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ORIGINAL RESEARCH

Baricitinib Efficacy Through 4 Years in Responders and Safety up to 5 Years in Adults with Severe Alopecia Areata: Final Results from BRAVE-AA1 and BRAVE-AA2

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ABSTRACT

Introduction: Long-term efficacy and safety data are imperative for therapies used to treat severe alopecia areata (AA) because the disease is chronic, loss of response can be devastating to patients, and the safety profile needs to support long-term therapy. Baricitinib, a selective JAK inhibitor, has been approved for severe AA in adults and is being studied in pediatric patients. This study evaluates the final long-term efficacy and safety of baricitinib in adults with severe AA.

Methods: Efficacy was assessed for patients randomized to baricitinib 4 mg or 2 mg who achieved response (Severity of Alopecia Tool [SALT] score ≤ 20) at Week 52 (4 mg, $N = 133$; 2 mg, $N = 72$) and stayed on the same dose through Week 200. Proportions of patients maintaining a SALT score ≤ 20 and achieving a Clinician-Reported Outcome Measure for Eyebrow/Eyelash (EB/EL) Hair Loss™ score of 0 or 1 with ≥ 2-point improvement from baseline were reported using the modified last-observation-carried-forward method. Safety is reported as incidence rates (IR) per 100 patient-years at risk for the All BARI AA group ($N = 1303$) and Extended BARI AA group ($N = 948$) through 248 weeks of exposure

Results: For baricitinib 4 mg and 2 mg, respectively, among Week 52 responders, 115/133 (86.5%) and 61/72 (84.7%) maintained a SALT score ≤ 20 at Week 200. Regrowth of EB/EL hair continued beyond Week 52 and was maintained through Week 200. In up to 5 years of exposure

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with baricitinib, the IR for serious infections, nonmelanoma skin cancer malignancies, deep vein thrombosis/pulmonary embolism, and major adverse cardiovascular events remained low relative to background rates. No deaths occurred, and adverse event rates remained stable over time.

Conclusions: Within this population, ~ 85% of responders maintained SALT scores ≤ 20 through approximately 4 years with continued benefit for EB/EL. Baricitinib's safety profile remained consistent over 5 years of treatment, in line with prior BRAVE program findings.

Trial Registration Number: BRAVE-AA1, ClinicalTrials.gov number, NCT03570749, start date, September 24, 2018; BRAVE-AA2, ClinicalTrials.gov number, NCT03899259, start date, July 8, 2019.

PLAIN LANGUAGE SUMMARY

Alopecia areata is an autoimmune disease caused when the immune system mistakenly attacks hair follicles, causing patchy or complete hair loss on the scalp, face, and body. The disease can be emotionally devastating to those affected, and severe cases do not usually improve without treatment. Since the disease often requires long-term treatment to maintain hair regrowth, studies examining the long-term benefits and risks of treatment are important. Baricitinib is a medication taken by mouth which is approved to treat severe alopecia areata in adults and is also being studied for use in children. This report describes the results from two studies in adults with alopecia areata, BRAVE-AA1 and BRAVE-AA2, that tested baricitinib's efficacy in regrowing hair and maintaining that regrowth over 4 years of treatment. Among patients who regrew their hair after 1 year of treatment with baricitinib, 85% maintained that regrowth for approximately 4 years of continued treatment. Hair regrowth in other areas such as the eyebrows and eyelashes continued to improve and be maintained over time. The observed profile remains consistent with the previously reported baricitinib safety profile in the BRAVE program. Overall, this long-term study provides evidence that ~ 9 out of 10 adults with severe alopecia areata who are treated with baricitinib maintain hair regrowth once they achieve it, and the safety profile remains consistent for up to 5 years of treatment.

Keywords: Alopecia areata; Baricitinib; Immunology; Eyebrow; Eyelash

Key Summary Points

Why carry out this study?

Severe alopecia areata (AA) has a chronic course without spontaneous remission, often requiring long-term treatment, which underscores the importance of a positive risk/benefit profile over time

This study evaluates the final long-term efficacy through Week 200 in Week 52 responders and safety through Week 248 of baricitinib in adults with severe AA

What was learned from the study?

This analysis shows maintenance of therapeutic response through ~ 4 years of treatment in patients who showed therapeutic response to baricitinib at Week 52 and a consistent safety profile in patients with severe alopecia areata treated with up to 5 years of continuous baricitinib therapy

INTRODUCTION

Alopecia areata (AA) is an autoimmune disorder characterized by nonscarring hair loss that can affect any hair-bearing site [1] and often leads to emotional and psychosocial distress [2–5]. Severe AA is unlikely to resolve without treatment [6, 7]. Baricitinib, an oral, selective, reversible Janus kinase (JAK) inhibitor targeting pathways involved in the pathogenesis of the disease, is the first systemic treatment approved globally for adults with severe AA [8]. Development is ongoing for pediatric patients from 6 years to <

18 years of age with severe AA (BRAVE-AA-PEDS, NCT05723198).

