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ORIGINAL RESEARCH

Cumulative Disease Control with Upadacitinib in Moderate-to-Severe Atopic Dermatitis—A 52-Week Multicenter Real-World Study: IL-AD (Italian Landscape Atopic Dermatitis)

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ABSTRACT

Introduction: Fixed-timepoint endpoints may not fully capture longitudinal treatment benefit in atopic dermatitis (AD). We evaluated the 52-week real-world effectiveness and safety of upadacitinib, focusing on cumulative disease control.

Methods: This multicenter retrospective analysis of prospectively collected LANDSCAPE

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registry data included patients with moderate-to-severe AD receiving stable upadacitinib 15 mg or 30 mg once daily. Patients who underwent dose modification from 15 to 30 mg or from 30 to 15 mg during the 52-week observation period were excluded from the present analysis to ensure that longitudinal outcomes and cumulative disease-control estimates could be consistently attributed to a stable upadacitinib dose. Outcomes were assessed at baseline and weeks 16, 32, and 52. Moderate disease control was defined as EASI75 plus peak pruritus numerical rating scale (pp-NRS) ≤ 4, and optimal disease control/minimal disease activity (MDA) as EASI90 plus pp-NRS ≤ 1. Cumulative control was estimated as equivalent days in target using a time-in-target approach.

***Results*:** Overall, 433 patients were included; 315 (72.7%) received 15 mg and 118 (27.3%) received 30 mg. At week 52, EASI75 and EASI90 were achieved by 85.7% and 72.7% of patients, respectively; moderate and optimal disease control/MDA were achieved by 80.6% and 62.6%. Patients spent a mean of 253.3 ± 101.9 equivalent days in moderate disease control and 176.1 ± 124.4 days in optimal control/MDA. Sustained moderate and optimal disease control from weeks 16 to 52 were achieved by 63.0% and 38.3%, respectively. Overall, 27.0% experienced at least one adverse event, with no permanent treatment discontinuations due to adverse events.

***Conclusion*:** Upadacitinib provided sustained real-world disease control over 52 weeks. Time-in-target measures may complement conventional endpoints by better reflecting persistence of therapeutic benefit.

Keywords: Atopic dermatitis; Upadacitinib; Real-world evidence; Minimal disease activity; Time-in-target

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Key Summary Points

Why carry out this study?

Conventional fixed-timepoint endpoints may not fully capture the longitudinal therapeutic benefit experienced by patients with chronic relapsing atopic dermatitis, particularly the persistence of clinically meaningful disease control over time.

Although upadacitinib has demonstrated high effectiveness in clinical trials and real-world studies, evidence quantifying cumulative disease control over a full year of treatment in routine clinical practice remains limited.

This study aimed to evaluate the 52-week real-world effectiveness and safety of upadacitinib, with a specific focus on quantifying cumulative moderate and optimal disease control using a time-in-target approach.

What was learned from the study?

At week 52, EASI75 and EASI90 were achieved by 85.7% and 72.7% of patients, respectively, while moderate and optimal disease control/minimal disease activity were achieved by 80.6% and 62.6%. Patients spent an estimated mean of 253 days in moderate disease control and 176 days in optimal disease control during the first treatment year.

Sustained moderate and optimal disease control from week 16 through week 52 were achieved by 63.0% and 38.3% of patients, respectively, indicating that a substantial proportion of patients maintained clinically meaningful control over time.

These findings suggest that time-in-target measures may complement conventional fixed-timepoint endpoints by providing additional information on the persistence of therapeutic benefit in routine clinical practice.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a relapsing course and a substantial impact on quality of life, sleep, daily activities and psychosocial well-being [1, 2]. The treatment landscape of moderate-to-severe AD has rapidly evolved with the introduction of targeted systemic therapies, including biologics and oral Janus kinase (JAK) inhibitors [1, 3]. Upadacitinib, an oral selective JAK1 inhibitor, has demonstrated rapid and sustained efficacy on both clinician-reported and patient-reported outcomes in randomized clinical trials [4–6]. Real-world studies have subsequently confirmed its effectiveness and safety in broader clinical populations, including patients previously exposed to systemic agents and biologics [7, 8]. However, most available evidence relies on fixed-timepoint endpoints such as EASI75, EASI90, Investigator Global Assessment (IGA) 0/1 or pruritus numerical rating scale responses [7, 8]. Although clinically relevant, these measures may not fully reflect the longitudinal experience of patients with a chronic relapsing disease [9, 10].

Treat-to-target and AHEAD recommendations have emphasized the importance of combining clinician-reported and patient-reported outcomes and of pursuing ambitious treatment goals, including minimal disease activity (MDA) [9, 10]. Similarly, recent International Eczema Council definitions of low disease activity and remission support the use of composite disease-control states [11]. Importantly, single-visit response rates do not distinguish transient improvement from sustained control over time. A recent post hoc analysis of phase 3 trials addressed this limitation by quantifying the time patients spent with clear or almost clear skin and no or minimal itch during treatment with upadacitinib [12]. However, real-world evidence on cumulative disease control with upadacitinib over a full year remains limited [7, 8, 11–14].

Therefore, this multicenter real-world study evaluated the 52-week effectiveness and safety of upadacitinib in patients with moderate-to-severe AD, with a specific focus on cumulative disease control. In addition to conventional endpoints such as EASI75 and EASI90, we assessed moderate disease control, defined as EASI75 plus pp-NRS ≤ 4, and optimal disease control/MDA, defined as EASI90 plus pp-NRS ≤ 1, and estimated the equivalent days spent in each disease-control state using a time-in-target approach.

METHODS

Study Design and Population

This was a multicenter, real-world, retrospective analysis of prospectively collected data from the ongoing LANDSCAPE clinical registry, including patients with moderate-to-severe atopic dermatitis treated with upadacitinib and followed for up to 52 weeks. Clinical and treatment data were prospectively recorded within the registry during routine clinical practice. Patients were stratified according to the prescribed upadacitinib dose, namely 15 mg or 30 mg once daily. The initial upadacitinib dose was selected by the treating physician as part of routine clinical practice, taking into account the approved prescribing information and individual patient characteristics, including age, disease severity, previous systemic treatment exposure, comorbidities, and patient-specific safety considerations. No study-specific algorithm or random allocation procedure was used to determine the starting dose. Patients who underwent dose modification from 15 to 30 mg or from 30 to 15 mg during the 52-week observation period were excluded from the present analysis to ensure that longitudinal outcomes and cumulative disease-control estimates could be consistently attributed to a stable upadacitinib dose. Demographic and clinical characteristics, disease phenotype, difficult-to-treat area involvement, atopic and non-atopic comorbidities, previous systemic treatments, clinical severity scores, patient-reported outcomes, treatment response, and adverse events (AEs) were collected.

Baseline characteristics included age, sex, body mass index, disease duration, clinical phenotype, head/neck, hand and genital involvement, family history of atopy, allergic comorbidities, cardiovascular/metabolic comorbidities, and previous exposure to conventional systemic agents, dupilumab, tralokinumab, and JAK inhibitors. Baseline disease severity was assessed using EASI, IGA, peak pruritus numerical rating scale (pp-NRS), and sleep NRS.

