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Upadacitinib Leads in Efficacy: A Bayesian Network Meta-Analysis of Four JAK Inhibitors in Moderate-To-Severe Atopic Dermatitis

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ABSTRACT

Background: Janus kinase inhibitors (JAKis) have revolutionized the management of moderate-to-severe atopic dermatitis (AD). Although agents approved by the United States Food and Drug Administration (FDA), such as upadacitinib and abrocitinib, are widely used, and baricitinib and ivarmacitinib are under investigation, direct head-to-head randomized clinical trials (RCTs) comparing these agents are lacking.

Objective: Our aim was to rank the short-term efficacy of four oral JAKis, upadacitinib (15/30 mg), abrocitinib (100/200 mg), baricitinib (2/4 mg), and ivarmacitinib (4/8 mg), in moderate-to-severe AD using a Bayesian Network Meta-Analysis (BNMA).

Methods: Conducted per PRISMA 2020 guidelines and registered in PROSPERO (CRD420251116775), this study systematically reviewed phase 2 and 3 RCTs evaluating JAKi monotherapy in adults with moderate-to-severe AD. Primary endpoints included: (1) ≥75% improvement in Eczema Area and Severity Index (EASI-75), (2) Investigator's Global Assessment (IGA-AD 0/1), and (3) ≥4-point reduction in itch numeric rating scale (Itch NRS) at 12–16 weeks. Bayesian hierarchical modeling estimated odds ratios (ORs) with 95% credible intervals (CrIs), and surface under the cumulative ranking curve (SUCRA) probabilities defined the treatment hierarchy.

Results: Nine RCTs ($n = 4261$) were included. Upadacitinib 30 mg demonstrated the greatest efficacy across all endpoints, EASI-75 (OR = 12.3; 95% CrI 7.9–18.7), IGA-AD 0/1 (OR = 18.9; 95% CrI 12.0–29.7), and Itch NRS (OR = 11.1; 95% CrI 7.2–17.5), followed by upadacitinib 15 mg, abrocitinib 200 mg, and ivarmacitinib 8 mg. Baricitinib 2 mg and 4 mg consistently ranked lowest. SUCRA values confirmed upadacitinib 30 mg as the top performer (97%–98%).

Conclusion: Among oral JAKis, upadacitinib 30 mg, followed by upadacitinib 15 mg, achieved the most consistent short-term efficacy, providing superior skin clearance and itch relief. Abrocitinib 200 mg and ivarmacitinib 8 mg showed intermediate benefits, whereas baricitinib displayed modest effects. These findings support a provisional efficacy preference for upadacitinib in managing moderate-to-severe AD unresponsive to biologic or topical therapies.

1 | Introduction

Atopic dermatitis (AD) is a highly debilitating, common, non-contagious skin disorder with a relapsing–remitting course. It is characterized by eczematous lesions, severe and often unremitting pruritus, and significant sleep disturbance, each of which independently compromises physical, emotional, and social well-being [1–4]. Pruritus is the defining symptom and most disabling

Summary

Question

Among the oral Janus kinase inhibitors (JAKis) currently approved or under evaluation for moderate-to-severe atopic dermatitis (AD), which agent demonstrates the greatest short-term efficacy in achieving skin clearance and itch reduction?

Findings

In this Bayesian network meta-analysis of nine randomized controlled trials including 4261 patients, upadacitinib 30 mg demonstrated the highest efficacy across all endpoints (EASI-75, IGA-AD 0/1, and ≥ 4-point Itch NRS improvement), followed by upadacitinib 15 mg and abrocitinib 200 mg. Ivarmacitinib 8 mg showed intermediate efficacy, while baricitinib 2 mg and 4 mg consistently ranked lowest across outcomes.

Meaning

Upadacitinib demonstrated superior short-term efficacy compared with other oral JAKis for moderate-to-severe AD, supporting its preferential consideration when systemic JAKi therapy is indicated and highlighting the need for head-to-head and long-term comparative studies.

feature of AD, often intensifying at night and contributing to sleep disruption, daytime fatigue, and impaired health-related quality of life [5–7]. AD imposes a considerable economic and psychosocial burden on patients and caregivers, particularly among those with moderate-to-severe disease who often require sustained systemic therapy to achieve adequate disease control [8, 9].

Until recently, pharmacotherapy for AD has relied on topical corticosteroids, topical calcineurin inhibitors, and systemic immunosuppressants such as cyclosporine, methotrexate, azathioprine, and mycophenolate [10]. The advent of monoclonal antibodies targeting the interleukin (IL)-4/13 pathway (dupilumab, tralokinumab, lebrikizumab) and oral Janus kinase inhibitors (JAKis) targeting the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (abrocitinib, upadacitinib) has represented a therapeutic breakthrough [11]. Biologics provide long-term disease control and little laboratory monitoring need, whereas JAKis (e.g., upadacitinib, abrocitinib, baricitinib, and ivarmacitinib, which is approved in China only) provide immediate symptom relief, particularly for pruritus, and oral convenience [12–20]. JAK inhibitors, on the other hand, are associated with greater safety concerns, including boxed warnings of serious infections, cancer, death, major adverse cardiovascular events (MACE), and thrombosis. They are therefore reserved for moderate-to-severe AD that is not adequately controlled with systemic treatments such as biologics, or when safety concerns, comorbidities, or cost limits the use of biologics [21–31]. Upadacitinib and abrocitinib are approved in adults and adolescents with AD; baricitinib is approved in the United Kingdom, the European Union, and Japan but not in the United States or China, and ivarmacitinib has only recently gained approval in China [19, 32, 33]. With the unlikelihood of well-powered head-to-head RCTs due to cost and logistical limitations, indirect comparisons such as Bayesian network meta-analysis (BNMA) are important in an effort to compare efficacy and guide therapeutic decisions [34–39].

Network meta-analysis (NMA) provides a strong statistical framework for comparing multiple interventions, even in the absence of direct studies [40, 41]. Earlier NMAs in AD have concentrated chiefly on biologics, and prior NMAs of oral JAK inhibitors have excluded data on certain agents, or have incorporated findings from non-RCTs, multiple pharmacologic drug classes, topical agents, drugs given in combination, agents and dosing regimens that were previously abandoned, demonstrated to be clinically ineffective or not approved for any immune-mediated or inflammatory disease in a major regulatory market [42–47]. Furthermore, NMAs published before June 2025 did not include ivarmacitinib, as its phase 3 data in AD and regulatory approvals in China for AD only became available in 2025 [24]. To address these gaps, we conducted a Bayesian network meta-analysis (BNMA) evaluating the short-term efficacy of four JAK inhibitors (abrocitinib, upadacitinib, baricitinib, and ivarmacitinib) as monotherapy for moderate-to-severe AD. The study aimed to rank their comparative efficacy, identify the most effective regimen across EASI-75, IGA-AD 0/1, and Itch NRS ≥ 4 endpoints, and inform evidence-based clinical decision-making.

