# Supplemental Online Content

Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the Measure Up 1 and Measure Up 2 randomized clinical trials. *JAMA Dermatol*. Published online March 9, 2022. doi:10.1001/jamadermatol.2022.0029

This supplemental material has been provided by the authors to give readers additional information about their work.

## Supplemental Methods

### Study Design and Participants

Eligible patients were adolescents (aged 12-17 years, bodyweight ≥40 kg) or adults (aged 18-75 years) with diagnosed AD per Hanifin and Rajka criteria, eligible for systemic therapy (patients with a history of inadequate response to topical AD treatments, patients who were using systemic therapy for AD, or patients for whom topical AD treatments were medically inadvisable), in addition to having ≥10% of body surface area affected by AD, EASI ≥16, validated Investigator's Global Assessment for AD [vIGA-AD] ≥3, and Worst Pruritus Numerical Rating Scale [WP-NRS] ≥4 [weekly average]).

### Procedures

During the double-blind treatment period, patients received oral upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily for 16 weeks. At screening, patients were required to apply an additive-free, bland emollient twice daily for at least 7 days before baseline and during the study until week 16. Patients were required to discontinue systemic atopic dermatitis treatments at least 4 weeks before baseline and discontinue topical corticosteroids or topical calcineurin inhibitors 7 days before baseline.

### Operational Accommodations for COVID-19

With the advent of the coronavirus disease 2019 (COVID-19) pandemic, operational accommodations for clinical trial continuity were incorporated to provide for temporary site disruptions and secure-in-place measures. These included providing for remote visits, using local laboratories to perform sample analyses, and using couriers to deliver the study drug to patients, where allowed and in accord with local regulations. Remote efficacy assessments of the skin were not allowed, and in-person visits were required at baseline and week 16.

**Efficacy End Points Assessed**

The following efficacy end points were assessed at all study visits through week 52: the proportion of patients who achieved ≥75% improvement in Eczema Area and Severity Index (EASI-75), validated Investigator's Global Assessment-Atopic Dermatitis (vIGA-AD) of clear/almost clear with ≥2 grades of improvement (vIGA-AD 0/1), Worst Pruritus Numerical Rating Scale (WP-NRS) improvement ≥4 in patients with WP-NRS ≥4 at baseline, ≥90% improvement in EASI (EASI-90), 100% improvement in EASI (EASI-100), vIGA-AD of 0 with a reduction from baseline of ≥2 points (vIGA-AD 0), and WP-NRS of 0 or 1 in patients with WP-NRS >1 at baseline (WP-NRS 0/1), and the percent change from baseline in EASI and WP-NRS. The following patient-reported outcomes were also assessed: improvement (reduction) in Dermatology Life Quality Index (DLQI) ≥4 in patients with DLQI ≥4 at baseline; DLQI 0/1 in patients with DLQI >1 at baseline; Hospital Anxiety and Depression Scale (HADS) for anxiety (HADS-A) <8 and depression (HADS-D) <8 in patients with HADS-A ≥8 or HADS-D ≥8 at baseline; and improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) Sleep ≥12 in patients with ADerm-IS Sleep ≥12 at baseline, Emotional State ≥11 in patients with ADerm-IS Emotional State ≥11 at baseline, and Daily Activities ≥14 in patients with ADerm-IS Daily Activities ≥14 at baseline. Among responders, defined as patients who achieved EASI-75 and vIGA-AD 0/1 at week 16, the proportion of patients who experienced a loss of response after week 16 up to week 52 was assessed at each study visit and overall; loss of response was defined as reduction of ≥50% of week 16 EASI response and vIGA-AD score ≥2 after week 16. The proportion of patients who achieved EASI-75 at week 16 (responders) and maintained EASI-75 response at week 52, and the proportion of patients who did not achieve EASI-75 at week 16 (nonresponders) and did achieve EASI-75 at week 52 were also assessed.

**Safety Assessments**

Treatment-emergent adverse events were defined as any adverse event that began or worsened in severity after the first dose of study drug, but within 30 days after the last dose. All adverse events of special interest were prespecified on the basis of previous observations in patients treated with upadacitinib or other JAK inhibitors. Mean change from baseline and the proportion of patients who met criteria for potentially clinically

significant laboratory assessments (ie, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade 3 or higher, and increase in NCI CTCAE grade from baseline) and vital signs were also recorded.

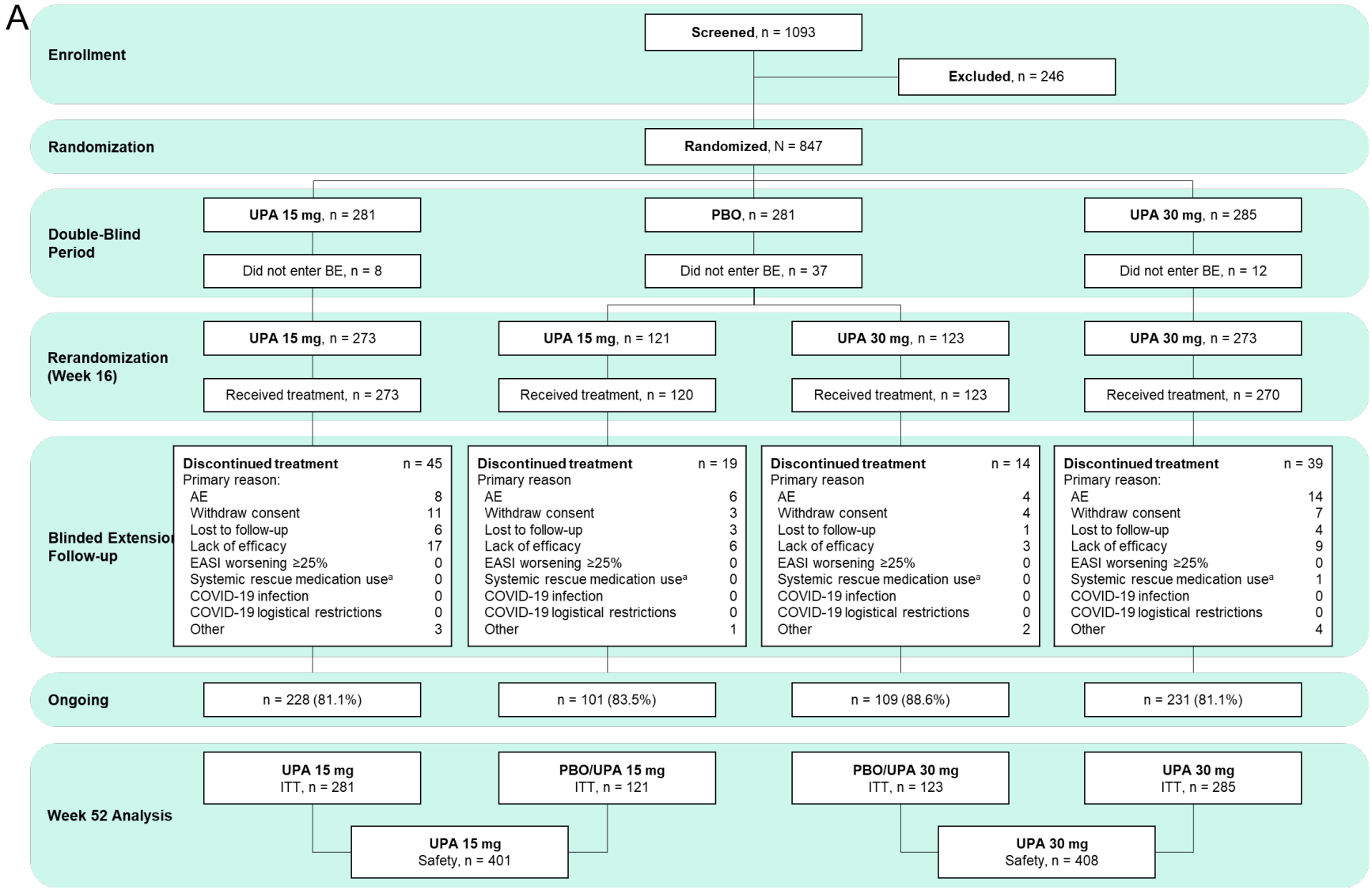
**Additional Statistical Analyses**

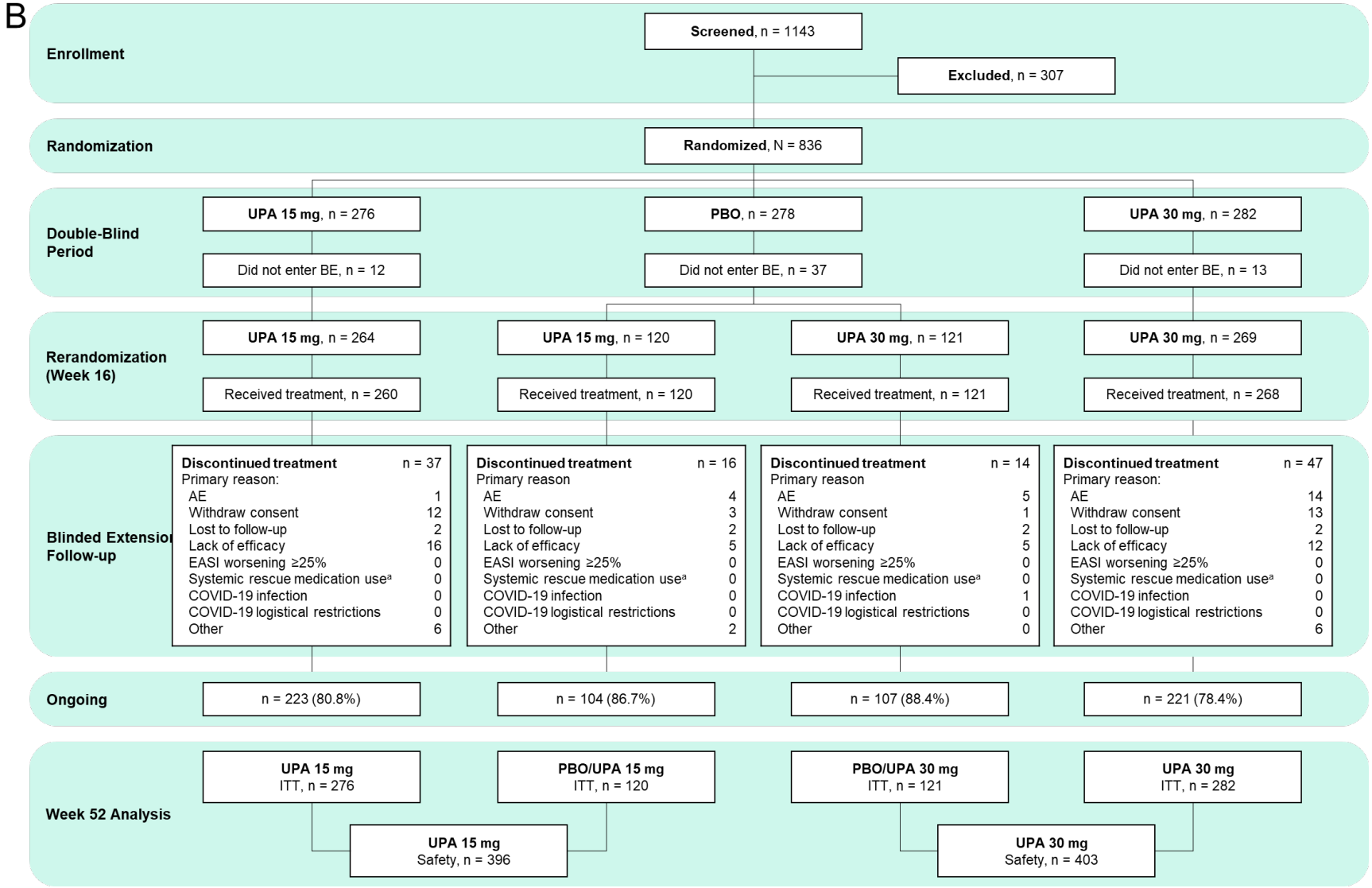
On the basis of findings from previous trials, a sample size of 810 adolescent and adult patients (270 per treatment group) was required to provide at least 90% power to detect a 32% difference in EASI-75 response rates between either upadacitinib dose and placebo, and a 21% difference in vIGA-AD response rates between either upadacitinib dose and placebo, at a two-sided 5% significance level.

