



Impact of Previous Alopecia Areata Treatment on Efficacy Responses up to Week 48 Following Ritlecitinib Treatment: A Post Hoc Analysis

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ABSTRACT

Introduction: Patients with alopecia areata (AA) may have received several therapies for management of AA during their lives. In the ALLEGRO phase 2b/3 (NCT03732807) study, the oral JAK3/TEC family kinase inhibitor ritlecitinib demonstrated efficacy and an acceptable safety profile in patients aged ≥ 12 years with AA and $\geq 50\%$ scalp hair loss. This post hoc

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analysis investigated associations between prior use of AA therapies and Severity of Alopecia Tool (SALT) responses in patients receiving ritlecitinib for AA.

Methods: Patients receiving ritlecitinib 30 mg or 50 mg once daily with or without an initial 4-week 200-mg daily loading dose were grouped by previous exposure to AA treatments, including topicals, intralesional corticosteroids (ILCS), topical immunotherapy, and systemic immunosuppressants or any prior AA treatment. Multivariable logistic regression analyses evaluated the association between response based on a SALT score of ≤ 20 and any prior treatment for AA at weeks 24 and 48.

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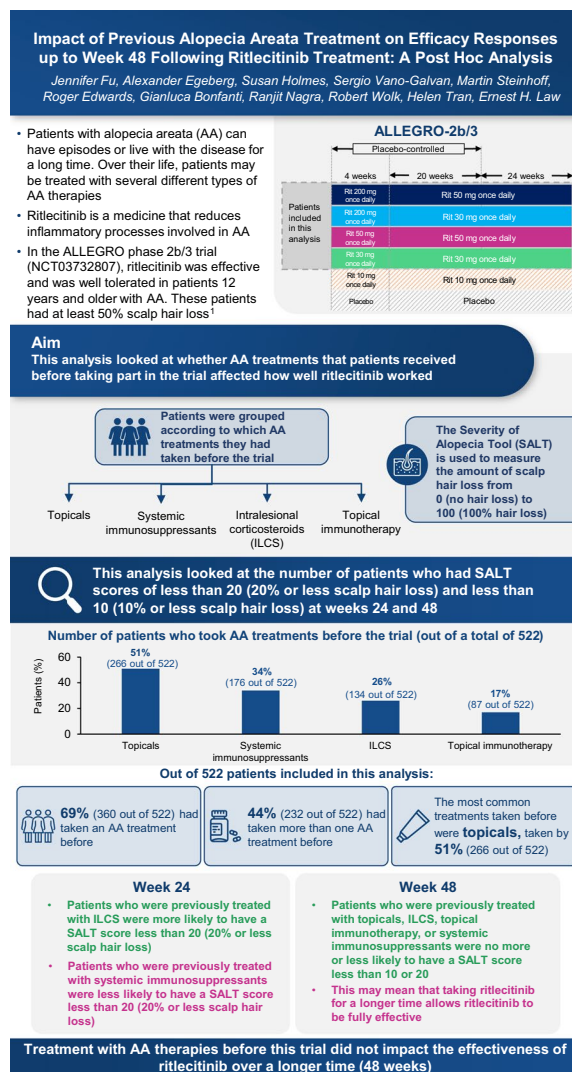
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Results: Of 522 patients, 360 (69.0%) had previous exposure to any AA treatment. At Week 24, SALT ≤ 20 response was positively associated with prior use of ILCS (odds ratio [OR], 2.12; 95% confidence interval [CI], 1.23–3.65; $P < 0.05$) and negatively associated with prior use of systemic immunosuppressants (OR 0.50; 95% CI 0.28–0.88; $P < 0.05$). Prior use of topicals or topical immunotherapy was not associated with SALT ≤ 20 response at Week 24. By Week 48, no association was identified between SALT ≤ 20 response and prior use of topicals, ILCS, topical immunosuppressants, or systemic immunosuppressants (all $P > 0.05$). Previous exposure to any AA therapy was not associated with SALT ≤ 20 response at weeks 24 or 48 (all $P > 0.05$).

Conclusions: Prior AA treatment history had no effect on longer-term treatment response to ritlecitinib.

