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ORIGINAL RESEARCH

Impact of Achieving Optimal Treatment Targets and Minimal Disease Activity on Health-Related Quality of Life and Satisfaction in Patients with Atopic Dermatitis

Jonathan I. Silverberg · Melinda Gooderham · Andreas Wollenberg · Andrew E. Pink · Diego Ruiz Dasilva · Shawn G. Kwatra · Yousef Binamer · Norito Katoh · Valeria Aoki · Alvaro Moreira · Ayman Grada · Chao Li · Brian Calimlim · Wan-Ju Lee · Christopher G. Bunick

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ABSTRACT

Introduction: Guidance from the Aiming Higher in Eczema/Atopic Dermatitis initiative identified moderate and optimal treatment targets for clinician-reported outcomes (ClinROs) and patient-reported outcomes (PROs) and defined minimal disease activity (MDA) as simultaneously meeting optimal targets in ClinRO and PRO. This post hoc analysis investigates the impact of achieving individual optimal targets or MDA on patient health-related quality of life (HRQoL) outcomes in patients with atopic dermatitis.

Methods: Patients from phase 3 Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD UP (NCT03568318) were randomized 1:1:1 to receive daily oral upadacitinib at either 15 mg or 30 mg, or placebo for the first 16 weeks. Patients were pooled for this analysis regardless of intervention and stratified into three mutually exclusive response groups meeting optimal, moderate, or neither treatment target for each ClinRO or PRO, and the achievement of MDA at week 16. Impact on the patient's HRQoL was measured across eight outcomes: itch, skin symptoms, quality of life, sleep, daily activities, emotional state, work productivity, and treatment satisfaction.

Results: Patients who achieved optimal treatment targets, compared with those achieving moderate or neither treatment target, reported greater improvement in patient HRQoL outcomes (1.1–20.2-fold for optimal versus moderate, 1.3 to >50-fold for optimal versus neither

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J. I. Silverberg (✉)
Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA
e-mail: jonathanisilverberg@gmail.com

M. Gooderham
SKiN Centre for Dermatology, Peterborough, ON, Canada

target, and 1.2–16.3-fold for moderate versus neither target groups). In addition, patients who achieved MDA, versus those achieving optimal ClinRO or PRO alone, were more likely to report improved patient HRQoL outcomes.
***Conclusions*:** These results highlight the value of reaching optimal treatment targets and MDA in disease management of atopic dermatitis.

Keywords: Atopic dermatitis; Quality of life; Optimal treatment target; Patent-reported outcome; Clinician-reported outcome; Minimal disease activity

Key Summary Points

Why carry out this study?

Optimal and moderate treatment targets have been identified for atopic dermatitis to raise the standard of care and fully address the burden of the disease on patients and their health-related quality of life.

In this study we evaluated the impact of achieving optimal versus moderate treatment targets on patient health-related quality of life.

What was learned from the study?

Patients who achieved optimal treatment targets, compared with those meeting moderate or neither treatment target, were more likely to report improved patient health-related quality of life.

Particularly, health-related quality of life improvements were greatest in patients who achieved minimal disease activity (simultaneous achievement of one optimal clinician-reported and one optimal patient-reported outcome).

These results demonstrate that achievement of skin clearance alone may be insufficient in fully meeting patient needs and that simultaneous achievement of both optimal clinician- and patient-reported outcomes is needed to attain the best patient outcomes.

M. Gooderham
Probity Medical Research, Peterborough, ON, Canada

M. Gooderham
Division of Dermatology, Queen's University, Peterborough, ON, Canada

A. Wollenberg
Department of Dermatology and Allergy, University Hospital Augsburg, Augsburg, Germany

A. Wollenberg
Comprehensive Center for Inflammation Medicine, University of Luebeck, Luebeck, Germany

A. Wollenberg
Department of Dermatology and Allergy University Hospital, Ludwig Maximilian University of Munich, Munich, Germany

A. E. Pink
St John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust and King's College London, London, UK

D. Ruiz Dasilva
Department of Dermatology, Forefront Dermatology and Eastern Virginia Medical School, Virginia Beach, VA, USA

S. G. Kwatra
Department of Dermatology, University of Maryland School of Medicine, Baltimore, MD, USA

Y. Binamer
Department of Dermatology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Y. Binamer
College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

N. Katoh
North Campus, Kyoto Prefectural University of Medicine, Kyoto, Japan

V. Aoki
Department of Dermatology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

A. Moreira · A. Grada · C. Li · B. Calimlim · W.-J. Lee
AbbVie Inc, North Chicago, IL, USA

C. G. Bunick
Program in Translational Biomedicine, Yale University School of Medicine, New Haven, CT, USA

C. G. Bunick
Department of Dermatology, Yale University School of Medicine, New Haven, CT, USA

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Patients with AD often suffer from an intensely itchy, sometimes painful rash that can have major detrimental impacts on a patient's quality of life [1]. In addition to the itch and pain associated with the rash, patients often report sleep disturbance [2], anxiety and depression [3], and associated reduced health-related quality of life (HRQoL) impacting both themselves and their families [4].

There are a variety of treatments available for AD ranging from topical to systemic therapies, including biologics and Janus kinase inhibitors as the most recently approved systemic targeted therapies [5]. With the entry of these targeted therapies in recent years, patients now have more options to effectively manage their AD. Meanwhile, treatment goals in AD are evolving as more effective therapies become available.

Aiming Higher in Eczema/Atopic Dermatitis (AHEAD), a workgroup focused on raising the standard of care in AD, comprising 87 expert dermatologists from 44 countries, used qualitative patient research to introduce a novel treat-to-target approach to guide dermatology clinicians in establishing treatment goals for patients [6]. This approach places special emphasis on involving a patient's needs when setting treatment objectives. One of the most important considerations of the AHEAD recommendations is the development of a concept for minimal disease activity (MDA) as a preferred treatment goal [6]. The AHEAD recommendations outline both moderate and optimal treatment targets for clinician-reported outcomes (ClinRO) and patient-reported outcomes (PRO). Achievement of MDA is defined as simultaneous achievement of at least one optimal treatment target for ClinRO (e.g., Eczema Area and Severity Index [EASI] 90% improvement) and PRO (e.g., peak pruritus numerical rating scale [NRS] 0/1) [6].

We aim to evaluate the impact of achieving optimal versus moderate treatment targets and achievement of MDA on patient outcomes using clinical trial data from Measure Up 1, Measure Up 2, and AD UP.

METHODS

This post hoc analysis combines observed case data from the phase 3 studies Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD UP (NCT03568318). Complete methodology for these studies was previously reported [7–9]. Briefly, adolescent and adult patients were originally randomized 1:1:1 to receive daily oral upadacitinib at either 15 mg or 30 mg, or placebo for the first 16 weeks. Patients in Measure Up 1 and 2 received only their randomized treatment, while patients enrolled in AD UP also received topical corticosteroids. Beginning at week 4, rescue treatment could be provided at the discretion of the investigator. All treatment groups were pooled into a single cohort regardless of intervention.