The BRAVE-AA1 and BRAVE-AA2 Phase 2/3 and Phase 3 trials [9, 10] respectively demonstrated significant efficacy for baricitinib 4 mg and 2 mg versus placebo in achieving the primary endpoint of Severity of Alopecia Tool (SALT) score ≤ 20 (at least 80% scalp coverage) by Week 36 and achieved significance by Week 16 with baricitinib 4 mg and by Week 24 with baricitinib 2 mg. The proportion of patients achieving SALT scores ≤ 20 continued to increase through Week 52 and was maintained through 3 years of treatment among responders [9, 10]. Eyebrow (EB) and eyelash (EL) regrowth also occurred early and continued to increase through Week 52 and, similar to scalp hair regrowth, was maintained through 3 years of treatment. Baricitinib has been extensively studied across several indications and in AA pediatric populations and adults up to 70 years old [11–15]. In adults with severe AA, safety data up to 4 years of exposure have been published [16]. In this analysis, the efficacy (up to approximately 4 years) and safety of baricitinib in patients with severe AA at baseline (SALT score ≥ 50) treated for up to 5 years from the BRAVE-AA1 and BRAVE-AA2 clinical trials were evaluated.

METHODS

Trial Design

BRAVE-AA1 and BRAVE-AA2 were Phase 2/3 and Phase 3, double-blind, parallel-group, randomized, placebo-controlled trials, respectively, conducted at 169 centers in 10 countries [9]. The primary trial design for the trials and study investigators were previously published [9].

Briefly, patients were initially randomized to receive placebo, baricitinib 2 mg, or baricitinib 4 mg in a 2:2:3 ratio for 52 weeks, with placebo nonresponder patients (SALT > 20) rescued at Week 36.

At Week 52, BRAVE-AA1 responders who were randomized at baseline to receive active treatment were rerandomized 3:1 to continue taking their current dose of baricitinib or transition to placebo (randomized withdrawal). In BRAVE-AA2, baricitinib 4 mg responders were rerandomized 1:1 to stay on assigned treatment or to down-titrate to baricitinib 2 mg, and baricitinib 2 mg responders stayed on baricitinib 2 mg. In both trials, patients who lost treatment benefit after dose change (SALT score change of > 20 points) were rescued to their original randomized treatment. Baricitinib patients who were nonresponders (SALT score > 20) at Weeks 52 and 76 were automatically discontinued at Week 76 unless they had at least a 2-point improvement from baseline in the clinician-reported outcome measure (ClinRO) for eyebrow or eyelash hair loss.

The efficacy analyses presented in this manuscript include patients who were responders at Week 52 and were continuously treated with baricitinib 4 mg or 2 mg from baseline through Week 200. The safety analyses presented in this article include all randomized patients who received at least one dose of baricitinib up to Week 200 in most countries and up to Week 248 in Mexico and Argentina, where a study addendum was implemented up to Week 248 to allow continued access to baricitinib for an additional 48 weeks. The efficacy and safety analyses also include patients enrolled in China under the Maximized Extended Enrollment addendum in BRAVE-AA2.

Patient Eligibility

A full description of inclusion and exclusion criteria has been previously published [9]. In summary, patients aged ≥ 18 to ≤ 60 years and ≥ 18 to ≤ 70 years for male and female individuals, respectively, with a SALT score of ≥ 50 (≥ 50% scalp hair loss) and a current AA episode lasting > 6 months to < 8 years without spontaneous improvement (that is, ≤ 10-point spontaneous reduction in SALT score) over the 6 months before screening were enrolled.

Endpoints

Efficacy outcomes included the proportion of patients maintaining a SALT score ≤ 20 (≤ 20% scalp hair loss or ≥ 80% scalp coverage), the proportion of patients achieving SALT score ≤ 10

(≤ 10% scalp hair loss or ≥ 90% scalp coverage), the proportion of patients achieving Clinician-Reported Outcome (ClinRO) Measure for Eyebrow Hair Loss™ score of 0 or 1 (full coverage or minimal gaps) with ≥ 2-point improvement from baseline among patients with baseline scores 2 or 3 (significant gaps or no notable EB), and the proportion of patients achieving ClinRO Measure for Eyelash Hair Loss™ score of 0 or 1 (no or minimal gaps) with ≥ 2-point improvement from baseline among patients with baseline scores 2 or 3 (significant gaps or no notable EL) [17].

Patient-reported outcomes (PROs) included the proportion of patients achieving a Scalp Hair Assessment (SHA) PRO™ score of 0 or 1 (0–20% missing scalp hair) with ≥ 2-point improvement from baseline among patients with baseline scores ≥ 3 (50% to 100% missing scalp hair); the proportion of patients achieving a PRO Measure for Eyebrows™ score of 0 or 1 (full coverage or minimal gaps) with ≥ 2-point improvement from baseline among patients with baseline scores 2 or 3 (large gaps or no notable EB); and the proportion of patients achieving a PRO Measure for Eyelashes™ score of 0 or 1 (no or minimal gaps) with ≥ 2-point improvement from baseline among patients with baseline scores 2 or 3 (large gaps or no notable EL) [17, 18].

Safety assessments included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory analyses, and adverse events (AEs) of special interest (AESIs). The AESIs were serious infections, major cardiovascular events (MACEs), deep vein thrombosis (DVT)/pulmonary embolism (PE), and malignancies.

The PRO and ClinRO measures developed by Eli Lilly and Company are proprietary instruments owned by Eli Lilly and Company.

