# Comparative safety of oral Janus kinase inhibitors versus dupilumab in patients with atopic dermatitis: A population-based cohort study



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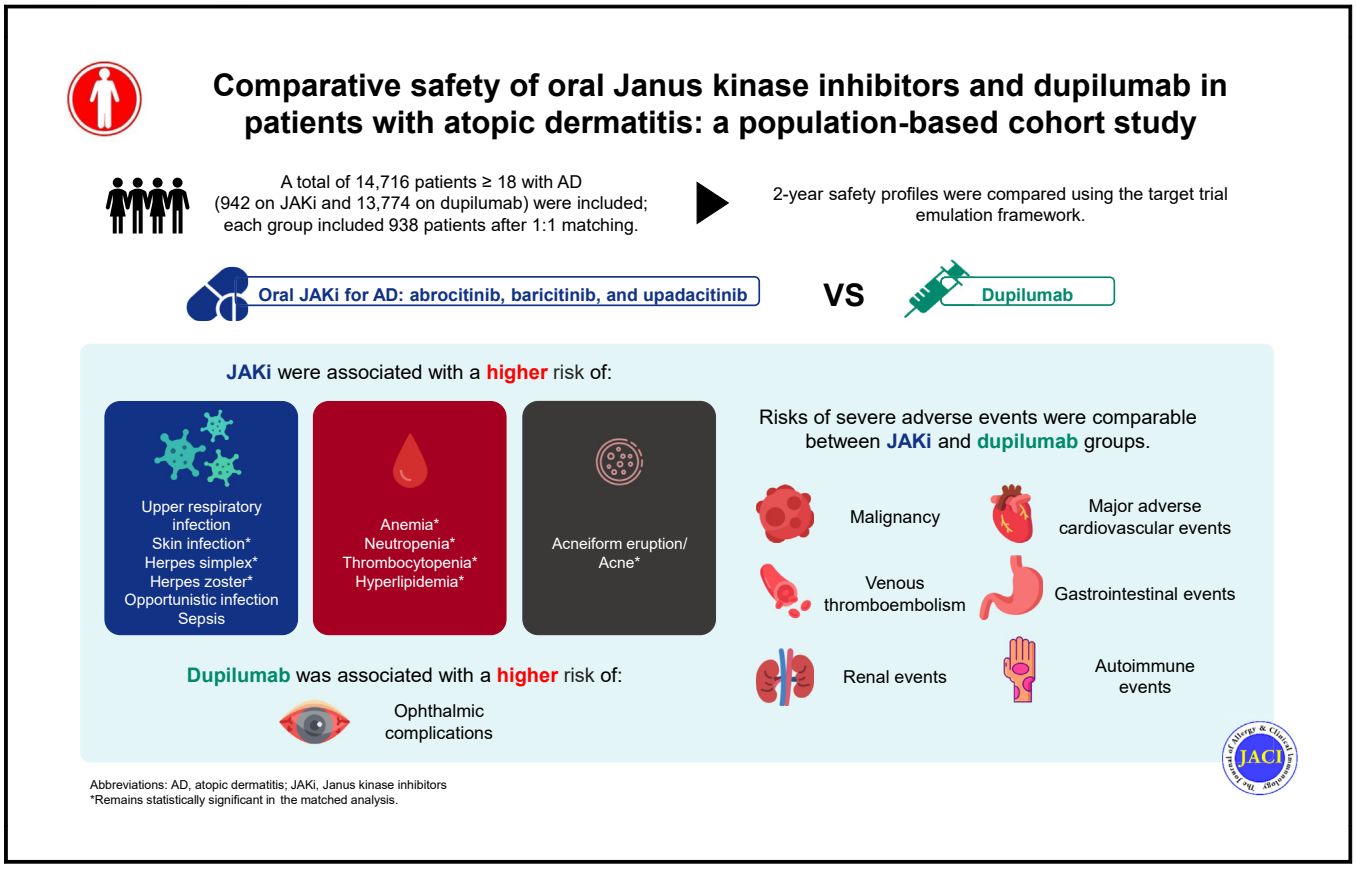
## GRAPHICAL ABSTRACT




**Capsule summary:** The US Food and Drug Administration has placed a boxed safety warning on all Janus kinase inhibitors (JAKi). This population-based study provides real-world evidence regarding the safety of JAKi for atopic dermatitis compared to dupilumab. Known adverse events in the existing literature were confirmed, but without indicating an increase in malignancies, major adverse cardiovascular events, venous thromboembolism, renal events, or serious gastrointestinal events.

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# Comparative safety of oral Janus kinase inhibitors versus dupilumab in patients with atopic dermatitis: A population-based cohort study

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**Background: Systemic Janus kinase inhibitors (JAKi) and dupilumab both have emerged as promising therapeutics for atopic dermatitis (AD). Dupilumab has a favorable safety profile, but oral JAKi therapy has been established in other diseases that carry potential comorbid susceptibilities that influence safety.**
**Objective: We sought to provide real-world evidence of the comparative safety of oral JAKi versus dupilumab in patients with AD.**
**Methods: The study used observational data from multiple healthcare organizations in the US. Patients with AD treated with either oral JAKi (upadacitinib, abrocitinib, and baricitinib) or dupilumab were enrolled. The 2 treatment groups were propensity score matched 1:1 on the basis of demographics, comorbidities, and prior medications. Safety outcomes within 2 years after the initiation of medications were measured by hazard ratios (HRs) with 95% confidence intervals (CIs).**
**Results: A total of 14,716 patients were included, with 942 patients treated with oral JAKi and 13,774 with dupilumab. The 2 treatment groups respectively included 938 patients after matching. Treatment with oral JAKi was not associated with increased risks of mortality, malignancies, major adverse cardiovascular events, venous thromboembolism, renal events, or serious gastrointestinal events. However, patients receiving oral JAKi showed significantly higher risks of skin and subcutaneous tissue infection (HR = 1.35, 95% CI = 1.07-1.69), herpes infection (herpes simplex, HR = 1.64, 95% CI = 1.03-2.61; herpes zoster, HR = 2.51, 95% CI = 1.14-5.52), acne (HR = 2.09, 95% CI = 1.54-2.84), cytopenia (anemia, HR = 1.83, 95% CI = 1.39-2.41; neutropenia, HR = 4.02, 95% CI = 1.91-8.47; thrombocytopenia, HR = 1.76, 95% CI = 1.08-2.89), and hyperlipidemia (HR = 1.45, 95% CI = 1.09-1.92); the risk of ophthalmic complications was higher in those receiving dupilumab (HR = 1.49, 95% CI = 1.03-2.17).**
**Conclusion: Oral JAKi did not exhibit concerning safety issues in treating patients with AD but increased the risk of infections and abnormalities in laboratory findings. Long-term follow-up data are required to validate these results. (J Allergy Clin Immunol 2024;154:1195-203.)**