According to the AHEAD recommendations, clinician-reported measures assessed in this study include EASI, SCORing Atopic Dermatitis (SCORAD), Investigators' Global Assessment (IGA), and affected body surface area (BSA). Patient-reported measures include Worst Pruritus NRS (WP-NRS), Patient-Oriented Eczema Measure (POEM), Atopic Dermatitis Impact Scale (ADerm-IS), sleep NRS, Atopic Dermatitis Symptom Scale (ADerm-SS), skin pain NRS, Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS). All measures were assessed at week 16.

For each individual ClinRO or PRO measurement, patients were stratified into three mutually exclusive response groups in the following order: achievement of optimal treatment target, moderate treatment target, or achievement of neither target. Optimal and moderate treatment targets are outlined in Table 1.

MDA is defined as the concurrent achievement of at least one optimal ClinRO and one optimal PRO. We evaluated selected MDA combinations on the basis of Harmonizing Outcome Measures (HOME)-endorsed core outcome set for AD clinical trials (i.e., EASI, WP-NRS, DLQI, and POEM) to understand the benefit of achieving MDA versus not achieving MDA. The MDA in this analysis is defined as EASI 90 + WP-NRS 0/1, EASI 90 + DLQI 0/1, and EASI 90 + POEM 0–2, respectively.

Table 1 Optimal and moderate treatment targets for clinician- and patient-reported outcomes

Measurement	Optimal target	Moderate target (excluding patients who achieved the optimal target)
Clinician-reported outcomes		
EASI response	Improvement ≥ 90%	Improvement ≥ 75% to < 90%
EASI category	≤ 3	4 to ≤ 7
SCORAD response	Improvement ≥ 75%	Improvement ≥ 50% to < 75%
SCORAD category	≤ 10	11 to ≤ 24
IGA and BSA	IGA 0/1 and BSA ≤ 2%	IGA ≤ 2 and BSA improvement ≥ 50%
Patient-reported outcomes		
Itch (WP-NRS)	≤ 1	Improvement (reduction) ≥ 4
Skin pain (pain NRS)[a]	≤ 1	Improvement (reduction) ≥ 3
Skin condition (POEM)	≤ 2	Improvement (reduction) ≥ 4
Sleep disturbance (sleep NRS)[b]	≤ 1	Improvement (reduction) ≥ 3
Impact on daily activities (DLQI/CDLQI)[c]	≤ 1	Improvement (reduction) ≥ 4
Mental health (HADS)	HADS-A < 8 and HADS-D < 8	HADS-A < 11 and HADS-D < 11

[a]ADerm-SS item on skin pain ("During the past 24 hours, how bad was your worst skin pain due to AD?") was used, reported on an 11-point scale, with higher numbers representing worse outcomes

[b]ADerm-IS item on sleep disturbance ("During your sleep hours, how much did your AD impact your sleep?") was used and reported on an 11-point scale, with higher numbers representing worse outcomes

[c]DLQI for patients aged > 16 years and CDLQI for patients aged 4–16 years. IDQOL for patients aged < 4 years was not available and was not included in this analysis

ADerm-IS Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *BSA* body surface area, *CDLQI* Children's Dermatology Life Quality Index, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *HADS* Hospital Anxiety and Depression Scale, *HADS-A* HADS-Anxiety, *HADS-D* HADS-Depression, *IDQOL* Infants' Dermatitis Quality of Life, *IGA* Investigators' Global Assessment, *MDA* minimal disease activity, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *SCORAD* SCORing Atopic Dermatitis, *WP-NRS* worst pruritus numerical rating scale

The impact of achieving optimal target or MDA on patients' HRQoL outcomes was evaluated using PRO measures assessing the following: patient-reported itch, skin symptoms, quality of life, sleep, daily activities, emotional state, work productivity, and treatment satisfaction, as outlined in Table 2.

Statistical Analysis

Descriptions of the impact on the patients' HRQoL outcomes were assessed for patients who achieved optimal target, moderate target, or neither target response, as well as for those who achieved MDA versus not achieving MDA. In addition, to further understand the association between skin clearance and itch on

Table 2 Impact on patients' health-related quality of life outcomes

Impact	Questionnaire	Outcome assessment
Itch	Worst Pruritus NRS	0/1[a]
DLQI[b]	Dermatology Live Quality Index	0/1[a]
Sleep	ADerm-IS sleep NRS	0/1[a]
Daily activities	ADerm-IS Daily Activities domain[c]	0–2[d]
Emotional state	ADerm-IS Emotional State domain[e]	0–2[d]
Work productivity	WPAI overall work impairment[f]	≥ 20 point improvement[g]
Treatment satisfaction	Patient Global Impression of Treatment[h]	"Extremely satisfied" or "very satisfied"
Skin symptoms	ADerm-SS TSS-7[i]	0–11[j]

[a]Assessed in patients with baseline score ≥ 1

[b]DLQI for patients aged > 16 years and CDLQI for patients aged 4–16 years

[c]Scored on a scale of 0–40, with 40 being the most severe impact on daily activities

[d]Assessed in patients with baseline score ≥ 2

[e]Scored on a scale of 0–40, with 40 being the most severe impact on emotional state

[f]Overall work impairment represents the percentage of work time missed and the percentage of time with work impairment due to AD, with higher values indicating greater impairment

[g]Assessed in patients with baseline score ≥ 20

[h]Patients were asked: "Overall, how satisfied or dissatisfied are you with your current treatment for AD?" Responses range from 1 = "extremely dissatisfied" to 7 = "extremely satisfied"

[i]Scored on scale of 0–70, with 70 being the most severe skin symptoms

[j]Assessed in patients with baseline score ≥ 11

AD atopic dermatitis, *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS TSS-7* Atopic Dermatitis Symptom Scale 7-item total symptom score, *CDLQI* Children's Dermatology Life Quality Index, *DLQI* Dermatology Life Quality Index, *NRS* numeric rating scale, *WPAI* Work Productivity and Activity Impairment

patients' HRQoL outcomes, additional analyses were conducted among EASI 90 responders where WP-NRS was broken down into 0/1, 2–3, 4–6, and 7–10. Similar analyses were conducted among WP-NRS 0/1 responders where EASI responses were further stratified into EASI 90, 75 to < 90, 50 to < 75, and < 50. Statistical analysis was conducted using chi-squared tests for categorical variables when assessing the difference in patient HRQoL outcomes for optimal versus moderate, optimal versus neither target, and moderate versus neither target. *P* value < 0.05 was considered statistically significant. Results are reported by observed cases with no imputation.

Ethical Approval

The original studies that collected the data analyzed within this manuscript were approved by the institutional review board (IRB), were conducted in accordance with the Declaration of

Helsinki, and informed consent was obtained for participants.

