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DRUG PROFILE



# Baricitinib as the first systemic treatment for severe alopecia areata

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**ABSTRACT**

**Introduction:** Alopecia areata is a heterogenous, immune-mediated hair loss disorder that can affect any hair-bearing site on the body. Despite being one of the most prevalent autoimmune skin diseases, treatments have historically been limited to off-label medications that have demonstrated limited efficacy, especially in more severe forms of disease. Thus, there has long been an unmet need for rigorously studied therapeutics in alopecia areata.

**Areas covered:** Janus kinase inhibitors have proven to be an effective class of drugs for treating several inflammatory disorders. One such drug, baricitinib, has recently demonstrated significant hair regrowth in phase 2 and 3 alopecia areata trials. It has since become the first systemic therapy approved for treating severe alopecia areata. This review examines the role of Janus kinase pathways in alopecia areata's pathogenesis and the safety and efficacy of baricitinib for treating severe alopecia areata.

**Expert opinion:** The approval of baricitinib for treating severe alopecia areata marks a major milestone in the disease's history. While baricitinib has proven to be efficacious for this indication and has demonstrated an overall good safety profile, patients' individual risk factors for serious adverse events should be assessed during shared decision-making with patients before initiating treatment.

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**KEYWORDS**
Alopecia areata; baricitinib; Janus kinase; Janus kinase inhibitor; tofacitinib

## 1. Introduction

### 1.1. Alopecia areata

Alopecia areata (AA) is a heterogenous, immune-mediated condition that primarily affects hair follicles and results in non-scarring hair loss [1,2]. AA most commonly affects the scalp and may occur in small, well-circumscribed patches, the entire scalp (alopecia totalis), or even the entire body (alopecia universalis) [1]. Hair loss secondary to AA is not limited to the scalp, as it may occur virtually anywhere, including the eyebrows, eyelashes, body, or facial hair [2]. The disease course for all AA subtypes is unpredictable, with some patients experiencing spontaneous resolution and others experiencing a more chronic, relapsing course [3]. Until recently, there were no Food and Drug Administration (FDA)-approved therapies for AA.

The estimated lifetime risk for AA is approximately 2% worldwide, with an average age of onset between 25 and 36 years [1,2,4]; however, AA can occur at virtually any age and has no clear sex predominance [3]. AA is a systemic immune-mediated condition commonly associated with other inflammatory disorders such as atopic dermatitis, thyroid disease, psoriasis, vitiligo, and systemic lupus erythematosus, among others [5–7]. Perhaps the most underestimated association yet most impactful to patients is the psychosocial effects of AA. Studies have found that nearly half of patients with AA experience poor health-related quality of life, and up to 74% experience psychiatric disorders such as depression and anxiety [8–10]. The unpredictable disease course and variable treatment response rates are additional sources of distress for patients experiencing AA, highlighting the need for more efficacious therapies for this common immune-mediated disease.

The extent of disease in AA has traditionally been assessed using the Severity of Alopecia Tool (SALT), which assesses the percentage of hair loss in each of the four quadrants of the scalp, multiplied by the surface area of each respective quadrant [11]. While this validated tool is widely used in AA clinical trials, it only evaluates scalp hair loss, necessitating the use of separate scales to assess eyebrows and eyelashes [12,13]. Expert clinicians have recently proposed a new scale – the Alopecia Areata Scale (AAS) – which also reports on psychosocial impact, eyebrow and eyelash loss, treatment response, and disease progression, in addition to percentage of scalp-hair loss, when grading the severity of AA [12]. The AAS uses the designations 'mild AA,' 'moderate AA,' and 'severe AA' to better capture more individualized and variable manifestations of this heterogenous condition.

### 1.2. Pathogenesis

Under normal circumstances, hair follicles are a site of immune privilege due to several factors such as the downregulation of major histocompatibility complex (MHC) class I proteins and the local production of immunosuppressant molecules like transforming growth factor beta 1 (TGF$\beta$1) [14–16]. Additionally, the antigen presenting cells (e.g. Langerhans cells) of hair follicles downregulate MHC class II proteins [17].

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**Article highlights**

- Alopecia areata is a heterogenous, autoimmune hair loss disorder with considerable psychosocial comorbidity
- Janus kinase inhibitors interfere with inflammatory cascades thought to be central to alopecia areata's pathogenesis
- The JAK-inhibitor, baricitinib, has proven to be efficacious in AA patients with extensive hair loss and is now the first systemic therapy to be FDA-approved for adults with severe AA.
- Baricitinib has generally demonstrated a good safety profile in AA; however, patients' individual risk factors for SAEs should be assessed during shared decision-making with patients before initiating treatment.

Together, these factors serve to prevent recognition and destruction of anagen hair follicles by autoreactive CD8+ T cells and natural killer (NK) cells. The breakdown of these immune-privilege systems, and subsequent activation of CD8 + and NK cells, is theorized to be central in the pathogenesis of AA [14,15,18]. This immune dysregulation results in hair follicle dystrophy and early transition to catagen phase [18].

### 1.3. The role of Janus kinase pathways

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathways are known to play an important role in maintaining both innate and adaptive immunity [15]. The JAK-STAT signaling cascade is initiated when the associated receptor binds its respective ligand, such as cytokines and interleukins. Upon binding, the receptor oligomerizes, which allows the receptor-associated JAK to phosphorylate its own tyrosine residue and subsequently activate its kinase function. The activated JAK then phosphorylates STAT proteins, allowing them to dimerize and translocate to the nucleus where they can act as transcription factors.