For continuous end points, percent change from baseline was analyzed using the mixed-effects model for repeated measures, which included categorical fixed effects of treatment, visit, and treatment-by-visit interaction; the continuous fixed covariates of baseline measurement; stratification factors of vIGA-AD at randomization (moderate, severe) and age group for the double-blinded period; and ≥50% improvement in EASI (EASI-50) response at week 16 and age group for the masked extension period up to week 52.

For categorical end points, multiple imputation (MI) analysis was also performed: missing values were imputed using the Markov Chain Monte Carlo method and SAS PROC MI (SAS Institute, Cary, NC), and included the following variables: treatment group, major stratum (vIGA-AD categories [for non–vIGA-AD-related endpoints], age group, and region), gender, and measurements at baseline and each visit in the double-blinded Period. The variables to be included in the imputation model for the blind extension (BE) period are treatment group, major stratum (EASI 50 responder [Yes/No], age [adolescent vs adult] if applicable, and regions), gender, study, and measurements at baseline and each visit in the BE period up to week 52. For response rates, 95% CIs were based on a Student's *t* distribution using SAS PROC MIANALYZE (SAS Institute). All assessments after the start of rescue medications were not included in the analyses; patients were counted as nonresponders after receiving rescue medication and data were not imputed by MI.

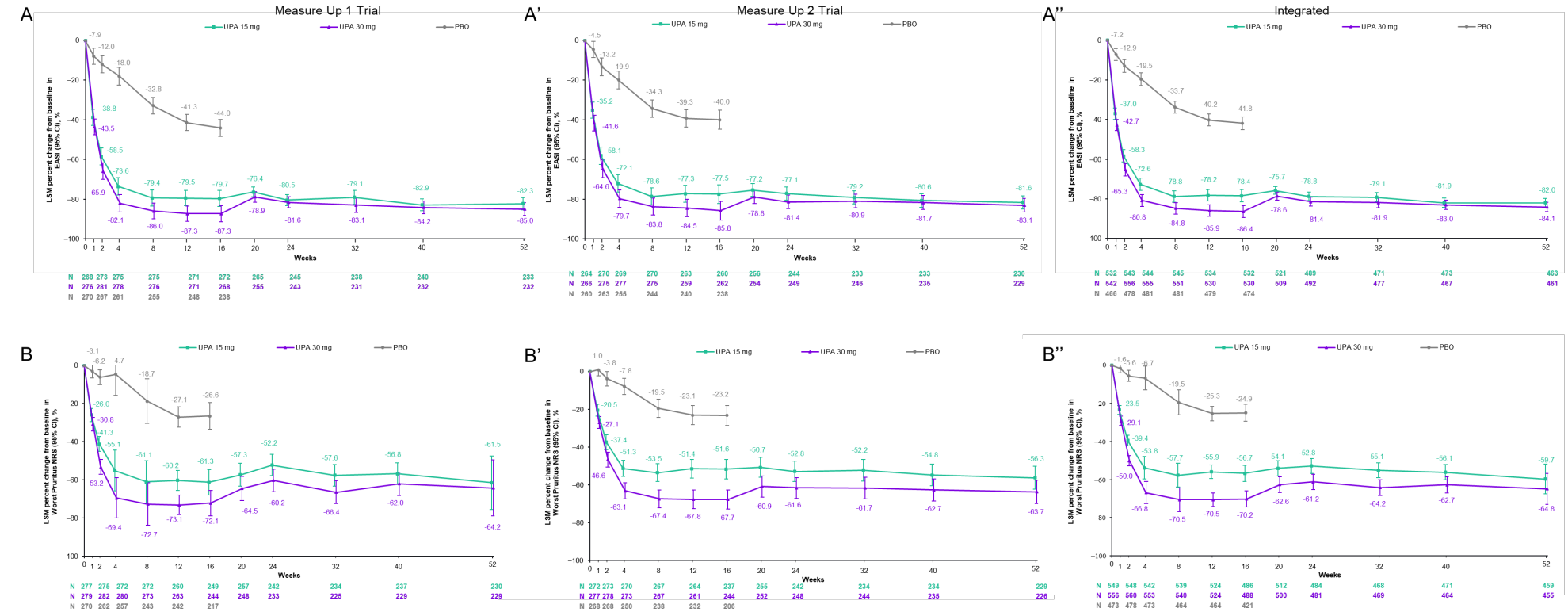
## eFigure 1. Patient Disposition






A, Measure Up 1 trial. B, Measure Up 2 trial.
Abbreviations: AE, adverse event; BE, blinded extension; COVID-19, coronavirus 2019; EASI, Eczema Area and severity Index; ITT, intent to treat in the main study; PBO, placebo; UPA, upadacitinib.

**eFigure 2. Efficacy Over Time: A, percent Change From Baseline in EASI and B, Percent Change From Baseline in Worst Pruritus NRS[a] Through Week 52 (ITT Population and Integrated[b] Data, OC Analysis)**



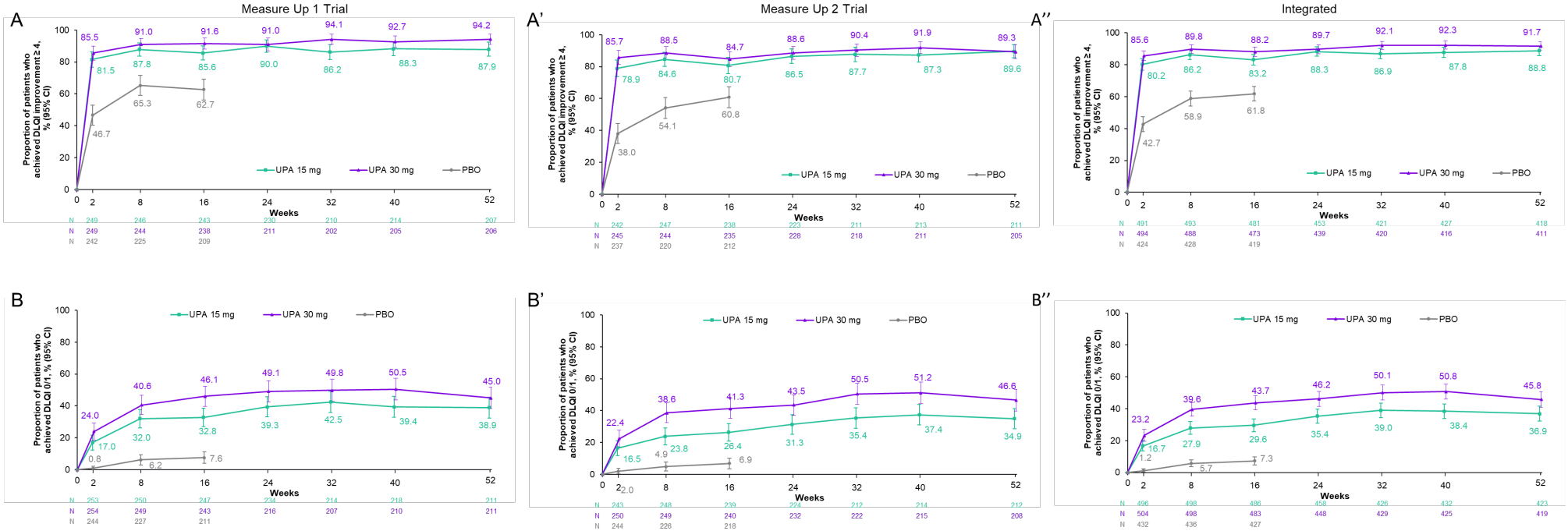

A, Least squares mean (95% CI) percent change in EASI; B, worst pruritus NRS in the Measure Up 1 trial; A' and B', Measure Up 2 trial; A'' and B'', integrated data set.

[a]Based on weekly average (through week 16); based on study visit (weeks 20 through 52).

[b]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI 75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; NRS, Numerical Rating Scale; OC, observed case; PBO, placebo; UPA, upadacitinib.

**eFigure 3. Efficacy Over Time: A, DLQI Improvement ≥4[a]; B, DLQI 0/1[b] Through Week 52 (ITT Population and Integrated[c] Data, OC Analysis)**




A, Response rates at each visit for DLQI improvement ≥4; B, DLQI 0/1 in the Measure Up 1 trial; A' and B', Measure Up 2 trial; and A'' and B'', integrated data set.

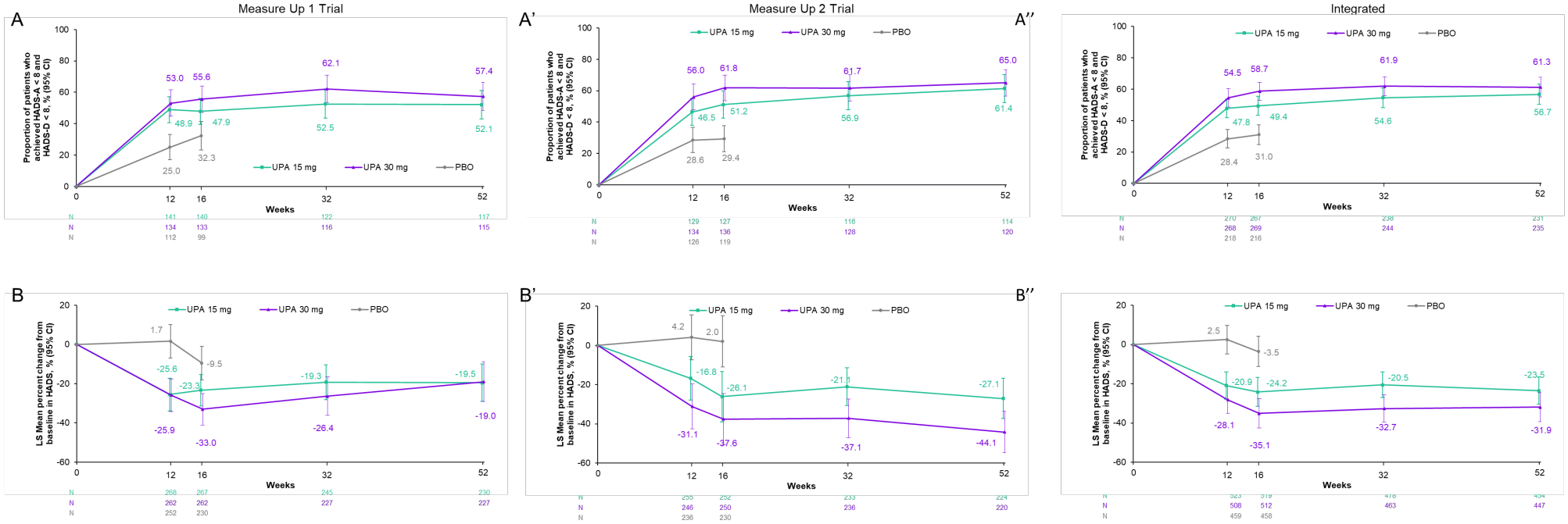
[a]In patients with DLQI ≥4 at baseline.

[b]In patients with DLQI >1 at baseline.