***Key words:*** *Janus kinase inhibitors, dupilumab, atopic dermatitis, safety*

*Abbreviations used*
AD: Atopic dermatitis
BH: Benjamini-Hochberg
FDA: US Food and Drug Administration
HR: Hazard ratio
ICD-10: International Classification of Diseases, Tenth Revision
JAKi: Janus kinase inhibitors
MACE: Major adverse cardiovascular event
RA: Rheumatoid arthritis
SD: Standard deviation
SMD: Standardized mean difference
VTE: Venous thromboembolism

Atopic dermatitis (AD) is an inflammatory skin disease that typically manifests in early childhood and can persist into adulthood. Current recommendations for AD treatment follow a stepwise strategy, starting with trigger avoidance and skin moisturization (ie, emollients and bathing). In mild-to-moderate AD, topical treatments, such as corticosteroids, calcineurin inhibitors, and the phosphodiesterase 4 inhibitor crisaborole, are recommended.[1] Severe or refractory cases, or cases in which topical treatments fail to control AD symptoms effectively, may require systemic therapies. Conventional immunomodulating drugs (azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil), although not officially approved for AD, are effective options but have significant adverse effects.[2] Newer therapies include monoclonal antibodies such as dupilumab, and targeted disease-modifying small molecule agents such as Janus kinase inhibitors (JAKi). The goals of therapy for these patients include not only a significant reduction in AD symptoms and long-term disease control but, more importantly, acceptable safety.

Dupilumab, targeting IL-4 and IL-13, was the first biologic approved by the US Food and Drug Administration (FDA) for moderate-to-severe AD; it is also indicated for asthma, prurigo

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nodularis, chronic sinusitis with nasal polyposis, and eosinophilic esophagitis.[3,4] The safety of dupilumab has been established in both adults and children,[5] with its main adverse effects being injection-site reactions and conjunctivitis.[6,7] JAKi have emerged as a promising option for AD treatment based on their capacity to modulate AD-related cytokines (eg, IL-4, IL-13, IL-31, and thymic stromal lymphopoietin). Currently, one topical JAKi (ruxolitinib) has been approved for mild-to-moderate AD; 3 oral JAK1 inhibitors (upadacitinib, abrocitinib, and baricitinib) have been approved for moderate-to-severe AD. Of note, baricitinib has secured approval for AD from the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency in Japan but not from the FDA. Dupilumab therapy has primarily focused on atopic disorders, but JAKi have broader applications across immune and inflammatory diseases, including rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease.

In a network meta-analysis of 75 systemic treatments for AD, high-dose upadacitinib (30 mg per day), high-dose abrocitinib (200 mg per day), and low-dose upadacitinib (15 mg per day) were among the most effective regimens for improving multiple AD-related outcomes.[8] However, despite the greater efficacy of these oral JAKi over other systemic treatments demonstrated in clinical trials, clinicians remain conservative in prescribing them for AD because of safety concerns surrounding JAKi. The FDA has previously placed black box warnings on all approved JAKi, even though the reported adverse events primarily came from rheumatologic indications rather than dermatologic ones.[9] Frequently reported adverse events in clinical trials investigating oral JAKi for AD included both mild, transient side effects, such as headache and nausea, and more concerning complications, including serious infections, opportunistic infections, herpes zoster, herpes simplex, nasopharyngitis, acne, anemia, neutropenia, thrombocytopenia, elevated creatine phosphokinase levels, and elevated cholesterol levels.[10,11] Malignant neoplasms and cardiovascular events have rarely been found throughout the monitoring periods. The evidence remains uncertain because these clinical trials only provided short-term follow-up data. More data on the real-world incidence of adverse events associated with JAKi for AD are warranted, especially comparisons of their safety profiles with other systemic therapies.[12]

Our objective was to supplement the evidence of the safety profile of oral JAKi in AD treatment using multicenter observational data in the United States. Dupilumab was selected as the active comparator in the current study because of its widespread use as the primary systemic treatment for AD by far following approval.[13]

## METHODS

We conducted a population-based cohort study utilizing electronic health records from multiple healthcare organizations in the US within the TriNetX network (Cambridge, Mass).[14] Given that the study exclusively used deidentified information, it received an exemption from institutional review board approval and was granted a waiver of informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist.

### Study participants

We used coding systems from the International Classification of Diseases, Tenth Revision (ICD-10), and RxNorm to establish cohorts and select outcomes for this study. Detailed codes and definitions for the diagnoses and outcomes are provided in Table E1 in this article's Online Repository (available at www.jacionline.org). All patients diagnosed with AD between January 1, 2022, and January 31, 2024, were included in the present study and assigned to 1 of 2 treatment groups: those who newly initiated therapy with oral JAKi (abrocitinib, baricitinib, or upadacitinib) and those who newly initiated therapy with dupilumab. Enrollment commenced around the time when abrocitinib and upadacitinib were approved by the FDA in January 2022, while baricitinib had already been approved in other countries in 2020. The index date was defined as the date when the JAKi or dupilumab therapy was first initiated in patients (new recipients). To ensure that the treatment was intended for AD, at least one AD diagnosis should be present within 6 months before the index date. To minimize indication bias, patients who had a diagnosis of an alternative indication for JAKi (alopecia areata, RA, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, ulcerative colitis, and Crohn disease) and dupilumab (asthma, prurigo nodularis, chronic sinusitis with nasal polyposis, and eosinophilic esophagitis) within 6 months before the index date were excluded in both groups. Individuals with a history of receiving of JAKi were excluded from the dupilumab group. Emulating a target trial, we followed an intention-to-treat approach.[15] Baseline characteristics, including age at index date, race, sex, history of atopic comorbid diseases (food allergy, asthma, and allergic rhinitis), chronic diseases or comorbidities (hypertensive diseases, type 2 diabetes mellitus, chronic kidney disease, ischemic heart disease, and stroke), and historical receipt of systemic immunomodulating drugs (methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine) were recorded. The flowchart of study sample selection and the study design are illustrated in Fig 1 and in Fig E1 in the Online Repository.

