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ORIGINAL RESEARCH

Efficacy of Baricitinib in Patients with Various Degrees of Alopecia Areata Severity: Post-Hoc Analysis from BRAVE AA1 and BRAVE AA2

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ABSTRACT

Background: Baricitinib, an oral selective JAK1/JAK2 inhibitor, is approved for the treatment of adults with severe alopecia areata (AA).
Objective: To evaluate differences in response up to week 52 among subgroups based on the baseline severity of AA assessed with the Severity of Alopecia Tool (SALT) score.
Methods: Data were pooled from BRAVE-AA1 and BRAVE-AA2, two randomized, placebo-controlled, phase 3 trials, which enrolled adults with a SALT score ≥ 50. Patients were subdivided by the degree of AA severity at baseline.
Results: Among the 855 patients treated with baricitinib 2 mg and 4 mg, improvements in scalp hair growth continued through to week 52. A superior response was observed in patients with a SALT score of 50–94 versus a score of 95–100. Patients on baricitinib 4 mg had a faster and higher response rate compared to baricitinib 2 mg.
Conclusion: Across all degrees of severity for baricitinib 2 mg and 4 mg doses, the proportion of patients responding was yet to plateau up to week 52. Response to treatment was longer for patients with a baseline SALT score 95–100. Further studies are needed to analyze other

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parameters that may impact observed response rates.

Keywords: Adults; Alopecia areata; Alopecia totalis; Alopecia universalis; Baricitinib; Clinician-reported outcome; Efficacy; Hair loss; Janus kinase; Randomized; Severity of alopecia tool

Key Summary Points

Why carry out this study?

Alopecia areata (AA) is an autoimmune condition characterized by rapid hair loss.

Extensive scalp hair loss is associated with poorer prognosis in AA; however, little is known about the actual impact of baseline severity of hair loss on treatment response with baricitinib.

What was learned from the study?

No meaningful difference in response to treatment was observed across the groups of patients with severe AA (SALT score 50–94). Response to treatment was delayed, and response rates were lower for patients with very severe alopecia areata (SALT score 95–100).

These data suggest that baseline severity of hair loss should be factored into consideration when setting expectations about treatment response.

INTRODUCTION

Alopecia areata (AA) is a chronic, autoimmune condition characterized by nonscarring hair loss with a broad spectrum of clinical presentations from localized patches to more extensive scalp hair loss [1–3]. While it predominantly affects the scalp, the disease can affect any hair-bearing region of the body [4, 5]. AA is associated with comorbid immune-mediated diseases (e.g., thyroid disease, lupus erythematosus, diabetes mellitus, atopic dermatitis, sinusitis, and coronary artery disease) and has psychosocial implications (e.g., anxiety, depression, and suicidality), increasing the burden of disease for patients and reducing their quality of life [6–8].

Extensive AA [9, 10], which includes AA subtypes such as alopecia totalis and alopecia universalis [11], is linked to poor prognosis [12]. However, there is no clear consensus on the definition of extensive or severe AA, although a threshold of at least 50% scalp hair loss is present in the scientific literature [13, 14]. Several years ago, the National Alopecia Areata Foundation (NAAF) sponsored investigation guidelines introduced severity categories based on baseline Severity of Alopecia Tool (SALT) scores, but provided no specific rationale for the proposed cut-off for groupings [15]. Building on the SALT score, AA experts developed the AA-Investigator Global Assessment (AA-IGA) [16] providing five clinical gradations of AA severity based on SALT scores, including level 3 or 'Severe' category for SALT ranging from 50 to 94 and Level 4 ('Very severe') for SALT between 95–100, representing patients with complete, or almost complete scalp hair loss. These terms help to address the ambiguity associated with previous terms used to describe extensive hair loss [13]. In parallel to the development of the AA-IGA, clinicians and patients were aligned that hair regrowth resulting in $\leq$ 20% scalp hair loss (i.e., at least 80% scalp hair coverage) was a successful treatment outcome for patients presenting with $\geq$ 50% scalp hair loss at baseline [16].