There are four members of the JAK family: JAK1, JAK2, JAK3, and TYK2 [15]. Different JAKs can associate with different receptor subunits, allowing for distinct signaling pathways depending on the ligand. For instance, receptors that are associated with gamma chain ($\gamma_c$) cytokines are known to preferentially signal through JAK1/3 while IFN-γ receptors signal through JAK 1/2 [14,19].

In mouse models of AA, activated CD8+ T and NK cells have been shown to produce high levels of IFN-γ, which signal through JAK1/2 to upregulate several $\gamma_c$ cytokines such as IL-15 [20]. IL-15 subsequently binds to CD8+ T-cells and further enhances IFN-γ production through the JAK1/3 signaling cascade [20]. The result of this signaling loop is thought to allow for the survival and maintenance of the CD8+ T and NK cells that underlie AA's pathogenesis.

## 2. Treatments

### 2.1. Traditional treatments

Treatment options for AA are typically guided by the age of the patient and extent of disease; however, there are no formal treatment guidelines for AA leading to a wide variability in clinical practice [21,22]. Randomized control trials examining the efficacy of historically first-line AA therapies are limited [22], and most of the evidence exists for patients with patchy AA disease, limiting the ability for clinicians to extrapolate treatment efficacy in other subtypes of AA. For mild disease with patchy hair loss, initial regimens most commonly consist of intralesional corticosteroids which may be combined with topical corticosteroids and/or topical minoxidil. In a meta-analysis of 543 patients with focal AA treated with intralesional triamcinolone, hair regrowth was reported as 62%, 80%, and 76% for concentrations of <5 mg/mL, 5 mg/mL, and 10 mg/mL, respectively [23]. The most commonly reported side effect in addition to pain is skin atrophy, which is reported more frequently at higher triamcinolone concentrations [23].

Topical corticosteroid formulations are also commonly used to treat AA, especially in those who cannot tolerate intralesional steroid injections or have widespread disease. In a randomized trial of 0.05% clobetasol propionate solution versus placebo in 34 patients with moderate-to-severe AA, hair regrowth was noted in 89% of sites treated with clobetasol propionate compared to 11% with placebo [24]. Side effects uncommonly include folliculitis, skin atrophy, itching, burning, and telangiectasias [22]. Topical corticosteroids are inferior to intralesional injections and less effective in treating more extensive types of AA and ophiasis-pattern hair loss [21,22].

Topical minoxidil is an effective adjunct treatment in limited AA, although it is insufficient to achieve complete hair regrowth as monotherapy [22,25]. A meta-analysis on the effectiveness of 5% minoxidil versus placebo reported hair regrowth of 60% versus 6%, respectively [25]. Side effects are typically mild, including scalp itching, dermatitis, and hypertrichosis [22].

For those who fail initial therapies or who have more extensive disease, treatment options have classically been limited to systemic corticosteroids, contact immunotherapy, or (less commonly) immunomodulators such as methotrexate [26]. Few randomized control trials have examined these off-label therapies in extensive AA.

### 2.2. Janus kinase inhibitors

In recent years, Janus kinase inhibitors (JAKis) have emerged as a promising class of drugs for the treatment of alopecia areata [27]. JAKis are small molecule, immunomodulating therapies available in topical and oral formulations that exert their effect by interfering with JAK-STAT pathways which are central to a number of inflammatory conditions [27]. To date, systemic JAKis have been approved for rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis, non-segmental vitiligo, and myelofibrosis. Numerous JAKis have been developed, each with selectivity for one or more Janus kinase enzymes. For example, upadacitinib, baricitinib, and ruxolitinib exhibit selectivity for JAK1/2, while deucravacitinib exhibits selectivity for TYK2.

As described above, grafted mouse models have demonstrated that IFN- γ and IL-15, cytokines upregulated through JAK-STAT pathways, appear to be central to the pathogenesis

of AA [20]. In mouse models, systemic JAKis prevent development of AA, while both systemic and topical formulations achieved hair regrowth [20]. These findings have since garnered significant interest in JAKis as a potential treatment for AA in humans.

After early case reports demonstrated preliminary efficacy of JAKis for AA, an open-label study on the safety and efficacy of 5 mg oral tofacitinib twice daily for 3 months in 66 patients with severe AA demonstrated that 64% of subjects responded to treatment, with 32% achieving a 50% or greater improvement in SALT score [28]. All of the 20 patients available for follow-up at the conclusion of the trial experienced relapse within 3 months of JAKi cessation. In a subsequent retrospective study of 90 AA patients treated with tofacitinib, a clinical response was noted in 77% of subjects, and 58% achieved a 50% or greater improvement in SALT score [29]. Multiple JAKis have been examined in the treatment of AA, including tofacitinib, ruxolitinib, and baricitinib. A pooled meta-analysis of 289 patients with AA who were treated with a systemic JAKi demonstrated that 72.4% of subjects experienced a clinical response and 45.7% of subjects experienced 50% or more hair regrowth [30].

