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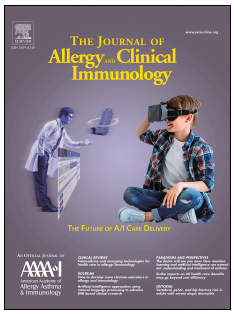

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PII: S0091-6749(21)01212-4

DOI: https://doi.org/10.1016/j.jaci.2021.07.036

Reference: YMAI 15228

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 30 March 2021

Revised Date: 9 July 2021

Accepted Date: 29 July 2021

Please cite this article as: Silverberg JI, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Costanzo A, Rosmarin D, Lynde C, Liu J, Gamelli A, Zeng J, Ladizinski B, Chu AD, Reich K, Upadacitinib plus topical corticosteroids in atopic dermatitis: week-52 AD Up study results, *Journal of Allergy and Clinical Immunology* (2021), doi: https://doi.org/10.1016/j.jaci.2021.07.036.

Upadacitinib plus topical corticosteroids in atopic dermatitis: week-52 AD Up study results

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Declaration of interests

JIS is an advisor, speaker, or consultant for AbbVie, Asana Biosciences, Dermavant, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Realm Pharma, and Regeneron-Sanofi. He is also a researcher for GlaxoSmithKline. **MdB-W** has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Arena, Eli

Lilly, Galderma, Janssen, LEO Pharma, Pfizer, Regeneron, and Sanofi Genzyme. **TB** is an advisor, speaker, and researcher for AbbVie, Almirall, AnaptysBio, Arena, Asana Biosciences, Bayer Health, BioVerSys, Boehringer Ingelheim, Bristol-Myers Squibb, Domain Therapeutics, Galapagos/MorphoSys, Galderma, Glenmark, GlaxoSmithKline, Incyte, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, Lilly, L´Oréal, Menlo Therapeutics, Novartis, Vifor Pharma, Pfizer, Pierre Fabre, Sanofi/Regeneron, and UCB. He is a founder of the non-profit biotech company "Davos Biosciences" within the International Kühne-Foundation. **WS** is a consultant for AbbVie, Pfizer, Regeneron, and Sanofi. He is a speaker for Regeneron and Sanofi, and has received research grants from AbbVie, AB Biosciences, Genentech, Glenmark, LEO Pharma, Regeneron, Sanofi, and Vanda. **KK** has received consulting fees, honoraria, or grant support or lecturing fees from AbbVie, Japan Tobacco, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Procter & Gamble, Sanofi, Taiho Pharmaceutical, and Torii Pharmaceutical. **AC** is an advisor, speaker, and researcher for AbbVie, Almirall, Boehringer Ingelheim, Celgene, Galderma, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi/Regeneron, and UCB. **DR** has received honoraria as a consultant for AbbVie, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals Inc; and has served as a paid speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. **CL** has been a consultant, speaker, and investigator for AbbVie, Amgen, AnaptysBio, Bausch Health, BMS, BI, Celgene, Eli Lilly, Galderma, Genentech, GSK, Janssen, Leo Pharma, L'Oreal, Merck, Novartis, Pfizer, Sanofi Genzyme, UCB; and an investigator for Asana Biosciences, Concert, Dermira, Glenmark, Incyte, Kyowa. **JL**, **AG**, **JZ**, **BL**, and **ADC** are full-time employees of AbbVie Inc., and may hold AbbVie stock or stock options. **KR** has served as advisor and/or paid speaker for and/or

participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Bausch Health (Valeant), Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Lilly, Medac, Merck, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, and XenoPort.

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Financial Support: Provided by AbbVie Inc.

Word Count: 3483

References: 29

Figures/Tables: 4/2

Supplementary figures: 11

Supplementary tables: 2

ABSTRACT

Background Primary (week 16) results from the ongoing phase 3, double-blind AD Up study (NCT03568318) demonstrate a positive benefit-risk profile for upadacitinib+TCS in patients with moderate-to-severe AD.

Objective Evaluate efficacy and safety of UPA+TCS through 52 weeks.

Methods Patients (12-75y) with chronic AD (≥10% of body surface area affected, EASI ≥16, vIGA-AD™ ≥3, and WP-NRS score ≥4) were randomized 1:1:1 to once-daily upadacitinib 15mg+TCS, upadacitinib 30mg+TCS, or PBO+TCS (re-randomized at week 16 to upadacitinib+TCS). Safety and efficacy, including proportion of patients achieving ≥75% improvement in EASI (EASI-75), vIGA-AD of clear/almost clear with improvement ≥2 grades (vIGA-AD 0/1), and WP-NRS improvement ≥4, were assessed through week 52. Missing data were primarily handled by nonresponder imputation incorporating multiple imputation for missing values due to COVID-19.

Results Of 901 patients, 300 were randomized to upadacitinib 15mg+TCS, 297 to upadacitinib 30mg+TCS, and 304 to PBO+TCS. For all endpoints, efficacy for upadacitinib 15mg+TCS and upadacitinib 30mg+TCS at week 16 was maintained through week 52. At week 52, the proportions of patients treated with upadacitinib 15mg+TCS and upadacitinib 30mg+TCS who achieved EASI-75 were 50.8% and 69.0%, respectively; 33.5% and 45.2%, respectively, achieved vIGA-AD 0/1; and 45.3% and 57.5%, respectively, achieved WP-NRS improvement ≥4. upadacitinib+TCS was well tolerated through 52 weeks; no new important safety risks beyond the current label were observed. No deaths were reported; events of MACE and VTE were infrequent (≤0.2/100 PY).

Conclusion Results through 52 weeks demonstrate long-term maintenance of efficacy and a favorable safety profile of upadacitinib+TCS in patients with moderate-to-severe AD.

Abstract word count: 250 (maximum 250 words)

CLINICAL IMPLICATIONS

Phase 3 AD Up study results through 52 weeks support the potential of upadacitinib + topical corticosteroids as an effective and well-tolerated long-term treatment option for patients with moderate-to-severe atopic dermatitis.

CAPSULE SUMMARY

Upadacitinib (UPA) + topical corticosteroids (TCS) provides long-term (52 weeks) efficacy and favorable safety in moderate-to-severe atopic dermatitis. UPA 15 mg + TCS and 30 mg + TCS were well tolerated; no new important safety signals were observed.

Keywords: Atopic dermatitis, randomized clinical trial, upadacitinib, topical corticosteroids, Janus kinase inhibitors

Abbreviations used: AD, atopic dermatitis; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in Eczema Area and Severity Index; EASI-90, ≥90% improvement in Eczema Area and Severity Index; EASI-100, 100% improvement in Eczema Area and Severity Index; JAK, Janus kinase; MACE, major adverse cardiovascular event; NRS; Numerical Rating Scale; PBO, placebo; PY, patient years; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator's Global Assessment for AD of clear or almost clear with ≥ 2 grades of improvement; VTE, venous thromboembolic event.

