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ORIGINAL RESEARCH ARTICLE

Patient-Reported Hair Loss and Its Impacts as Measured by the Alopecia Areata Patient Priority Outcomes Instrument in Patients Treated with Ritlecitinib: The ALLEGRO Phase 2b/3 Randomized Clinical Trial

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Abstract

Background The ALLEGRO phase 2b/3 study investigated the efficacy and safety of ritlecitinib in patients with alopecia areata (AA).

Objective To describe the impact of ritlecitinib on patient-reported hair loss using the Alopecia Areata Patient Priority Outcomes (AAPPO) instrument and evaluate the relationship between clinically meaningful hair regrowth and improvements in patient-reported impacts.

Methods In ALLEGRO-2b/3, patients aged ≥ 12 years with AA and ≥ 50% scalp hair loss received once-daily ritlecitinib 50 or 30 mg (± 4-week 200-mg daily loading dose), 10 mg, or placebo for 24 weeks and then continued ritlecitinib or switched from placebo to ritlecitinib 200/50 or 50 mg for 24 weeks. The AAPPO instrument evaluated improvement in hair loss, emotional symptoms (ES), and activity limitations (AL) from weeks 4 to 48 (secondary endpoint). Mean changes in ES and AL domain scores and individual items at weeks 24 and 48 were calculated for Severity of Alopecia Tool (SALT) score ≤ 20 responders and nonresponders (exploratory endpoint).

Results Overall, 718 patients were randomized. At week 24, 5–36% of patients receiving ritlecitinib 10–200/50 mg reported improvement in scalp hair loss versus 9% receiving placebo. The results for eyebrow, eyelash, and body hair loss were similar. Mean change from baseline in ES and AL scores at weeks 24 and 48 was small and similar between groups. Mean change was larger for individual hair loss and ES items at weeks 24 and 48 in SALT score ≤ 20 responders versus nonresponders.

Conclusions The AAPPO instrument demonstrated the beneficial impact of ritlecitinib on patient-reported hair growth, which was consistent with improvements in clinician-reported outcomes.

Clinical Trial Registration NCT03732807.

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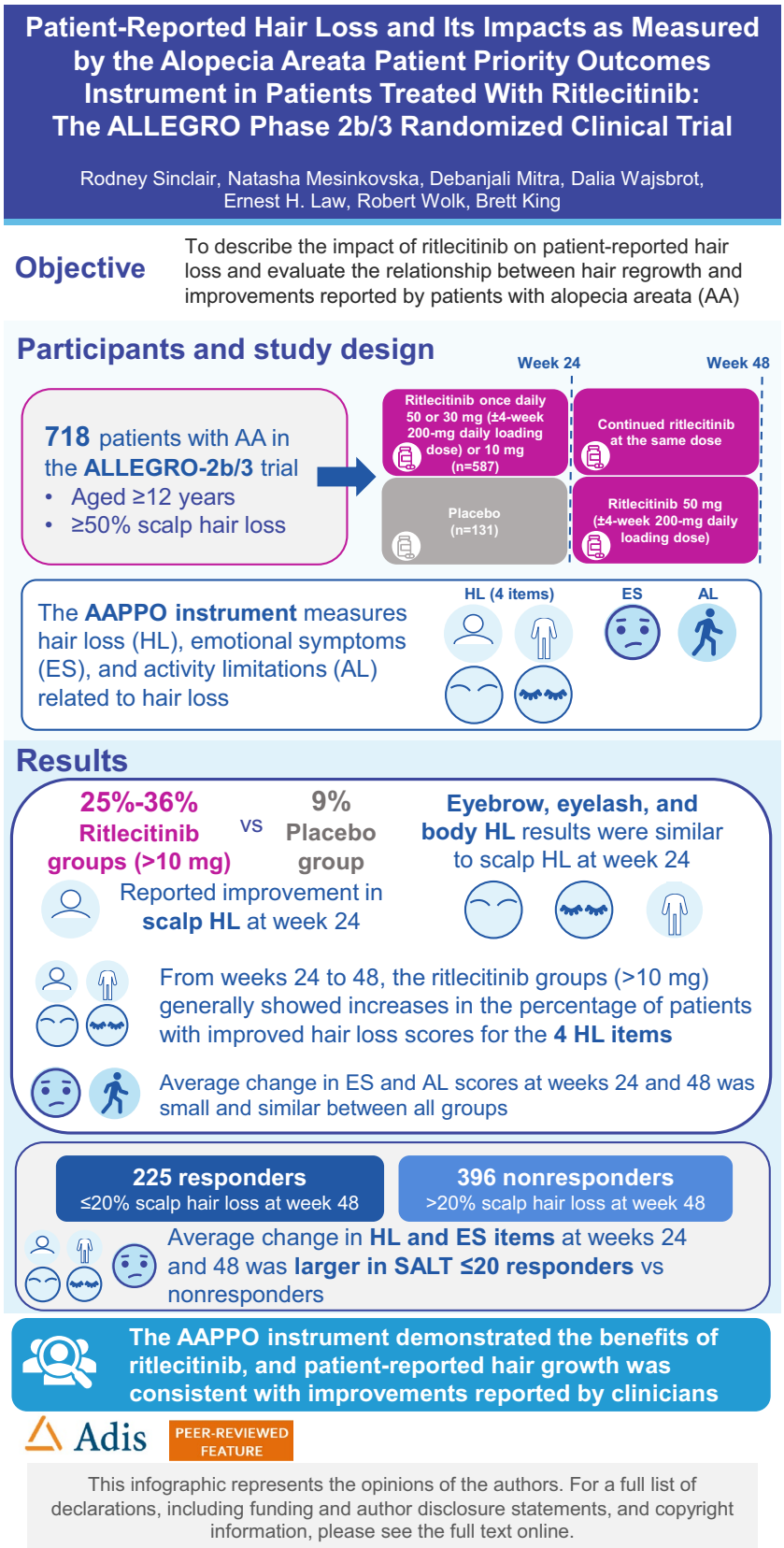
Infographic