The most common adverse events reported in patients with AA who were treated with JAKis are low-grade infections such as upper respiratory tract infections, urinary tract infections, or herpes simplex. One meta-analysis reported total infections at a rate of 24.6% [30]. Other adverse events associated with systemic JAKi therapy include hyperlipidemia, transaminitis, and leukopenia. Serious adverse events have been reported in clinical trials examining systemic JAKi for various indications, resulting in the FDA-mandated addition of boxed warnings to systemic JAKis, including increased risk of major adverse cardiovascular events, malignancy, serious infections, thrombosis, and mortality. However, it is important to note that the risk for such events is likely dependent on the population being treated and may vary across indications. For example, the mandated boxed warnings stemmed from findings in JAKi trials for rheumatoid arthritis, a population that is generally thought to be older and with more risk-modifying comorbidities than patients with alopecia areata.

Topical JAKis offer a favorable side effect profile given limited systemic absorption; however, studies supporting their efficacy in AA are limited and often inconsistent [31]. In a pilot trial of 10 AA patients treated with topical tofacitinib 2% twice daily for 24 weeks, three subjects reported hair regrowth [32]. Side effects were limited and included scalp irritation and folliculitis. In a meta-analysis, oral JAKis were associated with four times higher odds of achieving clinical response compared to topical JAKis [30].

To date, six different oral JAKis have been studied in AA clinical trials with positive results: baricitinib, deuruxolitinib (CTP-543), ritlecitinib, brepocitinib, tofacitinib, and ruxolitinib [33]. While oral tofacitinib appears to be most frequently reported early in the literature, only results from baricitinib, CTP-543, ritlecitinib, and brepocitinib phase 2 trials in AA have been published to date [34–37]. Recently, baricitinib became the first JAKi to report phase 3 results. It has since become the first systemic JAKi to be approved by the FDA for the indication of treating severe AA [36]. The remainder of this review will focus on baricitinib, including its pharmacokinetics, pharmacodynamics, and results from clinical trials.

## 3. Baricitinib

### 3.1. Pharmacodynamics and pharmacokinetics

Baricitinib, marketed as *Olumiant* by Eli Lilly, is an orally administered, small molecule (371.41 Da) adenosine triphosphate competitive inhibitor that selectively and reversibly inhibits the JAK1 and JAK2 enzymes [38]. The *in-vitro* half maximal inhibitory concentrations ($IC_{50}$) for JAK1 and JAK2 are 5.9 nM and 5.7 nM, respectively [39]. Given that the $IC_{50}$ for JAK3 is 560 nM, baricitinib demonstrates a roughly 100-fold selectivity for JAK1 and JAK2 [39]. Additionally, baricitinib was found to have an $IC_{50}$ of TYK2 of 53 nM while demonstrating no inhibition of a panel of 28 additional kinases. As JAK3 is mainly expressed in lymphocytes, baricitinib's selectivity for JAK1 and JAK2 may allow for less immunosuppression compared to pan-JAK inhibitors [39,40]. In human peripheral blood mononuclear cells, baricitinib was shown to inhibit both IL-6 and IL-23-stimulated STAT3 phosphorylation, which resulted in decreased downstream production of chemokine MCP-1 and pro-inflammatory cytokines IL-17 and IL-22 [39].

Clinical trials in healthy volunteers have demonstrated a dose-proportional pharmacokinetic profile, with single and multiple-dose administrations of 1–20 mg oral baricitinib exhibiting linear systemic drug accumulation over time [41]. Following oral administration, maximum plasma concentration is reached in roughly 1 hour [38]. In a multiple-dose study in healthy patients, steady-state plasma concentrations were reached within 48 hours of first-dose administration [41]. The bioavailability of baricitinib in approximately 80% and administration with meals does not appear to have a clinically relevant effect on exposure [42].

Clearance of baricitinib is roughly 11 L/hr for patients with AA, with a half-life of approximately 12 to 16 hours [42,43]. Metabolism of baricitinib is mediated by CYP3A4, although less than 10% of the dose undergoes oxidative biotransformation. It has not been found to induce or inhibit cytochrome P450 enzymes. It is primarily excreted in urine (75%) and in feces (20%), the majority of which is eliminated as unchanged active substance [42]. Baricitinib has been demonstrated to be a substrate of breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), P-glycoprotein, and multidrug and toxin extrusion protein 2-k (MATE2-K) transporters in *in-vitro* studies. Additionally, it has been found to inhibit OAT1, OAT2, OAT3, organic cationic transporter 1 (OCT1), OATB1B3, BCRP, MATE-1, and MATE2-K *in-vitro*. Administration of probenecid, a strong OAT3 inhibitor, resulted in a twofold increase in area under the curve (AUC) of baricitinib, suggesting that dosing of baricitinib should be adjusted accordingly. However, coadministration of baricitinib with several other transporter and enzymatic substrates has not yielded clinically meaningful changes in baricitinib exposure, including ketoconazole, fluconazole, rifampicin, and cyclosporine. Conversely, baricitinib had no clinically meaningful effect on serum levels of digoxin, methotrexate, simvastatin, ethinyl estradiol, or levonorgestrel when co-administered [42–44].

### 3.2. Clinical efficacy

Jabbari *et al*. first reported the efficacy of baricitinib in the treatment of AA in 2015 when they noted marked improvement of AA in a patient enrolled in a clinical trial examining baricitinib for the treatment of CANDLE syndrome [45]. Since then, several case reports, followed by the seminal phase II trial and two phase III trials, have demonstrated the efficacy of baricitinib in the treatment of AA [29,34,36,46,47].

