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Effect of upadacitinib on atopic hand eczema in patients with moderate-to-severe atopic dermatitis: Results from two randomized phase 3 trials

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Funding information
AbbVie

Abstract

Background: Approximately 60% of patients with atopic dermatitis have involvement of the hands adding to the burden of disease.

Objective: This analysis aims to evaluate the effect of upadacitinib monotherapy on atopic hand eczema in patients with moderate-to-severe AD over 16 weeks in the Measure Up 1 and 2 studies.

Methods: Data from patients (ages 12–75) randomized 1:1:1 to receive upadacitinib 15 mg, 30 mg, or placebo once daily in the Measure Up 1 and 2 studies were analysed for impact on atopic hand eczema assessed using the Hand Eczema Severity Index (HECSI). The percent change from baseline in HECSI score was a prespecified additional endpoint at all visits. The proportion of patients with at least a 75% improvement in HECSI score (HECSI 75) was evaluated post hoc.

Results: Patients treated with upadacitinib 15 mg or 30 mg experienced greater improvement in HECSI score compared with placebo as early as Week 1, which was maintained through Week 16. At Week 16, the mean change from baseline in HECSI score for patients receiving upadacitinib 15 mg, 30 mg, and placebo was −68%, −74%, and −15% in Measure Up 1 and −68%, −74% and +21% (positive change indicates worsening for placebo) in Measure Up 2, respectively. A greater proportion of upadacitinib-treated patients achieved HECSI 75 compared with placebo at all timepoints beginning at Week 1 through Week 16.

Conclusions: Upadacitinib 15 mg and 30 mg monotherapy provided rapid and sustained improvement in atopic hand eczema compared with placebo through Week 16 in patients with moderate-to-severe AD. At Week 16, the observed mean improvements in HECSI score in upadacitinib-treated patients were clinically meaningful based on previous interpretability studies. These results suggest that upadacitinib may be an effective treatment option for atopic hand eczema in patients with moderate-to-severe AD.

INTRODUCTION

Hand eczema is a common condition with an estimated lifetime prevalence of 14.5% in individuals of any age in the general population.[1] Symptoms include pruritus, pain, inflammation, oedema, redness, cracking and skin erosions, with the wrists, palms, back of hands and fingers being most commonly affected.[2,3] The causes of hand eczema are often multifactorial and include irritant or allergic contact dermatitis, and atopic dermatitis (AD).[4] Notably, analyses found

an estimated 3–4-fold increase in the prevalence of hand eczema in patients with AD compared to those without AD[5] and that up to one-third of patients with hand eczema have a history of AD.[6] Likewise, up to 60% of patients with active AD have concomitant hand eczema.[7] Connections between lifestyle factors and hand eczema have been explored in a meta-analysis as well, with results finding inconsistencies and low-quality evidence for associations with many lifestyle factors such as smoking.[8] Given the frequent use and high visibility of the hands, patients with hand eczema may have impaired functioning and encounter social stigmas, which can reduce the quality of life[9,10] and lead to avoidance of jobs where they are exposed to irritants, particularly those requiring frequent use of liquids, soaps, or water.[4,11,12] In a multicentre study of European patch test clinics, hand eczema severity was significantly associated with quality of life impact.[13] Dermatologic conditions involving the hands are often difficult to treat,[14,15] and current treatment options are limited and include emollients, phototherapy, topical glucocorticoids or calcineurin inhibitors, oral immunosuppressive agents, and the oral retinoid alitretinoin (approved in some European countries and Canada only).[4] Though few clinical studies of systemic treatment options have been conducted,[1] studies of alitretinoin have reported that treatment of hand eczema with 10 mg or 30 mg daily resulted in 28%–48% of patients achieving 'clear' or 'almost clear' skin at the end of 24 weeks of therapy, suggesting that many patients continued to experience signs and symptoms.[16]

Upadacitinib is an oral, once-daily, selective Janus kinase (JAK) inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3 or tyrosine kinase 2 and is approved in the US, EU and other countries for the treatment of moderate-to-severe AD and other immune-mediated inflammatory conditions. In two large phase 3, randomized, controlled studies (Measure Up 1 and Measure Up 2), upadacitinib 15 mg or 30 mg daily for 16 weeks was superior to placebo for the treatment of moderate-to-severe AD in adults and adolescents.[17]

Given the negative impact of hand eczema on quality of life, lack of systemic treatment options and the increased occurrence of hand eczema in patients with AD, there is a need for safe and effective therapies that provide rapid and sustained relief. Here, we assess the efficacy of upadacitinib monotherapy 15 mg or 30 mg versus placebo on atopic hand eczema (AD localized on the hands), as measured by the Hand Eczema Severity Index (HECSI), in patients with moderate-to-severe AD in the Measure Up 1 and Measure Up 2 studies.