RESULTS

Effects of Optimal Target Achievement on Patient HRQoL Outcomes

Across all reported measures, a higher proportion of patients who achieved the optimal treatment target attained stringent patient HRQoL compared with those meeting moderate or neither treatment targets (Figs. 1, 2, 3, 4, 5, and 6). Similarly, a higher proportion of patients who achieved moderate versus neither treatment target achieved stringent patient HRQoL outcomes (Figs. 1, 2, 3, 4, 5, and 6). These differences were significant for optimal versus moderate, optimal versus neither target, and moderate versus neither target reported in Figs. 1, 2, 3, 4, 5, and 6, with one exception (optimal versus moderate WP-NRS + work productivity improvement; Figs. 1, 2, 3, 4, 5 and 6). The ratio of achieving HRQoL outcomes was 1.1–20.2-fold for optimal versus moderate, 1.3 to >50-fold for optimal versus neither target, and 1.2–16.3-fold for moderate versus neither target groups.

Specifically, in the EASI response assessment (Fig. 1), patients who achieved the optimal treatment target (EASI 90) obtained greater improvement in patient HRQoL outcomes (50.6–86.5%),

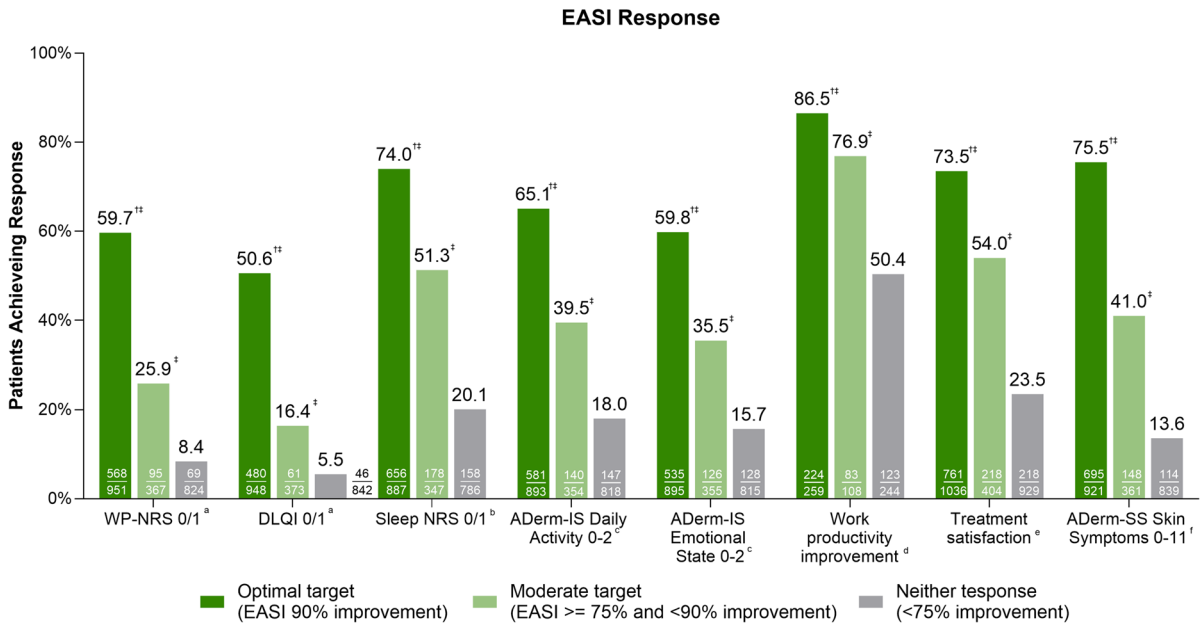

Fig. 1 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by EASI response. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e] Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

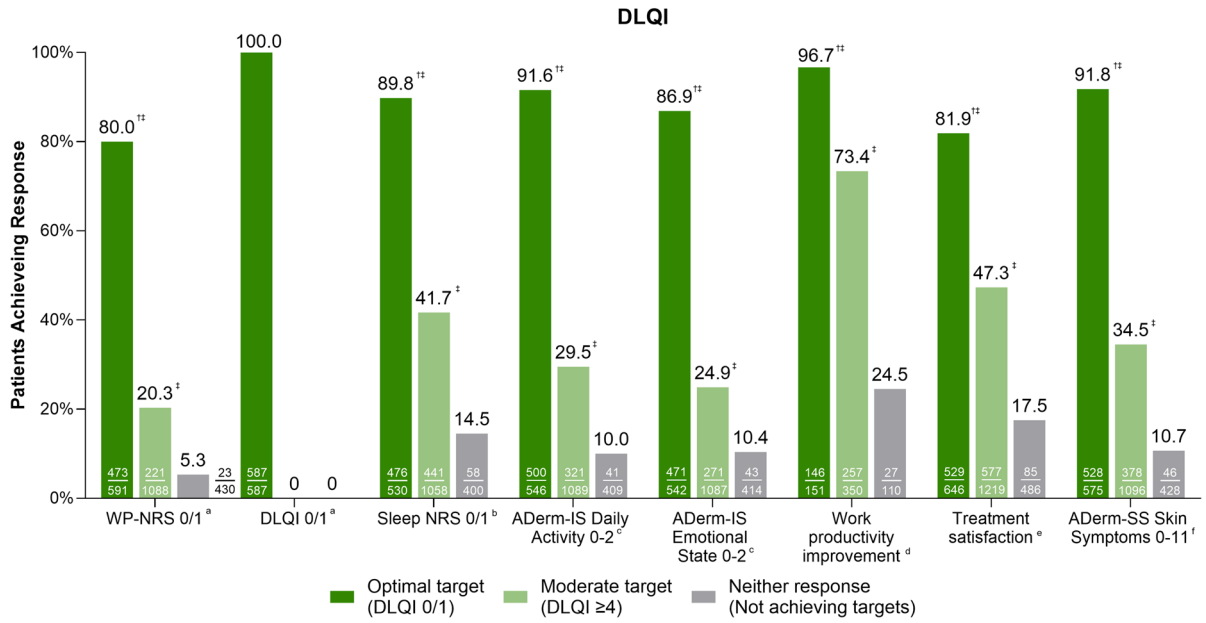

Fig. 2 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by DLQI. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

compared with those achieving moderate (EASI 75 to < 90; 16.4–76.9%) or neither treatment target (EASI < 75; 5.5–50.4%). A consistent trend was observed in other measures, including IGA + BSA, WP-NRS, DLQI, sleep NRS, and POEM (Figs. 2, 3, 4, 5, and 6) as well as SCORAD, skin pain NRS, and HADS-A and HADS-D (Supplementary Figs. 1–5).

Effects of MDA Achievement on Patient HRQoL Outcomes

A higher proportion of patients who achieved MDA, when compared with only PRO or ClinRO optimal treatment targets, or neither treatment targets, reported greater improvement in patient HRQoL outcomes (Figs. 7, 8, and 9).