Clinical Assessments and Outcomes

Patients were evaluated at baseline and during follow-up, including weeks 16, 32, and 52. Because disease-control status was assessed only at scheduled visits, the resulting time-in-target values should be interpreted as estimates based on intermittent observations rather than as directly observed daily disease-control status. The week 32 assessment provided an intermediate anchor between weeks 16 and 52, thereby reducing the duration over which interpolation was required. Clinical disease severity was assessed using EASI and IGA, while symptom burden was evaluated using pp-NRS and sleep NRS. The main efficacy endpoints were EASI75 and EASI90, defined as at least 75% and 90% improvement from baseline EASI, respectively. Moderate disease control was defined as simultaneous achievement of EASI75 and pp-NRS ≤ 4. Optimal disease control/minimal disease activity (MDA) was operationalized as simultaneous achievement of EASI90 and pp-NRS ≤ 1. To capture the longitudinal burden of disease control beyond single timepoint responses, cumulative disease control was assessed using a time-in-target approach. For each patient, moderate disease control and optimal disease control/MDA were coded as binary variables at each follow-up visit. The estimated number of equivalent days spent in target from baseline to week 52 was calculated using the trapezoidal rule across the scheduled time intervals, assuming linear changes in disease-control status between consecutive assessments. Accordingly, these values represent estimated equivalent days in target rather than directly observed daily disease-control status. The maximum theoretical value was 364 days,

corresponding to 52 weeks of continuous target achievement. Sustained response was defined as achievement of the respective endpoint at week 16, week 32, and week 52. Sustained endpoints included sustained EASI75, sustained EASI90, sustained moderate disease control, and sustained optimal disease control/MDA.

Safety Assessment

AEs were evaluated cumulatively over the 52-week observation period, without stratification by visit date. Events reported at different follow-up visits were pooled, and repeated reporting of the same AE in the same patient was counted once for each AE category. The proportion of patients experiencing at least one AE and the frequency of individual AEs were reported overall and according to upadacitinib dose.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation, while categorical variables were reported as number and percentage. Percentages were calculated on available data. Comparisons between upadacitinib 15 mg and 30 mg groups were performed using Welch's *t* test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. All statistical tests were two-sided, and p values <0.05 were considered statistically significant. Given the observational nature of the study and the non-randomized dose allocation, comparisons between dose groups were considered exploratory.

Ethical Approval

Ethical approval for the present analysis was obtained within the framework of the ongoing LANDSCAPE clinical registry. The specific amendment covering the present analysis was approved by the Territorial Ethics Committee of the Calabria Region (Comitato Etico Territoriale Regione Calabria; Protocol No. 164/2026) on June 22, 2026. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants had provided written informed consent for the use of their anonymized clinical data within the registry.

RESULTS

Study Population and Baseline Characteristics

Patients who underwent upadacitinib dose modification from 15 to 30 mg or from 30 to 15 mg during the 52-week observation period were excluded from the analytical cohort, as predefined in the study design. This approach was adopted to ensure that longitudinal clinical outcomes and cumulative time-in-target measures could be consistently attributed to a stable upadacitinib dose throughout follow-up. A total of 433 patients receiving a stable upadacitinib dose were therefore included in the present analysis, of whom 315 (72.7%) received upadacitinib 15 mg and 118 (27.3%) received 30 mg. Baseline demographic and clinical characteristics are summarized in Table 1. The overall mean age was 40.5 ± 15.5 years, mean BMI was 24.4 ± 3.8 kg/m^2 and mean disease duration was 23.5 ± 13.8 years. Male patients accounted for 59.1% of the cohort.

At baseline, mean EASI was 20.3 ± 11.2, mean IGA was 3.2 ± 0.9, mean pp-NRS was 7.2 ± 2.5, and mean sleep NRS was 5.7 ± 3.4. Baseline disease severity was generally comparable between patients receiving upadacitinib 15 mg and 30 mg, with no significant differences in age, BMI, disease duration, EASI, IGA, pp-NRS, or sleep NRS.

The most common clinical phenotype was classic AD, observed in 86.4% of patients, followed by generalized inflammatory, nummular eczema, palmoplantar, prurigo nodularis, erythrodermic, and generalized lichenoid phenotypes. Clinical phenotype distribution did not significantly differ between the upadacitinib 15 mg and 30 mg groups ($p=0.096$). Difficult-to-treat area involvement was frequent, particularly head/neck involvement, which was comparable between groups (63.2% vs 65.3%), and

Table 1 Baseline demographic and clinical characteristics of the study population

Characteristic	Overall, *n* = 433	UPA 15 mg, *n* = 315	UPA 30 mg, *n* = 118	*p* value
Age, years	40.5 ± 15.5	41.1 ± 16.0	39.1 ± 14.0	0.205
Sex				
Male	256 (59.1%)	182 (57.8%)	74 (62.7%)	0.352
Female	177 (40.9%)	133 (42.2%)	44 (37.3%)	0.352
BMI, kg/m^2	24.4 ± 3.8	24.2 ± 3.6	24.8 ± 4.3	0.179
Disease duration, years	23.5 ± 13.8	23.4 ± 13.9	24.0 ± 13.8	0.688
Family history of atopy	131 (30.3%)	90 (28.6%)	41 (34.7%)	0.213
Difficult-to-treat area involvement				
Head/neck involvement	276 (63.7%)	199 (63.2%)	77 (65.3%)	0.689
Hand involvement	199 (46.0%)	151 (47.9%)	48 (40.7%)	0.177
Genital involvement	54 (12.5%)	46 (14.6%)	8 (6.8%)	0.028*
Allergic comorbidities				
Allergic conjunctivitis	96 (22.2%)	61 (19.4%)	35 (29.7%)	0.022*
Allergic rhinitis	133 (30.7%)	88 (27.9%)	45 (38.1%)	0.041*
Allergic asthma	90 (20.8%)	63 (20.0%)	27 (22.9%)	0.511
Food allergy	43 (9.9%)	26 (8.3%)	17 (14.4%)	0.057
Other comorbidities				
Hypertension	44 (10.2%)	34 (10.8%)	10 (8.5%)	0.477
Type II diabetes	3 (0.7%)	3 (1.0%)	0 (0.0%)	0.566
Dyslipidemia	23 (5.3%)	18 (5.7%)	5 (4.2%)	0.542
MACE	6 (1.4%)	6 (1.9%)	0 (0.0%)	0.196
Previous systemic therapy				
Conventional systemic therapy	228 (52.7%)	165 (52.4%)	63 (53.4%)	0.851
Dupilumab	205 (47.3%)	151 (47.9%)	54 (45.8%)	0.687
Tralokinumab	30 (6.9%)	24 (7.6%)	6 (5.1%)	0.355
JAK Inhibitors	15 (3.5%)	6 (1.9%)	9 (7.6%)	0.007*
Clinical phenotype				
Classic	374 (86.4%)	271 (86.0%)	103 (87.3%)	0.096[a]
Nummular eczema	13 (3.0%)	10 (3.2%)	3 (2.5%)	
Erythroderma	8 (1.8%)	8 (2.5%)	0 (0.0%)	
Generalized inflammatory	14 (3.2%)	9 (2.9%)	5 (4.2%)	
Generalized lichenoid	6 (1.4%)	4 (1.3%)	2 (1.7%)	

Table 1 continued

Characteristic	Overall, $n = 433$	UPA 15 mg, $n = 315$	UPA 30 mg, $n = 118$	p value
Palmoplantar	9 (2.1%)	4 (1.3%)	5 (4.2%)	
Prurigo nodularis	9 (2.1%)	9 (2.9%)	0 (0.0%)	

