



BRIEF REPORT

Clinical Trial Eligibility in Atopic Dermatitis: Data from a Large Real-World International Cohort

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ABSTRACT

Introduction: Randomized clinical trials (RCTs) in atopic dermatitis (AD) often exclude older adults and patients with comorbidities, limiting the generalizability of trial findings to real-world populations. Despite the growing use of biologics and Janus kinase inhibitors (JAKis) in clinical

practice, the extent to which real-world patients meet RCT eligibility criteria and their associated safety outcomes remains unclear.

Methods: We conducted a retrospective analysis of a large, multicenter international cohort of adolescents and adults with AD treated with biologics (dupilumab, tralokinumab) or systemic JAKis (abrocitinib, baricitinib, upadacitinib) between October 2017 and March 2023 across 16 dermatology centers. Eligibility was defined

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according to commonly applied RCT criteria. Patients meeting ≥ 1 exclusion criterion were classified as ineligible. Demographic, clinical, and safety outcomes were analyzed.

Results: Among 2154 patients, 514 (23.9%) were ineligible. The most frequent reasons were Eczema Area and Severity Index (EASI) < 16 (67.9%), age ≥ 75 years (21.8%), and cardiovascular disease (13.0%). Ineligibility patterns differed across treatments: patients receiving JAKis were most often ineligible because of EASI < 16 (92.8%), whereas ineligibility among biologic users more commonly reflected also age or cardiovascular comorbidity. Ineligible patients were older, had more non-atopic comorbidities, and had lower measured baseline disease activity. Safety profiles were generally favorable. Among biologic-treated patients, adverse event rates were similar between eligible and ineligible groups. In the JAKi cohort, overall adverse events were more frequent in ineligible patients (52.9% vs. 42.6%; $p=0.051$), with acneiform eruption and lipid abnormalities emerging as the most distinct differences. No unexpected safety signals were identified in either treatment group.

Conclusion: Nearly one-quarter of real-world patients with AD would not have met eligibility

criteria for pivotal RCTs, yet both biologics and JAK inhibitors demonstrated acceptable safety profiles in these populations. While adverse events were more frequent among ineligible patients receiving JAKis, findings require further investigation to determine their clinical relevance, particularly regarding long-term cardiovascular outcomes.

Keywords: Atopic dermatitis; Biologic therapy; Clinical trials; Eligibility criteria; Janus kinase inhibitors; Real-world evidence

Key Summary Points

Why carry out this study?

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Real-world patients with atopic dermatitis (AD) often differ substantially from those enrolled in randomized clinical trials (RCTs), which commonly exclude older individuals and those with comorbidities.

It remains unclear what proportion of real-world patients with AD would meet eligibility criteria for pivotal RCTs and whether safety outcomes differ between eligible and ineligible patients.

We hypothesized that a substantial proportion of real-world patients would not meet RCT eligibility criteria and that that safety profiles might vary between eligible and ineligible groups.

What was learned from the study?

Almost one in four real-world patients treated with targeted systemic therapies for AD would not have met eligibility criteria for key RCTs.

Biologic therapies showed comparable safety in eligible and ineligible patients, whereas ineligible patients receiving JAK inhibitors experienced a higher frequency of adverse events, most notably acneiform eruption and lipid abnormalities.

No unexpected safety concerns emerged, supporting the use of targeted therapies in broader patient populations than those typically included in trials.

These findings reinforce the value of real-world evidence and highlight the need for more inclusive trial designs that better reflect the diversity of patients treated in everyday clinical practice.

INTRODUCTION

Randomized clinical trials (RCTs) in atopic dermatitis (AD) have been pivotal in establishing the efficacy and safety of targeted systemic therapies. However, their strict inclusion and exclusion criteria frequently restrict enrollment to a narrowly defined population, potentially

limiting the external validity of their results. These eligibility criteria commonly exclude older adults, patients with multiple comorbidities, or those receiving concomitant medications, even though such individuals represent a significant proportion of patients encountered in daily clinical practice [1–4]. Therefore, the outcomes and safety profiles reported in pivotal trials may not fully capture the therapeutic experience in real-world settings.

