Received: 8 November 2022 | Accepted: 15 February 2023

DOI: 10.1111/jdv.18995

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Higher levels of response on clinical atopic dermatitis severity measures are associated with meaningful improvements in patient-reported symptom and quality of life measures: Integrated analysis of three Upadacitinib phase 3 trials

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Funding information
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Abstract

Background: It is not fully understood how different degrees of improvements in atopic dermatitis (AD) clinical outcome measures translate to improvements in patient-reported outcome (PRO) measures, such as those assessing itch, symptoms, sleep, anxiety, depression, quality of life (QoL), and work productivity.

Objectives: This post hoc analysis of three clinical studies assessed how more robust improvements in clinical responses are associated with improvements in PROs and QoL.

Methods: Data from three randomized, double-blind, placebo-controlled, phase 3 trials in adults and adolescents with moderate to severe atopic dermatitis (Measure Up 1, Measure Up 2, and AD Up) were included. Patients were randomly assigned (1:1:1) to upadacitinib (15 or 30 mg) or placebo once daily (alone or in combination with topical corticosteroids). The mean percentage improvement from baseline to week 16 and percentage of patients achieving responses at week 16 were summarized by the Eczema Area and Severity Index (EASI) and validated Investigator Global Assessment of Atopic Dermatitis (vIGA-AD) response level categories.

Results: A total of 2392 patients from the three trials were included in the analysis. Increasingly greater mean percentage improvement and proportion of patients achieving response was observed at higher clinical response levels (i.e., stepwise pattern). Mean percentage improvement and proportion of patients achieving response exceeded 69% and 70% at EASI ≥ 90 and vIGA-AD 0/1, respectively, for most PROs including Worst Pruritus Numeric Rating Scale, Patient Oriented Eczema Measure, and Dermatology Life Quality Index.

Conclusions: Greater degrees of clinical responses are related to more robust improvements across multiple dimensions impacted by AD, including itch, skin pain, sleep, anxiety, depression, and QoL.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with multiple skin manifestations, including itch, pain, redness, and dryness. AD symptoms can cause sleep disruptions, decreased work productivity, and a decline in overall quality of life (QoL).[1]

The Eczema Area and Severity Index (EASI) and the validated Investigator Global Assessment of Atopic Dermatitis (vIGA-AD) are key disease outcome measures for assessing responses to treatment in AD clinical trials.[2] An EASI 75 response is a commonly used coprimary or primary endpoint in AD clinical trials per regulatory agency preference. A real-world study demonstrated EASI 50 to align with

minimal, EASI 75 moderate, and EASI 90 major clinical improvement across all EASI severities.[3] However, it is not fully understood how different degrees of improvements in outcome measures such as EASI and vIGA-AD in clinical trials translate to improvements in patient-reported outcome (PRO) measures, such as those assessing itch, symptoms, sleep, anxiety, depression, QoL, and work productivity.

The objective of this post hoc analysis was to characterize how incremental improvements in clinical response are associated with improvements in other outcome measures using data from three phase 3 clinical trials in adult and adolescent patients with moderate to severe AD.

METHODS

Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318) are ongoing randomized, phase 3, double-blind, placebo-controlled, multicenter studies evaluating upadacitinib in adolescents and adults (aged 12–75 years) with moderate to severe AD. The primary results of these studies have been published previously.[4,5] The study designs, key inclusion and exclusion criteria, and coprimary endpoints are illustrated in Figure S1. In these trials, patients were randomly assigned (1:1:1) in a double-blinded fashion to oral upadacitinib (15 or 30 mg) or placebo once daily. The AD Up trial included study treatment in combination with topical corticosteroids for all study arms.