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Key Points

In this randomized clinical trial of 718 patients with alopecia areata and at least 50% scalp hair loss, a higher proportion of ritlecitinib-treated patients reported improvements in hair growth, as measured by the Alopecia Areata Patient Priority Outcomes (AAPPO) instrument, than placebo-treated patients.

Patient-reported improvement in hair loss and emotional symptoms, as demonstrated by the AAPPO, was seen in patients who achieved 20% or less scalp hair loss (80% scalp hair coverage) versus those who did not achieve 20% or less scalp hair loss.

This is the first study using the AAPPO to demonstrate the beneficial impact of ritlecitinib on patient-reported hair growth, which was consistent with improvements in clinician-reported outcomes.

1 Introduction

Alopecia areata (AA) is an autoimmune disease that has an underlying immuno-inflammatory pathogenesis and is characterized by nonscarring hair loss involving the scalp, face, and/or body [1]. AA affects both children and adults and has an estimated global lifetime prevalence of ~ 2% [2]. Hair loss due to AA may occur in patches or be more extensive and involve complete loss of scalp hair [alopecia totalis (AT)] or complete loss of scalp, facial, and body hair [alopecia universalis (AU)] [1]. Hair loss episodes are unpredictable. AA may negatively impact patients' psychological well-being and quality of life and is associated with depression and anxiety [3–9].

Currently, there are two approved treatment options for patients with AA: baricitinib [Janus kinase (JAK) 1 and 2 inhibitor], which is approved in the USA, Japan, European Union (EU), China, and several other countries for adult patients with severe AA [10] and ritlecitinib, an oral, selective dual inhibitor of JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, which is approved for adolescent (12–17 years of age) and adult patients with severe AA in the USA, Japan, EU, China, and several other countries [11]. In the ALLEGRO phase 2b/3 trial (NCT03732807), significant scalp hair regrowth, as measured by the clinician-assessed Severity of Alopecia Tool (SALT), was demonstrated in patients aged ≥ 12 years with AA who received ritlecitinib over 24 weeks [11].

The evaluation of patient-reported outcomes (PROs) and health-related quality of life (HRQOL) measures is important for understanding treatment impact on patients. HRQOL measures, such as the Dermatology Life Quality Index (DLQI) and Skindex, have been adapted to AA [12, 13]; however, these and other AA-specific PRO measures, such as the Alopecia Areata Symptom Impact Scale (AASIS) and AA Quality of Life Index (AA-QLI) [14–16], may be missing constructs that are important to patients or may not be validated in clinical trials in patients with AA [17].

The Alopecia Areata Patient Priority Outcomes (AAPPO) instrument, a fit-for-purpose, validated tool, assesses hair loss, emotional symptoms, and activity limitations in both adults and adolescents with AA [17, 18]. The evaluation of AAPPO scores was a secondary endpoint in the ALLEGRO phase 2b/3 trial [11]. The objective of this analysis was to describe the impact of treatment with ritlecitinib on patient-reported hair loss at weeks 24 and 48, as measured by the AAPPO, and to evaluate the relationship between clinically meaningful hair regrowth and improvements in patient-reported impacts due to hair loss.

2 Methods

2.1 Study Design, Patients, and Treatment

ALLEGRO-2b/3 was an international, randomized, double-blind, placebo-controlled, combined dose-ranging and pivotal phase 2b/3 study that enrolled patients aged ≥ 12 years with AA and ≥ 50% scalp hair loss [measured by the SALT, a clinician assessment of the amount of scalp hair loss, with scores ranging from 0 (no scalp hair loss) to 100 (complete scalp hair loss)], including AT and AU [11]. The study design and inclusion and exclusion criteria have been described previously [11]. Briefly, patients had no evidence of terminal hair regrowth within 6 months at both the screening and baseline visits and a current episode of hair loss that had been present for ≤ 10 years. Patients with other causes of alopecia and previous use of any JAK inhibitor were excluded. Patients were randomly assigned to receive daily ritlecitinib (± a 4-week 200-mg daily loading dose) 200/50, 200/30, 50, 30, or 10 mg (10 mg was assessed for dose ranging only) or placebo for 24 weeks. The ritlecitinib groups continued to receive the same maintenance dose throughout a 24-week extension period. Patients randomized to placebo at the beginning of the study switched to ritlecitinib 200/50 mg or 50 mg during the extension period.