#### 3.2.1. Phase II trials

BRAVE-AA1 was the first randomized trial to examine baricitinib in adults with AA. Published in 2021, this phase 2 trial was a double-blind, placebo-controlled study on the safety and efficacy of baricitinib in adults with AA who had a SALT score ≥50% [34]. In total, 110 patients were enrolled and subsequently randomized into one of the four groups: placebo ($n = 28$), baricitinib 1 mg ($n = 28$), 2 mg ($n = 27$), and 4 mg ($n = 27$), each daily. An interim analysis was conducted at 12 weeks to select the optimal 2 doses to roll over to the phase 3 portion of the trial, as well as a separate phase 3 trial (BRAVE-AA2). A second analysis was performed at 36 weeks of treatment, with the primary efficacy endpoint defined as the proportion of patients achieving a SALT score ≤20%. Patients with severe (SALT score 50–94%) and very severe (SALT score 95–100%) AA, and whose current AA episode had lasted over 6 months but under 8 years and without evidence of spontaneous remission, were included. Study patients were not permitted to use other treatments for AA during the trial, although oral and topical minoxidil were permitted if patients had been on a stable dose for over 12 months. Notably, subjects who had previously failed an oral JAKi for the treatment of AA were excluded from the study. Mean age of subjects was 41 years, 75% of subjects were female, and mean SALT scores across treatment arms ranged from 83.4% to 90% at baseline. Results of the phase 2 trial are summarized below and in Table 1.

At the week-12 interim analysis, the proportions of patients achieving a ≥30% improvement in SALT score from baseline ($SALT_{30}$) were as follows: placebo (10.7%), baricitinib 1 mg (17.9%), 2 mg (29.6%), 4 mg (33.3%). At week-16, an endpoint of ≥50% improvement in SALT score from baseline ($SALT_{50}$) was used, with results again suggesting greater efficacy of 2 mg (31.8%) and 4 mg (38.1%) doses compared to 1 mg (18.2%) and placebo (4.5%). Thus, daily dosages of 2 mg and 4 mg were chosen to be studied in subsequent phase 3 trials.

After 36 weeks of treatment, the proportion of patients with a SALT score ≤20 was greater in both the 2 mg (33.3%; $P = 0.016$) and 4 mg (51.9%; $P = 0.001$) groups compared to placebo (3.6%). Furthermore, the proportion of patients with a SALT score ≤10 was greater in the 2 mg (25.9%; $P = 0.046$) and 4 mg (40.7%; $P = 0.008$) groups compared to placebo (0%). Similar efficacy was also shown for regrowth of eyelashes and eyebrows in patients with significant involvement at baseline. Specifically, 28.6% ($P = 0.034$) in the 2 mg group and 39.1% ($P = 0.012$) in the 4 mg group achieved a clinician reported outcome (ClinRO) measure for eyebrow hair loss of 0 (normal) or 1 (minimal gaps) compared to 4.3% in the placebo group at 36 weeks. Similarly, 40% in the 2 mg group and 60% in the 4 mg group achieved a ClinRO measure for eyelash hair loss of 0 or 1, compared to 5.9% in the placebo group at 36 weeks – though only the 4 mg group achieved statistical significance ($P = 0.041$) compared to placebo.

The results of BRAVE-AA1 supported baricitinib 2 mg and 4 mg as significantly more effective compared to placebo for the treatment of alopecia areata in patients with at least 50% hair loss, thus these two dosages were subsequently examined in two phase 3 trials.

#### 3.2.2. Phase III trials

Two phase 3 trials of baricitinib were carried out after the conclusion of the phase 2 portion of BRAVE-AA1: phase 3 of BRAVE-AA1, and BRAVE-AA2 [36]. The study design of both phase 3 trials, including inclusion and exclusion criteria, was similar to that of phase 2 of BRAVE-AA1. However, patients in the phase 3 trials were randomized in a 3:2:2 ratio to receive either baricitinib 4 mg, 2 mg, or placebo. Over 50% of patients in each treatment arm had very severe AA (SALT score 95–100) and 34–43% had an atopic background at baseline. Of note, this trial was conducted during the COVID-19 pandemic and so 10–15% of data for primary and secondary outcomes were missing – either due to missed visits or limitations of remote visits – thus requiring multiple imputation for data analysis. The results of each trial are summarized below and in Table 2.

A total of 654 patients were newly enrolled in the phase 3 portion of BRAVE-AA1, as none of these subjects were enrolled in the phase 2 portion of this trial. Of these patients, 598 completed 36 weeks of treatment with baricitinib or placebo.