Baricitinib is an oral JAK inhibitor that primarily inhibits JAK1 and JAK2, regulating the cytokines known to promote the activation and survival of CD8(+) T cells, preventing disease development, and achieving hair regrowth [17]. Baricitinib has demonstrated efficacy and safety in treating patients with severe AA (presenting with $\geq$ 50% hair loss) after 36 weeks of treatment [9, 17]. Currently, baricitinib is approved for moderately to severely active rheumatoid arthritis and moderate-to-severe atopic dermatitis for adults in over 70 countries. Additionally, baricitinib has been approved in countries including the US, Europe, and Japan for adults with severe AA.

This post hoc analysis is to evaluate whether trends in response to baricitinib treatment could be observed dependent on baseline severity of scalp hair loss. For this purpose, efficacy was assessed, up to week 52, in the very severe subgroup (SALT score 95–100) and subdivisions in the severe subgroup (SALT score 50–94). These data will help physicians to discuss treatment expectations with patients based on their baseline severity at presentation.

METHODS

Data are included from phase 3 cohorts of BRAVE-AA1 (NCT03570749) and phase 3 BRAVE-AA2 (NCT03899259), two randomized, double-blind, parallel-group, placebo-controlled studies evaluating the efficacy and safety of baricitinib in patients with severe AA (SALT score 50–94) and very severe AA (SALT score 95–100). Patients with a current episode of AA lasting for > 6 months to < 8 years and no spontaneous improvement (≤ 10-point reduction in SALT score) over the past 6 months were included. Additional inclusion and exclusion criteria were reported previously for both BRAVE-AA1 and BRAVE-AA2 [9]. Patients were randomized 2:2:3 to receive once-daily PBO (up to week 36) or baricitinib 2 mg or 4 mg (through to week 52). For the purpose of this analysis, the 'severe' group was further divided into five subgroups based on the percentage of hair loss (50–59%, 60–69%, 70–79%, 80–89%, and 90–94%). Key outcomes included the proportion of patients achieving SALT ≤ 20, SALT ≤ 10, and the percentage of SALT improvement from baseline (50% [$SALT_{50}$], 75% [$SALT_{75}$], and 90% [$SALT_{90}$]) up to week 52.

For this exploratory post hoc analysis, frequencies and percentages were reported as descriptive statistics for categorical response variables. For the percentage's indicative, confidence intervals were constructed using the Newcombe-Wilson method. For missing values non-responder imputation was performed. This included data collected after permanent study drug discontinuation or remotely due to the COVID-19 pandemic.

All patients provided written informed consent. Ethical review boards approved the study protocol at each study site. This study was conducted in accordance with consensus ethics principles from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation, and other applicable laws.

RESULTS

Patients

Patient demographics and clinical characteristics were balanced across treatment arms and between BRAVE-AA1 and BRAVE-AA2 (Table 1). Patients were randomly assigned to PBO or baricitinib 4 mg or 2 mg. Furthermore, 89.4% (N = 338) of patients on baricitinib 4 mg and 85.7% (N = 251) of patients on baricitinib 2 mg completed 52 weeks of treatment. Patients who were non-responders on PBO at week 36 were re-randomized to baricitinib 4 mg or 2 mg and therefore do not appear in this analysis, which examined patients on continuous treatment through week 52. Of note, in the PBO cohort, the SALT ≤ 20 response rate at week 36 was low, and spontaneous regrowth was observed more frequently in the severe subgroup (13/166 [7.8%]) than in the very severe subgroup (1/178 [0.6%]) (Figure S1).

Within the baricitinib cohorts, the distribution of baseline SALT score was overall comparable between the 4 mg and 2 mg cohort (Fig. 1). The largest group in both cohorts was those with a baseline SALT score of 95–100 (baricitinib 4 mg, N = 267 [51.8%] and baricitinib 2 mg, N = 193 [56.8%]). This was followed by those with a baseline SALT score of 50–59 (baricitinib 4 mg, N = 86 [16.7%] and baricitinib 2 mg, N = 55 [16.2%]) (Fig. 1).

