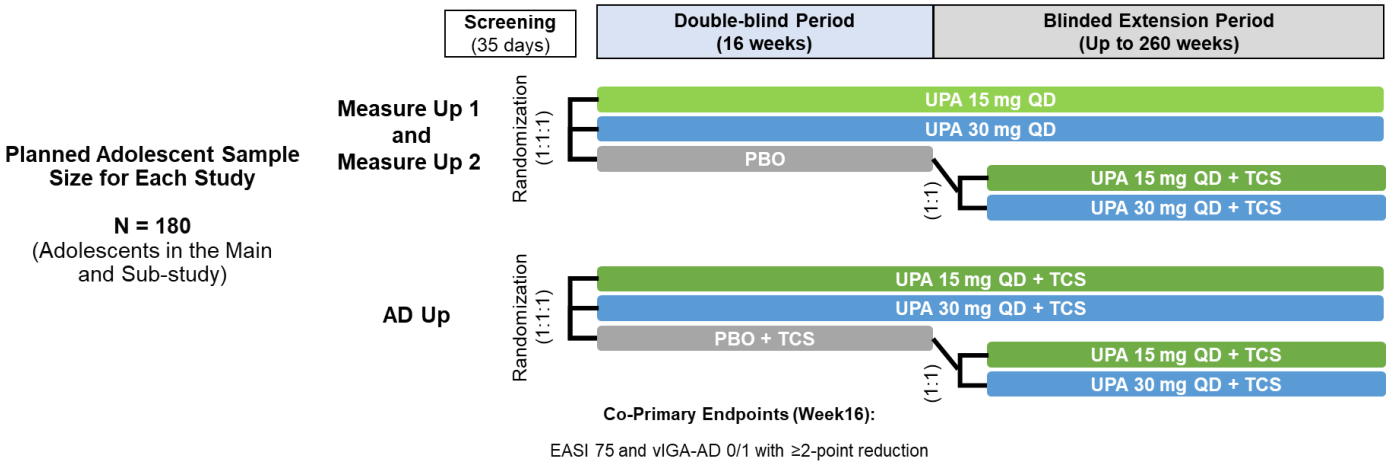
Supplemental Online Content

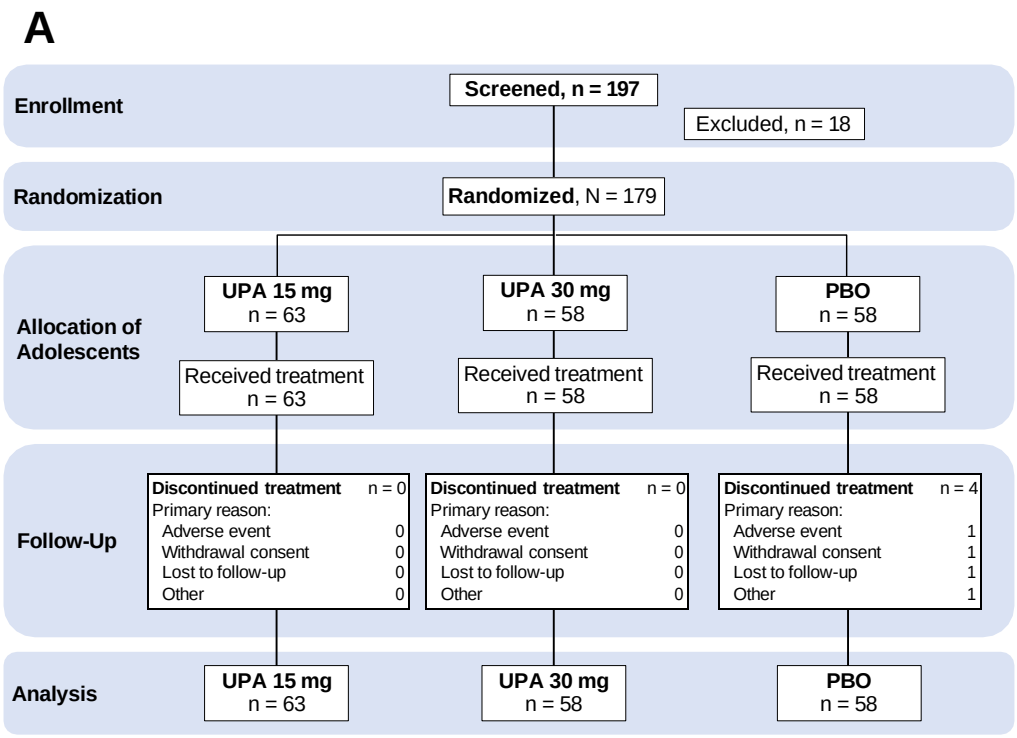
Paller AS, Ladizinski B, Mendes-Bastos P, et al. Efficacy and safety of upadacitinib treatment in adolescents with moderate-to-severe atopic dermatitis: analysis of the Measure Up 1, Measure Up 2, and AD Up randomized clinical trials. *JAMA Dermatol.* Published online April 12, 2023. doi:10.1001/jamadermatol.2023.0391

