ORIGINAL REPORT

Targeted Combined Endpoint Improvement in Patient and Disease Domains in Atopic Dermatitis: A Treat-to-Target Analysis of Adults with Moderate-to-Severe Atopic Dermatitis Treated with Upadacitinib

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A treat-to-target approach was recently developed to guide systemic treatment for adults with atopic dermatitis (AD). Recommendations outlined criteria for a 3-month initial acceptable treatment target and a 6-month optimal target, evaluated using global assessment of patient-reported disease severity, as well as Eczema Area and Severity Index, itch assessed on an 11-point numerical rating scale, Dermatology Life Quality Index, or Patient-Oriented Eczema Measure. Achievement of these targets with once-daily upadacitinib (15 mg and 30 mg) monotherapy was evaluated using integrated adult data from the Measure Up 1 and 2 phase 3 studies. Among the 852 patients treated with upadacitinib 15 mg or 30 mg, the 3-month initial acceptable target was achieved by >80%, >78%, and ≥87% of patients, and the 6-month optimal target was achieved by ≥53%, >61%, and >73% of patients at weeks 2, 16, and 52, respectively. Achievement of all 6 individual criteria for each of the target goals also increased over time. These findings suggest that upadacitinib 15 mg and 30 mg may help improve standards of care in patients with moderate-to-severe AD by achieving 6-month target goals at 16 weeks and as early as 2 weeks for most patients.

Key words: atopic dermatitis; itch; Janus kinase inhibitor; skin clearance; treat-to-target; upadacitinib.

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SIGNIFICANCE

Upadacitinib is used to treat atopic dermatitis, a condition that causes itchy and inflamed skin. This analysis evaluated the proportion of patients who achieved "treatment targets" with upadacitinib, using a framework encompassing multiple criteria including improvements in skin, itch, and quality of life. When treated with upadacitinib 15 mg or 30 mg, over half of patients achieved the targets after 2 weeks of treatment, and over three-quarters of patients achieved the targets after 1 year of treatment. These findings highlight the positive effects of upadacitinib across multiple aspects of patients' lives and may improve standards of care for atopic dermatitis.

Atopic dermatitis (AD) is a chronic, inflammatory disease characterized by eczematous lesions and intense pruritus, both of which are associated with substantial disease burden and impaired health-related quality of life (HRQoL) (1, 2). New targeted systemic treatments (such as biologic interleukin inhibitors and small-molecule oral Janus kinase inhibitors) are currently recommended for patients with moderate or severe forms of AD whose symptoms are insufficiently controlled with standard topical treatments (3, 4). Systemic therapies have transformed the AD treatment landscape and improved the standard of care for patients with moderate-to-severe AD; however, uniform agreement is lacking regarding optimal AD treatment goals and targets.

A treat-to-target approach was recently developed by de Bruin-Weller et al. (5) to guide shared decision-making concerning disease control with systemic therapy in adults with AD. This framework includes a patient-reported global assessment of overall disease severity, as well as assessments made by patients and/or their physicians of specific disease domains such as skin signs, itch, and HRQoL using established instruments (5). Treatment goals include an initial acceptable target to be reached within 3 months and an optimal treatment target to be reached within 6 months of systemic therapy initiation, each defined as improvements in patient-reported global severity of disease ("patient domain") plus at least 1 specific disease domain (**Fig. 1**) (5). This treat-to-target framework may be a valuable aid to guide AD treatment continuation, modification, and optimization and can guide patients and their healthcare providers in setting achievable treatment goals (5).

Upadacitinib is an oral selective Janus kinase inhibitor (6, 7). Upadacitinib demonstrated superior efficacy com-

Patient Domain	3-Month Initial Acceptable Target Goal	6-Month Optimal Target Goal
PGIS-5[a]	Reduction from baseline ≥ 1	Absolute score ≤ 2 (mild)
Disease Domains	AND ≥ 1 Specific Disease Domain Target	
EASI	≥ 50% improvement from baseline	≥ 75% improvement from baseline OR EASI ≤ 7
SCORAD	≥ 50% reduction	≥ 75% reduction OR SCORAD ≤ 24
WP-NRS	Reduction from baseline ≥ 3	Absolute score ≤ 4
DLQI	Reduction from baseline ≥ 4	Absolute score ≤ 5
POEM	Reduction from baseline ≥ 4	Absolute score ≤ 7