After 36 weeks of treatment, the proportion of patients achieving a SALT score of 20 or less was 38.8% for 4 mg

Table 1. Summary of efficacy endpoints for phase 2 trial of baricitinib for alopecia areata.

| | BRAVE-AA1 (phase 2) | | | |
|---|---|---|---|---|
| | Placebo ($n = 28$) | 1 mg ($n = 28$) | 2 mg ($n = 27$) | 4 mg ($n = 27$) |
| **Interim Analysis** | | | | |
| $SALT_{30}$ at week 12, % | 10.7 | 17.9 | 29.6 | 33.3 |
| $SALT_{50}$†, % | 4.5 | 18.2 | 31.8 | 38.1* |
| **Week 36** | | | | |
| $SALT_{90}$, % | 0 | NR | 18.5 | 40.7** |
| SALT≤20, % | 3.6 | NR | 33.3* | 51.9*** |
| SALT≤10, % | 0 | NR | 25.9* | 40.7** |
| ClinRO 0 or 1 Eyebrow‡, % | 4.3 | NR | 28.6* | 39.1* |
| ClinRO 0 or 1 Eyelash‡, % | 5.9 | NR | 40 | 60* |
| PRO 0 or 1 Scalp, % | 3.6 | NR | 33.3* | 37.0** |
| PRO 0 or 1 Eyebrow‡, % | 0 | NR | 40* | 45.8** |
| PRO 0 or 1 Eyelash‡, % | 0 | NR | 27.8 | 57.9* |

Note: *$p < 0.05$; **$p \le 0.01$; ***$p \le 0.001$.
†Based on 87 patients who had completed 16 weeks or were discontinued.
‡Analysis in patients with ClinRO and PRO baseline measures of ≥2 (significant gaps or no notable eyebrows/eyelashes).
- SALT score ranges from 0 (no scalp hair loss) to 100 (complete scalp hair loss).
- ClinRO/PRO measures for eyebrow/eyelash of 0 and 1 correspond to full coverage and minimal gaps, respectively.
- PRO measure for scalp hair of 0 and 1 correspond to no missing hair and limited area of missing hair (1% to 20% of scalp), respectively.

Abbreviations: NR = not reported; SALT = Severity of Alopecia Tool; $SALT_{30}$ = SALT score improvement of at least 30% from baseline; $SALT_{50}$ = SALT score improvement of at least 50% from baseline; SALT ≤ 20 = SALT score of 20 points or less; SALT ≤ 10 = SALT score of 10 or less; $SALT_{90}$ = SALT score improvement of at least 90% from baseline; ClinRO = clinician reported outcome; PRO = patient-reported outcome.

Table 2. Summary of efficacy endpoints for phase 3 trials of baricitinib for alopecia areata.

| | BRAVE-AA1 (phase 3) | | | BRAVE-AA2 (phase 3) | | |
|---|---|---|---|---|---|---|
| | Placebo ($n = 189$) | 2 mg ($n = 184$) | 4 mg ($n = 281$) | Placebo ($n = 156$) | 2 mg ($n = 156$) | 4 mg ($n = 234$) |
| **Week 12** | | | | | | |
| $SALT_{30}$, % | NR | NR | NR | NR | NR | NR |
| $SALT_{50}$, % | 5 | 11.3* | 22.4*** | 3.4 | 11.9 | 24.6 |
| **Week 24** | | | | | | |
| SALT ≤ 20, % | 5.7 | 13** | 28.4*** | 2.5 | 13 | 30.6*** |
| SALT ≤ 10, % | 3.2 | 8.4* | 15.8*** | 1.2 | 8.8 | 20.3 |
| **Week 36** | | | | | | |
| $SALT_{90}$, % | 3.3 | 11.7** | 23.8*** | 0.8 | 9 | 22.9*** |
| SALT ≤ 20, % | 6.2 | 22.8*** | 38.8*** | 3.3 | 19.4*** | 35.9*** |
| SALT ≤ 10, % | 4.1 | 13** | 27.9*** | 1 | 12 | 25.6*** |
| ClinRO 0 or 1 Eyebrow†, % | 4.4 | 22*** | 35.2*** | 5.5 | 13.2 | 38.9*** |
| ClinRO 0 or 1 Eyelash†, % | 4.4 | 14.8 | 36.2*** | 6.9 | 12.3 | 36.8*** |
| PRO 0 or 1 Scalp‡, % | 5.9 | 17.1*** | 35.8*** | 5.1 | 18.5** | 37.8*** |
| PRO 0 or 1 Eyebrow, % | NR | NR | NR | NR | NR | NR |
| PRO 0 or 1 Eyelash, % | NR | NR | NR | NR | NR | NR |

Note: *$p < 0.05$; **$p \le 0.01$; ***$p \le 0.001$. P-values marked statistically significant as calculated with multiplicity adjustments.
†Analysis in patients with ClinRO baseline measures of ≥2 (significant gaps or no notable eyebrows/eyelashes) who achieved at least a 2-point score improvement.
‡Analysis in patients with a PRO scalp score of 3 (≥50% of scalp is missing hair) or higher at baseline who achieved at least a 2-point score improvement.
- ClinRO/PRO measures for eyebrow/eyelash of 0 and 1 correspond to full coverage and minimal gaps, respectively.
- PRO measure for scalp hair of 0 and 1 correspond to no missing hair and limited area of missing hair (1% to 20% of scalp), respectively.
Abbreviations: NR = not reported; SALT = Severity of Alopecia Tool; $SALT_{30}$ = SALT score improvement of at least 30% from baseline; $SALT_{50}$ = SALT score improvement of at least 50% from baseline; SALT ≤ 20 = SALT score of 20 points or less; SALT ≤ 10 = SALT score of 10 or less; $SALT_{90}$ = SALT score improvement of at least 90% from baseline; ClinRO = clinician reported outcome; PRO = patient-reported outcome.