2 | Methods

2.1 | Study Selection and Data Sources

A systematic review following PRISMA 2020 and registered in PROSPERO (CRD420251116775) [48] included phase 2 and 3 randomized, double-blind, placebo-controlled trials of oral JAK inhibitors for moderate-to-severe AD. Searches of PubMed, Embase, Cochrane, and ScienceDirect through August 2025, plus key references and congress abstracts, identified eligible studies (Table S1).

2.2 | Eligibility Criteria

Eligible treatments included baricitinib (2/4 mg), upadacitinib (15/30 mg), abrocitinib (100/200 mg), and ivarmacitinib (4/8 mg). Age criteria aligned with pivotal programs: abrocitinib (JADE MONO-1, NCT03349060; JADE MONO-2, NCT03575871; JADE Phase 2b, NCT02780167; ≥ 12 years), upadacitinib (MEASURE UP-1, NCT03569293; MEASURE UP-2, NCT03607422; 12–75 years), baricitinib (BREEZE-AD1, NCT03334396; BREEZE-AD2, NCT03334422; BREEZE-AD5, NCT03435081; ≥ 18 years), and ivarmacitinib (Phase 3, NCT04875169; 12–75 years) [12–14, 16]. These four JAK inhibitors were chosen for their clinical and regulatory importance as systemic monotherapies for moderate-to-severe AD.

2.3 | Efficacy Outcomes

Efficacy outcomes of interest were consistent across all RCTs. Included studies either employed the validated Investigator's Global Assessment for AD (vIGA-AD) scale [21–23] or did not specify the source of their IGA scale [24, 25, 27, 28]. The primary

endpoints were: (i) the proportion of patients achieving at least 75% improvement from baseline in Eczema Area and Severity Index (EASI-75) [49]; (ii) the proportion achieving a score of 0 (clear) or 1 (almost clear) on the IGA-AD 0/1, with a minimum two-point improvement from baseline [50]; (iii) the proportion of patients with a ≥4-point reduction in the pruritus numeric rating scale (Itch NRS) score [51]. Baseline disease severity eligibility criteria are shown in Table S2. These endpoints were assessed at Week 16 (upadacitinib, baricitinib, and ivarmacitinib) and at Week 12 (abrocitinib).

2.4 | Statistical Analysis

A Bayesian network meta-analysis (BNMA) compared the relative efficacy of four oral JAK inhibitors versus placebo. Analyses were performed using OpenBUGS v3.2.3 in R v4.2.2 with the R2OpenBUGS package [52–54]. Fixed- and random-effects models, with and without baseline risk adjustment, were compared using the Deviance Information Criterion (DIC) [55]. Odds ratios (ORs) with 95% credible intervals (CrIs) were estimated, and treatment hierarchy assessed using P-scores and SUCRA values [56–61]. Risk of bias was evaluated using Cochrane RoB 2.0 [62, 63], following established methodological and Bayesian NMA reporting guidelines [64, 65]. To examine the impact of differing follow-up durations, we performed a sensitivity analysis excluding all Week-12 abrocitinib trials (JADE MONO-1, JADE MONO-2, and the phase 2 abrocitinib study), retaining only Week-16 trials of upadacitinib, ivarmacitinib, and baricitinib.

2.5 | Ethics Statement

Ethical approval and patient consent were not required because this was a network meta-analysis of previously published studies.

3 | Results

3.1 | Systematic Literature Review

By means of the systematic literature search, 7910 records were found. Of these, 1258 records had their eligibility evaluated, and 255 records had unique findings. Nine RCTs from seven publications were eventually included in the NMA (Figure 1). For moderate-to-severe AD, these nine studies included 4261 patients who were given either a placebo or one of the following JAKi: ivarmacitinib 4 mg or 8 mg, baricitinib 2 mg or 4 mg once a day (QD), upadacitinib 15 mg or 30 mg QD, or abrocitinib 100 mg QD or 200 mg QD [21–25, 27, 28]. All nine studies were double-blind, randomized, placebo-controlled clinical trials, published between 2019 and 2025. One study was a phase 2 trial [27], while the remaining eight were phase 3 trials. Three studies had 12-week placebo-controlled outcomes duration, each evaluating abrocitinib 100 mg QD and 200 mg QD [25, 27, 28]. The remaining six studies, which evaluated upadacitinib, baricitinib and ivarmacitinib [21–24] had a 16-week placebo-controlled outcomes duration (Table S3). All studies involving baricitinib included a 1 mg dose, approved only for patients with moderate renal impairment or those receiving organic anion transporter-3 (OAT3) inhibitors such as probenecid, requiring a 50% dose reduction; this dose was excluded. No abrocitinib trials evaluated the 50 mg dose, which is approved only for moderate renal impairment, poor CYP2C19 metabolizers, or concomitant strong CYP2C19 inhibitors. The pooled population had a balanced sex distribution (33.3%–62.5% female), mean age 29.9–44.3 years, and racially diverse representation. Baseline EASI scores (24.6–35) and IGA-AD scores (44–55.3) reflected moderate-to-severe disease, with mean disease duration 9.9–30.2 years (Table 1).

3.2 | Feasibility Assessment, Network Fit, and Risk of Bias

BNMAs were feasible for all selected efficacy outcomes. The availability of reported endpoints across the included RCTs determined the network structure (Figure S1). All studies provided data for all three outcomes: EASI-75, IGA (or IGA-AD), and pruritus/itch NRS. All nine included studies contributed data for these endpoints. Risk of bias assessment revealed limited concerns overall. Five studies [21, 22, 24] were rated as having "some concerns", one study [23] was assessed as "high risk", and the remaining three [25, 27, 28] were judged to have "low risk" of bias. Every trial included full data and used appropriate blinding, allocation concealment, and randomization techniques (Figure S2).

3.3 | Efficacy Endpoints

Upadacitinib 30 mg demonstrated the highest efficacy at the 16-week endpoint, achieving EASI-75 response rates of 72.9%–79.7% (95% CI: 54.4–84.4) compared with 13.3%–16.3% for placebo ($p < 0.0001$). IGA-AD 0/1 responses (clear or almost clear skin) were seen in 52%–62% of patients versus 4.7%–8.4% with placebo ($p < 0.0001$), while ≥4-point Itch NRS improvement occurred in ~60% versus 9.1%–11.8% of placebo ($p < 0.0001$), confirming a strong treatment effect. Abrocitinib 200 mg at Week 12 yielded EASI-75 in 61%–64.6% versus 10.4%–15.4% with placebo ($p \leq 0.01$), IGA-AD 0/1 in 38.1%–44% versus 5.8%–9.1% ($p < 0.0001$), and Itch NRS improvement in 55.3%–63.6% versus 11.5%–25.5% ($p < 0.0001$). For ivarmacitinib, 4 mg and 8 mg achieved EASI-75 rates of 54% and 66.1% compared with 21.6% for placebo ($p < 0.001$); IGA-AD 0/1 rates were 36.3% and 42% versus 9%, and Itch NRS improvement 37.2% and 40.2% versus 12.6% ($p < 0.001$). Baricitinib 4 mg showed modest efficacy with EASI-75 rates of 21.1%–24.8% versus 6.1%–8.8% for placebo ($p \leq 0.001$). IGA-AD 0/1 and Itch NRS responses were 13.8%–16.8% and 18.7%–21.5%, respectively, lower than selective JAK1 inhibitors (Table 2). Overall, efficacy was dose-dependent, with upadacitinib 30 mg ranking highest, followed by upadacitinib 15 mg, abrocitinib 200 mg, and ivarmacitinib 8 mg, while baricitinib remained least effective [19, 31, 66–70].