Fig. 1. Criteria for the 3-month initial acceptable target goal and the 6-month optimal target goal. DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; PGIS-5: Patient Global Impression of Severity 5-point scale; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing of Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale. [a]PGIS-5 is a 5-point scale measure (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe).

pared with placebo in patients with moderate-to-severe AD in 2 phase 3 studies (Measure Up 1 and Measure Up 2) and is approved for the treatment of moderate-to-severe AD (8, 9). In this analysis, we used the treat-to-target framework and integrated data from the Measure Up 1 and Measure Up 2 studies to investigate improvements in AD symptoms and quality of life with once-daily oral upadacitinib (15 mg or 30 mg) monotherapy in adults with moderate-to-severe AD.

MATERIALS AND METHODS

Study design, treatment, and patients

Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422) are identical, randomized, placebo-controlled, multicentre, phase 3 studies evaluating the efficacy and safety of upadacitinib in treating patients with moderate-to-severe AD (8, 10). Enrolment criteria for the Measure Up 1 and Measure Up 2 studies have been reported; in brief, eligible patients were adolescents (aged 12–17 years, weight ≥40 kg) or adults (aged 18–75 years) who had AD symptoms for ≥3 years, were candidates for systemic therapy, and had moderate-to-severe AD at screening (defined as Eczema Area and Severity Index [EASI] scores ≥16, validated Investigator Global Assessment for AD [vIGA-AD] scores ≥3, rolling average of Worst Pruritus Numerical Rating Scale [WP-NRS] scores ≥4, and ≥10% of body surface area affected) (8). Eligible patients were randomized 1:1:1 to receive daily, orally administered upadacitinib 15 mg, upadacitinib 30 mg, or placebo from baseline to week 16 (8). At week 16, patients randomized to placebo were re-randomized 1:1 to upadacitinib 15 mg or upadacitinib 30 mg; all patients continued blinded upadacitinib treatment to week 260 (8, 10).

The study was conducted in accordance with the protocol; International Council for Harmonisation guidelines; and applicable regulations, guidelines, and ethical principles originating from the Declaration of Helsinki. All patients provided written informed consent.

Assessments and target criteria

Patient-reported global severity of disease was assessed using the Patient Global Impression of Severity 5-point scale (PGIS-5; 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). PGIS-5 is derived from the 7-point PGIS scale (Table SI) (11). Five disease domains were used to assess AD signs and symptom severity and HRQoL: EASI, SCORing of Atopic Dermatitis (SCORAD), WP-NRS, Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM).

This analysis included patients from the Measure Up 1 and Measure Up 2 studies who met the following inclusion criteria at baseline: age ≥18 years, PGIS-5>2 (i.e., moderate or severe), EASI>7, SCORAD>24, WP-NRS>4, DLQI>5, and POEM>7. Integrated patient data from the Measure Up 1 and Measure Up 2 studies were used to evaluate the proportion of patients who achieved the 3-month initial acceptable target goal and the 6-month optimal target goal at weeks 2, 16, and 52 (time points at which all assessments were collected during the Measure Up 1 and 2 studies).

Statistical analysis

Data are reported as observed cases based on non-missing measurements at the time patients were receiving the study drug; statistical comparisons between upadacitinib and placebo were not performed for observed cases data. Analyses were conducted at time points at which all patient and disease domain assessments were conducted in the Measure Up 1 and Measure Up 2 studies (weeks 2, 16, and 52). For statistical comparisons of upadacitinib vs placebo (weeks 2 and 16), missing data were imputed using non-responder imputation with no special handling for data missing owing to COVID-19 (NRI-NC). *P*-values and 95% confidence intervals for the adjusted difference were calculated according to