The current post hoc pooled analysis of the three trials focuses on the first 16 weeks of treatment. In addition to EASI and vIGA-AD, 21 other outcome assessments encompassing AD severity, symptoms, impacts of AD, and QoL were evaluated (Table S1),[6–11] including the novel Atopic Dermatitis Symptom Scale (ADerm-SS) and Impact Scale (ADerm-IS), which are validated PRO measures designed to assess the severity of AD-specific symptoms at their worst and effects on patient QoL.[7,12,13] Both questionnaires include daily items assessed during a 24-h recall period and weekly items assessed every 7 days. For both the ADerm-SS and ADerm-IS, response options are based on an 11-point scale ranging from 0 (no signs/symptoms and not difficult, respectively) to 10 (worst imaginable signs/symptoms and extremely difficult, respectively).[14]

Statistical analysis

Observed data, regardless of drug discontinuation, for the intent-to-treat (ITT) population were pooled across the three phase three trials. The mean percentage improvement at week 16 relative to baseline and the proportion of patients achieving meaningful improvement were summarized by EASI and vIGA-AD response level categories. For EASI, the percentage improvement from baseline response categories were <50%, 50% to <75%, 75% to <90%, 90% to <100%, and 100%. For vIGA-AD, the response categories were 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). Spearman correlations among these measures were also estimated.

Mean work productivity and activity impairment (WPAI) component scores related to work (absenteeism, presenteeism, and work productivity loss) were translated to work hours per week, with the assumption of 40 work hours per week. Statistical calculations were based on available data for each outcome.

Additional exploratory analyses evaluated other stratification schemes, including absolute EASI, absolute Worst Pruritus Numeric Rating Scale (WP-NRS) score, WP-NRS response, and composite EASI 90 and WP-NRS 0–1 scores.

RESULTS

A total of 2392 patients from the three trials were included in the analysis (Table 1). The sample sizes by percentage of EASI improvement and vIGA-AD category at week 16 were EASI < 50 (n = 559), EASI 50 to <75 (n = 378), EASI 75 to <90 (n = 411), EASI 90 to <100 (n = 709), EASI 100 (n = 335), vIGA-AD severe (n = 201), vIGA-AD moderate (n = 638), vIGA-AD mild (n = 598), vIGA-AD almost clear (n = 604), and vIGA-AD clear (n = 351). Improvements in EASI and vIGA-AD at week 16 were correlated with improvements in the assessed measures (Table S2). Generally, correlations between PRO measures and WP-NRS were numerically greater compared with correlations between PRO measures and EASI and vIGA-AD.

Mean improvements in clinical and QoL endpoints

Mean percentage improvements in SCORing Atopic Dermatitis (SCORAD), objective SCORAD, SCORAD itch, WP-NRS, Patient-Oriented Eczema Measure (POEM), and ADerm-SS skin pain and 7-Item Total Symptom Score measures were incrementally greater for higher EASI and vIGA-AD responses (Figure 1a). At EASI 90 to <100 and vIGA-AD almost clear response levels, the mean percentage improvement exceeded 70% across all outcomes except for POEM.

Similarly, mean percentage improvements in SCORAD sleep, Dermatology Life Quality Index (DLQI), ADerm-IS, and Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscales were incrementally greater at higher EASI and vIGA-AD responses (Figure 1b). At EASI ≥ 90 and vIGA-AD clear or almost clear response levels, the mean percentage improvement was ≥74% across all outcomes except for HADS; for HADS anxiety and depression, the mean percentage improvement exceeded 27%.

The proportions of patients achieving clinically meaningful improvement in clinical and QoL endpoints were incrementally greater at higher EASI and vIGA-AD response category levels (Figure 2a,b). At EASI ≥ 90 and vIGA-AD clear or almost clear response levels, the proportions of patients achieving clinically meaningful improvement exceeded 90% for POEM and DLQI and were ≥74% for the other endpoints. Patterns were similar for EASI and vIGA-AD response categories for more stringent response definitions, such as WP-NRS 0–1,

TABLE 1 Demographics and baseline clinical characteristics (ITT population).