Efficacy Outcomes

Treatment efficacy was observed across the spectrum of disease severity, with baricitinib

Table 1 Summary of baseline demographics and alopecia areata clinical characteristics pooled week 52 efficacy population

Severity subgroup	**SALT score 50–94**			**SALT score 95–100**		
Characteristics	**Placebo (*N* = 166)**	**Baricitinib 2 mg (*N* = 147)**	**Baricitinib 4 mg (*N* = 248)**	**Placebo (*N* = 178)**	**Baricitinib 2 mg (*N* = 193)**	**Baricitinib 4 mg (*N* = 267)**
Age (years), mean (SD)	37.8 (13.0)	38.4 (12.8)	38.6 (13.2)	36.7 (12.3)	38.4 (13.0)	35.7 (12.7)
Genetic gender, *N* (%)						
Female	105 (63.3)	89 (60.5)	161 (64.9)	102 (57.3)	123 (63.7)	148 (55.4)
Male	61 (36.7)	58 (39.5)	87 (35.1)	76 (42.7)	70 (36.3)	119 (44.6)
Race, *N* (%)						
Asian	62 (37.6)	49 (33.6)	76 (30.8)	67 (37.6)	76 (39.4)	105 (39.3)
Black or African American	18 (10.9)	8 (5.5)	28 (11.3)	15 (8.4)	11 (5.7)	18 (6.7)
White	76 (46.1)	85 (58.2)	132 (53.4)	92 (51.7)	100 (51.8)	135 (50.6)
Other[§]	9 (5.4)	4 (2.7)	11 (4.4)	4 (2.2)	6 (3.1)	9 (3.4)
Region, *N* (%)						
North America	79 (47.6)	73 (49.7)	126 (50.8)	78 (43.8)	83 (43.0)	109 (40.8)
Asia	51 (30.7)	45 (30.6)	67 (27.0)	61 (34.3)	67 (34.7)	103 (38.6)
Rest of world	36 (21.7)	29 (19.7)	55 (22.2)	39 (21.9)	43 (22.3)	55 (20.6)
Duration of the current episode of AA (years), mean (SD)	3.8 (4.0)	4.0 (5.6)	3.5 (3.2)	4.3 (5.1)	4.2 (5.2)	3.9 (3.5)
Age of onset of AA (years), Mean (SD)	25.8 (14.7)	26.0 (15.4)	27.5 (15.5)	24.0 (14.5)	25.8 (14.3)	23.0 (13.7)
Atopic background *, *N* (%)						
Yes	59 (35.5)	45 (30.6)	79 (31.9)	80 (44.9)	85 (44.0)	105 (39.3)
No	107 (64.5)	102 (69.4)	169 (68.1)	98 (55.1)	108 (56.0)	162 (60.7)
Classified as ophiasis (yes), *N* (%)	22 (13.3)	22 (15.0)	34 (13.7)	3 (1.7)	11 (5.7)	17 (6.4)
Classified as universalis (yes), *N* (%)	32 (19.3)	30 (20.4)	46 (18.5)	108 (60.7)	123 (63.7)	192 (71.9)
Prior therapy, *N* (%)						
Naïve	10 (6.3)	18 (13.5)	26 (11.3)	12 (7.0)	15 (8.2)	31 (13.0)