This study was approved by the institutional review boards or ethics committees of the participating institutions. The study was conducted in accordance with the general principles set forth in 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. Written informed consent was obtained from each patient, parent, or patient's legal representative.

2.2 Outcomes

Hair loss and its impact on patients were assessed using the novel AAPPO instrument (Fig. 1), a fit-for-purpose, validated, 11-item PRO tool developed by Pfizer [17, 18]. Four items evaluate hair loss (scalp, eyebrows, eyelashes, and body), four items evaluate emotional symptoms (self-consciousness, embarrassment, sadness, and frustration), and three items evaluate activity limitations (outdoor activity, physical activity, and interactions with others). Patients described the current amount of hair loss in different body areas using a 5-point response scale scored from 0 (no hair loss) to 4 (complete hair loss). Patients rated the emotional symptoms and activity limitations due to hair loss over the past week. The extent of emotional symptoms and activity limitations was described using a 5-point scale ranging from never to always (emotional symptoms) and not at all to completely (activity limitations). The emotional symptoms score is determined by the mean score of items 5, 6, 7, and 8 on the AAPPO. The activity limitations score is determined by the mean score of items 9, 10, and 11 on the AAPPO (missing rule: requires ≥ 2 nonmissing responses; otherwise missing). Higher scores indicate more frequent emotional symptoms and more activity limitations due to hair loss.

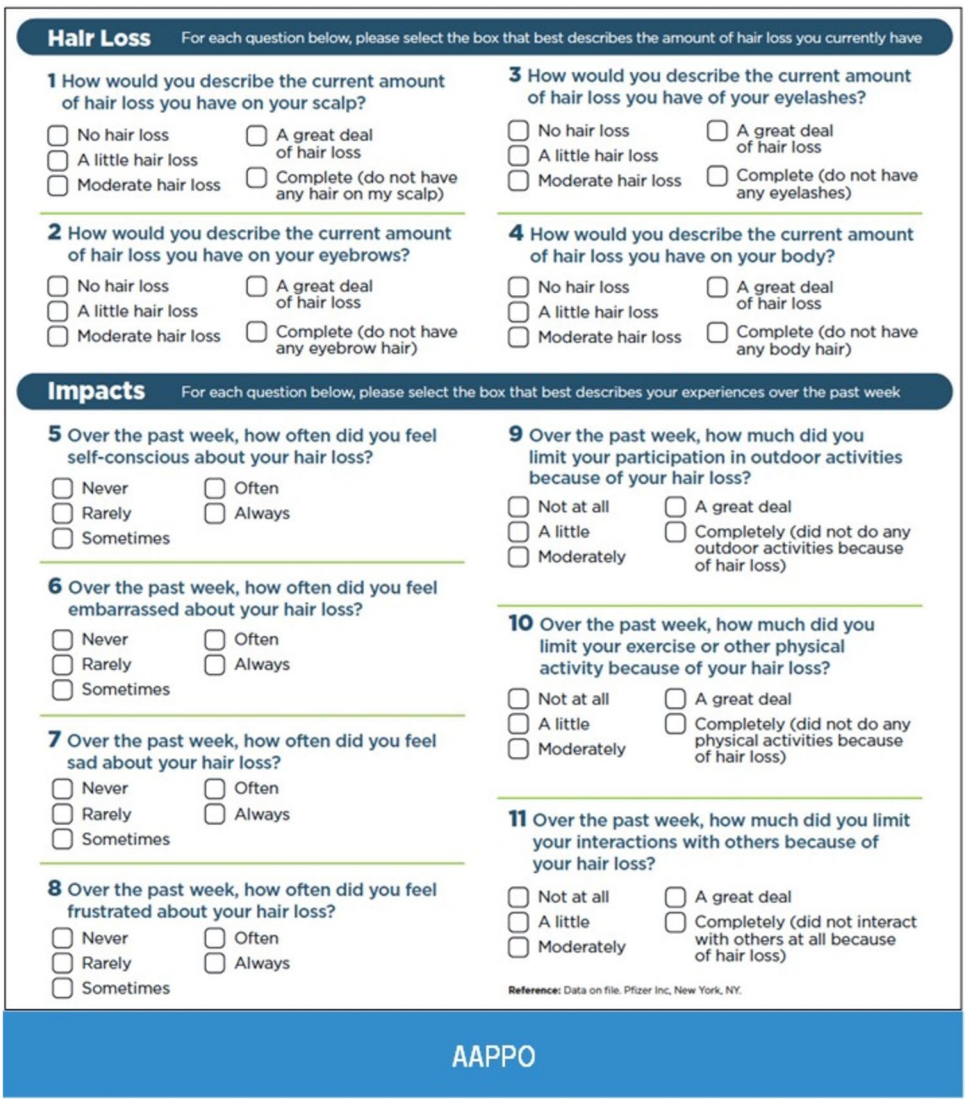

Fig. 1 AAPPO v2.0. US English Pfizer Inc. 2021, All rights reserved. *AAPPO* Alopecia Areata Patient Priority Outcomes