[c]Data from Measure Up 1 and Measure Up 2 studies.

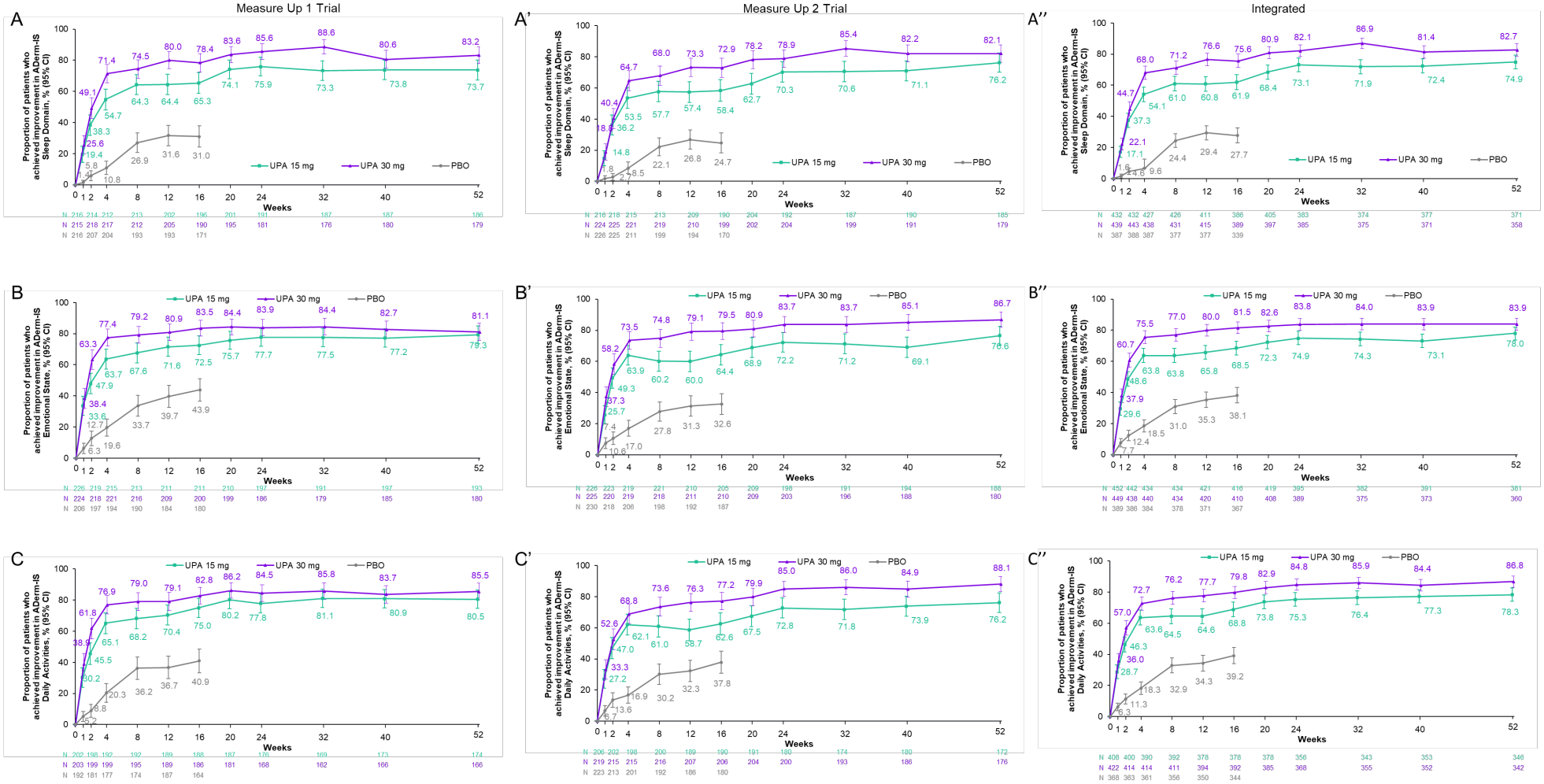
Abbreviations: DLQI, Dermatology Life Quality Index; ITT, intent-to-treat in the main study; PBO, placebo; UPA, upadacitinib.

**eFigure 4. Efficacy Over Time: A, HADS-A <8 and HADS-D <8[a]; B, Percent Change in HADS From Baseline Through Week 52 (ITT Population and Integrated[b] Data, OC Analysis)**




A, Response rates at each visit for HADS-A <8 and HADS-D <8; B, percent change in HADS from baseline in the Measure Up 1 trial; A' and B', Measure Up 2 trial; and A'' and B'', integrated data set.
[a]In patients with HADS-A ≥8 or HADS-D ≥8 at baseline.
[b]Data from Measure Up 1 and Measure Up 2 studies.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale for Anxiety; HADS-D, Hospital Anxiety and Depression Scale for Depression; ITT, intent-to-treat in the main study; OC, observed case; PBO, placebo; UPA, upadacitinib.

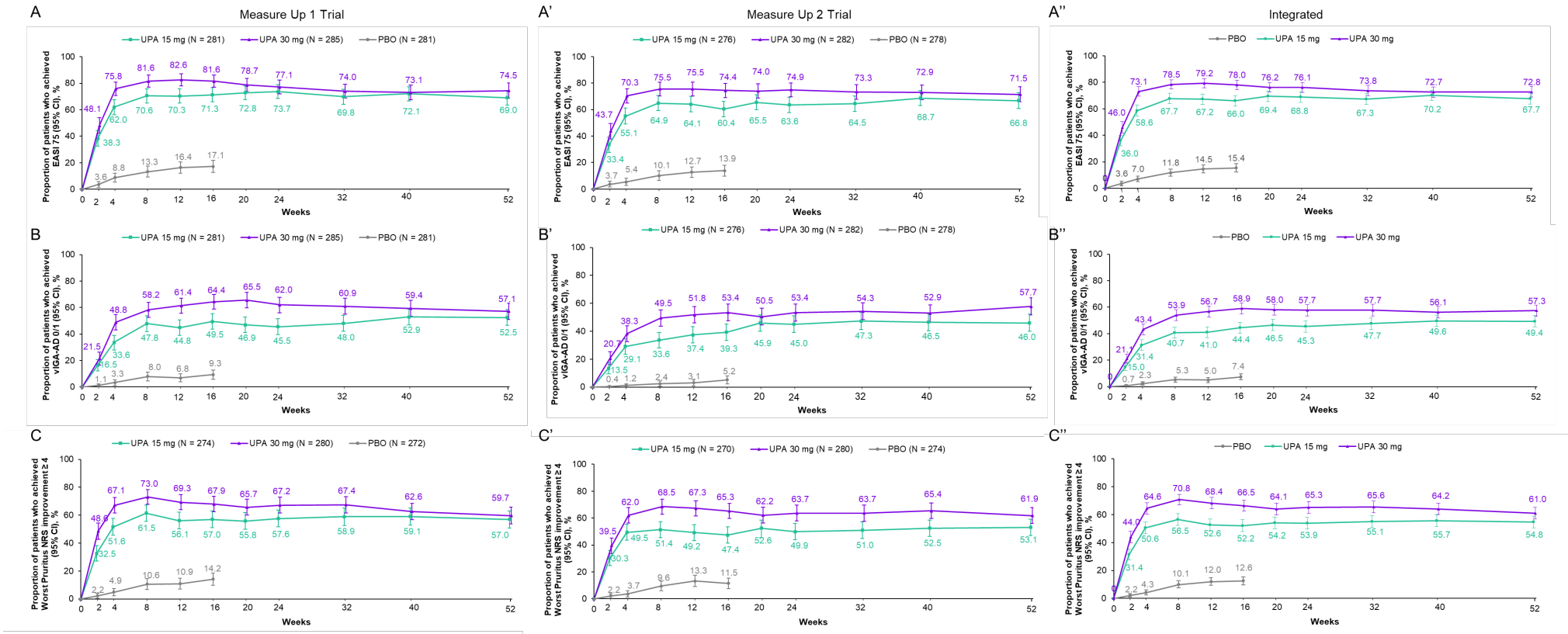
**eFigure 5. Efficacy Over Time: A, ADerm-IS Sleep[a]; B, Emotional State[b]; and C, Daily Activities[c] Through Week 52 (ITT Population and Integrated[d] Data, OC Analysis)**




A, Response rates at each visit for ADerm-IS Sleep domain; B, Emotional State domain; and C, Daily Activities domain in the Measure Up 1 trial; A' and B', Measure Up 2 trial; A'' and B'', integrated data set.
[a]In patients with ADerm-IS Sleep ≥12 at baseline.
[b]In patients with ADerm-IS Emotional State ≥11 at baseline.
[a]In patients with ADerm-IS Daily Activities ≥14 at baseline.
[d]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: ADerm-IS, Atopic Dermatitis Impact Scale; ITT, intent-to-treat in the main study; OC, observed case; PBO, placebo; UPA, upadacitinib.

**eFigure 6. Efficacy Over Time: A, EASI 75; B, vIGA-AD 0/1; and C, Worst Pruritus NRS[a] Improvement ≥4 Through Week 52 (ITT Population and Integrated[b] data, MI analysis)**



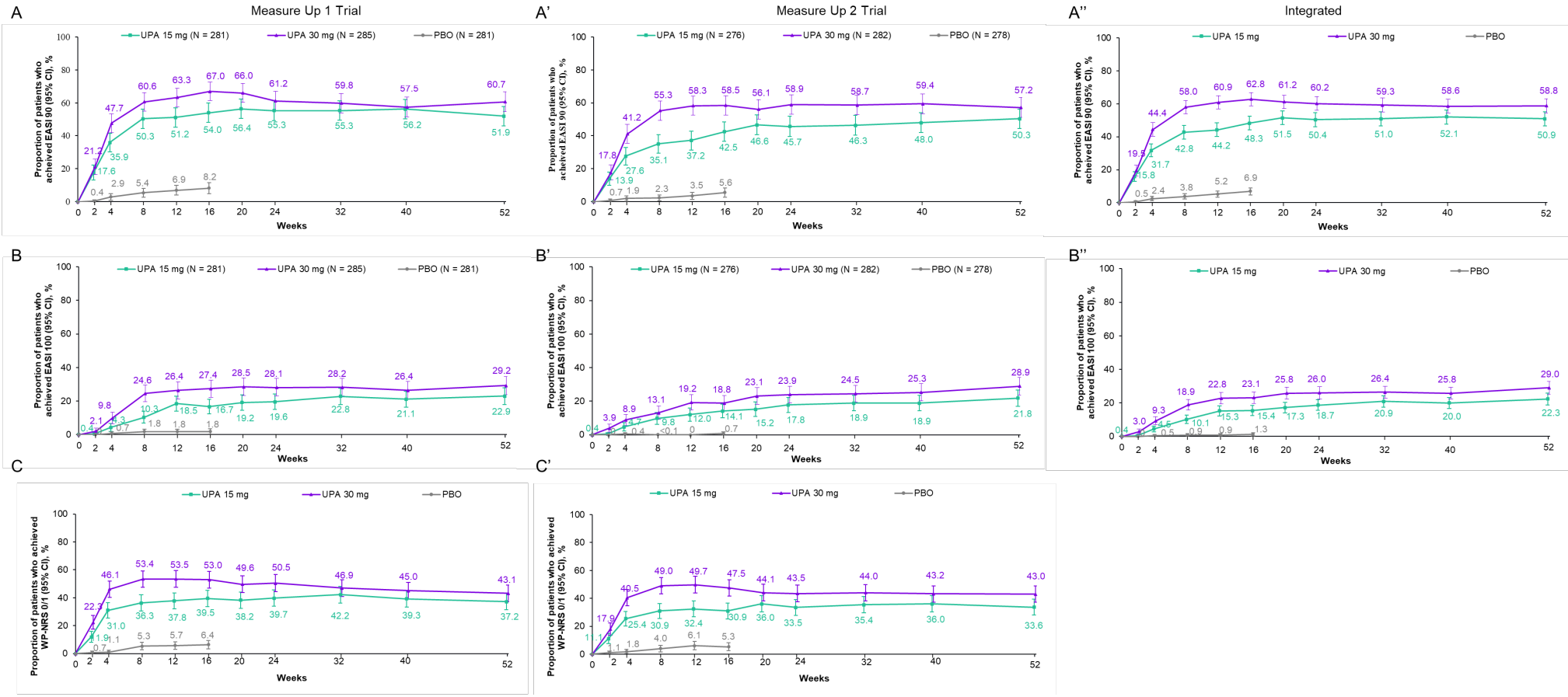

A, Response rates at each visit for EASI 75; B, vIGA-AD 0/1; and C, worst pruritus NRS improvement ≥4 in the Measure Up 1 trial; A', B', and C', Measure Up 2 trial; A'', B'', and C'', integrated data set.

