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

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Background: Primary (week 16) results from the ongoing phase 3, double-blind AD Up study (NCT03568318) demonstrate a positive benefit–risk profile for upadacitinib + topical corticosteroid (TCS) in patients with moderate-to-severe atopic dermatitis.
Objective: We evaluated the efficacy and safety of upadacitinib + TCS through 52 weeks.
Methods: Patients aged 12 to 75 years with chronic moderate-to-severe atopic dermatitis (≥10% of body surface area affected, Eczema Area and Severity Index [EASI] ≥16, Validated Investigator's Global Assessment for atopic dermatitis [vIGA-AD] ≥3, and Worst Pruritus Numerical Rating Scale [WP-NRS] score ≥4) were randomized 1:1:1 to once-daily upadacitinib 15 mg + TCS, upadacitinib 30 mg + TCS, or placebo (PBO) + TCS (rerandomized at week 16 to upadacitinib + TCS). Safety and efficacy, including proportion of patients experiencing ≥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 nonresponse imputation incorporating multiple imputation for missing values due to coronavirus disease 2019 (COVID-19).
Results: Of 901 patients, 300 were randomized to upadacitinib 15 mg + TCS, 297 to upadacitinib 30 mg + TCS, and 304 to PBO + TCS. For all end points, efficacy for upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS at week 16 was maintained through week 52. At week 52, the proportions of patients treated with upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS who experienced EASI-75 were 50.8% and 69.0%, respectively; 33.5% and 45.2%, respectively, experienced vIGA-AD 0/1; and 45.3% and 57.5%, respectively, experienced WP-NRS improvement ≥4. Upadacitinib + TCS was well tolerated through

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52 weeks; no new important safety risks beyond the current label were observed. No deaths were reported; major adverse cardiovascular events and venous thromboembolic events were infrequent (≤0.2/100 patient-years).
Conclusions: 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. (J Allergy Clin Immunol 2022;149:977-87.)

Key words: *Atopic dermatitis, randomized clinical trial, upadacitinib, topical corticosteroids, Janus kinase inhibitors*

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; symptoms of AD can persist, reemerge, 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 that provide prolonged clinical response without high levels of treatment discontinuation due to 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–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, an oral JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, is approved in the United States, the European Union, 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 upadacitinib 15 mg and upadacitinib 30 mg versus placebo (PBO). As monotherapy, both upadacitinib doses are well tolerated; markedly improve skin signs, itch, skin pain, and health-related quality of life; and consistently exhibit 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, a pivotal, phase 3, randomized, double-blind study, provide evidence that upadacitinib + 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 upadacitinib dose plus TCS experience ≥75% improvement in EASI (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 favorable benefit–risk profile of upadacitinib in AD. Exploration of the long-term benefit–risk profile of adding standard TCS to upadacitinib continues in the ongoing blinded extension (BE) period of AD Up; here we report results through 52 weeks.

Abbreviations used

AD:	Atopic dermatitis
AE:	Adverse event
BE:	Blinded extension
COVID-19:	Coronavirus disease 2019
CPK:	Creatine phosphokinase
EASI:	Eczema Area and Severity Index
EASI-50, -75, -90, -100:	Improvement from baseline in EASI of ≥50%, ≥75%, ≥90%, 100%
HZ:	Herpes zoster
JAK:	Janus kinase
LSM:	Least squares mean
MI:	Multiple imputation
NRI-C:	Nonresponse imputation incorporating MI to handle missing data due to COVID-19
PBO:	Placebo
PY:	Patient-year
RA:	Rheumatoid arthritis
TCS:	Topical corticosteroid
TEAE:	Treatment-emergent adverse event
vIGA-AD 01:	Validated Investigator's Global Assessment for AD of clear or almost clear with ≥2 grades of improvement
WP-NRS:	Worst Pruritus Numerical Rating Scale

METHODS

Study design and patients

Study design and patient population details have been previously reported.[26] Briefly, AD Up (NCT03568318) was a pivotal, phase 3, randomized, double-blind, PBO-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-blind 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 to 75 years (weight ≥40 kg) with chronic AD (onset ≥3 years before 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 forms, and recruitment materials before patient enrollment. 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 before any screening or study-related procedures. The adolescent substudy was added after protocol initiation to allow enrollment of additional adolescents to fulfill a regulatory commitment.

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 (see the Methods in this article's Online Repository at www.jacionline.org).

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 upadacitinib 15 mg, upadacitinib 30 mg, or PBO once daily, all in combination with TCS. At week 16, PBO + TCS–treated patients were rerandomized 1:1 to receive upadacitinib 15 mg or 30 mg plus TCS; patients initially randomized to upadacitinib 15 mg + TCS or upadacitinib 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 (United States/Puerto Rico/Canada, Japan, China, Other), and age group (adolescent, adult). Rerandomization 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 unaware of their treatment regimen throughout the study; the upadacitinib 15 mg, upadacitinib 30 mg, and PBO tablets were identical in appearance.

Procedures

Patients took a single oral tablet of upadacitinib 15 mg, upadacitinib 30 mg, or PBO (AbbVie, North Chicago, Ill) once daily. Twice-daily use of an additive-free, bland emollient was required for ≥7 days before 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 for sensitive skin areas) was applied once daily to areas with active lesions for ≤3 consecutive weeks or until lesions were clear or almost clear; then low-potency TCS was applied once daily for 7 days and stopped if lesions were no longer active (for sensitive skin areas, low-potency TCS or topical calcineurin inhibitor 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 the Methods in this article's Online Repository).

Outcomes

The co–primary efficacy end points (multiplicity controlled) were the proportion of patients who experienced EASI-75 and the proportion of patients who experienced vIGA-AD 0/1, both at week 16. The primary and following key secondary efficacy end points were assessed at all visits through week 52: the proportions of patients who experienced WP-NRS improvement ≥4, EASI-90 and EASI-100, and the percentage changes from baseline in EASI and WP-NRS. Among those with response, defined as patients experiencing 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 adverse events; deaths; adverse events (AEs) leading to discontinuation of study treatment; prespecified AEs of special interest, which were based on the known upadacitinib safety profile[21] and previous safety observations for upadacitinib[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 end points of 38% and 20%, respectively, and to allow for adequate characterization of safety.[26] After all patients in the main study completed the therapy regimen at week 52, efficacy analyses were conducted in the intent-to-treat population for the main study, 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 rerandomized at week 16 were combined into their respective upadacitinib 15 mg + TCS or upadacitinib 30 mg + TCS groups for the safety analyses.

For categorical end points, the primary approach for handling missing data was nonresponse imputation incorporating multiple imputation (MI) for missing values due to COVID-19 (NRI-C).[26] For response rates, 95% CIs were based on a Student *t* distribution from the SAS PROC MIANALYZE procedure (SAS Institute, Cary, NC). NRI-C was the primary approach for categorical end points in the double-blind period and for co–primary end points and WP-NRS in the BE 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 the BE period up to week 52 using Markov chain Monte Carlo and PROC MI, and included the following: treatment group, major stratum (vIGA-AD categories [for end points 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 having nonresponsive disease after receiving rescue medication, and data were not imputed by MI (see the Methods in this article's Online Repository).

For continuous end points, change and percentage change from baseline in each treatment group were analyzed using the mixed-effects model for repeated measures. This 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 those with response at week 16 and was performed for all variables in addition to NRI-C and MI. Further, *post hoc* analyses for percentage change of EASI and WP-NRS were conducted for the upadacitinib treatment groups from baseline through week 52 with treatment (upadacitinib 15 mg and upadacitinib 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 August 9, 2018, and December 20, 2019, a total of 901 patients were randomized to the double-blind period (300 to upadacitinib 15 mg + TCS, 297 to upadacitinib 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, a total of 283 PBO + TCS–treated patients were rerandomized—144 to upadacitinib 15 mg + TCS (143 were treated) and 139 to upadacitinib 30 mg + TCS (139 were treated)—while 289 upadacitinib 15 mg + TCS–treated and 287 upadacitinib 30 mg + TCS–treated patients continued to receive their initial treatment in the BE period (Fig 1). During the BE period, 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 due to COVID-19 are listed in Table E1 in this article's Online Repository at www.jacionline.org. Rescue medication was initiated in the BE period by 15.0%, 8.1%, 4.2%, and 5.0% of patients receiving upadacitinib 15 mg + TCS, upadacitinib 30 mg + TCS, PBO + TCS/upadacitinib 15 mg + TCS, and PBO + TCS/upadacitinib 30 mg + TCS, respectively.