Trial Registration Number: NCT03732807.

Graphical Abstract:



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Keywords: Alopecia areata; Ritlecitinib; SALT; Treatment; JAK inhibitor; Post hoc analysis

Key Summary Points

Why carry out this study?

Alopecia areata (AA) often follows a prolonged disease course, meaning that patients, particularly those with severe disease, may receive several therapies for management of AA during their lives.

This post hoc analysis of the ALLEGRO-2b/3 study investigated the impact of prior AA treatments on the efficacy of ritlecitinib at weeks 24 and 48 in patients with AA.

What was learned from the study?

After adjustment for potential confounders, no associations were found between prior AA treatment history and efficacy of ritlecitinib at Week 48.

In patients who received prior treatment for AA, continuation of ritlecitinib therapy for at least 48 weeks is important to evaluate ritlecitinib's therapeutic effect.

DIGITAL FEATURES

This article is published with digital features, including a Graphical Abstract to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.26520259>.

INTRODUCTION

Alopecia areata (AA) is an autoimmune disease driven by an immune attack on the hair follicles, causing non-scarring hair loss [1–4]. AA can affect many aspects of a patient's life, including emotional/psychosocial and health-related quality of life [5–7], and patients with AA appear to have higher rates of anxiety and depression compared with the general population [8]. The clinical course of AA is unpredictable; AA can be acute and self-limiting or follow a prolonged

and relapsing–remitting course that can persist for many years [9]. In approximately 23–40% of patients with AA, the disease may last for longer than 1 year [9–11], after which prognosis is less favorable, with patients developing further patches of hair loss that result in more severe subtypes of AA, such as alopecia totalis (AT) and alopecia universalis (AU) [9].

In June 2022, the US Food and Drug Administration approved the Janus kinase (JAK) inhibitor baricitinib for the treatment of adult patients with severe AA [12]. This was followed by approval in the USA, Europe, and several other countries of ritlecitinib, an oral JAK3/TEC family kinase inhibitor [13], for individuals aged ≥ 12 years with severe AA [14]. These new treatments have the potential to change the treatment landscape for AA; prior to their approval, treatments for AA were limited to off-label use of other medications, such as topical corticosteroids, topical calcineurin inhibitors, intralesional corticosteroid (ILCS) injections, systemic corticosteroids, systemic immunosuppressants, and contact immunotherapy [15–18]. These treatments have shown variable clinical efficacy and high relapse rates, highlighting the unmet need for effective treatments that induce durable remission [17, 19–23]. In addition, oral corticosteroids and other systemic immunosuppressants may lead to significant adverse effects [23, 24]; therefore, long-term administration is not recommended [22, 23].

Given the prolonged disease course of AA, a large proportion of patients who initiate treatment with recently approved ritlecitinib or baricitinib are expected to have been previously treated with one or more off-label therapies [25]. Therefore, with the increasing use of these new treatments, it is practically and clinically relevant to determine whether prior AA treatments have an impact on their efficacy.

The ALLEGRO phase 2b/3 (NCT03732807) study demonstrated that ritlecitinib was efficacious and had an acceptable safety profile in patients aged ≥ 12 years with AA and $\geq 50\%$ scalp hair loss [26]. This post hoc analysis of the ALLEGRO-2b/3 study investigated associations between prior use of AA therapies and hair regrowth response as measured by the Severity

of Alopecia Tool (SALT) in patients receiving ritlecitinib for AA over 48 weeks.

METHODS

Study Design

The design and primary results of the international, randomized, double-blind, placebo-controlled, combined dose-ranging, and pivotal ALLEGRO-2b/3 study have been previously described [26]. Patients were aged ≥ 12 years with a diagnosis of AA and $\geq 50\%$ scalp hair loss, including AT or AU; had no evidence of terminal hair regrowth within 6 months at both the screening and baseline visits; and had a current AA episode duration of 6 months to 10 years. Patients with other causes of alopecia or previous use of any JAK inhibitor were excluded.

Of 718 patients included in the ALLEGRO-2b/3 study, 446 (62%) were female, 105 (15%) were adolescents, and 330 (46%) had AT/AU.

