulmonary embolism	50 mg	169	178	SARS-CoV-2 positive test (Day 60; resolved); monoclonal gammapathy; morbid obesity; sleep apnea; cardiovascular disease (hypertension, hyperlipidemia)	Recovered / resolved	Not related (per investigator) Related (per sponsor)
New events adjudicated as major adverse cardiovascular events or venous thromboembolism since the previous data cut (King et al. 2024)									
38	White	Female	Cerebrovascular accident	50 mg	Day 838	Day 842	Chiropractic manipulation; long flight journey	Recovered / resolved with sequelae	Not related (per investigator)

67	White	Female	Acute myocardial infarction	50 mg	Day 819	822	Ex-smoker; obesity; peripheral swelling; varicose vein; hypertension	Recovered / resolved	Not related (per investigator)
37	White	Male	Acute myocardial infarction	50 mg	Day 935	Day 942	Dyslipidemia; smoking; alcohol use; maternal history of cardiac ischemic disease; atherosclerosis	Recovered / resolved	Not related (per investigator)
62	White	Male	Myocardial infarction	Last dose (50 mg) taken on Day 842	Day 903	Day 903	Hypercholesterolemia; stage 2 hypertension; smoking; family history of cardiac ischemic disease	Resolved with sequelae	Related to study intervention (per investigator) Not related (per sponsor)

AE, adverse event.

Table S4. Summary of select laboratory abnormalities.

	Ritlecitinib 50-mg ± 200-mg (N=1228)[a]	Any ritlecitinib (N=1294)[a]
Hemoglobin		
CTCAE Grade 2: 8.0 - <10 g/dL, n/N1[b] (%)	24/1223 (2.0)	26/1285 (2.0)
CTCAE Grade ≥3: <8.0 g/dL, n/N1[c] (%)	1/1223 (<0.1)[v]	1/1285 (<0.1)[v]
Neutrophils		
CTCAE Grade 2: 1000 - <1500/mm^3, n/N1[d] (%)	63/1207 (5.2)	76/1268 (6.0)
CTCAE Grade ≥3: <1000/mm^3, n/N1[e] (%)	13/1220 (1.1)	14/1282 (1.1)
Lymphocytes		
CTCAE Grade 2: 500 - <800/mm^3, n/N1[f] (%)	269/1219 (22.1)	281/1283 (21.9)
CTCAE Grade ≥3: <500/mm^3, n/N1[g] (%)	42/1223 (3.4)	44/1285 (3.4)
Platelets		
CTCAE Grade 2: 50.0 - <75 × 10^3/mm^3, n/N1[h] (%)	1/1223 (<0.1)	1/1285 (<0.1)
CTCAE Grade ≥3: <50 × 10^3/mm^3, n/N1[i] (%)	0/1223 (0)[v]	0/1285 (0)[v]
Creatine kinase		
CTCAE Grade 2, n/N1[j] (%)	76/1215 (6.3)	82/1276 (6.4)
CTCAE Grade ≥3, n/N1[k] (%)	78/1218 (6.4)	91/1282 (7.1)
HDL cholesterol		
<0.8x LLN, n/N1[l] (%)	5/1146 (0.4)	7/1211 (0.6)
LDL cholesterol		
>1.2x ULN, n/N1[l] (%)	21/1146 (1.8)	22/1210 (1.8)
Total cholesterol		
>1.3x ULN, n/N1[l] (%)	11/1146 (1.0)	12/1211 (1.0)
Triglycerides		
>1.3x ULN, n/N1[l] (%)	93/1146 (8.1)	107/1210 (8.8)
AST		
>3.0 – 5.0 x ULN, n/N1[m] (%)	16/1220 (1.3)	21/1282 (1.6)
>5.0 – 20.0 x ULN, n/N1[n] (%)	17/1221 (1.4)	19/1282 (1.5)
>20.0 x ULN, n/N1[o] (%)	0/1221 (0)	0/1282 (0)

ALT		
>3.0 – 5.0 x ULN, n/N1[p] (%)	25/1219 (2.1)	27/1280 (2.1)
>5.0 – 20.0 x ULN, n/N1[q] (%)	10/1221 (0.8)	12/1282 (0.9)
>20.0 x ULN, n/N1[r] (%)	0/1221 (0)	0/1282 (0)
Total bilirubin		
>1.5 – 3.0 x ULN, n/N1[s] (%)	29/1210 (2.4)	31/1269 (2.4)
>3.0 – 10.0 x ULN, n/N1[t] (%)	0/1221 (0)	0/1282 (0)
>10.0 x ULN, n/N1[u] (%)	0/1221 (0)	0/1282 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; ULN, upper limit of normal.

Worst post-baseline category is shown for hematological parameters, creatine kinase, liver enzymes, and bilirubin. Lipid test abnormalities are shown among all patients with a post-baseline observation.

N1 represents the number of patients who contributed to the calculation of the percentages, while n represents the number of patients with post baseline values meeting the criteria for each lab parameter.

[a] The analysis groups are not additive and are overlapping populations; the any ritlecitinib group includes all patients.

