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Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicentre, phase 2b–3 trial

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Summary

Background Alopecia areata is characterised by non-scarring loss of scalp, face, or body hair. We investigated the efficacy and safety of ritlecitinib, an oral, selective dual JAK3/TEC family kinase inhibitor, in patients with alopecia areata.

Methods In this randomised, double-blind, multicentre, phase 2b–3 trial done at 118 sites in 18 countries, patients aged 12 years and older with alopecia areata and at least 50% scalp hair loss were randomly assigned to oral ritlecitinib or placebo once-daily for 24 weeks, with or without a 4-week loading dose (50 mg, 30 mg, 10 mg, 200 mg loading dose followed by 50 mg, or 200 mg loading dose followed by 30 mg), followed by a 24-week extension period during which ritlecitinib groups continued their assigned doses and patients initially assigned to placebo switched to ritlecitinib 50 mg or 200 mg loading dose followed by 50 mg. Randomisation was done by use of an interactive response system and was stratified by baseline disease severity and age. The sponsor, patients, and investigators were masked to treatment, and all patients received the same number of tablets to maintain masking. The primary endpoint was Severity of Alopecia Tool (SALT) score 20 or less at week 24. The primary endpoint was assessed in all assigned patients, regardless of whether they received treatment. This study was registered with ClinicalTrials.gov, NCT03732807.

Findings Between Dec 3, 2018, and June 24, 2021, 1097 patients were screened and 718 were randomly assigned to receive ritlecitinib 200 mg+50 mg (n=132), 200 mg+30 mg (n=130), 50 mg (n=130), 30 mg (n=132), 10 mg (n=63), placebo to 50 mg (n=66), or placebo to 200 mg+50 mg (n=65). 446 (62%) of 718 patients were female and 272 (38%) were male. 488 (68%) were White, 186 (26%) were Asian, and 27 (4%) were Black or African American. Of 718 patients randomly assigned, 104 patients discontinued treatment (34 withdrew, 19 adverse events [AEs], 12 physician decision, 12 lack of efficacy, 13 lost to follow up, five rolled over to long-term study transfer, four pregnancies, two protocol deviations, one declined to attend follow-up due to COVID-19, one attended last visit very late due to COVID-19, and one non-compliance). At week 24, 38 (31%) of 124 patients in the ritlecitinib 200 mg+50 mg group, 27 (22%) of 121 patients in the 200 mg+30 mg group, 29 (23%) of 124 patients in the 50 mg group, 17 (14%) of 119 patients in the 30 mg group, and two (2%) of 130 patients in the placebo group had a response based on SALT score 20 or less. The difference in response rate based on SALT score 20 or less between the placebo and the ritlecitinib 200 mg+50 mg group was 29·1% (95% CI 21·2–37·9; p<0·0001), 20·8% (13·7–29·2; p<0·0001) for the 200 mg+30 mg group, 21·9% (14·7–30·2; p<0·0001) for the 50 mg group, and 12·8% (6·7–20·4; p=0·0002) for the 30 mg group. Up to week 48 and including the follow-up period, AEs had been reported in 108 (82%) of 131 patients in the ritlecitinib 200 mg+50 mg group, 105 (81%) of 129 patients in the 200 mg+30 mg group, 110 (85%) of 130 patients in the 50 mg group, 106 (80%) of 132 patients in the 30 mg group, 47 (76%) of 62 patients in the 10 mg group, 54 (83%) of 65 patients placebo to ritlecitinib 200 mg+50 mg in the extension period, and 57 (86%) of 66 patients in the placebo to 50 mg group. The incidence of each AE was similar between groups, and there were no deaths.

Interpretation Ritlecitinib was effective and well tolerated in patients aged 12 years and older with alopecia areata. Ritlecitinib might be a suitable treatment option for alopecia areata in patients who are candidates for systemic therapy.

Funding Pfizer.

Introduction

Alopecia areata is a T-cell mediated autoimmune, non-scarring form of hair loss that has an underlying immuno-inflammatory pathogenesis. It affects both children and adults,[1] with a prevalence of about 2% globally.[1,2] Alopecia areata can have a substantial impact on quality of life,[3,4] including psychosocial burden such as anxiety or depression.[5,6] Although spontaneous hair regrowth can occur, it is unlikely in more extensive forms of alopecia areata, including alopecia totalis (complete loss of scalp hair) and alopecia universalis (complete loss of scalp, face, and body hair).[7]

Research in context

Evidence before this study

Alopecia areata is an autoimmune disease characterised by nonscarring hair loss of the scalp, face, or body, for which there are few effective treatments. We searched PubMed for clinical trials published in English between Jan 1, 2000, and Sept 12, 2022, using the search terms "alopecia areata" AND "phase 3" or "phase III" or "phase 2" or "phase II". We found one phase 3 study on the only approved treatment for alopecia areata (baricitinib) and 14 phase 2 studies.

Added value of this study

Ritlecitinib 30 mg and 50 mg daily (with or without a 4-week 200 mg daily loading dose) resulted in significant hair regrowth compared with placebo. Ritlecitinib had a favourable safety profile over 48 weeks, and no major adverse cardiovascular events, opportunistic infections, or deaths were reported.

Implications of all the available evidence

Oral ritlecitinib 30 mg or 50 mg once a day (with or without a 4-week 200 mg loading dose) was efficacious and generally safe and well tolerated over 48 weeks in patients with alopecia areata. Long-term evaluation of ritlecitinib is ongoing. Ritlecitinib might be a treatment option for alopecia areata in patients aged 12 years and older.

Treatment options for alopecia areata are few. Off-label treatments such as corticosteroids (topical, intralesional, and systemic) and other immunosuppressants have variable tolerability and efficacy for severe disease.[8] Baricitinib, an oral inhibitor of the Janus kinases (JAKs) JAK1 and JAK2, received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval to treat adults with severe alopecia areata in June, 2022, and is the only approved treatment option in adults. Not all patients respond to baricitinib, and the clinical trials did not include adolescents, so there remains a significant unmet need for treatment in patients with alopecia areata.

Pathophysiology of alopecia areata involves immune privilege collapse in the hair follicle, which is thought to render the hair follicle susceptible to attack by natural killer and autoreactive CD8+ T cells.[9] Activation and proliferation of immune cells involve multiple cytokines, including interferon-γ and interleukin (IL)-15, which have been described as important drivers of alopecia areata.[10,11] Both of these cytokines perpetrate an inflammatory feed-forward loop and signal through cytoplasmic JAK1, JAK2, and JAK3, therefore providing therapeutic rationale for targeting each of these kinases.[11,12] The immune attack by CD8+ T cells is thought to also require recognition of autoantigens by the T-cell receptor (TCR).[13,14] Engagement of the TCR by antigen presented by major histocompatibility complex triggers a complex downstream signalling cascade crucial for T-cell differentiation and function.[15] Dysregulation of this pathway has been shown to contribute to the development of various autoimmune diseases, including those driven by CD8+ T cells.[16] The tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases, which are primarily expressed in haematopoietic cells, includes five members of which three play a central role in the TCR signalling cascade: IL-2-inducible T-cell kinase, TEC, and resting lymphocyte kinase.[15] IL-2-inducible T-cell kinase, the predominant TEC kinase expressed in T cells, is involved in a specific TCR signalling signature identified in activated T cells from the scalps of patients with alopecia areata, making this kinase also a potential target for drug development in this disease.[17]

Hair regrowth in patients with alopecia areata observed in open-label studies and phase 2–3 studies with the JAK inhibitors deuruxolitinib[18] and ruxolitinib[19] (JAK1 and JAK2), tofacitinib[20,21] (JAK1 and JAK3), and baricitinib[22,23] (JAK1 and JAK2) supports the role of JAK inhibition in the treatment of alopecia areata. Ritlecitinib is an orally administered, covalent small-molecule selective dual inhibitor of JAK3 and the TEC kinase family.[24] In vitro studies showed ritlecitinib covalently binds to JAK3 and is more than 10 000 times more potent against JAK3 than against JAK1, JAK2, and tyrosine kinase 2.[25] Ritlecitinib also inhibits the five members of the TEC kinase family.[24]

In a placebo-controlled, phase 2a clinical trial, ritlecitinib was efficacious and generally well tolerated in adults with alopecia areata.[26] We aimed to assess the efficacy and safety of multiple ritlecitinib dose regimens over 48 weeks in adults and adolescents with alopecia areata.