3.4 | Bayesian Network Meta-Analysis

The BNMA evaluated the comparative efficacy of four oral JAK inhibitors, upadacitinib, abrocitinib, ivarmacitinib, and

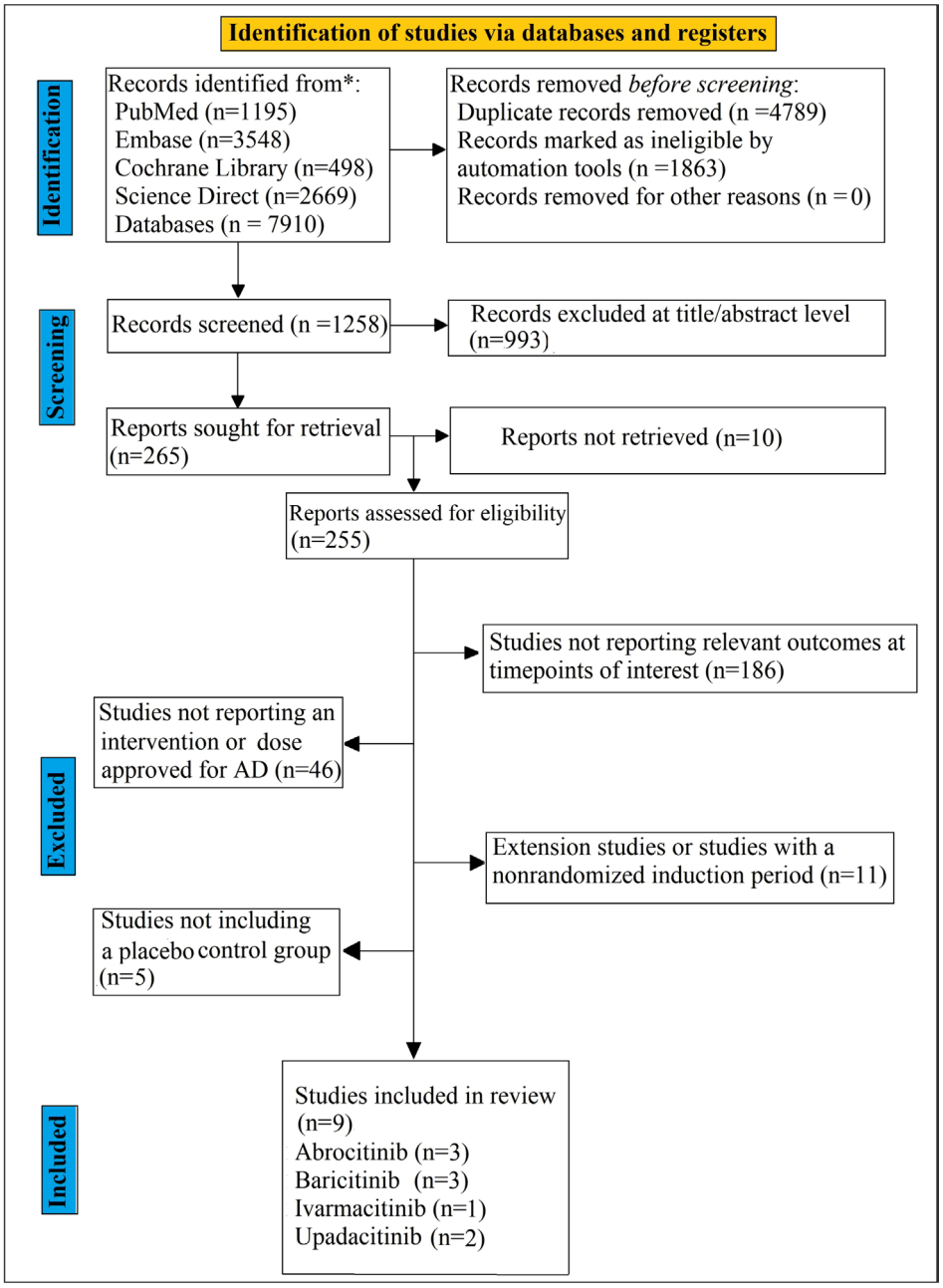

FIGURE 1 | PRISMA flow diagram.

baricitinib, across three key outcomes: EASI-75, IGA-AD 0/1, and a ≥4- Itch NRS. Upadacitinib 30 mg consistently demonstrated the highest efficacy across all outcomes.

For the EASI-75 response, upadacitinib 30 mg achieved an OR of 12.3 (95% CrI, 7.9–18.7), followed by upadacitinib 15 mg (OR = 12.0 [7.5–18.9]) and abrocitinib 200 mg (OR = 10.7 [6.1–17.3]). Ivarmacitinib 8 mg (OR = 7.1 [4.1–12.5]) and 4 mg (OR = 5.4 [3.0–9.6]) also showed significant efficacy, while baricitinib 4 mg (OR = 1.6 [1.1–2.5]) and 2 mg (OR = 2.1 [1.3–3.4]) ranked lowest.

For the IGA-AD 0/1 endpoint, which reflects achievement of clear or almost clear skin, upadacitinib 30 mg again ranked highest (OR = 18.9 [12.0–29.7]), followed by upadacitinib 15 mg (OR = 12.1 [7.6–19.8]), abrocitinib 200 mg (OR = 9.0 [5.4–14.7]), and ivarmacitinib 8 mg (OR = 6.8 [3.9–12.0]). Baricitinib 4 mg (OR = 2.0 [1.2–3.2]) and 2 mg (OR = 1.6 [1.0–2.7]) again demonstrated modest efficacy.

For ≥4-point improvement in Itch NRS, which captures patient-reported relief from pruritus, upadacitinib 30 mg remained superior (OR = 11.1 [7.2–17.5]), followed by upadacitinib 15 mg (OR = 8.7 [5.3–14.2]) and ivarmacitinib 8 mg (OR = 9.4 [5.6–15.7]). Abrocitinib 200 mg (OR = 8.0 [4.7–13.5]) and baricitinib 4 mg (OR = 2.2 [1.3–3.6]) showed intermediate responses, while baricitinib 2 mg (OR = 1.8 [1.0–3.2]) again ranked lowest.

Across all endpoints, upadacitinib 30 mg consistently achieved the highest odds of clinical improvement, confirming its superior efficacy relative to other JAK inhibitors included in the

TABLE 1 | Baseline demographic and clinical characteristics of patients across included randomized controlled trials of oral JAK inhibitors for moderate-to-severe atopic dermatitis.