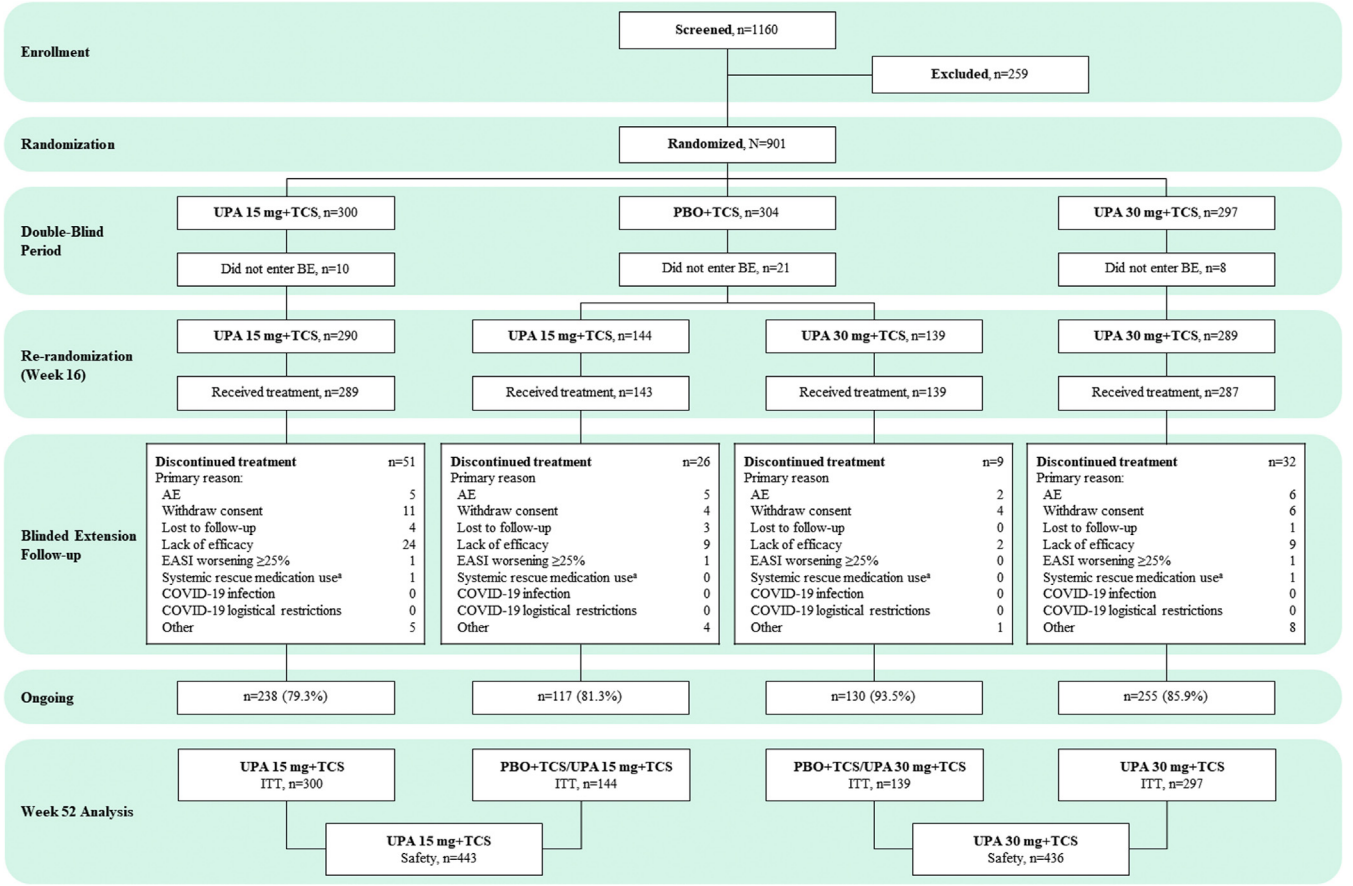

FIG 1. Patient disposition. *ITT,* Intention to treat for the main study; *UPA,* upadacitinib.

At week 16 (primary end point), significantly greater proportions of patients treated with upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS versus PBO + TCS experienced EASI-75, vIGA-AD 0/1, and WP-NRS improvement ≥4 ($P <$ .001 for all, Fig 2).[26] Likewise, at week 16, greater proportions of upadacitinib 15 mg + TCS– and upadacitinib 30 mg + TCS–treated patients experienced the more stringent end points of EASI-90 and EASI-100 ($P <.001$ for all, Fig 3) and marked improvements from baseline in EASI and WP-NRS scores ($P <.001$ for all, Fig 4) compared with PBO + TCS–treated patients.[26]

Overall, efficacy demonstrated for upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS at week 16 was maintained through week 52. At week 52, the proportions (95% CI) of patients treated with upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS who experienced EASI-75 were 50.8% (45.1%, 56.5%) and 69.0% (63.7%, 74.3%), respectively (Fig 2, *A*). The proportion (95% CI) of patients who experienced vIGA-AD 0/1 at week 52 was 33.5% (28.1%, 38.9%) for upadacitinib 15 mg + TCS and 45.2% (39.5%, 50.9%) for upadacitinib 30 mg + TCS (Fig 2, *B*). At week 52, 45.3% (95% CI: 39.5%, 51.0%) of patients receiving upadacitinib 15 mg + TCS and 57.5% (51.8%, 63.2%) receiving upadacitinib 30 mg + TCS experienced WP-NRS improvement ≥4 (Fig 2, *C*).

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

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

Overall, few patients experiencing response at week 16 lost response after that time and up to week 52 (see Table E2 in this article's Online Repository at www.jacionline.org). Overall, 8 patients (7.0%) with response at week 16 receiving upadacitinib 15 mg + TCS experienced loss of response after week 16; 5 (2.9%) in the upadacitinib 30 mg + TCS group lost response.

At week 52, 79.1% (71.7%, 86.6%) in the PBO + TCS/upadacitinib 15 mg + TCS group and 84.7% (77.3%, 92.1%) in the PBO + TCS/upadacitinib 30 mg + TCS group experienced EASI-75 (see Fig E1, *A,* in this article's Online Repository at www.jacionline.org); 56.9% (47.8%, 66.0%) and 65.5% (55.7%, 75.2%), respectively, experienced vIGA-AD 0/1 (Fig E1, *B*); and 61.3% (52.2%, 70.3%) and 70.7% (61.3%, 80.2%), respectively, experienced WP-NRS improvement ≥4 (Fig E1, *C*).

EASI-90 was experienced by 60.8% (51.8%, 69.8%) of patients in the PBO + TCS/upadacitinib 15 mg + TCS group

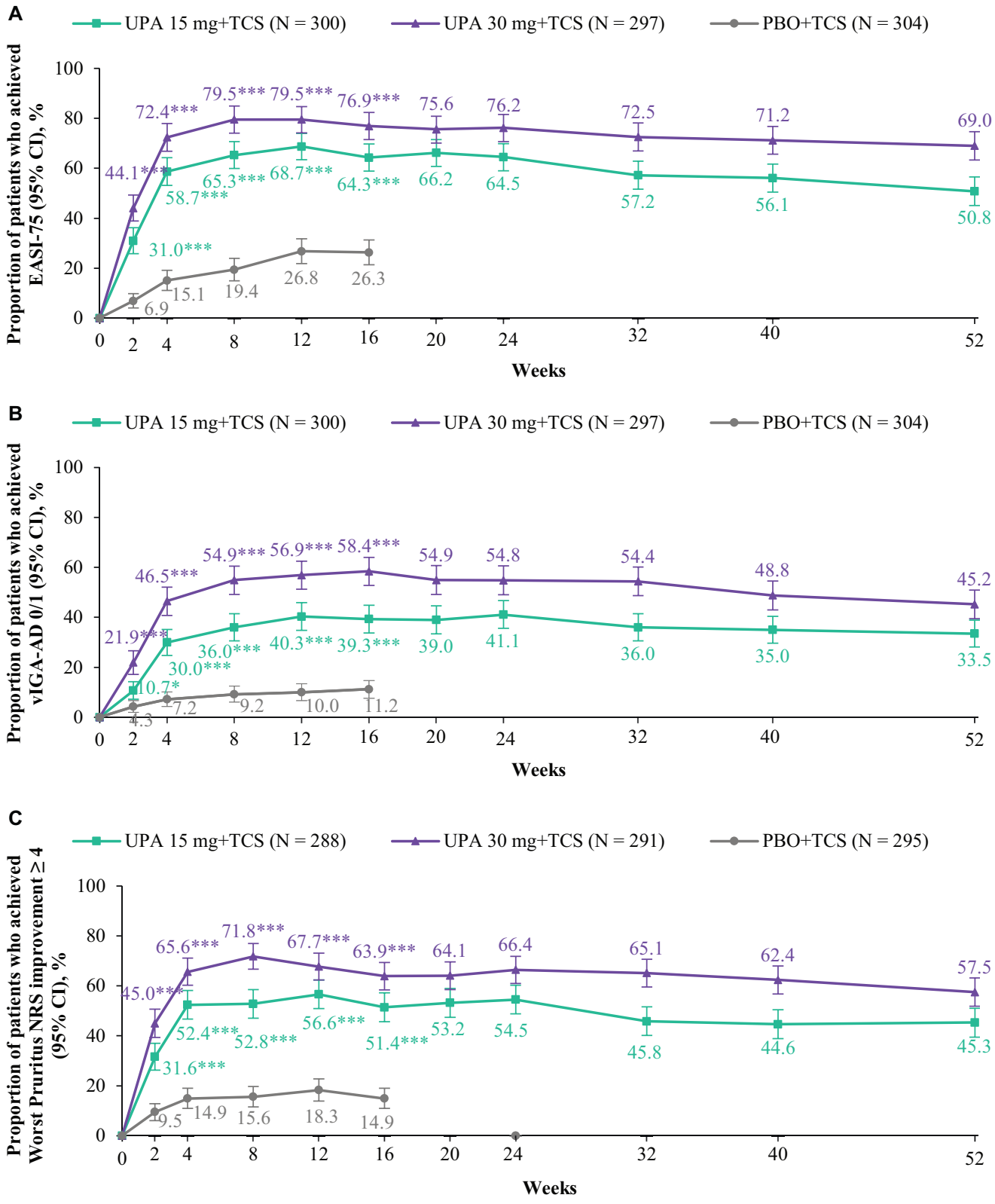

FIG 2. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥4 (ITT population, NRI-C). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *UPA*, upadacitinib. *$P < .01$, ***$P < .001$ vs PBO + TCS; *P* values were multiplicity 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.