In the analyses where MDA is defined as EASI 90 + WP-NRS 0/1 (Fig. 7), the proportion of patients achieving stringent patient HRQoL outcomes was greatest in patients who achieved MDA (72.6–98.8%) compared with those meeting WP-NRS 0/1 only (40.4–95.3%), EASI 90 only (18.0–72.3%), and those achieving neither

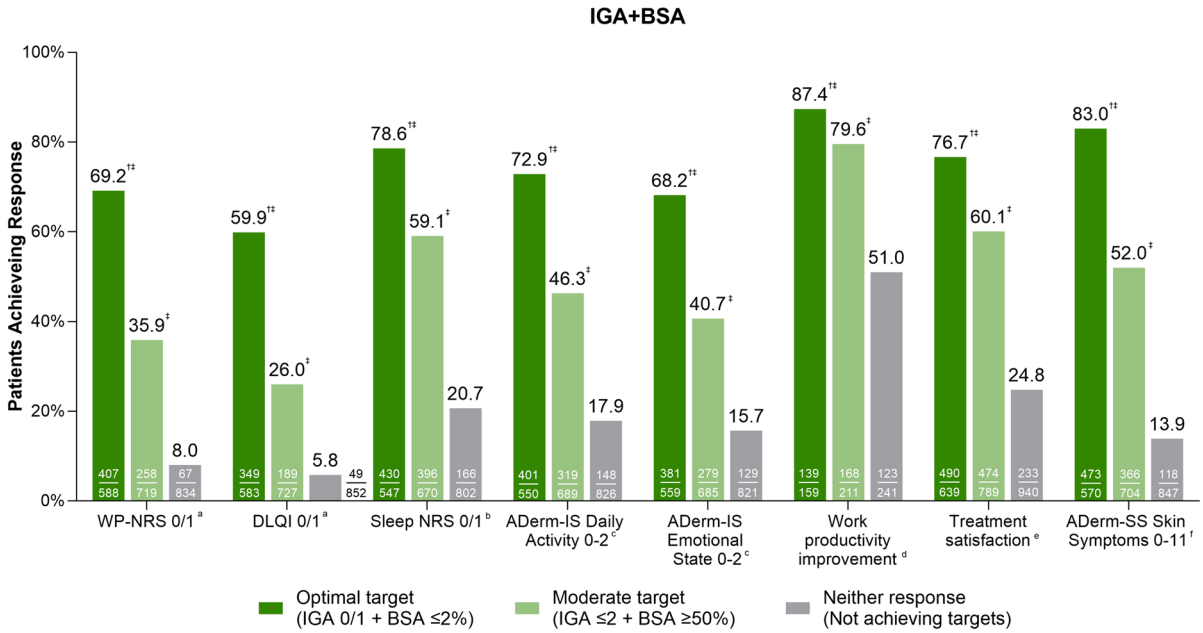

Fig. 3 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by IGA and BSA. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

target (4.4–53.1%; Fig. 2a). Consistent trends were observed when assessing the effect of MDA on the basis of EASI + DLQI (Fig. 8) and EASI + POEM (Fig. 9).

Effect of WP-NRS and EASI Improvement on Patient HRQoL Outcomes

Among patients achieving EASI 90 (optimal ClinRO target), the proportion of patients obtaining the HRQoL outcomes was greatest among those who also achieved WP-NRS 0/1 (i.e., MDA), ranging from 72.6 to 98.8% (Fig. 10). Proportions decreased as WP-NRS scores increased (Fig. 10), with a significantly lower proportion of patients with WP-NRS 2–3, compared with WP-NRS 0/1 achieving the patient HRQoL outcomes. Achievement rates were between approximately 10 and 58 percentage points lower in patients with WP-NRS 2–3 compared with those reported in patients with WP-NRS 0/1. At WP-NRS scores 7–10, achievement of HRQoL outcomes was generally < 25%, despite achieving EASI 90 (Fig. 10).

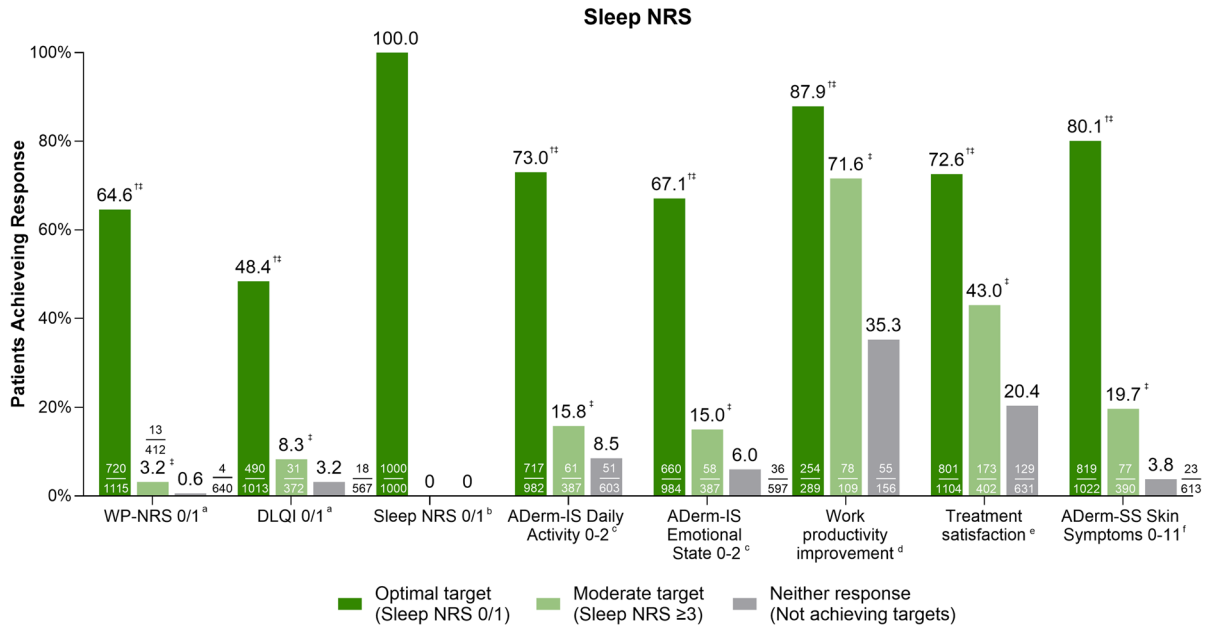

Fig. 4 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by sleep NRS. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

Among patients achieving WP-NRS 0/1 (optimal PRO target), the variation in the proportion of patients achieving the stringent patient HRQoL outcomes was lower across patients with different levels of EASI response (Fig. 11). Generally, patients who achieved MDA (i.e., EASI 90 + WP-NRS 0/1) obtained greater improvement in patient HRQoL outcomes (72.6–98.8%) compared with others with different levels of EASI response.