Patients were randomized to receive once-daily (QD) ritlecitinib 50 mg or 30 mg (with or without a 4-week 200-mg loading dose), ritlecitinib 10 mg, or placebo for 24 weeks. Randomization was stratified by AA severity (with a target of $\sim 40\%$ of patients with AT/AU in each group) and age (with a target of $\sim 15\%$ adolescents, aged 12–17 years, in each group) (Supplementary Fig. S1). During the 24-week extension period, patients in the ritlecitinib groups continued their 50-, 30-, or 10-mg maintenance doses, and patients initially randomized to placebo were switched to ritlecitinib 50 mg QD with or without a 200-mg, 4-week loading dose.

This post hoc analysis included patients in the ritlecitinib 30-mg or 50-mg QD (with or without a 200-mg loading dose) groups only. Patients were grouped by previous exposure to AA treatments, including ILCS, topical immunotherapy (diphenylcyclopropenone, dinitrochlorobenzene), systemic immunosuppressants [oral immunosuppressants (azathioprine, cyclosporin, methotrexate); oral, intramuscular, or intravenous steroids; non-oral methotrexate], other topicals (topical calcineurin inhibitors, minoxidil, corticosteroids, anthralin, dithranol),

or more than one of these AA treatments. SALT score ≤ 20 ($\leq 20\%$ scalp hair loss) and SALT score ≤ 10 ($\leq 10\%$ scalp hair loss) responses at weeks 24 and 48 were assessed.

The protocols were reviewed and approved by the institutional review boards or ethics committees of the participating institutions. 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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and Declaration of Helsinki. Written informed consent was obtained from each patient, patient's parent, or patient's legal representative.

Statistical Analysis

Multivariable logistic regression analyses evaluated the association between response on the basis of a SALT score of ≤ 20 and a SALT score of ≤ 10 and any prior use of ILCS, systemic immunosuppressants, topical immunotherapy, or other topicals (including glucocorticosteroids), adjusting for patient and clinical covariates at both Week 24 and Week 48. Covariates included age, sex, race, body mass index (continuous), AA episode duration (continuous), AA disease duration (continuous), extent of AA (AT/AU versus non-AT/AU), prior use of ILCS, prior use of topical/systemic immunosuppressants, prior use of topical immunotherapy, prior use of topicals, eyelash assessment at baseline, eyebrow assessment at baseline, active hair shedding, and treatment arm. Sensitivity analyses were performed to evaluate the impact of different model selection methods (forward, backward, and stepwise). All analyses were implemented using R.

RESULTS

Patients

Of 522 patients included in this analysis, 360 (69.0%) had previous exposure to any AA

Table 1 Proportion of patients previously exposed to AA treatments

<i>n</i> (%)	Ritlecitinib (<i>N</i> = 522)
Any prior AA treatment	360 (69.0)
Topicals	266 (51.0)
ILCS	134 (25.7)
Topical immunotherapy	87 (16.7)
Systemic immunosuppressants ^a	176 (33.7)

Patients may have used more than one AA treatment

AA alopecia areata, ILCS intralesional corticosteroids

^aOral immunosuppressants (azathioprine, ciclosporin, methotrexate); oral, intramuscular, or intravenous steroids; or non-oral methotrexate

treatment. The proportions of patients who had been exposed to the different AA treatments are presented in Table 1. The most common prior treatments were topicals (51.0%), followed by systemic immunosuppressants (33.7%), ILCS (25.7%), and topical immunotherapy (16.7%). The numbers of patients exposed to different combinations of AA treatments are presented in Supplementary Table S1. Of the 522 patients,

232 (44.4%) had received more than one prior treatment. Patient baseline characteristics are presented in Table 2.