Data are shown overall and stratified by upadacitinib dose. Continuous variables are reported as mean ± standard deviation and categorical variables as *n* (%). Percentages were calculated on available data. *P* values refer to comparisons between the upadacitinib 15 mg and 30 mg groups and were calculated using Welch's *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate

AD atopic dermatitis, *BMI* body mass index, *EASI* Eczema Area and Severity Index, *IGA* Investigator Global Assessment, *JAK* Janus kinase, *MACE* major adverse cardiovascular events, *NRS* numerical rating scale, *pp-NRS* peak pruritus numerical rating scale, *UPA* upadacitinib

*Nominal p values < 0.05 are considered statistically significant

[a]p value refers to the overall chi-square test comparing the distribution of mutually exclusive clinical phenotype categories between dose groups

hand involvement (47.9% vs 40.7%). Genital involvement was significantly more frequent in patients receiving upadacitinib 15 mg than in those receiving 30 mg (14.6% vs 6.8%, $p = 0.028$). Conversely, allergic conjunctivitis (19.4% vs 29.7%, $p = 0.022$), allergic rhinitis (27.9% vs 38.1%, $p = 0.041$), and previous exposure to JAK inhibitors (1.9% vs 7.6%, $p = 0.007$) were more frequent in the upadacitinib 30 mg group. Previous exposure to conventional systemic therapies, dupilumab, and tralokinumab did not significantly differ between groups. The cumulative number of prior systemic therapies per patient was not systematically recorded and therefore could not be reliably compared between dose groups. Overall, baseline clinical severity and phenotype distribution were broadly comparable between dose groups, although selected categorical variables showed significant between-group differences. Baseline characteristics and between-group comparisons are shown in Table 1.

Clinical Response and Disease Control

Clinical response and disease control endpoints are reported in Table 2. At week 16, EASI75 was achieved by 357/433 patients (82.4%), while EASI90 was achieved by 278/433 patients (64.2%). At week 52, response rates remained high, with EASI75 and EASI90 achieved by 371/433 patients (85.7%) and 315/433 patients (72.7%), respectively.

Moderate disease control was achieved by 334/433 patients (77.1%) at week 16 and by 349/433 patients (80.6%) at week 52. Optimal disease control/MDA was achieved by 235/433 patients (54.3%) at week 16 and by 271/433 patients (62.6%) at week 52. Among patients achieving EASI90, 43/278 (15.5%) at week 16 and 44/315 (14.0%) at week 52 did not achieve optimal disease control/MDA because pp-NRS remained > 1, indicating residual pruritus despite high-level skin response in a minority of EASI90 responders.

At week 16, treatment response was already high in both groups, although patients receiving upadacitinib 15 mg achieved significantly higher rates of EASI75 than those receiving 30 mg (84.8% vs 76.3%, $p = 0.039$) and significantly higher rates of moderate disease control (80.6% vs 67.8%, $p = 0.005$). By contrast, no significant between-group differences were observed at week 16 for EASI90 (65.7% vs 60.2%, $p = 0.284$) or optimal control/MDA (56.8% vs 47.5%, $p = 0.081$). At week 52, clinical response and disease control were sustained, with EASI75, EASI90, moderate disease control,and optimal control/MDA achieved in the overall population by 85.7%, 72.7%, 80.6%, and 62.6% of patients, respectively. At this timepoint, no significant differences were observed between upadacitinib 15 mg and

Table 2 Efficacy outcomes and cumulative disease control

Endpoint	Overall	UPA 15 mg	UPA 30 mg	*p* value
EASI75 W16	357 (82.4%)	267 (84.8%)	90 (76.3%)	0.039*
EASI75 W52	371 (85.7%)	273 (86.7%)	98 (83.1%)	0.339
EASI90 W16	278 (64.2%)	207 (65.7%)	71 (60.2%)	0.284
EASI90 W52	315 (72.7%)	233 (74.0%)	82 (69.5%)	0.352
Moderate control W16	334 (77.1%)	254 (80.6%)	80 (67.8%)	0.005*
Moderate control W52	349 (80.6%)	257 (81.6%)	92 (78.0%)	0.396
Optimal control/MDA W16	235 (54.3%)	179 (56.8%)	56 (47.5%)	0.081
Optimal control/MDA W52	271 (62.6%)	201 (63.8%)	70 (59.3%)	0.390
Moderate control days W0–W52	253.3 ± 101.9	261.0 ± 96.2	232.8 ± 113.6	0.018*
Optimal/MDA days W0–W52	176.1 ± 124.4	180.9 ± 123.2	163.1 ± 127.0	0.192
Sustained EASI75 W16–W52	308 (71.1%)	228 (72.4%)	80 (67.8%)	0.349
Sustained EASI90 W16–W52	211 (48.7%)	159 (50.5%)	52 (44.1%)	0.235
Sustained moderate control W16–W52	273 (63.0%)	207 (65.7%)	66 (55.9%)	0.060
Sustained MDA W16–W52	166 (38.3%)	124 (39.4%)	42 (35.6%)	0.472

Data are shown overall and stratified by upadacitinib dose. Categorical outcomes are reported as *n* (%), and cumulative disease control outcomes as mean ± standard deviation. Moderate disease control was defined as EASI75 plus pp-NRS ≤ 4, and optimal control/MDA as EASI90 plus pp-NRS ≤ 1. Sustained response required target achievement at weeks 16, 32, and 52. *P* values refer to comparisons between upadacitinib 15 mg and 30 mg groups

EASI Eczema Area and Severity Index, *MDA* minimal disease activity, *pp-NRS* peak pruritus numerical rating scale, *UPA* upadacitinib

*p values < 0.05 are considered statistically significant

30 mg for EASI75 (86.7% vs 83.1%, $p = 0.339$), EASI90 (74.0% vs 69.5%, $p = 0.352$), moderate disease control (81.6% vs 78.0%, $p = 0.396$), or optimal control/MDA (63.8% vs 59.3%, $p = 0.390$). These longitudinal response patterns are shown in Fig. 1.

Longitudinal Changes in Clinical Scores

At baseline, disease severity was comparable between upadacitinib 15 mg and 30 mg groups, with no significant differences in EASI, IGA, pp-NRS, or sleep NRS. Mean EASI, IGA, pp-NRS, and sleep NRS progressively decreased throughout the 52-week observation period, as shown in Table 3. In the overall population, mean EASI decreased from 20.3 ± 11.2 at baseline to 2.6 ± 4.5 at week 16, 2.0 ± 3.9 at week 32, and 1.9 ± 4.2 at week 52. Similarly, mean IGA decreased from 3.2 ± 0.9 at baseline to 0.7 ± 0.9 at week 16, 0.6 ± 0.8 at week 32, and 0.5 ± 0.8 at week 52. Patient-reported outcomes also improved markedly, with pp-NRS decreasing from 7.2 ± 2.5 at baseline to 1.5 ± 2.2 at week 16, 1.5 ± 2.3 at week 32, and 1.4 ± 2.3 at week 52, while sleep NRS decreased from 5.7 ± 3.4 to 0.7 ± 1.7, 0.6 ± 1.7, and 0.5 ± 1.5, respectively. At week 16, patients receiving upadacitinib 15 mg had significantly lower EASI (2.2 ± 3.9 vs 3.5 ± 5.9, $p = 0.021$), IGA (0.6 ± 0.8 vs 0.9 ± 1.0, $p = 0.036$), and pp-NRS scores (1.3 ± 2.1 vs