baricitinib, 22.8% for 2 mg, and 6.2% for placebo in BRAVE-AA1. The difference between the baricitinib groups and placebo was 32.6 percentage points for 4 mg ($P < 0.001$) and 16.6 for 2 mg ($P < 0.001$). Secondary outcomes similar to the phase 2 trials were assessed, all of which differed significantly between the 4 mg dose and placebo. Interestingly, a significant proportion (19.4%) of patients in the 4 mg arm had achieved a SALT score of 20 or less by 16 weeks (less than halfway through the trial). Regrowth of eyebrows was seen with baricitinib treatment; 22.0% (2 mg group) and 35.2% (4 mg) of patients achieved a ClinRO measure of 0 or 1 compared to 4.4% in the placebo arm ($P < 0.001$ both groups). A similar efficacy in eyelash regrowth was reported in the 4 mg group; however, there was no significant difference in regrowth in the 2 mg cohort at 36 weeks with multiplicity adjustments.

A total of 546 patients were enrolled in BRAVE-AA2, 490 of which completed the 36-week trial. Similar primary outcomes to BRAVE-AA1 were reported, with 19.4% of the 2 mg group and 35.9% of the 4 mg group achieving SALT score of 20 or less compared to 3.3% in the placebo group. While the 4 mg group again demonstrated significant improvement in the majority of secondary outcome categories compared to placebo, the 2 mg group failed to show a significant improvement in most secondary outcomes with multiplicity adjustments, including eyebrow and eyelash regrowth.

Overall, both 2 mg and 4 mg daily oral baricitinib demonstrated efficacy of hair regrowth in adult patients with severe AA, with a significant proportion of patients (19.4–51.9%) achieving a SALT score of 20 or less when compared to placebo after 36 weeks. Notably, in both phase 3 trials, 22.9–23.8% of subjects receiving baricitinib 4 mg daily achieved a 90% or greater improvement in SALT score. Significant regrowth of eyebrows and eyelashes was also observed in those receiving baricitinib 4 mg daily.

These studies were limited by a potential selection bias given that patients who had previously failed JAKi therapy for AA were excluded from the trials. Additionally, patients were permitted to use topical or oral minoxidil and oral finasteride throughout the trial, which may augment the efficacy of hair regrowth. However, patients were required to be on a stable dose of these medications for at least 12 months to be permitted to continue treatment in the trials and only 1.3% of trial patients were on these medications concomitantly.

### 3.3. Safety and tolerability

Baricitinib was generally well tolerated across all three clinical trials (Table 3). In the phase 2 portion of BRAVE-AA1, AEs were reported in 77.8% in the 4 mg baricitinib group, 70.4% 2 mg group, and 60.7% in the placebo group [34]. The most commonly reported AEs were upper respiratory tract infection, acne, and nausea. No SAEs or deaths were reported.

A more comprehensive side-effect profile was detailed in the phase 3 trials [36]. The percentages of any adverse event across all treatment arms (including placebo) appeared to be similar, ranging from 50.8% to 68.4% of patients. The most commonly reported AEs were upper respiratory tract infections, headache, nasopharyngitis, elevated creatine phosphokinase (CPK), and acne.

However, only acne appeared to occur more frequently with both baricitinib groups than placebo. Changes in several laboratory values were also reported. Elevated levels of low-density lipoprotein (LDL) were reported in up to 30.3% for baricitinib groups versus 17.7% for placebo, and elevated high-density lipoprotein (HDL) were reported in up to 43.0% for baricitinib versus 13.5% for placebo. Elevated creatine kinase levels were seen more commonly in the 4 mg groups (up to 5.7%) compared to the 2 mg group (up to 1.6%) and placebo (up to 1.6%). Other laboratory abnormalities included anemia, neutropenia, leukopenia, and thrombocytosis. The majority of these were considered low grade or transient, and thus patients remained in the trial. The exception was

Table 3. Summary of safety outcomes for phase 2 and 3 trials of baricitinib for alopecia areata. Phase 2 safety was up to 52 weeks, while phase 3 data was up to 36 weeks of treatment.