2.3 Statistical Analysis

All AAPPO analyses were based on the full analysis set (i.e., all patients who had been randomized, regardless of whether they received study medication, and analyzed in the treatment groups as they were randomized). Improvement in AAPPO hair loss items (scalp, eyebrow, eyelash, and body hair) from baseline was measured as the proportion of patients with a baseline score of 2–4 (moderate to complete hair loss) who achieved a score of 0–1 (none or little hair loss). The change from baseline in AAPPO emotional symptoms and activity limitations scores was assessed at weeks 4, 8, 12, 18, 24, 34, 40, and 48, and least-squares means were reported at weeks 24 and 48. An analysis was conducted for the visits up to week 24 (with six treatment groups) and another for all visits through week 48 (with seven treatment groups). The analysis method used mixed-effects models for repeated measures, which included effects for treatment group (six or seven groups), baseline value, visit (five or eight visits), and treatment by visit interaction. An unstructured covariance matrix was used for the model errors.

In a post hoc analysis, mean changes from baseline in AAPPO emotional symptoms and activity limitations domain scores, as well as mean changes at the individual item level (for each AAPPO instrument item 1–11) at weeks 24 and 48, were calculated for patients with a SALT score of ≤ 20 ($\leq 20\%$ scalp hair loss; responders) at weeks 24 or 48 and for patients who had a SALT score > 20 (nonresponders) at weeks 24 or 48, irrespective of treatment assignment. For this analysis, only observed data were used. To be included in the analysis, patients were required to have SALT response data and AAPPO data at baseline and at the weeks 24 and 48 visits; if they did not, the data were considered missing and were excluded from the particular assessment time point for this PRO.

All analyses were conducted using Statistical Analysis System software (SAS Institute, Cary, NC, USA) for Windows (Microsoft Corp., Redmond, WA, USA). All *P* values are two-sided unless otherwise noted and were not adjusted for multiplicity.

3 Results

3.1 Patients

Overall, 718 patients were randomized at 118 sites across 18 countries (ritlecitinib 10 mg, $n = 63$; 30 mg, $n = 132$; 50 mg, $n = 130$; 200/30 mg, $n = 130$; 200/50 mg, $n = 132$; placebo, $n = 131$). Patient disposition and baseline demographics were described previously [11]. The study baseline characteristics were generally well balanced across all six treatment groups; the majority of patients were female and white (Supplementary Table 1 in Supplementary Information 1). Across the treatment groups, the mean duration of each patient's current AA episode was between 3.2 and 3.6 years. In each treatment group, the number of patients with AT or AU (i.e., baseline SALT score of 100) was $\geq 45\%$ by study design; in patients without AT or AU, the mean SALT score was between 78.3 and 87.0 across the six groups.

Table 1 Baseline AAPPO patient-reported outcomes

	Placebo ($n = 131$)	Ritlecitinib QD				
		10 mg ($n = 63$)	30 mg ($n = 132$)	50 mg ($n = 130$)	200/30 mg ($n = 130$)	200/50 mg ($n = 132$)
Hair loss score, moderate to complete, *n* (%)[a]						
Scalp	129 (98.5)	60 (95.2)	129 (97.7)	123 (95.3)	129 (99.2)	125 (95.4)
Eyebrows	96 (73.3)	47 (74.6)	100 (75.8)	96 (74.4)	100 (76.9)	101 (77.1)
Eyelashes	84 (64.1)	39 (61.9)	90 (68.2)	81 (62.8)	90 (69.2)	89 (67.9)
Body	93 (71.0)	48 (76.2)	98 (74.2)	98 (76.0)	100 (76.9)	98 (74.8)
Emotional symptoms score, mean (SD)	1.98 (1.13)	1.74 (1.21)	1.68 (1.21)	1.81 (1.10)	1.78 (1.01)	1.70 (1.05)
Activity limitations score, mean (SD)	0.80 (0.96)	0.71 (0.93)	0.69 (0.94)	0.64 (0.85)	0.66 (0.86)	0.68 (0.85)

Score of 2–4 indicated moderate to complete hair loss

AAPPO Alopecia Areata Patient Priority Outcomes, *SD* standard deviation, *QD* once daily

[a] *n* and percent (%) indicate the count and percentage of patients with moderate to complete hair loss

3.2 AAPPO

3.2.1 Hair Loss

At baseline, the proportion of patients with an AAPPO scalp hair loss score of 2 to 4 (moderate to complete hair loss) was ≥ 95% across all treatment groups; between 73 and 77% of patients reported moderate to complete eyebrow hair loss, 62–69% reported moderate to complete eyelash hair loss, and 71–77% reported moderate to complete body hair loss (Table 1). At week 24, all ritlecitinib treatment groups that were planned to be tested against placebo had a significantly greater proportion of patients with improved patient-reported hair loss AAPPO scores from baseline for scalp, eyebrows, and eyelashes versus placebo (Fig. 2). The comparison versus placebo for improvement in the AAPPO body hair loss item score at week 24 was statistically significant for the ritlecitinib groups that received a loading dose of 200 mg but not for the ritlecitinib groups that did not receive a loading dose. From weeks 24 to 48, the ritlecitinib 30-, 50-, 200/30-, and 200/50-mg groups showed increases in the proportion of patients with improved hair loss scores for the four hair loss items (except eyelashes in the 200/30-mg group) (Fig. 2). The proportion of patients with improvement in the four hair loss items of the AAPPO was generally similar when assessed at week 48 in patients initially randomized to placebo who switched to ritlecitinib 200/50 or 50 mg at week 24 compared with results at week 24 in patients initially randomized to the same ritlecitinib dose, respectively (50 mg and 200/50 mg).