METHODS

Full methodological details for the Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422) studies, including study dates and size, inclusion/exclusion criteria, randomization and blinding, and endpoints assessed, have been published previously[17] and are provided in brief below.

Study design and patients

Measure Up 1 and Measure Up 2 are replicate double-blind, placebo-controlled, multicentre, phase 3 studies that include a main study and adolescent substudy. Data reported herein are from the main study portion. Patients were enrolled from 151 clinical centres in 24 countries for Measure Up 1 and 154 centres in 23 countries for Measure Up 2. Adolescents (aged 12–17 years) and adults (aged 18–75 years) with moderate-to-severe AD (≥10% of affected body surface area, Eczema Area and Severity Index [EASI] ≥16, validated Investigator's Global Assessment for AD [vIGA-AD™] ≥3, and Worst Pruritus Numerical Rating Scale [NRS] score ≥4) were randomly assigned (1:1:1) to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily for 16 weeks, stratified by baseline disease severity, geographic regions and age categories.

Independent ethics committees or institutional review boards at each study site approved the study protocol, informed consent form(s) and recruitment materials before patient enrolment. The study was conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations and the Declaration of Helsinki. Patients or their guardians were provided written informed consent before screening.

With the advent of the coronavirus disease 2019 (COVID-19) pandemic, operational accommodations for clinical trial continuity were incorporated for temporary site disruptions and secure-in-place measures, including remote visits, local lab collections and courier delivery of study drug to the patient, where allowed and in accordance with local regulations. Remote efficacy assessments of the skin were not allowed, and in-person visits were required at baseline and Week 16.

Outcomes

Efficacy was assessed as upadacitinib 15 mg or 30 mg compared with placebo, based on the percentage change from baseline in HECSI score at each visit over 16 weeks. The HECSI score is a widely used and validated instrument with scores ranging from 0 to 360 (Clear: 0, Almost Clear: 1–16, Moderate: 17–37, Severe: 38–116, Very Severe: ≥117) that grades the extent and severity of the physical signs of hand eczema for each region of the hand[18,19] (Figure 1). A higher proportion of patients attaining 75% (HECSI 75) or greater improvement in HECSI score at each study visit with upadacitinib 15 mg or 30 mg was achieved compared with placebo.

Statistical analysis

The per cent change from baseline in HECSI score was a prespecified additional endpoint at all visits through Week 16 and was analysed using mixed-effect model repeat

measurement (MMRM) analysis. For each measurement at each visit, patients with nonmissing measurements at the specific visit and nonzero measurements at baseline were included in the analysis. Measurements after receiving rescue medication were considered as missing.

Categorical variables were analysed using the Cochran–Mantel–Haenszel and the primary approach for evaluating categorical endpoints, including HECSI 75, was nonresponder imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C). The NRI-C categorized any subject who did not have an evaluation during a prespecified visit window (either due to missing assessment or due to early withdrawal from the study) as a nonresponder for the visit. The only exceptions were as follows: (1) when the subject was a responder both before and after the visit window, the subject was categorized as a responder for the visit or (2) missing data due to COVID-19 infection or logistical restriction was handled by MI. As these prespecified additional endpoints and post hoc endpoints were not multiplicity-controlled, all p-values are nominal.

FIGURE 1 Hand Eczema Severity Index (HECSI) Scoring. Scores are assigned for the intensity (0—no skin changes, 1—mild disease, 2—moderate disease and 3—severe disease) of each of the clinical signs of hand eczema (erythema, infiltration/papulation, vesicles, fissures, scaling and oedema) for each area of the hand (fingertips, fingers [except tips], palm of hand, back of hand and wrist) and summed to create an intensity score. The extent of disease for each area of the hand is scored based on the per cent of area affected (0: 0%, 1: 1%–25%, 2: 26%–50%, 3: 51%–75% and 4: 76%–100%) and is multiplied by the sum of the intensity scores to create individual HECSI scores for each hand area. HECSI scores for each hand area are then summed to create a total HECSI score (0–360), which is stratified based on severity (0—clear skin, 1 to 16—almost clear, 17 to 37—moderate, 38 to 116—severe and ≥117—very severe). Higher HECSI scores indicate greater intensity, severity and extent of involvement of hand eczema.