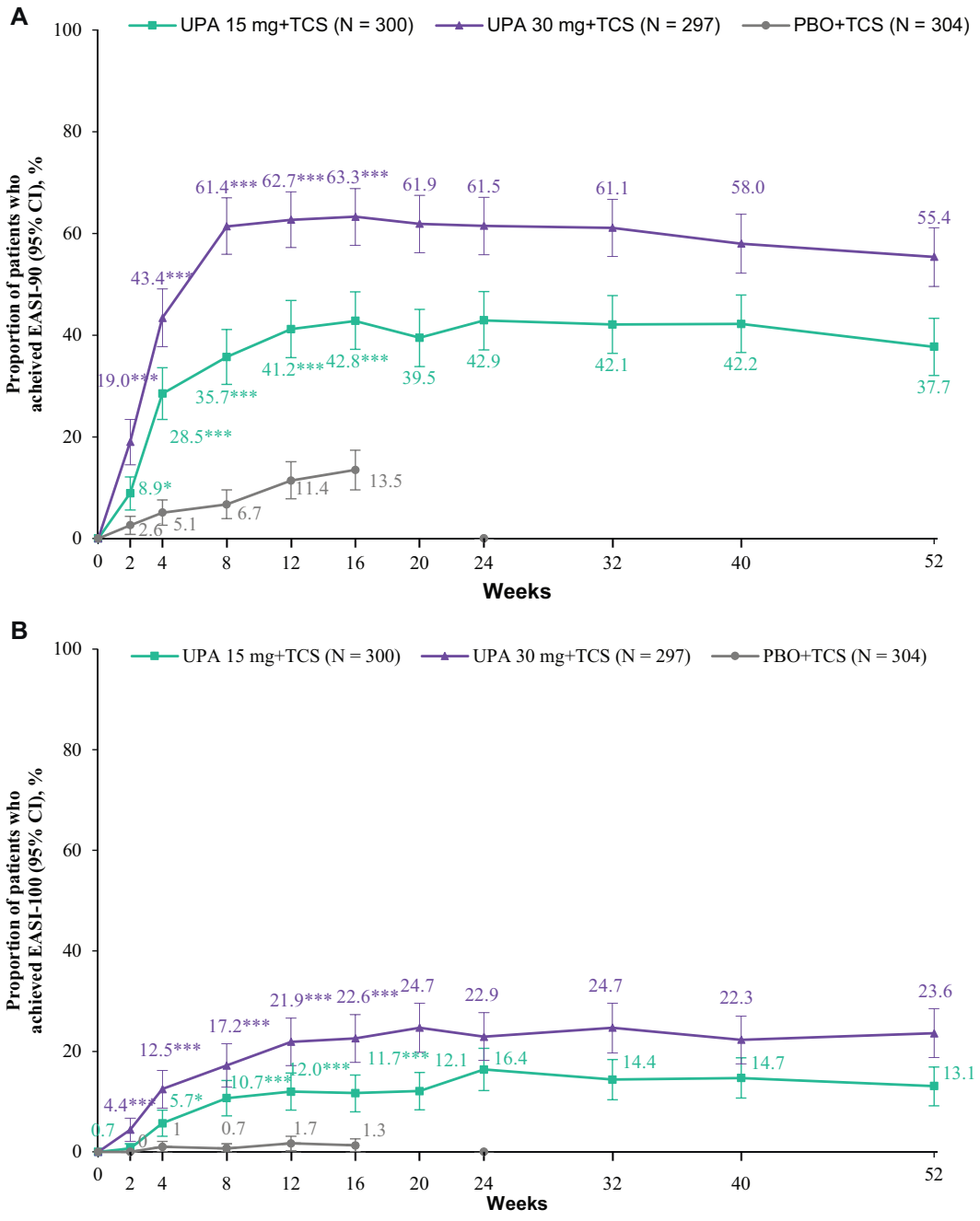

FIG 3. Efficacy over time for (**A**) EASI-90 and (**B**) EASI-100 (ITT population, MI). *ITT*, Intention to treat for the main study; *UPA*, upadacitinib. *$P < .01$, ***$P < .001$ vs PBO + TCS; *P* values were multiplicity controlled for EASI-90 only at weeks 4 and 16, and for EASI-100, only for upadacitinib 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.

and 71.8% (62.2%, 81.5%) in the PBO + TCS/upadacitinib 30 mg + TCS group at week 52 (see Fig E2, *A*, in this article's Online Repository at www.jacionline.org); EASI-100 was experienced by 27.0% (18.9%, 35.1%) and 26.3% (17.3%, 35.3%), respectively (Fig E2, *B*).

The LSM (95% CI) percentage change from baseline in EASI at week 52 was −82.2% (−86.7%, −77.8%) for PBO + TCS/upadacitinib 15 mg + TCS and −89.4% (−94.4%, −84.4%) for PBO + TCS/upadacitinib 30 mg + TCS (see Fig E3, *A*, in this article's Online Repository at www.jacionline.org); the percentage change from baseline in WP-NRS was −55.2% (−63.3%, −47.1%) and −69.8% (−78.9%, −60.6%), respectively (Fig E3, *B*).

Overall, similar results were obtained with NRI-C, MI, and observed case analyses (see Figs E4 to E11).

As of the 52-week data analysis cutoff, both upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS were well tolerated (Table I). The exposure-adjusted event rates (E/100 PY) of any TEAE, serious AEs, and AEs leading to discontinuation of study

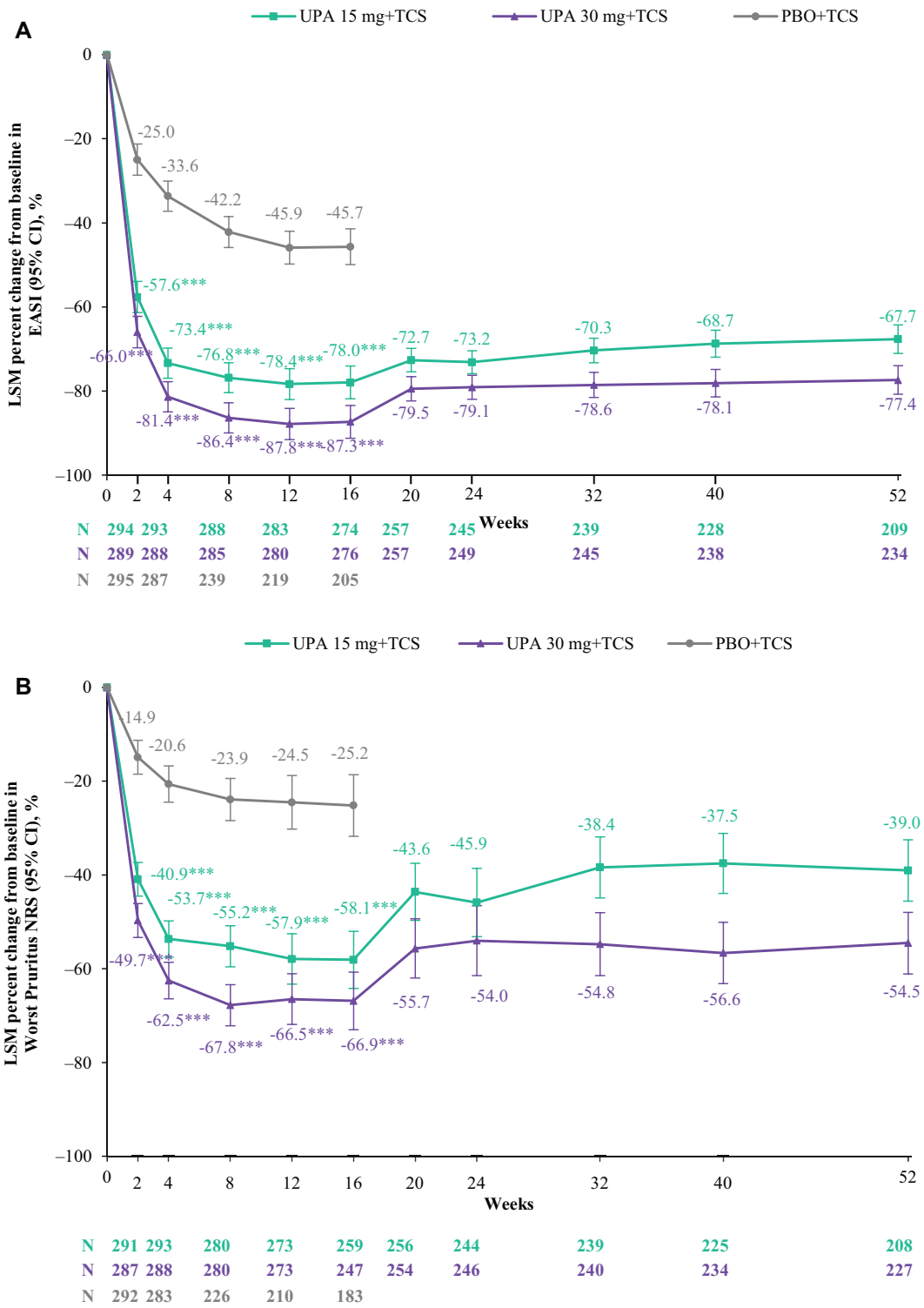

FIG 4. Efficacy over time for (**A**) percentage change from baseline in EASI and (**B**) percentage change from baseline in WP-NRS (ITT population, MMRM). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *MMRM*, Mixed-effects model for repeated measures; *UPA*, upadacitinib. ***$P <$ .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.

drug were similar between upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS groups (Table I). No deaths were reported through 52 weeks of the BE period (Table I).