Efficacy

The proportions of patients with SALT ≤ 20 and ≤ 10 responses at weeks 24 and 48 in each of the prior-treatment groups are shown in Figs. 1 and 2, respectively. At Week 24, SALT ≤ 20 response was positively associated with prior use of ILCS (OR 2.12; 95% CI 1.23–3.65; *P* < 0.05) and negatively associated with prior use of systemic immunosuppressants (OR 0.50; 95% CI 0.28–0.88; *P* < 0.05) (Fig. 3A). Prior use of topicals (OR 1.47; 95% CI 0.88–2.47; *P* > 0.05) or topical immunotherapy (OR 0.82; 95% CI 0.41–1.57; *P* > 0.05) was not associated with SALT ≤ 20 response at Week 24 (Fig. 3A). By Week 48, no association was identified between SALT ≤ 20 response and prior use of topicals, ILCS, topical immunosuppressants, or systemic immunosuppressants (all *P* > 0.05) (Fig. 3B).

At Week 24, SALT ≤ 10 response was positively associated with prior use of a topical therapy (OR 2.13; 95% CI 1.17–3.95; *P* < 0.05) (Fig. 4A); however, by Week 48, no association was observed (Fig. 4B). Prior use of ILCS,

Table 2 Patient baseline characteristics

	Ritlecitinib 200/50 mg ^a (<i>n</i> = 132)	Ritlecitinib 200/30 mg ^a (<i>n</i> = 130)	Ritlecitinib 50 mg (<i>n</i> = 130)	Ritlecitinib 30 mg (<i>n</i> = 132)
Age, mean (SD), years	34.5 (15.0)	33.7 (13.8)	32.4 (13.4)	33.7 (14.8)
Female, <i>n</i> (%)	81 (61.4)	85 (65.4)	71 (54.6)	80 (60.6)
White, <i>n</i> (%)	92 (69.7)	90 (69.2)	79 (60.8)	91 (68.9)
Patients with AT or AU, <i>n</i> (%)	60 (45.5)	60 (46.2)	60 (46.2)	61 (46.2)
BMI, mean (SD), kg/m ²	25.2 (4.9)	25.3 (5.4)	24.7 (5.0)	24.9 (4.7)
Disease duration since diagnosis, mean (SD), years	9.9 (10.8)	11.6 (11.7)	8.7 (8.7)	8.8 (8.9)
Duration of current AA episode, mean (SD), years	3.5 (2.9)	3.4 (2.8)	3.2 (2.7)	3.6 (2.8)

AA alopecia areata, AT alopecia totalis, AU alopecia universalis, BMI body mass index, SD standard deviation

^aOne patient in the 200/50-mg group and one in the 200/30-mg group did not receive treatment and were therefore not included in this post hoc analysis

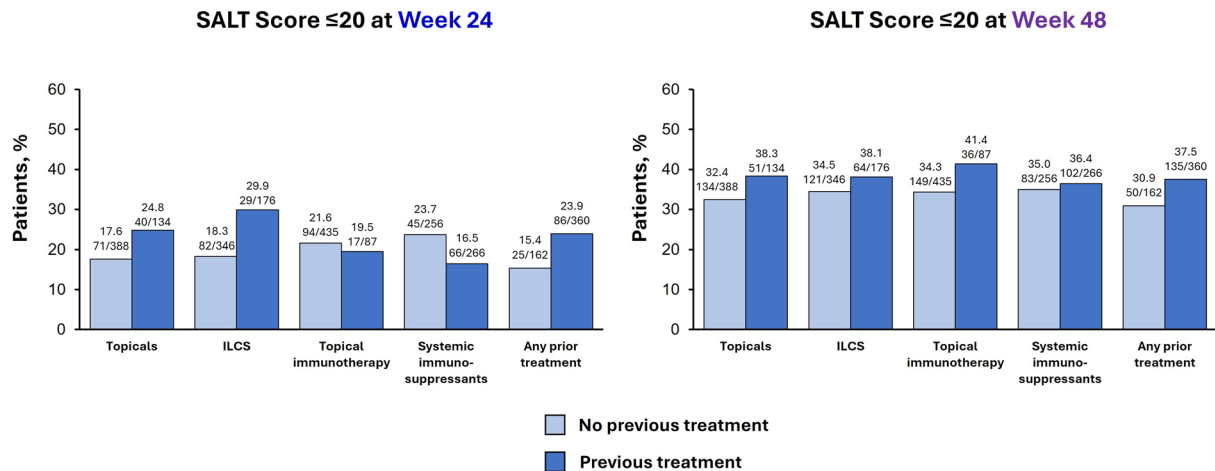


Fig. 1 SALT ≤ 20 response at weeks 24 and 48 by prior exposure to AA therapies in patients receiving ritlecitinib ≥ 30 mg. AA alopecia areata, ILCS intralesional corticosteroids, SALT Severity of Alopecia Tool