Statistical Analysis

Data were integrated from both trials. Efficacy analyses included all patients randomized to baricitinib (baricitinib 4 mg or 2 mg) at baseline who were responders at Week 52 and randomized to remain on the same dose of baricitinib at Week 52. Data were censored after permanent study drug discontinuation or rescue. Missing data were imputed using the modified last-observation-carried-forward (mLOCF) approach, using the most recent non-missing post-baseline assessment. For long-term efficacy, mLOCF maximizes the number of randomized patients assessed post-baseline, which strengthens the intent-to-treat principle and avoids progressive misclassification of patients who discontinued for reasons unrelated to efficacy or treatment failures over the 200-week follow-up.

Safety was assessed in all patients receiving ≥ 1 dose of baricitinib and who did not discontinue for the reason "lost to follow-up" at the first post-baseline visit, up to 30 days after the last dose of baricitinib. Two integrated safety analysis sets were evaluated. The extended baricitinib 4 mg and 2 mg analysis set (Extended BARI AA) includes patients continuously treated with the same baricitinib dose from baseline, using data from the 36-week placebo-controlled periods plus the long-term extensions up to 30 days after the last dose of baricitinib; data were censored at treatment or dose change and are presented irrespective of the Week 52 response. The all baricitinib AA analysis set (All BARI AA) includes all patients who ever received ≥ 1 dose of baricitinib (1 mg, 2 mg, or 4 mg) at any time from randomization or switch from placebo (including patients who are in the Extended BARI AA dataset), up to 30 days after the last dose of baricitinib. Incidence rates (IRs) per 100 patient-years were calculated based on event-specific exposure time at risk.

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. The trials were reviewed and approved by ANMAT, Argentina (#DI-2019-1569-APN-ANMAT#MSYDS), Therapeutic Goods Administration, Australia (#CT-2019-CTN-00918-1), CONEP, Brazil (#3.499.010), NMPA/CDE, China (#JXHL1900252), Israeli Ministry of Health, Israel (#6087-19-SMC), PMDA, Japan

(#30-2603 and 31-0156), COFEPRIS (Secretaría de Salud), Mexico (#193300410A0031/2019), Ministry of Food and Drug Safety, South Korea (#20190199878), Taiwan Food and Drug Administration, Taiwan (#1081490776), and Advarra, USA (#Pro00025373 and Pro00034650). The full list of ethics review boards is shown in Table S5.

Patients were not involved in the protocol development.

RESULTS

Patients

For the maintenance-of-efficacy analyses, 133 patients on baricitinib 4 mg and 72 patients on baricitinib 2 mg who had achieved SALT scores ≤ 20 at Week 52 were re-randomized to remain on the same dose for the remainder of the trial. The maintenance-of-efficacy analyses include nine patients (4 on baricitinib 4 mg and 5 on baricitinib 2 mg) not included in previous reports who were enrolled as part of a Maximized Extended Enrollment addendum in China and had achieved a SALT score of ≤ 20 at Week 52. Among responders at Week 52, completion through Week 248 occurred for 75.9% of patients on baricitinib 4 mg treatment and 63.9% of patients within the 2 mg group; no patients discontinued baricitinib 4 mg treatment because of lack of efficacy, while four (5.6%) patients in the 2-mg group discontinued because of lack of efficacy. Baseline characteristics of Week 52 responders are presented in Table 1.

For the safety analyses, the total number of patients in the Extended BARI AA and All BARI AA were 948 and 1303, respectively. In Extended BARI AA, 565 patients (1184.77 patient-years of exposure [PYE]) and 383 patients (546.11 PYE) were exposed to baricitinib 4 mg and 2 mg, respectively. In All BARI AA, 1303 patients were exposed to any dose of baricitinib, reflecting 3047.73 PYE (median: 2.6 years; maximum: 5 years). Overall, 23 (4.1%) patients treated with baricitinib 4 mg and 11 (2.9%) patients treated with baricitinib 2 mg discontinued treatment because of an AE. The baseline characteristics of the patients across these safety datasets and dose groups were published previously [16].

Maintenance of Efficacy in Week 52 Responders

Within the long-term efficacy population, for baricitinib 4 mg and baricitinib 2 mg, respectively, 86.5% and 84.7% maintained a SALT score ≤ 20 at Week 200 (Fig. 1A and B, Table S4). The proportion of patients who achieved a SALT score ≤ 10 at Week 52 (74.4% and 68.1%, respectively, for baricitinib 4 mg and 2 mg), indicating a deeper response, was also maintained through Week 200 for baricitinib 4 mg (75.9%) and increased slightly for baricitinib 2 mg (72.2%, Fig. 1C, D, Table S4).

The proportion of patients who achieved 90% improvement in SALT score from baseline also increased from 70.7% and 52.8% at Week 52 with baricitinib 4 mg and 2 mg, respectively, to 73.7% and 65.3% at Week 200 (Table S4). In addition, the maintenance of scalp hair regrowth over time was stable, as demonstrated by the mean change in SALT score from Week 52 to Week 200; mean change was + 2.2 points for the baricitinib 4 mg group and + 2.6 points for the baricitinib 2 mg group (Fig. 2).

Among the 18 patients on baricitinib 4 mg and 11 patients on baricitinib 2 mg who lost response (SALT score > 20), approximately 66.7% and 63.6%, respectively, had very severe AA (SALT score ≥ 95) at baseline (compared with 33.9% and 26.2%, respectively, of those who maintained response). Among patients who lost response, the median change in SALT score from Week 52 to Week 200 was 23.5 and 25.0 in the baricitinib 4 mg and 2 mg groups, respectively.