RESULTS

A total of 847 and 836 patients were enrolled in Measure Up 1 and Measure Up 2, respectively; demographics, baseline disease characteristics, efficacy and safety for these pivotal trials have been previously published.[17] Of all patients in the Measure Up 1 and Measure Up 2 trials, 803/847 (94.8%) and 774/836 (92.6%) had HECSI measurements at baseline. The mean HECSI score at baseline for patients treated with upadacitinib 15 mg, 30 mg or placebo was 46.4, 48.3 and 41.6 in Measure Up 1 and 43.8, 46.1, and 40.7 in Measure Up 2, respectively, among patients with HECSI measurements at baseline. Baseline severity stratified by HECSI score (almost clear, moderate, severe and very severe) is detailed in Table 1.

Patients who received upadacitinib 15 mg or 30 mg experienced greater reduction ($p \leq 0.001$) in their HECSI score compared with placebo across 16 weeks (Figure 2). Among

TABLE 1 Baseline atopic hand eczema disease characteristics for the measure up 1 and measure up 2 studies.

Baseline hand eczema disease characteristics	Measure Up 1			Measure Up 2		
	UPA 15 *n* = 281	UPA 30 *n* = 285	PBO *n* = 281	UPA 15 *n* = 276	UPA 30 *n* = 282	PBO *n* = 278
Patients with hand eczema at baseline, *n* (%)	281 (100)	285 (100)	280 (99.6)	275 (99.6)	282 (100)	276 (99.3)
Baseline HECSI score						
Mean [SD]	46.4 [47.8]	48.3 [55.5]	41.6 [46.8]	43.8 [50.44]	46.1 [48.6]	40.7 [46.0]
Median [min, max]	34.0 [0, 274]	28.0 [0, 296]	26.5 [0, 296]	29.0 [0, 300]	32.0 [0, 324]	26.5 [0, 240]
Baseline severity, *n* (%)						
Almost clear (HECSI 1 to <17)	105 (37.4)	111 (38.9)	107 (38.2)	107 (38.9)	89 (31.6)	103 (37.3)
Moderate (HECSI 17 to <38)	46 (16.4)	50 (17.5)	58 (20.7)	62 (22.5)	66 (23.4)	61 (22.1)
Severe (HECSI 38 to <117)	103 (36.7)	89 (31.2)	91 (32.5)	79 (28.7)	101 (35.8)	94 (34.1)
Very severe (HECSI ≥117)	27 (9.6)	35 (12.3)	24 (8.6)	27 (9.8)	26 (9.2)	18 (6.5)

Abbreviations: HECSI, Hand Eczema Severity Index; PBO, placebo; UPA, upadacitinib.
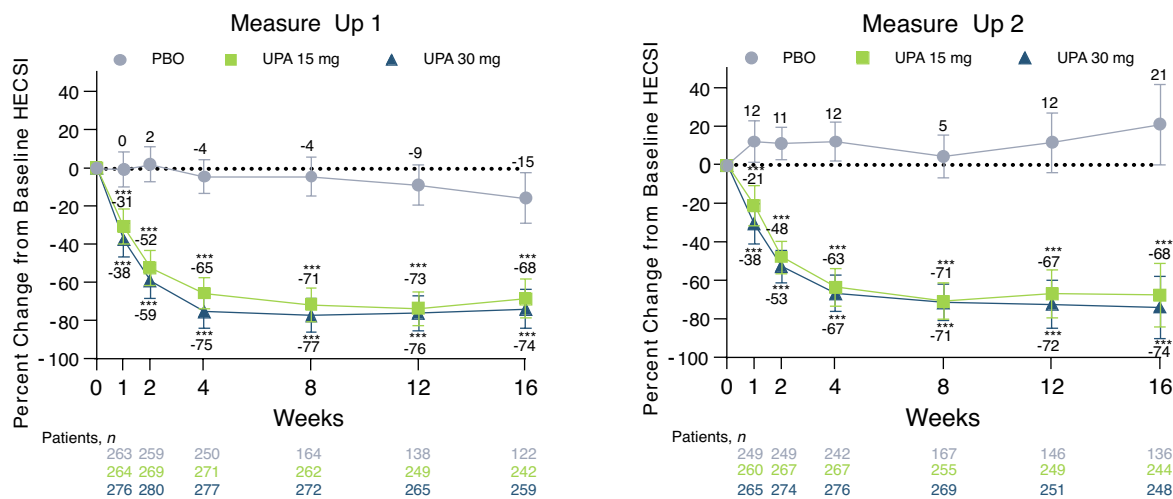
FIGURE 2   Mean Per cent Change in HECSI Score from Baseline (MMRM) through Week 16. Mean per cent change from baseline in overall HECSI score at each study visit through Week 16 as defined by investigator assessment for patients treated with upadacitinib 15 mg (UPA 15 mg), upadacitinib 30 mg (UPA 30 mg) or placebo (PBO). ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$, UPA versus PBO; MMRM; ITT population; nominal p-values are shown and were not multiplicity-controlled. HECSI, Hand Eczema Severity Index; ITT, intent-to-treat; MMRM, mixed-effect model repeat; UPA, upadacitinib; PBO, placebo.