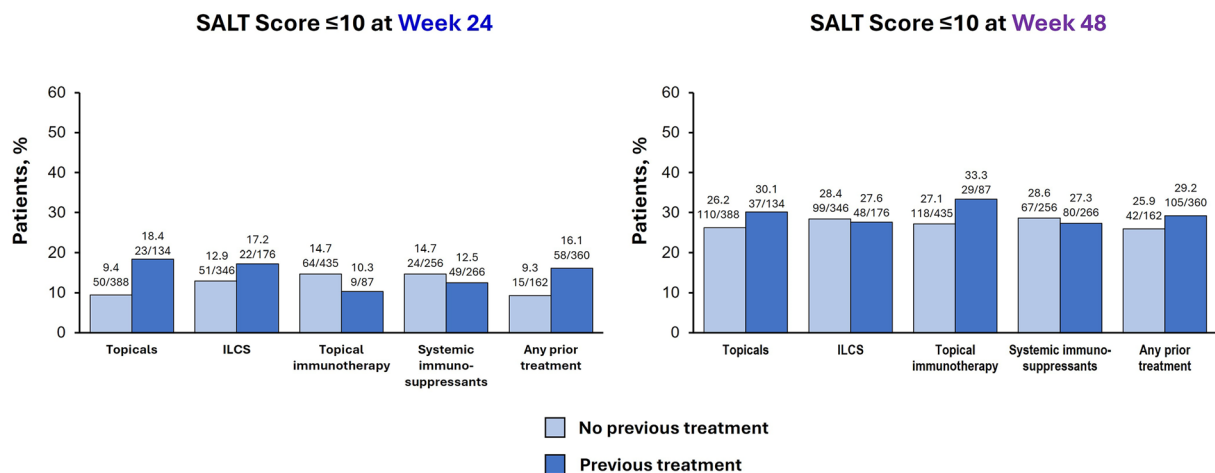


Fig. 2 SALT ≤ 10 response at weeks 24 and 48 by prior exposure to AA therapies in patients receiving ritlecitinib ≥ 30 mg. AA alopecia areata, ILCS intralesional corticosteroids, SALT Severity of Alopecia Tool

topical immunotherapy, or systemic immunosuppressants was not associated with SALT ≤ 10 response at Week 24 or Week 48 (all $P > 0.05$) (Fig. 4).

Previous exposure to any AA therapy was not associated with SALT ≤ 20 or SALT ≤ 10 response at Week 24 or Week 48 (all $P > 0.05$) (Fig. 5).

Results of all sensitivity analyses did not differ meaningfully from the results of the base-case analysis (data not shown).

DISCUSSION

This post hoc analysis of the ALLEGRO phase 2b/3 study found that in patients treated with ritlecitinib ≥ 30 mg QD, prior exposure to ILCS or systemic immunotherapy was associated with differences in the likelihood of clinically meaningful scalp hair regrowth (defined as SALT ≤ 20 or ≤ 10 response) at Week 24; however, by Week 48, no association was found between prior use of any AA therapies and scalp hair regrowth. These