INTRODUCTION

Atopic dermatitis (AD) causes long-term skin-related disability and burden.(1-6) AD onset, most often occurring in childhood before 5 years of age,(7) can occur at any age; and symptoms of AD can persist, re-emerge, or worsen (flare) throughout a patient's lifetime.(8, 9) Long-term persistence of AD is more likely in patients with moderate-to-severe disease.(10) Most patients with AD report symptoms and continue medication use over 2 to 3 decades of life, an important consideration for effective disease management.(11) There is a need for additional AD treatments that are acceptable for long-term use and provide prolonged clinical response without high levels of treatment discontinuation because of adverse effects.(12, 13)

Systemic therapies are often used in combination with topical corticosteroids (TCS) to control moderate-to-severe AD symptoms.(14) Adding TCS to dupilumab (anti–interleukin [IL]-4 and -13 receptor alpha monoclonal antibody), tralokinumab (anti–IL-13 monoclonal antibody), or baricitinib (selective Janus kinase [JAK]1 and JAK2 inhibitor) increases response rates over that observed for monotherapy in patients with moderate-to-severe AD.(15-20)

Upadacitinib (UPA), an oral JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, is approved in the US, EU, and other countries to treat moderately or severely active rheumatoid arthritis (RA)(21) and is in development for the treatment of immune-mediated inflammatory conditions, including AD.(22)·(23) Results from 2 ongoing, phase 3, randomized, double-blind, replicate studies (Measure Up 1 [NCT03569293] and Measure Up 2 [NCT03607422]) demonstrate superiority of UPA 15 mg and UPA 30 mg vs placebo (PBO). As monotherapy, both UPA doses are well tolerated; markedly improve skin signs, itch, skin pain, and health-related quality of life (QOL); and consistently achieve higher thresholds of skin improvement (ie, ≥90%/≥100% improvement in Eczema Area and Severity Index [EASI-90/EASI-100]) through 16 weeks in adolescents and adults with moderate-to-

severe AD.(24) Primary results from AD Up, this pivotal, phase 3, randomized, double-blind study, provide evidence that UPA+TCS is well tolerated and superior to PBO+TCS in adolescents and adults with moderate-to-severe AD—significantly greater proportions of patients receiving either UPA dose plus TCS achieve EASI-75, EASI-90, and EASI-100 and validated Investigator's Global Assessment of AD™ (vIGA-AD)(25) of clear or almost clear with ≥2 grades of improvement (vIGA-AD 0/1) compared with PBO+TCS.(26) No new important safety signals have been observed in the phase 3 AD program beyond those reported in the RA clinical program,(21) demonstrating an overall favourable benefit-risk profile of UPA in AD. Exploration of the long-term benefit-risk profile of adding standard TCS to UPA continues in the ongoing blinded extension (BE) period of AD Up; here we report results through 52 weeks.

METHODS

Study design and patients

Study design and patient population details were previously reported.(26) Briefly, AD Up (NCT03568318) was a pivotal, phase 3, randomized, double-blinded, placebo-controlled, multicenter study conducted in 171 clinical centers globally, consisting of a main study (reported here) and an adolescent substudy (ongoing; to be reported elsewhere). The study had a 35-day screening period and 16-week double-blinded period (reported previously),(26) followed by a BE period for up to 260 weeks of treatment with a 30-day follow-up (ongoing; results up to week 52 reported here).

Eligible patients were aged 12–75 years (weight ≥40 kg) with chronic AD (onset ≥3 years prior to baseline) per Hanifin and Rajka criteria(27) that was moderate to severe (≥10% of body surface area affected, EASI ≥16, vIGA-AD ≥3, and baseline weekly average Worst Pruritus Numerical Rating Scale [WP-NRS] score ≥4).

Independent ethics committees/institutional review boards at each study site approved the study protocol, informed consent form(s), and recruitment materials prior to patient enrolment. The study was conducted in agreement with the International Conference for Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Adult patients and parents/legal guardians of adolescent patients provided written informed consent prior to any screening or study-related procedures. The adolescent substudy was added after protocol initiation to allow enrolment of additional adolescents to fulfil a regulatory commitment.

With the advent of the COVID-19 pandemic, operational accommodations for clinical trial continuity were incorporated for temporary site disruptions and secure-in-place measures (see Supplemental Methods for more details).

Randomization and masking

Eligible patients were randomized 1:1:1 using an interactive response technology system according to a schedule generated by statisticians at AbbVie to receive UPA 15 mg, UPA 30 mg, or PBO once daily, all in combination with TCS. At week 16, PBO+TCS–treated patients were re-randomized 1:1 to receive UPA 15 mg or 30 mg plus TCS; patients initially randomized to UPA 15 mg+TCS or UPA 30 mg+TCS continued treatment as originally assigned. Randomization in the main study was stratified by baseline vIGA-AD score (moderate, 3; severe, 4), geographic region (US/Puerto Rico/Canada, Japan, China, Other), and age group (adolescents, adults). Re-randomization was stratified by EASI-50 (≥50% improvement from baseline in EASI) response at week 16, age group, and region for the BE up to week 52. Study investigators, study site personnel, and patients remained blinded to treatment throughout the study: UPA 15 mg, UPA 30 mg, and PBO tablets were identical in appearance.

Procedures

Patients took a single oral tablet of UPA 15 mg, UPA 30 mg, or PBO (AbbVie Inc., North Chicago, Illinois, US) once daily. Twice-daily use of an additive-free, bland emollient was required for ≥7 days prior to baseline and during the study until week 52. Protocol-mandated TCS was applied through week 52 according to a step-down regimen described previously.(26) Briefly, medium-potency TCS (low-potency TCS or topical calcineurin inhibitor [TCI] for sensitive skin areas) were applied once daily to areas with active lesions for ≤3 consecutive weeks or until lesions were clear or almost clear, then low-potency TCS were to be applied once daily for 7 days and stopped if lesions were no longer active (for sensitive skin areas, low-potency TCS or TCI was tapered and stopped); if lesions returned or persisted, this step-down approach was repeated until lesion resolution or evidence of local or systemic TCS toxicity (eg, striae, skin

atrophy, bruising). Although the TCS potency was mandated, the selection of TCS within each potency category was per investigator choice; no specific TCS was mandated. As needed therapy was not permitted, but starting at week 4, rescue therapy was permitted based on lack of EASI response. Starting at week 52, TCS use was per investigator discretion. See **Supplemental Methods** for more details.

Outcomes

The coprimary efficacy endpoints (multiplicity controlled) were the proportion of patients who achieved EASI-75 and proportion of patients who achieved vIGA-AD 0/1, both at week 16. The primary and following key secondary efficacy endpoints were assessed at all visits through week 52: the proportions of patients who achieved WP-NRS improvement ≥4, EASI-90 and EASI-100, and the percent changes from baseline in EASI and WP-NRS. Among responders, defined as patients achieving vIGA-AD 0/1 and EASI-75 at week 16, the proportion of patients experiencing a loss of response after week 16 until week 52 was assessed by visit and overall; loss of response was defined as a loss of ≥ 50% of the EASI response at week 16 and vIGA-AD score ≥2 after week 16.

Safety data were presented as of the data cutoff for the week-52 analysis. The following safety parameters were assessed: treatment-emergent adverse events (TEAEs); serious AEs (SAEs); deaths; AEs leading to discontinuation of study treatment; prespecified AEs of special interest (AESIs), which were based on the known UPA safety profile(21) and previous safety observations for UPA(23) and other JAK inhibitors(28) in patients with AD; laboratory assessments; and vital signs.

Statistical analysis

A sample size of 810 patients (270 per treatment group) was estimated to provide >90% power to detect treatment differences for the 2 primary endpoints of 38% and 20%, respectively, and allow for adequate characterization of safety.(26) After all patients in the main study completed week 52, efficacy analyses were conducted in the intent-to-treat population for the main study (ITT), defined as all patients who were randomized into the main study. Safety analyses were conducted in the safety population for the main study up to the cutoff date of the week 52 analysis, defined as all randomized patients who received ≥1 dose of study drug. PBO+TCS–treated patients re-randomized at week 16 were combined into their respective UPA 15 mg+TCS or UPA 30 mg+TCS groups for the safety analyses.