[a]Based on weekly average (through week 16); based on study visit (weeks 20 through 52) for patients with worst pruritus NRS ≥4 at baseline.

[b]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI 75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; MI, multiple imputation; NRS, Numerical Rating Scale; PBO, placebo; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥2 grades of reduction.

**eFigure 7. Efficacy Over Time: A, EASI 90; B, EASI 100; and C, Worst Pruritus NRS 0/1[a] Through Week 52 (ITT Population and Integrated[b] Data, MI Analysis)**



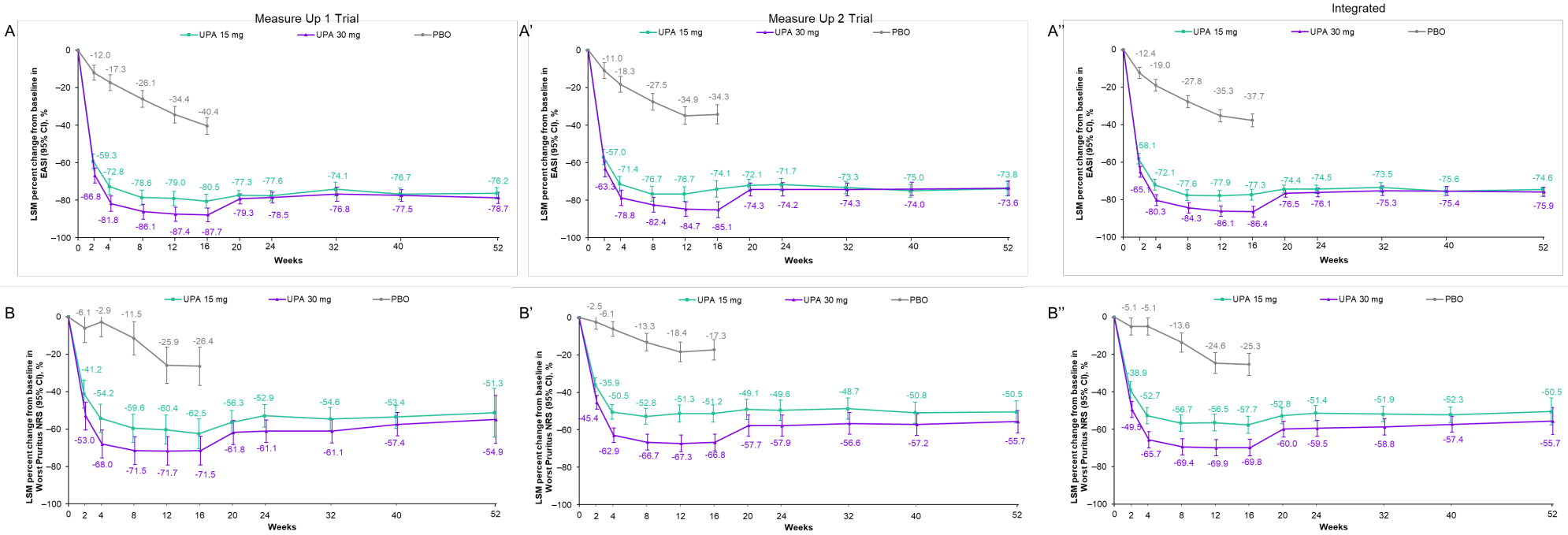

A, EASI 90; B, EASI 100; and C, worst pruritus NRS 0/1 in the Measure Up 1 trial; A', B', and C', in Measure Up 2 trial; and A'' and B'', integrated data set.

[a]For patients with worst pruritus NRS >1 at baseline.

[b]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI 90/100, ≥90%/100% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; MI, multiple imputation; NRS, Numerical Rating Scale; PBO, placebo; UPA, upadacitinib.

**eFigure 8. Efficacy Over Time: A, Percent Change From Baseline in EASI; B, Percent Change From Baseline in Worst Pruritus NRS[a] Through Week 52 (ITT Population and Integrated[b] Data, MMRM Analysis)**



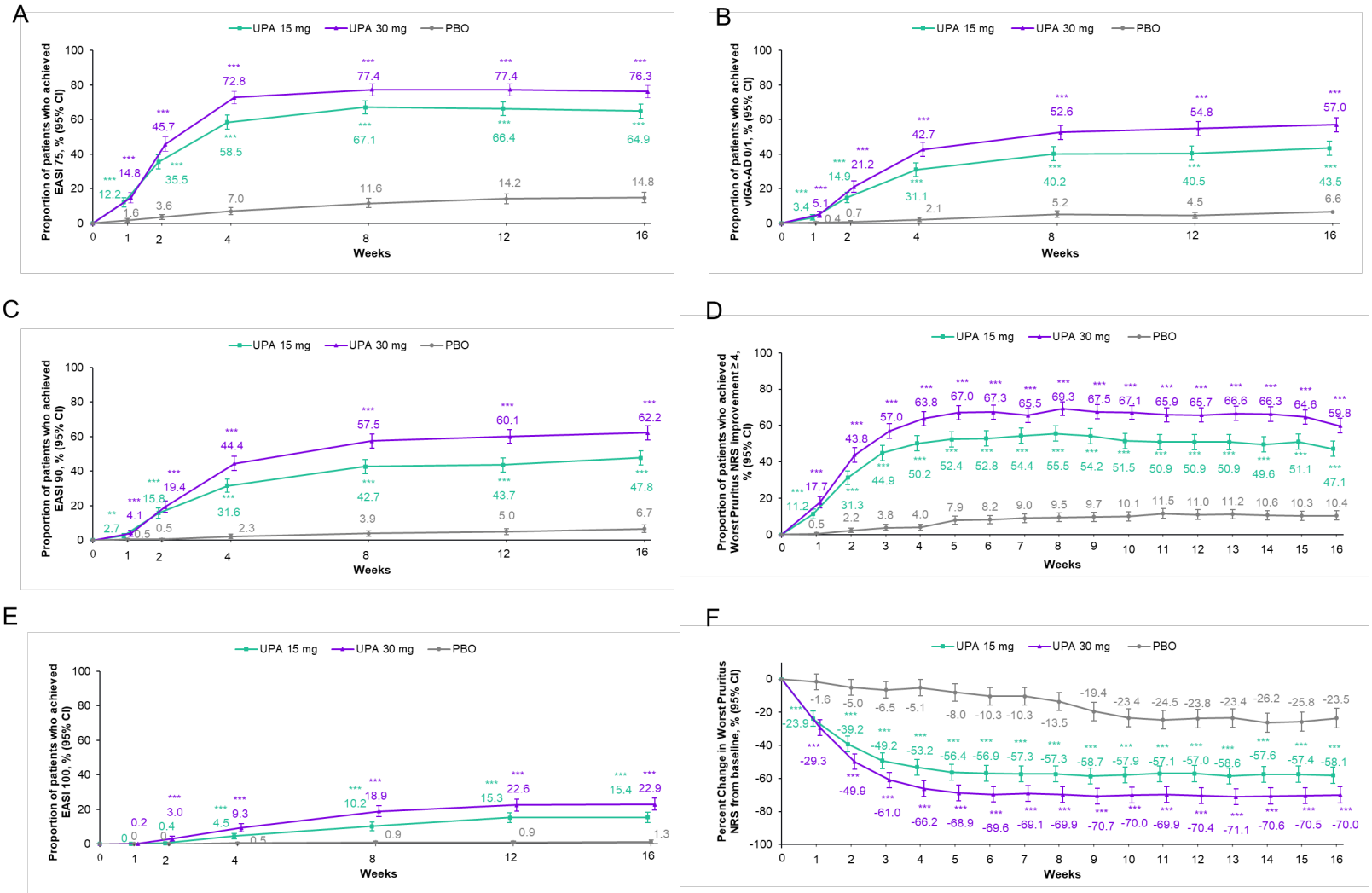

A, Least squares mean (95% CI) percent change in EASI; B, worst pruritus NRS in the Measure Up 1; A' and B', Measure Up 2 trials; and A" and B", integrated data set.

[a]Based on weekly average (through week 16); based on study visit (weeks 20 through 52).

[b]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI, Eczema Area and Severity Index; ITT, intent to treat for the main study; LSM, least squares mean; MMRM, mixed-model repeated measure; NRS, Numerical Rating Scale; PBO, placebo; UPA, upadacitinib.

**eFigure 9. Efficacy Over Time: A, EASI 75; B, vIGA-AD 0/1; C, EASI 90; D, Worst Pruritus NRS[a] Improvement ≥4; E, EASI 100; and F, Percent Change in Worst Pruritus NRS From Baseline by Visit Through Week 16 (Placebo-controlled Population, Integrated[b] Data)**