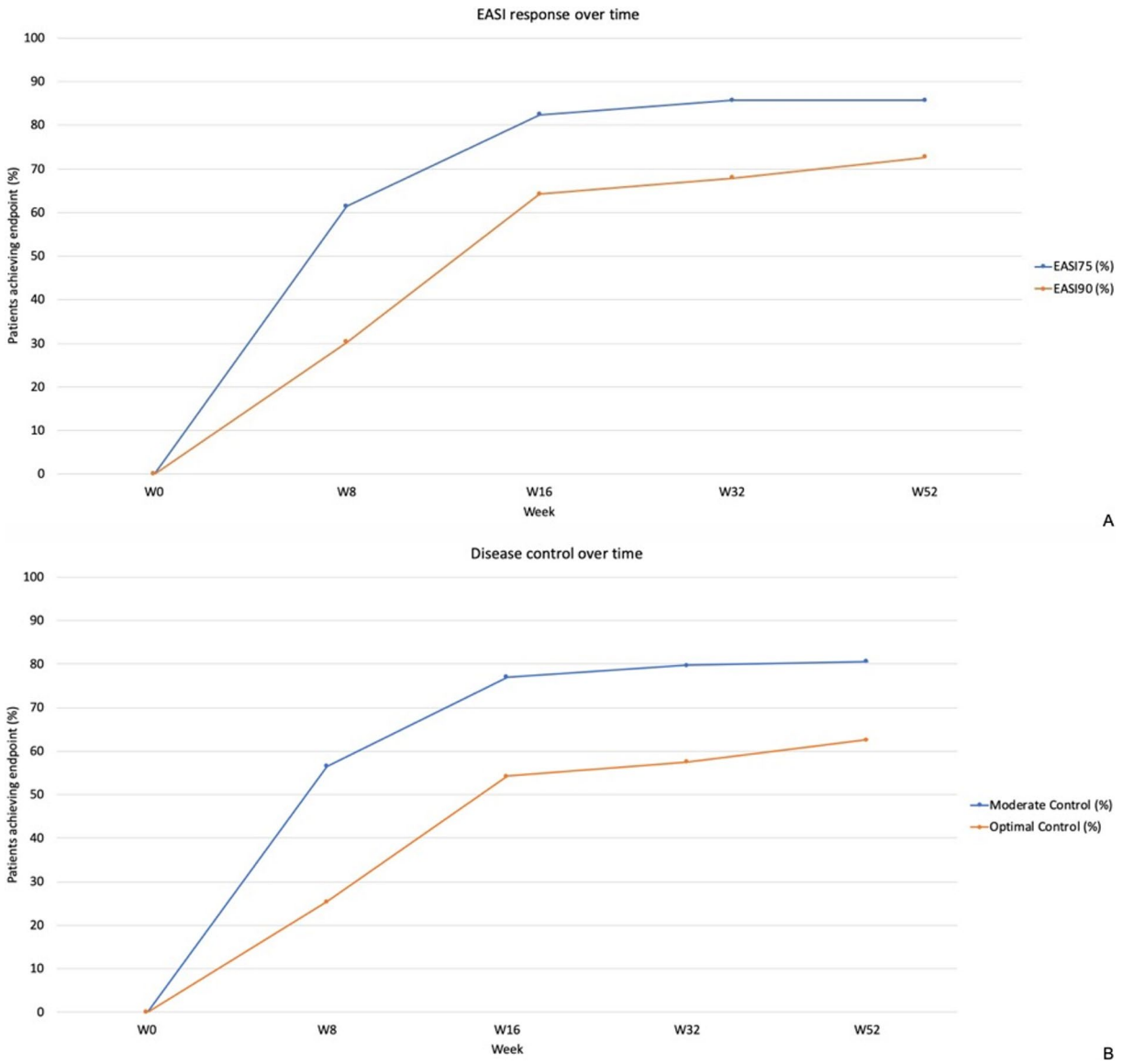

Fig. 1 Longitudinal achievement of clinical response and disease control targets during upadacitinib treatment. **a** Proportion of patients achieving EASI75 and EASI90 from baseline to week 52. **b** Proportion of patients achieving moderate disease control and optimal disease control/minimal disease activity from baseline to week 52. *EASI75* ≥ 75% improvement in Eczema Area and Severity Index, *EASI90* ≥ 90% improvement in Eczema Area and Severity Index

1.9 ± 2.5, $p = 0.023$) than those receiving 30 mg, whereas sleep NRS did not differ significantly. At week 32, only IGA remained significantly lower in the 15 mg group (0.5 ± 0.8 vs 0.8 ± 0.9, $p = 0.016$). By week 52, no significant differences between dose groups were observed for any clinical or patient-reported score.

Cumulative Disease Control and Sustained Response

When the time-in-target approach was used, patients spent a mean of 253.3 ± 101.9 equivalent days in moderate disease control during the first year of treatment, while the

Table 3 Longitudinal clinical scores during upadacitinib treatment

Outcome	Week	Overall	UPA 15 mg	UPA 30 mg	*p* value
EASI	W0	20.3 ± 11.2	20.0 ± 11.3	21.1 ± 11.1	0.342
	W16	2.6 ± 4.5	2.2 ± 3.9	3.5 ± 5.9	0.021*
	W32	2.0 ± 3.9	1.8 ± 3.5	2.7 ± 4.7	0.078
	W52	1.9 ± 4.2	1.9 ± 4.4	2.0 ± 3.6	0.784
IGA	W0	3.2 ± 0.9	3.2 ± 0.9	3.1 ± 1.0	0.530
	W16	0.7 ± 0.9	0.6 ± 0.8	0.9 ± 1.0	0.036*
	W32	0.6 ± 0.8	0.5 ± 0.8	0.8 ± 0.9	0.016*
	W52	0.5 ± 0.8	0.5 ± 0.8	0.6 ± 0.9	0.115
pp-NRS	W0	7.2 ± 2.5	7.2 ± 2.5	7.2 ± 2.4	0.969
	W16	1.5 ± 2.2	1.3 ± 2.1	1.9 ± 2.5	0.023*
	W32	1.5 ± 2.3	1.4 ± 2.2	1.8 ± 2.6	0.179
	W52	1.4 ± 2.3	1.3 ± 2.2	1.6 ± 2.5	0.307
Sleep NRS	W0	5.7 ± 3.4	5.7 ± 3.4	5.5 ± 3.4	0.527
	W16	0.7 ± 1.7	0.7 ± 1.8	0.8 ± 1.7	0.724
	W32	0.6 ± 1.7	0.5 ± 1.5	0.9 ± 2.1	0.096
	W52	0.5 ± 1.5	0.5 ± 1.5	0.6 ± 1.6	0.403

Data are shown overall and stratified by upadacitinib dose. Values are reported as mean ± standard deviation with available *n*. *P* values refer to comparisons between upadacitinib 15 mg and 30 mg groups at each timepoint

EASI Eczema Area and Severity Index, *IGA* Investigator Global Assessment, *NRS* numerical rating scale, *pp-NRS* peak pruritus numerical rating scale, *UPA* upadacitinib

*p values < 0.05 are considered statistically significant

corresponding value for optimal disease control/MDA was 176.1 ± 124.4 days. When stratified by dose, patients receiving upadacitinib 15 mg spent significantly more days in moderate disease control than those receiving 30 mg (261.0 ± 96.2 vs 232.8 ± 113.6 days, $p = 0.018$). By contrast, no significant difference between dose groups was observed for optimal control/MDA days (180.9 ± 123.2 vs 163.1 ± 127.0 days, $p = 0.192$). These cumulative disease control outcomes are reported in Table 2 and displayed in Fig. 2.