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

eFigure 1. Study design of Measure Up 1, Measure Up 2, and AD Up. These schematics apply to both the main study and the adolescent sub-study. Abbreviations: EASI, Eczema Area and Severity Index; PBO, placebo; QD, daily; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.



eFigure 2. Disposition of Adolescents. A, Measure Up 1. B, Measure Up 2. C, AD Up. Abbreviations: PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.



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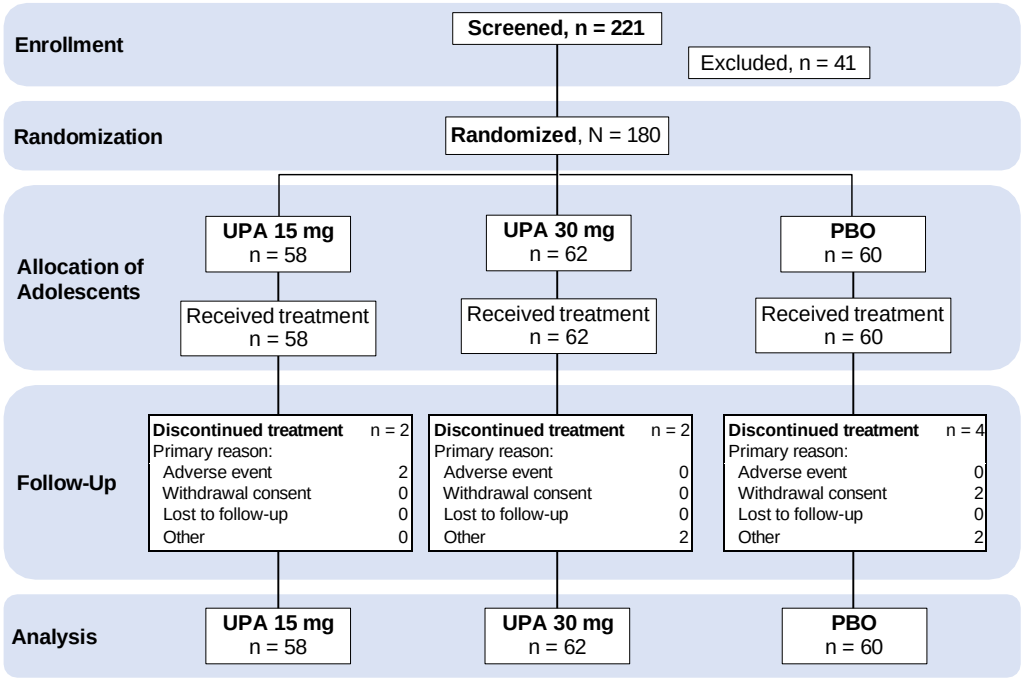