Table 1 continued

Severity subgroup	SALT score 50–94			SALT score 95–100		
Characteristics	**Placebo (*N* = 166)**	**Baricitinib 2 mg (*N* = 147)**	**Baricitinib 4 mg (*N* = 248)**	**Placebo (*N* = 178)**	**Baricitinib 2 mg (*N* = 193)**	**Baricitinib 4 mg (*N* = 267)**
Systemic agents (all immunosuppressant/ immunomodulator)	90 (57.0)	66 (49.6)	107 (46.3)	108 (63.2)	107 (58.8)	155 (64.9)
Systemic agents(corticosteroids)	68 (43.0)	45 (33.8)	84 (36.4)	77 (45.0)	83 (45.6)	121 (50.6)
Systemic agents(JAK inhibitor)	6 (3.8)	3 (2.3)	12 (5.2)	15 (8.8)	10 (5.5)	13 (5.4)
Systemic agents(others)	47 (29.7)	30 (22.6)	55 (23.8)	64 (37.4)	57 (31.3)	85 (35.6)
Other systemic (non-immunosuppressant)	16 (10.1)	19 (14.3)	18 (7.8)	16 (9.4)	17 (9.3)	28 (11.7)
Intralesional therapy	99 (62.7)	81 (60.9)	125 (54.1)	90 (52.6)	93 (51.1)	131 (54.8)
Topical therapy excluding immunotherapy	101 (63.9)	81 (60.9)	161 (69.7)	105 (61.4)	118 (64.8)	160 (66.9)
Topical immunotherapy	39 (24.7)	29 (21.8)	58 (25.1)	47 (27.5)	59 (32.4)	89 (37.2)
Procedures	33 (20.9)	28 (21.1)	46 (19.9)	32 (18.7)	44 (24.2)	66 (27.6)
Phototherapy	24 (15.2)	22 (16.5)	37 (16.0)	27 (15.8)	36 (19.8)	54 (22.6)

*Atopic background is defined as medical history of or ongoing atopic dermatitis, or allergic rhinitis, or allergic conjunctivitis, or allergic asthma

§For race, the term 'Other' accounted for patients who defined themselves as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Multiple; SD = standard deviation, AA = alopecia areata, SALT = Severity of Alopecia Tool

4 mg consistently providing a numerically higher level of response than baricitinib 2 mg (Figs. 2, 3, 4, and S2-3; Table S1-3).

For patients with baseline SALT score 50–94 treated with baricitinib 4 mg, the efficacy over the 52 weeks was overall comparable across subgroups, with response rates at week 52 ranging from 41.5–57.6% for SALT $\leq$ 20 and 29.3–45.5% for SALT $\leq$ 10 (Figs. 2, 3; Table S1–2). The response in the SALT 95–100 cohort was characterized by a slower onset of efficacy and a lower response rate in the baricitinib 4 mg cohort at week 52 (SALT $\leq$ 20, 27.7%; SALT $\leq$ 10, 19.1%) (Figs. 2, 3). For the baricitinib 2 mg treated patients, overall comparable efficacy was observed from the SALT 50–59 cohort up to SALT 80–89 cohort, with response rates at week 52 ranging between 26.1–44.4% for SALT $\leq$ 20 and 17.4%-29.6% for SALT $\leq$ 10 (Figs. 2, 3; Table S1-2). The efficacy for patients in the SALT 90–94 subgroup was markedly lower on baricitinib 2 mg (SALT $\leq$ 20, 11.1%; SALT $\leq$ 10, 11.1%) and comparable to the SALT 95–100 group (SALT $\leq$ 10. 7.8%; SALT $\leq$ 20, 12.4%) (Figs. 2, 3; Table S1–2).

Comparable trends were observed for the various thresholds of SALT improvement from baseline. For patients treated with baricitinib 4 mg, the response rates across the different baseline SALT subgroups ranging from 50 to 94 were consistent at week 52 for the respective percentages of SALT improvement from

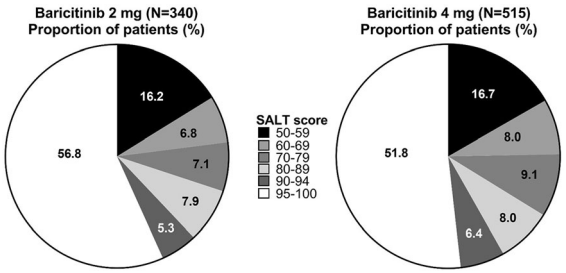

Fig. 1 Distribution of baseline SALT score across baricitinib 2 mg and 4 mg treatment arms