Proportions of patients achieving EB and EL complete hair coverage or minimal gaps after Week 52 increased through Week 200. Among baricitinib 4 mg-treated patients, the proportions increased from 70.2 to 84.5% for EB and from 71.4 to 78.6% for EL, and for baricitinib 2 mg-treated patients from 54.8% to 69.0% for EB and 55.9% to 82.4% for EL through Week 200 (Fig. 3).

Clinician assessment of hair regrowth corresponded to PROs. The PRO measures for scalp

Table 1 Baseline characteristics of Week 52 responders

	Week 52 responders	
	Baricitinib 2 mg (*N* = 72)	**Baricitinib 4 mg (*N* = 133)**
Age, years, mean (SD)	37.2 (10.96)	36.5 (12.25)
Female, *n* (%)	50 (69.4)	82 (61.7)
Male, *n* (%)	22 (30.6)	51 (38.3)
Race[a], *n* (%)		
White, *n* (%)	37 (51.4)	71 (53.4)
Asian, *n* (%)	33 (45.8)	52 (39.1)
Korean	15 (45.5)	40 (76.9)
Chinese	7 (21.2)	5 (9.6)
Japanese	5 (15.2)	3 (5.8)
Taiwanese	4 (12.1)	3 (5.8)
Asian*	1 (3.0)	1 (1.9)
Asian Indian	1 (3.0)	0
Black or African American	1 (1.4)	7 (5.3)
Other	1 (0.8)	1 (1.4)
Geographic region[b], n (%)		
North America	27 (37.5)	62 (46.6)
Asia	31 (43.1)	50 (37.6)
Rest of world	14 (19.4)	21 (15.8)
Duration since AA onset, years, mean (SD)	10.6 (9.52)	10.5 (10.22)
Duration of current episode of AA, years, mean (SD)		
< 4 years, *n* (%)	60 (83.3)	102 (76.7)
≥ 4 years, *n* (%)	12 (16.7)	31 (23.3)
Proportion of patients with alopecia universalis[c], *n* (%)	23 (31.9)	49 (36.8)
Proportion of patients with atopic background[d], *n* (%)	28 (38.9)	50 (37.6)
Weight, kg, mean (SD)	69.9 (16.03)	70.9 (15.32)
Body mass index, mean (SD)	25.3 (5.06)	25.2 (4.81)
SALT score, mean (SD)	76.8 (19.44)	80.3 (19.01)

Table 1 continued

	Week 52 responders	
	Baricitinib 2 mg (*N* = 72)	**Baricitinib 4 mg (*N* = 133)**
SALT score, median	78.0	87.0
Severity, *n* (%)		
Severe (SALT 50–94)	49 (68.1)	82 (61.7)
Very severe (SALT 95–100)	23 (31.9)	51 (38.3)
ClinRO Measure for Eyebrow Hair Loss™ score of 2 or 3[e], *n* (%)	42 (58.3)	84 (63.2)
ClinRO Measure for Eyelash Hair Loss™ score of 2 or 3[e], *n* (%)	34 (47.2)	70 (52.6)
Scalp Hair Assessment PRO™ score ≥ 3[f], *n* (%)	65 (90.3)	128 (96.2)

Percentages are based on non-missing values. *Participants based in North America

AA alopecia areata, *ClinRO* clinician-reported outcome, *n* number of patients in the specified category, *N* total population size, *PRO* patient-reported outcome, *SALT* Severity of Alopecia Tool, *SD* standard deviation

[a]Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple races

[b]Geographic regions include North America (USA), Asia (South Korea, Japan, Taiwan, China), and rest of the world (Mexico, Israel, Australia, Brazil, Argentina)

[c]Diagnosis of alopecia universalis was according to the investigator's assessment

[d]Atopic background is defined as medical history or current atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or allergic asthma

[e]A ClinRO or PRO score of 2 indicates significant gaps in eyebrow(s)/eyelash(es), and a score of 3 indicates no notable eyebrow(s)/eyelash(es)

[f]A score of 2 indicates 21–49% scalp hair is missing, a score of 3 indicates 50–94% scalp hair is missing, and a score of 4 indicates 95–100% scalp hair is missing

hair, EB, and EL showed an increase in response rates from Week 52 through Week 200 (Table S4).

Overview of Safety

In Extended BARI AA, TEAEs were reported in 449 (IR = 116.5) and 274 (IR = 132.1) of patients in the baricitinib 4 mg and baricitinib 2 mg groups, respectively; TEAEs occurred in 1035 (IR = 105.0) of patients in All BARI AA (Table 2). Most TEAEs were mild or moderate in severity. SAEs occurred in 34 (IR = 2.8) baricitinib 4 mg-treated and 12 (IR = 2.1) baricitinib 2 mg-treated patients in Extended BARI AA and 77 (IR = 2.5) of All BARI AA patients. In All BARI AA, most SAEs were infections or fractures due to injury (Table S1, supplement). Since the previous report, one additional patient reported a serious infection (worsening of chronic rhinitis), and one additional patient reported a serious fracture (hand). The frequency and IR of study drug discontinuation due to AEs was low and similar across groups with no new AEs leading to study drug discontinuation since the last report (Table 2) [16].