| | BRAVE-AA1 (phase 2) | | | BRAVE-AA1 (phase 3) | | | BRAVE-AA2 (phase 3) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo ($n = 28$) | 2 mg ($n = 27$) | 4 mg ($n = 27$) | Placebo ($n = 189$) | 2 mg ($n = 183$) | 4 mg ($n = 280$) | Placebo ($n = 154$) | 2 mg ($n = 155$) | 4 mg ($n = 233$) |
| **Adverse Events, n(%)** | | | | | | | | | |
| At Least one AE | 17 (60.7) | 19 (70.4) | 21 (77.8) | 97 (51.3) | 93 (50.8) | 167 (59.6) | 97 (63.0) | 106 (68.4) | 154 (66.1) |
| Mild | 8 (28.6) | 14 (51.9) | 14 (51.9) | 49 (25.9) | 60 (32.8) | 106 (37.9) | 65 (42.2) | 60 (38.7) | 81 (34.8) |
| Moderate | 9 (31.2) | 5 (18.5) | 6 (22.2) | 41 (21.7) | 31 (16.9) | 54 (19.3) | 28 (18.2) | 42 (27.1) | 60 (25.8) |
| Severe | 0 | 0 | 1 (3.7) | 7 (3.7) | 2 (1.1) | 7 (2.5) | 4 (2.6) | 4 (2.6) | 13 (5.6) |
| Serious AE | 0 | 0 | 0 | 3 (1.6) | 4 (2.2) | 6 (2.1) | 3 (1.9) | 4 (2.6) | 8 (3.4) |
| AE leading to discontinuation | 0 | 0 | 1 (3.7) | 2 (1.1) | 3 (1.6) | 5 (1.8) | 4 (2.6) | 4 (2.6) | 6 (2.6) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Frequently Reported, n(%)** | | | | | | | | | |
| URI | 5 (17.9) | 3 (11.1) | 6 (22.2) | 10 (5.3) | 9 (4.9) | 21 (7.5) | 11 (7.1) | 12 (7.7) | 15 (6.4) |
| Acne | 0 | 2 (7.4) | 3 (11.1) | 1 (0.5) | 10 (5.5) | 16 (5.7) | 3 (1.9) | 9 (5.8) | 11 (4.7) |
| Nausea | 0 | 2 (7.4) | 2 (7.4) | NR | NR | NR | NR | NR | NR |
| Headache | NR | NR | NR | 9 (4.8) | 8 (4.4) | 14 (5.0) | 10 (6.5) | 12 (7.7) | 21 (9.0) |
| Nasopharyngitis | NR | NR | NR | 12 (6.3) | 12 (6.6) | 21 (7.5) | 7 (4.5) | 2 (1.3) | 15 (6.4) |
| UTI | NR | NR | NR | 3 (1.6) | 2 (1.1) | 7 (2.5) | 2 (1.3) | 12 (7.7) | 11 (4.7) |
| Creatine Kinase Elevations | NR | NR | NR | 3 (1.6) | 3 (1.6) | 16 (5.7) | 2 (1.3) | 0 | 7 (3.0) |
| **Infections, n(%)** | | | | | | | | | |
| At least one infection | 10 (35.7) | 13 (48.1) | 10 (37) | 53 (28.0) | 46 (25.1) | 88 (31.4) | 45 (29.2) | 58 (37.4) | 69 (29.6) |
| Serious Infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1.3) | 1 (0.4) |
| Opportunistic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Herpes Zoster | 0 | 1 (3.7) | 1 (3.7) | 1 (0.5) | 1 (0.5) | 2 (0.7) | 1 (0.6) | 3 (1.9) | 3 (1.3) |
| Herpes Simplex | 0 | 3 (11.1) | 1 (3.7) | 4 (2.1) | 0 | 5 (1.8) | 8 (5.2) | 6 (3.9) | 2 (0.9) |
| Tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Leading to drug interruption | 0 | 2 (7.4) | 1 (3.7) | NR | NR | NR | NR | NR | NR |
| Leading to drug discontinuation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) | 0 |
| **Other, n(%)** | | | | | | | | | |
| MACE | NR | NR | NR | 0 | 1 (0.5) | 0 | 0 | 0 | 0 |
| Venous Thromboembolism | NR | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| Cancer, other than NMSC | NR | NR | NR | 0 | 0 | 0 | 1 (0.6) | 0 | 1 (0.4) |
| NMSC | NR | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal perforation | NR | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| **Lipids, n/total (%)‡** | | | | | | | | | |
| LDL ≥ 130 mg/dl | NR | NR | NR | 19/132 (14.4) | 27/132 (20.5) | 57/206 (27.7) | 20/113 (17.7) | 27/109 (24.8) | 54/178 (30.3) |
| HDL ≥ 60 mg/dl | NR | NR | NR | 14/104 (13.5) | 41/97 (42.3) | 68/163 (41.7) | 11/83 (13.3) | 31/87 (35.6) | 58/135 (43.0) |
| Triglycerides ≥ 500 mg/dl | NR | NR | NR | 3/173 (1.7) | 1/169 (0.6) | 4/268 (1.5) | 0 | 0 | 0 |

Note: ‡Percentages calculated based on the total number of patients at risk for each lipid derangement.

Abbreviations: AE = adverse event; URI = upper respiratory tract infection; UTI = urinary tract infection; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; LDL = low-density lipoprotein; HDL = low-density lipoprotein.

one patient with a history of gastrointestinal bleeding who developed grade 4 anemia while on 4 mg baricitinib and subsequently dropped out of the trial.

The percentages of any infection occurred at similar rates across all groups and were relatively common (range 25.1–37.4%, all groups). Types of infections reported included upper respiratory tract, urinary tract infection, herpes zoster, and herpes simplex. Serious infections were rare (0.4–1.3%, baricitinib groups) and included COVID-19 pneumonia and pyelonephritis.

Serious adverse events (SAE) were reported in a minority of patients, ranging from 2.1% to 3.4% in the baricitinib groups versus 1.6–1.9% in the placebo group. The most common SAEs were fractures secondary to injury ($n = 6$, all groups), followed by infection ($n = 3$, all groups). Of note, three cardiac-related SAEs occurred in patients with cardiac comorbidities on baricitinib: ventricular tachycardia, congestive heart failure, and acute myocardial infarction.