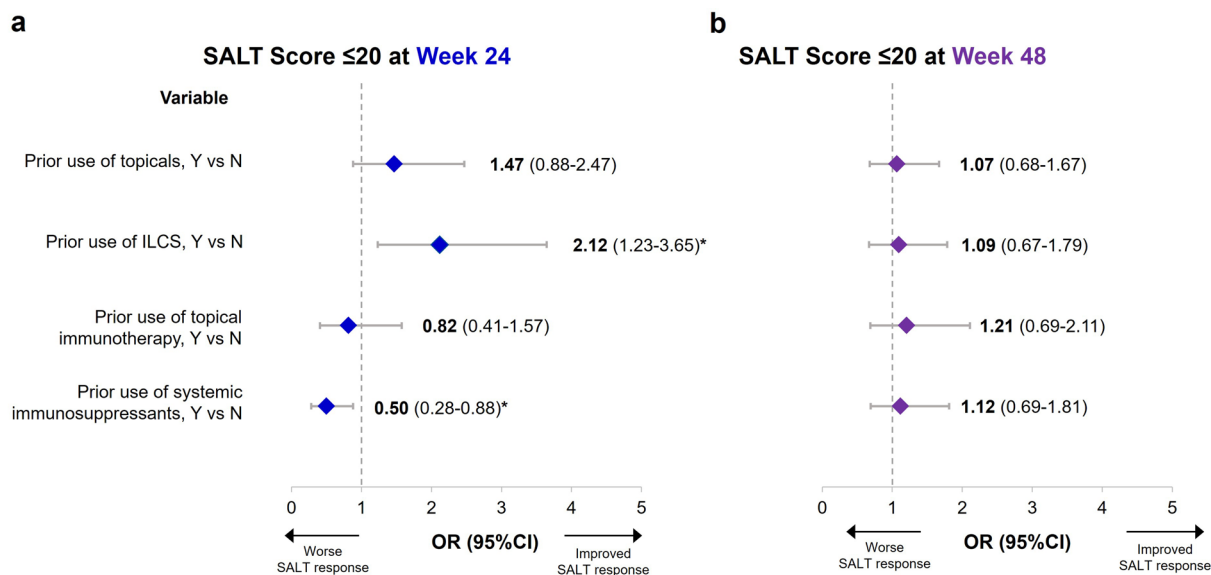


Fig. 3 Multivariate analysis of the effect of prior treatment on SALT ≤ 20 response at **a** Week 24 and **b** Week 48. *AA* alopecia areata, *AT* alopecia totalis, *AU* alopecia universalis, *CI* confidence interval, *ILCS* intralesional corticosteroids, *N* no, *OR* odds ratio, *SALT* Severity of Alopecia Tool, *Y* yes. Covariates included age, sex, race, body mass index

(continuous), episode duration (continuous), disease duration (continuous), extent of AA (*AT/AU* versus non-*AT/AU*), prior use of *ILCS*, prior use of systemic immunosuppressants, prior use of topical immunotherapy, prior use of topicals, eyelash assessment at baseline, eyebrow assessment at baseline, active shedding, and treatment arm. **P* < 0.05