The most frequently reported TEAEs (≥10% in either treatment group) were acne, nasopharyngitis, blood creatine phosphokinase (CPK) increase, dermatitis atopic, and upper respiratory tract

TABLE I. Treatment-emergent adverse events (safety population*)

Characteristic	Upadacitinib 15 mg + TCS (n = 443)	Upadacitinib 30 mg + TCS (n = 436)
	Events (events/100 PY)	
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
	Events (events/100 PY)	
Adverse event of special interest	PY = 511.9	PY = 533.1
Serious infections	14 (2.7)	12 (2.3)
Opportunistic infections†	7 (1.4)	18 (3.4)
Eczema herpeticum	6 (1.2)	12 (2.3)
Kaposi 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‡	41 (8.0)	26 (4.9)
Adjudicated gastrointestinal perforation	0	0
Anemia‡	7 (1.4)	13 (2.4)
Neutropenia‡	10 (2.0)	15 (2.8)
Lymphopenia‡	2 (0.4)	1 (0.2)
CPK elevation‡	45 (8.8)	54 (10.1)
Renal dysfunction‡	1 (0.2)	0
Adjudicated MACE§	1 (0.2)	1 (0.2)
Adjudicated venous thromboembolic event	1 (0.2)	0

	PY = 511.9		PY = 533.1	
	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)
Most frequently reported TEAEs (≥5% in any treatment group)				
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‡	37 (8.4)	45 (8.8)	49 (11.2)	54 (10.1)
Dermatitis atopic‖	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)

MACE, Major adverse cardiovascular event; *NMSC*, Nonmelanoma skin cancer. Except for keratoacanthoma, all other malignancies were deemed unrelated to the study drug by the investigator.

*Safety in the main study up to week 52.

†Excluding tuberculosis and HZ.

‡Includes laboratory investigations reported as TEAEs.

§MACE defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

‖AD 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.

infection (Table I). No acne events were serious, and 1 mild acne event in the upadacitinib 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 upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS, respectively) (Table I). All opportunistic infections reported, excluding tuberculosis and herpes zoster (HZ), were cases of eczema herpeticum (Kaposi varicelliform eruption); the exposure-adjusted event rates were 2.7 and 2.3 E/100 PY in the upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS treatment groups, respectively. All eczema herpeticum events were nonserious, and 2 events reported in the upadacitinib 30 mg + TCS group lead to treatment discontinuation. The event rate of HZ was higher in the upadacitinib 30 mg + TCS group compared with upadacitinib 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 central nervous system, lung, or liver. One squamous cell carcinoma of the oral cavity was reported in the upadacitinib 15 mg + TCS group; 3 malignancies were reported in the upadacitinib 30 mg + TCS group, with 1 case each of nonmelanoma skin cancer (a keratoacanthoma), colon adenocarcinoma, and melanoma-in-situ of the digit. Colon adenocarcinoma and keratoacanthoma

TABLE II. Potentially clinically important laboratory values in the BE period (safety population)

Parameter	Grade (Criteria)	No. (%) for: Upadacitinib 15 mg + TCS (n = 443)	Upadacitinib 30 mg + TCS (n = 436)
Hemoglobin (g/L)	3 (<80)	0	4 (0.9)
Lymphocytes (× 10^9/L)	3 (0.2 to <0.5)	4 (0.9)	2 (0.5)
	4 (<0.2)	0	0
Neutrophils (× 10^9/L)	3 (0.5 to <1.0)	5 (1.1)	5 (1.1)
	4 (<0.5)	0	0
Platelets (× 10^9/L)	3 (25 to <50)	0	0
	4 (<25)	0	0
ALT (U/L)	3 (>5.0 to 20.0× ULN)	2 (0.5)	2 (0.5)
	4 (>20.0× ULN)	0	0
AST (U/L)	3 (>5.0 to 20.0× ULN)	1 (0.2)	4 (0.9)
	4 (>20.0× ULN)	1 (0.2)	0
Creatinine (μmol/L)	3 (>3.0 to 6.0× ULN or >3.0× baseline)	0	1 (0.2)
	4 (>6.0× ULN)	0	0
CPK (U/L)	3 (>5.0 to 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; *ULN*, upper limit of normal. Safety in the main study up to week 52.

were diagnosed less than 2 months from the first dose of upadacitinib. Adjudicated major adverse cardiovascular events were reported for a 60-year-old patient treated with upadacitinib 15 mg + TCS (nonfatal subarachnoid hemorrhage) and a 69-year-old patient treated with upadacitinib 30 mg + TCS (nonfatal stroke); both were classified as serious events and were deemed unrelated to study drug with cardiovascular risk factors, and the patients were withdrawn from study treatment. One adjudicated venous thromboembolic event (venous thromboembolic event [grade 2 pulmonary embolism]) was reported for a 66-year-old white male patient with a history of obesity and hypercholesterolemia in the upadacitinib 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 as a result of 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 and aspartate aminotransferase increased were 3.3 and 1.8 E/100 PY with upadacitinib 15 mg + TCS and 1.5 and 1.3 E/100 PY with upadacitinib 30 mg + TCS, respectively. AEs of anemia, neutropenia, and CPK elevations were reported more frequently with upadacitinib 30 mg + TCS versus upadacitinib 15 mg + TCS. These laboratory-related AEs were generally nonserious and did not lead to treatment discontinuation. Most CPK elevations occurred after exercise or other vigorous physical activity (76.6% in upadacitinib 15 mg + TCS and 64.0% in upadacitinib 30 mg + TCS groups); most (≥84%) did not have any associated symptoms. Overall, potentially clinically important laboratory test results were infrequent (Table II). 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 upadacitinib + 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 upadacitinib 30 mg + TCS consistently experienced numerically better results compared with upadacitinib 15 mg + TCS. This trend was also observed in PBO + TCS–treated patients who were rerandomized to receive upadacitinib 15 mg + TCS or upadacitinib 30 mg + TCS from week 16 to week 52. Upadacitinib + 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, were related to vigorous physical activity, and did not lead to treatment discontinuation. Safety results were similar between upadacitinib doses, with clinically irrelevant differences between the upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS groups. These results reinforce the primary (week 16) efficacy and safety results[26] and demonstrate efficacy and favorable safety of upadacitinib + 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-blind, PBO-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 experienced vIGA-AD 0/1 (36% [n = 32] with dupilumab 300 mg every 2 weeks + TCS and 40% [n = 108] with dupilumab 300 mg once weekly + TCS vs 13% [n = 33] with PBO + TCS) and EASI-75 (65% [n = 58] with dupilumab 300 mg every 2 weeks + TCS and 64% [n = 173] with dupilumab 300 mg every week + TCS vs 22% [n = 57] with PBO + TCS) ($P < .001$ 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 upadacitinib in AD. Compared with the 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 together, may inform the clinical use of the drug. The primary NRI-C analysis is a stringent analysis that cumulatively applies nonresponse forward into subsequent time points; the accumulation of nonresponse over time could contribute to a downward response rate trend. PBO + TCS–treated patients who switched to upadacitinib 15 mg + TCS or upadacitinib 30 mg + TCS had high response rates (based on those who received ≥1 dose of study drug in the BE period) 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 the double-blind period and the BE period up to week 52 as a result of changes in stratification factors and 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 upadacitinib 15 mg from week 16 to week 20 for percentage change of WP-NRS. Of note, WP-NRS was administered on electronic handheld 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 response analyses. This was not the case, as this did not occur in different thresholds of EASI response (EASI-75/-90/-100), vIGA-AD 0/1, and WP-NRS ≥4. Additionally, no patient in any group experienced loss of response at week 20 (Table E2).

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) versus subjective outcomes (ie, patient-reported outcomes and quality-of-life assessments).

Future analyses will investigate the long-term impact of upadacitinib + TCS on patient-reported outcomes and health-related quality of life, 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 upadacitinib + TCS through 260 weeks are planned, as well as subgroup analyses (eg, age group). Though upadacitinib + TCS closely mimics real-world treatment paradigms for patients with moderate-to-severe AD, upadacitinib + TCS experienced similar efficacy for the same end points (eg, skin improvement, itch reduction) with upadacitinib monotherapy in the short term.[24] Therefore, it will be important to compare long-term efficacy and safety of upadacitinib + TCS with the long-term upadacitinib 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 upadacitinib + 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.

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.

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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.

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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 experience EASI-50 at any 2 consecutive scheduled study visits, rescue therapy with high- or superhigh-potency TCS (unless higher-potency TCS was considered unsafe) or other topical AD medications (eg, topical calcineurin inhibitor or crisaborole) was allowed as needed, escalating to systemic rescue medication only for disease that did not respond adequately after 7 days of topical treatment. From weeks 24 to 52, rescue therapy was allowed as needed if EASI-50 was not recorded at any scheduled visit. Patients who received any rescue therapy were considered to have nonresponsive disease for subsequent visits; however, patients who received rescue therapy with topical AD treatments or oral corticosteroids for $\leq$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, nonbiologic, 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.