Table I. Baseline demographics and characteristics

Characteristic	UPA 30 mg (*n*=424)	UPA 15 mg (*n*=428)	PBO (*n*=430)
Age, years, mean (SD)	36.3 (14.9)	35.9 (14.6)	36.8 (14.0)
Sex, *n* (%)			
Female	191 (45.0)	183 (42.8)	196 (45.6)
Male	233 (55.0)	245 (57.2)	234 (54.4)
Race, *n* (%)			
White	290 (68.4)	278 (65.0)	281 (65.3)
Black	17 (4.0)	29 (6.8)	30 (7.0)
Asian	102 (24.1)	109 (25.5)	104 (24.2)
Other	15 (3.5)	12 (2.8)	15 (3.5)
Body mass index, kg/m^2, mean (SD)	26.3 (5.8)	26.1 (5.7)	26.9 (6.0)
BSA affected, %, mean (SD)	47.4 (22.5)	47.3 (22.4)	47.0 (22.5)
Previous systemic treatment, *n* (%)	214 (50.5)	232 (54.2)	238 (55.3)
Disease duration, years, mean (SD)	24.6 (14.3)	24.3 (14.7)	25.6 (14.1)
vIGA-AD score, *n* (%)			
Moderate (score of 3)	200 (47.2)	209 (48.8)	206 (47.9)
Severe (score of 4)	224 (52.8)	219 (51.2)	224 (52.1)
PGIS-5, *n* (%)			
Moderate (score of 3)	193 (45.5)	201 (47.0)	181 (42.1)
Severe (score of 4)	231 (54.5)	227 (53.0)	249 (57.9)
EASI, mean (SD)	29.8 (11.7)	29.9 (12.3)	29.0 (12.1)
SCORAD, mean (SD)	68.1 (12.3)	68.1 (12.5)	67.8 (12.1)
WP-NRS, mean (SD)	7.5 (1.4)	7.3 (1.5)	7.5 (1.5)
DLQI, mean (SD)	17.6 (6.3)	17.6 (6.6)	18.2 (6.3)
POEM, mean (SD)	22.2 (4.8)	21.9 (4.4)	22.6 (4.5)

BSA: body surface area; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; PGIS-5: Patient Global Impression of Severity 5-point scale; PBO: placebo; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing of Atopic Dermatitis; UPA: upadacitinib; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale. PGIS-5 is derived from the 7-point PGIS (Table SI) (11).

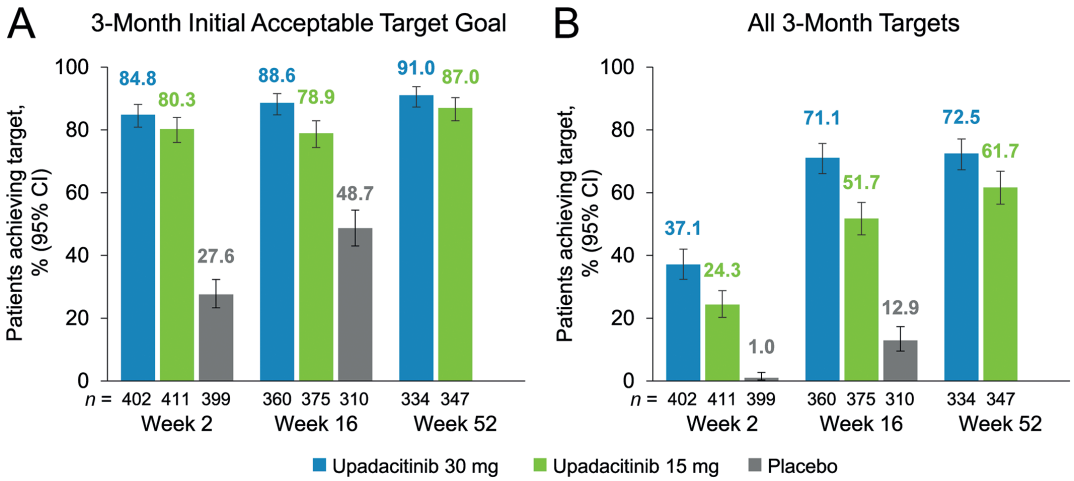

Fig. 2. Proportion of patients achieving 3-month targets over time (OC). OC: observed cases. (A) Data presented for patients achieving the 3-month initial acceptable target goal and (B) patients achieving all 6 individual 3-month targets.

the Cochran–Mantel–Haenszel test adjusted for strata (study and baseline vIGA-AD).

RESULTS

Patients

Overall, this analysis included 1,282 adults (upadacitinib 30 mg, $n=424$; upadacitinib 15 mg, $n=428$; placebo, $n=430$). Baseline demographics and disease characteristics were generally well balanced across treatment groups (**Table I**). Patients' mean (SD) age was 36.3 (14.5) years; 44.5% of patients were female; and most patients (66.2%) were White. At baseline, the mean (SD) EASI score was 29.6 (12.1); 52.0% of patients had a vIGA-AD score of 4 (severe); and the mean (SD) WP-NRS score was 7.4 (1.5).