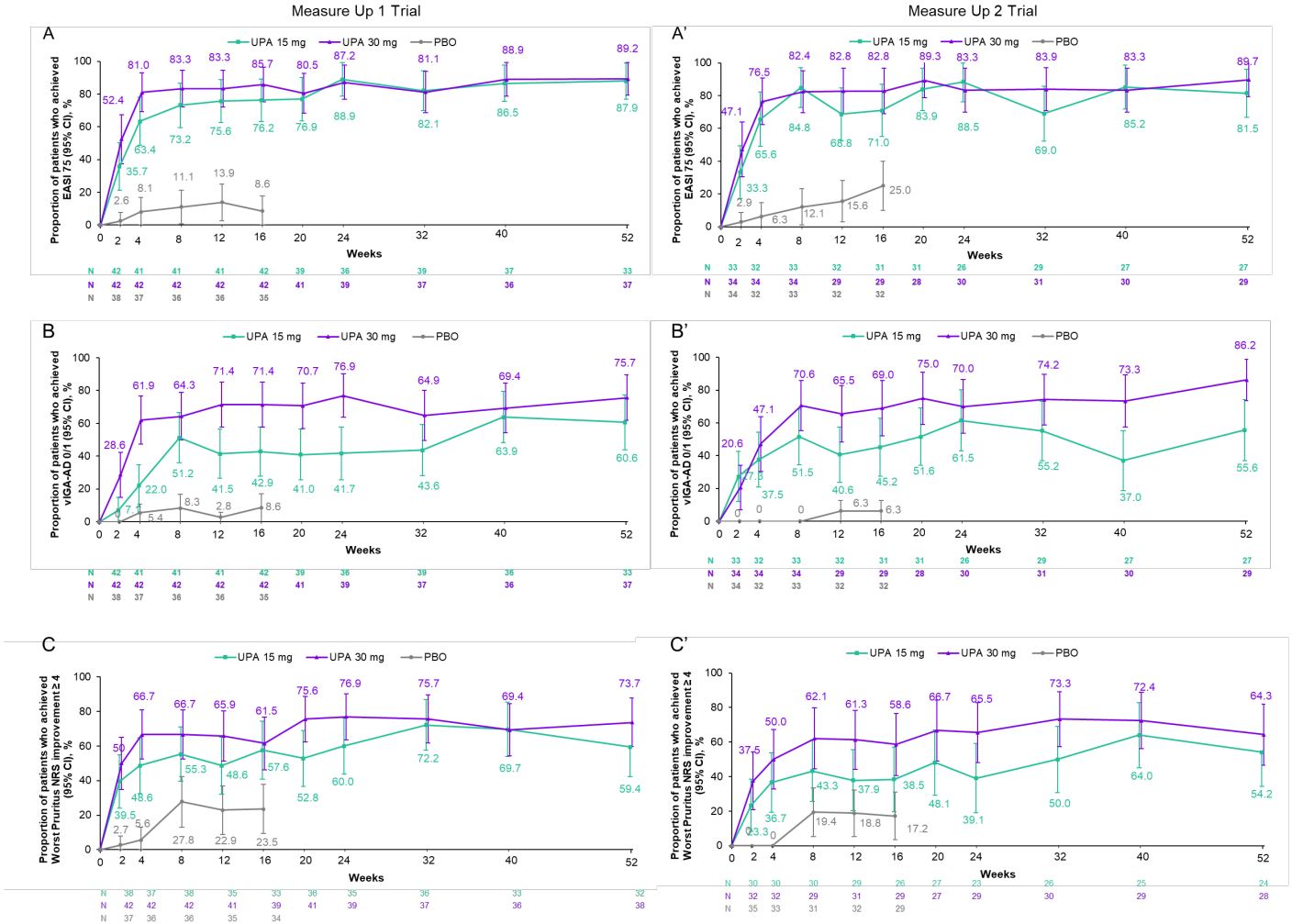

Response rates at each visit for A, EASI 75 (NRI-C); B, vIGA-AD 0/1 (NRI-C); C, EASI 90 (NRI-C); D, worst pruritus NRS improvement ≥4 (NRI-C); E, EASI 100 (NRI-C); and F, percent change in worst pruritus NRS from baseline (MMRM) in the integrated data set from Measure Up 1 and Measure Up 2.

[a]Based on weekly average for patients with worst pruritus NRS ≥4 at baseline.

[b]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI 75/90/100, ≥75%/≥90%/≥100% improvement in Eczema Area and Severity Index; NRI-C, nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19; MMRM, mixed-model repeated measures; NRI-C, nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRS, Numerical Rating Scale; PBO, placebo; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥2 grades of reduction.

**eFigure 10. Efficacy Over Time: A, EASI 75; B, vIGA-AD 0/1; and C, Worst Pruritus NRS[a] Improvement ≥4 Through Week 52 (Adolescent Population, OC Analysis)**

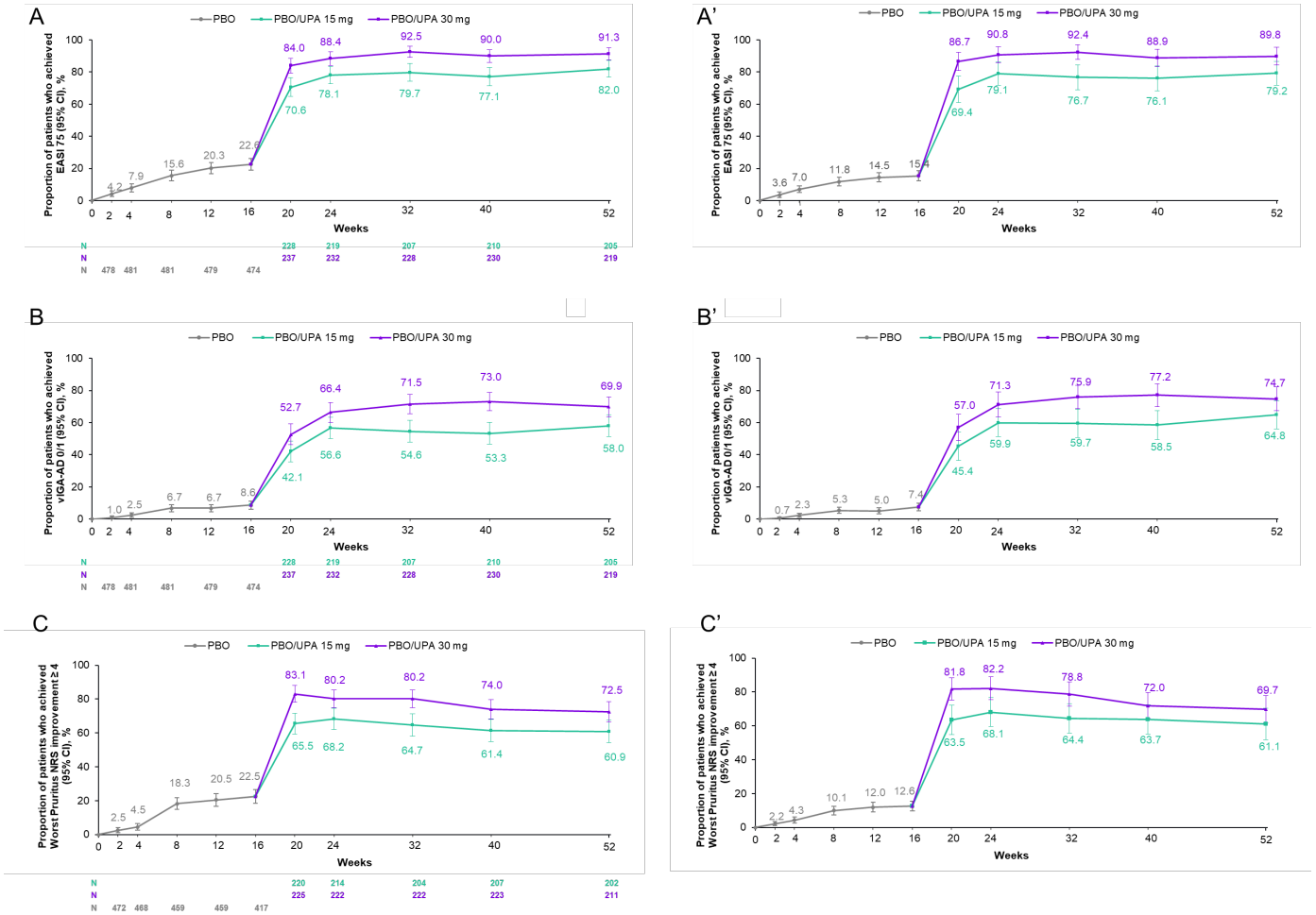



A, Response rates at each visit for EASI 75; B, vIGA-AD 0/1; and C, worst pruritus NRS improvement ≥4 in the Measure Up 1 trial; and A', B', and C', Measure Up 2 trial (OC analysis).

[a]Based on weekly average (through week 16); based on study visit (weeks 20 through 52) for patients with worst pruritus NRS ≥4 at baseline.

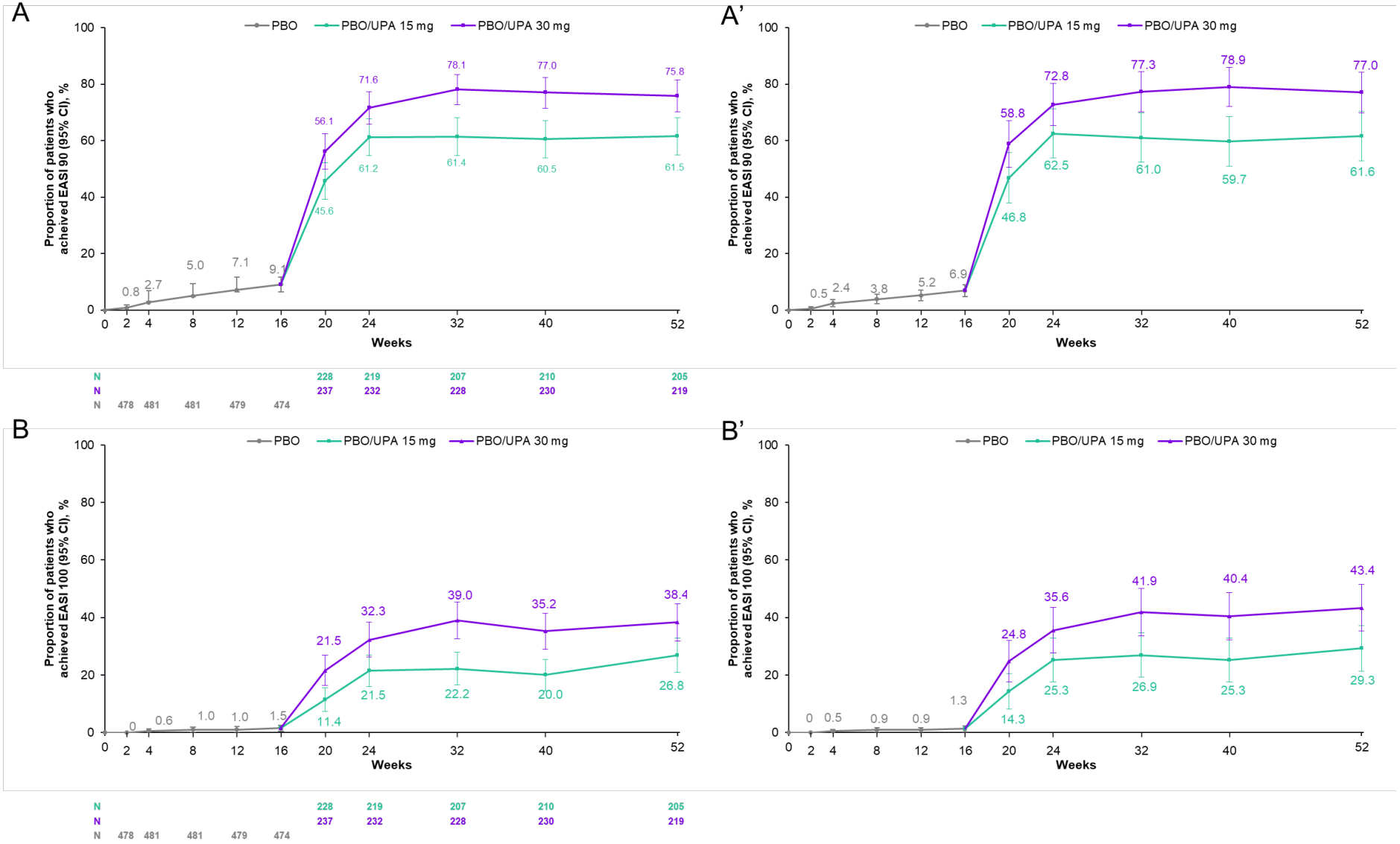
Abbreviations: EASI 75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent to treat for the main study; MI, multiple imputation; NRI-C, nonresponder imputation incorporating Multiple Imputation to handle missing data due to COVID-19; NRS, Numerical Rating Scale; OC, observed case; PBO, placebo; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥ 2 grades of reduction.

**eFigure 11. Efficacy Over Time for Crossover Cohort[a]: A, EASI 75; B, vIGA-AD 0/1; and C, Worst Pruritus NRS[b] Improvement ≥4 Through Week 52 (Integrated[c] Data, OC and MI Analysis)**




A, Response rates at each visit for EASI 75; B, vIGA-AD 0/1; and C, worst pruritus NRS improvement ≥4 OC analysis; A', B', and C', MI analysis.
[a]Data from patients treated with placebo from weeks 1–16, then rerandomized at week 16 to receive UPA 15 mg or UPA 30 mg from weeks 16–52.
[b]Based on weekly average (through week 16); based on study visit (weeks 20 through 52) for patients with worst pruritus NRS ≥4 at baseline.
[c]Data from Measure Up 1 and Measure Up 2 studies.
Abbreviations: EASI 75, ≥75% improvement in Eczema Area and Severity Index; MI, multiple imputation; NRS, Numerical Rating Scale; PBO, placebo; OC, observed case; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥2 grades of reduction.