[b] N1 = number patients with baseline hemoglobin ≥10.0 g/dL (Grade 0 or 1).

[c] N1 = number patients with baseline hemoglobin ≥8.0 g/dL (Grade 0, 1, or 2).

[d] N1 = number of patients with baseline neutrophils ≥1500/mm^3 (Grade 0 or 1).

[e] N1 = number of patients with baseline neutrophils ≥1000/mm^3 (Grade 0, 1, or 2).

[f] N1 = number of patients with baseline lymphocytes ≥800/mm^3 (Grade 0 or 1).

[g] N1 = number of patients with baseline lymphocytes ≥500/mm^3 (Grade 0, 1, or 2).

[h] N1 = number of patients with baseline platelets ≥75.0 × 10^3/mm^3 (Grade 0 or 1).

[i] N1 = number of patients with baseline platelets ≥50.0 × 10^3/mm^3 (Grade 0, 1, or 2).

[j] N1 = number of patients with baseline creatine kinase ≤2.5x ULN (≤500 U/L, Grade 0 or 1).

[k] N1 = number of patients with baseline creatine kinase ≤5x ULN (≤1000 U/L, Grade 0, 1, or 2).

[l] N1 = the total number of patients with at least one post-baseline observation of the given laboratory test.

[m] N1 = number of patients with baseline AST ≤3.0 x ULN.

[n] N1 = number of patients with baseline AST ≤5.0 x ULN.

[o] N1 = number of patients with baseline AST ≤20.0 x ULN.

[p] N1 = number of patients with baseline ALT ≤3.0 x ULN.

[q] N1 = number of patients with baseline ALT ≤5.0 x ULN.

[r] N1 = number of patients with baseline ALT ≤20.0 x ULN.

[s] N1 = number of patients with baseline total bilirubin ≤1.5 x ULN.

[t] N1 = number of patients with baseline total bilirubin ≤3.0 x ULN.

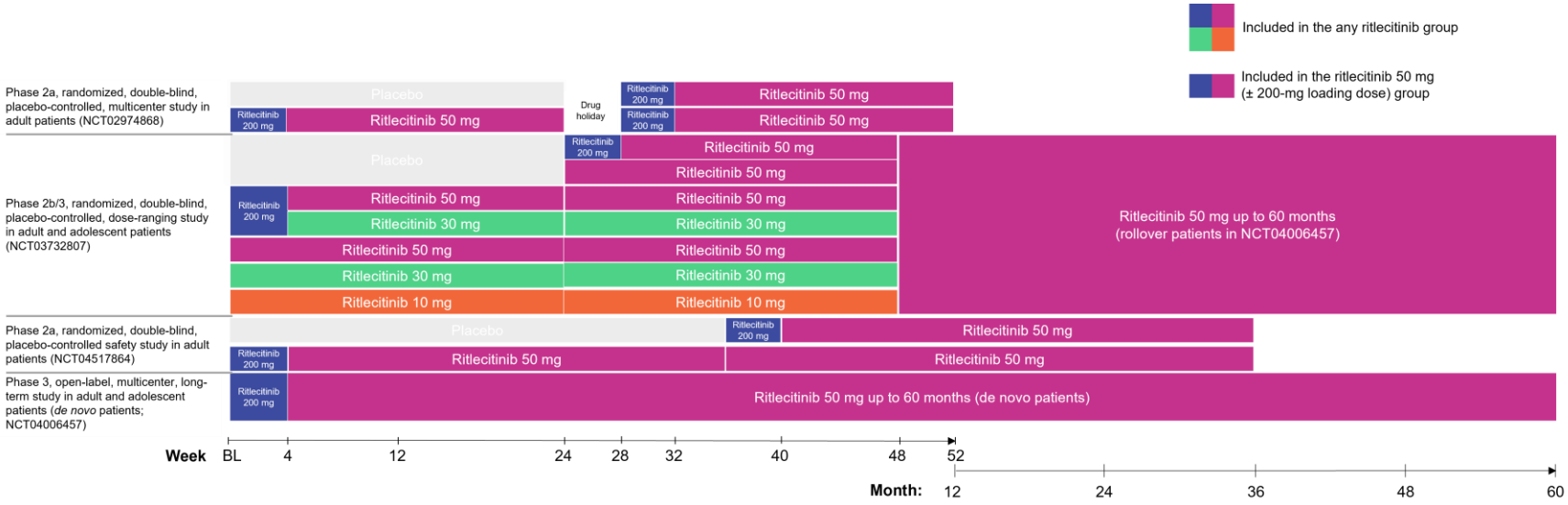
[u] N1 = number of patients with baseline total bilirubin ≤10.0 x ULN.

[v] All cases were Grade 3; there were no cases of Grade 4 or higher decreases in platelets or hemoglobin.