Achievement of the 3-month initial acceptable target goal

More than 78% of patients treated with either dose of upadacitinib achieved the 3-month initial acceptable target goal as early as week 2, with similar results observed at week 16 and week 52; a substantially higher proportion of patients achieved the 3-month initial acceptable target goal with upadacitinib than with placebo (**Fig. 2**A). More than 24% of patients who received upadacitinib achieved all 6 of the individual criteria for the 3-month initial acceptable target goal as early as week 2, and over 51% of patients achieved all 6 individual criteria at weeks 16 and 52 (Fig. 2B). Results were generally consistent using NRI-NC methodology; more patients achieved the 3-month initial acceptable target goal with upadacitinib 15 mg or 30 mg than with placebo at weeks 2 and 16 (nominal $p<0.001$; Fig. S1). When considering the full distribution of patient responses for the 3-month initial acceptable target goal, the proportion of patients achieving a higher number of individual target criteria increased over time; response rates were substantially higher with upadacitinib than with placebo (**Fig. 3**). Among subgroups of patients who achieved the 3-month patient domain target (≥1-point improvement in PGIS-5) and ≥1 or exactly 1, 2, 3, or 4 individual 3-month target

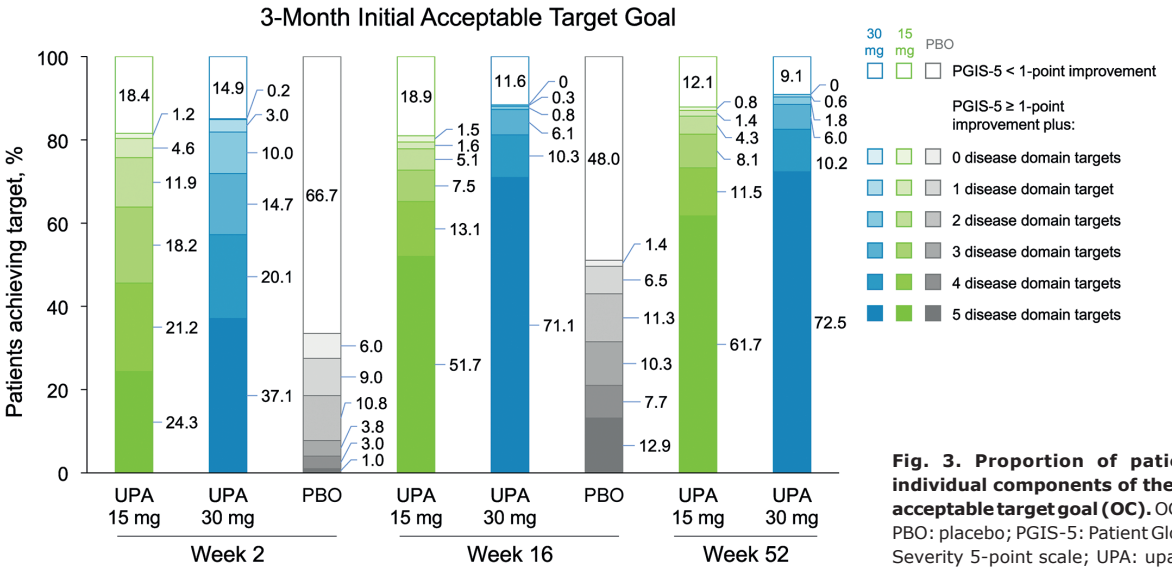

Fig. 3. Proportion of patients achieving individual components of the 3-month initial acceptable target goal (OC). OC: observed cases; PBO: placebo; PGIS-5: Patient Global Impression of Severity 5-point scale; UPA: upadacitinib.