### Study outcomes

Comparative safety outcomes occurring within 2 years of the tracking period after the index date (January 1, 2022) or the last date of the study period (June 18, 2024), whichever came first, were assessed. The diagnoses of the following safety outcomes, prespecified on the basis of safety profiles of JAKi or dupilumab reported in previous clinical trials or cohort studies, were compared between the 2 groups: all-cause mortality, malignancies (all malignancies, nonmelanoma skin cancer, lymphoma, cutaneous T-cell lymphoma, and gastrointestinal cancer), cardiovascular events (major adverse cardiovascular events [MACEs] and venous thromboembolism [VTE]), renal events (acute kidney injury and chronic kidney disease), gastroenterologic events (gastrointestinal perforation, acute pancreatitis, and inflammatory bowel disease), autoimmune rheumatic events (psoriasis, arthritis, and alopecia areata), infections (upper respiratory tract infection, lower respiratory tract infection, urinary tract infection, skin and subcutaneous tissue infection, herpes simplex infection, herpes zoster infection, tuberculosis, opportunistic infection [excluding tuberculosis and herpes zoster], and sepsis), and other adverse events (ophthalmic complications, acneiform eruption/acne, anemia, neutropenia, thrombocytopenia, and hyperlipidemia).

### Statistical analysis

The distribution of baseline characteristics along with standardized mean differences (SMDs) of the covariates were compared between participants treated with JAKi and dupilumab. To minimize confounding effects, 1:1 propensity score matching

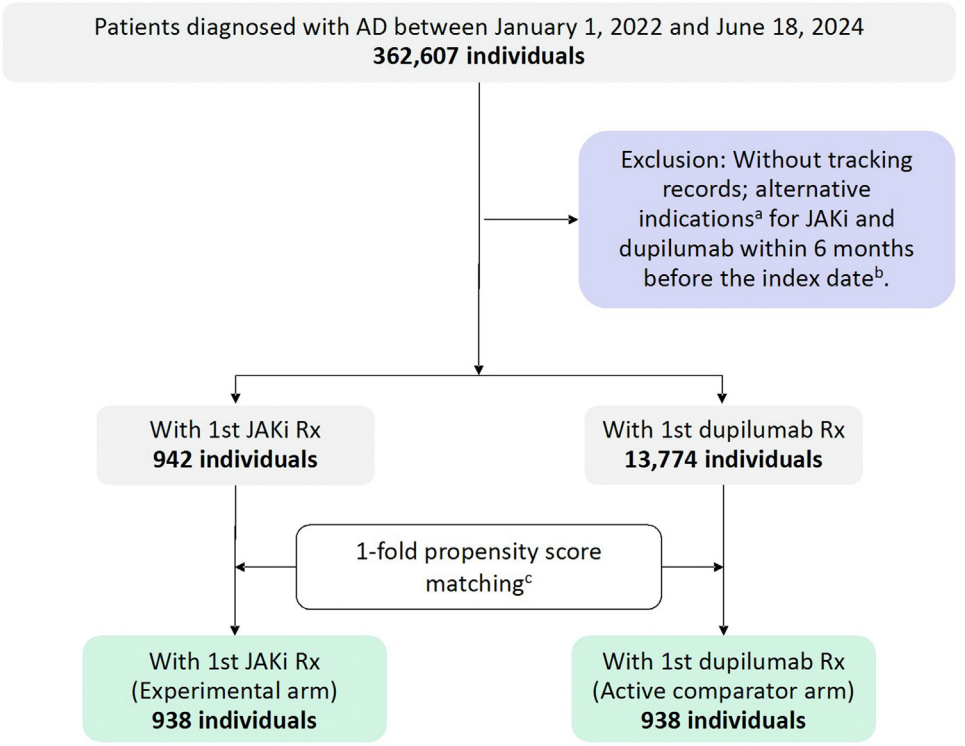


**FIG 1.** Study flow diagram. [a]Alternative diagnoses include: alopecia areata, RA, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, ulcerative colitis, Crohn disease, asthma, prurigo nodularis, chronic sinusitis with nasal polyposis, and eosinophilic esophagitis. [b]Index date is defined as the date of first prescription of JAKi (abrocitinib, baricitinib, and upadacitinib) or dupilumab in each cohort. [c]Onefold propensity score matching for age, sex, race, medical history, atopic comorbid diseases (food allergy, allergic rhinitis, and asthma), and receipt of conventional immunomodulating drugs (azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil). *Dx,* Diagnosis; *Rx,* prescription.

was used using greedy nearest-neighbor algorithms with a caliper of 0.1 pooled standard deviation (SD).[16] The estimated propensity score was calculated by logistic regression based on the unbalanced covariates at baseline (SMD > 0.1).[17] If the outcome was acute and would typically result in full recovery, we did not exclude patients with the event before the treatment index date; for outcomes with chronic tendencies, we excluded those who experienced the event before the treatment index date. The unmatched analysis investigated the time to occurrence of prespecified outcomes within 2 years from the baseline. The sensitivity analysis was conducted using matched cohorts based on the estimated propensity score. We estimated hazard ratios (HRs) with 95% CIs by the Cox proportional hazards model. The proportional hazard assumption was tested using the generalized Schoenfeld approach. Two-sided log-rank $P < .05$ was considered statistically significant. In the unmatched analysis, to control the inflation of type I error rates, or false discovery rates, that occur with multiple comparisons, the Benjamini-Hochberg (BH) procedure was applied to correct for $P$ values; false discovery rate–adjusted $P < .05$ was designated as statistical significance.[15] Statistical analyses were conducted by the built-in Advanced Analytics in TriNetX research platform and RStudio v2023.12.1+402.