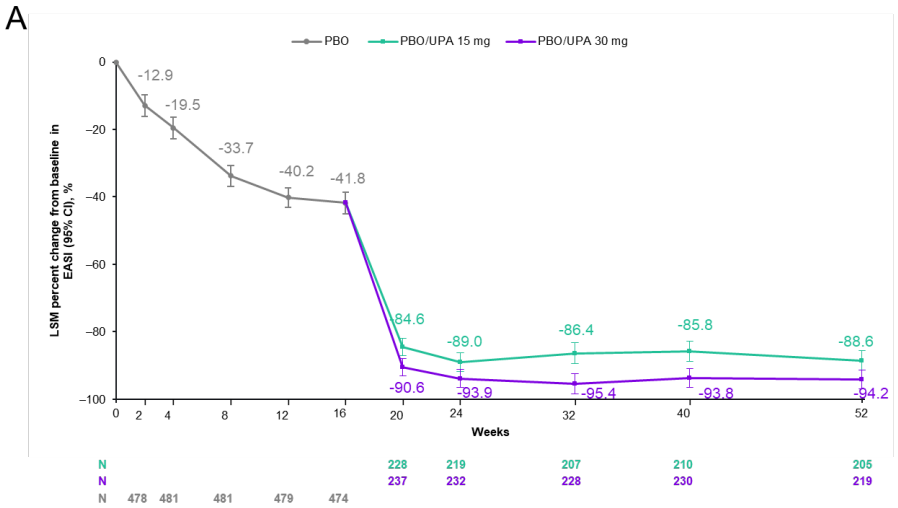
**eFigure 12. Efficacy Over Time for Crossover Cohort[a]: A, EASI 90; B, EASI 100 Through Week 52 (Integrated[b] Data, OC and MI Analyses)**

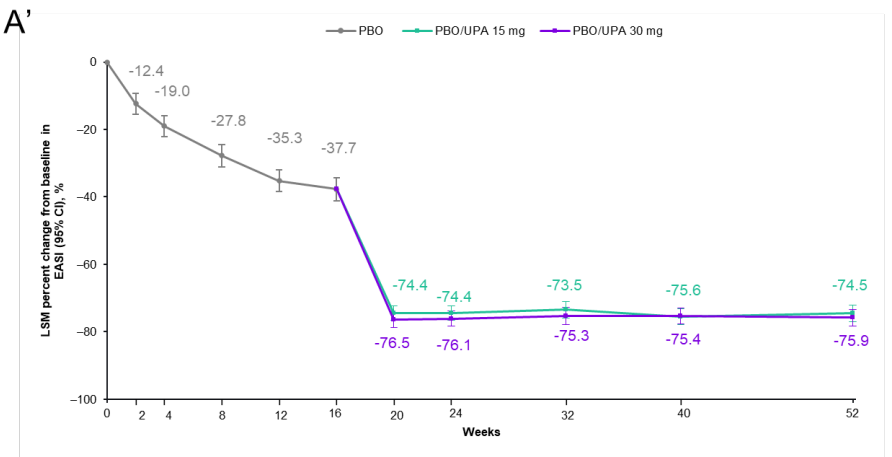


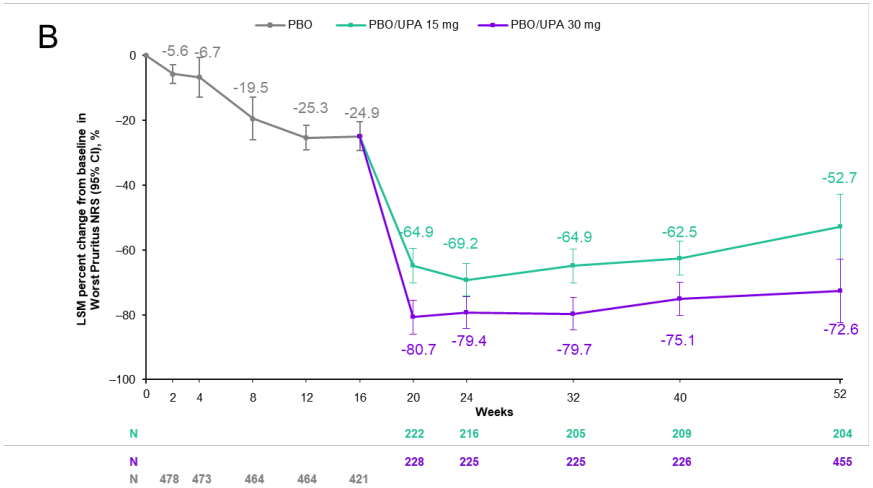

A, EASI 90; B, EASI 100 in OC analysis; A' and B', MI analysis.
[a]Data from patients treated with placebo from weeks 1–16, then rerandomized at week 16 to receive UPA 15 mg or UPA 30 mg from weeks 16–52.
[b]Data from Measure Up 1 and Measure Up 2 studies.

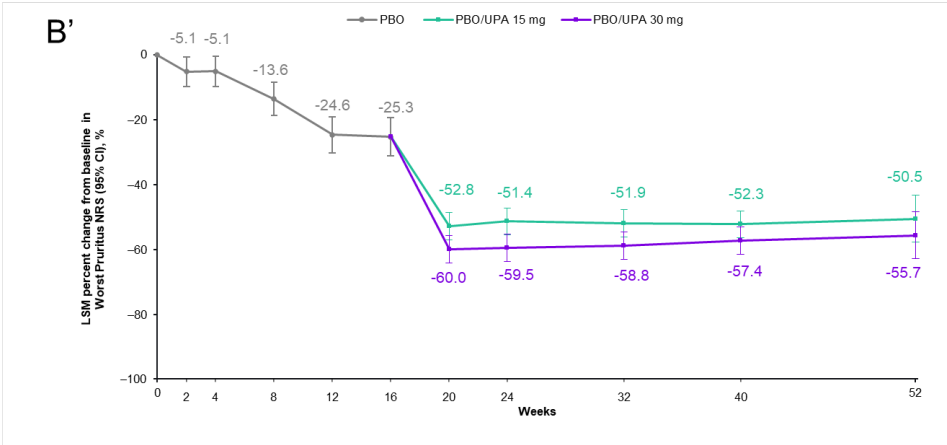
Abbreviations: EASI 90/100, ≥90%/100% improvement in Eczema Area and Severity Index; MI, multiple imputation; OC, observed case; PBO, placebo; UPA, upadacitinib.

**eFigure 13. Efficacy Over Time for Crossover Cohort[a]: A, Percent Change From Baseline in EASI; B, Percent Change From Baseline in Worst Pruritus NRS[b] Through Week 52 (Integrated[c] Data, OC and MMRM Analyses)**