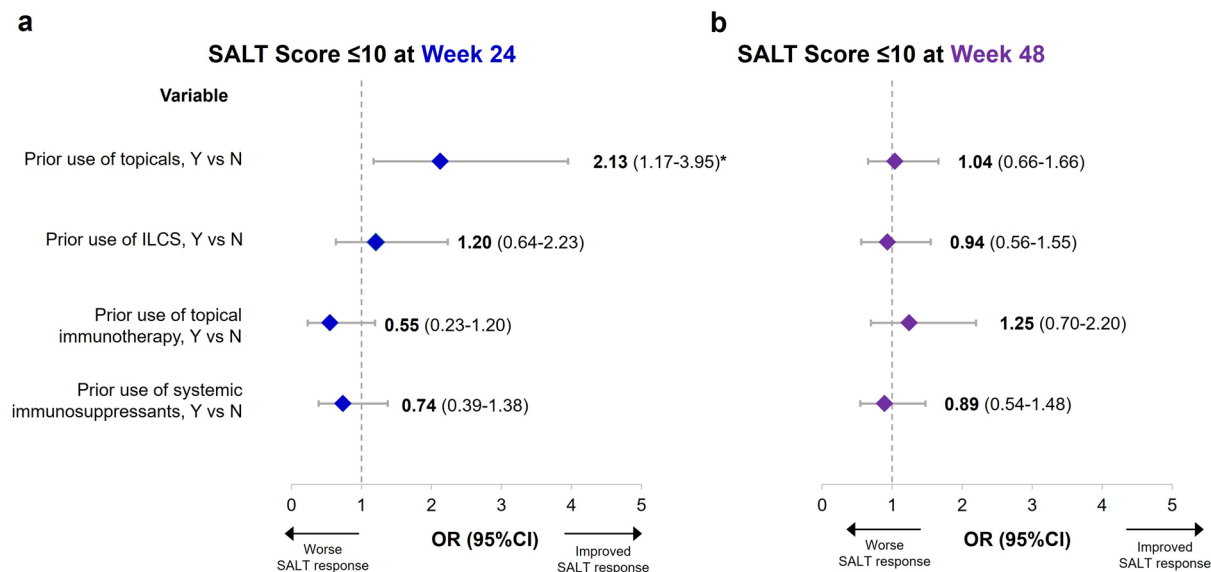


Fig. 4 Multivariate analysis of the effect of prior treatment on SALT ≤ 10 response at **a** Week 24 and **b** Week 48. *AA* alopecia areata, *AT* alopecia totalis, *AU* alopecia universalis, *CI* confidence interval, *ILCS* intralesional corticosteroids, *N* no, *OR* odds ratio, *SALT* Severity of Alopecia Tool, *Y* yes. Covariates included age, sex, race, body mass index

(continuous), episode duration (continuous), disease duration (continuous), extent of AA (*AT/AU* versus non-*AT/AU*), prior use of *ILCS*, prior use of systemic immunosuppressants, prior use of topical immunotherapy, prior use of topicals, eyelash assessment at baseline, eyebrow assessment at baseline, active shedding, and treatment arm. **P* < 0.05

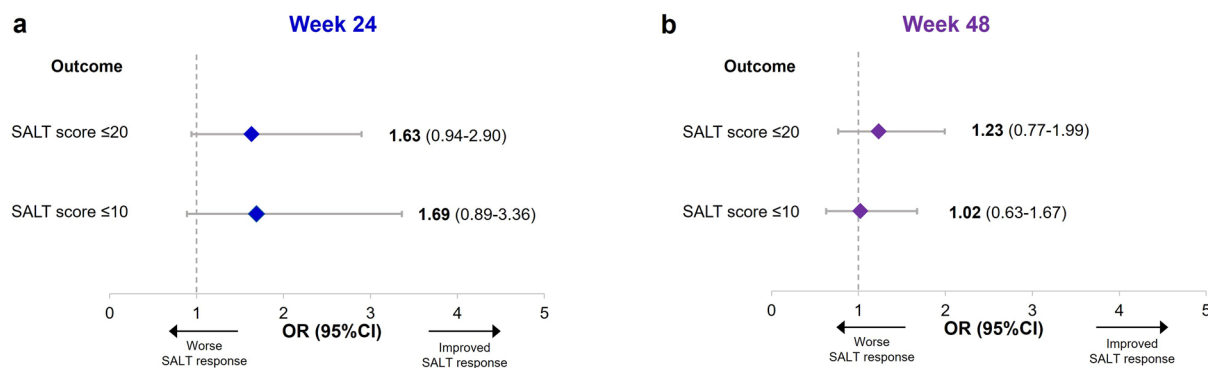


Fig. 5 Effect of any prior AA treatment on SALT ≤ 10 and SALT ≤ 20 responses at **a** Week 24 and **b** Week 48. AA alopecia areata, AT alopecia totalis, AU alopecia universalis, CI confidence interval, ILCS intralesional corticosteroids, OR odds ratio, SALT Severity of Alopecia Tool. Logistic regression model using a single binary variable indicating prior use of ILCS, systemic immunosuppressants, topical immunotherapy, or topicals. Covariates included age, sex,

race, body mass index (continuous), episode duration (continuous), disease duration (continuous), extent of AA (AT/AU versus non-AT/AU), prior use of ILCS, prior use of systemic immunosuppressants, prior use of topical immunotherapy, prior use of topicals, eyelash assessment at baseline, eyebrow assessment at baseline, active shedding, and treatment arm

results suggest that prior treatment history has no effect on longer-term treatment response to ritlecitinib and that long-term use of ritlecitinib allows it to reach its full therapeutic potential.