## RESULTS

The study comprised 14,716 eligible patients with AD, of whom 942 were treated with oral JAKi (abrocitinib, baricitinib, or upadacitinib) and 13,774 with dupilumab before matching. On the one hand, compared to unmatched individuals treated with dupilumab, those who received JAKi were older (mean ± SD age at index for JAKi group, 38.2 ± 20.1 years; for dupilumab group, 34.1 ± 24.2 years) and more likely to have been treated with azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil (SMD > 0.1). On the other hand, those who received dupilumab were more likely to be Black or African American (18.3% in the dupilumab group vs 12.4% in the JAKi group, SMD > 0.1). After propensity score matching, 938 AD patients who received JAKi and 938 who received dupilumab were included in the study. The mean ± SD age of patients in the JAKi group was 38.2 ± 20.1 years, with 52.1% female and 50.2% White individuals. The mean ± SD age of patients in the dupilumab group was 38.6 ± 20.5 years, with 54.9% female and 53.6% White individuals. Baseline characteristics were well balanced between the 2 groups after propensity score matching (Table I).

### Primary analysis

In the unmatched analysis, patients treated with JAKi were mainly associated with a significantly higher risk of multiple infections compared to those treated with dupilumab. These infections included skin and subcutaneous tissue infection (cellulitis, panniculitis, erysipelas, folliculitis, and impetigo; HR = 1.26; 95% CI = 1.07-1.48; BH-adjusted $P = .019$), herpes simplex infection (HR = 2.05; 95% CI = 1.48-2.83; BH-adjusted $P < .001$), herpes zoster infection (HR = 2.26; 95% CI = 1.36-3.74; BH-adjusted $P = .004$), and sepsis (HR = 2.19; 95% CI = 1.23-3.89; BH-

**TABLE I.** Baseline characteristics of patients with AD receiving therapy with JAKi or dupilumab

| Characteristic | Before propensity score matching | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | JAKi group (n = 942) | Dupilumab group (n = 13,774) | SMD | JAKi group (n = 938) | Dupilumab group (n = 938) | SMD |
| Age at index (years), mean ± SD years | 38.2 ± 20.1 | 34.1 ± 24.2 | 0.183* | 38.2 ± 20.1 | 38.6 ± 20.5 | 0.021 |
| Female sex | 491 (52.1) | 7,120 (51.7) | 0.009 | 489 (52.1) | 515 (54.9) | 0.056 |
| Race | | | | | | |
| White | 475 (50.4) | 7,030 (51.0) | 0.012 | 471 (50.2) | 503 (53.6) | 0.068 |
| Asian | 107 (11.4) | 1,323 (9.6) | 0.057 | 107 (11.4) | 101 (10.8) | 0.020 |
| Black or African American | 149 (12.4) | 3,002 (18.3) | 0.166* | 127 (13.5) | 120 (12.8) | 0.022 |
| American Indian or Alaska Native | 10 (1.1) | 45 (0.3) | 0.089 | 10 (1.1) | 10 (1.1) | <0.001 |
| Native Hawaiian or other Pacific Islander | 10 (1.1) | 88 (0.6) | 0.046 | 10 (1.1) | 10 (1.1) | <0.001 |
| Other | 54 (5.7) | 772 (5.6) | 0.006 | 54 (5.8) | 57 (6.1) | 0.014 |
| Medical history | | | | | | |
| Hypertensive diseases | 179 (19.0) | 2,371 (17.2) | 0.046 | 179 (19.1) | 145 (15.5) | 0.096 |
| Type 2 diabetes mellitus | 76 (8.1) | 984 (7.1) | 0.035 | 75 (8.0) | 61 (6.5) | 0.058 |
| Hyperlipidemia | 113 (12.0) | 1,506 (10.9) | 0.033 | 113 (12.0) | 99 (10.6) | 0.047 |
| Ischemic heart disease | 35 (3.7) | 714 (5.2) | 0.071 | 35 (3.7) | 47 (5.0) | 0.063 |
| Cerebral infarction | 14 (1.5) | 312 (2.3) | 0.057 | 14 (1.5) | 25 (2.7) | 0.082 |
| Chronic kidney disease | 32 (3.4) | 533 (3.9) | 0.025 | 32 (3.4) | 35 (3.7) | 0.017 |
| Atopic comorbid disease | | | | | | |
| Food allergy | 75 (8.0) | 1,305 (9.5) | 0.054 | 74 (7.9) | 56 (6.0) | 0.076 |
| Asthma | 155 (16.5) | 2,058 (14.9) | 0.042 | 154 (16.4) | 137 (14.6) | 0.050 |
| Allergic rhinitis | 145 (15.4) | 1,963 (14.3) | 0.032 | 142 (15.1) | 129 (13.8) | 0.039 |
| Receipt of other systemic AD medications | | | | | | |
| Azathioprine | 47 (5.0) | 162 (1.2) | 0.222* | 43 (4.6) | 34 (3.6) | 0.048 |
| Cyclosporine | 213 (22.6) | 970 (7.0) | 0.449* | 209 (22.3) | 220 (23.5) | 0.028 |
| Methotrexate | 199 (21.1) | 1,269 (9.2) | 0.337* | 195 (20.8) | 177 (18.9) | 0.048 |
| Mycophenolate mofetil | 109 (11.6) | 539 (3.9) | 0.290* | 105 (11.2) | 106 (11.3) | 0.003 |

Data are presented as nos. (%) unless otherwise indicated.
*SMD > 0.1.

adjusted $P = .019$). Additionally, patients treated with JAKi showed a higher risk of other adverse events, including acneiform eruption/acne (HR = 2.73; 95% CI = 2.22-3.35; BH-adjusted $P < .001$), anemia (HR = 1.83; 95% CI = 1.52-2.20; BH-adjusted $P < .001$), neutropenia (HR = 2.96; 95% CI = 1.97-4.44; BH-adjusted $P < .001$), and thrombocytopenia (HR = 1.82; 95% CI = 1.29-2.57; BH-adjusted $P = .004$). Conversely, the risk of ophthalmic complications (conjunctivitis, blepharitis, keratitis, dry eye, ocular pain, and other ocular surface diseases) was lower in the JAKi group (HR = 0.59; 95% CI = 0.44-0.80; BH-adjusted $P < .001$) compared to the dupilumab group. The risk of upper respiratory tract infection, opportunistic infection, and hyperlipidemia was nominally significantly higher in the JAKi group, but none was statistically significant after multiple-testing correction (Table II).