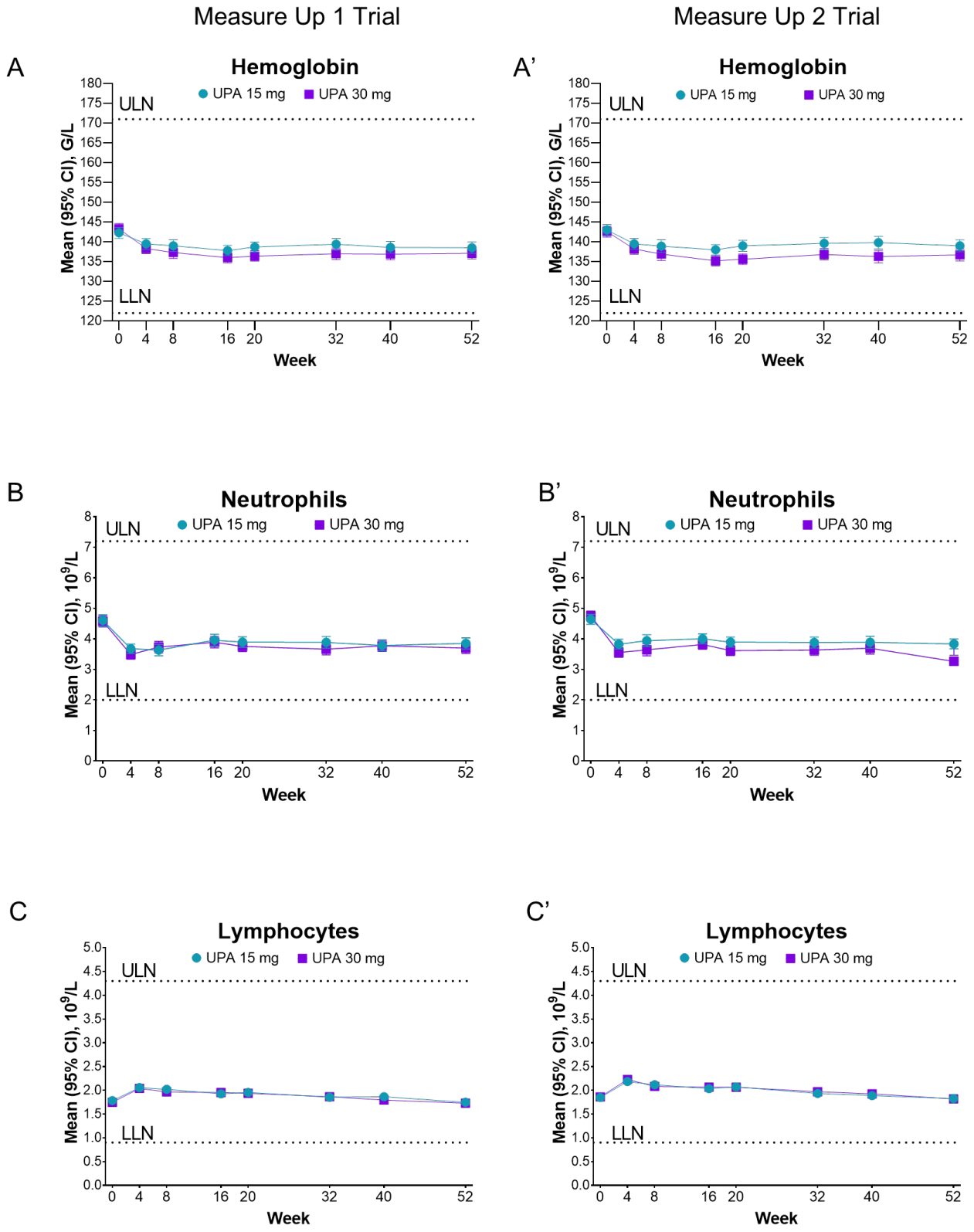



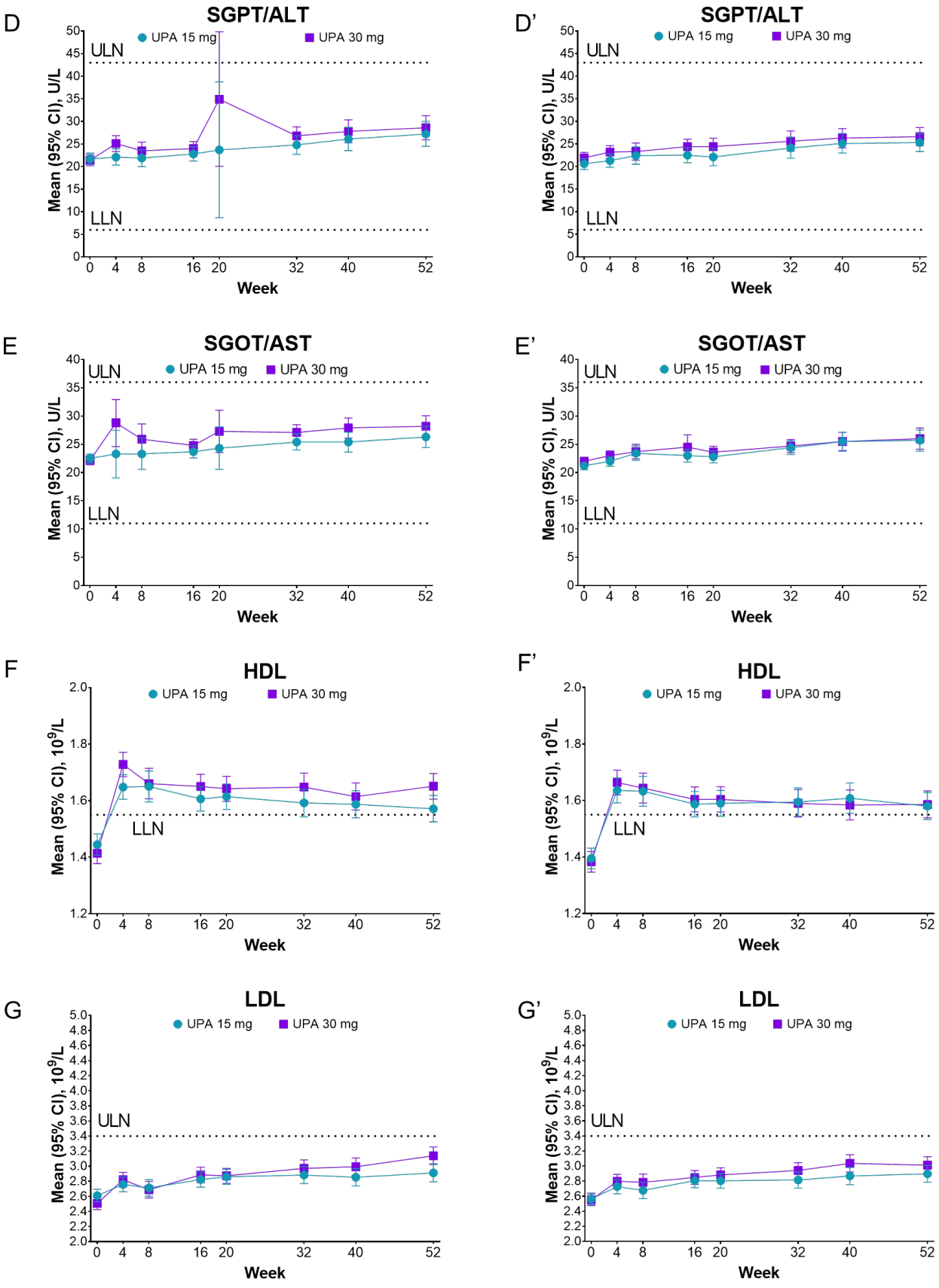




A, Least squares mean (95% CI) percent change in EASI; B, worst pruritus NRS in the OC and MMRM analyses (A' and B').
[a]Data from patients treated with placebo from weeks 1–16, then rerandomized at week 16 to receive UPA 15 mg or UPA 30 mg from weeks 16–52.
[b]Based on weekly average (through week 16); based on study visit (weeks 20 through 52).
[c]Data from Measure Up 1 and Measure Up 2 studies.

Abbreviations: EASI, Eczema Area and Severity Index; LSM, least squares mean; MMRM, mixed-model repeated measure; NRS, Numerical Rating Scale; OC, observed case; PBO, placebo; UPA, upadacitinib.

**eFigure 14. Hematology and Chemistry Parameters Over Time Through Week 52 (ITT Population)**





A, Mean (95% CI) hemoglobin; B, neutrophils; C, lymphocytes; D, ALT; E, AST; F, HDL; and G, LDL in Measure Up 1 and (A' – G') Measure Up 2 trials.
Summaries presented for patients who had both baseline and postbaseline values. Baseline was defined as the last nonmissing observation on or before the first dose date of upadacitinib dose. Visit mean and 95% CI are based on analysis of variance model with treatment as a fixed factor.
In panel D, the elevated value at week 20 related to a patient who had a markedly elevated ALT of 4068 U/L that was due to acute hepatitis B.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; ITT, intent to treat for the main study; LDL, low-density lipoprotein; LLN, lower limit of normal; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal; UPA, upadacitinib.

**eTable 1. Treatment-emergent Adverse Events Through Week 16 (Safety Population[a])**

| Events (events/100 PY) | 15 mg UPA | | | 30 mg UPA | | | PBO | | |
|---|---|---|---|---|---|---|---|---|---|
| | Measure Up 1 (N = 281) | Measure Up 2 (N = 276) | Combined (N = 557) | Measure Up 1 (N = 285) | Measure Up 2 (N = 282) | Combined (N = 567) | Measure Up 1 (N = 281) | Measure Up 2 (N = 278) | Combined (N = 559) |
| | PY = 85.1 | PY = 82.8 | PY = 167.9 | PY = 85.2 | PY = 84.7 | PY = 169.9 | PY = 78.8 | PY = 77.2 | PY = 156.0 |
| Any TEAE | 451 (529.9) | 419 (506.0) | 870 (518.1) | 620 (727.8) | 462 (545.7) | 1082 (637.0) | 382 (484.8) | 328 (424.9) | 710 (455.2) |
| Serious AEs | 6 (7.0) | 7 (8.5) | 13 (7.7) | 8 (9.4) | 9 (10.6) | 17 (10.0) | 8 (10.2) | 10 (13.0) | 18 (11.5) |
| AEs leading to D/C of study drug | 6 (7.0) | 11 (13.3) | 17 (10.1) | 14 (16.4) | 8 (9.4) | 22 (13.0) | 12 (15.2) | 12 (15.5) | 24 (15.4) |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AESIs | | | | | | | | | |
| Serious infections | 2 (2.3) | 1 (1.2) | 3 (1.8) | 2 (2.3) | 2 (2.4) | 4 (2.4) | 0 | 3 (3.9) | 3 (1.9) |
| Opportunistic infection excluding tuberculosis and herpes zoster | 0 | 5 (6.0) | 5 (3.0) | 4 (4.7) | 0 | 4 (2.4) | 4 (5.1) | 0 | 4 (2.6) |
| Herpes zoster[b] | 5 (5.9) | 6 (7.2) | 11 (6.6) | 6 (7.0) | 3 (3.5) | 9 (5.3) | 0 | 2 (2.6) | 2 (1.3) |
| Active tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NMSC | 1 (1.2) | 2 (2.4) | 3 (1.8) | 0 | 1 (1.2) | 1 (0.6) | 0 | 0 | 0 |
| Malignancy other than NMSC | 0 | 0 | 0 | 2 (2.3) | 1 (1.2) | 3 (1.8) | 0 | 0 | 0 |
| Lymphoma | 0 | 0 | 0 | 0 | 1 (1.2) | 1 (0.6) | 0 | 0 | 0 |
| Hepatic disorder | 6 (7.0) | 2 (2.4) | 8 (4.8) | 11 (12.9) | 4 (4.7) | 15 (8.8) | 2 (2.5) | 5 (6.5) | 7 (4.5) |
| Adjudicated gastrointestinal perforations | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anemia | 1 (1.2) | 2 (2.4) | 3 (1.8) | 5 (5.9) | 5 (5.9) | 10 (5.9) | 1 (1.3) | 2 (2.6) | 3 (1.9) |
| Neutropenia | 4 (4.7) | 2 (2.4) | 6 (3.6) | 16 (18.8) | 6 (7.1) | 22 (13.0) | 2 (2.5) | 1 (1.3) | 3 (1.9) |

| Events (events/100 PY) | 15 mg UPA | | | 30 mg UPA | | | PBO | | |
|---|---|---|---|---|---|---|---|---|---|
| | Measure Up 1 (N = 281) | Measure Up 2 (N = 276) | Combined (N = 557) | Measure Up 1 (N = 285) | Measure Up 2 (N = 282) | Combined (N = 567) | Measure Up 1 (N = 281) | Measure Up 2 (N = 278) | Combined (N = 559) |
| | PY = 85.1 | PY = 82.8 | PY = 167.9 | PY = 85.2 | PY = 84.7 | PY = 169.9 | PY = 78.8 | PY = 77.2 | PY = 156.0 |
| Lymphopenia | 3 (3.5) | 0 | 3 (1.8) | 2 (2.3) | 1 (1.2) | 3 (1.8) | 4 (5.1) | 0 | 4 (2.6) |
| CPK elevation | 19 (22.3) | 9 (10.9) | 28 (16.7) | 18 (21.1) | 12 (14.2) | 30 (17.7) | 7 (8.9) | 6 (7.8) | 13 (8.3) |
| Renal dysfunction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adjudicated MACE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adjudicated venous thromboembolic event | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3) | 1 (0.6) |

Most frequently reported TEAEs (≥ 5% of patients in any treatment group)

| | Events (events/100 PY) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | PY = 85.1 | PY = 82.8 | PY = 167.9 | PY = 85.2 | PY = 84.7 | PY = 169.9 | PY = 78.8 | PY = 77.2 | PY = 156.0 |
| Acne | 20 (23.5) | 36 (43.5) | 56 (33.4) | 51 (59.9) | 43 (50.8) | 94 (55.3) | 6 (7.6) | 6 (7.8) | 12 (7.7) |
| Upper respiratory tract infection | 27 (31.7) | 20 (24.2) | 47 (28.0) | 43 (50.5) | 22 (26.0) | 65 (38.3) | 23 (29.2) | 14 (18.1) | 37 (23.7) |
| Nasopharyngitis | 22 (25.8) | 19 (22.9) | 41 (24.4) | 40 (47.0) | 18 (21.3) | 58 (34.1) | 18 (22.8) | 22 (28.5) | 40 (25.6) |
| Headache | 16 (18.8) | 22 (26.6) | 38 (22.6) | 20 (23.5) | 22 (26.0) | 42 (24.7) | 14 (17.8) | 12 (15.5) | 26 (16.7) |
| Blood CPK increased | 19 (22.3) | 9 (10.9) | 28 (16.7) | 18 (21.1) | 12 (14.2) | 30 (17.7) | 7 (8.9) | 6 (7.8) | 13 (8.3) |
| Dermatitis atopic | 9 (10.6) | 8 (9.7) | 17 (10.1) | 4 (4.7) | 4 (4.7) | 8 (4.7) | 28 (35.5) | 28 (36.3) | 56 (35.9) |

[a]Safety in the main study during the double-blinded period.
[b]Searched using a prespecified grouped term and herpes zoster presented under common AEs was based on the single preferred term of herpes zoster.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; D/C, discontinuation; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