All oral JAKis carry boxed warnings including increased risk of major adverse cardiovascular events, malignancy, serious infections, thrombosis, and mortality. No deaths, thromboembolic events, or non-melanoma skin cancers were reported in any of the above trials. However, one myocardial infarction in a 48-year-old patient with cardiovascular risk factors (tobacco use, atrial fibrillation, hypercholesterolemia, and hypertension) was reported after 9 months of 2 mg baricitinib therapy. Additionally, two cancers were diagnosed during phase 3 trials: B-cell lymphoma in a 40-year-old patient receiving 4 mg baricitinib for 4 months and prostate cancer in a 58-year-old patient receiving placebo. Because follow-up time in these trials is limited, the true long-term risk of these serious adverse events in patients AA is unknown. Overall, the safety profile demonstrated in these trials is consistent with that reported in trials of other conditions such as RA and atopic dermatitis [48]. However, some have argued that because JAKi boxed warnings are based on trials in patients with RA – a population that tends to be older and with more baseline risk factors – the side effect profile may prove to be safer in AA [48].

Given the recency in which baricitinib was awarded FDA approval for the treatment of severe AA, post-market surveillance is limited. In total, there have been 21 cases of adverse events reported on the FDA Adverse Events Reporting System (FAERS) as of a search performed in January 2023. Of these cases, eight were considered serious, including lung adenocarcinoma, atrial fibrillation, sensorineural deafness, seizures, oral herpes, COVID-19 infection, myasthenia gravis, and diverticulitis.

### 3.4. Regulatory affairs

Prior to its latest use in alopecia areata, baricitinib was FDA-approved for treating adults with moderately to severe rheumatoid arthritisand hospitalized adults with COVID-19 infection who required supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Additionally, baricitinib is approved for the treatment of atopic dermatitis in the E.U. and Japan. Eli Lilly has recently discontinued phase 3 trials of baricitinib in system lupus erythematosus for failure to meet the study's primary endpoint. Since completing phase 3 trials, baricitinib is now approved in the United States, European Union, and Japan for the treatment of adult patients with severe alopecia areata.

## 4. Conclusion

Phase 2 and 3 trials support the safety and efficacy of baricitinib in treating patients with AA who have at least 50% hair loss. Baricitinib has thus become the first FDA-approved pharmaceutical for the treatment of adults with severe AA. Post-marketing, real-world data is now needed to assess its long-term efficacy and safety in patients with AA, with particular attention given to the risk of serious adverse events associated with JAKis in this population. Safety monitoring will be especially important as studies of JAKis in AA have suggested that ongoing treatment, and thus prolonged drug exposure, is required to sustain results. With several other JAKi candidates now in phase 3 trials, additional research will be needed to assess which therapy is most efficacious in AA while minimizing adverse events.

## 5. Expert opinion

Despite being one of the most common autoimmune diseases worldwide, there were no FDA-approved therapies for severe AA until recently. While AA may present with patchy hair loss that can spontaneously regrow in some patients, others may have persistent and extensive hair loss which has less tendency to spontaneously remit and is more resistant to the previously available standards of care. Previous first-line treatments, such as intralesional and topical glucocorticoids, have demonstrated variable efficacy in extensive forms of AA. Additionally, their off label-use in AA is most effective in patchy subtypes which are more likely to remit spontaneously compared to severe AA. Regardless of the extent of disease, AA is often accompanied by considerable emotional and psychosocial distress, as patients struggle with uncertainty of an unpredictable disease course. Taken together, these factors highlight the need for more effective, FDA-approved treatments for severe AA.

Baricitinib's latest indication for treating severe AA in adults represents a major milestone in AA's history as it is the first therapy of any kind to be FDA-approved for this condition. Baricitinib, a JAK1/2 inhibitor, demonstrated efficacy in treating AA patients with at least 50% hair loss, with up to 38% of patients achieving 80% or more scalp hair coverage after 36 weeks. Baricitinib is likely the first of several JAKis approved for this indication, as several phase 3 trials are currently underway. This will pave the way for eventual head-to-head in-class drug comparisons, allowing for the identification of optimal JAK-STAT targets and dosages.

The recent approval may give patients who have struggled with severe AA hope for a cure. However, it is important to clarify with patients that successful treatment will likely require ongoing, long-term treatment, as smaller studies have reported relapses of AA after drug cessation [28,30]. This will make drug monitoring especially important as the effects of long-term exposure in this population are largely

unknown. While the side effects reported in phase 3 trials were overall acceptable and in-line with those reported in trials across other indications, one case of malignancy and one case of a major adverse cardiovascular event were reported in patients receiving baricitinib – both of which are boxed warnings of JAKis. While causality in these cases is difficult to ascertain and the absolute risk of these events appears to be low, long-term studies and post-market surveillance will be key in clarifying these risks in patients with AA who tend to be relatively young. In the meantime, clinicians should familiarize themselves with these potential serious side effects and evaluate each patient's individual risk factors, such as age and malignancy history, when considering them for JAKi treatment.

Additional phase 3 studies and long-term open-label studies of different JAKis for AA are currently underway. Thus, we anticipate additional JAKis to be granted similar indications as baricitinib within the next 2 years. As more JAKi formulations are approved, we would expect future trials to compare the efficacy and safety profiles of formulations within the JAKi drug class. As different JAKis target different Janus kinase pathways, it is reasonable to expect that different formulations may emerge as offering an optimal balance of efficacy and safety. Additional trials are necessary to identify patients most likely to respond to JAKi therapy, as well as possible maintenance dosing so that treatment efficacy may be optimized against drug exposure.

## Declaration of interest

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