For categorical endpoints the primary approach for handling missing data was nonresponder imputation incorporating multiple imputation (MI) for missing values due to COVID-19 (NRI-C).(26) For response rates, 95% confidence intervals (CIs) were based on a Student's t-distribution from the SAS PROC MIANALYZE procedure. NRI-C was the primary approach for categorical endpoints in the double-blind period and for coprimary endpoints and WP-NRS in the blinded extension period up to week 52. MI was also performed as a confirmatory sensitivity analysis for EASI 75/90/100, vIGA-AD 0/1, and WP-NRS in BE Period up to Week 52, using Markov Chain Monte Carlo and PROC MI, and included: treatment group, major stratum (vIGA-AD categories [for endpoints other than vIGA-AD 0/1], age group, and region), gender, and measurements at baseline and each visit up to the end of the analysis period. All assessments after the start of rescue medication were not included in the analyses; patients were counted as nonresponders after receiving rescue medication and data were not imputed by MI (see Supplemental Methods for more details). For continuous endpoints, change and percent change from baseline in each treatment group were analyzed using the mixed-effects model for repeated measures (MMRM). The MMRM included categorical fixed effects of treatment, visit,

and treatment-by-visit interaction; the continuous fixed covariates of baseline measurement; and stratification factors of vIGA-AD categories at randomization (moderate vs severe) and age group for the double-blind period, and EASI-50 response at week 16 and age group for the BE period up to week 52. Observed case analysis, which did not impute values for missing evaluations, was used to assess loss of response among week-16 responders and performed for all variables in addition to NRI-C and MI described above. Further, post-hoc analyses for percentage change of EASI and WP-NRS were conducted for the UPA treatment groups from baseline through week 52 with treatment (UPA 15 mg and UPA 30 mg), treatment-by-visit interaction, vIGA-AD categories at baseline, age (adolescent vs adult), and baseline value in the model. Using descriptive statistics only, safety data were reported as the number of AEs divided by the total exposure in 100 patient-years (PY), and potentially clinically significant changes from baseline in laboratory assessments were reported as the number and proportion of patients.

RESULTS

Between Aug 9, 2018, and Dec 20, 2019, 901 patients were randomized to the double-blind period (300 to UPA 15 mg+TCS, 297 to UPA 30 mg+TCS, and 304 to PBO+TCS). As previously reported, demographics and baseline disease characteristics were well balanced between groups.(26) At week 16, 283 PBO+TCS–treated patients were re-randomized—144 to UPA 15 mg+TCS (143 were treated) and 139 to UPA 30 mg+TCS (139 were treated)—while 289 UPA 15 mg+TCS–treated and 287 UPA 30 mg+TCS–treated patients continued to receive their initial treatment in the BE period (**Figure 1**). During the BE, no patients discontinued treatment for primary reasons related to COVID-19. The number of patients for whom missing EASI-75 and/or vIGA-AD 0/1 data were imputed using MI because of COVID-19 are listed in **Supplemental Table 1**. Rescue medication was initiated in the BE by 15.0%, 8.1%, 4.2%, and 5.0% of patients receiving UPA 15 mg+TCS, UPA 30 mg+TCS, PBO+TCS/UPA 15 mg+TCS, and PBO+TCS/UPA 30 mg+TCS, respectively.

At week 16 (primary endpoint), significantly greater proportions of patients treated with UPA 15 mg+TCS and UPA 30 mg+TCS vs PBO+TCS achieved EASI-75, vIGA-AD 0/1, and WP-NRS improvement ≥4 ($P < 0.001$ for all, **Figure 2**).(26) Likewise, at week 16, greater proportions of UPA 15 mg+TCS– and UPA 30 mg+TCS–treated patients achieved the more stringent endpoints of EASI-90 and EASI-100 ($P < 0.001$ for all, **Figure 3**) and marked improvements from baseline in EASI and WP-NRS scores ($P < 0.001$ for all, **Figure 4**) compared with PBO+TCS–treated patients.(26)

Overall, efficacy demonstrated for UPA 15 mg+TCS and UPA 30 mg+TCS at week 16 was maintained through week 52. At week 52, the proportions (95% CI) of patients treated with UPA 15 mg+TCS and UPA 30 mg+TCS who achieved EASI-75 were 50.8% (45.1%, 56.5%) and 69.0% (63.7%, 74.3%), respectively (**Figure 2A**). The proportion (95% CI) of patients who

achieved vIGA-AD 0/1 at week 52 was 33.5% (28.1%, 38.9%) for UPA 15 mg+TCS and 45.2% (39.5%, 50.9%) for UPA 30 mg+TCS (**Figure 2B**). At week 52, 45.3% (95% CI: 39.5%, 51.0%) of patients receiving UPA 15 mg+TCS and 57.5% (51.8%, 63.2%) receiving UPA 30 mg+TCS achieved WP-NRS improvement ≥4 (**Figure 2C**).

Similar results were demonstrated for EASI-90 and EASI-100. At week 52, the proportions (95% CI) of patients who achieved EASI-90 were 37.7% (32.1%, 43.3%) and 55.4% (49.7%, 61.2%) for UPA 15 mg+TCS and UPA 30 mg+TCS, respectively (**Figure 3A**) and for EASI-100 were 13.1% (9.2%, 16.9%) for UPA 15 mg+TCS group and 23.6% (18.8%, 28.5%) for UPA 30 mg+TCS, respectively (**Figure 3B**).

At week 52, the least squares mean (LSM [95% CI]) percent change from baseline in EASI was −67.7% (−71.0%, −64.3%) for UPA 15 mg+TCS and −77.4% (−80.8%, −74.0%) for UPA 30 mg+TCS (**Figure 4A**); the LSM (95% CI) percent change from baseline in WP-NRS was in −39.0% (−45.6%, −32.5%) for UPA 15 mg+TCS and −54.5% (−61.1%, −48.0%) for UPA 30 mg+TCS (**Figure 4B**).

Overall, few patients experiencing response at week 16 lost response after that time and up to week 52 (**Supplemental Table 2**). Overall, 8 (7.0%) week-16 responders receiving UPA 15 mg+TCS experienced loss of response after week 16; 5 (2.9%) in the UPA 30 mg+TCS group lost response.

At week 52, 79.1% (71.7%, 86.6%) in the PBO+TCS/UPA 15 mg+TCS group and 84.7% (77.3%, 92.1%) in the PBO+TCS/UPA 30 mg+TCS group achieved EASI-75 (**Supplemental Figure 1A**); 56.9% (47.8%, 66.0%) and 65.5% (55.7%, 75.2%), respectively, achieved vIGA-AD 0/1 (**Supplemental Figure 1B**); and 61.3% (52.2%, 70.3%) group and 70.7% (61.3%, 80.2%), respectively, achieved WP-NRS improvement ≥4 (**Supplemental Figure 1C**).

EASI-90 was achieved by 60.8% (51.8%, 69.8%) of patients in the PBO+TCS/UPA 15 mg+TCS group and 71.8% (62.2%, 81.5%)in the PBO+TCS/UPA 30 mg+TCS group at week 52 (**Supplemental Figure 2A**); and EASI-100 was achieved by 27.0% (18.9%, 35.1%) and 26.3% (17.3%, 35.3%), respectively (**Supplemental Figure 2B**).

The LSM (95% CI) percent change from baseline in EASI at week 52 was −82.2% (−86.7%, −77.8%) for PBO+TCS/UPA 15 mg+TCS and −89.4% (−94.4%, −84.4%)for PBO+TCS/UPA 30 mg+TCS (**Supplemental Figure 3A**); and the percent change from baseline in WP-NRS was −55.2% (−63.3%, −47.1%) and −69.8% (−78.9%, −60.6%), respectively (**Supplemental Figure 3B**).

Overall, similar results were obtained with NRI-C, MI, and observed case analyses (see **Supplemental Figures 4-11**).

As of the 52-week data analysis cutoff, both UPA 15 mg+TCS and UPA 30 mg+TCS were well tolerated (**Table 1**). The exposure-adjusted event rates (EAER, E/100 PY) of any TEAE, SAEs, and AEs leading to discontinuation of study drug were similar between UPA 15 mg+TCS and UPA 30 mg+TCS groups (**Table 1**). No deaths were reported through 52 weeks of the BE (**Table 1**).