baseline. Response rates ranged from 48.8–70.7% ($SALT_{50}$), 39.0–60.6% ($SALT_{75}$), and 26.8–45.5% ($SALT_{90}$) at week 52 (Figs. 2, 3, 4 and S2-3; Table S3). The response in the SALT score 95–100 cohort was characterized by a slower onset of efficacy and a lower response rate in the baricitinib 4 mg cohort at week 52 for $SALT_{50}$ (43.4%), $SALT_{75}$ (30.0%), and $SALT_{90}$ (19.1%) (Figs. 2, 3, 4 and S2-3; Table S3). For patients treated with baricitinib 2 mg and a baseline of SALT 50–89, response rates ranged from 34.8–55.6% ($SALT_{50}$), 26.1–44.4% ($SALT_{75}$), and 17.4–25.9% ($SALT_{90}$) at week 52 (Figs. 2, 3, 4, and S2-3; Table S3). At week 52, a slower onset of efficacy and lower response rate were found in the SALT score 90–94 subgroup with response rates for $SALT_{50}$ (22.2%), $SALT_{75}$ (11.1%), and $SALT_{90}$ (5.6%), comparable to those observed with the SALT 95–100 subgroup: $SALT_{50}$ (23.8%), $SALT_{75}$ (14.5%), and $SALT_{90}$ (7.3%) (Figs. 2, 3, 4 and S2-3; Table S3).

DISCUSSION

The efficacy and safety of baricitinib 4 mg and 2 mg in patients with severe and very severe AA were previously reported [9]. Here, we have investigated more precisely the impact of baseline severity on response rates over 52 weeks of continuous treatment. This extended treatment period was important to help understand whether the differences in efficacy between subgroups at earlier time points were due to differences in the time to onset of efficacy or truly reflected differences in responsiveness to treatment.

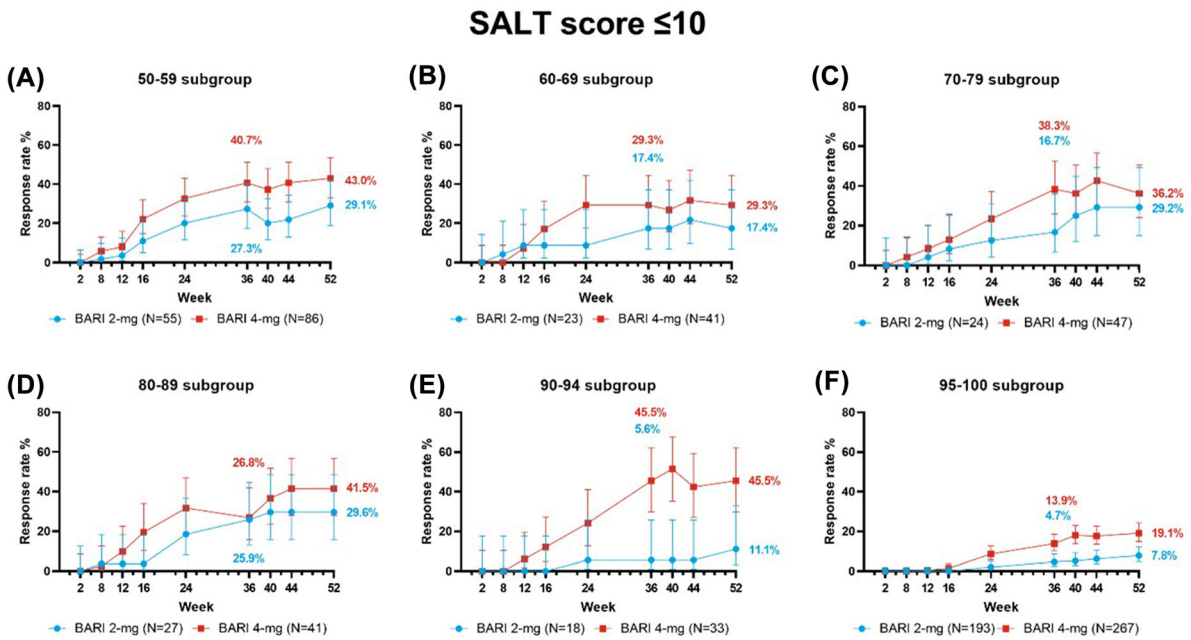

Fig. 2 SALT score of 10 or less through to Week 52, in degrees of AA severity. Primary censoring rule excludes data collected after permanent study drug discontinuation or data collected at remote visits because of the COVID-19 pandemic. SALT score ≤ 10 = $\leq 10\%$ improvement from the patient's baseline SALT score