patients with HECSI scores at baseline, the mean change from baseline HECSI score for patients receiving upadacitinib 15 mg, 30 mg and placebo was −68%, −74% and −15% in Measure Up 1 and −68%, −74%, and +21% (positive change indicates worsening for placebo) in Measure Up 2 at Week 16, respectively. Representative clinical trial photographs over the 16-week treatment period with upadacitinib 30 mg demonstrate the improvements in atopic hand eczema associated with decreasing HECSI scores (Figure 3).

Greater proportions ($p \leq 0.001$) of patients receiving either upadacitinib 15 mg or 30 mg achieved HECSI 75 compared with placebo as early as Week 1, which was maintained through Week 16 (Figure 4). When stratified by baseline HECSI severity, greater proportions ($p \leq 0.05$) of patients receiving upadacitinib 15 mg or 30 mg with baseline clear to almost clear hand eczema (HECSI <17; Figure 5a) or moderate-to-very-severe hand eczema (HECSI ≥17; Figure 5b) achieved HECSI 75 compared with placebo as early as Week 1 and through Week 16.

Safety

Safety outcomes for Measure Up 1 and Measure Up 2 have been previously reported[17] and were consistent with the known safety profile for upadacitinib with no new safety signals identified.

DISCUSSION

In this analysis of the replicate phase 3 Measure Up 1 and 2 studies, nearly all patients with AD had some degree of comorbid atopic hand eczema at baseline, with average

baseline HECSI scores consistent with severe disease. By Week 16, mean improvement in HECSI score was well above the minimally important change of 59%[18] for patients treated with upadacitinib 15 mg or 30 mg, but not for patients in the placebo group, indicating a clinically meaningful improvement in atopic hand eczema.

HECSI 75 is increasingly being incorporated into clinical trials evaluating the treatment of hand eczema and provides a meaningful threshold of clinical improvement.[17,20] A greater proportion of patients in both dosing groups achieved HECSI 75 compared with placebo as early as Week 1, with maximum improvement achieved as early as Week 4, which was sustained through Week 16. Importantly, this finding suggests that monotherapy with upadacitinib was sufficient to provide rapid and sustained improvement in atopic hand eczema compared with placebo through Week 16, which parallels findings for the treatment of AD previously reported.[21] Furthermore, the subgroup analysis demonstrated that upadacitinib (15 and 30 mg) was effective in patients with both mild and moderate-to-severe atopic hand eczema. Taken together, these results suggest that upadacitinib may be an effective treatment option for hand eczema in patients with moderate-to-severe AD.