The most frequently reported TEAEs (≥10% in either treatment group) were acne, nasopharyngitis, blood creatine phosphokinase (CPK) increase, dermatitis atopic, and upper respiratory tract infection (**Table 1**). No acne events were serious, and 1 mild acne event in the UPA 30 mg+TCS group led to study drug discontinuation on study day 22.

Rates of serious infections were similar between treatment groups (2.7 and 2.3 E/100 PY with UPA 15 mg+TCS and UPA 30 mg+TCS, respectively) (**Table 1**). All opportunistic infections reported, excluding tuberculosis and herpes zoster (HZ), were cases of eczema herpeticum

(Kaposi's varicelliform eruption); the EAERs were 1.4 and 3.4 E/100 PY in the UPA 15 mg+TCS and UPA 30 mg+TCS treatment groups, respectively. All eczema herpeticum events were nonserious and 2 events reported in the UPA 30 mg+TCS group lead to treatment discontinuation. The event rate of HZ was higher in the UPA 30 mg+TCS group compared with UPA 15 mg+TCS (6.2 vs 4.1 E/100 PY). Most HZ events involved a single dermatome and did not lead to treatment discontinuation. There were no HZ events involving CNS, lung, or liver. One squamous cell carcinoma of the oral cavity was reported in the UPA 15 mg+TCS group; 3 malignancies were reported in the UPA 30 mg+TCS group: 1 case each of nonmelanoma skin cancer (a keratoacanthoma), colon adenocarcinoma, and melanoma in situ of the digit. Colon adenocarcinoma and keratoacanthoma were diagnosed less than 2 months from the first dose of UPA. Adjudicated major adverse cardiovascular events (MACE) were reported for a 60-year-old patient treated with UPA 15 mg+TCS (nonfatal subarachnoid hemorrhage) and a 69-year-old patient treated with UPA 30 mg+TCS (nonfatal stroke); both were classified as serious events and deemed unrelated to study drug with cardiovascular risk factors, and the patients were withdrawn from study treatment. One adjudicated venous thromboembolic event (VTE [grade 2, pulmonary embolism]) was reported for a 66-year-old white male patient with a history of obesity and hypercholesterolemia in the UPA 15 mg+TCS group. This event was an incidental finding based on results from a routine chest X-ray specified by the protocol for the week 52 visit, and was deemed not serious and possibly related to study drug by the study physician; the patient was withdrawn from the study due to this event. There were no reports of active tuberculosis, adjudicated gastrointestinal perforation, or lymphoma.

Most AEs of hepatic disorders were transient, asymptomatic transaminase elevations. The event rates of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased were 3.3 and 1.8 E/100 PY with UPA 15 mg+TCS and 1.5 and 1.3 E/100 PY with UPA 30 mg+TCS, respectively. AEs of anemia, neutropenia, and CPK elevations were reported more

frequently with UPA 30 mg+TCS vs UPA 15 mg+TCS. These laboratory-related AEs were generally nonserious and did not lead to treatment discontinuation. Most CPK elevations occurred following exercise or other vigorous physical activity (76.6% in UPA 15 mg+TCS and 64.0% in UPA 30 mg+TCS); most (≥84%) did not have any associated symptoms. Overall, potentially clinically important laboratory test results were infrequent (**Table 2**). The incidence of grade 3 or higher elevations in CPK showed a dose-related increase with upadacitinib treatment.

DISCUSSION

This report provides the first evidence of long-term efficacy and safety of UPA+TCS through 52 weeks of treatment. Although there were no statistical comparisons between doses, a clear dose response was observed from week 2 through week 52: patients treated with UPA 30 mg+TCS consistently achieved numerically better results compared with UPA 15 mg+TCS. This trend was also observed in PBO+TCS-treated patients who were re-randomized to receive UPA 15 mg+TCS or UPA 30 mg+TCS from week 16 to week 52. UPA+TCS provides meaningful clinical responses (ie, vIGA-AD 0/1 and EASI-75) as well as extensive responses (ie, EASI-90 and EASI-100) in adolescents and adults with moderate-to-severe AD. Notably, no new important safety risks were observed through 52 weeks of treatment beyond those described in the current label for RA.(21) The only laboratory-related AE anomaly was CPK elevations, which were generally nonserious, related to vigorous physical activity, and did not lead to treatment discontinuation. Safety results were similar between UPA dosages, with clinically irrelevant differences between the UPA 15 mg+TCS and UPA 30 mg+TCS groups. These results reinforce the primary (week 16) efficacy and safety results(26) and demonstrate efficacy and favorable safety of UPA+TCS is maintained long term through 52 weeks of treatment.

There is an overall lack of long-term efficacy and safety data for systemic-plus-TCS treatments in patients with AD. CHRONOS was the first randomized, double-blinded, placebo-controlled, phase 3 study of long-term (1-year) systemic dupilumab treatment in combination with TCS in patients with moderate-to-severe AD and inadequate response to TCS. Primary (week 16) improvements with dupilumab+TCS were sustained over 52 weeks of treatment. At week 52, significantly more patients who received dupilumab+TCS achieved IGA 0/1 (36% [n=32] with dupilumab 300 mg every 2 weeks [q2w]+TCS and 40% [108] with dupilumab 300 mg once weekly [qw]+TCS vs 13% [33] with PBO+TCS) and EASI-75 (65% [58] with dupilumab 300 mg q2w+TCS and 64% [173] with dupilumab 300 mg qw+TCS vs 22% [57] with PBO+TCS) ($P <$

0.001 for all). Several studies of long-term efficacy and safety of JAK inhibitors in combination with TCS to treat moderate-to-severe AD are ongoing.(19, 20, 23, 29) Though preliminary short-term results are promising, limited data are available for long-term efficacy and safety of JAK inhibitors in combination with TCS to treat moderate-to-severe AD. The 52-week results from AD Up reported here provide the first evidence of long-term efficacy and acceptable safety profile of UPA in AD. Compared to RA program,(21) no new important safety risks were observed; however, the rate of acne was higher in the AD study. These acne events were nonserious and rarely led to treatment discontinuation.

Results obtained with each individual imputation method provide different and relevant information that, when taken altogether, may inform the clinical use of the drug. The primary NRI-C analysis is a stringent analysis that cumulatively applies nonresponders forward into subsequent time points; and the accumulation of nonresponders over time could contribute to a downward response rate trend. PBO+TCS–treated patients who switched to UPA 15 mg+TCS or UPA 30 mg+TCS had high response rates (based on those who received ≥1 dose of study drug in the BE) from weeks 20 to 52. This population may have been enriched for patients who made it through the PBO-controlled period without rescue medication or EASI score worsening of ≥25% at any 2 consecutive visits.

EASI and WP-NRS percentage change appeared to rebound after week 16, which may be related to the analysis model. In the prespecified analysis for the percentage change of EASI and WP-NRS, separate models were used for double-blind period and the blinded extension period up to week 52 due to the changes in the stratification factors and the number of treatment groups. Results from a post-hoc analysis using a single model for baseline through week 52 did not show the striking rebound from week 16 to week 20 for the percentage change of EASI, while this increase was still observed for UPA 15 mg from week 16 to week 20 for percentage change of WP-NRS. Of note, WP-NRS was administered on electronic hand-held

devices from screening through week 16; starting at the week 20 visit, the frequency of administration was reduced from daily assessments to assessments only at scheduled site visits using a tablet at the site, which may have contributed to the rebound of LSM percentage change in WP-NRS after week 16. Further, if these rebounds in efficacy were meaningful and a true reflection of the drug's efficacy changes between week 16 and week 20, this would also have been captured by other measures based on responder analyses. This was not the case, as this did not occur in different thresholds of EASI response (EASI75/90/100), vIGA-AD 0/1, and WP-NRS ≥4. Additionally, no patient in any group experienced loss of response at week 20 (**Table S2**).