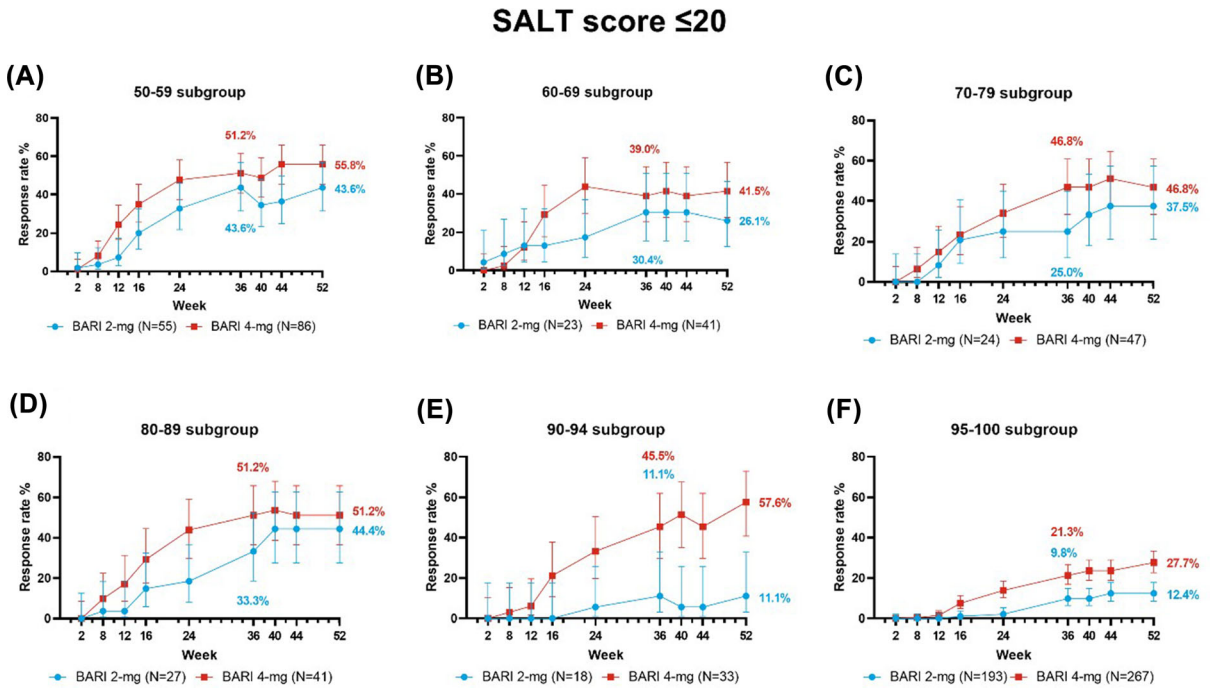

Fig. 3 SALT Score of 20 or less through to Week 52, in degrees of AA severity. Primary censoring rule excludes data collected after permanent study drug discontinuation or data collected at remote visits because of the COVID-19 pandemic. SALT score ≤ 20 = $\leq 20\%$ improvement from the patient's baseline SALT score

These data by baseline severity subgroups over 52 weeks of treatment confirmed the observations made on the overall cohort during the placebo period, showing superior efficacy of baricitinib 4 mg over baricitinib 2 mg for SALT ≤ 20, SALT ≤ 10, $SALT_{50}$, $SALT_{75}$, and $SALT_{90}$ and continuous improvement over the treatment period.