Table S5. Details of patients with creatine kinase elevations and reported treatment-emergent adverse events of rhabdomyolysis (new events since the previous data cut, King et al. 2024)

Age	Sex	Preferred Term	Dose at time of onset	Event start day	Event end day	Creatine kinase level on event start day	Severity	Event outcome	Causality assessment
20s	Male	Rhabdomyolysis	50 mg	Day 728	Day 749	4306 U/L	Mild	Resolved	Related to new exercise regimen
20s	Female	Rhabdomyolysis	50 mg	Day 968	Day 989	10,438 U/L	Mild	Resolved	Related to new exercise regimen
20s	Male	Rhabdomyolysis	50 mg	Day 966	Day 986	1211 U/L	Mild	Resolved	Related to physical activity

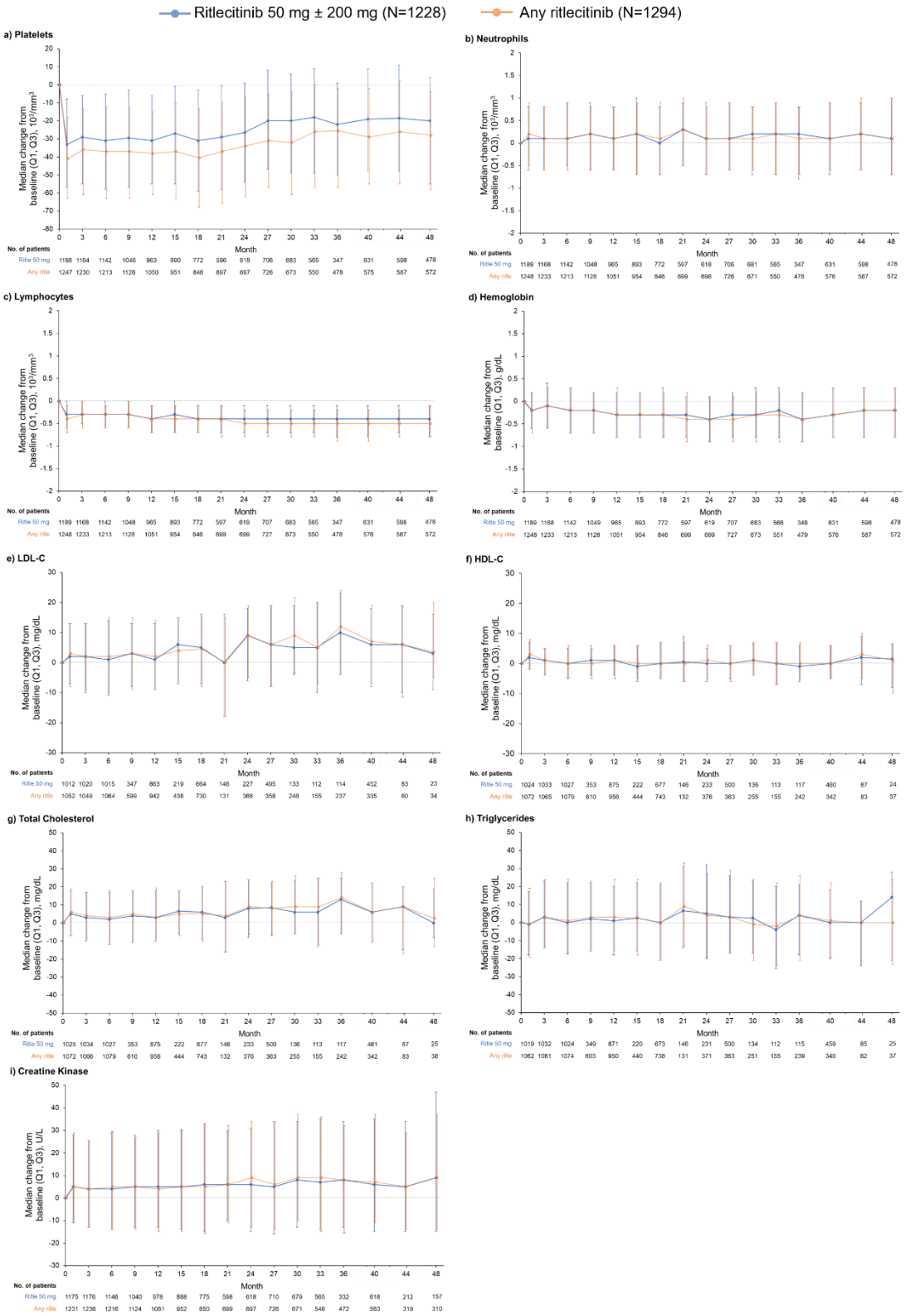
Fig. S1 Schematic of the study design of the four ALLEGRO studies including the two analysis populations (the any ritlecitinib and ritlecitinib 50-mg ± 200-mg groups)



This figure is not intended to depict the complete designs of each study; it highlights only those design elements relevant to the patients included in the safety analysis presented here.

BL, baseline. Adapted from King et al. Integrated Safety Analysis of Ritlecitinib, an Oral JAK3/TEC Family Kinase Inhibitor, for the Treatment of Alopecia Areata from the ALLEGRO Clinical Trial Program. *Am J Clin Dermatol* 2024; **25**(2): 299-314.

Fig. S2 Median change from baseline in **s**elect laboratory parameters.



HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.