This analysis has several limitations that should be considered. Measure Up 1 and 2 were not designed to study hand eczema (e.g. the presence of hand eczema was not an inclusion criterion for study entry), and the HECSI was the only outcome measure assessed that was specific to hand eczema; therefore, results may not be generalizable to the typical hand eczema patient or patients without comorbid moderate-to-severe AD. Hand eczema endpoints were not included in the ranking hierarchy and were not multiplicity-controlled; significant differences could therefore represent chance findings. Additional studies in underrepresented
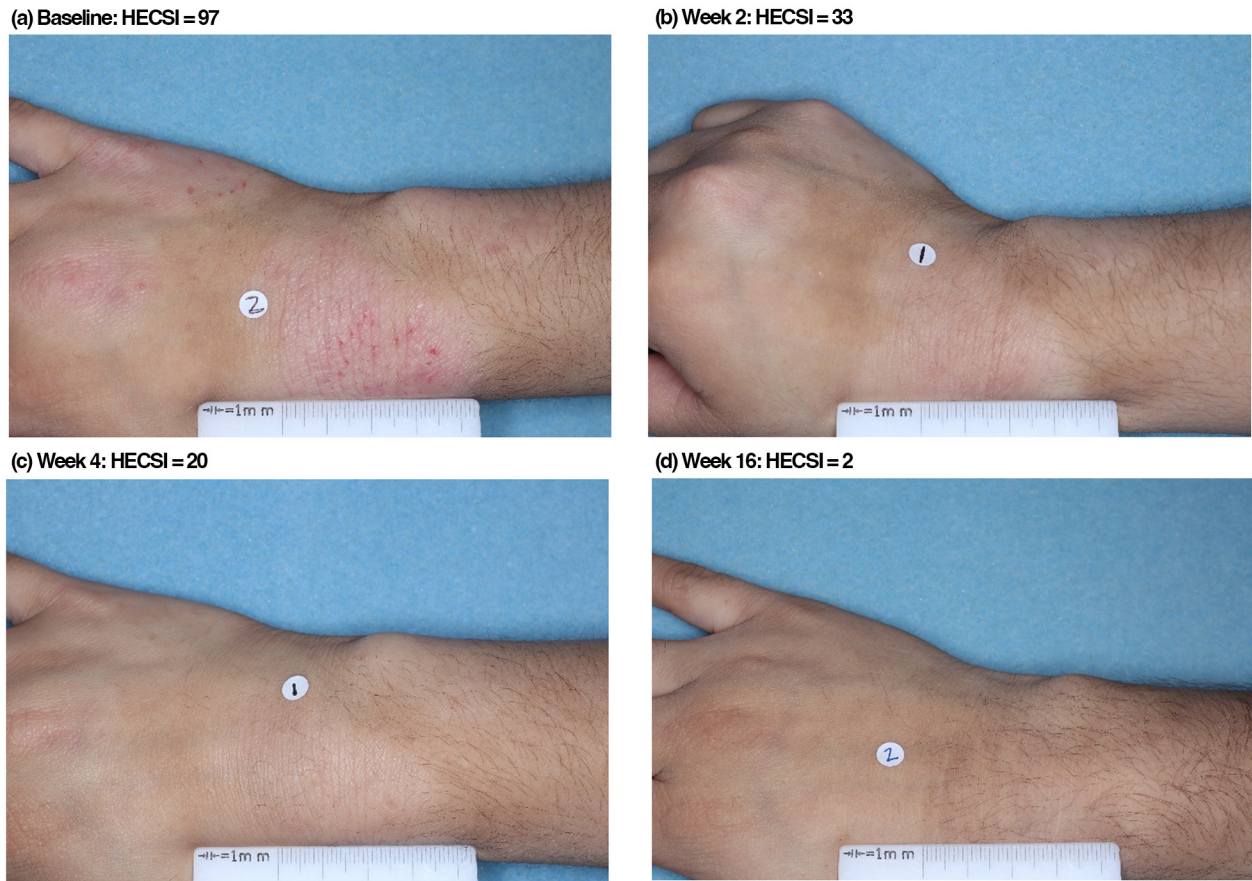
FIGURE 3   Clinical Images of HECSI assessment over time. Representative clinical study photographs of upadacitinib 30 mg treatment over time with corresponding HECSI scoring indicated at study visit. (a) Baseline HECSI score 97 (severe), (b) Week 2 HECSI score 33 (moderate), (c) Week 4 HECSI Score 20 (moderate) and (d) Week 16 HECSI score 2 (almost clear).
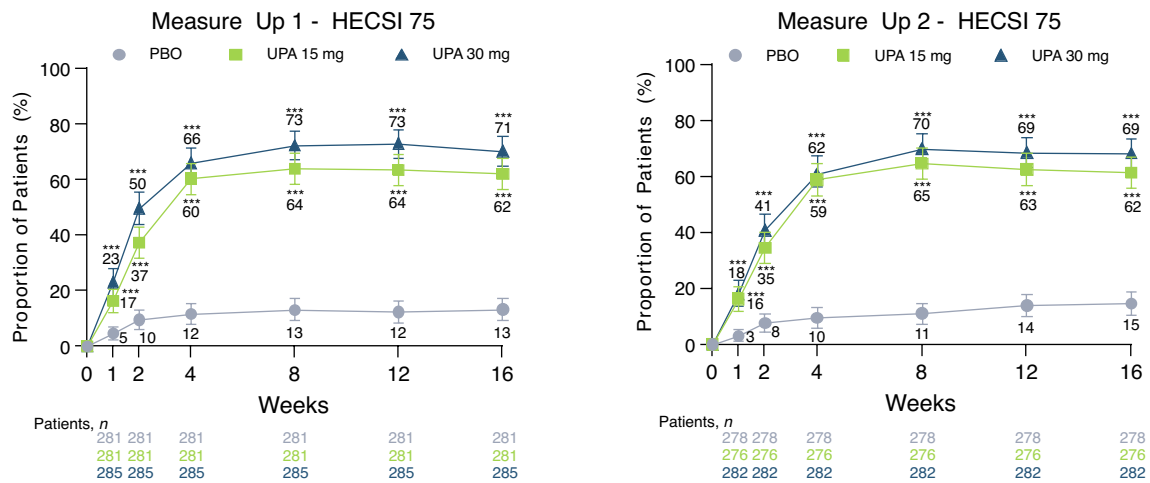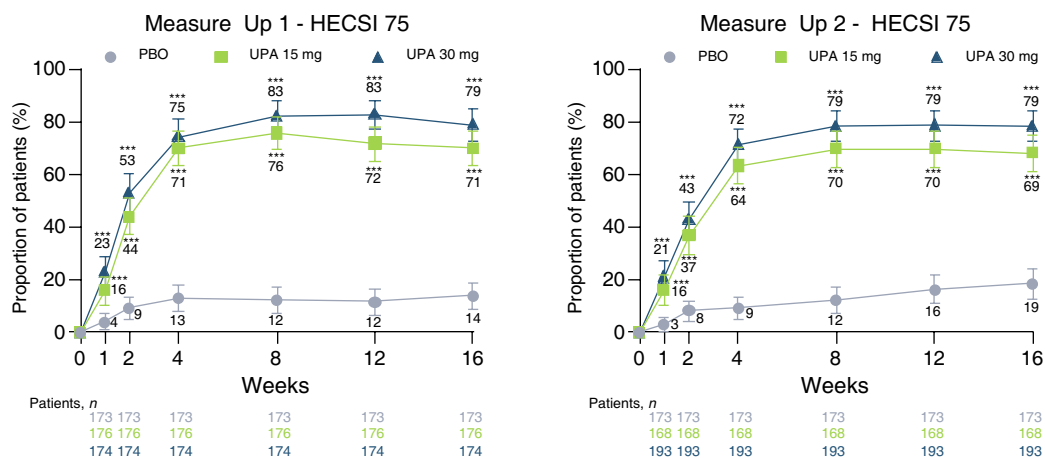