When developing the AA-IGA [16], the rationale for dividing the population of patients with $\geq 50\%$ scalp hair loss into two subgroups of SALT 50–94 and SALT 95–100 was the belief that patients with complete or almost complete scalp hair loss have a poorer prognosis. The data presented here confirm this assumption showing a lower response rate on all endpoints among the SALT 95–100 subgroup, while no particular trend was observed among the different subgroups constituting the SALT 50–94 cohort, at least when looking at baricitinib 4 mg treated patients. The lower response for all efficacy outcomes for the subgroup SALT 90–94 among baricitinib 2 mg treated patients may reflect a reduced efficacy of the baricitinib 2 mg dose in this degree of AA severity, which is not observed in the baricitinib 4 mg cohort. However, it is important to note the small sample size of this subgroup ($n = 18$). In addition to the lower response rate observed in the SALT 95–100 subgroup, it is also important to note the apparent delay in the onset of the response for these subjects.

These data are important for healthcare providers at the time of selecting the appropriate starting dose and setting initial treatment expectations. Understanding the different trajectories of response based on baseline disease characteristics and for the 2 mg vs. 4 mg doses may also help clinicians to make more informed choices about disease management during follow-up visits. This would hopefully lead to better patient outcomes, particularly for those with more extensive hair loss in whom response may be delayed. Improvement of AA with baricitinib treatment may reduce the psychosocial burden on patients, which exists because of the refractory disposition of AA and

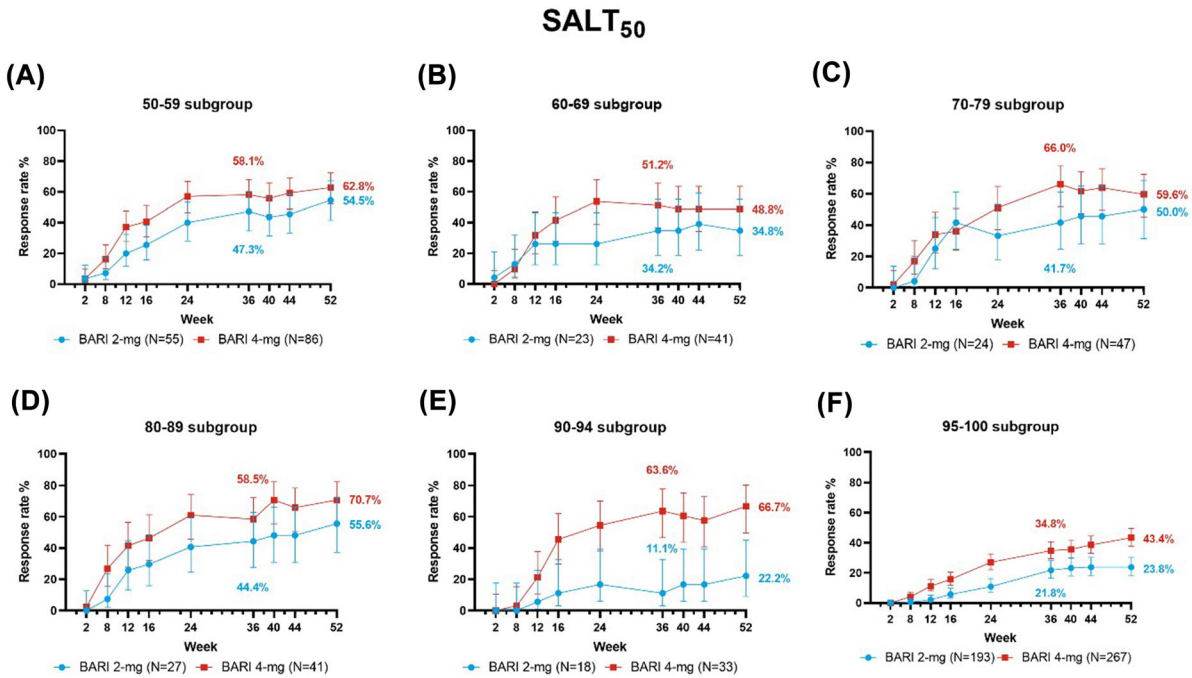

Fig. 4 A 50% reduction in SALT score through to Week 52, in degrees of AA severity. Primary censoring rule excludes data collected after permanent study drug discontinuation or data collected at remote visits due to the COVID-19 pandemic. $SALT_{50}$ = 50% improvement from the patient's baseline SALT score

the previous lack of efficacious treatment options [18, 19].