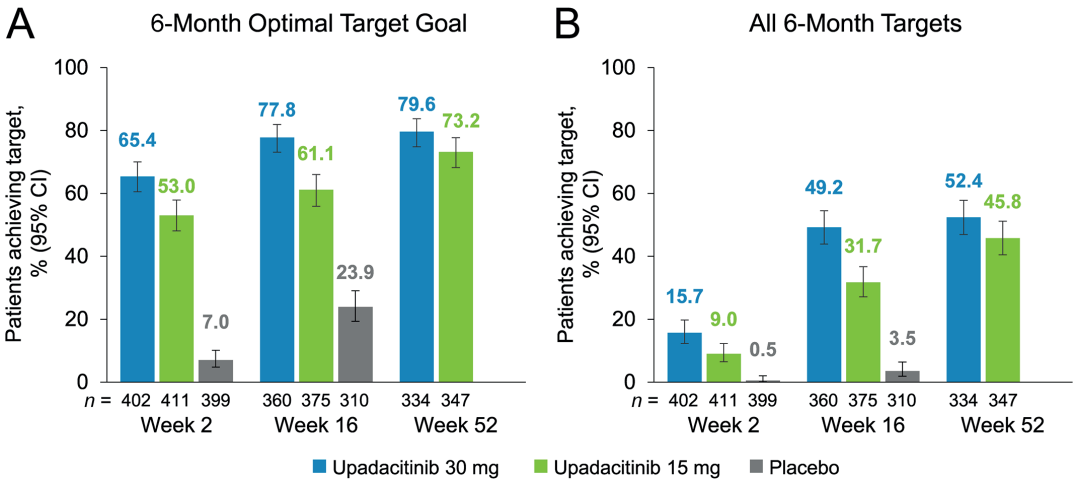

Fig. 4. Proportion of patients achieving 6-month targets over time (OC). OC: observed cases. (A) Data presented for patients achieving the 6-month optimal target goal and (B) patients achieving all 6 individual 6-month targets.

components, the proportion of patients who achieved specific individual 3-month target components is presented in Figs. S2–S6.

Achievement of the 6-month optimal target goal

Overall, results for the 6-month optimal target goal followed similar patterns to those observed for the 3-month initial acceptable target goal. At week 52, over 73% of patients who received upadacitinib achieved the 6-month optimal target goal (**Fig. 4**A) and over 45% achieved all 6 of the 6-month individual criteria (Fig. 4B). At weeks 2 and 16, using NRI-NC, more patients achieved the 6-month optimal target goal with upadacitinib 15 mg or 30 mg than with placebo (nominal $p<0.001$; Fig. S7). Similar to the 3-month initial acceptable target goal findings, the number of individual 6-month target criteria achieved by patients increased over time when looking across the full distribution of responses, and response rates were substantially higher with upadacitinib than with placebo (**Fig. 5**). Among subgroups of patients who achieved the 6-month patient domain target (PGIS-5 score ≤2) and ≥1 or exactly 1, 2, 3, or 4 individual 6-month target components, the proportion of patients who achieved specific individual 6-month target components is presented in Figs. S8–S12.

DISCUSSION

The treat-to-target approach, which suggests improvements in both the patient's assessment of overall disease severity and at least 1 specific disease domain assessed by the patients and/or physicians using established instruments, provides a framework to evaluate treatment goals for systemic therapies like upadacitinib and to define treatment success for AD. Overall, the 3-month initial acceptable target goal and the 6-month optimal target goal were achieved with upadacitinib by most patients at the time points studied. A numerically higher propor-