Nevertheless, the risk of all-cause mortality, all malignancies, lymphoma, cutaneous T-cell lymphoma, gastrointestinal cancer, MACEs, VTE, acute kidney injury, chronic kidney disease, acute pancreatitis, gastrointestinal perforation, inflammatory bowel disease, psoriasis, arthritis, alopecia areata, lower respiratory tract infection, urinary tract infection, and tuberculosis was comparable between the 2 groups (Table II).

### Sensitivity analysis

In the sensitivity analysis using the matched samples, patients treated with JAKi continued to show a significantly increased risk of skin and subcutaneous tissue infection (HR = 1.35; 95% CI = 1.07-1.69; $P = .01$), herpes simplex infection (HR = 1.64; 95% CI = 1.03-2.61; $P = .035$), herpes zoster infection (HR = 2.51; 95% CI = 1.14-5.52; $P = .018$), acneiform eruption/acne (HR = 2.09; 95% CI = 1.54-2.84; $P < .001$), anemia (HR = 1.83; 95% CI = 1.39-2.41; $P < .001$), neutropenia (HR = 4.02; 95% CI = 1.91-8.47; $P < .001$), thrombocytopenia (HR = 1.76; 95% CI = 1.08-2.89; $P = .023$), and hyperlipidemia (HR = 1.45; 95% CI = 1.09-1.92; $P = .009$). The risk of ophthalmic complications (HR = 0.67; 95% CI = 0.46-0.97; $P = .033$) remained significantly lower in patients treated with JAKi compared to those treated with dupilumab (Table III).

## DISCUSSION

The data presented in this study supported the potential risk of multiple infections and laboratory abnormalities reported in the clinical trials. No significant safety signals were seen in MACEs, VTE, renal events, or malignancies that have been problematic in patients treated with JAKi for other diseases.

The safety of JAKi is a foremost consideration for clinicians as a result of the immunosuppressive nature of this therapeutic class. In the ORAL Surveillance study, JAKi increased the risk of malignancies, MACEs, and VTE in patients with RA, further resulting in a consequential regulatory response from the FDA: black box warnings.[18] Apart from its implications in rheumatologic diseases, only sporadic cases of malignant neoplasms have been reported in clinical trials of JAKi for AD (Measure Up 1, Measure Up 2, AD Up). The cases were mostly nonmelanoma skin cancer, with a few instances of other malignancies such as lymphoma and gastrointestinal cancers, and none of them was determined to be directly related to the study medications.[10] In addition, the incidence rates were extremely low; in an

**TABLE II.** Comparative safety of JAKi and dupilumab for risk of adverse events in unmatched AD patients

| Outcome | No. of events in:† JAKi group (n = 942) | Dupilumab group (n = 13,774) | HR | 95% CI | *P* value | BH-adjusted *P* value |
|---|---|---|---|---|---|---|
| All-cause mortality | 10 | 123 | 1.19 | 0.55, 2.55 | .660 | .812 |
| Malignancies‡ | | | | | | |
| Malignancy | 17 | 280 | 1.29 | 0.79, 2.10 | .314 | .569 |
| Nonmelanoma skin cancer | 10 | 143 | 1.35 | 0.69, 2.65 | .383 | .653 |
| Lymphoma | 10 | 68 | 1.81 | 0.78, 4.18 | .159 | .329 |
| Cutaneous T-cell lymphoma | 10 | 26 | 1.23 | 0.16, 9.17 | .843 | .905 |
| Gastrointestinal cancer | 0 | 36 | NA | NA | NA | NA |
| Cardiovascular events‡ | | | | | | |
| MACEs | 10 | 131 | 1.23 | 0.60, 2.52 | .569 | .786 |
| VTE | 10 | 97 | 0.81 | 0.30, 2.19 | .672 | .812 |
| Renal events‡ | | | | | | |
| Acute kidney injury | 10 | 127 | 0.95 | 0.42, 2.16 | .907 | .915 |
| Chronic kidney disease | 10 | 111 | 0.90 | 0.37, 2.21 | .821 | .905 |
| Gastroenterologic events‡ | | | | | | |
| Acute pancreatitis | 10 | 42 | 1.85 | 0.66, 5.19 | .233 | .450 |
| Gastrointestinal perforation | 0 | 13 | NA | NA | NA | NA |
| Inflammatory bowel disease | 10 | 153 | 0.77 | 0.34, 1.73 | .521 | .755 |
| Autoimmune rheumatic events‡ | | | | | | |
| Psoriasis | 12 | 237 | 0.97 | 0.54, 1.73 | .915 | .915 |
| Arthritis | 26 | 602 | 0.91 | 0.61, 1.34 | .625 | .812 |
| Alopecia areata | 10 | 42 | 1.53 | 0.47, 4.95 | .473 | .742 |
| Infections | | | | | | |
| Upper respiratory tract | 132 | 2,818 | 1.19 | 1.00, 1.43 | .048* | .116 |
| Lower respiratory tract | 35 | 599 | 1.13 | 0.80, 1.59 | .486 | .742 |
| Urinary tract | 18 | 381 | 0.93 | 0.58, 1.49 | .754 | .875 |
| Skin and subcutaneous tissue§ | 153 | 2,314 | 1.26 | 1.07, 1.48 | .006* | .019** |
| Herpes simplex | 41 | 384 | 2.05 | 1.48, 2.83 | <.001* | <.001** |
| Herpes zoster | 18 | 145 | 2.26 | 1.36, 3.74 | .001* | .004** |
| TB | 10 | 28 | 2.48 | 0.87, 7.07 | .080 | .178 |
| Opportunistic infection (excluding TB and herpes zoster) | 21 | 337 | 1.60 | 1.02, 2.49 | .038* | .110 |
| Sepsis | 13 | 116 | 2.19 | 1.23, 3.89 | .006* | .019** |
| Other adverse events | | | | | | |
| Ophthalmic complications | 81 | 1,495 | 0.59 | 0.44, 0.80 | <.001* | <.001** |
| Acneiform eruption/acne | 105 | 771 | 2.73 | 2.22, 3.35 | <.001* | <.001** |
| Anemia | 124 | 1,311 | 1.83 | 1.52, 2.20 | <.001* | <.001** |
| Neutropenia | 27 | 180 | 2.96 | 1.97, 4.44 | <.001* | <.001** |
| Thrombocytopenia | 36 | 377 | 1.82 | 1.29, 2.57 | .001* | .004** |
| Hyperlipidemia | 105 | 1,523 | 1.22 | 1.00, 1.49 | .048* | .116 |