Limitations of this analysis include the relatively small sample size and lack of powered statistical comparison between groups from weeks 20 to 52. Given the inherent challenges of studying long-term outcomes in chronic diseases, these results must be examined in context. Also, efficacy results reported here are mostly based on objective outcomes (ie, physician assessment of disease severity) vs subjective outcomes (ie, patient-reported outcomes [PRO] and QOL assessments).

Future analyses will investigate the long-term impact of UPA+TCS on PROs and health-related QOL, rescue medication use, TCS-free days, and disease flare incidence during the BE period. Generalizability of AD Up results compared with other AD studies (eg, CHRONOS) is limited by the lack of a PBO+TCS treatment group from weeks 16 to 52. The AD Up BE is ongoing; analyses of results for efficacy and safety of UPA+TCS through 260 weeks are planned, as well as subgroup analyses (eg, age group). Though UPA+TCS closely mimics real-world treatment paradigms for patients with moderate-to-severe AD, UPA+TCS achieved similar efficacy for the same endpoints (eg, skin improvement, itch reduction) with UPA monotherapy in the short term.(24) Therefore, it will be important to compare long-term efficacy and safety of UPA+TCS with the long-term UPA monotherapy study efficacy and safety findings (report forthcoming).

In conclusion, results through 52 weeks from the phase 3 AD Up study further support the potential of UPA+TCS as a well-tolerated and effective long-term treatment option with a positive benefit-risk profile in adults and adolescents with moderate-to-severe AD.

CONTRIBUTIONS

All authors participated in data interpretation, critically reviewed this manuscript, and provided final approval for publication. **AC**, **DR**, **CL**, **JIS, MdB-W, TB, WS, KK,** and **KR** participated in data acquisition. **BL**, **AG**, and **ADC** participated in study concept/design and data acquisition. **JL** and **JZ** participated in statistical analysis.

Data sharing

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 (eg, 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 and execution of a data sharing agreement. 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.

Role of the funding source

The design, study conduct, analysis, and financial support for AD Up were provided by AbbVie Inc. AbbVie participated in the interpretation of data, review, and approval of the manuscript. All

authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Acknowledgments

AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. AbbVie funded the research for this study and provided writing support for this manuscript. Medical writing assistance, funded by AbbVie, was provided by Jennifer C Jaworski, MS, and Caroline W Cazares, PhD, of JB Ashtin.

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TABLES

Table 1. Treatment-emergent adverse events (safety population[a])

	UPA 15 mg + TCS n=443	UPA 30 mg + TCS n=436
	Patients (events/100PY)	
Overview	PY = 511.9	PY = 533.1
Any TEAE	1730 (338.0)	1848 (346.6)
Serious AEs	41 (8.0)	43 (8.1)
AEs leading to discontinuation of study drug	20 (3.9)	20 (3.8)
Deaths	0	0
	Patients (events/100PY)	
AESI	PY = 511.9	PY = 533.1
Serious infections	14 (2.7)	12 (2.3)
Opportunistic infections[b]	7 (1.4)	18 (3.4)
Eczema herpeticum	6 (1.2)	12 (2.3)
Kaposi's varicelliform eruption	1 (0.2)	6 (1.1)
Herpes zoster	21 (4.1)	33 (6.2)
Active tuberculosis	0	0
NMSC	0	1 (0.2)
Malignancy excluding NMSC	1 (0.2)	2 (0.4)
Lymphoma	0	0
Hepatic disorder[c]	41 (8.0)	26 (4.9)
Adjudicated gastrointestinal perforation	0	0
Anemia[c]	7 (1.4)	13 (2.4)
Neutropenia[c]	10 (2.0)	15 (2.8)
Lymphopenia[c]	2 (0.4)	1 (0.2)
CPK elevation[c]	45 (8.8)	54 (10.1)
Renal dysfunction[c]	1 (0.2)	0
Adjudicated MACE[d]	1 (0.2)	1 (0.2)
Adjudicated venous thromboembolic event	1 (0.2)	0

Most frequently reported TEAEs (≥5% in any treatment group)	n (%)	Patients (events/100PY) PY = 511.9	n (%)	Patients (events/100PY) PY = 533.1
Acne	62 (14.0)	68 (13.3)	81 (18.6)	100 (18.8)
Nasopharyngitis	76 (17.2)	128 (25.0)	73 (16.7)	90 (16.9)
Blood CPK increased[c]	37 (8.4)	45 (8.8)	49 (11.2)	54 (10.1)
Dermatitis atopic[e]	47 (10.6)	53 (10.4)	29 (6.7)	36 (6.8)
Upper respiratory tract infection	45 (10.2)	58 (11.3)	45 (10.3)	58 (10.9)
Oral herpes	20 (4.5)	42 (8.2)	36 (8.3)	66 (12.4)
Headache	29 (6.5)	35 (6.8)	28 (6.4)	35 (6.6)
Herpes zoster	18 (4.1)	18 (3.5)	28 (6.4)	28 (5.3)
Cough	23 (5.2)	25 (4.9)	26 (6.0)	27 (5.1)
Herpes simplex	23 (5.2)	42 (8.2)	24 (5.5)	31 (5.8)

AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; PY, patient-years; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
[a]Safety in the main study up to week 52.
[b]Excluding tuberculosis and herpes zoster.
[c]Includes laboratory investigations reported as TEAEs.
[d]MACE defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
[e]Atopic dermatitis with new onset or worsening on or after the first dose of upadacitinib and no more than 30 days after the last dose of upadacitinib in the study.
Except for keratoacanthoma, all other malignancies were deemed unrelated to the study drug by the investigator.

Table 2: Potentially clinically important laboratory values in BE period (safety population[a])

		n (%)	
Parameter	**Grade (Criteria)**	**UPA 15 mg + TCS n=443**	**UPA 30 mg + TCS n=436**
Hemoglobin, g/L	3 (<80)	0	4 (0.9)
Lymphocytes, × 10^9/L	3 (0.2–<0.5)	4 (0.9)	2 (0.5)
	4 (<0.2)	0	0
Neutrophils, × 10^9/L	3 (0.5–<1.0)	5 (1.1)	5 (1.1)
	4 (<0.5)	0	0
Platelets, × 10^9/L	3 (25–<50)	0	0
	4 (<25)	0	0
ALT, U/L	3 (>5.0–20.0 × ULN)	2 (0.5)	2 (0.5)
	4 (>20.0 × ULN)	0	0
AST, U/L	3 (>5.0–20.0 × ULN)	1 (0.2)	4 (0.9)
	4 (>20.0 × ULN)	1 (0.2)	0
Creatinine, µmol/L	3 (>3.0–6.0 × ULN or >3.0 × baseline)	0	1 (0.2)
	4 (>6.0 × ULN)	0	0
CPK, U/L	3 (>5.0–10.0 × ULN)	12 (2.7)	18 (4.1)
	4 (>10.0 × ULN)	7 (1.6)	10 (2.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, blinded extension; CPK, creatine phosphokinase; PBO, placebo; TCS, topical corticosteroids; ULN, upper limit of normal; UPA, upadacitinib.
[a]Safety in the main study up to week 52.

FIGURES

Figure 1. Patient disposition

AE, adverse event; BE, blinded extension; EASI, Eczema Area and Severity Index; ITT, intention to treat for the main study; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.

Figure 2. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) WP-NRS[a] improvement ≥4 (ITT population, NRI-C)

CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; NRI-C, nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.
*P<0.01, ***P<0.001 vs PBO+TCS; P values were multiplicity controlled for EASI-75 only at weeks 2, 4, and 16; for vIGA-AD 0/1, only at week 16; and for WP-NRS, only at weeks 1, 4, and 16; P values were nominal at all other time points. No statistical comparisons were made after week 16.