Trial	Drugs/dose	Endpoint	Trial size (*n*)	Age, mean (±SD), years	Female, *n* (%)	Race, *N* (%)	Baseline EASI, mean (SD)	Baseline severe IGA-AD score	Disease duration, mean (SD), years
Measure Up 1 [22] (NCT03569293)	Upadacitinib 15 mg	16 weeks	281	42 (15)	124 (44)	W: 182 (65), B: 26 (9), A: 63 (22), AI/AN: 0, NH/PI: 1 (< 1), M: 9 (3)	30.6 (12.8)	127 (45.2)	20.4 (14.3)
	Upadacitinib 30 mg		285	42 (15)	130 (46)	W: 191 (67), B: 8 (3), A: 71 (25), AI/AN: 3 (1), NH/PI: 1 (< 1), M: 14 (5)	29.0 (11.1)	131 (46.0)	21.3 (15.3)
	Placebo		281	40 (14)	137 (49)	W: 182 (65), B: 21 (7), A: 69 (25), AI/AN: 3 (1), NH/PI: 1 (< 1), M: 5 (2)	28.8 (12.6)	125 (44.5)	20.5 (15.9)
Measure Up 2 [22] (NCT03607422)	Upadacitinib 15 mg	16 weeks	276	33 (12)	121 (44)	W: 184 (67), B: 17 (6), A: 65 (24), AI/AN: 5 (2), NH/PI: 2 (1), M: 3 (1)	28.6 (11.7)	150 (54.3)	18.8 (13.3)
	Upadacitinib 30 mg		282	35 (12)	120 (43)	W: 198 (70), B: 18 (6), A: 62 (22), AI/AN: 2 (1), NH/PI: 0, M: 2 (1)	29.7 (12.2)	156 (55.3)	20.8 (14.3)
	Placebo		278	36 (13)	124 (45)	W: 195 (70), B: 16 (6), A: 56 (20), AI/AN: 5 (2), NH/PI: 1 (< 1), M: 5 (2)	29.1 (12.1)	153 (55.0)	21.1 (13.6)
JADE MONO-2 [28] (NCT03575871)	Abrocitinib 100 mg	12 weeks	158	37.4 (15.8)	67 (43.2)	W: 101 (63.9), B: 9 (5.7), A: 46 (29.1), M: 1 (0.6), NR: 1 (0.6)	28.4 (11.2)	51 (32.3)	21.1 (14.8)
	Abrocitinib 200 mg		155	33.5 (14.7)	64 (40.5)	W: 91 (58.7), B: 6 (3.9), A: 54 (34.8), M: 2 (1.3), NR: 2 (1.3)	29.0 (12.4)	49 (31.6)	20.5 (14.8)
	Placebo		78	33.4 (13.8)	31 (39.7)	W: 40 (51.3), B: 6 (7.7), A: 29 (37.2), M: 1 (1.3), NR: 2 (2.6)	28.0 (10.2)	26 (33.3)	21.7 (14.3)

(Continues)

TABLE 1 | (Continued)

Trial	Drugs/dose	Endpoint	Trial size (*n*)	Age, mean (±SD), years	Female, *n* (%)	Race, *N* (%)	Baseline EASI, mean (SD)	Baseline severe IGA-AD score	Disease duration, mean (SD), years
JADE MONO-1 [25] (NCT03349060)	Abrocitinib 100 mg	12 weeks	156	32.6 (15.4)	66 (42)	W: 113 (72), B: 15 (10), A: 26 (17), O: 2 (1)	31.3 (13.6)	64 (41)	24.9 (16.1)
	Abrocitinib 200 mg		154	33.0 (17.4)	73 (47)	W: 104 (68), B: 21 (14), A: 26 (17), O: 3 (2)	30.6 (14.1)	63 (41)	22.7 (14.5)
	Placebo		77	31.5 (14.4)	28 (36)	W: 62 (81), B: 6 (8), A: 6 (8), O: 2 (3)	28.7 (12.5)	31 (40)	22.5 (14.4)
Phase 2 Trial [27] (NCT02780167)	Abrocitinib 100 mg	12 weeks	56	41.1 (15.6)	25 (44.6)	W: 40 (71.4), B: 7 (12.5), A: 8 (14.3), O: 1 (1.8)	26.7 (11.8)	26 (47.3)	23.8
	Abrocitinib 200 mg		55	38.7 (17.6)	27 (49.1)	W: 37 (67.3), B: 13 (23.6), A: 5 (9.1), O: 0	24.6 (13.5)	20 (37.0)	19.6
	Placebo		56	42.6 (15.1)	35 (62.5)	W: 40 (71.4), B: 10 (17.9), A: 4 (7.1), O: 2 (3.6)	25.4 (12.9)	21 (38.2)	25.6
Phase 3 Trial [24] (NCT04875169)	Ivarmacitinib 4 mg	16 weeks	113	31.9 (16.0)	42 (37.2)	W: 10 (8.9), B: 1 (0.9), A: 96 (85.7), O: 5 (4.5)	29.5 (11.3)	49 (43.4)	9.9 (11.5)
	Ivarmacitinib 8 mg		112	31.4 (15.5)	39 (34.8)	W: 11 (9.7), B: 0, A: 95 (84.1), O: 7 (6.2)	29.8 (12.4)	46 (41.1)	12.5 (10.7)
	Placebo		111	29.9 (14.9)	42 (37.8)	W: 14 (12.6), B: 1 (0.9), A: 95 (85.6), O: 1 (0.9)	27.6 (10.6)	46 (41.4)	11.3 (11.8)
BREEZE-AD1 [21] (NCT03334396)	Baricitinib 1 mg	16 weeks	127	36 (12.4)	49 (38.6)	W: 74 (58.3), A: 40 (31.5)	29 (11.8)	53 (41.7)	27 (14.9)
	Baricitinib 2 mg		123	35 (13.7)	41 (33.3)	W: 75 (61.0), A: 35 (28.5)	31 (11.7)	52 (42.3)	25 (14.6)
	Baricitinib 4 mg		125	37 (12.9)	42 (33.6)	W: 70 (56.5), A: 41 (33.1)	32 (12.7)	51 (40.8)	25 (14.9)
	Placebo		249	35 (12.6)	101 (40.6)	W: 147 (59.5), A: 73 (29.6)	32 (13.0)	105 (42.2)	26 (15.5)
BREEZE-AD2 [21] (NCT03334422)	Baricitinib 1 mg	16 weeks	125	33 (10.0)	45 (36.0)	W: 85 (68.0), A: 36 (28.8)	33 (12.7)	63 (50.8)	24 (12.7)
	Baricitinib 2 mg		123	36 (13.2)	58 (47.2)	W: 85 (69.1), A: 37 (30.1)	35 (16.0)	62 (50.4)	24 (13.8)
	Baricitinib 4 mg		123	34 (14.1)	41 (33.3)	W: 82 (66.7), A: 38 (30.9)	33 (12.7)	63 (51.2)	23 (14.8)
	Placebo		224	35 (13.0)	90 (36.9)	W: 169 (69.3), A: 72 (29.5)	33 (12.8)	121 (49.6)	25 (13.9)

(Continues)

TABLE 1 | (Continued)

Trial	Drugs/dose	Endpoint	Trial size (*n*)	Age, mean (±SD), years	Female, *n* (%)	Race, *N* (%)	Baseline EASI, mean (SD)	Baseline severe IGA-AD score	Disease duration, mean (SD), years
BREEZE-AD5 [23] (NCT03435081)	Baricitinib 1 mg	16 weeks	146	40 (17)	72 (49)	W: 86 (59), A: 26 (18), AA: 26 (18), O: 8 (5)	27.7 (12)	62 (42)	24 (17)
	Baricitinib 2 mg		147	40 (15)	77 (53)	W: 85 (58), A: 22 (15), AA: 30 (21), O: 9 (6)	26.6 (11)	61 (42)	24 (16)
	Placebo		147	39 (17)	67 (46)	W: 80 (55), A: 24 (16), AA: 33 (23), O: 9 (6)	27.0 (11)	61 (41)	23 (17)

Abbreviations: A, Asian; AA, African American; AI/AN, American Indian or Alaska Native; BID, twice daily; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NH/PI, Native Hawaiian or Pacific Islander; QD, once daily; SD, standard deviation; W, White.

network. Baricitinib 2 mg and 4 mg demonstrated the least efficacy, reinforcing the comparative advantage of JAK1 inhibitors in moderate-to-severe AD (Figure 2).