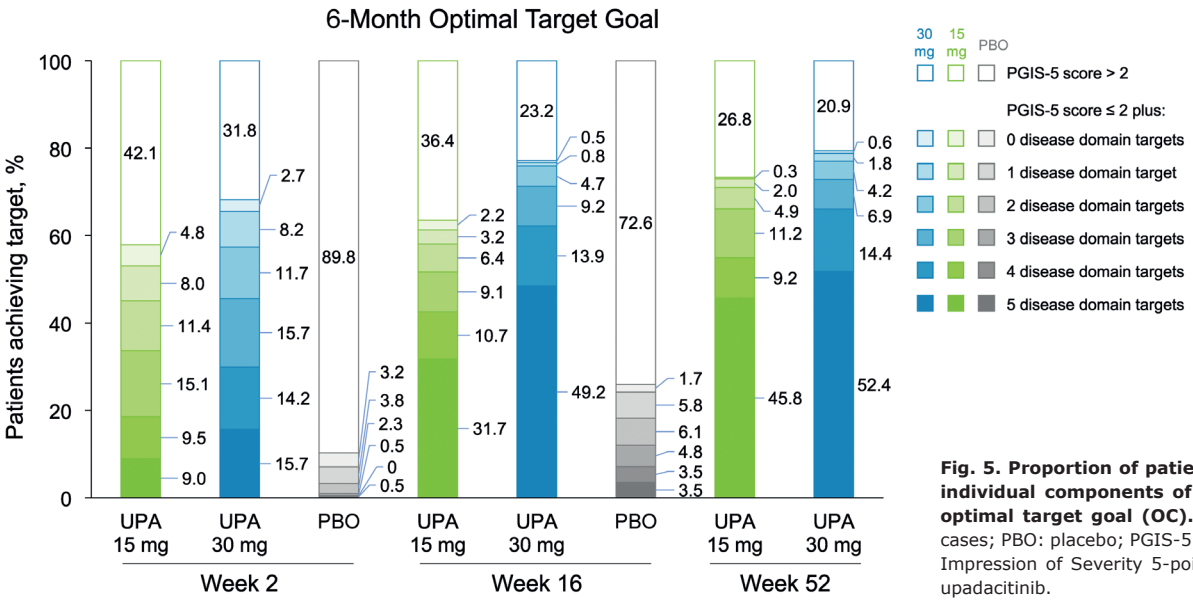

Fig. 5. Proportion of patients achieving individual components of the 6-month optimal target goal (OC). OC: observed cases; PBO: placebo; PGIS-5: Patient Global Impression of Severity 5-point scale; UPA: upadacitinib.

tion of patients achieved the 3-month and 6-month target goals with upadacitinib 30 mg than with upadacitinib 15 mg, a dose-dependent pattern consistent with previous upadacitinib studies (8, 10).

Patients rapidly achieved the treatment goals with upadacitinib 15 mg or 30 mg: most achieved the 3-month initial acceptable target goal and the more stringent 6-month optimal target goal at week 2, with consistent or improved achievement at weeks 16 and 52. Considering how quickly many patients achieved the 3-month and 6-month targets with upadacitinib therapy, these findings suggest that goal targets for AD may need to be re-evaluated as new treatments with improved and rapid efficacy become available and standards of care become elevated. Indeed, evolution and flexibility of the treat-to-target consensus criteria have been proposed to adapt to the rapidly evolving treatment landscape for AD or to account for limitations of different healthcare systems (12, 13).

Overall, the 3-month initial acceptable target goal and the 6-month optimal target goal were achieved by more than half of patients as early as week 2 and by three-quarters of patients at week 52. The proportion of patients achieving all 6 individual treatment targets also increased over time. As early as week 2, 24–37% of patients achieved all 6 individual 3-month targets and 9–16% of patients achieved all 6 individual 6-month targets. At week 52, approximately two-thirds of patients achieved all 6 individual 3-month targets and roughly half achieved all 6 individual 6-month targets. These findings highlight the compelling breadth of effects associated with upadacitinib therapy.

Numerous systemic therapies for AD have been developed and approved in recent years; however, no consensus exists on criteria for treatment selection and treatment success. Furthermore, factors guiding treatment decisions may be complex, and clinical assessments of treatment benefits may be subjective. The treat-to-target framework was designed to guide clinicians administering systemic therapies in various clinical settings and in diverse patient populations. Evaluation of prespecified target criteria provides a valuable tool to monitor treatment response across multiple dimensions and inform shared decision-making between patients and healthcare providers as appropriate treatments are selected to achieve optimal outcomes. Findings from this analysis highlight the importance of evaluating and controlling multiple dimensions of AD (including patient-reported outcomes in addition to clinician-reported outcomes) in impacting treatment selection, guiding individualized treatment plans, and optimizing patient care and outcomes.

The results reported herein are generally consistent with those in another treat-to-target analysis of a selective Janus kinase inhibitor, abrocitinib (14), which demonstrates the utility of this approach to evaluate the efficacy of various systemic AD treatments and optimize outcomes. Generally, a numerically higher proportion of patients achieved the individual 3-month and 6-month target components with upadacitinib treatment at week 16 than did patients receiving abrocitinib treatment at week 12 (although results for abrocitinib at week 16 have not been reported to date) (14). Here we also report the short-term (2-week) and long-term (52-week) achievement of 3-month and 6-month target goals with upadacitinib therapy, in addition to the proportion of patients achieving all 6 individual components of the 3-month and 6-month target goals; to our knowledge, this is the first such report for any systemic AD therapy.