With the advent of biologic agents and systemic Janus kinase inhibitors (JAKis), the therapeutic landscape of AD has expanded substantially. These agents differ in their mechanisms of action, safety considerations, and potential interactions with patient comorbidities. Understanding whether the populations typically excluded from RCTs can achieve comparable treatment outcomes and safety profiles is therefore of growing clinical importance.

Recent studies in psoriasis and other inflammatory diseases have highlighted discrepancies between trial and real-world populations, demonstrating that a substantial proportion of routine patients would have been ineligible for pivotal RCTs [5–7].

However, similar evidence in AD remains limited. To our knowledge, no large international study has systematically quantified the proportion of real-world patients with AD who would not meet RCT eligibility criteria or compared their safety outcomes across biologic and JAKi therapies. We conducted this retrospective study aiming to fill that gap.

METHODS

We analyzed data from a large, multicenter, international cohort of adolescent and adult patients with AD who initiated treatment with biologic agents (dupilumab, tralokinumab) or oral JAKis (abrocitinib, baricitinib, upadacitinib) between October 2017 and March 2023 across 16 dermatology centers in Canada, Czechia, Greece, Italy, Portugal, Spain, and Switzerland, with data collected up to a cutoff date of July 2024.

Eligibility was based on commonly applied inclusion and exclusion criteria in pivotal RCTs of systemic therapies for AD [3, 4]. Patients were classified as “ineligible” if they met at least one of the following: age ≥ 75 years, cardiovascular disease, chronic kidney/liver disease, current or prior malignancy except non-melanoma skin cancer (NMSC), latent/active tuberculosis, hepatitis B/C, HIV infection, active infection, or a baseline Eczema Area and Severity Index (EASI) < 16 . Remaining patients were considered “eligible.” Demographic, clinical, and safety data were compared between cohorts.

This study was a retrospective, non-interventional analysis conducted using fully de-identified, anonymized, and aggregated data collected as part of routine clinical practice. In accordance with applicable national and institutional regulations at the participating centers, formal ethics committee approval and informed consent were not required for this type of study. The study

was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Of 2154 patients, 514 (23.9%) were considered ineligible (Table 1). The most common reasons included EASI < 16 (67.9%), age ≥ 75 (21.8%), and cardiovascular disease (13.0%). Less frequent reasons for ineligibility included chronic kidney/liver disease (5.3%), current or prior malignancy except NMSC (4.9%), latent/active tuberculosis (1.8%), and hepatitis B/C (1.4%). The distribution of ineligibility criteria differed significantly between treatment groups ($p < 0.001$). Patients treated with systemic JAK inhibitors were most often excluded because of EASI < 16 (92.8% vs. 58.8%; $p < 0.001$), while those on biologic therapy were more commonly ineligible because of

Table 1 Distribution of ineligibility criteria across treatment groups

	Total ($n = 514$)	Biologics ^a ($n = 376$)	Systemic JAK inhibitors ^b ($n = 138$)	p value ^c
Reason for ineligibility				
EASI < 16 , n (%)	349	221 (58.8%)	128 (92.8%)	< 0.001
Age ≥ 75 , n (%)	112	104 (27.7%)	8 (5.8%)	< 0.001
Cardiovascular disease, n (%)	67	66 (17.6%)	1 (0.7%)	< 0.001
Chronic kidney/liver disease, n (%)	27	24 (6.4%)	3 (2.2%)	0.073
Current or prior malignancy except NMSC, n (%)	25	24 (6.4%)	1 (0.7%)	0.068
Latent TB, n (%)	9	8 (2.1%)	1 (0.7%)	1.000
Hepatitis B/C, n (%)	7	7 (1.9%)	0 (0.0%)	0.198
HIV, n (%)	0	0 (0.0%)	0 (0.0%)	NA
Active infection, n (%)	0	0 (0.0%)	0 (0.0%)	NA