In up to 5 years of exposure, in the All BARI AA group, the total number and IR for AESIs were: serious infections: *n* = 17, IR = 0.5; non-melanoma skin cancer (NMSC), *n* = 4, IR = 0.1; malignancies other than NMSC, *n* = 7, IR = 0.2; deep vein thrombosis/pulmonary embolism (DVT/PE), *n* = 2, IR = 0.06; MACE, *n* = 1, IR < 0.1 with IRs being stable over time for all AESIs. Since the last publication [16], there have been no new reports of MACE, DVT/PE, or malignancy

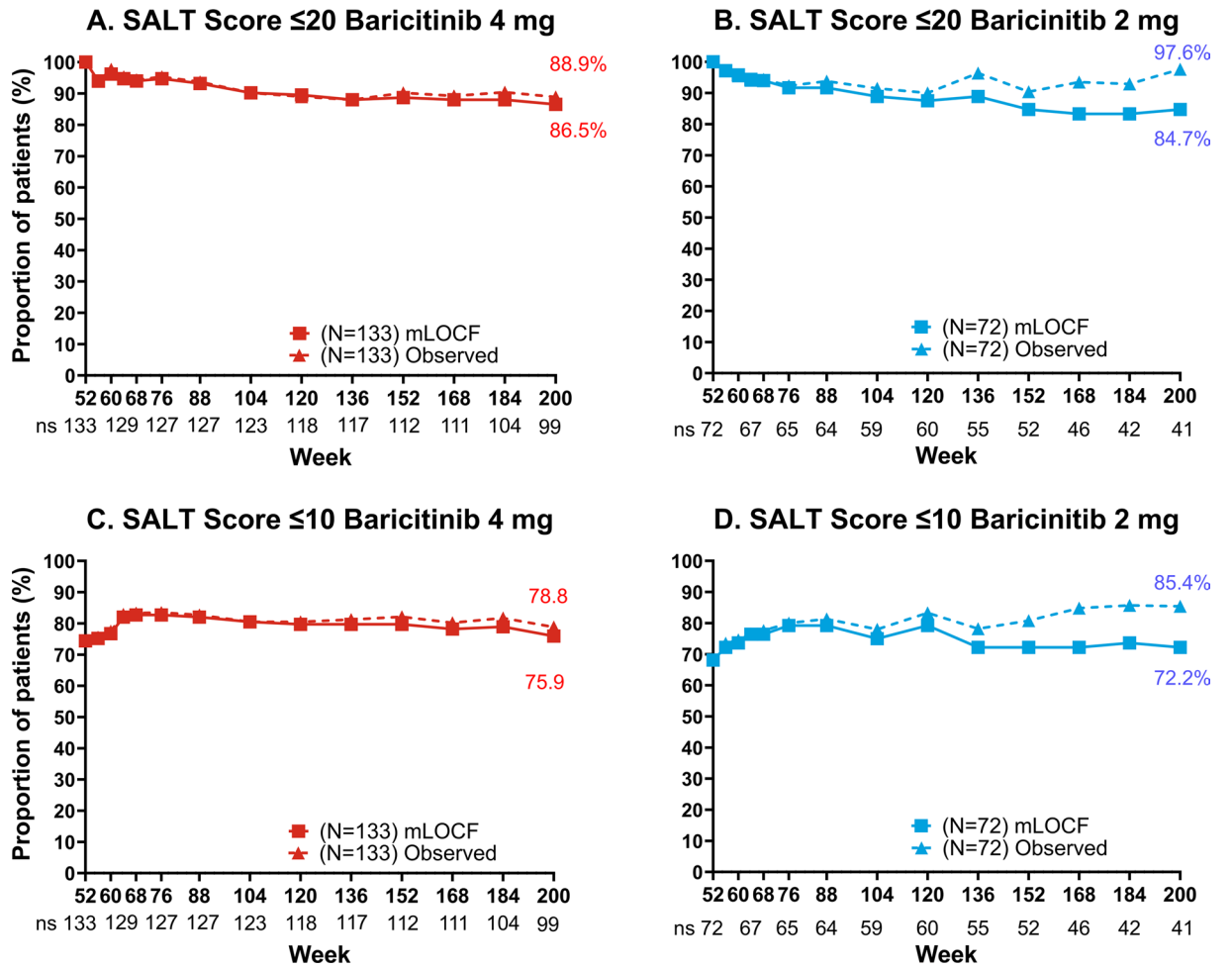


Fig. 1 Among Week 52 baricitinib responders achieving a SALT score ≤ 20, the proportion of patients who maintained this response with **A** baricitinib 4 mg and **B** baricitinib 2 mg; the proportion of patients achieving a SALT score ≤ 10 with **C** baricitinib 4 mg and **D** baricitinib 2 mg. Data reported as mLOCF and as observed. Note: A SALT score ≤ 20 indicates ≤ 20% scalp hair loss. A SALT score ≤ 10 indicates ≤ 10% scalp hair loss. *SALT* Severity of Alopecia Tool, *mLOCF* modified last observation carried forward, *N* population count

other than NMSC. One new participant reported NMSC. AESI patient cases from BRAVE-AA1 and BRAVE-AA2 up to Week 248 are summarized in Table S2. As previously noted, one new participant reported a serious infection (worsening of chronic rhinitis). In addition, a participant who had previously reported a serious COVID-19 event reported an unspecified viral infection that was serious. No deaths were reported.

The new participant (72 years of age at the time of event) reporting NMSC experienced three squamous cell carcinoma (SCC) events. The participant had fair skin with significant sun exposure. After 928 days on 4 mg baricitinib, the participant noted a SCC on the right foot and a SCC on the right hand. The participant had surgery to excise the SCCs. Both events resolved, and the participant remained on the study drug. On Study Day 1253, the participant reported an additional SCC on the upper chest. The event was mild, and the participant completed the study.