Sustained EASI75 from week 16 to week 52 was achieved by 308/433 patients (71.1%), while sustained EASI90 was achieved by 211/433 patients (48.7%). Sustained moderate disease control was observed in 273/433 patients (63.0%), and sustained optimal control/MDA was achieved by 166/433 patients (38.3%). When stratified by dose, no statistically significant differences were observed between upadacitinib 15 mg and 30 mg for sustained EASI75 (72.4% vs 67.8%, $p = 0.349$), sustained EASI90 (50.5% vs 44.1%, $p = 0.235$), sustained moderate disease control (65.7% vs 55.9%, $p = 0.060$), or sustained optimal control/MDA (39.4% vs 35.6%, $p = 0.472$). However, sustained moderate disease control was numerically higher in the 15 mg group, although this difference did not reach statistical significance. Sustained response outcomes are reported in Table 2 and displayed in Fig. 3.

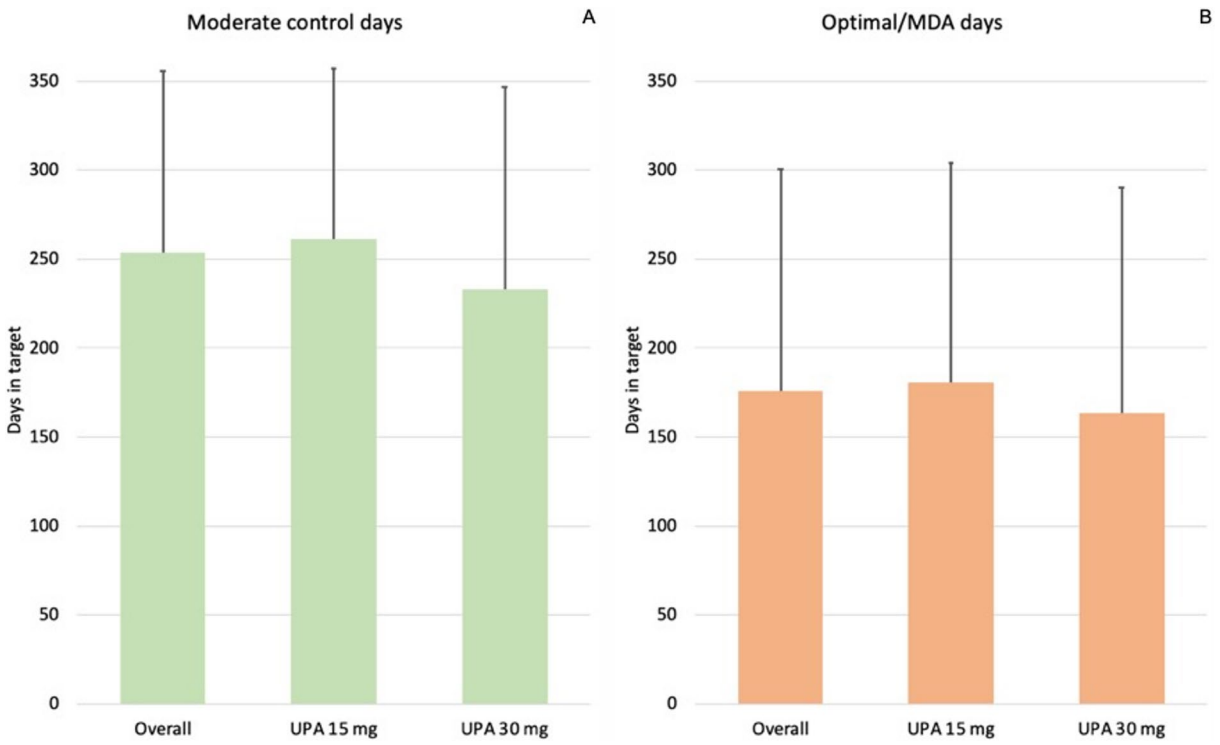

Fig. 2 Cumulative disease control during the first year of upadacitinib treatment. Moderate disease control and optimal control/minimal disease activity were quantified as the number of equivalent days spent in target from baseline to week 52 using a time-in-target approach. Data are shown as mean ± standard deviation in the overall population and according to upadacitinib dose. Moderate disease control days were significantly higher in patients receiving upadacitinib 15 mg compared with those receiving 30 mg ($p = 0.018$), whereas no significant difference was observed for optimal control/MDA days ($p = 0.192$). *MDA* minimal disease activity, *UPA* upadacitinib

Safety

AEs are summarized in Table 4. Overall, 117/433 patients (27.0%) reported at least one AE during the 52-week observation period, with comparable rates between the upadacitinib 15 mg and 30 mg groups (27.0% vs 27.1%, $p = 0.978$). The most frequently reported AEs were hypercholesterolemia (36/433, 8.3%), acne/JAKne (34/433, 7.9%), CPK increase (18/433, 4.2%), and hypertriglyceridemia (15/433, 3.5%). Less frequent AEs included upper respiratory tract infections (10/433, 2.3%), herpes zoster (9/433, 2.1%), recurrent herpes simplex (8/433, 1.8%), neutropenia (8/433, 1.8%), transaminase increase (6/433, 1.4%), and asthenia (5/433, 1.2%). No statistically significant differences were observed between the 15 mg and 30 mg groups for the overall AE rate or for any individual AE category. Of note, hypercholesterolemia was numerically more frequent in the 15 mg group than in the 30 mg group (9.8% vs 4.2%), although the difference did not reach statistical significance ($p = 0.060$), while acne/JAKne rates were similar between groups (8.3% vs 6.8%, $p = 0.612$). Rare adverse events reported in ≤2 patients included anemia, myalgia, red face, thrombocytosis, abdominal pain, arthralgia, asthma attack, dental abscess, leukocyte formula inversion, leukopenia, lymphopenia, oral candidiasis, paraesthesia, paronychia, seborrhoeic dermatitis, sexual impotence, urinary tract infection, and weight gain. None of the reported adverse events resulted in permanent discontinuation of upadacitinib.