3.5 | SUCRA Probability Analyses

The SUCRA heatmap and bar chart present the comparative rankings of relative efficacy for all treatments under analysis across three endpoints most relevant: EASI-75, IGA-AD 0/1, and a ≥4- Itch NRS by BNMA. Upadacitinib 30 mg was ranked highest consistently with SUCRA probabilities of 97%, 98%, and 97% across the respective endpoints. This was succeeded by upadacitinib 15 mg (93%–92%) and abrocitinib 200 mg (87%–86%), confirming their overall better performance.

Ivarmacitinib 8 mg also performed very well (82% to 89%), while intermediate-dose regimens such as abrocitinib 100 mg and ivarmacitinib 4 mg performed moderately (55%–70%). On the other hand, baricitinib 4 mg and 2 mg had the lowest SUCRA probabilities (16%–28%), with the lowest probability of being the most effective treatment at all endpoints. These rankings emphasize the reproducible therapeutic value of JAK1 inhibitors, and greater efficacy of upadacitinib 30 mg in skin clearance and the relief of pruritus in moderate-to-severe AD patients (Figure 3; Figure S3).

3.6 | Sensitivity and Meta-Regression Analyses

Sensitivity analyses and meta-regression confirmed the robustness of BNMA findings by comparing unadjusted and covariate-adjusted models for EASI-75, IGA-AD 0/1, and Itch NRS ≥4 improvement. For EASI-75, baseline EASI or IGA 4 adjustment modestly improved fit (DIC 418.2 → 415.4/416.1) and reduced variance (τ^2 0.081 → 0.074–0.076) with < 3% ΔSUCRA change. For IGA-AD 0/1, baseline IGA 4 adjustment improved fit (392.7 → 390.5), reduced τ^2 (0.069 → 0.065), and caused < 4% rank reordering. For Itch NRS, baseline EASI adjustment improved DIC (405.9 → 403.3), reduced τ^2 (0.084 → 0.078), and maintained hierarchy (< 5% ΔSUCRA). Rankings and convergence remained stable, confirming upadacitinib 30 mg as the top-performing treatment (Table S4). In the sensitivity analysis excluding all Week-12 abrocitinib trials, the treatment hierarchy remained essentially unchanged across EASI-75, IGA-AD 0/1, and Itch NRS ≥4 endpoints. Upadacitinib 30 mg remained the highest-ranked regimen, followed by upadacitinib 15 mg and ivarmacitinib 8 mg, whereas baricitinib 2 mg and 4 mg continued to rank lowest. Effect estimates and SUCRA values were similar in magnitude to the primary analysis (Figure S4), indicating that pooling Week-12 and Week-16 endpoints did not materially influence the BNMA conclusions.

4 | Discussion

This BNMA synthesized evidence from nine RCTs involving 4261 patients receiving one of four oral JAK inhibitors—upadacitinib, abrocitinib, ivarmacitinib, or baricitinib—or matching placebo to evaluate their efficacy for the management of moderate-to-severe AD. Upadacitinib 30 mg once daily consistently showed the best efficacy across all primary endpoints,

TABLE 2 | Primary efficacy outcomes from randomized controlled trials of oral JAK inhibitors for moderate-to-severe atopic dermatitis at Week 12 or 16.

Trial	Drugs/dose	EASI-75 responders, *n* (%; 95% CI)	Placebo % adjusted (95% CI)	IGA-AD responders, *n* (%; 95% CI)	Placebo % adjusted (95% CI)	Itch NRS ≥ 4 responders (%; 95% CI)	Placebo % adjusted (95% CI)
Measure Up 1 [22] (NCT03569293)	Upadacitinib 15 mg	196 (69.6; 64.2–75.0)	53.3 (46.4–60.2); $p < 0.0001$	135 (48.1; 42.3–54.0)	39.8 (33.2–46.4); $p < 0.0001$	52.2 (46.3–58.1)	40.5 (33.5–47.5); $p < 0.0001$
	Upadacitinib 30 mg	227 (79.7; 75.0–84.4)	63.4 (57.1–69.8); $p < 0.0001$	177 (62.0; 56.4–67.7)	53.6 (47.2–60.0); $p < 0.0001$	60.0 (54.3–65.7)	48.2 (41.3–55.0); $p < 0.0001$
	Placebo	46 (16.3; 12.0–20.7)		24 (8.4; 5.2–11.7)		11.8 (7.9–15.6)	
Measure Up 2 [22] (NCT03607422)	Upadacitinib 15 mg	166 (60.1; 54.4–65.9)	46.9 (39.9–53.9); $p < 0.0001$	107 (38.8; 33.0–44.5)	34.0 (27.8–40.2); $p < 0.0001$	41.9 (36.0–47.7)	32.6 (25.8–39.4); $p < 0.0001$
	Upadacitinib 30 mg	206 (72.9; 67.7–78.2)	59.6 (53.1–66.2); $p < 0.0001$	147 (52.0; 46.1–57.9)	47.4 (41.0–53.7); $p < 0.0001$	59.6 (53.9–65.4)	50.4 (43.8–57.1); $p < 0.0001$
	Placebo	37 (13.3; 9.3–17.3)		13 (4.7; 2.2–7.2)		9.1 (5.7–12.5)	
JADE MONO-2 [28] (NCT03575871)	Abrocitinib 100 mg	69 (44.5)	33.9 (23.3–44.4); $P < 0.001$	44 (28.4)	19.3 (9.6–29.0); $p < 0.001$	45.2 (37.1–53.3)	33.7 (33–34.3); $p < 0.0001$
	Abrocitinib 200 mg	94 (61)	50.5 (40.0–60.9); $p < 0.001$	59 (38.1)	28.7 (18.6–38.8); $p < 0.001$	55.3 (47.2–63.5)	43.8 (43.1–44.5); $p < 0.0001$
	Placebo	8 (10.4)		7 (9.1)		11.5 (4.1–19.0)	
JADE MONO-1 [25] (NCT03349060)	Abrocitinib 100 mg	62 (40)	27.9 (17.4–38.3); $p < 0.0001$	37 (24)	15.8 (6.8–24.8); $p = 0.0037$	55 (38)	22.5 (10.3–34.8); $p = 0.0003$
	Abrocitinib 200 mg	96 (63)	51.0 (40.5–61.5); $p < 0.0001$	67 (44)	36.0 (26.2–45.7); $p < 0.0001$	84 (57)	41.7 (29.6–53.9); $p < 0.0001$
	Placebo	9 (12)		6 (8)		11 (15)	
Phase 2 Trial [27] (NCT02780167)	Abrocitinib 100 mg	22 (40.7)	25.3 (1.77–8.41); $p \leq 0.01$	16 (29.6; 17.5–41.8)	—	25 (50.0)	2.84 (1.40–5.76); $p < 0.0001$
	Abrocitinib 200 mg	31 (64.6)	49.2 (4.26–21.19); $p \leq 0.01$	21 (43.8; 29.7–57.8)	—	28 (63.6)	38.1 (2.43–10.77); $p < 0.0001$
	Placebo	8 (15.4)		3 (5.8; 0.0–12.1)		13 (25.5)	