EASI Eczema Area and Severity Index, HIV human immunodeficiency virus, JAK Janus kinase, NMSC non-melanoma skin cancer, TB tuberculosis, VTE venous thromboembolism; Y years

^aDupilumab, tralokinumab

^bUpadacitinib, abrocitinib, baricitinib

^c p -values were calculated using individual Fisher's exact tests for each exclusion criterion; the global chi-square test of independence showed that the overall pattern of ineligibility reasons differed significantly between treatment groups (χ^2 , $p < 0.001$)

advanced age (27.7% vs. 5.8%; $p<0.001$) or cardiovascular disease (17.6% vs. 0.7%; $p<0.001$).

At baseline, significant demographic and clinical differences were observed between eligible and ineligible patients (Table 2). Ineligible patients were older (median 51.0 vs. 33.0 years; $p<0.001$) and displayed a significantly higher prevalence of non-atopic comorbidities, including hypertension, diabetes, dyslipidemia, and prior venous thromboembolism. In contrast, the prevalence of classic atopic comorbidities, such as asthma, allergic rhinitis, and food allergy, was significantly lower in the ineligible group. The median follow-up duration was significantly shorter among ineligible patients (12.0 vs. 18.0 months; $p<0.001$). Sex distribution and disease duration were comparable between cohorts.

Baseline disease severity was significantly lower among ineligible patients, with lower mean EASI and DLQI scores (both $p<0.001$). While the baseline pruritus NRS was slightly lower in the ineligible cohort (mean 7.7 vs. 8.1; $p=0.014$), the absolute difference of 0.4 points falls well below the established minimal clinically important difference (MCID) for this measure (approximately 2–3 points) [8], suggesting that it does not represent a clinically meaningful variation in itch intensity.

Prior treatment patterns were broadly similar between cohorts, except for cyclosporine, which was less commonly used among ineligible patients (44.8% vs. 53.6%; $p=0.001$), and biologics, which were more frequently used in this cohort (16.3% vs. 9.2%; $p<0.001$).

Of the full cohort, 1758 patients (81.6%) were treated with biologic therapy and 396 (18.4%) received systemic JAKis. Systemic JAKis were more frequently used in the ineligible group than in the eligible group (26.8% vs. 15.7%; $p<0.001$), whereas biologic therapies were more common among eligible patients (84.3% vs. 73.2%; $p<0.001$).

The overall incidence of adverse events was comparable between eligible and ineligible patients across both treatment groups (Table 3). Among patients receiving biologic therapies, no adverse event occurred in 29.8% of eligible and 31.1% of ineligible patients ($p=0.625$). No significant differences were found in hospitalization rates, alopecia, arthralgias, blepharitis/

conjunctivitis, or injection site reactions. However, herpetic infections were significantly more frequent among ineligible patients (6.4% vs. 3.9%; $p=0.039$), while non-herpetic infections were reported only in the eligible group (1.2% vs. 0%; $p=0.032$). In the systemic JAKi group, the proportion of patients experiencing at least one adverse event tended to be higher in the ineligible cohort (52.9% vs. 42.6%; $p=0.051$). Notably, acneiform eruption (18.8% vs. 9.3%; $p=0.006$) and lipid abnormalities (19.6% vs. 12.0%; $p=0.043$) were significantly more common among ineligible patients. No significant differences were observed for hematologic abnormalities, infections, or thromboembolic events between the two subgroups.