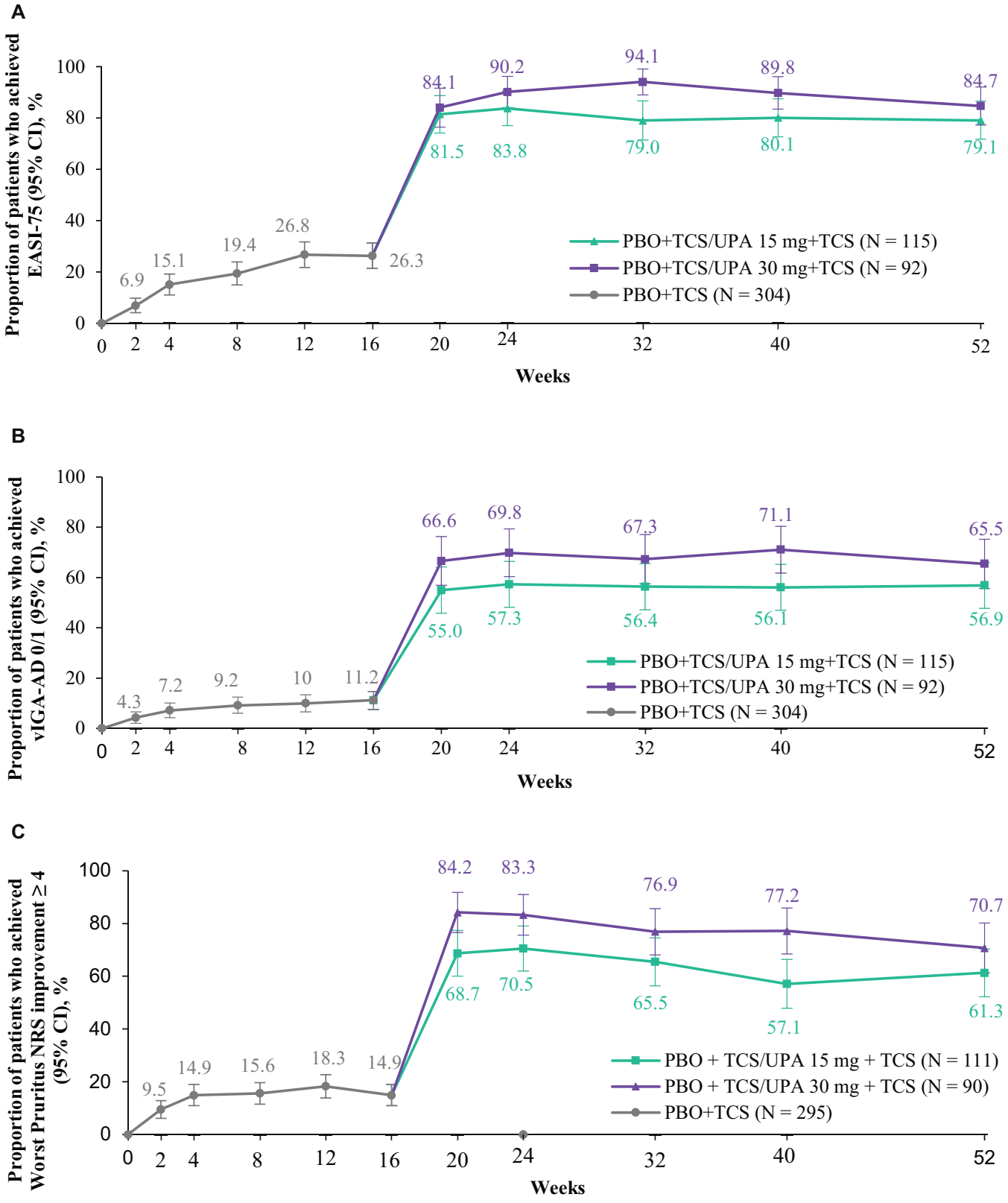

FIG E1. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥ 4 (ITT population, Crossover group, NRI-C). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *UPA*, upadacitinib.

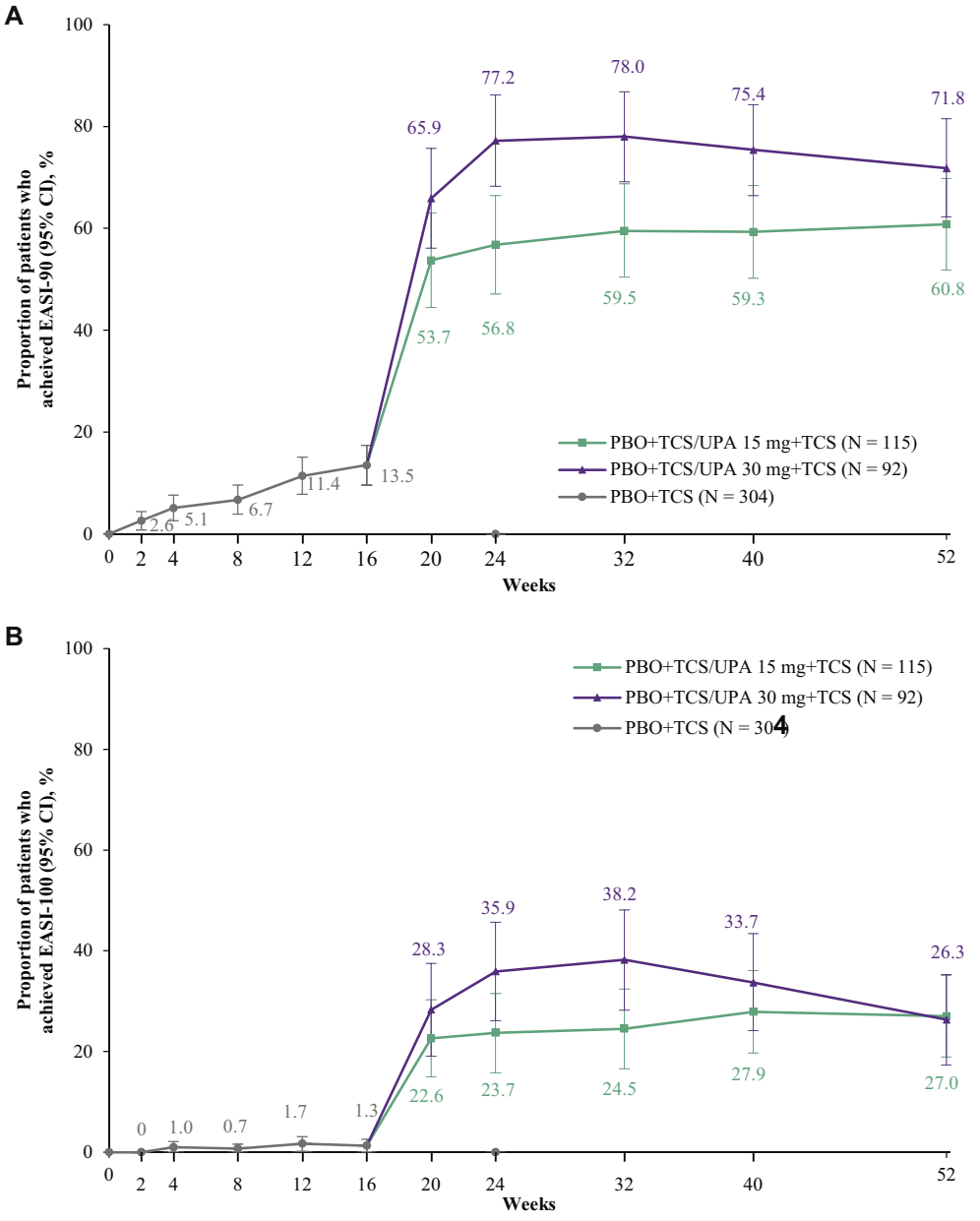

FIG E2. Efficacy over time for (**A**) EASI-90 and (**B**) EASI-100 (ITT population, Crossover group, MI). *ITT*, Intention to treat for the main study; *UPA*, upadacitinib.

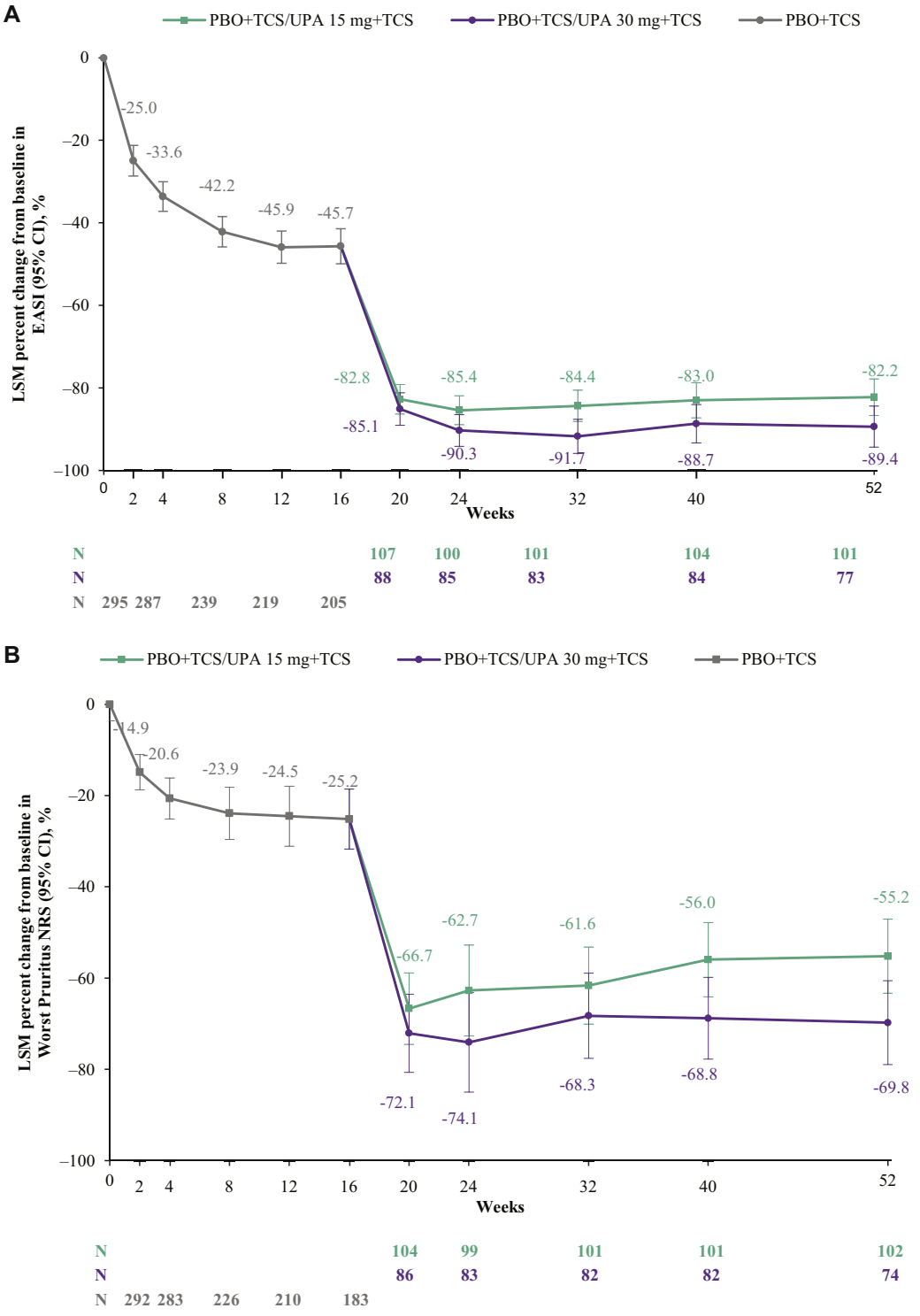

FIG E3. Efficacy over time for (**A**) percentage change from baseline in EASI and (**B**) percentage change from baseline in WP-NRS (ITT population, Crossover group, MMRM). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *MMRM*, Mixed effects model for repeated measures; *UPA*, upadacitinib.