(Continues)

TABLE 2 | (Continued)

Trial	Drugs/dose	EASI-75 responders, *n* (%; 95% CI)	Placebo % adjusted (95% CI)	IGA-AD responders, *n* (%; 95% CI)	Placebo % adjusted (95% CI)	Itch NRS ≥ 4 responders (%; 95% CI)	Placebo % adjusted (95% CI)
Phase 3 Trial [24] (NCT04875169)	Ivarmacitinib 4 mg	61 (54.0; 44.4–63.4)	30.5 (18.8–42.1); $p \leq 0.01$	41 (36.3; 27.5–45.9)	27.5 (17.2–37.8)	42 (37.2; 28.3–46.8)	24.6 (13.8–35.4); $p < 0.0001$
	Ivarmacitinib 8 mg	74 (66.1; 56.5–74.8)	43.2 (32.6–53.8); $p \leq 0.01$	47 (42.0; 32.7–51.7)	32.1 (22.1–42.2)	45 (40.2; 31.0–49.9)	26.6 (15.9–37.3); $p < 0.0001$
	Placebo	24 (21.6; 14.4–30.4)		10 (9.0; 4.4–15.9)		14 (12.6; 7.1–20.3)	
BREEZE-AD1 [21] (NCT03334396)	Baricitinib 1 mg	22 (17.3)	−8.5; $p \leq 0.01$	15 (11.8)	(7); $p \leq 0.05$	13 (10.5)	(3.3); $p \leq 0.05$
	Baricitinib 2 mg	23 (18.7)	−9.9; $p \leq 0.01$	14 (11.4)	(6.6); $p \leq 0.05$	15 (12)	(4.8); $p \leq 0.05$
	Baricitinib 4 mg	31 (24.8)	−16; $p \leq 0.001$	21 (16.8)	(12); $p \leq 0.001$	27 (21.5)	(14.3); $p \leq 0.001$
	Placebo	22 (8.8)		12 (4.8)		18 (7.2)	
BREEZE-AD2 [21] (NCT03334422)	Baricitinib 1 mg	16 (12.8)	−6.7; $p \leq 0.01$	11 (8.8)	(4.3); $p \leq 0.05$	8 (6)	(1.3); $p \leq 0.05$
	Baricitinib 2 mg	22 (17.9)	−11.8; $p \leq 0.01$	13 (10.6)	(6.1); $p \leq 0.05$	19 (15.1)	(10.4); $p \leq 0.05$
	Baricitinib 4 mg	26 (21.1)	−15; $p \leq 0.001$	17 (13.8)	(9.3); $p \leq 0.001$	23 (18.7)	(14); $p \leq 0.001$
	Placebo	14 (6.1)		10 (4.5)		11 (4.7)	
BREEZE-AD5 [23] (NCT03435081)	Baricitinib 1 mg	19 (13)	−5; $p \leq 0.01$	19 (13)	(08); $p \leq 0.001$	(23) 16	(10); $p \leq 0.001$
	Baricitinib 2 mg	44 (30)	−22; $p \leq 0.001$	35 (24)	(19); $p \leq 0.001$	(37) 25	(19); $p \leq 0.001$
	Placebo	12 (8)		7 (5)		(09) 6	

Abbreviations: AD, atopic dermatitis; BID, twice daily; CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IGA-AD, Investigator's Global Assessment for Atopic Dermatitis; JAK, Janus kinase; NRS, Numerical Rating Scale; QD, once daily; SD, standard deviation.