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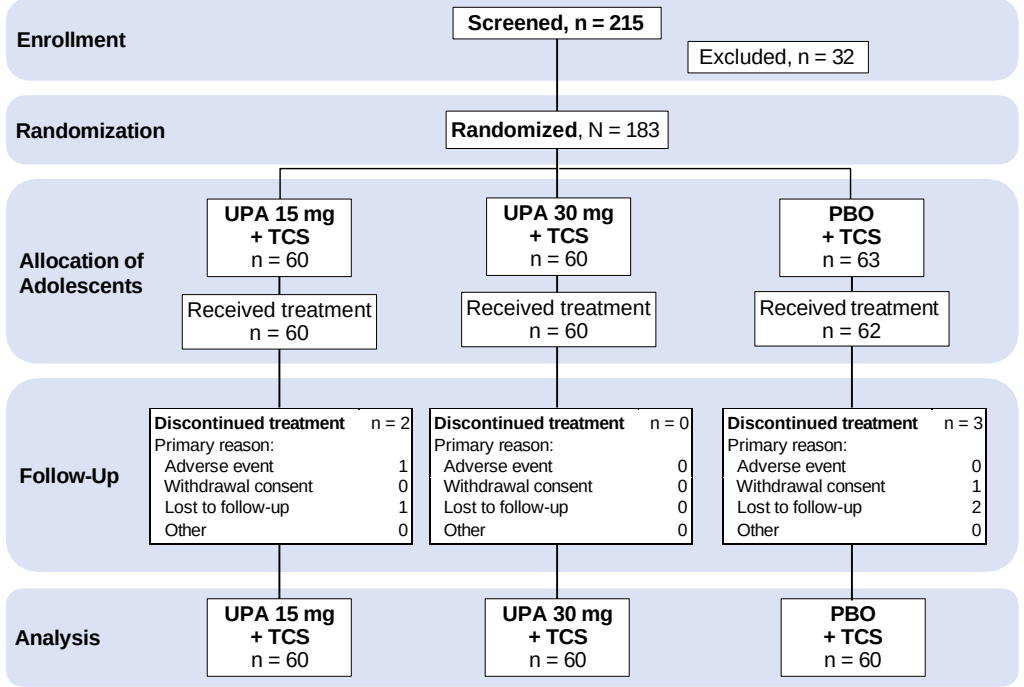