Characteristic	*N* = 2392
Sex, *n* (%)	
Male	1372 (57.4)
Female	1020 (42.6)
Age	
Mean (SD), years	33.8 (15.3)
<18 years, *n* (%)	321 (13.4)
BSA affected, %, mean (SD)	47.2 (22.5)
EASI, mean (SD)	29.4 (12.1)
vIGA-AD	
Moderate (score of 3), *n* (%)	1175 (49.1)
Severe (score of 4), *n* (%)	1217 (50.9)
SCORAD, mean (SD)	67.3 (12.5)
Objective SCORAD, mean (SD)	53.1 (11.1)
SCORAD Itch, mean (SD)	7.7 (1.7)
SCORAD Sleep, mean (SD)	6.4 (2.7)
WP-NRS[a], mean (SD)	7.2 (1.6)
POEM, mean (SD)	21.4 (5.0)
DLQI, mean (SD)	16.7 (7.0)
HADS Anxiety, mean (SD)	7.4 (4.2)
HADS Depression, mean (SD)	5.4 (4.0)
ADerm-SS Skin Pain[a], mean (SD)	6.4 (2.2)
ADerm-SS TSS-7, mean (SD)	46.5 (13.7)
ADerm-IS Sleep[a], mean (SD)	18.5 (7.6)
ADerm-IS daily activities, mean (SD)	23.2 (10.5)
ADerm-IS emotional state, mean (SD)	20.1 (8.0)
WPAI absenteeism[b], mean (SD)	11.7 (23.2)
WPAI presenteeism[b], mean (SD)	46.1 (26.7)
WPAI work productivity[b], mean (SD)	48.8 (28.0)
WPAI activity impairment[b], mean (SD)	53.6 (27.0)

Note: Based on non-missing values.

Abbreviations: AD, atopic dermatitis; ADerm-IS, Atopic Dermatitis Impact Scale; ADerm-SS, Atopic Dermatitis Symptom Scale; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; ITT, intent-to-treat; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; vIGA-AD, validated Investigator Global Assessment of Atopic Dermatitis; WP-NRS, Worst Pruritus Numeric Rating Scale; WPAI, Work Productivity and Activity Impairment.

[a]Weekly average.

[b]WPAI was not assessed in Measure Up 2.

POEM 0–2, and DLQI 0–1 (Figure 2c,d). Similar results were observed for patient global impression endpoints (Figure S2).

Work productivity and activity impairment

Mean improvements were incrementally greater at higher EASI and vIGA-AD response category levels for all WPAI outcome measures except absenteeism (Figure 3a). At EASI 90 to <100 and vIGA-AD almost clear response levels, the mean improvement was ≥30% for work productivity loss, which translated to an increase of ≥12 h/week, and ≥40% for activity impairment. At EASI 100 and vIGA-AD clear response levels, the mean improvement exceeded 35% for work productivity loss, which translated to an increase of ≥14 h/week, and exceeded 45% for activity impairment.

Mean impairment assessed at week 16 was incrementally greater for all WPAI outcomes at lower EASI and vIGA-AD response category levels (Figure 3b). At EASI 90 to <100 and vIGA-AD almost clear response levels, work productivity loss and activity impairment were 10% to 12% on average. At EASI 100 and vIGA-AD clear response levels, work productivity loss and activity impairment were 5% to 6% on average.

Other stratification schemes

Improvements and response rates at week 16 were incrementally greater for all outcomes and their respective domains for lower absolute EASI categories (Figure S3), lower WP-NRS score categories (Figure S4), and with higher WP-NRS improvement (Figure S5). When examining composite EASI 90 and WP-NRS 0–1 responses, improvements and response rates were highest among patients who achieved both EASI 90 and WP-NRS 0–1 (Figure S6). Patient global impression endpoints were consistent with these trends (Figure S2).

Similar results were observed in the pooled placebo group (*n* = 757) that demonstrated consistent stepwise patterns, although improvements were generally lower (data not shown).

DISCUSSION

In this secondary analysis of data collected from patients enrolled in three ongoing clinical trials,[4,5] we demonstrated that higher response categories of the EASI and vIGA-AD are associated with improvements in other outcome measures that assess a broad spectrum of AD-related signs, symptoms, and effects on QoL. Importantly, although the number of outcome measures used was large and diverse, there was notable consistency among the results. That is, higher levels of skin clearance translated to higher levels of improvement across multiple outcomes.