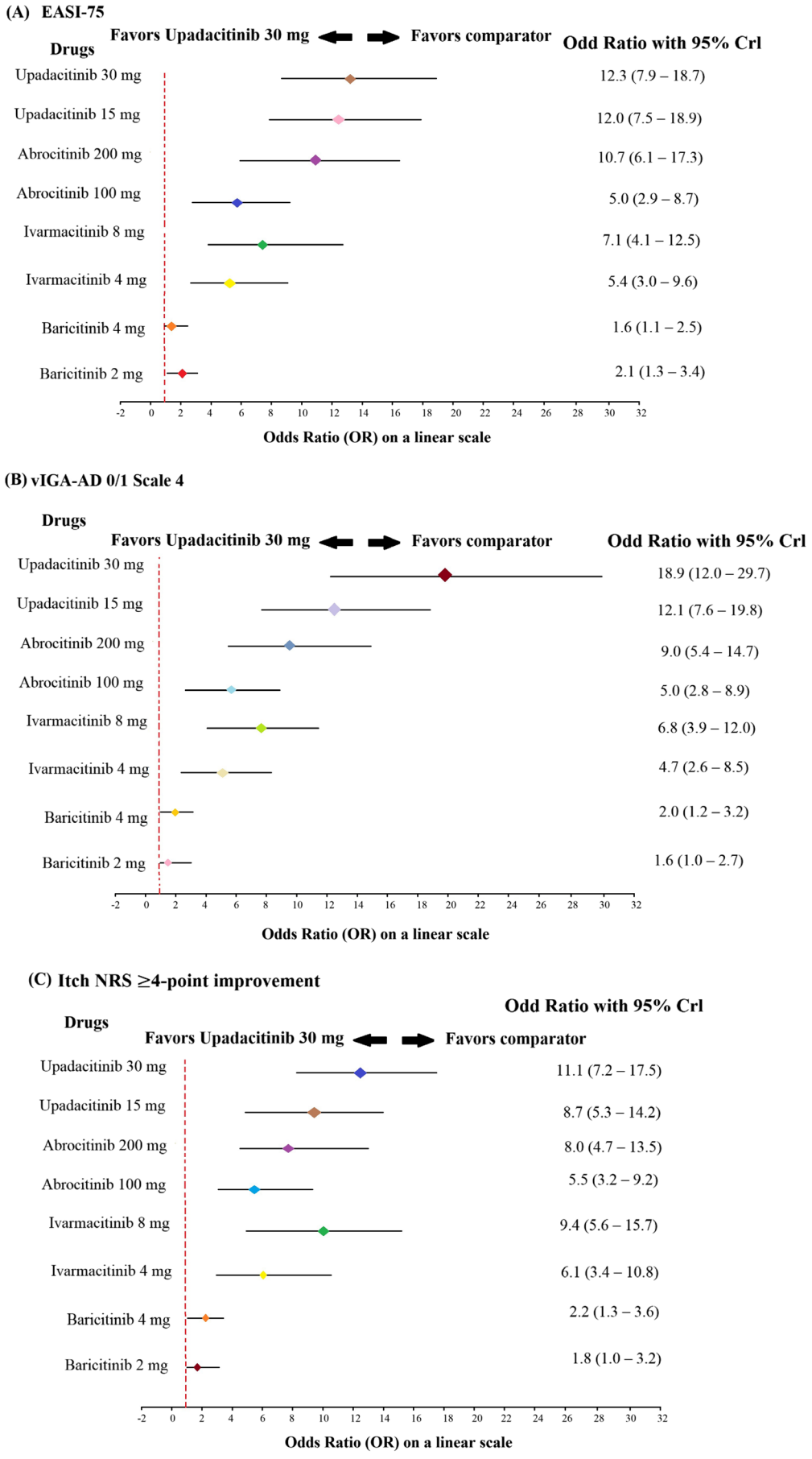

FIGURE 2 | Legend on next page.

FIGURE 2 | Bayesian network meta-analysis forest plots for primary efficacy outcomes. Forest plots displaying pooled odds ratios (ORs) with 95% credible intervals (CrI) for (A) EASI-75 response, (B) IGA-AD 0/1 response, and (C) Itch NRS ≥4-point improvement at 12–16 weeks. Upadacitinib 30 mg demonstrated the highest efficacy across all endpoints, followed by upadacitinib 15 mg and abrocitinib 200 mg, compared to placebo.

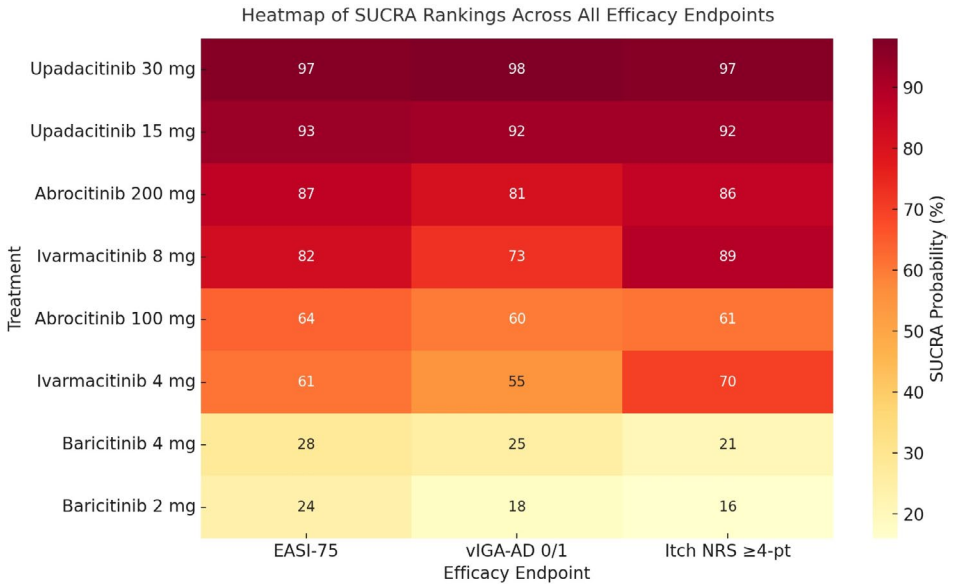

FIGURE 3 | Heatmap of SUCRA rankings across all efficacy endpoints. Surface under the cumulative ranking curve area (SUCRA) heatmap summarizing the probability of each treatment being the most effective across efficacy endpoints (EASI-75, IGA-AD 0/1, and Itch NRS ≥4-point improvement). Upadacitinib 30 mg consistently ranked highest, followed by upadacitinib 15 mg and abrocitinib 200 mg.

including EASI-75, IGA-AD 0/1, and ≥4-point improvement in Itch NRS. Upadacitinib 15 mg and abrocitinib 200 mg were next in line. These findings affirm the superior performance of upadacitinib in achieving both skin clearance and pruritus reduction. SUCRA probabilities (97%–98%) and robust pooled odds ratios (EASI-75 OR = 12.3; 95% CrI: 7.9–18.7) further support upadacitinib 30 mg as the most likely optimal treatment across evaluated endpoints.

Abrocitinib 200 mg achieved efficacy comparable to upadacitinib 15 mg, with a clear dose–response advantage over abrocitinib 100 mg. These findings are consistent with pivotal JADE MONO-1 and JADE MONO-2 trials and align with current United States Food and Drug Administration (FDA) labeling [12, 13, 25, 28]. Ivarmacitinib 8 mg, a newly approved oral JAK1 inhibitor in China (2025) indicated for AD, ankylosing spondylitis, rheumatoid arthritis, and severe alopecia areata, yielded effect sizes similar to abrocitinib 200 mg and consistently outperformed baricitinib 4 mg across all evaluated endpoints [16, 24].

Sensitivity and meta-regression analyses confirmed the robustness of these findings. Adjustments for baseline disease severity, specifically EASI scores and IGA 4, modestly improved model fit (ΔDIC ≈2–3) and reduced heterogeneity ($\Delta\tau^2$ ≈0.006–0.008), without materially altering treatment ranking (< 5% SUCRA shift). This suggests that between-study variation exerted minimal confounding influence.

Upadacitinib, abrocitinib, ivarmacitinib, and baricitinib were selected for their clinical relevance and regulatory significance in managing moderate-to-severe AD. Upadacitinib is approved for moderate-to-severe AD in the United States (US), Canada, the United Kingdom (UK), the European Union (EU), and Japan. Abrocitinib holds approvals in all of the above regions, as well as in China. Ivarmacitinib received National Medical Products Administration (NMPA) approval in China in 2025 for AD. Baricitinib, although not indicated for AD in the US or China, is approved in both markets for alopecia areata and rheumatoid arthritis and has been extensively evaluated in phase 3 AD trials. It is also approved for AD in the UK, EU, and Japan. Despite the demonstrated efficacy of all four JAK inhibitors, safety data from RCTs, real-world studies, pooled safety analyses, and FDA Adverse Event Reporting System (FAERS) highlight the need for continued vigilance, particularly for serious infections, mortality, MACE, and thrombosis [12–14]. As a result, all major regulatory authorities, including the FDA (US), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA, UK), the NMPA (China), and the Pharmaceutical and Medical Devices Agency (PMDA, Japan), recommend reserving oral JAK inhibitors for patients with moderate-to-severe AD who have had an inadequate response, intolerance, or contraindication to biologic therapy (e.g., dupilumab or tralokinumab) [16, 71–74].

In addition, biologic agents represent the first-line systemic therapy for moderate-to-severe AD; however, they were intentionally excluded from this network to preserve methodological consistency and maintain a homogeneous JAK-inhibitor monotherapy evidence network.