3.2.2 Emotional Symptoms and Activity Limitations

At baseline, mean scores reflected emotional symptoms that occurred never, rarely, or sometimes (Table 1). Across all groups, the mean emotional symptoms score was between 1.68 and 1.98. Similarly, mean baseline scores for activity limitations reflected limitations that occurred not at all or a little. The mean activity limitations score was between 0.64 and 0.80 across groups. Up to week 24, least-squares mean changes from baseline in emotional symptoms showed modest improvements in all groups, with no apparent difference between ritlecitinib and placebo groups. In the ritlecitinib 30-, 50-, 200/30-, and 200/50-mg groups, the mild improvement in emotional symptoms generally continued through week 48. Activity limitations scores showed minimal improvement over 48 weeks (Fig. 3).

At week 24, a total of 114 patients were classified as responders (SALT score ≤ 20), and 536 were classified as nonresponders (SALT score > 20); 225 and 396 were considered responders and nonresponders at week 48, respectively (Supplementary Table 2 in Supplementary Information 1). The baseline mean [standard deviation (SD)] overall SALT score was 90.6 (14.4); patients who were SALT score ≤ 20 responders at weeks 24 and 48 had a lower mean (SD) baseline SALT score than nonresponders [81.0 (17.2) versus 92.6 (12.8) and 84.7 (16.3) versus 93.6 (12.4), respectively]. Improvement from baseline in the AAPPO emotional symptoms and activity limitations mean scores was larger in SALT score ≤ 20 responders than in nonresponders at week 24 [emotional symptoms, − 1.1 (95% confidence interval [CI], − 1.3 to − 1.0) versus −0.5 (95% CI, − 0.5 to − 0.4); activity limitations, − 0.5 (95% CI, − 0.6 to − 0.4) versus −0.2 (95% CI, − 0.3 to − 0.2), respectively; Supplementary Fig. 1 in Supplementary Information 1]. Similar trends were seen at week 48. Overall, the mean change in each of the 11 AAPPO items score in patients who were SALT score ≤ 20 responders demonstrated a greater improvement (i.e., larger change from baseline) compared with nonresponders. The mean change in scores from baseline for the individual four hair loss items and four emotional symptoms items at week 24 was generally larger in SALT score ≤ 20 responders than in nonresponders (Fig. 4a). The mean change in scores for the individual activity limitation items was similar between SALT score ≤ 20 responders and nonresponders. Similar trends were observed at week 48 (Fig. 4b).

4 Discussion

In the ALLEGRO-2b/3 study, a higher proportion of patients who received ritlecitinib (doses > 10 mg) reported improvements in the four body areas of hair growth at week 24 than patients who received placebo, with an improvement at week 48 for most body sites. Mean changes from baseline in emotional symptoms and activity limitations scores showed minimal improvement over 48 weeks. Patients who were considered responders to ritlecitinib treatment based on SALT score ≤ 20, reported greater improvement in hair growth and emotional symptoms than nonresponders. Patient-reported improvements in hair growth were consistent with improvements in the clinician-reported outcomes based on SALT score ≤ 20 (primary outcome of ALLEGRO-2b/3 study) and eyebrow/eyelash response (≥ 2-grade improvement from baseline or a normal score in eyebrow assessment or eyelash assessment) [11]. The beneficial results with ritlecitinib in AAPPO hair loss scores were consistent with improvements in other PROs in the ALLEGRO-2b/3 trial, including patient perception of treatment benefit, as measured by the Patient Global Impression of Change (PGI-C) [11] and the Patient Satisfaction with Hair Growth (P-Sat) [19].