We used mutually exclusive EASI categories to evaluate the relationship between an incrementally greater response level and improvement in any given outcome measure. The results suggest that incrementally greater levels of response translate to meaningful differences. As a representative example, ≥20% more patients in the EASI 90 to <100 group reported WP-NRS 0–1, POEM 0–2, and DLQI 0–1 compared with patients in the EASI 75 to <90 group. The same pattern was observed with other outcomes measures. In addition, when comparing achievement of relative improvements in EASI with achievement of absolute EASI categories, the incremental responses on other outcome measures were similar, with identical or nearly identical responses noted for EASI 100 versus absolute EASI 0 and

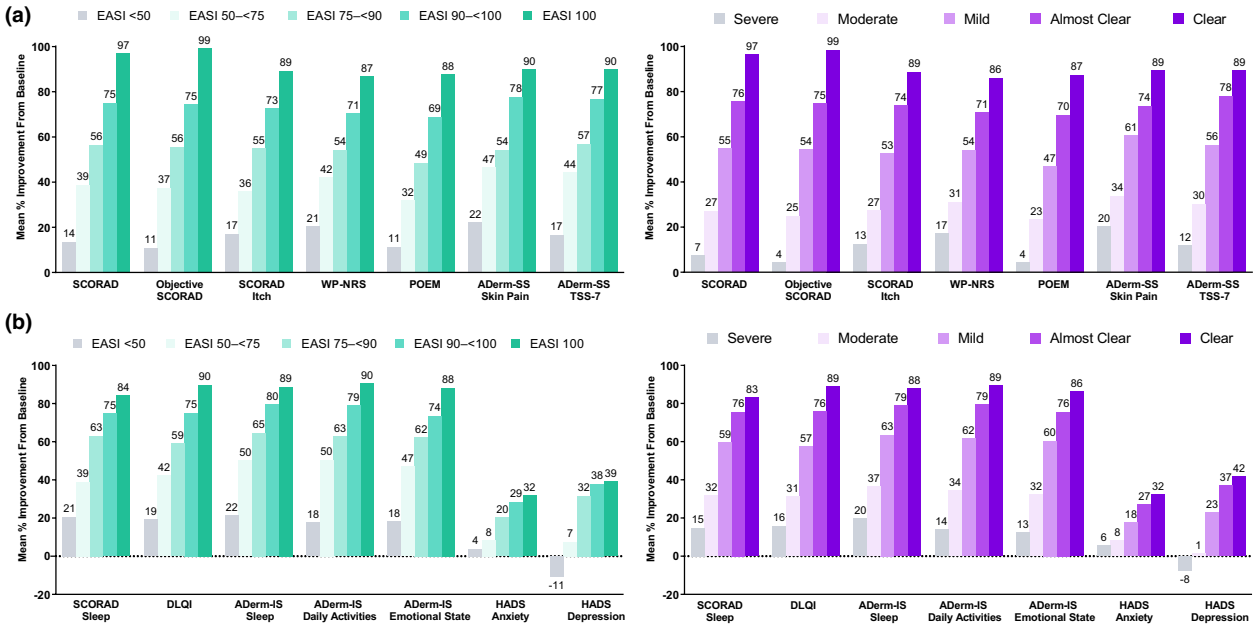

FIGURE 1 Mean percentage improvement in (a) clinical outcomes and (b) quality of life outcomes by EASI and vIGA-AD response category level at week 16 (ITT population). DLQI was assessed in patients aged ≥16 years at screening. ADerm-IS, Atopic Dermatitis Impact Scale; ADerm-SS, Atopic Dermatitis Symptom Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Activity and Severity Index; HADS, Hospital Anxiety and Depression Scale; ITT, intent-to-treat; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; TSS-7, 7-Item Total Symptom Score; vIGA-AD, validated Investigator Global Assessment of Atopic Dermatitis; WP-NRS, Worst Pruritus Numeric Rating Scale.