*NA,* Not applicable; *TB,* tuberculosis.
*Nominally significant (unadjusted $P < .05$).
†If patient is ≤10, results show count as 10.
‡Patients with outcome before time window are excluded.
§Includes cellulitis, panniculitis, erysipelas, folliculitis, and impetigo.
**Statistical significance after BH procedure for multiple comparisons (adjusted $P < .05$).

integrated safety analysis of 2,856 patients with moderate-to-severe AD treated with abrocitinib, the rates of nonmelanoma skin cancer, other malignancies, MACEs, and VTE were all less than 0.5 per 100 patient-years.[19] The pooling data from several meta-analyses also suggested that the risk of malignancies, MACEs, and VTE did not increase in AD patients treated with JAKi compared to those receiving placebo or dupilumab.[20-22] One explanation of these findings is that autoimmune diseases such as RA inherently harbor a greater risk of cardiovascular disease and thromboembolism, but AD does not typically exhibit the same elevated risk levels.[23,24] More serious adverse events once confirmed to be treatment related to JAKi for AD and alopecia areata were gastrointestinal perforation, acute pancreatitis, and inflammatory bowel disease, although the instances were limited to only a few cases.[25,26] Our data reassured us that JAKi, when used to treat AD, did not seem to confer a risk for malignancies, MACEs, VTE, renal diseases, or the aforementioned serious gastrointestinal events. However, this study only provided the outcomes within a 2-year follow-up; as a result, the evidence was rather constrained because certain chronic outcomes, such as neoplasms, may not manifest within this short observational period.

The increased susceptibility to infections is another significant hurdle in JAKi treatment. Infections commonly reported after initiating therapy with JAKi include nasopharyngitis, pneumonia, urinary tract infection, cellulitis, and herpes.[27] In a network meta-analysis pooling the safety of JAKi in AD from 18 studies, both abrocitinib and upadacitinib increased the risk of any infection and herpesvirus infection compared to placebo; upadacitinib results in an elevated risk of herpes zoster infection compared to

**TABLE III.** Comparative safety of JAKi and dupilumab for risk of adverse events in matched AD patients

| Outcome | No. of events in:† JAKi group (n = 938) | Dupilumab group (n = 938) | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| All-cause mortality‡ | 10 | 11 | 1.00 | 0.38, 2.64 | .998 |
| Malignancies‡ | | | | | |
| Malignancy‡ | 17 | 27 | 0.94 | 0.51, 1.74 | .844 |
| Nonmelanoma skin cancer | 10 | 14 | 1.10 | 0.47, 2.58 | .834 |
| Lymphoma | 10 | 10 | 1.06 | 0.36, 3.11 | .910 |
| Cutaneous T-cell lymphoma | 10 | 10 | 0.63 | 0.06, 6.68 | .697 |
| Gastrointestinal cancer | 0 | 10 | NA | NA | NA |
| Cardiovascular events‡ | | | | | |
| MACEs | 10 | 10 | 1.36 | 0.50, 3.70 | .543 |
| VTE | 10 | 12 | 0.41 | 0.13, 1.29 | .115 |
| Renal events‡ | | | | | |
| Acute kidney injury | 10 | 10 | 0.90 | 0.32, 2.56 | .845 |
| Chronic kidney disease | 10 | 10 | 0.88 | 0.29, 2.69 | .819 |
| Gastroenterologic events‡ | | | | | |
| Acute pancreatitis | 10 | 0 | NA | NA | NA |
| Gastrointestinal perforation | 0 | 0 | NA | NA | NA |
| Inflammatory bowel disease | 10 | 12 | 0.71 | 0.26, 1.92 | .498 |
| Autoimmune rheumatic events‡ | | | | | |
| Psoriasis | 11 | 18 | 0.92 | 0.43, 1.99 | .838 |
| Arthritis | 26 | 51 | 0.78 | 0.49, 1.27 | .318 |
| Alopecia areata | 10 | 10 | 3.00 | 0.46, 19.75 | .235 |
| Infections | | | | | |
| Upper respiratory tract | 132 | 172 | 1.02 | 0.81, 1.28 | .872 |
| Lower respiratory tract | 35 | 32 | 1.62 | 0.99, 2.64 | .051 |
| Urinary tract | 18 | 25 | 0.99 | 0.54, 1.84 | .983 |
| Skin and subcutaneous tissue§ | 153 | 159 | 1.35 | 1.07, 1.69 | .010* |
| Herpes simplex | 41 | 33 | 1.64 | 1.03, 2.61 | .035* |
| Herpes zoster | 18 | 11 | 2.51 | 1.14, 5.52 | .018* |
| TB | 10 | 10 | 1.56 | 0.35, 6.97 | .560 |
| Opportunistic (excluding TB and herpes zoster) | 21 | 27 | 1.57 | 0.85, 2.93 | .147 |
| Sepsis | 13 | 10 | 2.33 | 0.92, 5.85 | .065 |
| Other adverse events | | | | | |
| Ophthalmic complications | 81 | 121 | 0.67 | 0.46, 0.97 | .033* |
| Acneiform eruption/acne | 105 | 71 | 2.09 | 1.54, 2.84 | <.001* |
| Anemia | 123 | 90 | 1.83 | 1.39, 2.41 | <.001* |
| Neutropenia | 27 | 10 | 4.02 | 1.91, 8.47 | <.001* |
| Thrombocytopenia | 36 | 37 | 1.76 | 1.08, 2.89 | .023* |
| Hyperlipidemia | 105 | 96 | 1.45 | 1.09, 1.92 | .009* |

*NA,* Not applicable; *TB,* tuberculosis.
*Nominally significant (unadjusted $P < .05$).
†If patient is ≤10, results show count as 10.
‡Patients with outcome before time window are excluded.
§Includes cellulitis, panniculitis, erysipelas, folliculitis, and impetigo.

dupilumab.[22] Our findings were generally consistent, showing that JAKi for AD were correlated with a higher risk of upper respiratory tract infection, skin and subcutaneous tissue infection, herpes simplex infection, and herpes zoster infection. The results may also be attributed to the benefits of dupilumab. Prior studies have shown that dupilumab reduced the risk of serious infection, skin infection, and herpes infection in patients with AD.[28,29] Still, stringent pre-prescription screening and continuous monitoring for infectious diseases remain essential for patients considering or currently prescribed JAKi.