Methods

Study design

ALLEGRO phase 2b–3 was a randomised, double-blind, multicentre, phase 2–3 trial done at 118 hospitals and clinics in Argentina, Australia, Canada, Chile, China, Colombia, Czech Republic, Germany, Hungary, Japan, Korea, Mexico, Poland, Russia, Spain, Taiwan, the UK, and the USA. The protocol was reviewed and approved by the institutional review boards or ethics committees of each participating institution. The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council for Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki.

Patients

Eligible patients were adults (aged 18 years and older) and adolescents (aged 12–17 years) with a diagnosis of

alopecia areata with at least 50% scalp hair loss (including alopecia totalis and alopecia universalis), measured by the Severity of Alopecia Tool (SALT; investigator's assessment of the amount of scalp hair loss[27] ranging from 0 [no scalp hair loss] to 100 [total scalp hair loss]). Patients without evidence of terminal hair regrowth within 6 months at both the screening and baseline visits and with maximum duration of current episode of hair loss 10 years or less were included. Exclusion criteria included other causes of alopecia; clinically significant depression; auditory conditions considered acute, fluctuating, or progressive; previous use of any JAK inhibitor; history of disseminated herpes zoster, disseminated herpes simplex, or recurrent localised, dermatomal herpes zoster; or age 12 to <18 years without a documented history of varicella-zoster virus vaccination or presence of varicella-zoster virus IgG antibody (appendix p 6). Written informed consent was obtained from each patient, parent, or the patient's legal representative.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (2:2:2:2:1:1:1) to receive oral ritlecitinib 200 mg loading dose for 4 weeks followed by 50 mg (hereafter 200 mg+50 mg), 200 mg loading dose for 4 weeks followed by 30 mg (hereafter 200 mg+30 mg), 50 mg, 30 mg, 10 mg, placebo for 24 weeks followed by 200 mg loading dose for 4 weeks then 50 mg (hereafter placebo to 200 mg+50 mg), or placebo for 24 weeks followed by 50 mg. The 10 mg group was included for pharmacokinetic, dose-response, and safety assessments only and was not included in statistical comparisons versus placebo. Randomisation was stratified by scalp hair loss (target of about 40% of patients with alopecia totalis or alopecia universalis, defined by a SALT score of 100, to be able to analyse efficacy and safety in this subgroup) and age (12–17 years, target of about 15% of patients to support development for a paediatric [adolescent] indication, or 18 years or older). An interactive response technology system was used to ensure treatment assignments in each stratum were balanced. In regions enrolling both adolescents and adults, there were four strata (younger than 18 years and alopecia totalis or alopecia universalis; younger than 18 years and not alopecia totalis or alopecia universalis; 18 years or older and alopecia totalis or alopecia universalis; and 18 years or older and not alopecia totalis or alopecia universalis) and in regions enrolling only adults, there were two strata (18 years or older and alopecia totalis or alopecia universalis and 18 years or older and not alopecia totalis or alopecia universalis). Within each stratum, patients were randomly assigned to one of seven groups as described above. The study sponsor, patients, and investigators were masked to treatment. To maintain masking throughout the study, all patients, regardless of treatment sequence, received the same number of tablets per day.

Procedures

Treatment was given orally, once a day for 24 weeks during the placebo-controlled period and for 24 weeks during the extension period. During the extension period, patients assigned to placebo were switched to ritlecitinib 50 mg once a day with or without a 200 mg, 4-week loading dose. Patients assigned to one of the ritlecitinib regimens continued their maintenance dose (figure 1). Clinical assessments were done at screening, baseline, and week 4, 8, 12, 18, 24, 28, 34, 40, and 48 (or end of treatment) visits and included SALT score, eyebrows and eyelashes hair loss (eyelash assessment or eyebrow assessment by the investigator with 4-point scales from 0 [none] to 3 [normal]; appendix p 17), and patient self-administered Patient Global Impression of Change (PGI-C; seven responses ranging from greatly improved to greatly worsened compared with study start, appendix p 18). Safety was monitored throughout the study. The protocol included guidance for investigators and participants in handling adverse events. Guidelines for patient safety monitoring and discontinuation are provided in the appendix (p 10).

Outcomes

Primary and key secondary outcomes were evaluated at week 24 (end of the placebo-controlled period). The primary endpoint was response based on SALT score 20 or less (20% scalp hair loss or less), defined as a clinically meaningful treatment outcome by both clinicians and patients,[28] and the more stringent key secondary endpoint was response based on SALT score 10 or less (10% scalp hair loss or less). Secondary endpoints included PGI-C score of moderately improved or greatly improved to week 48 (appendix p 18), response based on SALT score 20 or less and 10 or less to week 48, change from baseline in SALT scores to week 48, measures of eyebrow and eyelash regrowth (appendix p 17), and exposure response based on SALT score 20 or less. Response based on 75% improvement in SALT score from baseline to week 48 and change from baseline in Alopecia Areata Patient Priorities Outcome scales to week 48 were secondary endpoints and will be reported in detail with exploratory outcomes and post hoc analyses at a later date.

Safety was monitored throughout the study for adverse events (AEs). AEs of interest (including opportunistic infections; malignancy; and cardiovascular, neurological, and audiological events) were reviewed by adjudication committees by use of predefined criteria. Audiology testing was done and neurological events were reviewed on the basis of a finding of reversible axonal dystrophy in the nervous system of dogs in nonclinical chronic toxicology studies (unpublished data).