EASI <50 versus absolute EASI ≥23 and overlapping values for other category comparisons. Overall, our results correspond to previous reports[15,16] and demonstrate that achieving a higher response on skin (EASI and vIGA-AD) and itch (WP-NRS) yielded high levels of improvement in other clinically meaningful measures; improvements were particularly high among patients who achieved both EASI 90 and WP-NRS 0–1.

The higher levels of improvement across multiple PRO and QoL measures associated with higher EASI, vIGA-AD, and WP-NRS thresholds indicate the clinical meaningfulness of attaining these higher thresholds. Although achieving EASI 100 may not have appeared feasible in the past, our results demonstrate that with newer therapies, such as upadacitinib, thresholds indicative of major clinical improvements are attainable, supporting the use of higher thresholds as targets for both clinical trials and treatment.

Interestingly, mean improvements in WPAI outcome measures were incrementally greater at higher EASI and vIGA-AD response category levels except for absenteeism. Overall, absenteeism in this population was relatively low and highly variable. However, the pattern was more consistent when assessing mean impairment at week 16, suggesting that greater improvements in EASI or vIGA-AD translate to lower degrees of absenteeism. These results are in line with a recent AD study, which demonstrated that more severe AD had greater impacts on the work productivity and daily activity of patients with AD; however, absenteeism only contributed 10% to total weekly work impairment due to AD, whereas presenteeism contributed nearly 90%, suggesting that presenteeism-induced productivity loss has a greater contribution to total work productivity loss than absenteeism in patients with AD.[17]

Similarly, overall improvement in HADS anxiety and depression was far lower than with the other PROs. HADS is not an AD- or dermatology-specific instrument, so it may be less sensitive in detecting relevant changes unique to the AD population. This is reflected in the patterns observed within HADS-A and HADS-D (i.e., mean percentage improvement is relatively lower compared with other outcomes, and the change at each increasing skin clearance level is not as pronounced compared with other outcomes). Thus, when assessing aspects of psychosocial health, AD-specific or dermatology-specific instruments (e.g., ADerm-IS, DLQI) may provide more refined details to the uniquely lived experience of patients with AD.

Our results are also consistent with previous QoL studies[18,19] and demonstrate that the symptoms and skin lesions of AD affect many different areas of a patient's QoL, resulting in a large negative burden of disease. Thus, it is critically important for AD treatments to optimize the clinical response associated with the appearance (i.e., clearance) of skin, resolve or mitigate bothersome symptoms, and improve the overall QoL of affected patients. The results of these analyses can be used to inform treatment goals and shared decision-making processes in AD, especially because multiple measures were used to assess these relationships from the patient perspective.

Strengths of the study include the large sample size, comprehensive nature of the measures used to assess clinical response from the patient's perspective, and the fact that the