Other less serious complications associated with JAKi can also occur, although they typically do not lead to treatment discontinuation. Acneiform eruption/acne has been reported as one of the most frequent treatment-emergent adverse events,[30] with a proportion ranging from 7% to 17% in patients receiving upadacitinib.[31] In addition, because the Janus activating kinase–signal transducer and activator of transcription (JAK-STAT) pathway has an established regulatory role in hematopoiesis, inhibition often leads to cytopenia.[32] Previous studies also linked JAKi to elevations in lipids and demonstrated a dose-dependent relationship.[11,33] Our data documented an increased incidence of acneiform eruption/acne, anemia, neutropenia, thrombocytopenia, and hyperlipidemia in AD patients undergoing JAKi treatment, although the duration of these side effects was unclear.

Compared to the highly publicized safety issues of JAKi, dupilumab has a relatively favorable safety profile.[34] The higher incidence of ocular surface diseases, primarily conjunctivitis, maintains the most common adverse effects in treating AD with dupilumab.[35] Dupilumab has also been reported to potentially cause the progression of cutaneous T-cell lymphoma, joint pain or arthritis, psoriasiform manifestations or psoriasis, and alopecia areata, although the causation requires further research.[7] Our data showed that dupilumab was only associated with an increased risk of ophthalmic complications, with no

significant association found with the risk of lymphoma, cutaneous T-cell lymphoma, psoriasis, arthritis, or alopecia areata. The differing results between our study and previous population-based studies assessing the risk of cutaneous T-cell lymphoma and joint pain in patients with AD treated with dupilumab may be explained by the different comparators (no dupilumab receipt, cyclosporine, or mycophenolate) and by the fact that JAKi are treatments for the outcomes of interest (psoriasis, arthritis, and alopecia areata).[36,37]

The major strength of our study is the size of the database, which provides significant statistical power relative to limited trial data. Moreover, by using propensity score matching and by using advanced causal inferences and the target trial emulation framework, the present study has established real-world evidence to offer a comprehensive evaluation of potential adverse effects associated with JAKi.[38] Nevertheless, there are several limitations to this study. First, this study relies on ICD-10 codes to identify exposures and outcomes, introducing the possibility of misclassification, which limits the validity of our findings. Second, despite strict restrictions on the time order of the AD diagnosis and the index date as well as exclusions of alternative indications in the study's eligibility criteria, there remains the possibility of indication bias. Third, although we have perfromed propensity score matching to minimize the effects of confounding, residual unmeasured confounding can still exist. Fourth, there is a lack of data on the severity assessment scoring system for AD (eg, Eczema Area and Severity Index [aka EASI], Severity Scoring Index of Atopic Dermatitis [aka SCORAD], and Six Area Six Sign Atopic Dermatitis Atopic Score [aka SASSAD]), and not all patients have their body surface area recorded in the registry. Fifth, we do not apply stratified log-rank test or variance estimation to account for the matched nature of the sample, which might have made the results less likely to reject the null hypothesis.[39] Finally, considering the recent approval of JAKi for AD and the limited 2-year tracking period of this study, there remains the possibility that diseases with longer latency periods, particularly tumorigenesis, may not yet have developed. Therefore, extended follow-up studies are necessary to thoroughly assess the long-term safety profile of JAKi.

In conclusion, this target trial emulation study demonstrated that compared to dupilumab, JAKi posed an increased risk of established adverse events, including infections, acneiform eruption/acne, anemia, neutropenia, thrombocytopenia, and hyperlipidemia. Regular monitoring for these complications is recommended.

**Key messages**

- **Oral JAKi, when used to treat AD, are associated with a higher risk of infections, acneiform eruption/acne, anemia, neutropenia, thrombocytopenia, and hyperlipidemia.**
- **Our study did not reveal any increased risks of malignancies, MACEs, VTE, renal events, or serious gastrointestinal events with the use of oral JAKi.**

## DISCLOSURE STATEMENT

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Disclosure of potential conflict of interest: E. B. Hawryluk is on the advisory board of Apogee; consults for Skin Analytics; and receives royalties from UpToDate as an author and reviewer. L. C. Schneider is an investigator for Regeneron and DBV Technologies; and is on the advisory boards of Sanofi, Triveni Bio, DBV, Alladapt Immunotherapeutics, BioThea Pharmaceuticals, Ukko, Leo Pharmaceuticals, DAIT/NIAID, and the National Eczema Association. The rest of the authors declare that they have no relevant conflicts of interest.