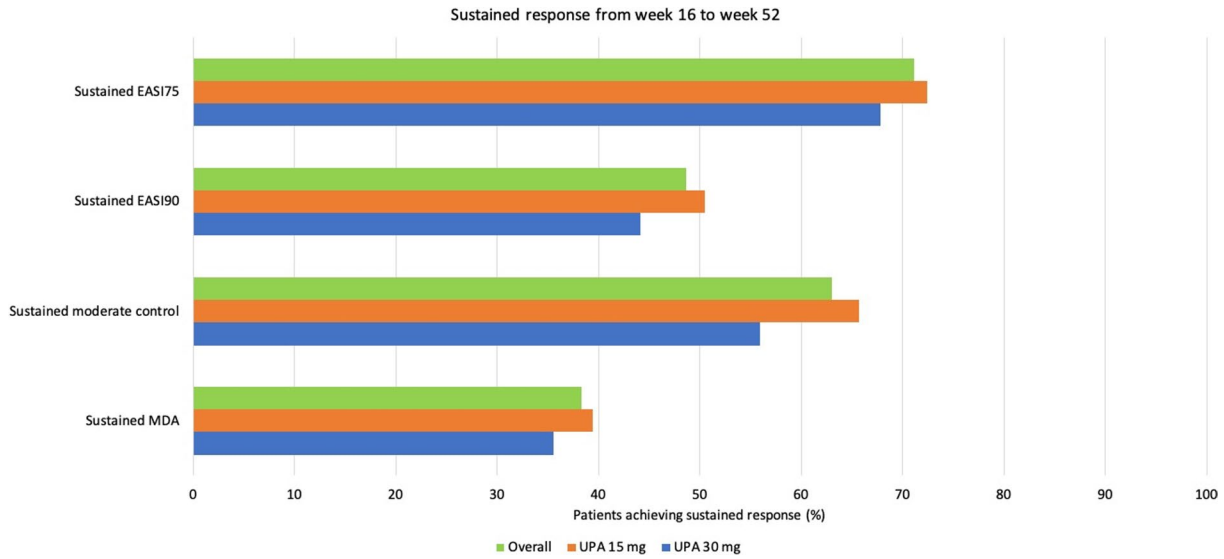

Fig. 3 Sustained clinical response and sustained disease control from week 16 to week 52. Sustained response was defined as achievement of the target at week 16, week 32, and week 52. Data are shown overall and according to upadacitinib dose. *EASI75* ≥75% improvement in Eczema Area and Severity Index, *EASI90* ≥90% improvement in Eczema Area and Severity Index, *MDA* minimal disease activity, *UPA* upadacitinib

DISCUSSION

In the current therapeutic landscape of AD, highly effective targeted therapies have shifted treatment goals from partial improvement toward more ambitious outcomes, including near-complete skin clearance, symptom control, and sustained disease control. This evolution highlights the limitations of relying exclusively on single timepoint endpoints and supports the assessment of how consistently patients remain in clinically meaningful control states over time. Although MDA and time-in-response concepts have recently been explored, real-world evidence quantifying cumulative disease control over 1 year of upadacitinib treatment remains limited. In this large multicenter cohort, upadacitinib provided rapid and sustained clinical improvement over 52 weeks, with high rates of conventional, composite, and sustained response. Importantly, patients spent a substantial proportion of the first treatment year in moderate or optimal disease control, supporting cumulative disease control as a complementary measure of long-term treatment benefit.

The conventional efficacy outcomes observed in our cohort were consistent with both pivotal trials and previous real-world studies. In Measure Up 1 and Measure Up 2, upadacitinib produced high EASI75 responses at week 16 that were maintained through week 52 [4, 15]. Similarly, Chiricozzi et al. reported EASI75 and EASI90 responses of 87.6% and 69.1%, respectively, at week 48 in a prospective real-world cohort [7], while another 52-week retrospective study further confirmed the long-term effectiveness of upadacitinib in routine clinical practice [8]. These findings are closely aligned with the week 52 EASI75 and EASI90 rates of 85.7% and 72.7% observed in our cohort.

Patient-reported symptoms also improved substantially, with marked reductions in pp-NRS and sleep NRS throughout follow-up. These results are consistent with the 52-week analyses of Measure Up 1 and Measure Up 2, in which improvements in itch, sleep, and quality-of-life outcomes were sustained over 1 year [16]. The parallel improvement in objective disease severity and patient-reported symptoms further supports the broad clinical benefit of upadacitinib in routine practice.

Table 4 Adverse events during upadacitinib treatment

Adverse event	Overall, *n* = 433	UPA 15 mg, *n* = 315	UPA 30 mg, *n* = 118	*p* value
Any AE	117 (27.0%)	85 (27.0%)	32 (27.1%)	0.978
Hypercholesterolemia	36 (8.3%)	31 (9.8%)	5 (4.2%)	0.060
Acne/JAKne	34 (7.9%)	26 (8.3%)	8 (6.8%)	0.612
CPK increase	18 (4.2%)	15 (4.8%)	3 (2.5%)	0.421
Hypertriglyceridemia	15 (3.5%)	13 (4.1%)	2 (1.7%)	0.375
URTIs	10 (2.3%)	6 (1.9%)	4 (3.4%)	0.471
Herpes zoster	9 (2.1%)	7 (2.2%)	2 (1.7%)	1.000
Neutropenia	8 (1.8%)	4 (1.3%)	4 (3.4%)	0.222
Recurrent herpes simplex	8 (1.8%)	6 (1.9%)	2 (1.7%)	1.000
Transaminase increase	6 (1.4%)	4 (1.3%)	2 (1.7%)	0.666
Asthenia	5 (1.2%)	4 (1.3%)	1 (0.8%)	1.000
AD flare	4 (0.9%)	2 (0.6%)	2 (1.7%)	0.300
Folliculitis	3 (0.7%)	2 (0.6%)	1 (0.8%)	1.000
Hypereosinophilia	3 (0.7%)	2 (0.6%)	1 (0.8%)	1.000
Nausea	3 (0.7%)	3 (1.0%)	0 (0.0%)	0.566

Adverse events were analyzed cumulatively over 52 weeks, without stratification by follow-up visit. Repeated occurrence of the same adverse event in the same patient was counted once. Data are reported as *n* (%) overall and by upadacitinib dose. *P* values refer to comparisons between the 15 mg and 30 mg groups

AD atopic dermatitis, *AE* adverse event, *CPK* creatine phosphokinase, *JAK* Janus kinase, *UPA* upadacitinib, *URTIs* upper respiratory tract infections

A key aspect of this study is the use of composite disease control endpoints combining physician-assessed disease severity and patient-reported itch. This approach is aligned with the treat-to-target framework in AD, which emphasizes the need to evaluate treatment success using both clinician-reported and patient-reported outcomes [9]. More recently, the AHEAD recommendations proposed a more ambitious management strategy based on shared decision-making and minimal disease activity, defined by the simultaneous achievement of at least one optimal clinician-reported outcome and one optimal patient-reported outcome [10]. Our pragmatic definition of optimal control/MDA, based on EASI90 plus pp-NRS ≤ 1, is consistent with this conceptual framework, although it should be interpreted as an MDA-like endpoint rather than a fully multidimensional MDA definition because quality-of-life measures were not included in the primary definition.

The proportion of patients achieving optimal control/MDA in our study was 54.3% at week 16 and 62.6% at week 52. These findings compare favorably with a recent integrated analysis of Measure Up 1 and 2, in which upadacitinib-treated patients achieved AHEAD-defined MDA at week 16 in 42.5% of the 15 mg group and 55.9% of the 30 mg group, and at week 52 in 57.4% and 69.9%, respectively [17]. In that same analysis, the specific combination of EASI90 plus WP-NRS 0/1 was achieved at week 52 by 38.1% of patients receiving 15 mg and 46.9% of those receiving 30 mg [17]. Direct comparison with our findings is limited by differences in study design, population, missing-data handling,

follow-up structure, and real-world treatment selection. However, taken together, these data support the clinical relevance of combining high-level skin clearance with minimal itch as a meaningful target in AD. Notably, residual pruritus appeared to limit optimal control in only a minority of patients achieving high-level skin clearance: 15.5% of EASI90 responders at week 16 and 14.0% at week 52 still had pp-NRS >1. These findings suggest that, although discordance between skin response and itch control persists in some patients, most patients achieving EASI90 also achieved minimal pruritus.