Changes in laboratory analytes were consistent with those previously reported for baricitinib (Table S3, supplement).

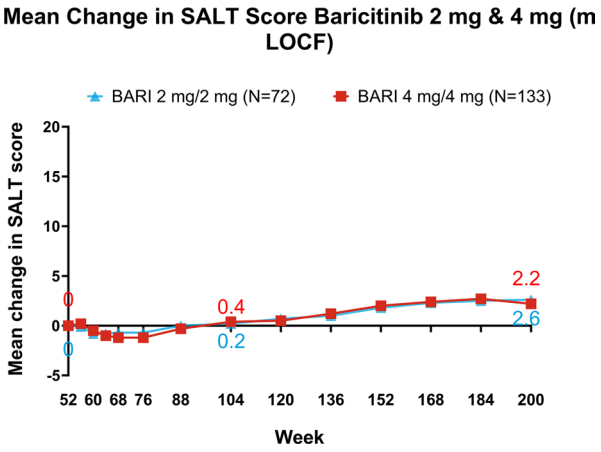


Fig. 2 Mean change in SALT score from Week 52 to Week 152 in Week 52 baricitinib 4 mg and baricitinib 2 mg responders (mLOCF). *BARI* baricitinib, *SALT* Severity of Alopecia Tool, *mLOCF* modified last observation carried forward, *N* population count

DISCUSSION

Severe AA is a chronic inflammatory condition that requires sustained systemic treatment [1]. Previous data have shown loss of response with treatment withdrawal [19], indicating treatment must be continued to maintain response. While JAK inhibitors have emerged as a standard of care, these therapies are relatively new for dermatologists treating severe AA, and clinical evidence supporting the benefits and risks of their long-term use continues to evolve, particularly given that JAK inhibitors carry class warnings related to certain AESIs [20]. These warnings were established as a class effect based on data for certain AESIs reported in higher-risk populations with moderate-to-severe rheumatoid arthritis (age ≥ 50 with cardiovascular risk factors) compared with tumor necrosis factor inhibitor therapy [21]. Failure to treat severe AA introduces its own risk given the profound quality of life impact of this disease on patients and caregivers [4], and delay in treating AA can make the disease more recalcitrant to treatment [22, 23]. Baricitinib has a well-established safety profile and is approved for treatment in adults with moderate-to-severe rheumatoid arthritis, atopic dermatitis (AD), and severe AA, and it is approved for use in children ≥ 2 years with juvenile idiopathic arthritis and moderate-to-severe AD and in adolescents ≥ 12 years with severe AA [24]. The BRAVE-AA trials are the largest and longest to date reporting long-term continuous therapy across approved doses. Approximately 87% of baricitinib 4 mg and 85% of baricitinib 2 mg patients who were Week 52 responders maintained clinical response of SALT score ≤ 20 through 200 weeks of continuous treatment. Many patients also saw a deepened response as assessed by SALT scores ≤ 10. The low percentage of patients who lost response had a much higher level of very severe AA at baseline compared with those who maintained response. To our knowledge, these are the longest-term maintenance-of-efficacy data for a JAK inhibitor used in the treatment of severe AA.

At Week 52, approximately 70% of participants with a scalp response (SALT score ≤ 20) achieved normal to near-normal EB and/or EL regrowth, and this increased further to ~ 80 to 85% at these sites by Week 200. Increases in regrowth from Week 52 to Week 200 were also observed in the baricitinib 2 mg group. These data suggest that longer-term treatment in some patients may further maximize benefit across hair-bearing sites.

The safety data reported here are comparable to those previously reported through 4 years of baricitinib exposure [16]. Most TEAEs were mild or moderate in severity, and the IRs of TEAEs and SAEs were similar to those previously reported [16, 25]. The observed profile remains consistent with the previously reported baricitinib safety profile in the BRAVE program [16]. No new cases of opportunistic infections, MACE, DVT, or PE were reported during the additional year of follow-up since the last report, while there was one new patient who reported a serious infection and one new patient who reported NMSC. Overall, AESI IRs remain similar to or lower than those reported through 4 years of follow-up in BRAVE-AA1/BRAVE-AA2 [16] and similar to or lower than background published rates [13]. No deaths have been reported for the BRAVE-AA trials. Laboratory analyte results remain consistent with previous reports [25].