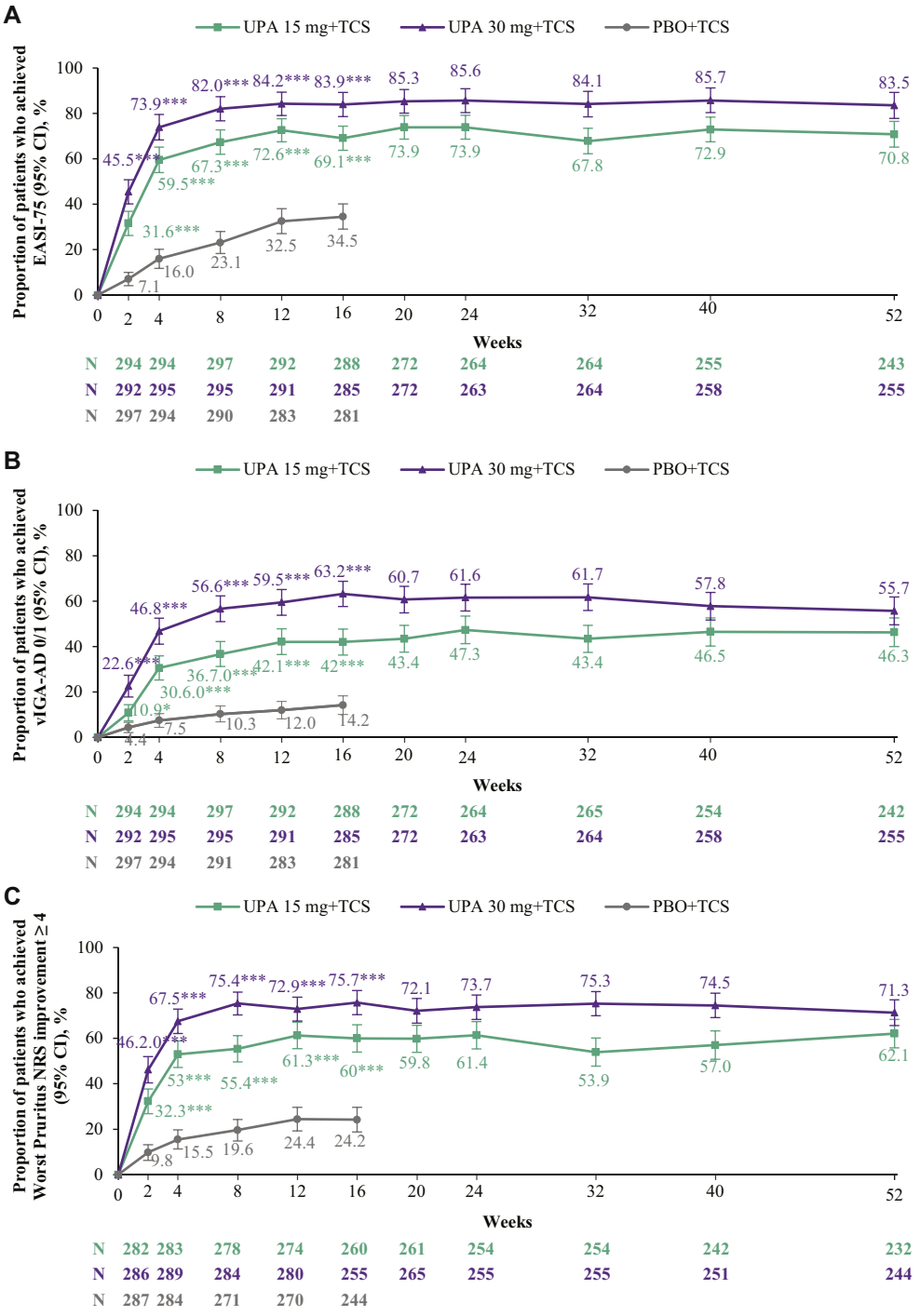

FIG E4. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥4 (ITT population, OC). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

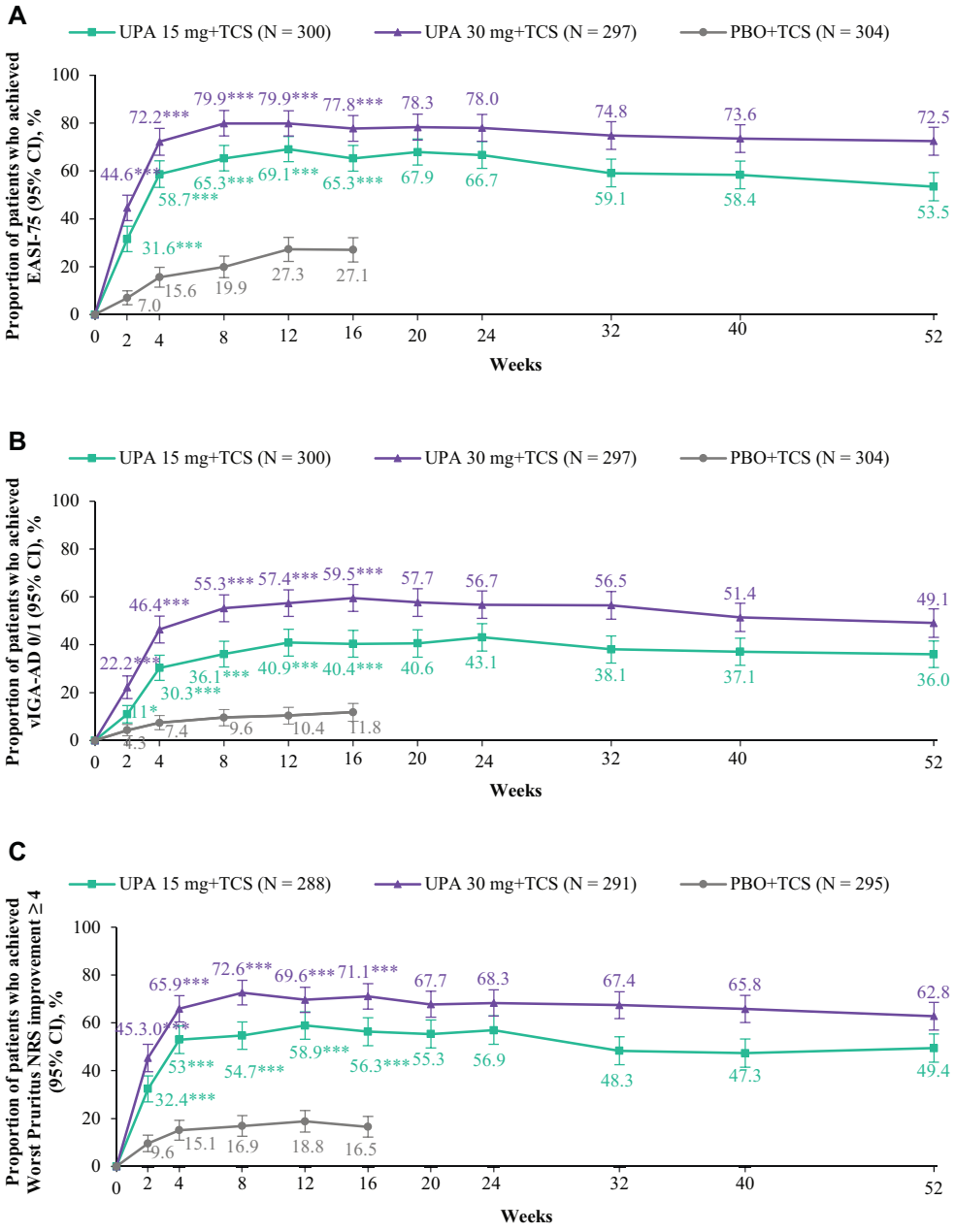

FIG E5. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥4 (ITT population, MI). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *UPA*, upadacitinib.