Our findings are also supported by emerging real-world evidence specifically focused on MDA with oral JAK inhibitors in AD. Rodriguez-Sanna et al. prospectively evaluated patients with moderate-to-severe AD treated with upadacitinib and defined pruritus-based MDA as EASI90 plus Worst Pruritus NRS ≤1; MDA was achieved by 62.3% of patients at week 16 and 46.2% at week 52, and early MDA achievement was associated with older age, shorter disease duration, and less prior systemic corticosteroid exposure [13]. In addition, Koumprentziotis et al. recently reported sustained MDA outcomes over 104 weeks in a real-world retrospective cohort of patients treated with upadacitinib or abrocitinib, further supporting the relevance of MDA as a long-term treatment target in routine clinical practice [14]. Compared with these studies, our analysis adds a cumulative time-in-target perspective over 52 weeks, quantifying not only whether patients achieved MDA-like control at selected visits but also how many equivalent days they spent in moderate or optimal disease control during the first year of treatment.

The most original contribution of our analysis is the quantification of cumulative disease control using a time-in-target approach. Traditional endpoints such as EASI75 or EASI90 at week 16 or week 52 provide clinically important information, but they do not distinguish between patients who transiently achieve response and those who remain controlled for most of the treatment year. In our cohort, the mean time spent in moderate disease control was 253.3 days, corresponding to approximately 70% of the first treatment year, while the mean time spent in optimal control/MDA was 176.1 days, corresponding to nearly half of the year. This provides a more dynamic and patient-centered measure of therapeutic benefit, particularly in a chronic relapsing disease such as AD.

This time-in-target perspective is supported by recent post hoc trial analyses. Blauvelt et al. evaluated time spent with clear or almost clear skin and no or minimal itch in Measure Up 1, Measure Up 2 and Heads Up, showing that patients receiving upadacitinib spent substantially more days with EASI90 response and WP-NRS 0/1 response than patients receiving placebo or dupilumab [12]. Through 16 weeks in Measure Up 1 and 2, upadacitinib-treated patients spent 9.8–13.4 times as many days with EASI90 response and 7.0–10.3 times as many days with WP-NRS 0/1 response compared with placebo [12]. In Heads Up, upadacitinib-treated patients also spent more time with EASI90 and WP-NRS 0/1 response than dupilumab-treated patients through weeks 16 and 24 [12]. Our study extends this concept to a real-world setting and over a longer 52-week observation period, using pragmatic composite disease control targets rather than isolated skin or itch endpoints.

When outcomes were stratified by dose, patients receiving upadacitinib 15 mg showed higher rates of EASI75 and moderate disease control at week 16 and spent significantly more days in moderate disease control than those receiving 30 mg. However, these findings should not be interpreted as evidence that 15 mg is more effective than 30 mg. In randomized trials and post hoc analyses, the 30 mg dose generally produced numerically higher or faster responses than 15 mg [4, 15, 16]. In our real-world cohort, dose allocation was not randomized but reflected routine clinical decision-making, making confounding by indication an important consideration. In particular, previous JAK inhibitor exposure was significantly more frequent in the 30 mg group, suggesting that this subgroup may have included more treatment-experienced or difficult-to-treat patients. Previous exposure to conventional systemic therapies, dupilumab, and tralokinumab was otherwise comparable between dose groups. However, the cumulative number of prior systemic therapies per patient was not systematically recorded and could not

be reliably reconstructed retrospectively. Consequently, a more granular assessment of previous treatment burden and an adjusted analysis accounting for this factor were not feasible. Other measured and unmeasured patient characteristics influencing both initial dose selection and treatment response may also have contributed to the observed early differences. Importantly, no significant between-dose differences were observed at week 52 for EASI75, EASI90, moderate disease control, or optimal control/MDA, nor for any sustained response endpoint. This interpretation is also supported by recent real-world evidence highlighting the dynamic and individualized use of upadacitinib dosing in clinical practice. In a multicenter study by Manzo Margiotta et al., dose escalation from 15 to 30 mg was driven by inadequate disease control, whereas dose reduction from 30 to 15 mg was mainly related to adverse events or achievement of minimal disease activity, emphasizing that dose selection may change over time according to individual effectiveness and tolerability [18]. Therefore, between-dose comparisons in the present study should be considered exploratory and hypothesis-generating rather than evidence of comparative effectiveness.

The sustained response analysis further supports the durability of upadacitinib effectiveness in routine practice. Sustained EASI75 and sustained EASI90 from week 16 to week 52 were achieved by 71.1% and 48.7% of patients, respectively, while sustained moderate disease control and sustained optimal control/MDA were achieved by 63.0% and 38.3%. These endpoints are stricter than single-visit responses because they require target achievement at week 16, week 32, and week 52. In this sense, they complement the cumulative disease control analysis by showing that a substantial proportion of patients maintained response across multiple visits, not merely at the final timepoint.

The safety profile observed in our study was consistent with the known safety profile of upadacitinib in AD. Overall, 27.0% of patients experienced at least one AE, with comparable rates between the 15 mg and 30 mg groups. The most frequently reported AEs were dyslipidemia, acne/JAKne, and CPK increase. Integrated safety analyses of upadacitinib phase 3 trials have identified acne, CPK elevation, herpes zoster, and laboratory abnormalities among relevant events during treatment, and have supported the use of both 15 mg and 30 mg doses in appropriate patients with moderate-to-severe AD [19]. Acne has also been specifically characterized as a dose-associated event in trial populations, occurring more frequently with upadacitinib 30 mg than 15 mg over 16 weeks [20]. In our cohort, acne/JAKne occurred in 7.9% of patients overall and did not significantly differ between dose groups, although real-world retrospective AE capture may underestimate mild or transient events.

Taken together, these findings confirm the long-term real-world effectiveness and safety of upadacitinib in moderate-to-severe AD and suggest that cumulative disease control may be a clinically useful outcome for future real-world studies. While conventional endpoints remain essential, time-in-target metrics may better reflect the stability and persistence of therapeutic benefit over time. This is particularly relevant in AD, where the goal of treatment is not only to achieve rapid improvement but also to maintain durable control of skin lesions, itch, and sleep disturbance over the long term.

Strengths and Limitations

This study has several strengths. First, it includes a large multicenter real-world cohort of patients with moderate-to-severe AD treated with upadacitinib and followed for up to 52 weeks. The availability of both clinician-reported outcomes, including EASI and IGA, and patient-reported outcomes, including pp-NRS and sleep NRS, allowed a comprehensive evaluation of treatment effectiveness over time. In addition, the study included patients treated with both approved upadacitinib doses, providing an exploratory assessment of outcomes in patients receiving 15 mg and 30 mg in routine clinical practice. A further strength of this analysis is the use of a cumulative disease control approach. Rather than focusing exclusively on response rates at fixed timepoints, this study quantified the number of equivalent days spent in moderate disease control and optimal disease control/

minimal disease activity during the first year of treatment. This time-in-target strategy may provide a more patient-centered and clinically meaningful estimate of therapeutic benefit, as it reflects the persistence and stability of disease control over time.