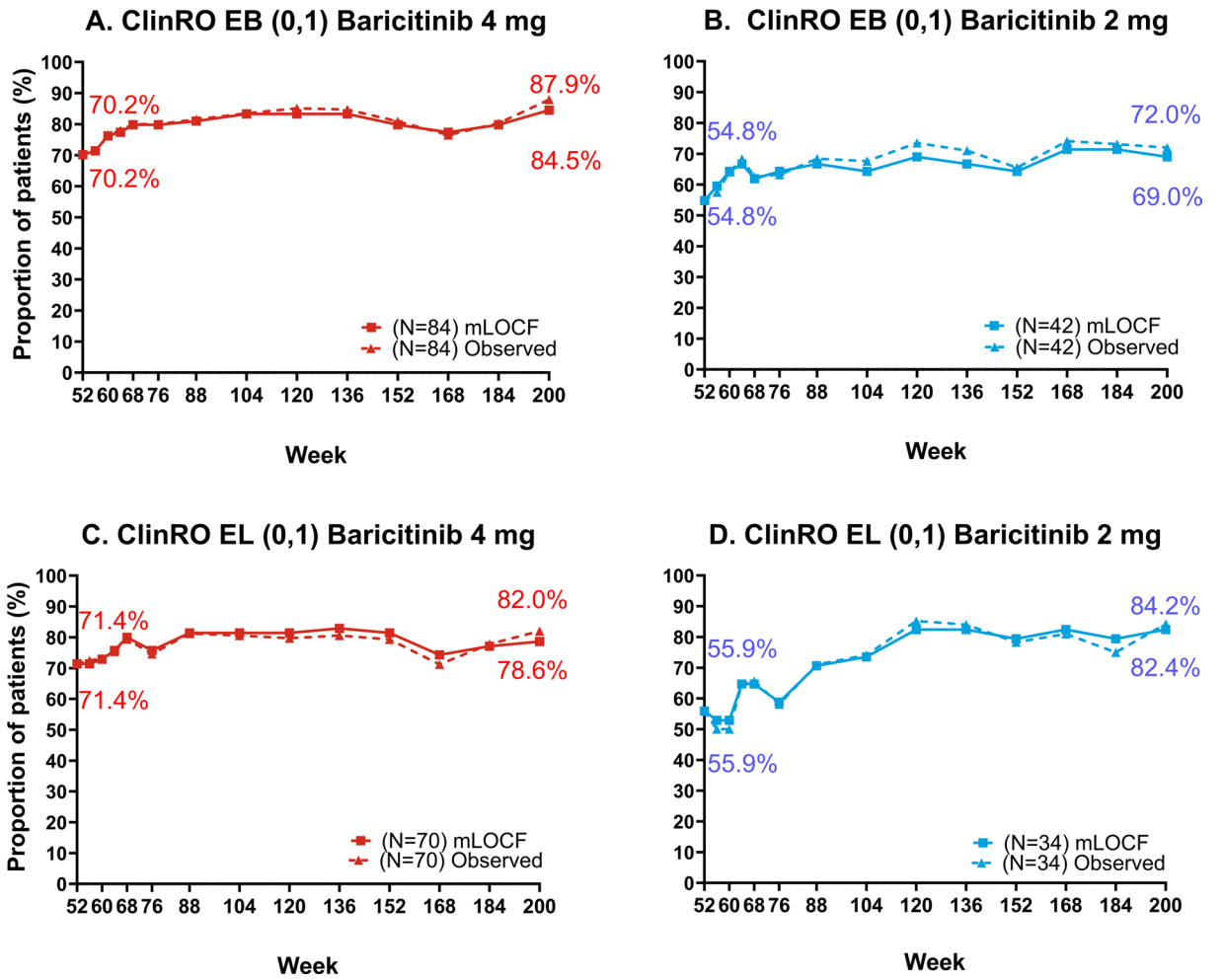


Fig. 3 Among Week 52 SALT score ≤ 20 responders with baseline ClinRO for EB or EL ≥ 2, proportion of patients achieving ClinRO EB or EL (0,1) and ≥ 2-point improvement from baseline from Week 52 to 200 among Week 52 scalp responders: **A** ClinRO EB, baricitinib 4 mg; **B** ClinRO EB, baricitinib 2 mg; **C** ClinRO EL, baricitinib 4 mg; **D** ClinRO EL, baricitinib 2 mg (mLOCF and observed). *EB ClinRO* Clinician-Reported Measure for Eyebrow Hair Loss™, *EL ClinRO* Clinician-Reported Measure for Eyelash Hair Loss™, *mLOCF* modified last observation carried forward, *N* population count

Limitations

This analysis did not include any comparisons to placebo as patients treated with placebo from baseline who had SALT scores > 20 at Week 36 were rescued to baricitinib per protocol. This lack of a placebo comparator limits the definitive conclusions that can be drawn about long-term safety data and risk for rare events such as VTE and malignancy. However, IRs for adverse events of special interest were similar to rates in the general AA population [16, 25]. This report focused only on the maintenance of efficacy throughout long-term continuous therapy among patients who had a SALT score ≤ 20 at Week 52. Due to study design, efficacy beyond Week 52 could not be assessed in the full cohort: 2 mg nonresponders were uptitrated [27], and 4 mg nonresponders could continue on the current dose only if they achieved an EB/EL response at Week 52 or a SALT score ≤ 20 before Week 52. A prior publication, Mostaghimi et al. (2024), addresses the