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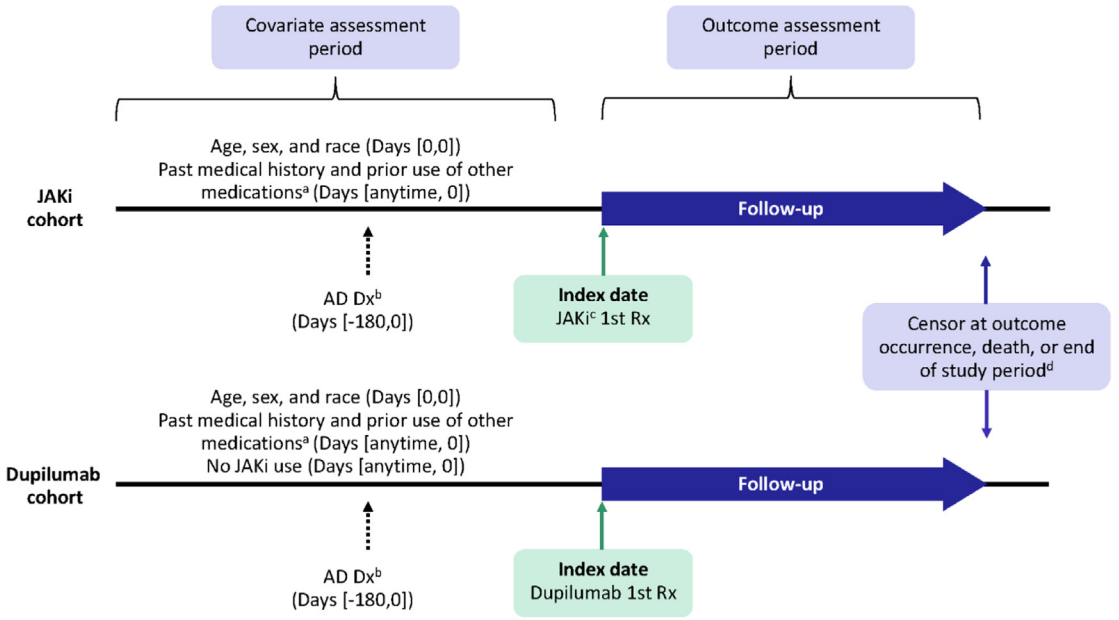


**FIG E1.** Study design. [a]Medical history includes hypertensive diseases, type 2 diabetes mellitus, hyperlipidemia, ischemic heart diseases, cerebral infarction, and chronic kidney disease; prior receipt of other medications includes systemic immunomodulating drugs (methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine). [b]Patients with diagnosis of alopecia areata, RA, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, ulcerative colitis, Crohn disease, asthma, prurigo nodularis, chronic sinusitis with nasal polyposis, and eosinophilic esophagitis were excluded within same time frame (days [−180,0]). [c]JAKi include abrocitinib, baricitinib, and upadacitinib. [d]Study period is 2 years from baseline. *Dx,* Diagnosis; *Rx,* prescription.

**TABLE E1.** List of ICD-10 codes and RxNorm codes for defining exposures, covariates, and outcomes

| Characteristic | ICD-10 | RxNorm |
|---|---|---|
| AD | L20 | |
| Exposures | | |
| Dupilumab | | 1876376 |
| Abrocitinib | | 2591476 |
| Baricitinib | | 2047232 |
| Upadacitinib | | 2196092 |
| Baseline characteristics | | |
| Hypertensive diseases | I10-I1A | |
| Type 2 diabetes mellitus | E11 | |
| Hyperlipidemia | E78 | |
| Ischemic heart diseases | I20-I25 | |
| Cerebral infarction | I63 | |
| Chronic kidney disease | N18 | |
| Food allergy | T78.0, T78.1, Z91.01 | |
| Asthma | J45 | |
| Allergic rhinitis | J30.1-J30.9 | |
| Medication outcomes | | |
| Azathioprine | | 1256 |
| Cyclosporine | | 3008 |
| Methotrexate | | 6851 |
| Mycophenolate mofetil | | 68149 |
| Diagnostic outcomes | | |
| Malignancies | C00-C96 | |
| Nonmelanoma skin cancers | C44-C4A | |
| Lymphomas | C81-C88 | |
| Cutaneous T-cell lymphoma | C84.A | |
| Gastrointestinal cancers | C15-C26 | |
| Major cardiovascular event (ischemic heart diseases, cardiovascular death, ischemic stroke) | I21-I25, I46, I63, G45 | |
| VTE (pulmonary embolism, venous embolism, thrombosis) | I26, I82 | |
| Acute kidney injury | N17 | |
| Chronic kidney disease | N18-N19 | |
| Acute pancreatitis | K85 | |
| Gastrointestinal perforation | K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K57.0, K57.2, K57.4, K57.8, K631 | |
| Inflammatory bowel diseases (Crohn disease, ulcerative colitis) | K50, K51 | |
| Upper respiratory infections | J00-J06, J36 | |
| Lower respiratory infections | J09-J18, J20-J22 | |
| Urinary tract infection (acute pyelonephritis, cystitis, urinary tract infection) | N10, N30, N39.0 | |
| Skin and soft tissue infection (erysipelas, viral skin infections, dermatophytosis, superficial mycoses, fungal skin infections, impetigo, cutaneous abscess, furuncle, carbuncle, cellulitis, acute lymphangitis, acute lymphadenitis, pilonidal cyst and sinus) | A46, B00-B09, B35-B36, B37.2, B38.3, B42.1, B43.0, B45.2, B46.3, L00-L08 | |
| Herpes simplex | B00 | |
| Herpes zoster | B01, B02 | |
| Tuberculosis | A15-A19 | |
| Opportunistic infections (cytomegaloviral disease, mycoses, protozoal diseases, helminthiases) | B25, B35-B49, B50-B64, B65-B83 | |
| Sepsis | A02.1, A22.7, A26.7, A32.7, A40, A41, A42.7, A54.86, B37.7, R65.2 | |
| Psoriasis | L40 | |
| Arthritis | M05-M14, M25.5 | |
| Alopecia areata | L63 | |
| Ophthalmic complications (blepharitis, conjunctivitis, keratitis, dry eye syndrome, ocular pain) | H00, H01, H04.12, H10, H11, H16, H57.1 | |
| Acneiform eruption/acne | L27.0-L27.1, L70 | |
| Anemia | D64.9; TNX:9014 Hemoglobin [Mass/volume] in Blood (at most 12.00 g/dL) | |

*(Continued)*

**TABLE E1**. *(Continued)*

| Characteristic | ICD-10 | RxNorm |
|---|---|---|
| Neutropenia | D70.9; TNX: 9018 Neutrophils [no./volume] in blood (at most $1.50 \times 10^3/\mu L$) | |
| Thrombocytopenia | D69.6; platelets [no./volume] in blood (at most $1.50 \times 10^5/\mu L$) | |
| Hyperlipidemia | E78 | |