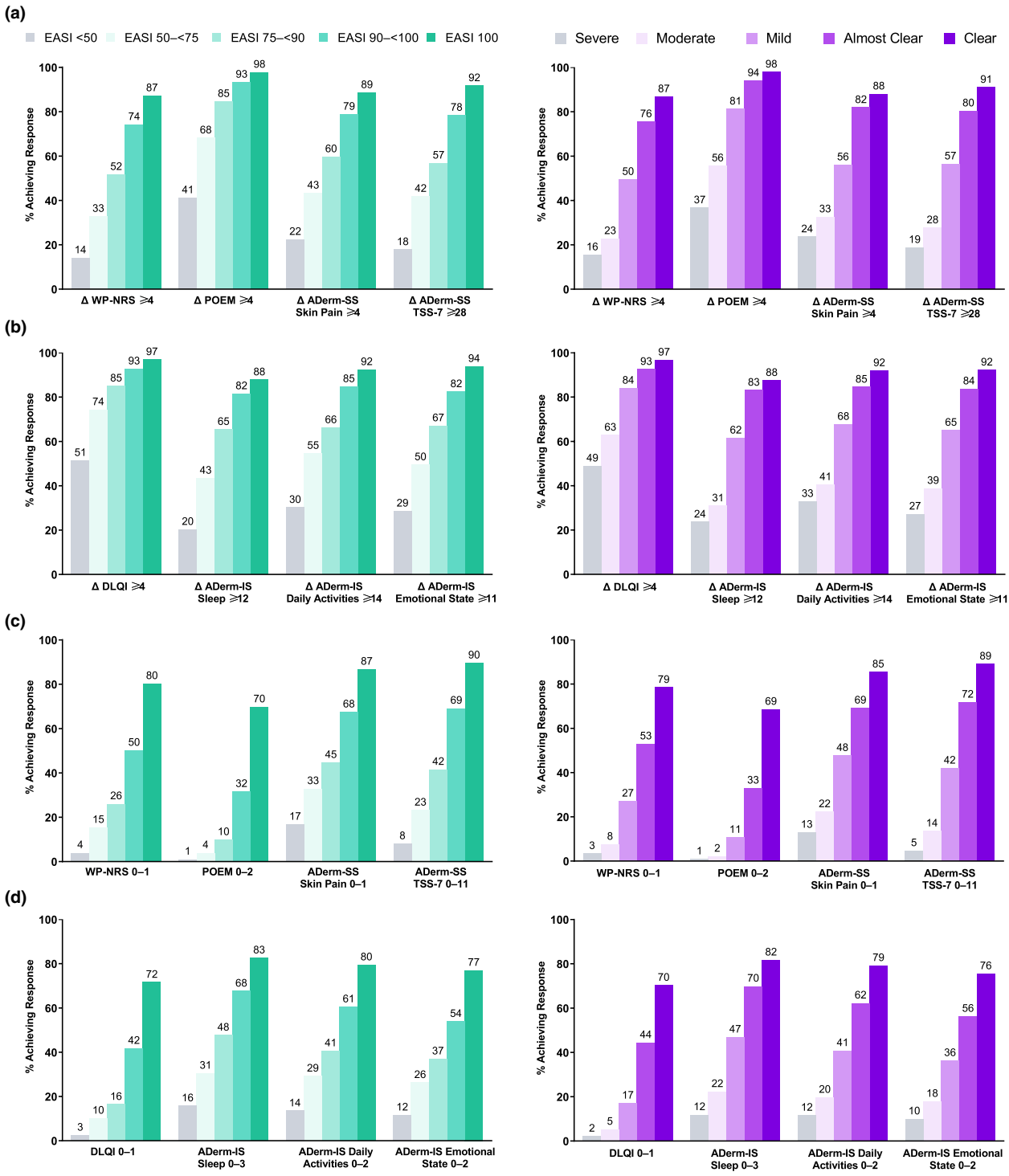

FIGURE 2 Response rates of (a, c) clinical outcomes and (b, d) quality of life outcomes by EASI and vIGA-AD response category level at week 16 (ITT population). Change score thresholds in panels a and b represent the MCID. DLQI was assessed in patients aged ≥16 years at screening. ADerm-IS, Atopic Dermatitis Impact Scale; ADerm-SS, Atopic Dermatitis Symptom Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Activity and Severity Index; ITT, intent-to-treat; MCID, minimal clinically important difference; POEM, Patient-Oriented Eczema Measure; TSS-7, 7-Item Total Symptom Score; vIGA-AD, validated Investigator Global Assessment of Atopic Dermatitis; WP-NRS, Worst Pruritus Numeric Rating Scale.

data were collected during rigorously designed clinical trial settings that controlled for potential biases, which are typically present in observational studies.