FIGURE 4   Proportion of Patients Achieving HECSI 75 by Visit (NRI-C). Proportion of patients achieving HECSI 75 at each study visit as defined by investigator assessment for patients treated with upadacitinib 15 mg (UPA 15 mg), upadacitinib 30 mg (UPA 30 mg) or placebo (PBO) over 16 weeks. Stratification based on severity at baseline was post hoc, and p-values are considered nominal. ***$p \leq 0.001$, UPA versus PBO; NRI-C, ITT population. HECSI, Hand Eczema Severity Index; ITT, intent-to-treat; NRI-C, nonresponder imputation incorporating MI to hand missing data due to COVID-19; UPA, upadacitinib; PBO, placebo.
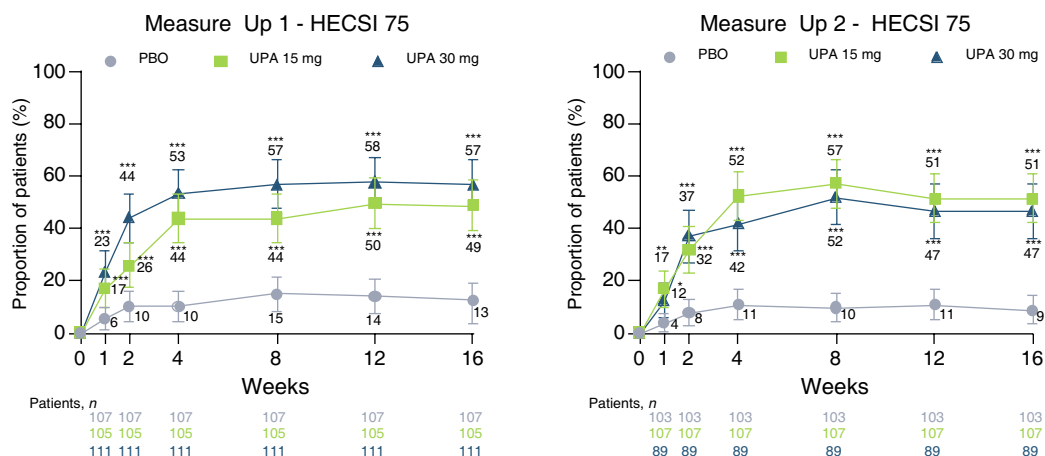
FIGURE 5 Proportion of Patients Achieving HECSI 75 by Visit Stratified by Baseline HECSI (NRI-C). Proportion of patients achieving HECSI 75 with (a) clear or almost clear (HECSI <17), or (b) moderate-to-very-severe (HECSI ≥17), hand eczema at baseline who received either upadacitinib 15, 30 mg or placebo at each study visit through Week 16. Stratification based on severity at baseline was post hoc, and p-values are considered nominal. ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$, UPA vs PBO; NRI-C, ITT population. HECSI, Hand Eczema Severity Index; ITT, intent-to-treat; NRI-C, nonresponder imputation incorporating MI to hand missing data due to COVID-19; UPA, upadacitinib; PBO, placebo. [Correction added on 8 July 2023 after first online publication: In the first graph under panel B, the number of patients in the section that reads Patient,n has been corrected.]