DISCUSSION

Here we present the first quantitative data supporting the value of achieving optimal treatment targets individually and MDA (simultaneous achievement of optimal treatment

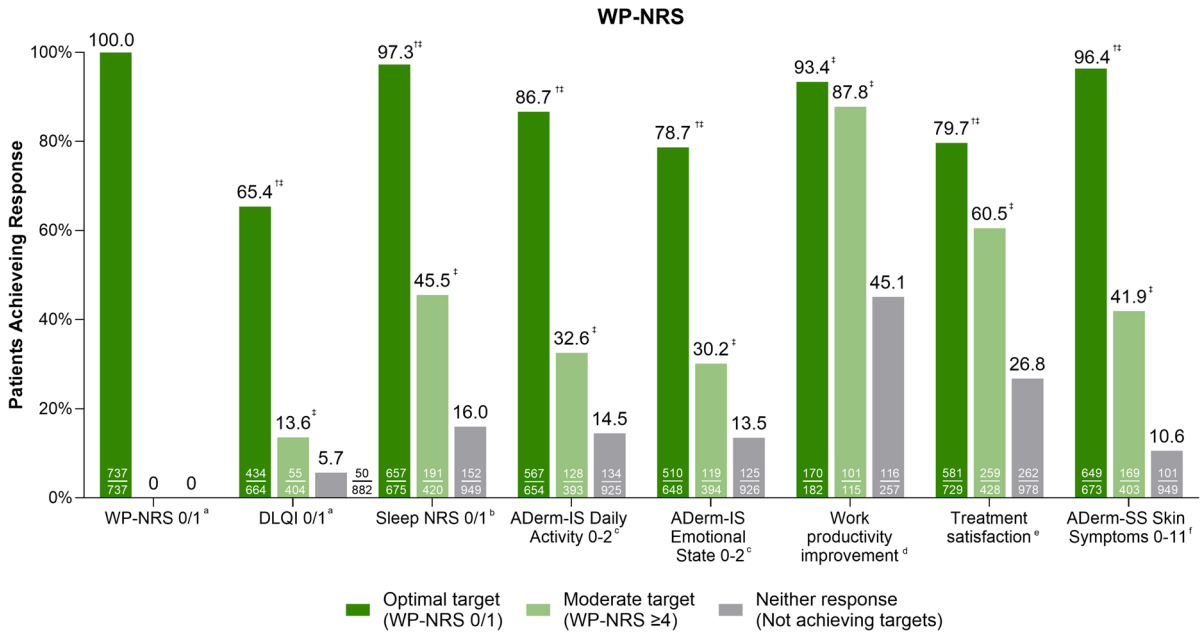

Fig. 5 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by WP-NRS. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

targets) from the AHEAD recommendations. Our analysis revealed that patients achieving optimal treatment targets, compared with those achieving moderate or neither treatment target, reported greater improvement in patient HRQoL outcomes, including quality of life, daily activities, emotional state, work productivity, and treatment satisfaction. The ratio of achieving stringent patient HRQoL outcomes for optimal versus moderate treatment targets was up to approximately a 20-fold difference. In addition, patients who achieved MDA, compared with achieving only one optimal ClinRO or PRO, also reported improved patient HRQoL outcomes, underscoring the importance of achieving both the patient's and physician's treatment targets simultaneously. The study findings stress the significance of aiming for optimal targets when treating patients with AD, as the analysis demonstrates a greater proportion of patients

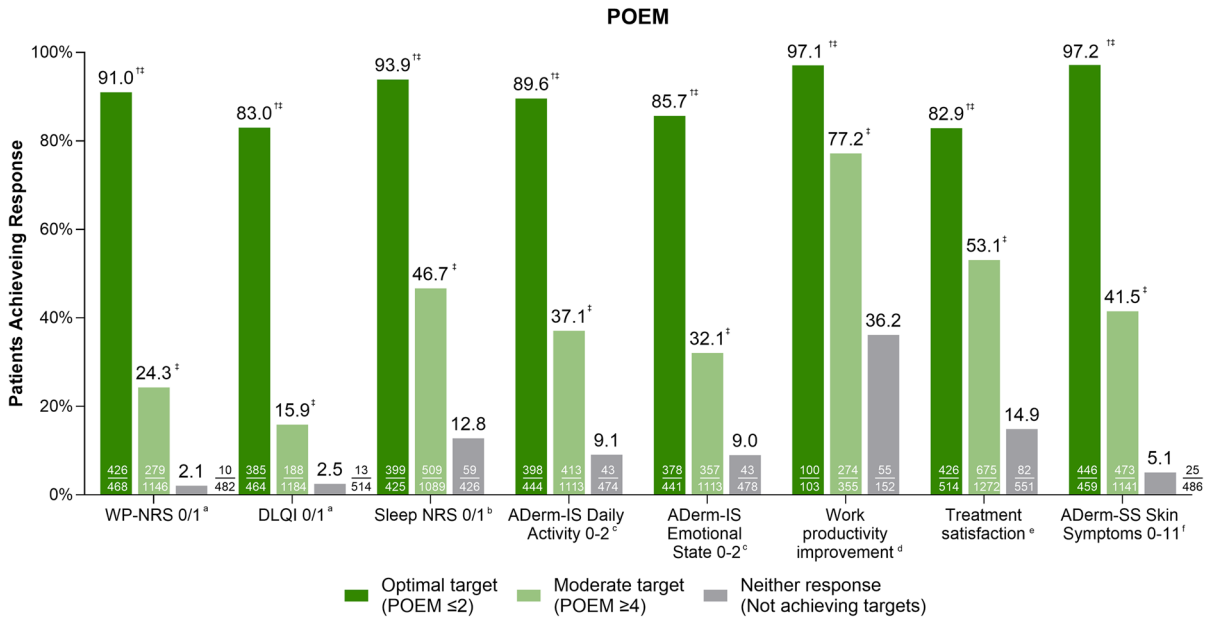

Fig. 6 Effect of achievement of optimal, moderate, and neither treatment targets on patient health-related quality of life outcomes by POEM. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. †$P < 0.05$ compared with moderate target. ‡$P < 0.05$ compared with inadequate response. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11. [g]Optimal and moderate targets are mutually exclusive, and patients achieving the optimal target are not included in those achieving the moderate target; *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, *IGA* Investigators' Global Assessment, *NRS* numeric rating scale, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

showing improvements across multiple dimensions of their lives. Our study aligns with the goals set out by the AHEAD recommendations to achieve optimal targets when possible.

The treatment agnostic results presented here are also supported by real-world analysis [10]. An analysis of the TARGET-Derm AD international observational registry reported that achieving optimal treatment targets for both itch relief and skin clearance markedly enhances PROs [10]. This study, along with the results presented here, further emphasizes the AHEAD recommendations of achieving optimal treatment targets.