We assessed efficacy using overall α=0·00125 as agreed with the FDA and 0·01 with the EMA. The primary endpoint was response based on SALT score 20 or less at week 24 for the FDA (no key secondary endpoint). The primary endpoint for the EMA was response based on

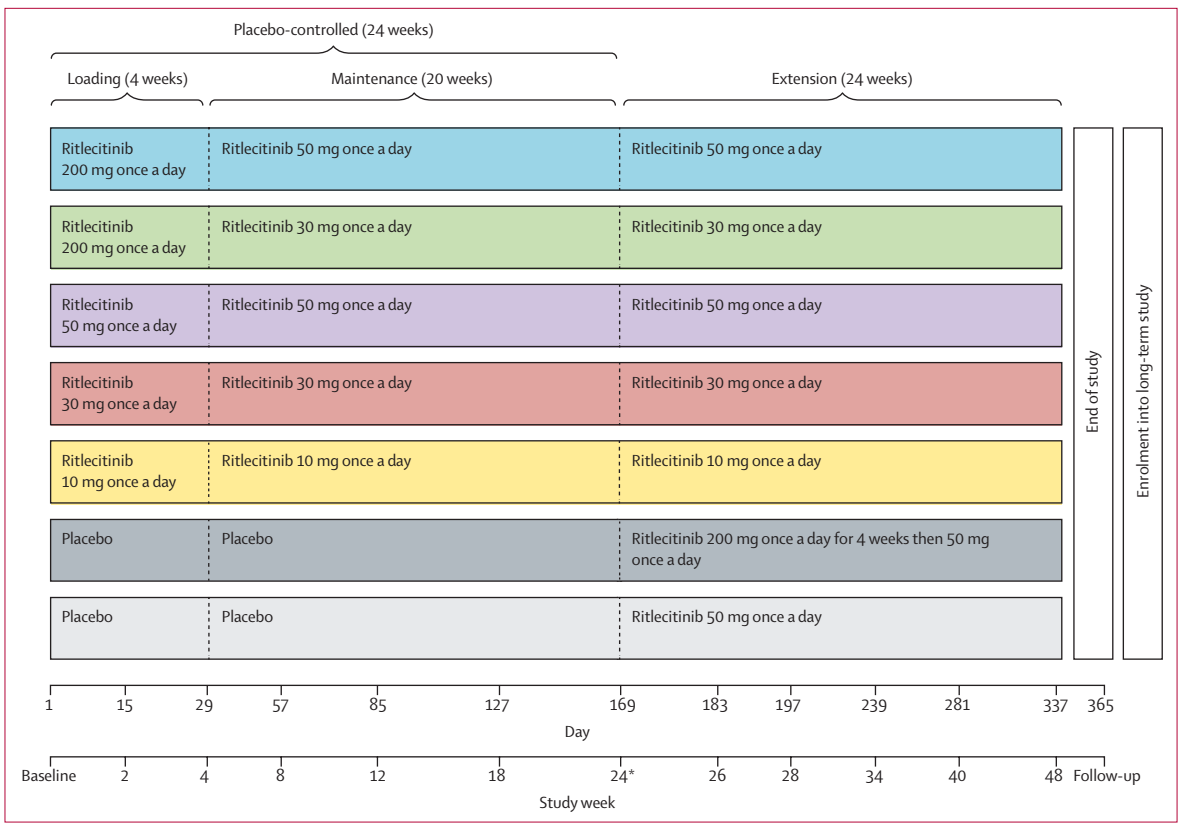

Figure 1: **Study design**
*Primary and key secondary endpoints were analysed at 24 weeks.

SALT score 10 or less at week 24 and the key secondary endpoint was PGI-C response, defined as a score of moderately improved or greatly improved at week 24.

Statistical analysis

The planned sample size of 120 patients per ritlecitinib group (200 mg+50 mg, 200 mg+30 mg, 50 mg, or 30 mg) was based on the consideration to have sufficient power to assess the primary endpoint at no less than 90% power to detect that ritlecitinib 200 mg+50 mg is superior to placebo by a difference of at least 24% in the proportion of responders with SALT score 20 or less at week 24, which assumes a placebo response rate 5% or less, at α=0·05, and accounted for multiplicity using a closed testing procedure (appendix p 19) to ensure control of type I error for all comparisons (active treatment *vs* placebo). The testing procedure for comparisons between each ritlecitinib group and placebo for the primary and key secondary endpoints is described and illustrated in the appendix (pp 7–8, 19). Placebo response and treatment response differences were informed by a previous phase 2a study.[26] The ritlecitinib 10 mg group was not included in statistical comparisons versus placebo; however, the sample size of 60 was chosen to allow for estimation of dose-response parameters. Efficacy endpoints were assessed in the full analysis set, defined as all randomly assigned patients regardless of whether they received study drug. Data from the two placebo groups were pooled for comparative analyses up to week 24. The Miettinen and Nurminen method was used for calculation of 95% CIs and the Farrington-Manning method was used for the calculation of p values. Missing data due to COVID-19-related reasons were excluded from this analysis, whereas patients with missing data due to other reasons were considered as non-responders. Statistical analyses and how missing data were handled for the FDA and EMA are included in the appendix (p 9). Dose-response analysis was done by use of a Bayesian three-parameter maximum drug effect (E_{max}) model (appendix p 21). Safety was analysed in all patients who received the study drug (safety analysis set) and was summarised descriptively. This study is registered with ClinicalTrials.gov, NCT03732807.

Role of the funding source

The study was designed, funded, and managed by the sponsor. The sponsor collected and analysed the data and funded editorial assistance. All authors participated in the data interpretation and had full access to the data in the study, and all read and approved the final version of the manuscript for publication.

Results

Between Dec 3, 2018, and June 24, 2021, 1097 patients were screened. Of the 379 screen failures, 376 did not meet entry criteria (196 did not meet inclusion criteria and 193 met exclusion criteria) and three failed screening due to COVID-19. 718 were randomly assigned to receive ritlecitinib 200 mg + 50 mg (n=132), 200 mg + 30 mg (n=130), 50 mg (n=130), 30 mg (n=132), 10 mg (n=63), placebo to 50 mg (n=66), or placebo to 200 mg + 50 mg (n=65). Of 715 patients treated, 104 patients discontinued