Limitations

There are a few limitations of this study. One limitation is a restriction to time points during the Measure Up 1 and 2 studies when all assessments were conducted; therefore, whether these targets were met before week 2 and the nature of the dynamics between weeks 16 and 52 are not known. Additionally, findings from this clinical trial population may not be generalizable to the real-world population of patients with AD seen in the clinic. The assessments needed to gauge the achievement of treat-to-target criteria may not be comprehensively evaluated and fully integrated into clinical practice owing to variables such as short clinic visits and clinician preferences for specific tools; thus, there may be an increased need to implement these assessments so that healthcare providers can determine whether targets are being met. In addition, these findings may not fully represent treatment benefits experienced by patients; current treat-to-target goals only reflect "acceptable" and "optimal" targets, but partial improvements in clinical and/or HRQoL outcomes that do not meet the treat-to-target criteria may still be meaningful to patients, especially when considering their disease history and journey. Current treat-to-target criteria do not include direct input from patients regarding their most bothersome symptoms; thus, additional tailoring and shared decision-making between patients and physicians may be needed to meet individualized treatment goals.

Conlusion

Upadacitinib 15-mg or 30-mg treatment led to rapid and durable improvements in AD symptoms and quality of life based on an evidence-based, treat-to-target approach, which may inform shared decision-making between patients and their healthcare providers and improve standards of care for AD.

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Data sharing statement: AbbVie is committed to responsible data sharing regarding the clinical trials it sponsors. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g. protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Disclosures: SGK has served as an advisory board member/consultant for AbbVie, Amgen, Arcutis, Aslan, Cara, Castle Biosciences, Celldex, Galderma, Genzada, Incyte, Johnson & Johnson, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi. He has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. MdB-W has served as a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Galderma, Janssen, LEO Pharma, Lilly, Pfizer, Regeneron, Sanofi-Genzyme, and UCB. JIS has received honoraria as a consultant, advisory board member, and/or speaker for AbbVie, AObiome, Arcutis, Alamar, Amgen, Arena, Arcutis, Asana, ASLAN, BI, BioMX, Biosion, Bodewell, Cara, Castle, Celgene, Connect, Dermavant, Dermira, Dermtech, Galderma, GSK, Incyte, Kiniksa, LEO Pharma, Lilly, Menlo, Novartis, Optum, Pfizer, RAPT, Regeneron, Sanofi-Genzyme, Shaperon, and Union. His institution has received grants from Galderma and Pfizer. PL has received research grants/funding from AbbVie, AOBiome, the National Eczema Association, and Regeneron/Sanofi Genzyme. He participates in speakers' bureaus for Galderma, Incyte, L'Oréal, LEO Pharma, Lilly, Pfizer, and Regeneron/Sanofi Genzyme. He reports payments for serving as a consultant or participating on advisory boards for AbbVie, Almirall, Amyris, AOBiome, Arbonne, Aslan, Bodewell, Bristol Myers Squibb, Burt's Bees, Concerto Biosciences (stock options), Dermavant, Exeltis, Galderma, IntraDerm, Johnson & Johnson, Kimberly-Clark, Kiniksa, L'Oréal, LEO Pharma, Lilly, Menlo Therapeutics, Merck, Micreos (stock options), My-Or Diagnostics, Pierre-Fabre, Pfizer, Realm Therapeutics, Regeneron/Sanofi Genzyme, Sibel Health, Theraplex, UCB, Unilever, and Verrica. In addition, he has a patent pending for a Theraplex product and receives royalty payments for the patent. He is also a board member and scientific advisory committee member of the National Eczema Association. MD has received research support and/or honoraria for lecturing, consulting, and/or advisory board responsibilities from AbbVie, Almirall, Arena, Aslan, Incyte, Kymab, La Roche Posay, LEO Pharma, Lilly, Pfizer, Pierre Fabre, Regeneron, and Sanofi Genzyme. HA, BMC, MCL, YL, and SO are full-time employees of AbbVie Inc., and may hold AbbVie stock, stock options, and/or patents. SW has received institutional research grants from LEO, Pfizer, and Sanofi; and has performed consulting work and lectures for AbbVie, Almirall, Boehringer, Galderma, Kymab, LEO Pharma, Lilly, Pfizer, Regeneron, and Sanofi Genzyme.

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