The MDA treatment goals were developed through the consensus of international clinicians on the basis of qualitative patient research to understand patient needs [6]. Patients were asked to identify 1–3 troublesome AD symptoms, and the appropriate PRO was selected to best measure these outcomes, and, additionally, clinicians selected at least one ClinRO to provide an objective measure of the patient's disease [6, 11]. These results highlight the benefit of achieving MDA and optimal treatment targets for patients and the importance of shared decision-making between the clinician and the patient in treatment management. However, patients'

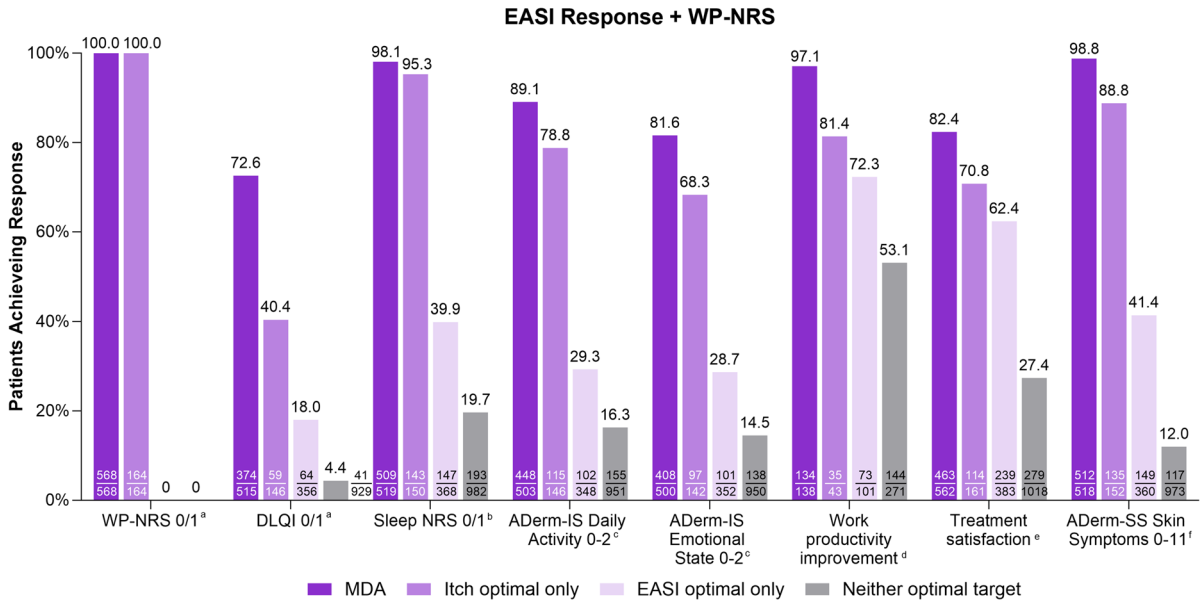

Fig. 7 Effect of achievement of MDA, PRO optimal only, ClinRO optimal only, and neither optimal targets on patient health-related quality of life outcomes by EASI and itch. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11; *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

voices are not always reflected in clinical practice. With the chronic nature of the disease and the debilitating symptoms associated with AD, patients have reported feeling that their physicians may downplay the impact of AD on their life [6]. In a qualitative patient research study, the majority of patients reported a large or moderate impact on their lives of depression or anxiety associated with their AD, skin changes (weeping, bleeding, dry/flaky/scaly skin, redness, or color changes), itch, pain, sleep disturbance, or treatment burden [11].

Moreover, our analysis demonstrated that achieving skin clearance alone (e.g., EASI 90 only) may not result in the best outcomes for patients, suggesting that skin manifestations alone as a treatment target may not be enough to optimize patient outcomes. Results presented here demonstrate that patients who achieved MDA with both optimal ClinRO and PRO targets were associated with the greatest improvement in patient HRQoL outcomes, followed by achieving optimal PRO target alone, and by achieving optimal ClinRO target only. In addition, our study showed that despite achieving EASI 90, patients' HRQoL outcomes vary largely by the level of itch relief, with better outcomes achieved among patients with MDA (i.e., EASI 90 + WP-NRS 0/1) compared with those with greater levels of itch (e.g., EASI 90 + WP-NRS

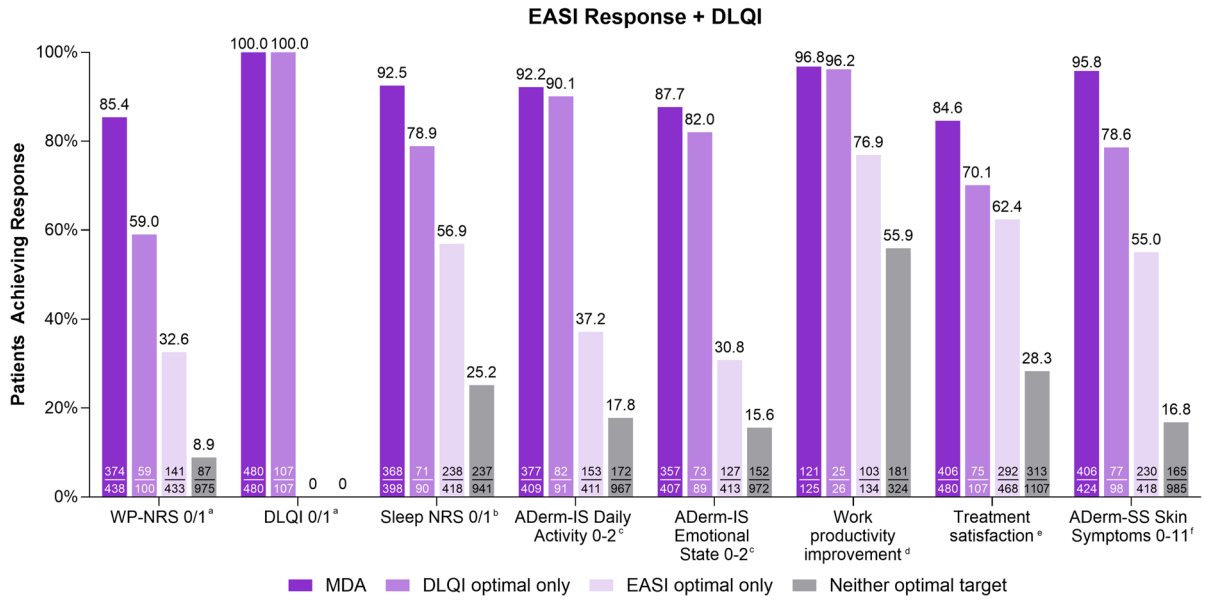

Fig. 8 Effect of achievement of MDA, PRO optimal only, ClinRO optimal only, and neither optimal targets on patient health-related quality of life outcomes by EASI and DLQI. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11; *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

7–10). Significantly fewer patients who obtained WP-NRS 2–3 compared with those achieving WP-NRS 0–1 met the patient HRQoL outcomes, suggesting that partial improvement alone may not fully meet patient HRQoL needs. There are obvious unmet patient needs and, hence, the AHEAD recommendations include patients' voices in setting up the treatment target and guiding disease management throughout.