groups may be informative given evidence of higher prevalence and greater severity of AD in Black/African American and Asian populations compared with White patients.[22,23] Importantly, new immunomodulatory drugs, both topical and systemic, are under investigation for the treatment of chronic hand eczema, with preliminary findings suggesting that regardless of subtype, patients benefit from treatment with JAK inhibitors.[24]

CONCLUSIONS

In summary, these results suggest that upadacitinib (15 and 30 mg) may be an effective treatment option for atopic hand eczema of any severity in patients with moderate-to-severe AD. Given the prevalence of hand eczema in patients with

AD and the substantial negative impact on quality of life, these are important results that may help inform clinical practice.

CONFLICT OF INTEREST STATEMENT

Financial arrangements of the authors with companies whose products may be related to the present manuscript are listed, as declared by the authors. **EL Simpson** received personal fees from AbbVie, Anacor, Bausch Health (Valeant), Boehringer Ingelheim, Dermavant, Forté Pharma, Incyte, Lilly, LEO Pharma, MedImmune, Menlo Therapeutics, Pfizer, Pierre Fabre, Regeneron, Roivant and Sanofi and received grants from AbbVie, Amgen, Celgene, Chugai, Galderma, Genentech, Kyowa Kirin, Lilly, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Sanofi, Tioga Pharmaceuticals and Vanda. **K Rahawi, X Hu, AD Chu and CL Nduaka** are full-time employees of AbbVie Inc., and may hold AbbVie stock and/or stock options. **S Jazayeri** has acted as the principal investigator and received research funding, speaker and/or consultant for/from: AbbVie, Amgen, Anaptys, Athenex, AbGenomics, Bausch Health Americas Valeant, Bellus, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Coherus Biosciences, Corrona, LLC, Dermavant, DermTech, Dermira, DS Biopharma, Eli Lilly and Company, Galderma, Genentech, Health Analytics, Innovaderm, IQVIA Biotech, Janssen Biotech, Kadmon, Kiniksa, Leo Pharmaceuticals, MC2 Therapeutics, Novartis, Novella, Pfizer, Regeneron. Sandoz, Tolmar, UCB Biopharma, Xenoport (now Arbor Pharmaceuticals) and Watson. **P Lio** reports research grants/funding from Regeneron/Sanofi Genzyme, AOBiome, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, LEO, Incyte, Eli Lilly, Pfizer, and Galderma; reports consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Kiniksa, Eli Lilly, Menlo Therapeutics, Galderma, IntraDerm, Exeltis and Realm Therapeutics. **C Lynde** has acted as a principal investigator, speaker and/or consultant for AbbVie, Amgen, AnaptysBio, Avillon, Arcutis, Bristol Myers Squibb, Celgene, Cipher, Genentech, GlenMark, Incyte, Janssen, Leo Pharma, Kyowa, Pfizer and Merck. **M-L Schuttelaar** received research funding from Regeneron/Sanofi Genzyme, Novartis and Pfizer and has acted as the principal investigator, advisory board member, speaker or consultant for AbbVie, Eli Lilly, Galderma, LEO Pharma 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 datasets), 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 US 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