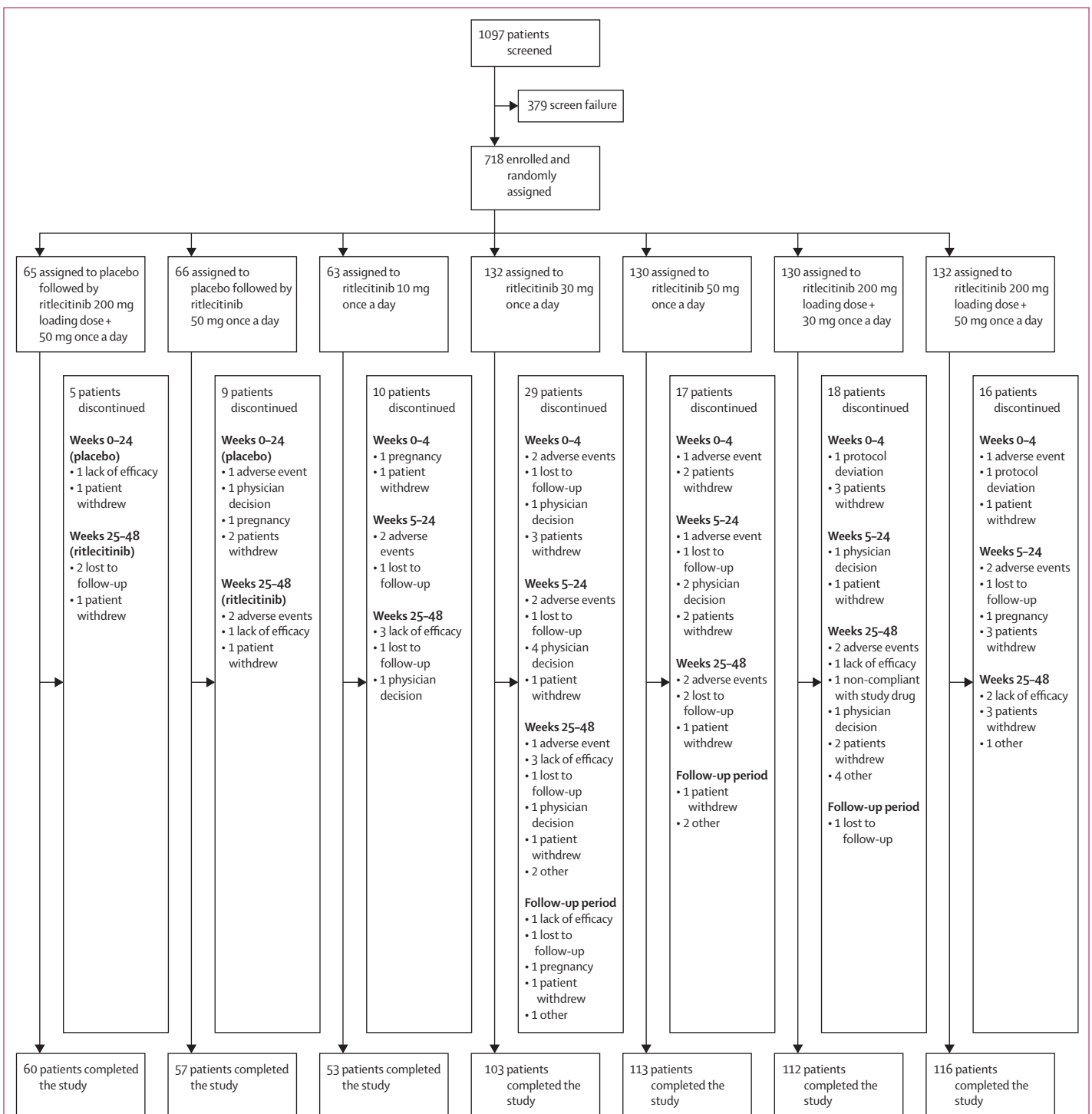

Figure 2: **Trial profile**

treatment (34 withdrew, 19 AEs, 12 physician decision, 12 lack of efficacy, 13 lost to follow up, five rolled over to long-term study transfer, four pregnancies, two protocol deviations, one declined to attend follow-up due to COVID-19, one attended last visit very late due to COVID-19, and one non-compliance) and 614 completed the study. Reasons for patient discontinuation from the study are shown in figure 2.

Baseline demographic and disease characteristics were well balanced across treatment groups (table 1). 105 (15%) of 718 patients were adolescents and 613 (85%) were adults. 446 (62%) of patients were female and 272 (38%) were male. 488 (68%) were White, 186 (26%) were Asian, and 27 (4%) were Black or African American. 330 (46%) had alopecia totalis or alopecia universalis. Mean SALT score at baseline ranged from

	Placebo* (n=131)	10 mg ritlecitinib (n=63)	30 mg ritlecitinib (n=132)	50 mg ritlecitinib (n=130)	200 mg then 30 mg ritlecitinib (n=130)	200 mg then 50 mg ritlecitinib (n=132)
Age, years						
Mean (SD)	34·0 (15·0)	34·3 (13·9)	33·7 (14·8)	32·4 (13·4)	33·7 (13·8)	34·5 (15·0)
Median (IQR; range)	32·0 (22·0–44·0; 12·0–73·0)	34·0 (21·0–48·0; 13·0–58·0)	32·5 (21·0–41·0; 12·0–73·0)	30·0 (22·0–42·0; 13·0–70·0)	31·5 (21·0–44·0; 12·0–65·0)	34·0 (22·0–46·5; 12·0–71·0)
Adolescents (12–17 years)	19 (15%)	9 (14%)	20 (15%)	18 (14%)	19 (15%)	20 (15%)
Adults (≥18 years)	112 (86%)	54 (86%)	112 (85%)	112 (86%)	111 (85%)	112 (85%)
Sex						
Female	86 (66%)	43 (68%)	80 (61%)	71 (55%)	85 (65%)	81 (61%)
Male	45 (43%)	20 (32%)	52 (39%)	59 (45%)	45 (35%)	51 (39%)
Race						
White	94 (72%)	42 (67%)	91 (69%)	79 (61%)	90 (69%)	92 (70%)
Black or African American	4 (3%)	2 (3%)	3 (2%)	5 (4%)	7 (5%)	6 (5%)
Asian	31 (24%)	17 (27%)	34 (26%)	43 (33%)	28 (22%)	33 (25%)
Other†	2 (2%)	1 (2%)	4 (3%)	1 (1%)	4 (3%)	0
Not reported	0	1 (2%)	0	2 (2%)	1 (1%)	1 (1%)
Patients with alopecia totalis or alopecia universalis‡	60 (46%)	29 (46%)	61 (46%)	60 (46%)	60 (46%)	60 (46%)
Alopecia totalis	24 (18%)	12 (19%)	26 (20%)	30 (23%)	34 (26%)	25 (19%)
Alopecia universalis	34 (26%)	13 (21%)	29 (22%)	24 (18%)	21 (16%)	26 (20%)
Not specified	2 (2%)	4 (6%)	6 (5%)	6 (5%)	5 (4%)	9 (7%)
Baseline SALT score						
50 to <75	14 (11%)	15 (24%)	27 (20%)	27 (21%)	22 (17%)	22 (17%)
75 to <100	57 (44%)	19 (30%)	44 (33%)	43 (33%)	48 (37%)	50 (38%)
100	60 (46%)	29 (46%)	61 (46%)	60 (46%)	60 (46%)	60 (46%)
All patients, mean (SD)	93·0 (11·5)	88·3 (16·9)	90·0 (15·1)	90·3 (14·7)	90·5 (14·3)	90·3 (15·1)
Non-alopecia totalis or alopecia universalis,‡ mean (SD)	87·0 (12·9)	78·3 (17·6)	81·5 (16·3)	82·0 (15·9)	82·4 (15·4)	82·2 (16·5)
Patients without normal eyebrow assessment score§	107 (82%)	52 (83%)	112 (85%)	106 (82%)	109 (84%)	110 (83%)
Patients without normal eyelash assessment score§	97 (74%)	45 (71%)	102 (77%)	95 (73%)	95 (73%)	102 (77%)
Disease duration since diagnosis, years						
Mean (SD)	11·0 (11·8)	10·8 (10·7)	8·8 (8·9)	8·7 (8·7)	11·6 (11·7)	9·9 (10·8)
Median (IQR; range)	7·4 (2·6–14·4; 0·1–58·2)	7·0 (3·1–17·2; 0·2–50·9)	5·8 (2·8–10·5; 0·0–53·4)	6·3 (2·6–10·9; 0·3–44·7)	7·3 (2·9–15·1; 0·0–57·1)	6·7 (2·5–11·3; 0·3–60·1)
Duration of current alopecia areata episode, years						
Mean (SD)	3·2 (2·7)	3·3 (2·7)	3·6 (2·8)	3·2 (2·7)	3·4 (2·9)	3·4 (2·9)
Median (IQR; range)	2·5 (1·1–4·9; 0·0–10·0)	2·2 (1·0–4·8; 0·3–9·7)	2·6 (1·1–5·5; 0·3–10·0)	2·2 (1·0–5·1; 0·2–9·9)	2·7 (1·1–5·1; 0·0–13·0)	2·3 (1·0–5·5; 0·0–10·0)

Data are n (%) unless otherwise specified. Full analysis set, n=718. SALT=Severity of Alopecia Tool. *Combined patients who received placebo for 24 weeks then switched to either ritlecitinib 50 mg or ritlecitinib 200 mg followed by 50 mg. †Includes self-reported American Indian or Alaska native, Native Hawaiian or other Pacific Islander, or multiracial. ‡Patients in the alopecia totalis or alopecia universalis category had a SALT score of 100% at baseline (regardless of the category in the alopecia areata history case report form). §See appendix (p 17) for eyebrow assessment and eyelash assessment scales.