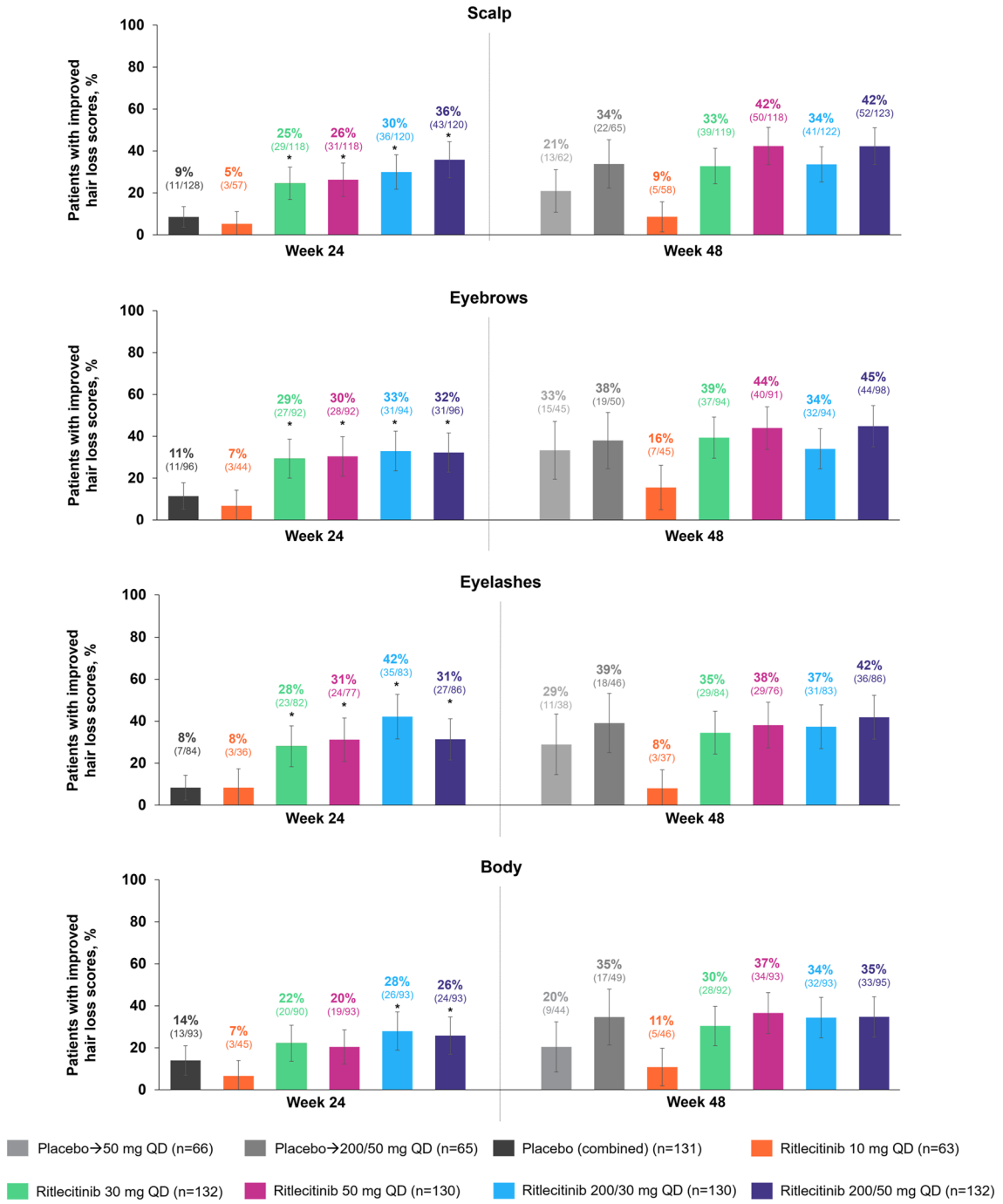

Fig. 2 Improvement from baseline in AAPPO hair loss scores at weeks 24 and 48[a] with ritlecitinib QD. *AAPPO* Alopecia Areata Patient Priority Outcomes, *QD* once daily. *$P \leq 0.05$ versus placebo (combined) without adjustment for multiplicity. [a] Among patients with hair loss scores of ≥ 2 at baseline in the full analysis set. Baseline is defined as the latest nonmissing value from the pretreatment period. Improvement in AAPPO hair loss items (scalp, eyebrow, eyelash, and body hair) from baseline was measured as the proportion of patients with a baseline score of 2–4 (moderate to complete hair loss) who achieved a score of 0–1 (none or little hair loss)

The burden of AA can have a detrimental effect on patients' HRQOL; patients with AA may experience psychological and psychosocial symptoms such as social phobia, depression, shame, stress, embarrassment, poor self-esteem, and anxiety as a result of their hair loss [3–9, 20–22]. Patients with AA are also more likely to have higher levels of dissatisfaction with their appearance, which may cause emotional distress that can lead to personal, social, and work-related issues [23]. Evaluation of therapies for AA using PRO measures, in addition to clinician-reported