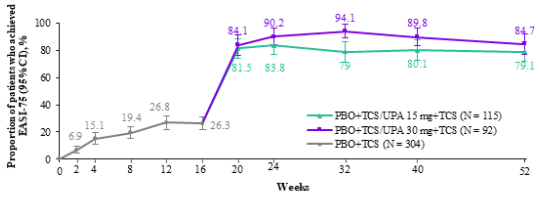
Figure 3. Efficacy over time for (A) EASI-90 and (B) EASI-100 (ITT population, MI)

CI, confidence interval; EASI-90/-100, ≥90%/100% improvement in Eczema Area and Severity Index; ITT, intention to treat for the main study; MI, multiple imputation; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.
*P<0.01, ***P<0.001 vs PBO+TCS; P values were multiplicity controlled for EASI-90 only at weeks 4 and 16 and for EASI-100, only for UPA 30+TCS vs PBO+TCS at week 16; P values were nominal at all other time points. No statistical comparisons were made after week 16.

Figure 4. Efficacy over time for (A) percent change from baseline in EASI and (B) percent change from baseline in WP-NRS[a] (ITT population, MMRM)

CI, confidence interval; EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; MMRM, mixed-effects model for repeated measures; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; WP-NRS, Worst-Pruritis Numerical Rating Scale.
[a]Based on weekly average.
***P<0.001 vs PBO+TCS; P values were multiplicity controlled only at week 16; P values were nominal at all other time points. No statistical comparisons were made after week 16.

A)



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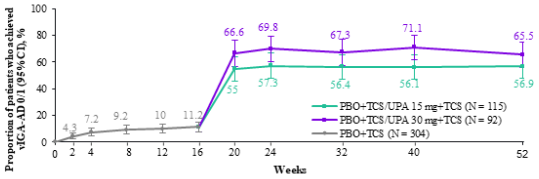

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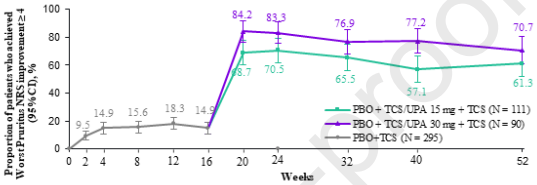

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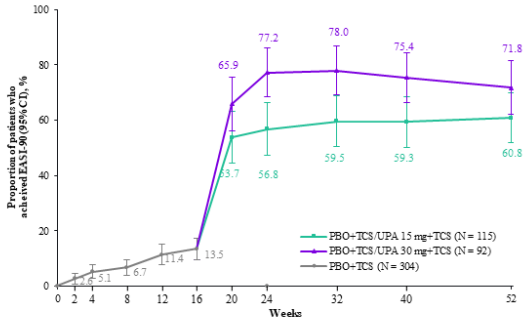

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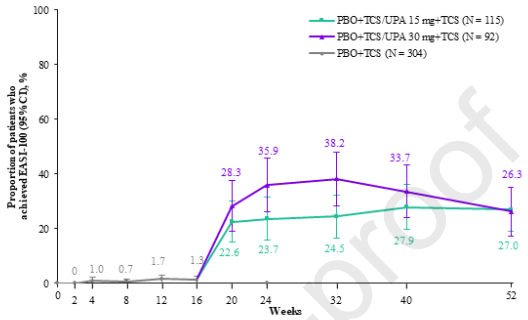

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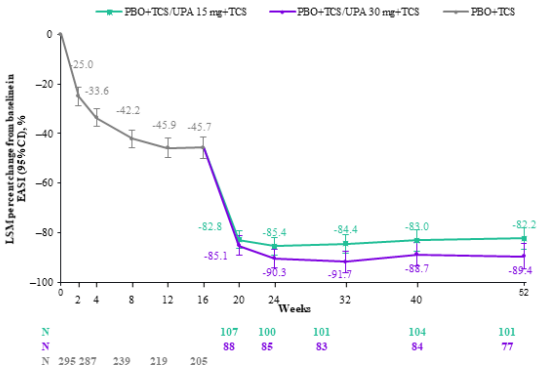

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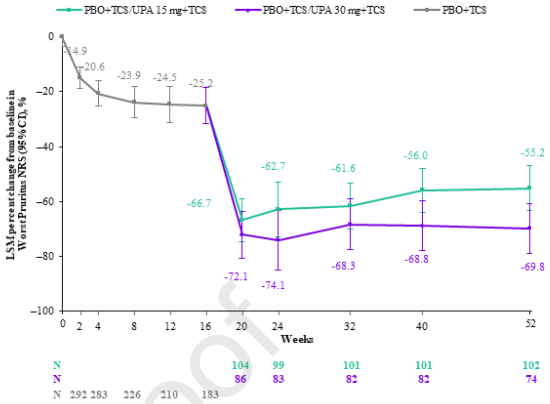

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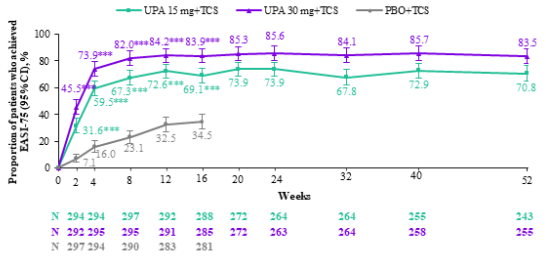

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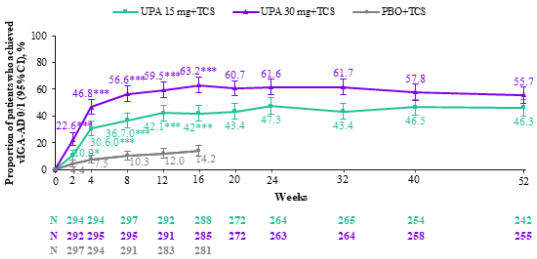

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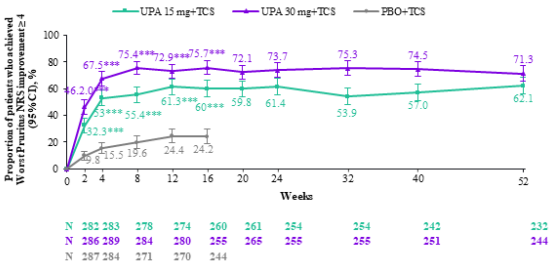

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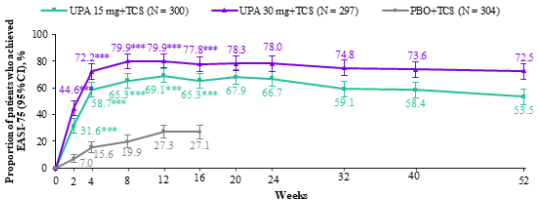

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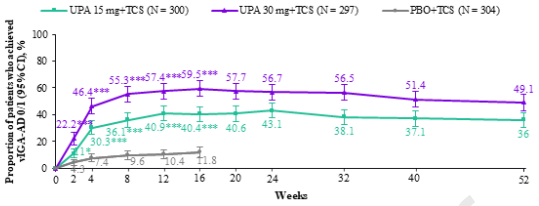

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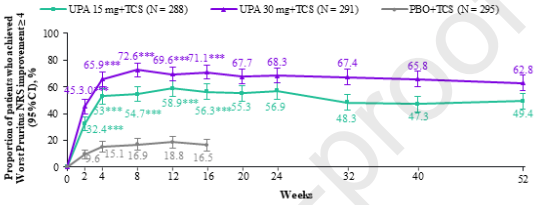

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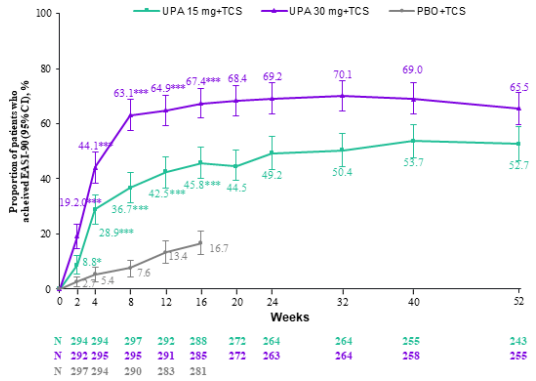