Table 1: **Baseline demographic and disease characteristics**

88·3 to 93·0; mean SALT score for those without alopecia totalis or alopecia universalis was 78·3 to 87·0. Patients enrolled into ALLEGRO phase 2b–3 were generally representative of patients with more extensive hair loss attributable to alopecia areata, and the patient population was enriched with patients with alopecia totalis or alopecia universalis to obtain a more precise estimate of efficacy of ritlecitinib in these patients (appendix p 12).

At week 24, 38 (31%) of 124 patients in the ritlecitinib 200 mg + 50 mg group, 27 (22%) of 121 patients in the 200 mg + 30 mg group, 29 (23%) of 124 patients in the 50 mg group, 17 (14%) of 119 patients in the 30 mg group, and two (2%) of 130 patients in the placebo group had a response based on SALT score 20 or less (table 2). The difference in response rate based on SALT score 20 or less between the placebo and the ritlecitinib 200 mg + 50 mg group was 29·1% (95% CI 21·2–37·9; p<0·0001), 20·8% (13·7–29·2; p<0·0001) for the 200 mg + 30 mg group, 21·9% (14·7–30·2; p<0·0001) for the 50 mg group, and 12·8% (6·7–20·4; p=0·0002) for the 30 mg group. A clear dose response was identified (appendix p 21). A significantly higher proportion of patients with SALT score 10 or less at week 24 was also observed in the ritlecitinib 200 mg + 50 mg, 200 mg + 30 mg, 50 mg, and 30 mg groups compared with placebo (table 2). The proportion of patients with SALT score 20 or less or 10 or less continued to increase until week 48 in the 200 mg + 50 mg, 200 mg + 30 mg, 50 mg, and 30 mg treatment groups (figure 3A,3B; appendix p 20).

At week 24, 42–52% of patients in the ritlecitinib 200 mg + 50 mg, 200 mg + 30 mg, 50 mg, and 30 mg treatment groups had a PGI-C response of moderately or greatly improved compared with 9% in the placebo group (figure 3C; table 2). PGI-C response rates continued to increase beyond week 24 for these four dose groups.

In prespecified subgroup analyses, ritlecitinib treatment demonstrated consistent results in adolescents as compared with adults at week 24 (appendix p 22), and a consistency of treatment effect in patients with alopecia totalis or alopecia universalis and in those without alopecia totalis or alopecia universalis (appendix p 23). In patients with alopecia totalis or alopecia universalis, response rates based on SALT score 20 or less at

	Placebo* (n=131)	10 mg ritlecitinib (n=63)	30 mg ritlecitinib (n=132)	50 mg ritlecitinib (n=130)	200 mg then 30 mg ritlecitinib (n=130)	200 mg then 50 mg ritlecitinib (n=132)
SALT score 20 or less response at week 24†‡						
n/N (%)	2/130 (2%)	1/59 (2%)	17/119 (14%)	29/124 (23%)	27/121 (22%)	38/124 (31%)
Difference from placebo (95% CI)	..	0·16 (–4·05 to 7·58)	12·75 (6·69 to 20·36)	21·85 (14·65 to 30·23)	20·78 (13·65 to 29·18)	29·11 (21·17 to 37·91)
p value	..	..	0·0002	<0·0001	<0·0001	<0·0001
SALT score 10 or less response at week 24‡§						
n/N (%)	2/130 (2%)	1/59 (2%)	13/119 (11%)	17/124 (14%)	16/121 (13%)	27/124 (22%)
Difference from placebo (95% CI)	..	0·16 (–4·05 to 7·58)	9·39 (3·86 to 16·46)	12·17 (6·27 to 19·53)	11·68 (5·82 to 19·07)	20·24 (13·23 to 28·49)
p value	..	..	0·0019	0·0002	0·0003	<0·0001
SALT score 10 or less response at week 24¶‖						
Estimated response rate (%)	1·54%	1·65%	10·62%	13·42%	12·87%	21·29%
Difference from placebo (95% CI)	..	0·12 (–3·67 to 3·91)	9·09 (3·10 to 15·07)	11·88 (5·42 to 18·33)	11·33 (4·93 to 17·74)	19·75 (11·91 to 27·59)
p value	..	..	0·0029	0·0003	0·0005	<0·0001
PGI-C response at week 24†‡**						
Estimated response rate (%)	9·23%	11·36%	41·95%	49·17%	45·40%	52·19%
Difference from placebo (95% CI)	..	2·15 (–6·91 to 11·22)	32·72 (21·95 to 43·50)	39·96 (28·85 to 51·06)	36·18 (25·22 to 47·14)	42·96 (31·68 to 54·25)
p value	..	..	<0·0001	<0·0001	<0·0001	<0·0001

Results are for the primary and key secondary efficacy endpoints across treatment groups for the overall clinical study, for the FDA, and for the EMA, based on the respective planned analysis and significance levels (full analysis set). All p values presented in this table are nominal. EMA=European Medicines Agency. FDA=Food and Drug Administration. n=number of patients with response based on SALT score 20 or less or SALT 10 or less, as appropriate. N=number of patients with valid data. PGI-C=Patient's Global Impression of Change. SALT=Severity of Alopecia Tool. *Both placebo groups were combined for week 24 analyses. †Primary endpoint for overall clinical study (α=0·05) and for the FDA (α=0·00125). ‡Miettinen and Nurminen method was used to calculate 95% CIs and Farrington-Manning method was used to calculate p values for testing the difference in the proportion of response between each active treatment group and placebo. Data missing due to COVID-19 were excluded from this analysis, whereas patients with missing data due to other reasons were included in the analysis as non-responders. §Key secondary endpoint for the overall clinical study (α=0·05). ¶Multiple imputation methods were based on generalised linear mixed model for longitudinal binary data up to week 24, with an assumption of missing at random for SALT scores missing at week 24 due to COVID-19. Patients with SALT scores missing due to other reasons were included in the analysis as non-responders. A single complete imputed data set for week 24 was analysed using the Miettinen and Nurminen method. ‖Primary endpoint for the EMA (α=0·01). **PGI-C response was defined as a PGI-C score of moderately improved or greatly improved. ††Key secondary endpoint for the EMA (α=0·01).