Table 2 Safety overview

	Extended baricitinib AA[a]		All baricitinib AA
	Baricitinib 2 mg (*N* = 383)	Baricitinib 4 mg (*N* = 565)	(*N* = 1303)
Exposure			
Total patient-years	546.1	1184.8	3047.7
Number of patients with ≥ 52 weeks, *n* (%)	268 (70.0)	451 (79.8)	1017 (78.1)
Number of patients with ≥ 104 weeks, *n* (%)	70 (18.3)	231 (40.9)	691 (53.0)
Number of patients with ≥ 152 weeks, *n* (%)	59 (15.4)	210 (37.2)	625 (48.0)
Number of patients with ≥ 200 weeks, *n* (%)	42 (11.0)	156 (27.6)	331 (25.4)
Median duration (days)	364.0	380.0	953.0
Maximum duration (days)	1742	1755	1826
Adverse events, n [IR]			
Any TEAE	274 [132.1]	449 [116.5]	1035 [105.0]
TEAE Severity[b]			
Mild	147 [38.0]	216 [24.4]	500 [22.7]
Moderate	117 [26.2]	197 [21.8]	461 [19.7]
Severe	10 [1.8]	36 [3.0]	74 [2.4]
Serious AE	12 [2.1]	34 [2.8]	77 [2.5]
Death	0	0	0
AE leading to study drug discontinuation[d]	11 [1.9]	23 [1.9]	47 [1.5]
AESIs n [IR]			
Any treatment-emergent infection	177 [50.8]	291 [41.8]	706 [39.9]
Serious infections	2 [0.3]	6 [0.5]	17 [0.5]
Herpes simplex	11 [2.0]	18 [1.5]	43 [1.4]
Herpes zoster	11 [2.0]	18 [1.5]	53 [1.7]
Opportunistic infections	0	0	1 [< 0.1]
Tuberculosis	0	0	0
Infection leading to permanent discontinuation	1 [0.2]	1 [0.1]	3 [0.1]
MACE	1 [0.2]	0	1 [< 0.1]
DVT and/or PE[c]	1 [0.0]	0	2 [0.1]
NMSC	1 [0.2]	0	4 [0.1]
Malignancies other than NMSC	0	2 [0.2]	7 [0.2]

Table 2 continued

	Extended baricitinib AA[a]		All baricitinib AA
	Baricitinib 2 mg (*N* = 383)	Baricitinib 4 mg (*N* = 565)	(*N* = 1303)
Gastrointestinal perforation			
Appendicitis with perforation	0	0	1 [< 0.1]

IRs were calculated per 100 patient-years

AA alopecia areata, *AE* adverse event, AESI adverse event of special interest, *DVT* deep vein thrombosis, *IR* incidence rate, *MACE* major adverse cardiovascular event, *n* number of patients in the specified category, *N* number of patients in the analysis set, *NMSC* non-melanoma skin cancer, *PE* pulmonary embolism, *TEAE* treatment-emergent adverse event

[a]Data censored at dose/treatment change

[b]Patients with multiple occurrences of the same event are counted under the highest severity

[c]One patient experienced both DVT and PE, and one patient had PE

[d]One patient who was reported as "discontinued treatment due to AE" in the Week 152 data cut is now reported as "discontinued study due to AE"

durability of response among delayed scalp responders and reported that ~ 40% of Week 52 nonresponders with EB/EL response achieved a scalp response after an additional year and maintained it 1 year later [26].

CONCLUSION

Data informing long-term continued therapy with baricitinib are important to inform patient management given the chronic nature of severe AA. This report shows a high level of maintained efficacy and additional improvements among Week 52 responders through ~ 4 years of treatment, such as deeper regrowth of hair across the scalp, EB, and EL with baricitinib. The observed profile remains consistent with the previously reported baricitinib safety profile in the BRAVE program, and data continue to support a positive benefit-risk profile for baricitinib. To our knowledge, these are the longest-term maintenance-of-efficacy data for a JAK inhibitor used in the treatment of severe AA.

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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 upon 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, blank, or annotated case report forms, will be provided in a secure data sharing environment. The datasets generated during and/or analyzed during the current study are available in the Vivli repository, www.vivli.org. For details on submitting a request, see the instructions provided at www.vivli.org.

Declarations

Conflict of Interest. Ruth Ann Vleugels is a paid consultant for ArgenX, Abbvie, Astra Zeneca, Priovant, and Lilly. Bianca Maria Piraccini has served as a consultant for Pierre fabre-Ducray, Difa Cooper, Dercos-L'Oreal, ISDIN, Legacy Healthcare, Pfizer, Olistic, Giuliani, and Almirall. Natasha Mesinkovska reported personal fees from Lilly, Pfizer, Sun Pharma, and AbbVie during the conduct of the study. Arash Mostaghimi is an Editorial Board member of Dermatology and Therapy. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. He receives honoraria or advisory fees from hims and hers, AbbVie, Sun Pharma, Pfizer, Digital Diagnostics, Lilly, Equillium, ASLAN, Boehringer Ingelheim, Figure 1, Dermatheory, Olaplex, and Legacy Healthcare. Yutaka Shimomura has been an investigator for Eli Lilly and Company. Brett King has received fees from Abbvie, AltruBio Inc, Almirall, Amgen, AnaptysBio, Apogee Therapeutics, Aquestive, Aslan Pharmaceuticals, Bristol Meyers Squibb, CAGE Bio Inc, Concert Pharmaceuticals Inc, Eli Lilly and Company, Equillium, Galderma, GSK, Horizon Therapeutics, Incyte Corp, Janssen Pharmaceuticals, LEO Pharma, Merck, Nektar, Novartis, Otsuka/Visterra Inc, Pfizer Inc, Q32 Bio Inc, Regeneron, Sanofi Genzyme, Soterios, Sun Pharmaceutical, Takeda, TWi Biotechnology Inc, and Ventyx Biosciences Inc. He has served on speaker bureaus for Abbvie, Incyte, Eli Lilly, Pfizer, Regeneron and Sanofi Genzyme. He is a scientific advisor for BiologicsMD. Angelina Sontag, Fionn McSwiney, Najwa Somani, Hitendra Pandey, and Karen Denning are employees and shareholders of Eli Lilly and Company.

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.

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