However, the results of this analysis should be interpreted in light of some limitations. First, the analyses were conducted using clinical trial data for patients

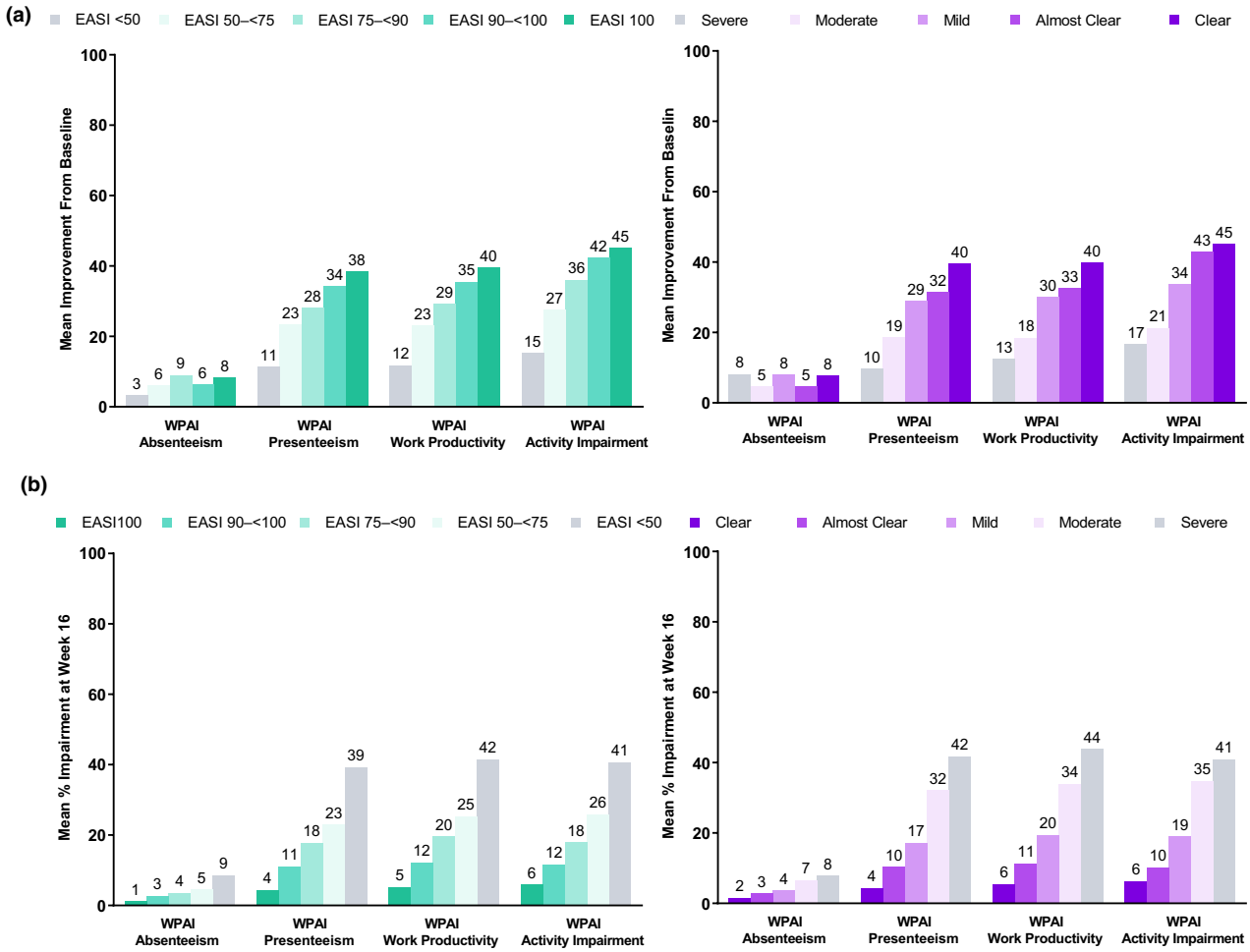

FIGURE 3 (a) Mean improvement and (b) mean percentage impairment in WPAI by EASI and vIGA-AD response category level at week 16 (ITT population). EASI, Eczema Activity and Severity Index; ITT, intent-to-treat; vIGA-AD, validated Investigator Global Assessment of Atopic Dermatitis; WPAI, Work Productivity and Activity Impairment.