Some limitations should be acknowledged. The observational, non-randomized design prevents causal inference, and between-dose differences may reflect clinical decision-making, previous treatment exposure, disease complexity, or other measured and unmeasured confounders. The exclusion of patients undergoing dose modification may also have introduced selection bias. In routine clinical practice, patients escalating from 15 to 30 mg may do so because of inadequate disease control; therefore, their exclusion may have preferentially retained patients who responded adequately to the initial 15 mg dose and removed patients with poorer outcomes. This could have resulted in an overestimation of effectiveness and cumulative disease control among patients remaining on a stable dose, particularly in the 15 mg group, and may have contributed to some of the observed between-dose differences. Conversely, patients reducing the dose from 30 to 15 mg because of adverse events or achievement of satisfactory disease control were also excluded, potentially affecting estimates in the opposite direction. The magnitude and direction of this selection bias cannot be quantified within the present analysis. Accordingly, the dose-stratified findings should be interpreted as outcomes among patients who remained on a stable dose rather than as comparative effectiveness estimates applicable to all patients initiating upadacitinib 15 mg or 30 mg. In addition, multiple comparisons were performed without adjustment for multiplicity, and between-dose analyses should therefore be considered exploratory and hypothesis-generating. Optimal disease control/MDA was pragmatically defined as EASI90 plus pp-NRS ≤ 1; because quality-of-life measures such as DLQI or ADCT were not consistently available, this endpoint should be regarded as MDA-like rather than a fully multidimensional definition of minimal disease activity. Cumulative disease control was estimated from assessments at weeks 16, 32, and 52 using linear interpolation. Accordingly, time-in-target values represent estimated equivalent days rather than directly observed days and cannot capture short-term fluctuations, transient flares, or brief losses of disease control between visits. More frequent assessments would provide a more precise estimate of cumulative disease control. The timing of AE onset was not available; therefore, AEs were analyzed cumulatively over 52 weeks, without detailed assessment of severity, laboratory trajectories, or causality. Finally, the 52-week follow-up does not allow assessment of longer-term durability or potential late loss of effectiveness, and longer follow-up is needed to determine whether disease control persists beyond the first treatment year. Despite these limitations, the study provides clinically relevant real-world evidence on the longitudinal effectiveness, cumulative disease control, and safety of upadacitinib in moderate-to-severe AD.

CONCLUSION

This multicenter real-world study confirms the sustained effectiveness and acceptable safety profile of upadacitinib in patients with moderate-to-severe atopic dermatitis during the first 52 weeks of treatment. Beyond conventional response endpoints, the time-in-target approach showed that patients spent a substantial proportion of the first treatment year in moderate or optimal disease control, highlighting the clinical relevance of cumulative disease control as a complementary outcome in routine practice. Longer-term follow-up is needed to determine whether this level of disease control is maintained beyond the first treatment year.

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Author Contribution. Luca Potestio and Diego Orsini contributed to the study conception and design. Luca Potestio contributed to methodology, data curation, formal analysis, interpretation of the results, and drafting and critical revision of the original manuscript.

Diego Orsini contributed to methodology, interpretation of the results, supervision, and critical revision of the manuscript. Matteo Bianco, Luca Mastorino, Francesca Maria Gaiani, Francesca Barei, Francesca di Vico, Stefano Bighetti, Raul Armando Luyo Saboya, Martina Maurelli, Eugenia Veronica Di Brizzi, Flavia Manzo Margiotta, Mattia Cristallo, Anna Francesca Cavaliere, Manfredi Magliulo, Andrea Carugno, Antonio Podo Brunetti, Ruggero Cascio Ingurgio, Giulia Carpentieri, Francesco Messina, Marco Campoli, Chiara Assorgi, Franco Rongioletti, Nicola Zerbinati, Massimo Gola, Francesco Loconsole, Maria Concetta Fargnoli, Maria Esposito, Anna Graziella Burroni, Eustachio Nettis, Marco Romanelli, Pietro Morrone, Anna Balato, Giampiero Girolomoni, Elena Pezzolo, Mario Bruno Guanti, Mariateresa Rossi, Cataldo Patruno, Maddalena Napolitano, Angelo Valerio Marzano, Silvia Mariel Ferrucci, Piergiorgio Malagoli, Michela Ortoncelli, Simone Ribero, Antonio Costanzo, and Alessandra Narcisi contributed to patient recruitment, data acquisition and/or data collection, interpretation of the findings, and critical revision of the manuscript. All authors contributed to the review and editing of the manuscript and approved the final version.

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Declarations

Conflict of Interest. Luca Potestio has been a consultant and/or speaker for AbbVie, Almirall, Johnson and Johnson, and UCB Pharma. Matteo Bianco has been a speaker for BMS. Luca Mastorino served as speaker and advisory board member for LEO Pharma, Almirall, Novartis, Eli Lilly, Accord, Pierre Fabre, UCB, and Johnson & Johnson. Francesca Maria Gaiani acted as a speaker or consultant for Novartis, AbbVie, Eli Lilly, Celgene, LEO Pharma, and Almirall. Stefano Bighetti received honoraria for lectures from Pfizer. Martina Maurelli has been a paid speaker for Almirall, Johnson & Johnson Innovative Medicine, and LEO Pharma. Flavia Manzo Margiotta declares conflicts of interest with Eli Lilly, AbbVie, Almirall, Sanofi, LEO Pharma, and Pfizer. Andrea Carugno has been a speaker and/or consultant for Almirall, Amgen, AbbVie, Boehringer Ingelheim, Eli Lilly, LEO Pharma, Janssen-Cilag, Novartis, and UCB Pharma. Ruggero Cascio Ingurgio has served as a consultant for UCB Pharma. Giulia Carpentieri declares no conflicts of interest. Franco Rongioletti declares conflicts of interest with AbbVie, Almirall, Sanofi, Lilly, and UCB. Nicola Zerbinati was a scientific director of Matex Lab. Maria Concetta Fargnoli has served on advisory boards and received honoraria for lectures and/or research grants from Amgen, Almirall, AbbVie, Boehringer Ingelheim, BMS, Galderma, Kyowa Kirin, Incyte, LEO Pharma, Pierre Fabre, UCB, Eli Lilly, Pfizer, Johnson & Johnson, MSD, Novartis, Sanofi, Regeneron, and Sun Pharma. Maria Esposito has served as speaker/consultant for AbbVie, Amgen, Almirall, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, UCB, and Sanofi-Regeneron. Marco Romanelli declares conflicts of interest with Eli Lilly, AbbVie, Novartis, Janssen, Almirall, Sanofi, LEO Pharma, UCB, and Urgo. Anna Balato has served as speaker and/or has received fees from AbbVie, Almirall, Amgen, BI, BMS, Eli Lilly, Janssen, Incyte, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB. Giampiero Girolomoni has received personal fees from AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Galderma, Eli Lilly, Incyte, Johnson & Johnson Innovative Medicine, LEO Pharma, Merck Serono, Novartis, Pfizer, Samsung Bioepis, and Sanofi. Elena Pezzolo has received personal fees from AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Galderma, Eli Lilly, Incyte, Johnson & Johnson, LEO Pharma, Novartis, Pfizer, and Sanofi outside the submitted work. Mario Bruno Guanti declares conflicts of interest with AbbVie, Pfizer, Sanofi, Lilly, Unifarco, LEO Pharma, Almirall, and Firma. Mariateresa Rossi has served on advisory boards and received honoraria for lectures from Almirall, AbbVie, LEO Pharma, Sanofi Genzyme,

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Ethical Approval. Ethical approval for the present analysis was obtained within the framework of the ongoing LANDSCAPE clinical registry. The specific amendment covering the present analysis was approved by the Territorial Ethics Committee of the Calabria Region (Comitato Etico Territoriale Regione Calabria; Protocol No. 164/2026) on June 22, 2026. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants had provided written informed consent for the use of their anonymized clinical data within the registry.

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