DISCUSSION

In this large, multicenter real-world cohort of patients with AD treated with targeted systemic therapies, nearly one in four patients (23.9%) would have been ineligible for pivotal RCT. This observation highlights a persistent gap between the highly selected populations enrolled in clinical trials and the heterogeneous patients encountered in routine clinical practice. The main reasons for ineligibility were low baseline disease activity ($EASI<16$), older age, and the presence of comorbidities, particularly cardiovascular disease, mirroring exclusion criteria commonly applied in AD RCTs. Similar findings have been reported across other inflammatory dermatoses, where restrictive eligibility criteria limit the external validity of trial results and reduce their applicability to real-world settings [1, 5–7].

It is important to acknowledge that the group classified as ‘ineligible’ in our study represents a heterogeneous population. The comorbidities used as exclusion criteria in pivotal RCTs vary greatly in severity and clinical significance, and age ≥ 75 years encompasses individuals with markedly different levels of frailty and physiological reserve. Our classification therefore reflects the formal exclusion criteria applied in RCTs rather than an assessment of clinical unsuitability.

Table 2 Baseline demographic, clinical, and treatment characteristics of eligible vs. ineligible patients

Characteristic	Total (<i>n</i> = 2154)	Eligible (<i>n</i> = 1640)	Ineligible (<i>n</i> = 514)	<i>p</i> value
Female sex, <i>n</i> (%)	1005 (47.7)	777 (47.4)	234 (45.5)	0.490
Male sex, <i>n</i> (%)	1149 (53.3)	863 (52.6)	280 (54.5)	
Age, median (IQR), years	36.0 (29.0)	33.0 (24.0)	51.0 (41.0)	< 0.001
Duration of AD, median (IQR), years	18.0 (25.0)	18.0 (24.0)	19.0 (26.0)	0.614
Atopic comorbidities				
Allergic rhinitis, <i>n</i> (%)	497 (23.1)	394 (24.0)	103 (20.0)	< 0.001
Asthma, <i>n</i> (%)	464 (21.5)	367 (22.4)	97 (18.9)	< 0.001
Allergic conjunctivitis, <i>n</i> (%)	342 (15.9)	258 (15.7)	84 (16.3)	0.129
Food allergy, <i>n</i> (%)	169 (7.9)	139 (8.5)	30 (5.8)	0.002
Other comorbidities				
Hypertension, <i>n</i> (%)	115 (5.3)	72 (4.4)	43 (8.4)	0.001
Diabetes, <i>n</i> (%)	53 (2.5)	21 (1.3)	32 (6.2)	< 0.001
Dyslipidemia, <i>n</i> (%)	85 (3.9)	46 (2.8)	39 (7.6)	0.001
Depression/anxiety, <i>n</i> (%)	163 (7.6)	128 (7.8)	35 (6.8)	0.031
History of VTE, <i>n</i> (%)	3 (0.1)	0 (0.0)	3 (0.6)	0.045
Latent TB, <i>n</i> (%)	9 (0.4)	0 (0.0)	9 (1.8)	< 0.001
Baseline EASI, mean (SD)	23.5 (9.9)	26.4 (7.8)	14.0 (10.2)	< 0.001
Baseline DLQI, mean (SD)	16.9 (6.2)	17.7 (5.7)	14.3 (6.9)	< 0.001
Baseline pruritus NRS, mean (SD)	8.0 (1.6)	8.1 (1.4)	7.7 (2.0)	0.014
Previous treatment exposures				
Topical agents, <i>n</i> (%)	1804 (83.8)	1371 (83.6)	433 (84.2)	0.782
Cyclosporine, <i>n</i> (%)	1109 (51.5)	879 (53.6)	230 (44.8)	0.001
Other conventional systemic therapies ^a , <i>n</i> (%)	1462 (67.9)	1118 (68.2)	344 (66.9)	0.636
Phototherapy, <i>n</i> (%)	352 (16.3)	267 (16.3)	85 (16.5)	0.945
Biologic therapies ^b , <i>n</i> (%)	235 (10.9)	151 (9.2)	84 (16.3)	< 0.001
Systemic JAK inhibitors ^c , <i>n</i> (%)	60 (2.8)	45 (2.7)	15 (2.9)	0.955
Current therapy				
Biologic therapies ^b , <i>n</i> (%)	1758 (81.6)	1382 (84.3)	376 (73.2)	< 0.001
Systemic JAK inhibitors ^c , <i>n</i> (%)	396 (18.4)	258 (15.7)	138 (26.8)	< 0.001
Follow-up time (months), median (IQR)	18.0 (18.0)	18.0 (16.0)	12.0 (18.0)	< 0.001