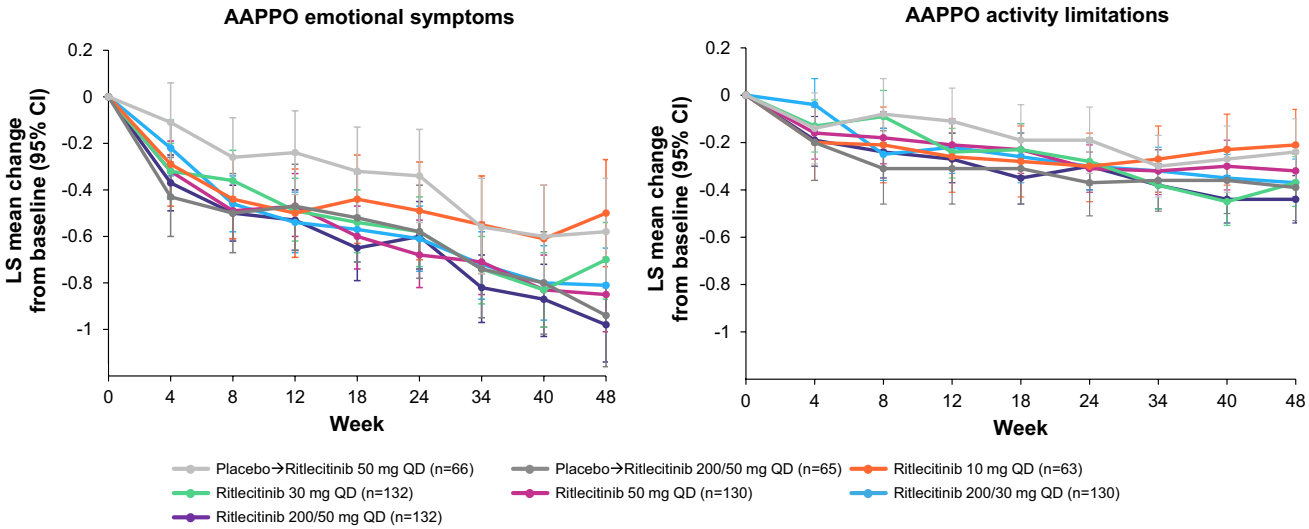

Fig. 3 Change from baseline in AAPPO emotional symptoms and activity limitations scores up to week 48. [a] *n*, number of patients in the full analysis set, *AAPPO* Alopecia Areata Patient Priority Outcomes, *CI* confidence interval, *LS* least squares, *QD* once daily. [a] Mixed-effects model for repeated measures included fixed effects for treatment group, baseline value, visit, and treatment by visit interaction. Unstructured covariance matrix was used for model errors. The baseline is defined as latest nonmissing value from the pretreatment period

outcomes, is important for understanding patients' experiences with therapies.

The AAPPO tool development met US Food and Drug Administration patient-focused guidance requirements and adhered to patient-focused drug development initiative principles [18]. The fit-for-purpose AAPPO instrument was developed to assess hair loss, emotional symptoms, and activity limitations from the perspective of patients [18]; it was validated using data collected in an observational study of 121 patients ≥ 12 years old with AA who had ≥ 25% scalp hair loss, as measured by SALT [17].

In the current study, several factors may have contributed to the small or absent change from baseline in emotional symptoms and activity limitations scores in the prespecified analysis. First, patients with AA may develop adaptive coping strategies over time, including acceptance, in response to AA [24]. Patients across treatment groups had a current AA episode that lasted for a mean duration of > 3 years [25]; therefore, they may have established coping mechanisms to adjust to their AA that resulted in low baseline emotional symptoms and activity limitations scores, even though almost half of patients had AT or AU and those without AT or AU had high baseline SALT scores. Second, qualitative research conducted during development of the AAPPO tool suggested that emotional symptoms and activity limitations are subsequent to the initial effect of hair loss [18]. It is possible that this relationship may also apply to hair regrowth, with improved psychosocial functioning being realized once the individual has adjusted to new hair. Further exploration of ALLEGRO-2b/3 data and analysis of the ongoing ALLEGRO-LT trial (NCT04006457) [26] may be revealing of this possibility.

Results of the analysis provide evidence to support that meaningful hair regrowth is associated with concurrent improvement in the psychosocial burden of AA, specifically emotional symptoms, and provide support for SALT score ≤ 20, which was the primary endpoint, as a clinically meaningful endpoint.

This analysis had several limitations. Patients with < 50% hair loss or an AA episode duration of > 10 years were excluded. The majority of patients were female and white; therefore, the results may not be representative of all patients with AA. Although the AAPPO instrument has been validated [17, 18], meaningful minimally important differences have not been established for the emotional symptoms and activity limitations domain scores; this limits the interpretation of these results, particularly those of the exploratory analysis. Finally, categorizing patients by SALT score ≤ 20 response in the post hoc analysis removed the effect of randomization, and potential confounders between SALT score ≤ 20 responders and nonresponders were not accounted for.