Table 2: **Summary of results**

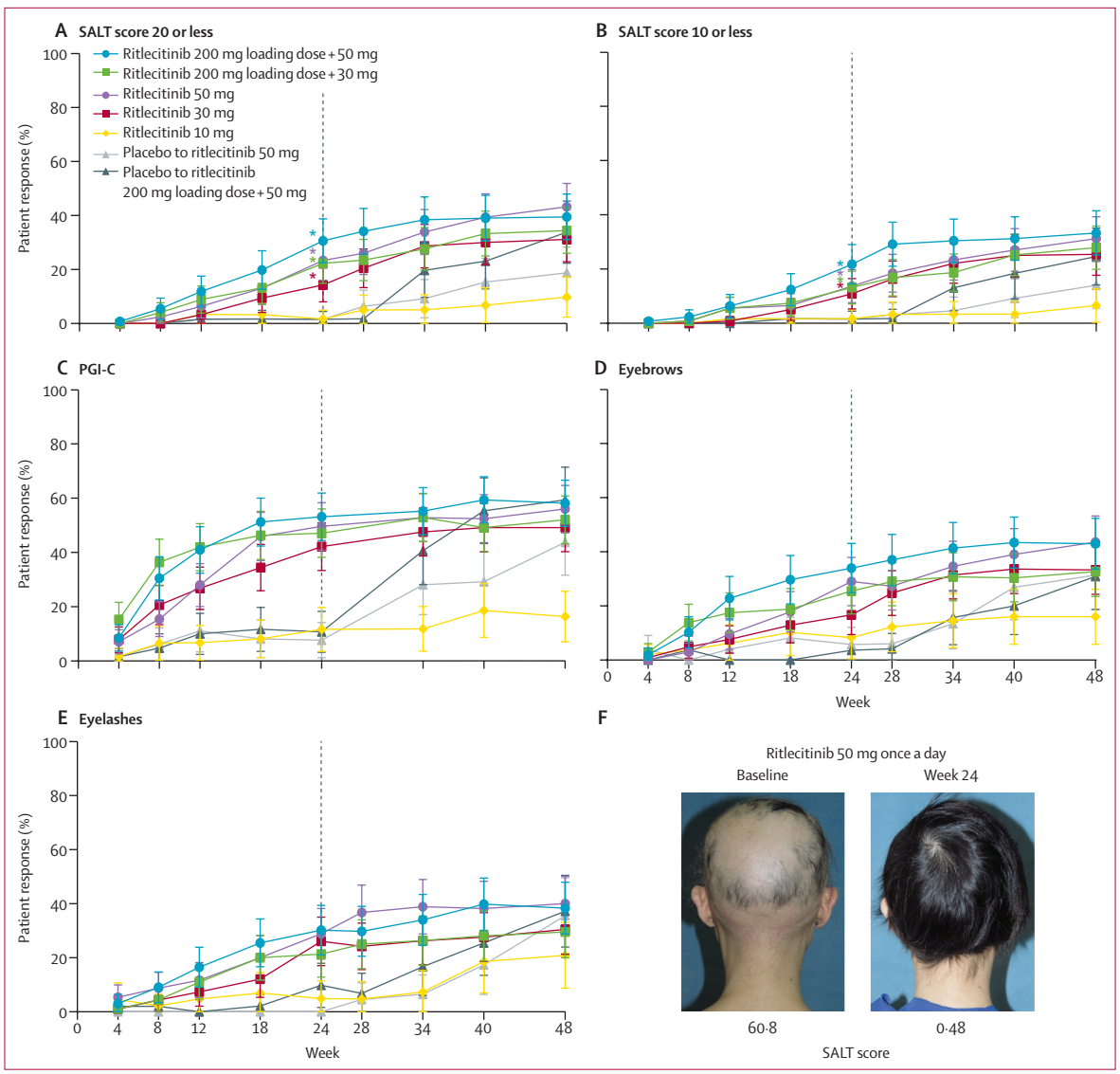

Figure 3: **Patient response by treatment group**
Vertical bars represent 95% CIs. (A) Response based on SALT score 20 or less. (B) Response based on SALT score 10 or less. (C) PGI-C response (score of moderately improved or greatly improved). (D) Eyebrow response (≥2 grade improvement or normal eyebrow assessment score of 3 in patients without normal eyebrows at baseline). (E) Eyelash response (≥2 grade improvement or normal eyelash assessment score of 3 in patients without normal eyelashes at baseline). (F) Representative photos of a single responder at screening and week 24. Photos from more patients are shown in the appendix (p 24). SALT=Severity of Alopecia Tool. PGI-C=Patient's Global Impression of Change. *Statistically significant versus placebo for the overall study at an overall significance level (α) of 0·05.

week 24 was 14% in the 200 mg + 50 mg group, 12% in the 200 mg + 30 mg group, 7% in the 50 mg group, 7% in the 30 mg group, and 0% in the placebo group. The treatment effect of ritlecitinib versus placebo was generally consistent across other subgroups for all doses (data not shown).

Among patients without normal eyebrow assessment or eyelash assessment scores at baseline, eyebrow and eyelash responses (≥2 grade improvement from baseline in eyebrow assessment score or a normal score in eyelash assessment score) increased over time with ritlecitinib 200 mg + 50 mg, 200 mg + 30 mg, 50 mg, and 30 mg (figures 3D and 3E; appendix p 20). Representative images of hair regrowth in patients responding to ritlecitinib are shown in figures 2F and the appendix (p 24).

During the placebo-controlled period (weeks 0–24), 14 patients permanently discontinued the study due to AEs, and 55 experienced dose interruptions due to AEs (table 3). AEs were reported by 96 (73%) of 131 patients in the ritlecitinib 200 mg + 50 mg group, 91 (71%) of 129 patients in the 200 mg + 30 mg group, 98 (75%) of 130 patients in the 50 mg group, 96 (73%) of 132 patients in the 30 mg group, 43 (69%) of 62 patients in the 10 mg

	Placebo (pooled) (n=131)	10 mg ritlecitinib (n=62)	30 mg ritlecitinib (n=132)	50 mg ritlecitinib (n=130)	200 mg then 30 mg ritlecitinib (n=129)	200 mg then 50 mg ritlecitinib (n=131)
Permanent discontinuations due to AEs	2 (2%)	2 (3%)	4 (3%)	2 (2%)	0	4 (3%)
Temporary dose interruptions due to AEs	7 (5%)	5 (8%)	9 (7%)	13 (10%)	9 (7%)	12 (9%)
Patients with AEs	93 (71%)	43 (69%)	96 (73%)	98 (75%)	91 (71%)	96 (73%)
AEs occurring in ≥10% of patients*						
Upper respiratory tract infection	10 (8%)	2 (3%)	11 (8%)	8 (6%)	10 (8%)	16 (12%)
Nasopharyngitis	8 (6%)	6 (10%)	16 (12%)	13 (10%)	18 (14%)	15 (11%)
Headache	11 (8%)	11 (18%)	20 (15%)	12 (9%)	10 (8%)	11 (8%)
Patients with SAEs†	3 (2%)	2 (3%)	1 (1%)	0	0	4 (3%)

Data are n (%). Summary of AEs, SAEs, discontinuations, and AEs of special interest with ritlecitinib or placebo (safety analysis set). AE=adverse event. SAE=serious adverse event. *Individual AEs (by preferred term) reported in at least 10% of patients in a given treatment group during the indicated period. †List of SAEs is shown in the appendix (p 15).

Table 3: **Adverse events in placebo-controlled period**

group, and 93 (71%) of 131 patients in the placebo groups. Most AEs were mild or moderate in severity. The most common AEs of any grade occurring in at least 10% of patients in any treatment group were upper respiratory tract infection, nasopharyngitis, and headache (table 3; appendix p 13). The incidence of nasopharyngitis during this period was higher with ritlecitinib than with placebo (10–14% of patients for ritlecitinib *vs* 6% for placebo). The incidence of upper respiratory tract infection, urticaria, and urinary tract infection was highest with 200 mg + 50 mg and the incidence of folliculitis and dizziness was highest in the 200 mg + 50 mg and 200 mg + 30 mg groups (appendix p 13).