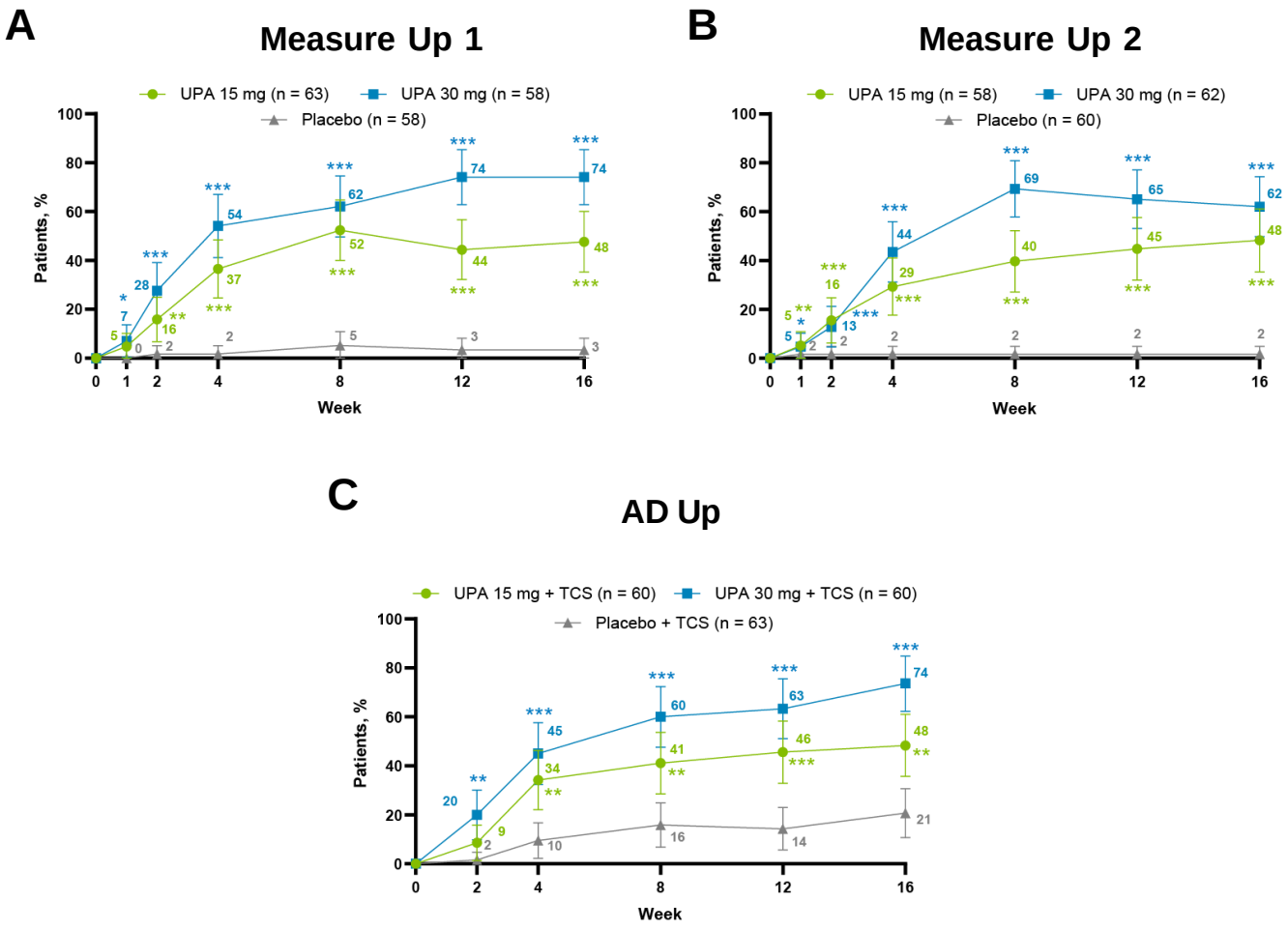
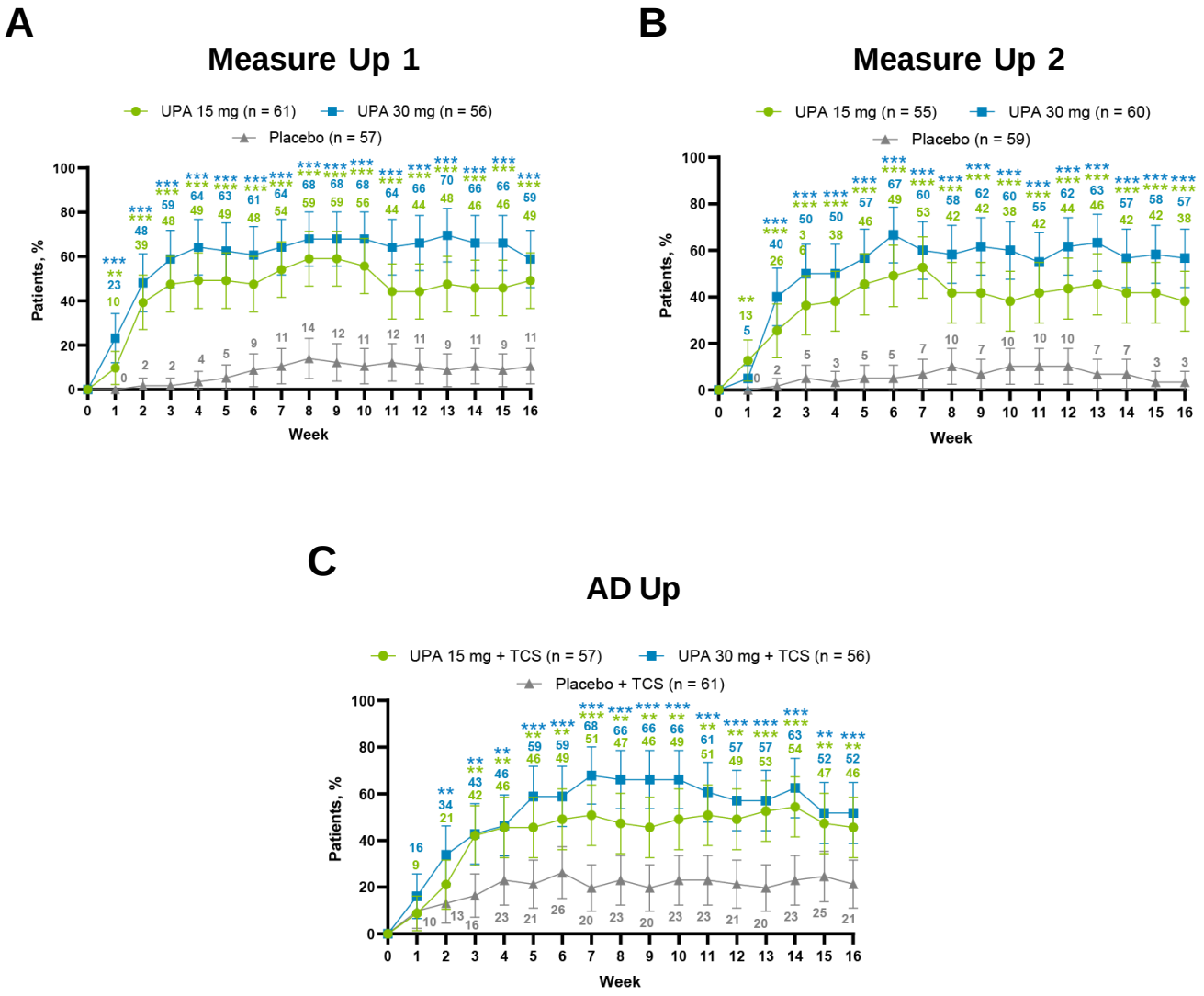