ETHICS STATEMENT

All authors were involved in the interpretation of the data, preparation and critical review of the manuscript and approved the final version of the manuscript. The patients in this manuscript have given written informed consent to publication of their case details.

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REFERENCES

1. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM, et al. Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis. 2022;86(5):357–78.
2. Veien NK, Hattel T, Laurberg G. Hand eczema: causes, course, and prognosis II. Contact Dermatitis. 2008;58(6):335–9.
3. Silverberg JI, Guttman-Yassky E, Agner T, Bissonnette R, Cohen DE, Simpson E, et al. Chronic hand eczema guidelines from an expert panel of the international eczema council. Dermatitis. 2021;32(5):319–26.
4. Coenraads PJ. Hand eczema. N Engl J Med. 2012;367(19):1829–37.
5. Ruff SMD, Engebretsen KA, Zachariae C, Johansen JD, Silverberg JI, Egeberg A, et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. Br J Dermatol. 2018;178(4):879–88.
6. Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population – a systematic review and meta-analysis. Contact Dermatitis. 2021;84(6):361–74.
7. Simpson EL, Thompson MM, Hanifin JM. Prevalence and morphology of hand eczema in patients with atopic dermatitis. Dermatitis. 2006;17(3):123–7.
8. Loman L, Brands MJ, Massella Patsea AAL, Politiek K, Arents BWM, Schuttelaar MLA. Lifestyle factors and hand eczema: a systematic review and meta-analysis of observational studies. Contact Dermatitis. 2022;87:211–32.
9. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Anatomical patterns of dermatitis in adult filaggrin mutation carriers. J Am Acad Dermatol. 2015;72(3):440–8.
10. Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. Br J Dermatol. 2009;161(2):397–403.
11. Brands MJ, Loman L, Schuttelaar MLA. Exposure and work-related factors in subjects with hand eczema: data from a cross-sectional questionnaire within the lifelines cohort study. Contact Dermatitis. 2022;86(6):493–506.
12. Diepgen TL. Occupational skin-disease data in Europe. Int Arch Occup Environ Health. 2003;76(5):331–8.
13. Agner T, Andersen KE, Brandao FM, Bruynzeel DP, Bruze M, Frosch P, et al. Hand eczema severity and quality of life: a cross-sectional,

multicentre study of hand eczema patients. Contact Dermatitis. 2008;59(1):43–7.

14. Elsner P, Agner T. Hand eczema: treatment. J Eur Acad Dermatol Venereol. 2020;34(Suppl 1):13–21.

15. Raposo I, Torres T. Palmoplantar psoriasis and palmoplantar pustulosis: current treatment and future prospects. Am J Clin Dermatol. 2016;17(4):349–58.

16. Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol. 2008;158(4):808–17.

17. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (measure up 1 and measure up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021;397(10290):2151–68.

18. Oosterhaven JAF, Schuttelaar MLA. Responsiveness and interpretability of the Hand Eczema Severity Index. Br J Dermatol. 2020;182(4):932–9.

19. Held E, Skoet R, Johansen JD, Agner T. The Hand Eczema Severity Index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302–7.

20. Worm M, Thyssen JP, Schliemann S, Bauer A, Shi VY, Ehst B, et al. The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial. Br J Dermatol. 2022;187(1):42–51.

21. Simpson EL, Papp KA, Blauvelt A, Chu CY, Hong HC, Katoh N, et al. Efficacy and safety of Upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the measure up 1 and measure up 2 randomized clinical trials. JAMA Dermatol. 2022;158(4):404–13.

22. Silverberg JI. Public health burden and epidemiology of atopic dermatitis. Dermatol Clin. 2017;35(3):283–9.

23. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol. 2018;27(4):340–57.

24. Cheng J, Facheris P, Ungar B, Guttman-Yassky E. Current emerging and investigational drugs for the treatment of chronic hand eczema. Expert Opin Investig Drugs. 2022;31(8):843–53.