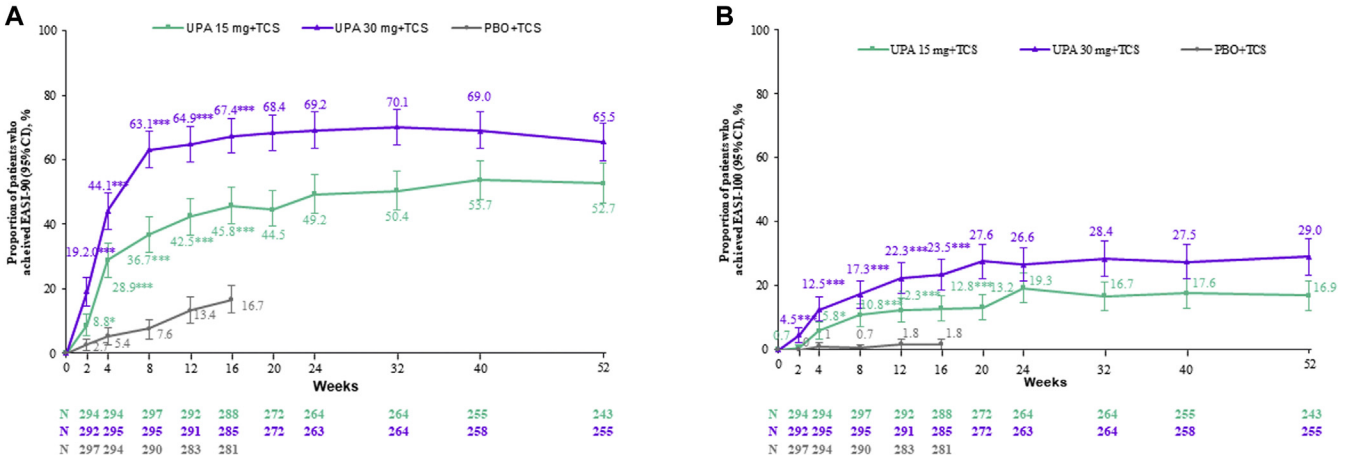

FIG E6. Efficacy over time for (**A**) EASI-90 and (**B**) EASI-100 (ITT population, OC). *ITT*, Intention to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

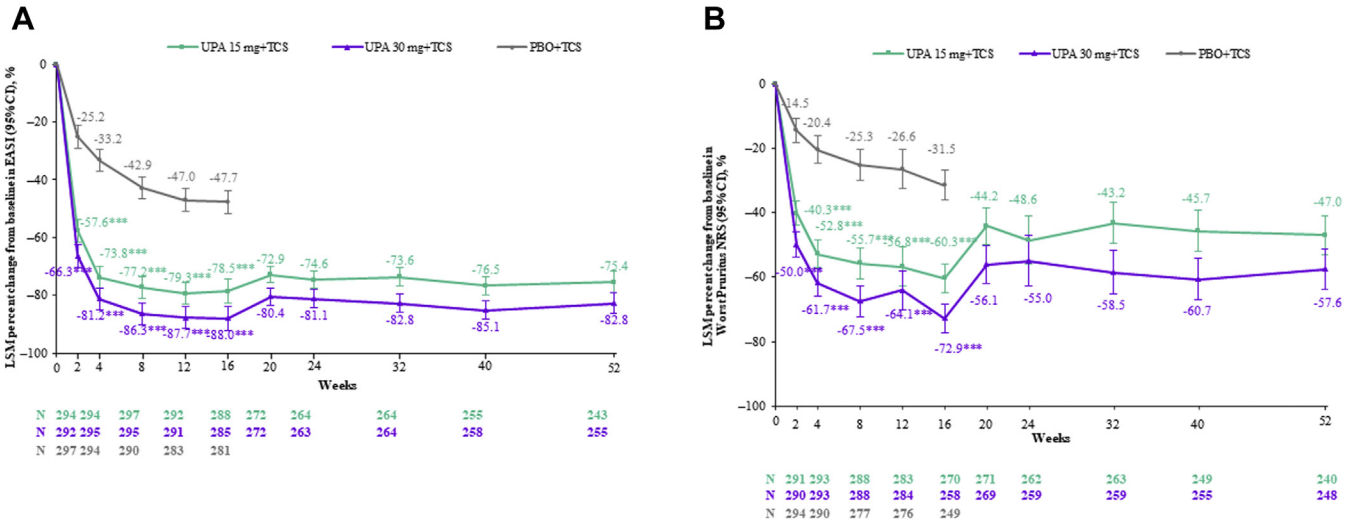

FIG E7. Efficacy over time for (**A**) percentage change from baseline in EASI and (**B**) percentage change from baseline in WP-NRS (ITT population, OC). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

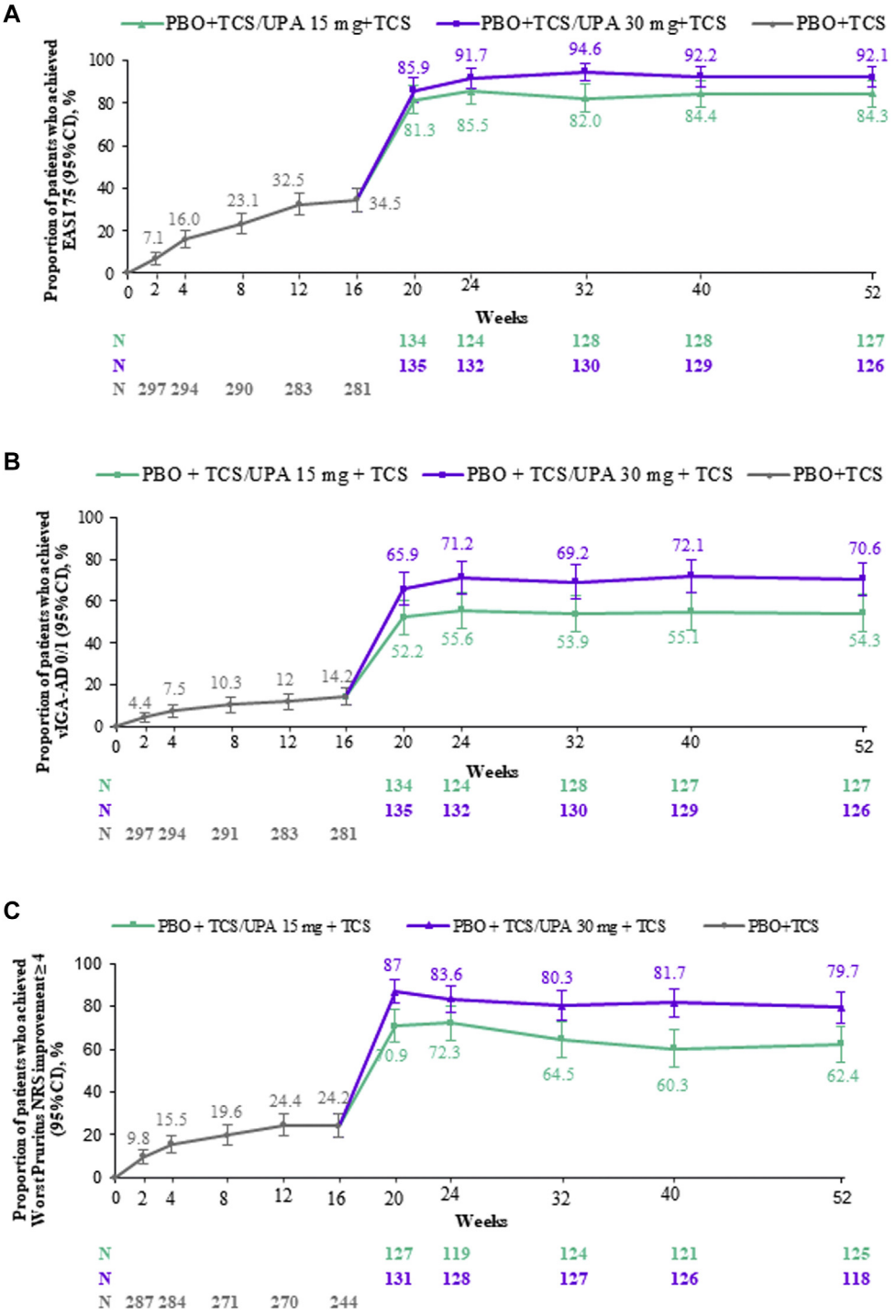

FIG E8. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥4 (ITT population, Crossover group, OC). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