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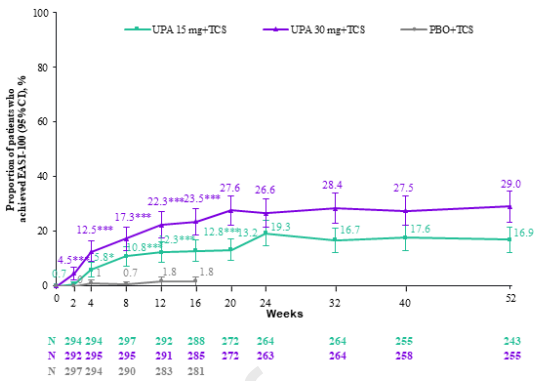

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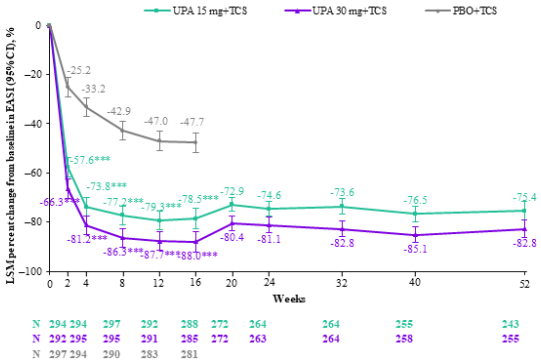

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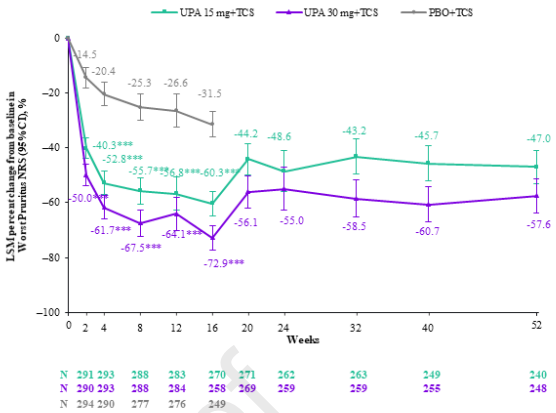

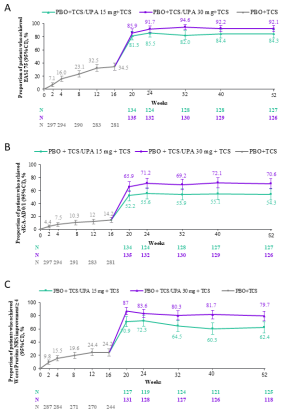

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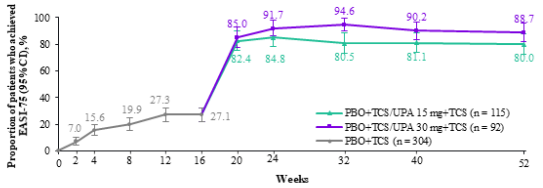

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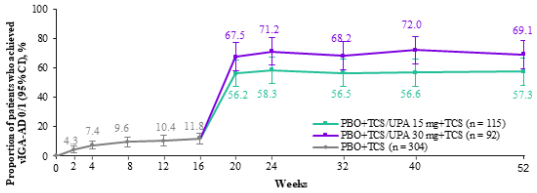

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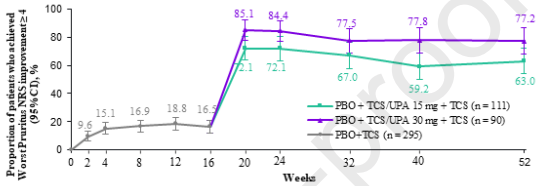

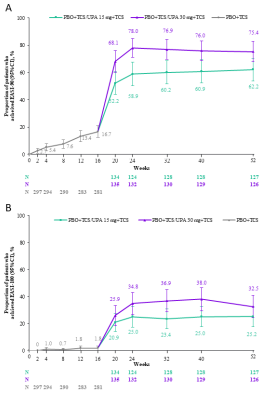

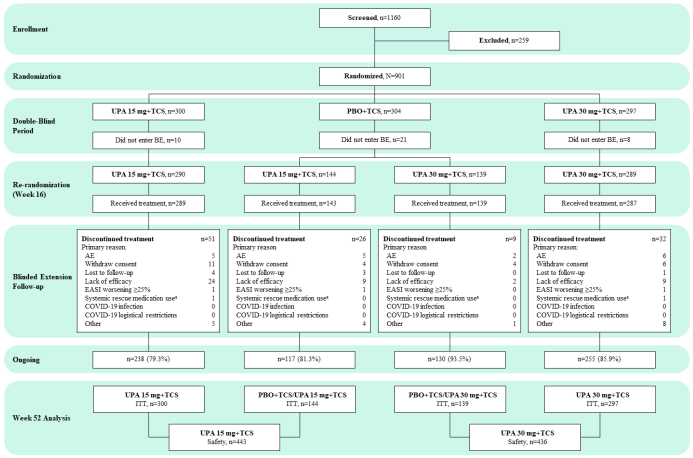

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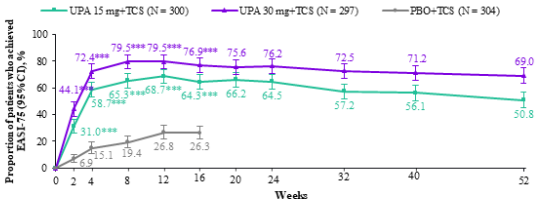

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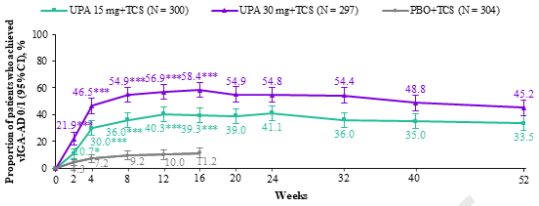

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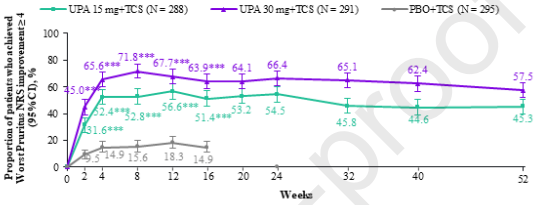

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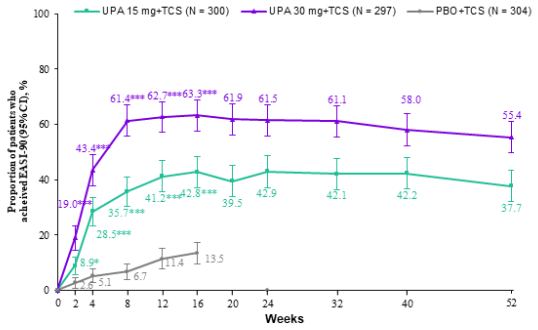

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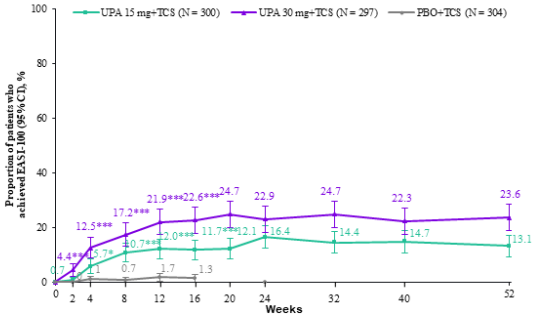