with moderate to severe AD and may not be generalizable to all AD patients, especially those with mild disease. Second, these analyses required the assumption that the relationships between a clinical response and other measures were independent of the assigned treatment. For example, an EASI 100 response translated to the same outcomes regardless of the treatment received. Consequently, treatment-specific effects may attenuate these results. Separate analyses conducted within the placebo study arms exhibited consistent stepwise patterns, although improvements were generally lower. This may suggest that upadacitinib independently affects these outcomes or improves other disease parameters simultaneously, hence enhancing improvements in PROs. Finally, these analyses only evaluated bivariate relationships. Multivariate and interaction effects were not investigated but may provide a more detailed understanding of the complex relationships among clinical responses and other AD-specific outcomes. These interrelationships, their direct and mediated effects, and the independent effects of treatment are areas of future research. The moderate levels of correlation between clinician-assessed measures and patient-reported measures suggest that there may be some disconnect. Future studies should assess characteristics of patients who selectively had greater improvements in EASI or IGA but not PROs.

CONCLUSIONS

The results from three phase 3 trials of patients with moderate to severe AD showed that attainment of greater degrees of clinical response is related to improvements across multiple dimensions impacted by AD, including itch, skin pain, and other symptoms, as well as sleep, anxiety, depression, and aspects of QoL. These results demonstrate the value of achieving higher levels of clinical response.

ACKNOWLEDGEMENTS

All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Maria Hovenden, PhD, and

Janet E. Matsuura, PhD, of ICON (Blue Bell, PA) and was funded by AbbVie.

FUNDING INFORMATION

AbbVie funded this research and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

CONFLICT OF INTEREST STATEMENT

Kristian Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB; and received travel reimbursement from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Galderma, Janssen-Cilag, LEO, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB. Professor Reich is a co-founder of Moonlake Immunotherapeutics. **Marjolein S. de Bruin-Weller** has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Arena, Aslan, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme. **Mette Deleuran** has received research support, has consulting/advisory board agreements, and/or has received honoraria for lecturing from AbbVie, Eli Lilly, LEO Pharma, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Incyte, Kymab Ltd, La Roche Posay, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, and Sanofi-Genzyme. **Brian M. Calimlim, Naijun Chen, and Xiaofei Hu** are full-time, salaried employees of AbbVie Inc. and own AbbVie stock or stock options. Naijun Chen may have also received travel reimbursement from AbbVie. **Allan R. Tenorio** is a former employee of AbbVie Inc. and owns AbbVie stock or stock options. **Jonathan I. Silverberg** has received honoraria as a consultant and/or advisory board member for AbbVie, AObiome, Arcutis, Alamar, Amgen, Arena, Arcutis, Asana, Aslan, BioMX, Biosion, Bodewell, Boehringer-Ingelheim, Cara, Castle Biosciences, Celgene, Connect Biopharma, Dermavant, Dermira, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Menlo, Novartis, Optum, Pfizer, RAPT, Regeneron, Sanofi-Genzyme, Shaperon, and Union; speaker for AbbVie, Eli Lilly, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme; and institution received grants from Galderma and Pfizer.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

ETHICS STATEMENT

For all three studies included in this analysis, independent ethics committees or institutional review boards at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrolment. All three studies were done in accordance with the International Conference for Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Adult patients or the parents or legal guardians of adolescent patients have given written informed consent before screening, including consent to publication of their case details.

CLINICAL TRIAL REGISTRATION

The three trials included in this analysis were registered at Clinicaltrials.gov: Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Reich K, de Bruin-Weller MS, Deleuran M, Calimlim BM, Chen N, Hu X, et al. Higher levels of response on clinical atopic dermatitis severity measures are associated with meaningful improvements in patient-reported symptom and quality of life measures: Integrated analysis of three Upadacitinib phase 3 trials. J Eur Acad Dermatol Venereol. 2023;37:1634–1641. https://doi.org/10.1111/jdv.18995