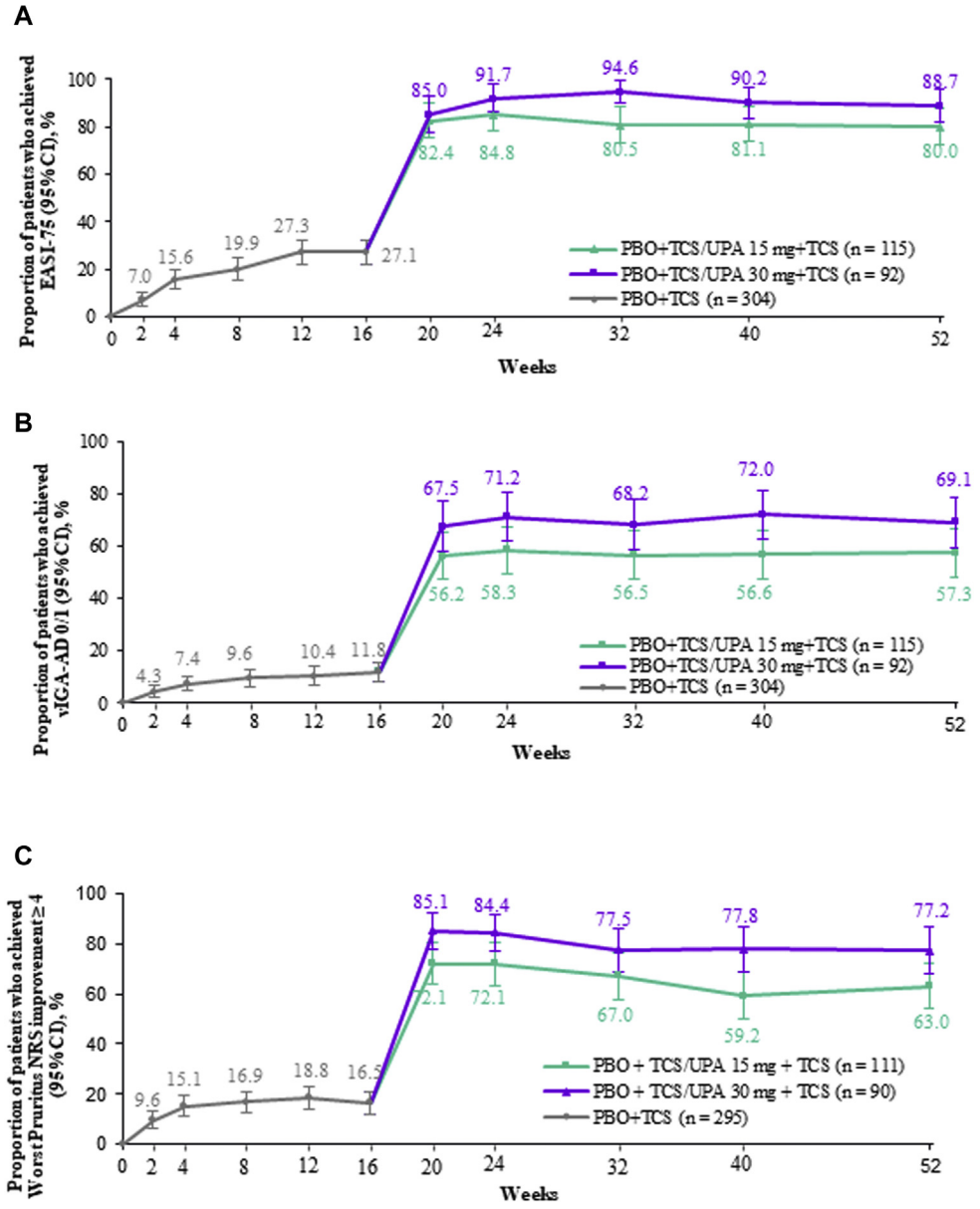

FIG E9. Efficacy over time for (**A**) EASI-75, (**B**) vIGA-AD 0/1, and (**C**) WP-NRS improvement ≥4 (ITT population, Crossover group, MI). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *UPA*, upadacitinib.

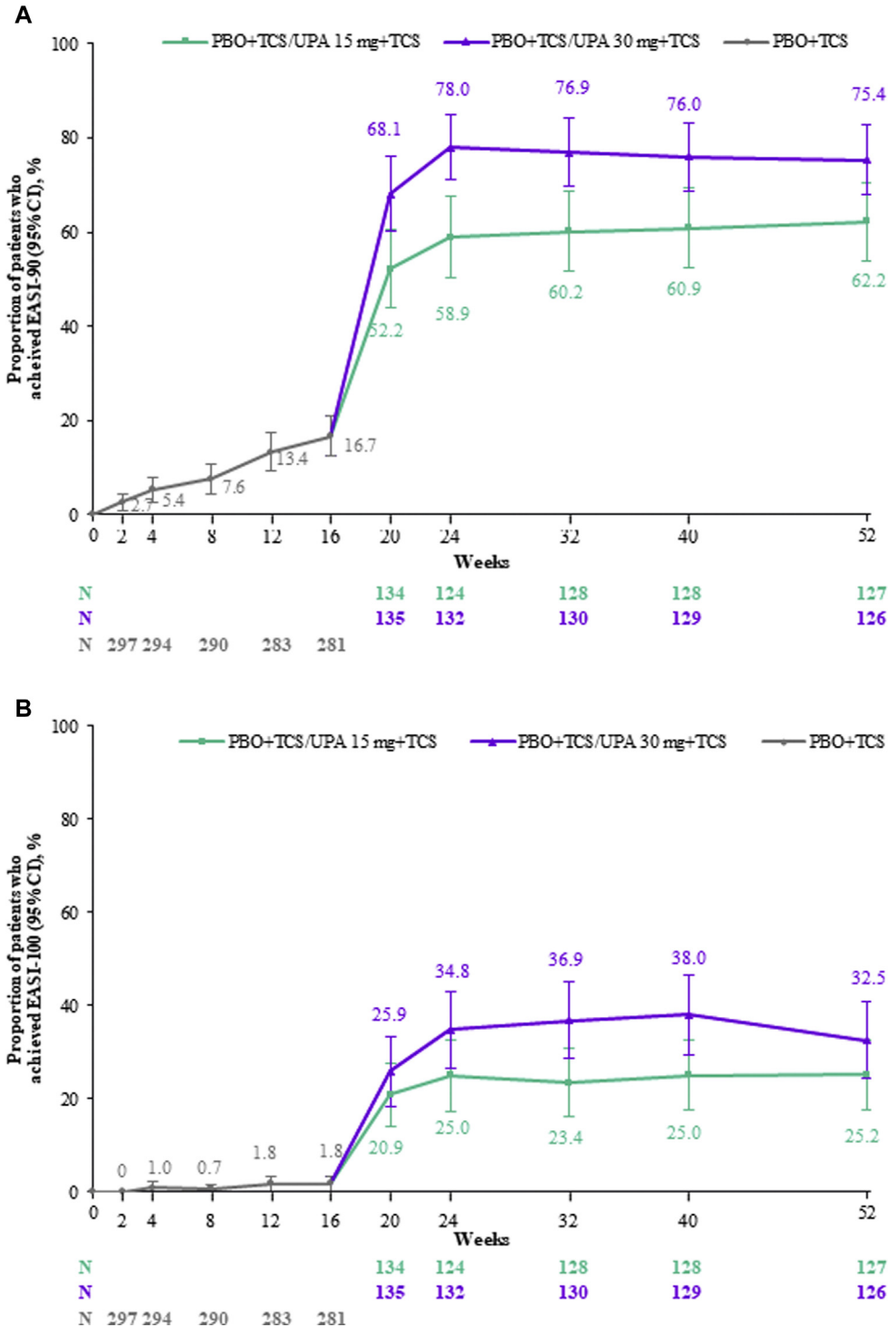

FIG E10. Efficacy over time for (**A**) EASI-90 and (**B**) EASI-100 (ITT population, Crossover group, OC). *ITT*, Intention to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

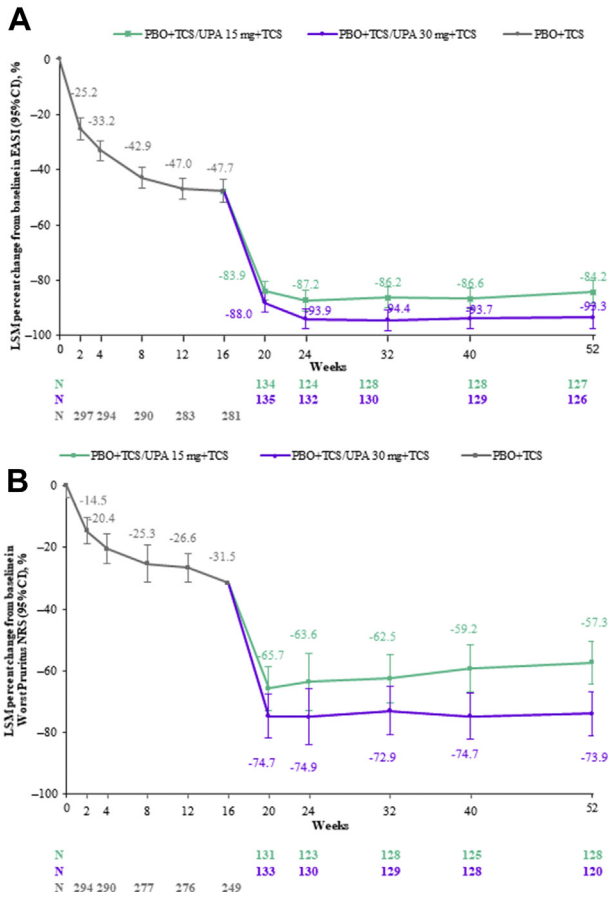

FIG E11. Efficacy over time for (**A**) percentage change from baseline in EASI and (**B**) percentage change from baseline in WP-NRS (ITT population, Crossover group, OC). WPNRS data are based on the weekly average. *ITT*, Intent to treat for the main study; *OC*, Observed cases; *UPA*, upadacitinib.

TABLE E1. Patients with missing data due to COVID-19 (ITT population)

End point	Time point	No. of patients with missing data due to COVID-19: Upadacitinib 15 mg + TCS	Upadacitinib 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

		Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS	PBO + TCS/ upadacitinib 15 mg + TCS	PBO + TCS/ upadacitinib 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

ITT, Intent to treat for the main study; *WP-NRS*, Worst Pruritis Numerical Rating Scale.

TABLE E2. Proportion of patients with response at week 16 who then lost response after week 16 up to week 52 (ITT population)

	Upadacitinib 15 mg + TCS			Upadacitinib 30 mg + TCS			PBO + TCS/ upadacitinib 15 mg + TCS			PBO + TCS/ upadacitinib 30 mg + TCS		
Time point	**N**	**n (%)**	**95% CI**	**N**	**n (%)**	**95% CI**	**N**	**n (%)**	**95% CI**	**N**	**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	—

ITT, Intent to treat for main study. Response was defined as experiencing vIGA-AD 0/1 with ≥2 grades of reduction from baseline and EASI-75 at week 16; loss of response was defined as loss of at least 50% of the week 16 EASI response and vIGA-AD score of ≥2 or higher.