Bold values indicate statistical significance (*p* 0.05)

AD atopic dermatitis, DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, IQR interquartile range, JAK Janus kinase, NRS Numeric Rating Scale, SD standard deviation, TB tuberculosis, VTE venous thromboembolism, Y years

^aCorticosteroids, methotrexate, azathioprine, and mofetil mycophenolate

^bDupilumab, tralokinumab

^cUpadacitinib, abrocitinib, baricitinib

Table 3 Distribution of adverse events by treatment and eligibility cohorts

Adverse event	Biologics ^a (<i>n</i> = 1758)			Systemic JAK inhibitors ^b (<i>n</i> = 396)		
	Eligible (<i>n</i> = 1382)	Ineligible (<i>n</i> = 376)	<i>p</i> value	Eligible (<i>n</i> = 258)	Ineligible (<i>n</i> = 138)	<i>p</i> value
Any adverse event	412 (29.8%)	117 (31.1%)	0.625	110 (42.6%)	73 (52.9%)	0.051
Hospitalization	2 (0.1%)	0 (0.0%)	1.000	1 (0.4%)	0 (0.0%)	1.000
Acneiform eruption	8 (0.6%)	0 (0.0%)	0.215	24 (9.3%)	26 (18.8%)	0.006
Alopecia	14 (1.0%)	2 (0.5%)	0.546	0 (0.0%)	0 (0.0%)	NA
Arthralgias	11 (0.8%)	7 (1.9%)	0.082	2 (0.8%)	3 (2.2%)	0.347
Blepharitis/ conjunctivitis	243 (17.6%)	71 (18.9%)	0.560	1 (0.4%)	1 (0.7%)	1.000
Hematologic abnormalities	17 (1.2%)	2 (0.5%)	0.397	23 (8.9%)	15 (10.9%)	0.529
Herpetic infection	54 (3.9%)	24 (6.4%)	0.039	17 (6.6%)	7 (5.1%)	0.547
Injection site reaction	12 (0.9%)	5 (1.3%)	0.383	NA	NA	NA
Facial erythema	57 (4.1%)	12 (3.2%)	0.410	0 (0.0%)	0 (0.0%)	NA
Lipid abnormalities	5 (0.4%)	4 (1.1%)	0.104	31 (12.0%)	27 (19.6%)	0.043
Non-herpetic infections	17 (1.2%)	0 (0.0%)	0.032	12 (4.7%)	6 (4.3%)	0.890
Venous thromboembolism	1 (0.1%)	0 (0.0%)	1.000	0 (0.0%)	2 (1.4%)	0.121
Other AE	109 (7.9%)	29 (7.7%)	0.911	41 (15.9%)	30 (21.7%)	0.148

AE adverse event, *JAK* janus kinase, *NA* not applicable

^aDupilumab, tralokinumab

^bUpadacitinib, abrocitinib, baricitinib

The pattern of ineligibility criteria differed between treatment classes. In the JAK inhibitor subgroup, most ineligible cases were excluded based on EASI < 16, whereas exclusions related to older age or cardiovascular comorbidities were uncommon. This contrasts with the biologic-treated cohort, in which ineligibility resulted from a broader combination of factors, including EASI < 16, age ≥ 75 years, and cardiovascular disease. Current safety communications advise caution when prescribing systemic JAKis in older patients or individuals with relevant cardiovascular risk factors, which likely contributes to the preferential use of biologics in these populations.