At Week 24, prior use of ILCS appeared to have a clinical benefit on the efficacy of ritlecitinib. This may be because ILCS is commonly used to treat patients with localized lesions rather than extensive hair loss [16]. Such patients may have a greater early response to ritlecitinib treatment [27] than those with more extensive involvement, who are likely to have been treated with systemic agents. Indeed, the prior use of systemic immunosuppressants was negatively associated with ritlecitinib efficacy at Week 24. This may be because these patients had more extensive scalp involvement at baseline and therefore could potentially be slower to respond to treatment with ritlecitinib [27, 28].

Patients with AA may receive multiple different treatments over the course of their disease [25]. This is true in this study, in which over two-thirds of patients had received a prior treatment and 44.4% had received more than one prior treatment. Prior to the approval of baricitinib and ritlecitinib, the majority of treatments for AA were administered off label, including corticosteroids; however, these treatments do

not demonstrate sustained efficacy [17, 19–23]. Oral corticosteroids are also not suitable for long-term use due to safety concerns [22–24]. In an integrated analysis of four studies in AA, ritlecitinib was shown to be well tolerated with an acceptable safety profile up to 24 months in patients aged ≥ 12 years with AA [29].

This study had some limitations. This was a post hoc analysis and therefore may be subject to inherent biases or confounding variables. Patient numbers in some of the subgroups were small, and the study was not powered to detect differences in efficacy between subgroups on the basis of prior treatment. There was a lack of more detailed information on prior treatment history, including temporality/sequencing, patient response, and reasons for discontinuation, including whether a therapy caused remission (for a limited time) before becoming ineffective or failed from the outset.

CONCLUSIONS

Among patients receiving ritlecitinib, prior therapies for AA were not associated with differences in SALT ≤ 20 response at Week 48, suggesting

that prior treatment history has no effect on the longer-term efficacy of ritlecitinib.

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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.

Declarations

Conflict of Interest. Jennifer Fu has received consultation fees from Pfizer. Alexander Egeberg has received research funding from Pfizer, Eli Lilly, Novartis, Bristol Myers Squibb, AbbVie, Janssen, and Boehringer Ingelheim and has received honoraria for work as a consultant and/or speaker from AbbVie, Almirall, LEO Pharma, Zuellig Pharma, Galapagos NV,

SUN Pharmaceuticals, Samsung Bioepis, Pfizer, Eli Lilly, Novartis, Union Therapeutics, Galderma, Dermavant, UCB, Mylan, Bristol Myers Squibb, McNeil Consumer Healthcare, Horizon Therapeutics, Boehringer Ingelheim, and Janssen. Susan Holmes is an investigator for Pfizer and has undertaken paid consultancy work for Pfizer. Sergio Vano-Galvan has received research funding and honoraria for work as a consultant and/or speaker from Pfizer and Eli Lilly. Martin Steinhoff has received honoraria or investigative or consultation fees from or was an investigator for AbbVie, Almirall, Avon, Algorithm, Allergan, Bayer Health, Bayersdorf, Bristol Myers Squibb, Celgene, Chugai, Ducray, Eli Lilly, Galderma, Genentech, GSK, Incyte, Janssen, Johnson & Johnson, Kiniksa, LEO Pharma, L'Oreal, Maruho, Menlo Therapeutics, Mitsubishi, Novartis, Pfizer, Pierre-Fabre, Qatar Pharma, Regeneron, Sanofi, Toray, Trevi, Vertex, and ZymoGenetics. Roger Edwards is an employee of Health Services Consulting Corporation and received consultancy fees from Pfizer in connection with this study. Gianluca Bonfanti is an employee of Engineering Ingegneria Informatica, which is a paid subcontractor to Health Services Consulting Corporation. Ranjit Nagra, Robert Wolk, Helen Tran, and Ernest Law are employees of, and hold stock or stock options in, Pfizer.

Ethical Approval. The protocol was reviewed and approved by the institutional review boards or ethics committees of the participating institutions. 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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and Helsinki Declaration of 1964 and its later amendments. Written informed consent was obtained from each patient, patient's parent, or patient's legal representative to participate in the study.

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