Limitations of these analyses include the lack of placebo arm up to week 52. However, data from the placebo-controlled period indicate that the chance of spontaneous remission is low, particularly for the most severe patients [9]. Severity was only defined by the extent of scalp hair loss and did not consider other locations for hair loss or patient-reported outcomes. Future examination of AA severity with a multidimensional framework, including eyebrow, eyelash, and patient-reported outcomes, may be of significant interest in assessing the efficacy of treatment for severe forms of the disease [20, 21]. An additional limitation is that many other parameters may influence the response to treatment, including the duration of the hair loss. Patients with an episode lasting ≥ 8 years without any hair regrowth were excluded. Furthermore, the population in these phase III trials was selective, excluding patients with a previous inadequate response to oral JAK inhibitors (defined as a failure to develop significant terminal hair growth after at least 12 weeks of treatment). Thus, the contribution of these other parameters in the response to treatment remains to be determined. Finally, while the enrollment criteria were designed to limit the influence of androgenetic alopecia (male pattern Grade IV or greater using Hamilton-Norwood classification or female pattern were excluded) in overall hair loss [9], it remains possible that it partially affected the evaluation of disease severity and response to treatment.

BRAVE-AA1 and BRAVE-AA2 are ongoing and will follow patients for up to 200 weeks. Longer periods of observation may be necessary to analyze further the patterns of response to treatment based on patients' baseline characteristics and provide further guidance to clinicians. A difference was observed between response rates among patients who presented with baseline severe AA (SALT score 50–94) and those with very severe AA (SALT score 95–100). Treatment response rates through week 52 were comparable across patients with severe AA and higher than in those who presented with very

severe AA. Patients with very severe AA at baseline required a longer period of treatment to achieve a SALT score ≤ 20, and the overall likelihood of treatment response may be lower in this patient subgroup, which is consistent with the less favorable prognosis reported for this cohort in the literature.

In general, there appears to be a dose-response relationship. Patients on baricitinib 4 mg had a faster and higher response rate compared to baricitinib 2 mg. These data offer insights into how patients may respond to treatment based on baseline disease severity and treatment dose, and this can help to inform patient care and management decisions.

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Data Availability. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Declarations

Conflict of Interest. Susan Taylor is an employee and is on the board of directors of Mercer Strategies. Susan Taylor is also a speaker for Beiersdorf, Inc., Evolus, Inc, MJH LifeSciences, and L'Oréal USA. Susan Taylor is on the advisory board for Beiersdorf, Inc., Biorez, Inc., Galderma Laboratories, L.P., GloGetter, Hugel America, Inc., Janssen, L'Oréal USA, Medscape/WebMD, Scientis US, and UCB. Susan Taylor is a consultant for Arcutis Biotherapeutics, Inc., Armis Scientific, Beiersdorf, Inc., Cara Therapeutics, Cara Therapeutics, Evolus, Inc., Johnson & Johnson Consumer Products Company, Piction Health, Regeneron, Vichy Laboratoires. Susan Taylor is an author for McGraw-Hill, and is on the editorial board for Practical Dermatology, Cutis, and Archives in Dermatologic Research. ST is also a peer reviewer for the British Journal of Dermatology and an investigator for Concert Pharmaceuticals, Croma-Pharma, Eli Lilly, and Pfizer. Neil J. Korman reported receiving grants and personal fees from AbbVie, Eli Lilly, Leo Pharma, Principia, and Trevi; grants from Amgen, Celgene, Chemocentryx, Dermira, Menlo Therapeutics, Syntimmune, and XBiotech; and personal fees from Genentech, Janssen, Novartis, Regeneron, Sun Pharma, and UCB. Tsen-Fang Tsai has conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, GSK-Stiefel, Janssen-Cilag, Leo Pharma, Merck, Novartis, Pfizer Inc., and UCB Pharma. Yukata Shimomura receives advisory

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Ethical Approval. The trials were conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and the research protocols were approved by each center's institutional review board or ethics committee. All patients provided written informed consent.

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