During the entire study (up to week 48 and including the follow-up period), AEs were reported by 108 (82%) of 131 patients in the ritlecitinib 200 mg + 50 mg group, 105 (81%) of 129 patients in the 200 mg + 30 mg group, 110 (85%) of 130 patients in the 50 mg group, 106 (80%) of 132 patients in the 30 mg group, 47 (76%) of 62 patients in the 10 mg group, 54 (83%) of 65 patients in the group who received placebo for 24 weeks and then switched to ritlecitinib 200 mg + 50 mg in the extension period, and 57 (86%) of 66 patients in the group who received placebo for 24 weeks and then switched to ritlecitinib 50 mg in the extension period (table 4). The incidence of each AE was similar across treatment groups, except for influenza, upper respiratory tract infection, and urinary tract infection, which were reported more frequently in the 200 mg + 50 mg group than in any other group. Folliculitis, urticaria, and dizziness were reported more frequently in the 200 mg + 50 mg and 200 mg + 30 mg groups.

16 serious AEs were reported in 14 patients (four in the ritlecitinib 200 mg + 50 mg group, two in the 200 mg + 30 mg group, two in the 50 mg group, one in the 30 mg group, two in the 10 mg group, and three while receiving placebo); ten of these patients reported 11 of the events during the placebo-controlled phase (appendix p 15). Five AEs of serious infection were reported in four patients (one patient in the ritlecitinib 200 mg + 50 mg group experienced two events [empyema (related to treatment) and sepsis (related to treatment)], one in the 200 mg + 50 mg group and one in the 200 mg + 30 mg group experienced appendicitis [not related to treatment], and one in the 30 mg group experienced diverticulitis [not related to treatment]), one pulmonary embolism (not related to treatment; patient in the 50 mg group), and two malignancies (both breast cancers, one in the 200 mg + 50 mg group [46 year-old female diagnosed with breast cancer on day 68 of ritlecitinib treatment, not related to treatment per the investigator] and one in the 50 mg group [58 year-old female diagnosed with breast cancer on day 198, related to treatment per the investigator]). Eight events of herpes zoster were reported in eight patients (one patient in the ritlecitinib 200 mg + 50 mg group, two in the 200 mg + 30 mg group, and five in the 50 mg group); none were serious. No deaths, major cardiovascular events, or opportunistic infections were reported during the study. Dose interruptions due to COVID-19 are shown in the appendix (p 16). The safety profile during the entire study was consistent with that of the placebo-controlled period (table 3, table 4; appendix p 13).

Throughout the entire study, 30 patients had neurological events of interest, evenly distributed across treatment groups. In 25 of these patients, AEs were reported up to week 24 (one patient receiving 200 mg + 50 mg, five receiving 200 mg + 30 mg, three receiving 50 mg, eight receiving 30 mg, four receiving 10 mg, and four receiving placebo). Audiological events were identified from protocol-specified audiological testing; none were spontaneously reported. Six patients with adjudicated audiological AEs met the criteria as non-serious events of interest of sensorineural hearing loss. Of these, two patients experienced audiological AEs up to week 24 (one patient each receiving 50 mg and 30 mg). No events were consistent with central hearing disorder.

Treatment with ritlecitinib was associated with changes in median haematological parameters. There were small, transient decreases in haemoglobin and small, variable changes in neutrophil concentrations, which were stable from week 4 onward after initiation of treatment with ritlecitinib up to week 48. Small, early decreases in platelets were observed with ritlecitinib treatment, regardless of dose (200 mg + 50 mg, median change $-45{\cdot}0\times10^3$/mm³ at week 2), which remained stable to week 48. Dose-dependent early decreases in absolute lymphocyte levels (200 mg + 50 mg, median change from baseline $-0{\cdot}5\times10^9$/L at week 4), T lymphocyte counts, and T lymphocyte subset counts were observed. After the initial

	Placebo to 50 mg (n=66)	Placebo to 200 mg then 50 mg (n=65)	10 mg ritlecitinib (n=62)	30 mg ritlecitinib (n=132)	50 mg ritlecitinib (n=130)	200 mg then 30 mg ritlecitinib (n=129)	200 mg then 50 mg ritlecitinib (n=131)
Permanent discontinuations due to AEs	4 (6%)	0	2 (3%)	6 (5%)	4 (3%)	2 (2%)	4 (3%)
Temporary dose interruptions due to AEs	8 (12%)	13 (20%)	5 (8%)	16 (12%)	20 (15%)	16 (12%)	17 (13%)
Patients with AEs	57 (86%)	54 (83%)	47 (76%)	106 (80%)	110 (85%)	105 (81%)	108 (82%)
AEs occurring in ≥10% of patients*							
Headache	8 (12%)	8 (12%)	12 (19%)	24 (18%)	16 (12%)	14 (11%)	17 (13%)
Nasopharyngitis	4 (6%)	7 (11%)	7 (11%)	21 (16%)	18 (14%)	21 (16%)	19 (15%)
Upper respiratory tract infection	6 (9%)	7 (11%)	2 (3%)	16 (12%)	11 (8%)	12 (9%)	18 (14%)
Nausea	1 (2%)	8 (12%)	3 (5%)	12 (9%)	3 (2%)	3 (2%)	11 (8%)
Acne	8 (12%)	5 (8%)	3 (5%)	12 (9%)	12 (9%)	10 (8%)	6 (5%)
Patients with SAEs†	3 (5%)	0	2 (3%)	1 (1%)	2 (2%)	2 (2%)	4 (3%)
AEs of special interest, n							
Herpes zoster	0	0	0	0	5	2	1
Serious infections	0	0	0	1‡	0	1§	2¶
Pulmonary embolism	0	0	0	0	1	0	0
Malignancies	0	0	0	0	1‖	0	1**

Data are n (%). Summary of AEs, SAEs, discontinuations, and AEs of special interest with ritlecitinib or placebo (safety analysis set). AE=adverse event. SAE=serious adverse event. *Individual AEs (by preferred term) reported in at least 10% of patients in a given treatment group during the indicated period. †List of SAEs is shown in the appendix (p 15). ‡Diverticulitis. §Appendicitis. ¶Empyema and sepsis (two events in one patient), appendicitis. ||Breast cancer. **Invasive lobular breast carcinoma.

Table 4: **Adverse events in overall study period**

decrease, concentrations recovered partly and remained stable up to week 48. There was no change in CD19 cells (B lymphocytes) in any treatment group. There was a dose-dependent early decrease in natural killer cell counts to week 24, which was most apparent in groups with the 200 mg loading dose of ritlecitinib (200 mg + 50 mg). There were no clinically meaningful effects of ritlecitinib on alanine aminotransferase, aspartate aminotransferase, bilirubin, or alkaline phosphatase, and no cases of drug-induced liver injury were reported. 50 patients had creatine kinase levels more than twice the upper limit of normal to week 24 (11 receiving 200 mg + 50 mg, ten receiving 200 mg + 30 mg, 14 receiving 50 mg, eight receiving 30 mg, three receiving 10 mg, and four receiving placebo). 78 patients had creatine kinase levels more than twice the upper limit of normal to week 48. No patient had creatine kinase level meeting the discontinuation criteria (more than ten times the upper limit of normal, confirmed by retest). Increases in creatine kinase were not clinically meaningful and no cases of rhabdomyolysis were reported. There were small, transient dose-dependent increases in total cholesterol, HDL cholesterol, and LDL cholesterol (relative to placebo), without a consistent pattern or association with dose up to week 48.