A limitation of this study is the assumption that the inter-relationships among outcomes are independent of treatment received. For example, the patterns observed are assumed to be similar regardless of whether patients received upadacitinib (15 mg or 30 mg) or placebo. In addition, results are reported as observed, and no imputation was used for missing data. Another limitation is that as data are only assessed at one time point, patients may have achieved a moderate or optimal treatment target or MDA before week 16 and subsequently lost this response. In addition, our analysis uses a clinical trial population that may not accurately reflect a real-world population. Finally, information about the most burdensome symptoms from patients was not assessed in the clinical trials. Owing to the high number of various combinations of ClinRO and PRO, we evaluated HOME-endorsed outcome sets as representative of the MDA definition in

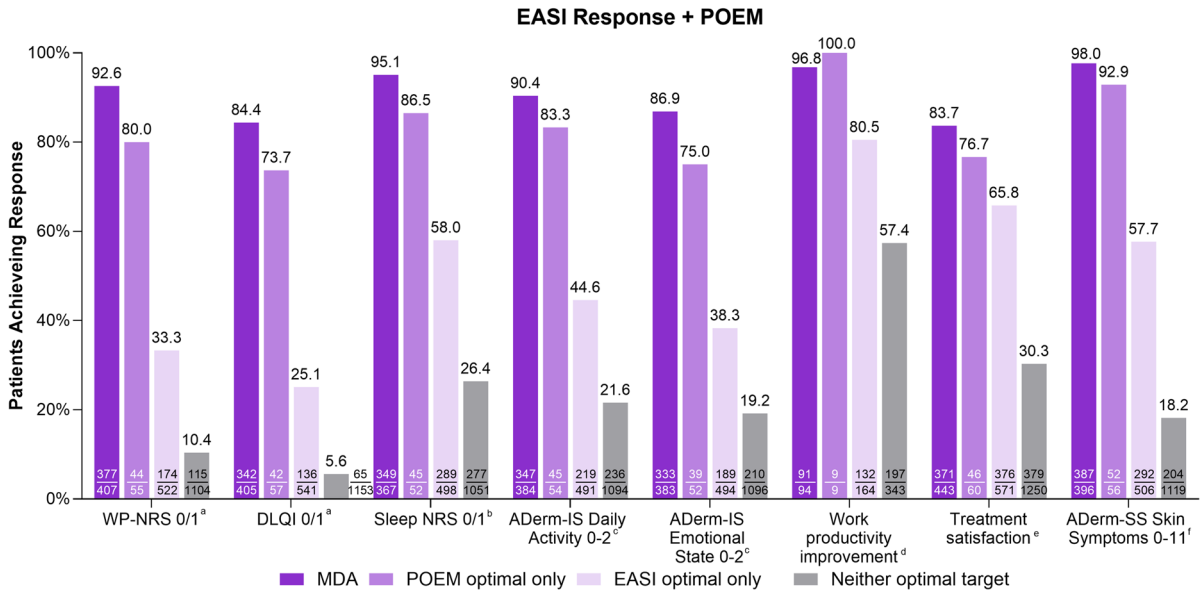

Fig. 9 Effect of achievement of MDA, PRO optimal only, ClinRO optimal only, and neither optimal targets on patient health-related quality of life outcomes by EASI and POEM. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11; *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

this study. Future studies are needed to further assess the impact of MDA with the combination of ClinRO with more than one PRO.

With the evolving AD treatment landscape, physicians and patients can aim for both ClinRO and PRO optimal treatment targets and achievement of MDA, increasing patients' HRQoL. Future clinical trials can raise the bar for AD treatment goals and include measures of MDA achievement as an endpoint, with some studies already employing the simultaneous achievement of EASI 90 + WP-NRS 0/1 as the primary endpoint. [12]

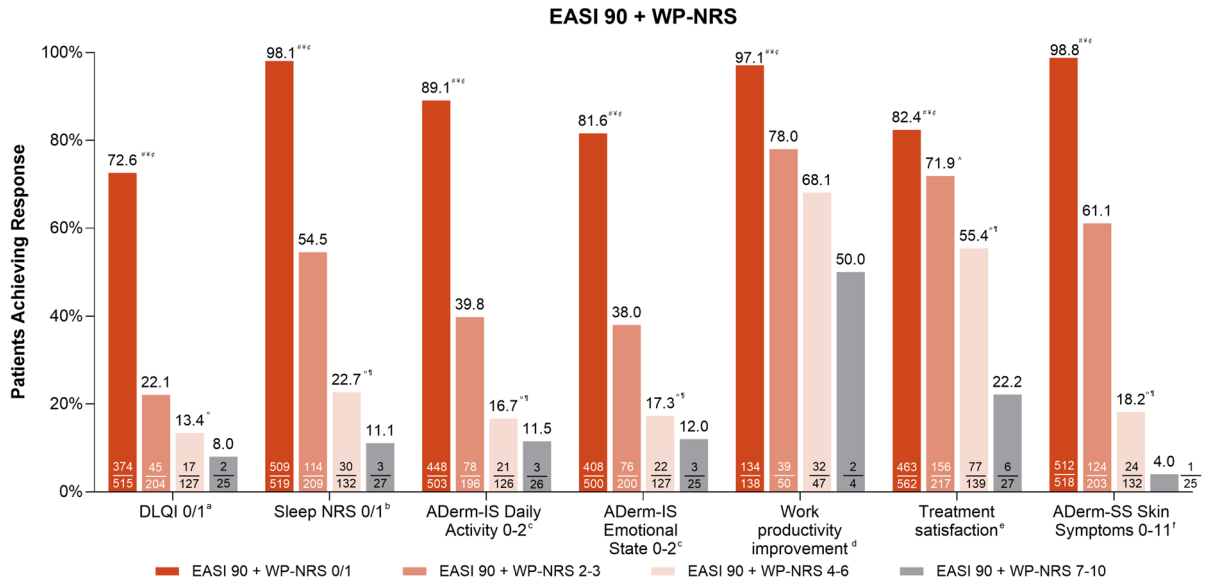

Fig. 10 Effect of improvements in WP-NRS on patient health-related quality of life outcomes among EASI 90 responders. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. $^{\#}P < 0.05$ comparing EASI 90 + WP-NRS 0/1 versus EASI 90 + WP-NRS 2–3. $^{¥}P < 0.05$ comparing EASI 90 + WP-NRS 0/1 versus EASI 90 + WP-NRS 4–6. $^{¢}P < 0.05$ comparing EASI 90 + WP-NRS 0/1 versus EASI 90 + WP-NRS 7–10. $^{¤}P < 0.05$ comparing EASI 90 + WP-NRS 2–3 versus EASI 90 + WP-NRS 4–6. $^{¶}P < 0.05$ comparing EASI 90 + WP-NRS 2–3 versus EASI 90 + WP-NRS 7–10. $^{\wedge}P < 0.05$ comparing EASI 90 + WP-NRS 4–6 versus EASI 90 + WP-NRS 7–10. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WPAI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11; *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