**eTable 2. Treatment-emergent Adverse Events Through Week 52 (Adolescent Population)**

| | 15 mg UPA | | 30 mg UPA | |
|---|---|---|---|---|
| **Patients (events/100 PY)** | **Measure Up 1 (N = 60)** | **Measure Up 2 (N = 49)** | **Measure Up 1 (N = 60)** | **Measure Up 2 (N = 52)** |
| | **PY = 73.3** | **PY = 59.6** | **PY = 77.4** | **PY = 61.2** |
| Any TEAE | 181 (246.8) | 173 (290.1) | 219 (282.8) | 162 (264.6) |
| Serious AEs | 3 (4.1) | 9 (15.1) | 4 (5.2) | 2 (3.3) |
| AEs leading to D/C of study drug | 4 (5.5) | 2 (3.4) | 6 (7.7) | 2 (3.3) |
| Deaths | 0 | 0 | 0 | 0 |
| AESIs | | | | |
| Serious infections | 1 (1.4) | 2 (3.4) | 4 (5.2) | 0 |
| Opportunistic infection excluding tuberculosis and herpes zoster[a] | 0 | 1 (1.7) | 0 | 1 (1.6) |
| Herpes zoster[b] | 1 (1.4) | 1 (1.7) | 4 (5.2) | 2 (3.3) |
| Active tuberculosis | 0 | 0 | 0 | 0 |
| NMSC | 0 | 0 | 0 | 0 |
| Malignancy other than NMSC | 0 | 0 | 0 | 0 |
| Lymphoma | 0 | 0 | 0 | 0 |
| Hepatic disorder | 5 (6.8) | 2 (3.4) | 0 | 3 (4.9) |
| Adjudicated gastrointestinal perforations | 0 | 0 | 0 | 0 |
| Anemia | 2 (2.7) | 1 (1.7) | 0 | 1 (1.6) |
| Neutropenia | 1 (1.4) | 2 (3.4) | 4 (5.2) | 4 (6.5) |
| Lymphopenia | 0 | 0 | 0 | 0 |
| Renal dysfunction | 0 | 0 | 0 | 0 |
| Blood CPK increased | 13 (17.7) | 4 (6.7) | 10 (12.9) | 5 (8.2) |

| | | | | |
|---|---|---|---|---|
| Adjudicated MACE | 0 | 0 | 0 | 0 |
| Adjudicated venous thromboembolic event | 0 | 0 | 0 | 0 |

| | 15 mg UPA | | | | 30 mg UPA | | | |
|---|---|---|---|---|---|---|---|---|
| | Measure Up 1 (N = 60) | | Measure Up 2 (N = 49) | | Measure Up 1 (N = 60) | | Measure Up 2 (N = 52) | |
| | Patients n (%) | PY = 73.3 Events (E/100 PY) | Patients n (%) | PY = 59.6 Events (E/100 PY) | Patients n (%) | PY = 77.4 Events (E/100 PY) | Patients n (%) | PY = 61.2 Events (E/100 PY) |
| Most frequently reported TEAEs (≥ 10% of patients in any treatment group) | | | | | | | | |
| Acne | 6 (10.0) | 6 (8.2) | 8 (16.3) | 11 (18.4) | 21 (35.0) | 22 (28.4) | 9 (17.3) | 10 (16.3) |
| Upper respiratory tract infection | 10 (16.7) | 17 (23.2) | 10 (20.4) | 14 (23.5) | 12 (20.0) | 15 (19.4) | 5 (9.6) | 6 (9.8) |
| Nasopharyngitis | 6 (10.0) | 7 (9.5) | 5 (10.2) | 5 (8.4) | 5 (8.3) | 6 (7.7) | 3 (5.8) | 3 (4.9) |
| Headache | 5 (8.3) | 6 (8.2) | 4 (8.2) | 6 (10.1) | 4 (6.7) | 5 (6.5) | 7 (13.5) | 12 (19.6) |
| Blood CPK increased | 5 (8.3) | 13 (17.7) | 3 (6.1) | 4 (6.7) | 9 (15.0) | 10 (12.9) | 5 (9.6) | 5 (8.2) |
| Cough | 8 (13.3) | 8 (10.9) | 2 (4.1) | 2 (3.4) | 1 (1.7) | 1 (1.3) | 3 (5.8) | 3 (4.9) |
| Dermatitis atopic | 6 (10.0) | 8 (10.9) | 3 (6.1) | 3 (5.0) | 2 (3.3) | 2 (2.6) | 4 (7.7) | 6 (9.8) |
| Pyrexia | 5 (8.3) | 5 (6.8) | 3 (6.1) | 3 (5.0) | 2 (3.3) | 2 (2.6) | 7 (13.5) | 10 (16.3) |
| Corona virus infection | 0 | 0 | 6 (12.2) | 6 (10.1) | 1 (1.7) | 1 (1.3) | 3 (5.8) | 3 (4.9) |

[a]All were cases of eczema herpeticum.
[b]Searched using a prespecified grouped term and herpes zoster presented under common AEs was based on the single preferred term of herpes zoster.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; D/C, discontinuation; E, events; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, patient-years; PBO, placebo; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

**eTable 3. Most Frequently Reported Treatment-emergent Adverse Events (≥ 5% of Patients in Any Treatment Group) During Administration of UPA Through Week 52**

| | Measure Up 1[a] (N = 401) | | Measure Up 2[a] (N = 396) | | Combined[b] (N = 797) | Measure Up[a] 1 (N = 408) | | Measure Up[a] 2 (N = 403) | | Combined[b] (N = 811) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients n (%) | PY = 490.9 Events (E/100 PY) | Patients n (%) | PY = 462.4 Events (E/100 PY) | PY = 953.3 Events (E/100 PY) | Patients n (%) | PY = 501.0 Events (E/100 PY) | Patients n (%) | PY = 477.2 Events (E/100 PY) | PY = 978.2 Events (E/100 PY) |
| Acne | 41 (10.2) | 49 (10.0) | 69 (17.4) | 76 (16.4) | 125 (13.1) | 99 (24.3) | 117 (23.4) | 76 (18.9) | 82 (17.2) | 199 (20.3) |
| Blood CPK increased | 22 (5.5) | 36 (7.3) | 28 (7.1) | 31 (6.7) | 67 (7.0) | 44 (10.8) | 58 (11.6) | 39 (9.7) | 51 (10.7) | 109 (11.1) |
| Cough | 20 (5.0) | 23 (4.7) | 20 (5.1) | 22 (4.8) | 45 (4.7) | 11 (2.7) | 11 (2.2) | 16 (4.0) | 17 (3.6) | 28 (2.9) |
| Dermatitis atopic | 41 (10.2) | 47 (9.6) | 36 (9.1) | 38 (8.2) | 85 (8.9) | 25 (6.1) | 29 (5.8) | 20 (5.0) | 23 (4.8) | 52 (5.3) |
| Headache | 23 (5.7) | 27 (5.5) | 28 (7.1) | 44 (9.5) | 71 (7.4) | 24 (5.9) | 27 (5.4) | 31 (7.7) | 39 (8.2) | 66 (6.7) |
| Herpes zoster[c] | 16 (4.0) | 16 (3.3) | 15 (3.8) | 15 (3.2) | 31 (3.3) | 24 (5.9) | 24 (4.8) | 20 (5.0) | 21 (4.4) | 45 (4.6) |
| Nasopharyngitis | 50 (12.5) | 61 (12.4) | 28 (7.1) | 33 (7.1) | 94 (9.9) | 49 (12.0) | 68 (13.6) | 34 (8.4) | 39 (8.2) | 107 (10.9) |
| Oral herpes | 13 (3.2) | 15 (3.1) | 14 (3.5) | 16 (3.5) | 31 (3.3) | 25 (6.1) | 38 (7.6) | 24 (6.0) | 31 (6.5) | 69 (7.1) |
| Upper respiratory tract infection | 53 (13.2) | 71 (14.5) | 34 (8.6) | 45 (9.7) | 116 (12.2) | 55 (13.5) | 72 (14.4) | 32 (7.9) | 40 (8.4) | 112 (11.4) |
| Urinary tract infection | 15 (3.7) | 20 (4.1) | 9 (2.3) | 12 (2.6) | 32 (3.4) | 21 (5.1) | 24 (4.8) | 19 (4.7) | 28 (5.9) | 52 (5.3) |

[a]Includes all patients in the main study who received at least 1 dose of UPA.
[b]Data from Measure Up 1 and Measure Up 2 studies.
[c]Based on the single preferred term of herpes zoster.
Abbreviations: CPK, creatine phosphokinase; PY, patient year; UPA, upadacitinib.

**eTable 4. Grades 3–4 Hematology and Chemistry Parameters Through Week 52 (All UPA Population[a])**

| | | UPA 15 mg | | | UPA 30 mg | | |
|---|---|---|---|---|---|---|---|
| | **Grade (Criteria)** | **Measure Up 1 (N = 401)** | **Measure Up 2 (N = 396)** | **Combined (N = 797)** | **Measure Up 1 (N = 408)** | **Measure Up 2 (N = 403)** | **Combined (N = 811)** |
| Hemoglobin, g/L | Grade 3 (<80) | 0/398 (0) | 1/393 (0.3) | 1/791 (0.1) | 1/406 (0.2) | 1/401 (0.2) | 2/807 (0.2) |
| Platelets, $\times 10^9$/L | Grade 3 (25 to <50) | 0/398 (0) | 0/393 (0) | 0/791 (0) | 0/406 (0) | 0/401 (0) | 0/807 (0) |
| | Grade 4 (<25) | 0/398 (0) | 0/393 (0) | 0/791 (0) | 0/406 (0) | 0/401 (0) | 0/807 (0) |
| Lymphocytes, $\times 10^9$/L | Grade 3 (0.2 to < 0.5) | 1/398 (0.3) | 3/393 (0.8) | 4/791 (0.5) | 6/406 (1.5) | 5/401 (1.2) | 11/807 (1.4) |
| | Grade 4 (<0.2) | 0/398 (0) | 0/393 (0) | 0/791 (0) | 0/406 (0) | 0/401 (0) | 0/807 (0) |
| Neutrophils, $\times 10^9$/L | Grade 3 (0.5 to <1.0) | 2/398 (0.5) | 3/393 (0.8) | 5/791 (0.6) | 9/406 (2.2) | 2/401 (0.5) | 11/807 (1.4) |
| | Grade 4 (<0.5) | 0/398 (0) | 0/393 (0) | 0/791 (0) | 1/406 (0.2) | 1/401 (0.2) | 2/807 (0.2) |
| ALT, U/L | Grade 3 (>5.0 to 20.0 × ULN) | 1/398 (0.3) | 2/393 (0.5) | 3/791 (0.4) | 5/406 (1.2) | 2/401 (0.5) | 7/807 (0.9) |
| | Grade 4 (>20.0 × ULN) | 1/398 (0.3) | 0/393 (0) | 1/791 (0.1) | 1/406 (0.2) | 0/401 (0) | 1/807 (0.1) |
| AST, U/L | Grade 3 (>5.0 to 20.0 × ULN) | 4/398 (1.0) | 2/393 (0.5) | 6/791 (0.8) | 8/406 (2.0) | 2/401 (0.5) | 10/807 (1.2) |
| | Grade 4 (>20.0 × ULN) | 1/398 (0.3) | 0/393 (0) | 1/791 (0.1) | 2/406 (0.5) | 0/401 (0) | 2/807 (0.2) |
| Creatinine, µmol/L | Grade 3 (>3.0 to 6.0 × ULN) | 0/399 (0) | 0/393 (0) | 0/792 (0) | 0/407 (0) | 0/401 (0) | 0/808 (0) |
| | Grade 4 (>6.0 × ULN) | 0/399 (0) | 0/393 (0) | 0/792 (0) | 1/407 (0.2) | 0/401 (0) | 1/808 (0.1) |
| Creatine kinase, U/L | Grade 3 (>5.0 to 10.0 × ULN) | 12/398 (3.0) | 11/393 (2.8) | 23/791 (2.9) | 18/407 (4.4) | 17/401 (4.2) | 35/808 (4.3) |
| | Grade 4 (>10.0 × ULN) | 9/398 (2.3) | 9/393 (2.3) | 18/791 (2.3) | 14/407 (3.4) | 13/401 (3.2) | 27/808 (3.3) |

Data are presented as n/N (%).
[a]Includes all patients in the main study who received at least 1 dose of UPA.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; UPA, upadacitinib.