At baseline, ineligible patients differed substantially from eligible ones in several demographic and clinical aspects that are likely to influence both treatment selection and safety outcomes. They were significantly older (median 51 vs. 33 years) and had a higher prevalence of non-atopic comorbidities, consistent with a more complex clinical profile and higher cardiovascular risk. Conversely, atopic comorbidities were generally less frequent in the ineligible group, possibly reflecting the shift from a classic “atopic phenotype” to a later-onset or comorbidity-driven disease subtype in older patients.

Baseline disease severity was lower among ineligible patients across all assessed measures. This likely reflects not only the broader use of

targeted systemic therapies in real-world practice, where treatment decisions are influenced by quality-of-life impact and comorbidity burden rather than strict EASI thresholds, but also fundamental differences in study design between clinical trials and real-world cohorts. In RCTs, long washout periods and the prohibition of topical therapy prior to enrollment often result in higher baseline EASI scores. Conversely, in clinical practice, patients typically transition directly between systemic or topical treatments without such washout intervals, leading to lower measured disease activity at treatment initiation. Consequently, many patients with EASI < 16 in this cohort may not necessarily represent mild disease but rather partial responders or those with secondary loss of efficacy to previous therapies.

When analyzing adverse events, distinct patterns emerged between treatment subgroups. Among patients treated with biologic therapies, the frequency and type of adverse events were largely similar between eligible and ineligible patients. No significant differences were observed in the overall rate of adverse events, hospitalizations, or most specific categories. A slightly higher frequency of herpetic infections was noted among ineligible patients, whereas non-herpetic infections were less common in this group. These findings suggest that the safety profile of biologics, such as dupilumab and tralokinumab, remains consistent even in populations with greater comorbidity burden.

In the systemic JAKi group, the overall rate of adverse events tended to be higher in ineligible patients compared with eligible ones, although this difference was only borderline significant ($p=0.051$). Within this subgroup, acneiform eruption and lipid abnormalities occurred more frequently in ineligible patients. Ineligible patients in our cohort carried a greater burden of non-atopic comorbidities, including dyslipidemia, which may increase susceptibility to metabolic adverse events and heighten the expression of known class effects of JAK inhibitors on lipid regulation. Although no major adverse cardiovascular events (MACE) events were identified in this cohort, this absence must be interpreted cautiously. Our follow-up duration and retrospective design limit the ability to

detect rare but clinically relevant cardiovascular outcomes.

Although a substantial proportion of patients in this cohort would not have qualified for participation in pivotal RCTs, the overall safety profile of both biologics and JAK inhibitors remained favorable. No new or unexpected safety signals emerged in these real-world populations, even among patients with significant comorbidities or advanced age. These findings support the feasibility of safely using targeted systemic therapies in broader, more heterogeneous clinical settings, reflecting their robustness and tolerability beyond the highly selected populations enrolled in clinical trials.

This study has inherent limitations typical of retrospective analyses, including potential underreporting of mild adverse events and heterogeneity in data recording across participating centers. The shorter follow-up duration among ineligible patients may have influenced adverse event detection, potentially underestimating event frequency in this group. Particularly, further prospective studies with longer follow-up will be required to clarify whether the numerically higher rate of adverse events in ineligible patients treated with JAK inhibitors has meaningful implications.

Real-world evidence (RWE) such as these are essential to complement RCT findings, refining our understanding of treatment safety, especially among older, comorbid, or polypharmacy populations often underrepresented in controlled studies.

CONCLUSION

Approximately one quarter of real-world patients with AD treated with targeted systemic therapies would not have fulfilled the eligibility criteria of pivotal RCTs. Ineligible patients had lower disease activity, were older, and presented with more non-atopic comorbidities.

Among those receiving biologic therapies, no major differences in safety outcomes were observed between eligible and ineligible patients, supporting a consistent tolerability profile across groups.