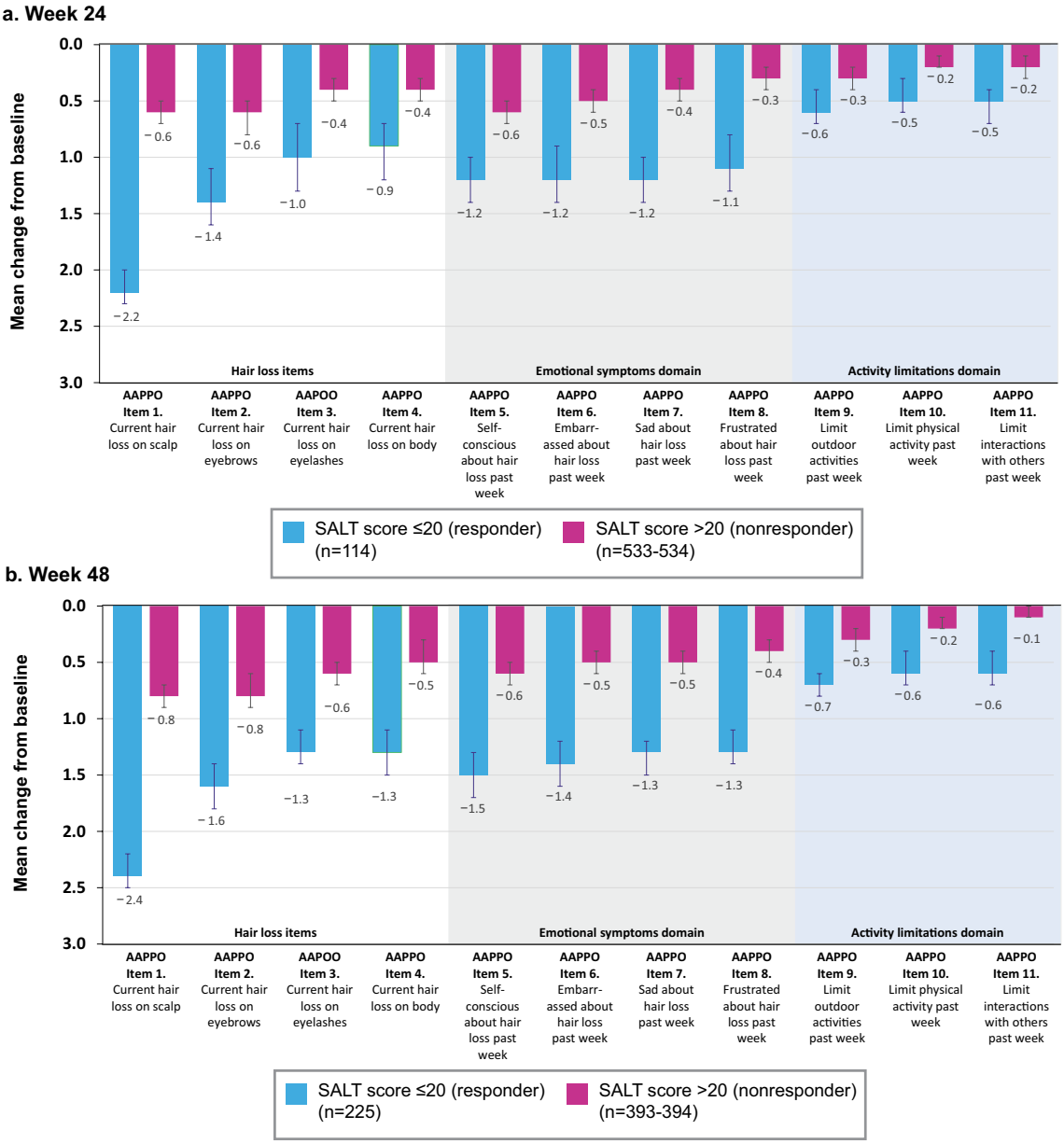

Fig. 4 ALLEGRO-2b/3: AAPPO item score changes by SALT score ≤ 20 response at **a** week 24 and **b** week 48. *AAPPO* Alopecia Areata Patient Priority Outcomes, *SALT* Severity of Alopecia Tool

5 Conclusions

This is the first known study using the fit-for-purpose, validated AAPPO instrument to demonstrate the beneficial impact of ritlecitinib on patient-reported hair growth, which was consistent with improvements in clinician-reported outcomes. Greater benefits in hair loss items, in particular, and to a lesser extent emotional symptoms, as demonstrated by the AAPPO instrument, were seen in SALT score ≤ 20 responders than in nonresponders, providing evidence to support the relationship between meaningful hair regrowth and improvement in the psychosocial burden of AA. Future research should evaluate the relationship between meaningful hair regrowth and its downstream impacts on patients over a longer period.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40257-024-00899-4.

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Declarations

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Conflict of interest R.S. reports professional services for AbbVie, Acrotech, Amgen, Arena, Arcutis, Aksebio, AstraZeneca, Ascend, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Coherus BioSciences, Cutanea, Connect, Demira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MedImmune, Merck, MSD, Novartis, Oncobiologics, Pfizer, Regeneron, Reistone, Roche, Sanofi, Samson Clinical, SUN Pharma, and UCB. N.M. reports professional services for AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Concert Pharmaceuticals, Eli Lilly, La Roche-Posay, and Pfizer. D.M., D.W., E.H.L., and R.W. are employees of or hold stock or stock options in Pfizer Inc. B.K. has received honoraria and/or consultation fees from AbbVie, AltruBio, Almirall, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Meyers Squibb, Concert Pharmaceuticals Inc, Equillium, Horizon Therapeutics, Eli Lilly and Company, Incyte, Janssen Pharmaceuticals, LEO Pharma, Otsuka/Visterra Inc, Pfizer Inc, Regeneron, Sanofi Genzyme, TWi Biotechnology Inc, and Viela Bio. He has previously served on speaker bureaus for AbbVie, Incyte, Eli Lilly, Pfizer, Regeneron, and Sanofi Genzyme.

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

Ethics approval This study was approved by the institutional review boards or ethics committees of the participating institutions. The study was conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from each patient, parent, or the patient's legal representative.

Consent to publish Not applicable.

Code availability Not applicable.

Author contributions E.H.L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. Conceptualization: D.M., D.W., E.H.L., R.W. Data curation: R.S., N.M., D.M., D.W., E.H.L, R.W., B.K. Writing—original draft: E.H.L. Writing—review and editing: R.S., N.M., D.M., D.W., E.H.L., R.W., B.K. Formal analysis: D.W.

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