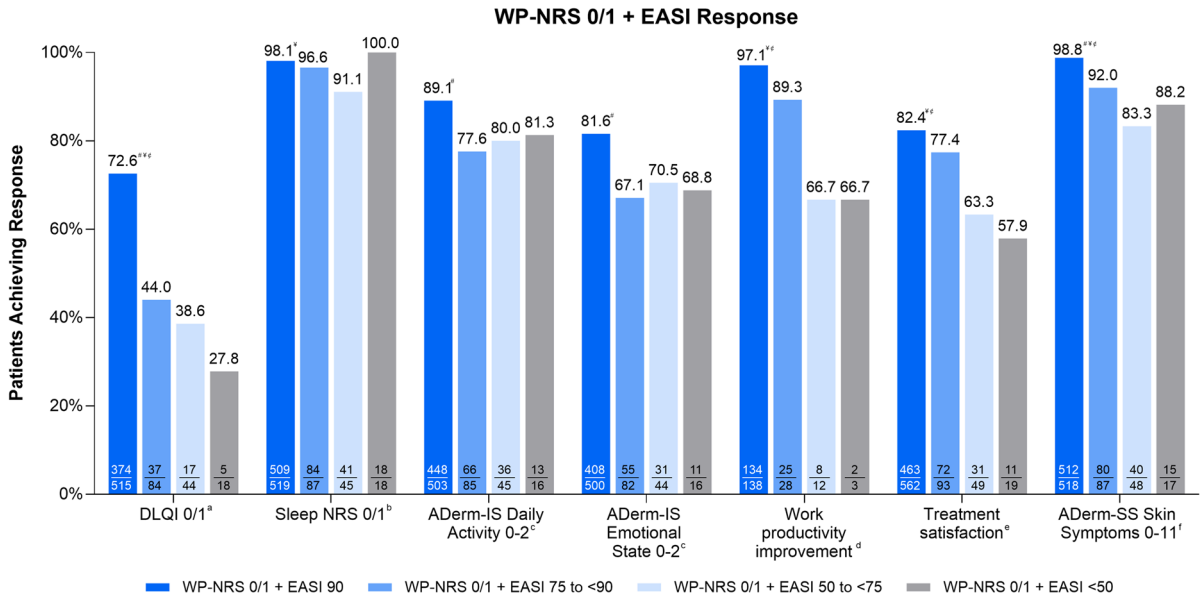

Fig. 11 Effect of improvements in EASI on patient health-related quality of life outcomes among WP-NRS 0/1 achievers. Analyses were based on available data for each outcome. Sample size may vary depending on data availability of the measures involved. Data are not adjusted for multiplicity. $^{\#}P < 0.05$ comparing WP-NRS 0/1 + EASI 90 versus WP-NRS 0/1 + EASI 75 to < 90. $^{¥}P < 0.05$ comparing WP-NRS 0/1 + EASI 90 versus WP-NRS 0/1 + EASI < 75–50. $^{¢}P < 0.05$ comparing WP-NRS 0/1 + EASI 90 versus WP-NRS 0/1 + EASI < 50. $^{¤}P < 0.05$ comparing WP-NRS 0/1 + EASI 75 to < 90 versus WP-NRS 0/1 + EASI < 75–50. $^{¶}P < 0.05$ comparing WP-NRS 0/1 + EASI 75 to < 90 versus WP-NRS 0/1 + EASI < 50. $^{\wedge}P < 0.05$ comparing WP-NRS 0/1 + EASI 75 to < 50 versus WP-NRS 0/1 + EASI < 50. [a]For patients with baseline score > 1. [b]ADerm-IS item no. 2 sleep 0/1 among those with baseline score > 1. [c]Among those with a baseline score > 2. [d]WAPI overall work impairment ≥ 20 point improvement among those with a baseline score ≥ 20. [e]Patient Global Impression of Treatment reporting "extremely satisfied" or "very satisfied." [f]Among those with baseline score > 11; *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *POEM* Patient-Oriented Eczema Measure, *WP-NRS* Worst Pruritus Numerical Rating Scale

CONCLUSIONS

Our analysis shows that patients achieving optimal targets or MDA reported greater improvements in skin symptoms, daily activities, emotional state, work productivity, and patient satisfaction. In addition, patients who achieved optimal treatment targets were more likely to report better patient HRQoL outcomes compared with those achieving moderate treatment targets, emphasizing the value in reaching these higher treatment targets and reinforcing the importance of including patient input and PROs in treatment decisions.

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Calimlim, and Wan-Ju Lee contributed to conceptualization. Formal analysis was conducted by Chao Li and Wan-Ju Lee. Investigation was conducted by Jonathan I Silverberg, Melinda Gooderham, Andreas Wollenberg, Andrew E. Pink, Diego Ruiz Dasilva, Shawn G. Kwatra, Yousef Binamer, Norito Katoh, Valeria Aoki, and Christopher G. Bunick. All authors contributed to the writing of this manuscript.

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Data Availability. 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, 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, and 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 USA 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."

Declarations

Conflicts of Interest. Jonathan Silverberg—has received honoraria as a consultant and/or advisory board member for AbbVie, Aldena, Aldena, Amgen, AObiome, Apollo, Arcutis, Arena, Asana, Aslan, Attovia, Bodewell, Boehringer Ingelheim, Bristol-Meyers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant, Eli Lilly, FIDE, Galderma, GlaxoSmithKline, Incyte, Inmagene, Invea, Kiniksa, LEO Pharma, Merck, Nektar, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sandoz, Sanofi Genzyme, Shaperon, TARGET-RWE, Teva, Triveni, Union, and UpToDate; is a speaker for AbbVie, Arcutis, Dermavant, Eli Lilly, Galderma, LEO Pharma, Pfizer, Regeneron, and Sanofi Genzyme; and George Washington School of Medicine received grants from Galderma, Incyte, and Pfizer. Valeria Aoki—has served as an investigator in clinical trials for Sanofi, Amgen, and Abbvie and as a consultant/advisory board member for Eli Lilly, Galderma, and Abbvie. Yousef Binamer—has received speaker honoraria for serving as a consultant and travel support from AbbVie, Eli Lilly, Janssen, Kyowa Kirin, NewBridge, Novartis, and Sanofi and has received research grants from Novartis and Sanofi. Diego Ruiz Dasilva—has served as an advisor and/or speaker for AbbVie, Arcutis, Dermavant, Eli Lilly, Galderma, Janssen, LEO pharma, Pfizer, Sanofi & Regeneron, UCB, Verrica. Norito Katoh—has received honoraria as a speaker/consultant for Sanofi, Maruho, AbbVie, Ely-Lilly Japan, Torii Pharmaceutical, Pfizer, and Otsuka Pharmaceutical and has received grants as an investigator from Maruho, Sun Pharma, and LEO Pharma. Shawn Kwatra—has received honoraria for serving on advisory boards for AbbVie, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celldex Therapeutics, Dermavant, Galderma, Genzada Pharmaceuticals, Incyte, Johnson & Johnson, Leo Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. Melinda Gooderham—has been an investigator, speaker, and/or advisor for AbbVie, Acelyrin, Alumis, Amgen, Akros, Arcutis, Aristea, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Cara, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, InMagene, JAMP Pharma, Janssen, LEO Pharma, L'Oreal, MedImmune, Meiji, Moonlake, Nektar, Nimbus, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union, Ventyx, and Vyne. Andrew Pink—has acted as

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Ethical Approval. The original studies that collected the data analyzed within this manuscript were approved by the IRB, were conducted in accordance with the Declaration of Helsinki, and informed consent was obtained for participants.

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