Conversely, in the JAKi group, there appeared to be a higher overall frequency of adverse events among ineligible patients, with acneiform eruption and lipid abnormalities emerging as the most distinct differences between cohorts.

These findings highlight the importance of further research to confirm this trend of increased adverse events among ineligible patients treated with JAKis and to determine whether such differences translate into clinically meaningful outcomes, particularly regarding cardiovascular risk and long-term safety.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jensen Yeung has been an advisor, consultant, speaker, and/or investigator for AbbVie, Amgen, Anacor, Apogee, Arcutis, Astellas, Bausche, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Centocor, Coherus, Dermira, Forward, Fresenius Kabi, Galderma, Incyte, Janssen, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Takeda, UCB, and Xenon. Vimal Prajapati has been an advisor, consultant, and/or speaker for AbbVie, Actelion, Amgen, Apogee Therapeutics, Aralez, Arcutis, Aspen, Bausch Health, BioScript Solutions, Boehringer Ingelheim, Bristol Myers Squibb, Canadian Psoriasis Network, Celgene, Celltrion, Cipher, CorEvitas, Eczema Society of Canada, Eli Lilly, Galderma, GlaxoSmithKline, Homeocan, Incyte, JAMP Pharma, J&J Innovative Medicine, Janssen, Johnson & Johnson, LEO Pharma, Medexus, Novartis, Organon, Pedipharm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, Tribute, UCB, and Valeant; investigator for AbbVie, AnaptysBio, Apogee Therapeutics, Arcutis, Arena, Asana, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CorEvitas, Dermavant, Dermira, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Meiji Pharma, Nektar Therapeutics, Nimbus Lakshmi, Novartis, Pfizer, RAPT Therapeutics, Regeneron, Reistone, Sanofi Genzyme, Sun Pharma, Takeda, and UCB; received grants from AbbVie, Bausch

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Ethical Approval. This study was a retrospective, non-interventional analysis conducted using fully de-identified, anonymized, and aggregated data collected as part of routine clinical practice. In accordance with applicable national and institutional regulations at the participating centers, formal ethics committee approval and informed consent were not required for this type of study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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advantages, and limitations. *Dermatol Ther*. 2022;35(12):e15909.

2. Schmitt-Egenolf M. The disruptive force of real-world evidence. *J Clin Med*. 2023;12(12):4026.
3. Lam M, Zhu JW, Maqbool T, et al. Inclusion of older adults in randomized clinical trials for systemic medications for atopic dermatitis: a systematic review. *JAMA Dermatol*. 2020;156(11):1240–5.
4. Sreekantaswamy SA, Tully J, Edelman LS, Supiano MA, Butler D. The underrepresentation of older adults in clinical trials of Janus kinase inhibitors in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2022;87(5):1174–6.
5. Garcia-Doval I, Carretero G, Vanaclocha F, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. *Arch Dermatol*. 2012;148(4):463–70. <https://doi.org/10.1001/archdermatol.2011.2768>.
6. Mason KJ, Barker JNWN, Smith CH, et al. Comparison of drug discontinuation, effectiveness, and safety between clinical trial eligible and ineligible patients in BADBIR. *JAMA Dermatol*. 2018;154(5):581–8.
7. Regnault MM, Castañeda-Sanabria J, Tran MHTD, et al. Users of biologics in clinical practice: would they be eligible for phase III clinical studies? Cohort study in the French Psoriasis Registry PSOBIOTEQ. *J Eur Acad Dermatol Venereol*. 2020;34(2):293–300.
8. Reich A, Riepe C, Anastasiadou Z, et al. Itch assessment with visual analogue scale and numerical rating scale: determination of minimal clinically important difference in chronic itch. *Acta Derm Venereol*. 2016;96(7):978–80.

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REFERENCES

1. Shen J, Liu Y. Real-world evidence of biological agents in dermatology: a review of its applications,