Although upadacitinib 30 mg demonstrated the highest short-term efficacy in this analysis, followed by upadacitinib 15 mg, it is important to note that 15 mg is the starting dose, with 30 mg for patients between the age of 12 and 64 with an inadequate response to the lower dose.

A major strength of this NMA is its exclusive use of phase 2 and phase 3, placebo-controlled monotherapy trials, minimizing bias from combination regimens and ensuring treatment homogeneity.

The Bayesian hierarchical modeling, supplemented by sensitivity and meta-regression adjustments, yielded stable and precise comparative estimates with strong convergence diagnostics [75, 76]. Earlier NMA in AD have primarily focused on biologic therapies, while prior NMAs of oral JAK inhibitors have either excluded data on certain agents or incorporated findings from non-randomized studies, heterogeneous pharmacologic classes, combination regimens, and doses that were clinically ineffective or not approved for any immune-mediated or inflammatory disease in major regulatory markets [42–47]. The available phase 2 and 3 monotherapy data for baricitinib, abrocitinib, upadacitinib, and ivarmacitinib are being included for the first time in this NMA. Notably, pivotal study data on ivarmacitinib has not been included in prior NMAs assessing JAK inhibitors and biologics as monotherapies for AD [16, 19, 24, 44, 70]. The treatment networks only contained approved doses to guarantee clinical relevance and policy application. Multinational research from North America, Asia, Europe, South America, and Oceania made up the majority of the included studies. Collectively, these strengths reinforce the internal validity of the NMA and support the generalizability of its conclusions across diverse clinical settings and geographic regions.

Several mechanistic factors may explain the differential efficacy observed among JAK inhibitors. In AD, JAK1-selective inhibitors (upadacitinib, abrocitinib, ivarmacitinib) primarily suppress Th2 cytokines such as IL-4, IL-13, and IL-31, accounting for their rapid effects on itch relief and skin improvement [77–79]. Baricitinib, with dual JAK1/JAK2 activity, exerts broader immunomodulatory effects but with less selectivity, which may influence both efficacy and safety. More generally, higher efficacy with JAK inhibitors and higher doses has been associated with increased toxicity, including a greater risk of herpes zoster [30, 80]. Finally, selectivity is relative: each agent inhibits all three JAK isoforms to some degree. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness and safety is not fully understood [12–14].

While methodologically rigorous, this analysis has limitations. First, the absence of head-to-head trials among upadacitinib, abrocitinib, baricitinib, and ivarmacitinib confines rankings to indirect, placebo-controlled comparisons. However, common placebo arms enabled a robust evidence network. Second, heterogeneity in baseline measures (EASI-75, IGA-AD 0/1, Itch NRS, ethnicity) may have influenced effect sizes, though sensitivity and meta-regression analyses yielded only marginal precision gains without altering treatment hierarchy. Third, abrocitinib trials reported outcomes at Week 12, whereas others used 16-week endpoints; however, Bieber et al. demonstrated comparable placebo-adjusted EASI-75 and IGA responses at both timepoints, mitigating temporal bias [81]. Fourth, assessment of publication bias was not feasible due to the small number of included studies per outcome. Funnel plot asymmetry tests and related quantitative methods require a larger dataset to yield reliable conclusions; therefore, potential publication bias cannot be ruled out. Fifth, as only short-term efficacy was evaluated, results may not reflect long-term durability, safety, and tolerability. Sixth, quality-of-life (QoL) outcomes were not included in this network because QoL instruments, timepoints, and reporting formats varied substantially across trials, preventing the construction of a consistent and connected evidence network. Future studies incorporating harmonized QoL endpoints are needed to provide a more holistic comparison of patient-reported outcomes across JAK inhibitors.

Finally, since this BNMA exclusively evaluated monotherapy, the findings primarily reflect short-term efficacy of JAK inhibitors when used alone. In clinical practice, JAK inhibitors are frequently administered in combination with topical therapies, which may produce different response patterns. Therefore, the comparative rankings reported here should be interpreted with caution, and future studies directly evaluating combination regimens are needed.

5 | Conclusion

This Bayesian network meta-analysis (BNMA) presents an absolute hierarchy of efficacy among the JAK inhibitors upadacitinib, abrocitinib, baricitinib, and ivarmacitinib in moderate-to-severe AD. Across different analytic models, such as BNMA, SUCRA probability rankings, sensitivity and meta-regression analyses, upadacitinib 30 mg most reliably demonstrated the superior short-term efficacy by EASI-75, IGA-AD 0/1, and a ≥4-point Itch NRS improvement. With the limitations of indirect comparison and short follow-up, this research addresses a significant gap in comparative effectiveness data for JAK inhibitors and provides timely, clinically relevant findings to guide evidence-based decision-making in moderate-to-severe AD. Future studies need to prioritize long-term outcomes and direct head-to-head comparisons to follow up on these findings.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Upon reasonable request, including a clearly defined research question with valid scientific rationale and, where applicable, a robust statistical analysis plan, and subject to a Data Use Agreement, the lead author will provide additional data that support the findings of this report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Network geometry of included interventions. Network plot illustrating the evidence structure among randomized controlled trials comparing oral JAK inhibitors for moderate-to-severe atopic dermatitis. Each node represents an intervention (drug and dose), with node size proportional to the number of participants. The number of trials included in each comparison is indicated by the thickness of the connecting lines, which show direct head-to-head comparisons between therapies. **Figure S2:** Risk of bias assessment of included studies. Summary of risk of bias evaluation using the Cochrane Risk of Bias Tool (RoB 2) for all included randomized controlled trials. Most studies demonstrated low risk across all domains, with minor concerns related to allocation concealment and blinding in a few trials. **Figure S3:** 95% confidence interval (CrIs) for reaching efficacy endpoints for all JAK inhibitors. A baseline-risk adjusted RE model was used to calculate the probability (95% CrI) of obtaining an EASI-75 response, validate the Investigator's Global Assessment of 0/1 (vIGA-AD 0/1) and ≥4-point improvement in the Itch Numerical Rating Scale (NRS) at Week 12/16, as well as the related 95% CrIs. The primary endpoint timepoint (Week 12 for abrocitinib and Week 16 for all other treatments) was used to measure outcomes for each trial. **Figure S4:** Ranking heatmaps for comparative efficacy across three primary outcomes after removal of all 12 week abrocitinib trials. Heatmaps display the network meta-analytic odds ratios (ORs) comparing each active JAK inhibitor dose against all others for: (A) EASI-75, (B) vIGA-AD response, and (C) Itch NRS ≥4-point improvement. Each cell represents the OR for the row treatment versus the column treatment, with color intensity reflecting effect magnitude. Values greater than 1 favor the row treatment, while values less than 1 favor the column comparator. **Table S1:** Search string across various databases. **Table S2:** Baseline disease-severity entry criteria across pivotal randomized trials in moderate-to-severe atopic dermatitis. **Table S3:** Summary of randomized controlled trials evaluating oral Janus kinase (JAK) inhibitors in patients with moderate-to-severe atopic dermatitis. **Table S4:** Sensitivity and meta-regression analyses comparing model fit, heterogeneity, and ranking stability across covariate-adjusted Bayesian network models.