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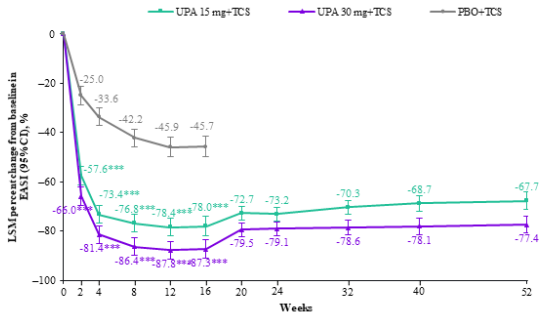

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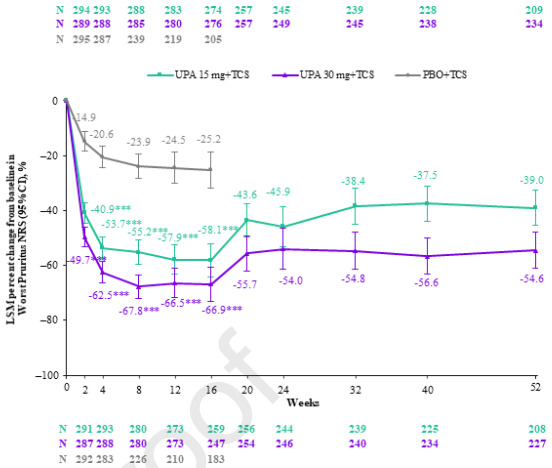

SUPPLEMENTARY MATERIAL

Supplemental Methods

Protocol-mandated TCS

The sponsor did not provide TCS, and choice of TCS aligned with potency was at the investigator's discretion; the protocol recommended triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment as medium-potency TCS and hydrocortisone 1% cream as low-potency TCS.

Rescue Therapy

From weeks 4 to 24, if a patient did not achieve EASI-50 at any 2 consecutive scheduled study visits, rescue therapy with high– or super-high–potency TCS (unless higher potency TCS was considered unsafe) or other topical AD medications (eg, TCI or crisaborole) was allowed as needed, escalating to systemic rescue medication only for patients who did not respond adequately after 7 days of topical treatment. From weeks 24 to 52, rescue therapy was allowed as needed if a patient failed to achieve EASI-50 at any scheduled visit. Patients with any rescue therapy were considered nonresponders for subsequent visits; however, patients who received rescue therapy with topical AD treatments or oral corticosteroids for ≤2 consecutive weeks could continue to receive study medication. Through week 52, rescue therapy was defined as any of the following: high potency TCS; other topical therapies (not including moisturizers or emollients); biologic, non-biologic, or other systemic therapies; or phototherapy.

COVID-19 Operational Accommodations

Measures included remote visits, local laboratory collections, and delivering study drugs to study participants via courier where allowed, in accord with local regulations. Remote assessments of the skin to determine efficacy were not allowed, and in-person visits were required at baseline and week 16.

Table S1. Patients with missing data because of COVID-19 (ITT population)

Endpoint	Time point	Patients with missing data because of COVID-19, n			
		UPA 15 mg + TCS	UPA 30 mg + TCS	PBO+TCS	
EASI-75 and vIGA-AD 0/1	Weeks 2–8	0	0	0	
	Week 12	0	0	1	
	Week 16	0	1	0	
WP-NRS ≥4	Weeks 1–16	0	0	0	
		UPA 15 mg + TCS	UPA 30 mg + TCS	PBO+TCS/ UPA 15 mg + TCS	PBO+TCS/ UPA 30 mg + TCS
EASI-75	Week 20	11	7	6	2
	Week 24	10	12	8	3
	Week 32	6	12	6	6
	Week 40	3	9	3	4
	Week 52	3	6	2	4
vIGA-AD 0/1	Week 20	11	7	6	2
	Week 24	10	12	8	3
	Week 32	6	12	6	6
	Week 40	4	9	4	4
	Week 52	3	6	2	4
WP-NRS ≥4	Week 20	9	6	5	3
	Week 24	9	11	7	4
	Week 32	5	12	6	6
	Week 40	4	9	4	4
	Week 52	3	7	0	4

EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.

Table S2. Proportion of week 16 responders[a] who experienced loss of response[b] after week 16 up to week 52 (ITT population)

	UPA 15 mg + TCS			UPA 30 mg + TCS			PBO+TCS/ UPA 15 mg + TCS			PBO+TCS/ UPA 30 mg + TCS		
Time point	**N[a]**	**n (%)**	**95% CI**	**N[a]**	**n (%)**	**95% CI**	**N[a]**	**n (%)**	**95% CI**	**N[a]**	**n (%)**	**95% CI**
Overall	115	8 (7.0)	2.3, 11.6	171	5 (2.9)	0.4, 5.4	19	1 (5.3)	0.0, 15.3	13	0	–
Week 20	109	0	–	164	0	–	18	0	–	13	0	–
Week 24	106	1 (0.9)	0.0, 2.8	162	2 (1.2)	0.0, 2.9	16	0	–	12	0	–
Week 32	111	3 (2.7)	0.0, 5.7	161	0	–	18	0	–	11	0	–
Week 40	111	4 (3.6)	0.1, 7.1	159	2 (1.3)	0.0, 3.0	19	1 (5.3)	0.0, 15.3	11	0	–
Week 52	108	5 (4.6)	0.7, 8.6	158	1 (0.6)	0.0, 1.9	19	0	–	12	0	–

CI, confidence interval; EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear.
[a]Responders were defined as patients achieving vIGA-AD 0/1 with ≥ 2 grades of reduction from baseline and EASI-75 at week 16.
[b]Loss of response was defined as a loss of at least 50% of the week 16 EASI response and vIGA-AD score of 2 or higher .

Supplemental Figure Legends

Figure S1. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) WP-NRS[a] improvement ≥ 4 (ITT population, Crossover group, NRI-C)

CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; NRI-C, nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S2. Efficacy over time for (A) EASI-90 and (B) EASI-100 (ITT population, Crossover group, MI)
CI, confidence interval; EASI-90/-100, ≥90%/100% improvement in Eczema Area and Severity Index; ITT, intention to treat for the main study; MI, multiple imputation; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.

Figure S3. Efficacy over time for (A) percent change from baseline in EASI and (B) percent change from baseline in WP-NRS[a] (ITT population, Crossover group, MMRM)
CI, confidence interval; EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; MMRM, mixed effects model for repeated measures; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S4. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) Worst Pruritus NRS[a] improvement ≥4 (ITT population, OC)
CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst-Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S5. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) Worst Pruritus NRS[a] improvement ≥ 4 (ITT population, MI)
CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; MI, multiple imputation; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S6. Efficacy over time for (A) EASI-90 and (B) EASI-100 (ITT population, OC)
CI, confidence interval; EASI-90/-100, ≥90%/100% improvement in Eczema Area and Severity Index; ITT, intention to treat for the main study; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.

Figure S7. Efficacy over time for (A) percent change from baseline in EASI and (B) percent change from baseline in WP-NRS[a] (ITT population, OC)

CI, confidence interval; EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S8. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) WP-NRS[a] improvement ≥4 (ITT population, Crossover group, OC)

CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S9. Efficacy over time for (A) EASI-75, (B) vIGA-AD 0/1, and (C) WP-NRS[a] improvement ≥4 (ITT population, Crossover group, MI)

CI, confidence interval; EASI-75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; MI, multiple imputation; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for atopic dermatitis of clear or almost clear with ≥2 grades of improvement; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.

Figure S10. Efficacy over time for (A) EASI-90 and (B) EASI-100 (ITT population, Crossover group, OC)

CI, confidence interval; EASI-90/-100, ≥ 90%/100% improvement in Eczema Area and Severity Index; ITT, intention to treat for the main study; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.

Figure S11. Efficacy over time for (A) percent change from baseline in EASI and (B) percent change from baseline in WP-NRS[a] (ITT population, Crossover group, OC)

CI, confidence interval; EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; OC, observed cases; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; WP-NRS, Worst Pruritis Numerical Rating Scale.
[a]Based on weekly average.