Discussion

In the ALLEGRO phase 2b–3 trial, ritlecitinib 50 mg and 30 mg daily, with or without 200-mg loading dose, was efficacious in patients aged 12 years and older with alopecia areata and at least 50% scalp hair loss. All four tested dose regimens met primary and key secondary endpoints at the overall study level and in the statistical testing hierarchy agreed with the FDA and EMA. Proportions of patients with response based on SALT score 20 or less and 10 or less were significantly higher among patients receiving ritlecitinib than in patients given placebo at week 24, and response rates continued to increase up to week 48 (end of study). Consistent with other placebo-controlled trials in alopecia areata with extensive scalp hair loss,[22,26] the placebo response was very low, confirming the low rate of spontaneous remission in patients with extensive scalp hair loss due to alopecia areata. Patients with alopecia totalis or alopecia universalis, who are often refractory to treatment,[3,29] had higher response rates with ritlecitinib than with placebo, although response rates were lower than in patients without alopecia totalis or alopecia universalis; patients with alopecia totalis or alopecia universalis comprised almost half of the study population. Considering that almost half of the trial population had alopecia totalis or alopecia universalis together with evidence that patients with longer episode of severe disease have a poorer prognosis (compared with those with short episode duration),[30] treating patients early in an episode of more extensive hair loss and before complete hair loss occurs might substantially increase response rates. However, further analyses are needed to determine patient and disease factors that are associated with response to ritlecitinib and

effect on long-term disease course. PGI-C responses were also greater with ritlecitinib treatment than with placebo. Regrowth of eyebrows and eyelashes was observed. This study was not powered for hypothesis testing in subgroups, such as adolescents and patients with alopecia totalis or alopecia universalis; however, treatment effects in these subgroups were nominally statistically significant and consistent with responses in the entire population, across all dose groups. Ritlecitinib was generally safe and well tolerated throughout this study (up to week 48 visit, and including the follow-up period) at all doses, and the safety profile was consistent with previous studies of ritlecitinib.[26] Audiology evaluation did not reveal any central hearing disorder from ritlecitinib, and no serious neurological AEs were observed.

Multiple dose regimens were assessed in this study, including the 200 mg + 50 mg dose shown to be effective and well tolerated in the previous phase 2a trial.[26] A dose-response was shown across efficacy endpoints, and all doses included in the statistical analyses were superior to placebo at week 24. Loading-dose regimens provided an earlier response than did no loading dose, but regimens with and without loading doses showed similar efficacy by week 48.

Hair regrowth observed with ritlecitinib might imply restoration of hair follicle immune privilege. This is supported by preliminary evidence from mouse model and skin biopsy studies that suggests modulation of cellular biomarkers toward maintenance of hair follicle immune privilege following treatment with ritlecitinib.[30,31] In a scalp biopsy study from patients with alopecia areata treated with ritlecitinib, gene expression revealed up-regulation of the immunoregulatory CD200 pathway associated with immune privilege maintenance and downregulation of the natural killer/T cell NKG2D-MICA/B danger signal pathway.[30] Reduction of NKG2D+ cells was also confirmed in lesional scalp following treatment. Furthermore, a consistent cluster of down-regulated expression of major histocompatibility complex class I genes was observed in patients given ritlecitinib, consistent with immunostaining of alopecic mice treated with ritlecitinib.[31]

Our study has some limitations, including the exclusion of patients with duration of current alopecia areata episode longer than 10 years. Although some data were missing due to COVID-19, the impact on study efficacy results was minimal; at week 24, 41 participants (5·7%) were excluded from the analysis of the primary endpoint because their missing SALT score was related to COVID-19. Although there was diversity among the trial participants, most (68%) were White.

In conclusion, ritlecitinib doses of 50 mg and 30 mg once a day (with or without loading dose of 200 mg once a day) were efficacious and generally safe and well tolerated over 48 weeks in patients with alopecia areata. A long-term study (ALLEGRO-LT; NCT04006457) is ongoing.

Contributors

BK, XZ, WGH, JCS, JS, CL, NAM, VP, and RS contributed to the data acquisition. BK, XZ, WGH, JCS, JS, CL, NAM, SHZ, LN, DW, RF, DM, VP, and RW contributed to the data analysis. BK, NAM, DW, AF, DM, VP, RS, and RW contributed to the writing. SHZ, LN, DW, AF, VP, RS, and RW contributed to the study design. DW did the statistical analysis. BK and DW directly accessed and verified the underlying data reported in the manuscript. All authors participated in the data interpretation and had full access to the data in the study, and all read and approved the final version of the manuscript for publication.

Declaration of interests

BK served on advisory boards or was a consultant or clinical trial investigator for AbbVie, AltruBio, Almirall, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, BMS, Concert Pharmaceuticals, Equillium, Horizon Therapeutics, Eli Lilly, Incyte, Janssen Pharmaceuticals, LEO Pharma, Otsuka/Visterra, Pfizer, Regeneron, Sanofi Genzyme, TWi Biotechnology, and Viela Bio. BK is on speaker bureaus for AbbVie, Incyte, Eli Lilly, Pfizer, Regeneron, and Sanofi Genzyme. WGH was a scientific advisor or clinical study investigator for Beiersdorf/Eucerin, BioNOOX, Eucerin, Galderma, GSK, Janssen, Johnson & Johnson, Pfizer, and Sanofi. JCS was scientific advisor or consultant for AbbVie, LEO Pharma, Novartis, Sandoz, Sanofi Genzyme, Trevi, and Viofor; speaker for AbbVie, Eli Lilly, Janssen-Cilag, LEO Pharma, and Sanofi Genzyme; and investigator for AbbVie, Amgen, BMS, Galderma, Galapagos, Incyte, InfraRx, Janssen-Cilag, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Trevi, and UCB. JS was a consultant or clinical study investigator for 30 Madison, Eirion, Eli Lilly, Pfizer, and Regenlab; and stockholder of 30 Madison. CL was speaker or consultant for AbbVie, Altius, Amgen, Aralez, Arcutis, Bausch Health, Bayer, Boehringer Ingelheim, BMS, Celgene, Cipher, Dermavant, Eli Lilly, Fresenius Kabi, GSK, Innovaderm, Intega Skin, Janssen, Kyowa, La Roche Posay, LEO Pharma, L'Oreal, Medexus, Merck, P&G, Pediapharm, Regeneron, Roche, Sanofi Genzyme, Sentrex, TEVA, Tribute, UCB, Valeant, and Viatris; and principal investigator for AbbVie, Amgen, Aralez, Arcutis, Bausch Health, Bayer, Boehringer Ingelheim, BMS, Celgene, Cipher, Dermavant, Eli Lilly, GSK, Innovaderm, Janssen, Kyowa, LEO Pharma, L'Oreal, Merck, Pediapharm, Regeneron, Roche, Sanofi Genzyme, Tribute, UCB, and Valeant. NAM provided professional services for AbbVie, Arena Pharmaceuticals, BMS, Concert Pharmaceuticals, Eli Lilly, La Roche Posay, and Pfizer. RS provided professional services to Aerotech, AbbVie, AstraZeneca, Akesobio, Amgen, Arcutis, Arena, Ascend, Bayer, BMS, Boehringer Ingelheim, Celgene, Coherus BioSciences, Connect, Cutanea, Dermira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MedImmune, Merck, MSD, Novartis, Oncobiologics, Pfizer, Regeneron, Reistone, Roche, Samson Clinical, Sanofi, Sun Pharma, and UCB. SHZ, LN, DW, AF, DM, VP, and RW are employees of and own stock in Pfizer. RF was an employee of and owned stock in Pfizer at the time of this study. XZ declares no competing interests.

Data sharing

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 deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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