eFigure 3. Proportion of Adolescents Achieving EASI 90 Response Over the Double-blind Period. A, Measure Up 1. B, Measure Up 2. C, AD Up. Abbreviations: EASI, Eczema Area and Severity Index; TCS, topical corticosteroids; UPA, upadacitinib. Nominal *P* values are calculated using Cochran-Mantel-Haenszel test with the adjustment of baseline vIGA-AD categories (3;4): **P* < .05, ***P* < .01, ****P* < .001. Based on nonresponder imputation incorporating multiple imputation to hand missing data due to COVID-19 or nonresponder imputation only if there were no missing data due to COVID-19.



eFigure 4. Proportion of Adolescents with Worse Pruritus NRS ≥4 (Weekly Average) Improvement From Baseline Over the Double-blind Period. A, Measure Up 1. B, Measure Up 2. C, AD Up. Abbreviations: NRS, numerical rating scale; TCS, topical corticosteroids; UPA, upadacitinib. Nominal *P* values are calculated using Cochran-Mantel-Haenszel test with the adjustment of baseline vIGA-AD categories (3;4): ***P* < .01, ****P* < .001. Based on nonresponder imputation incorporating multiple imputation to hand missing data due to COVID-19 or nonresponder imputation only if there were no missing data due to COVID-19.



eTable 1. Summary of Efficacy Endpoints and Patient-reported Outcome Measure Endpoints at Week 16 in Adults Aged 18–75 Years

Parameters, n/N% [95% CI]	Measure Up 1			Measure Up 2			AD Up		
	Upadacitinib 15 mg (n = 239)	Upadacitinib 30 mg (n = 243)	Placebo (n = 241)	Upadacitinib 15 mg (n = 243)	Upadacitinib 30 mg (n = 247)	Placebo (n = 242)	Upadacitinib 15 mg (n = 261)	Upadacitinib 30 mg (n = 260)	Placebo (n = 264)
EASI 75	166/239 (69.3) [63.4, 75.2][a]	192/243 (79.1) [73.9, 84.2][a]	43/241 (17.7) [12.8, 22.6]	144/243 (59.3) [53.1, 65.4][a]	180/247 (72.7) [67.2, 78.3][a]	32/242 (13.2) [9.0, 17.5]	172/261 (65.8) [60.0, 71.6][a]	201/260 (77.3) [72.2, 82.4][a]	68/264 (25.9) [20.6, 31.2]
vIGA-AD 0/1	119/239 (49.9) [43.6, 56.3][a]	148/243 (60.8) [54.6, 66.9][a]	21/241 (8.6) [5.0, 12.2]	93/243 (38.3) [32.2, 44.4][a]	125/247 (50.5) [44.3, 56.8][a]	12/242 (5.0) [2.2, 7.7]	107/261 (40.9) [35.0, 46.9][a]	150/260 (57.7) [51.7, 63.7][a]	30/264 (11.4) [7.6, 15.3]
EASI 90	131/239 (54.9) [48.6, 61.2][a]	156/243 (64.4) [58.3, 70.4][a]	22/241 (8.9) [5.3, 12.6]	102/243 (42.0) [35.8, 48.2][a]	142/247 (57.6) [51.4, 63.8][a]	15/242 (6.2) [3.2, 9.2]	112/261 (43.0) [37.0, 49.1][a]	161/260 (62.1) [56.2, 68.0][a]	33/264 (12.5) [8.5, 16.5]
WP-NRS ≥4 improvement	125/234 (53.4) [47.0, 59.8][a]	145/238 (60.9) [54.7, 67.1][a]	26/233 (11.2) [7.1, 15.2]	103/240 (42.9) [36.7, 49.2][a]	150/246 (61.0) [54.9, 67.1][a]	24/238 (10.1) [6.3, 13.9]	134/252 (53.2) [47.0, 59.3][a]	168/258 (65.1) [59.3, 70.9][a]	39/256 (15.2) [10.8, 19.6]
DLQI 0/1[c]	73/238 (30.7) [24.8, 36.6][a]	102/239 (42.8) [36.5, 49.0][a]	10/238 (4.3) [1.7, 6.8]	58/238 (24.4) [18.9, 29.8][a]	90/239 (37.7) [31.6, 43.9][a]	10/236 (4.2) [1.7, 6.8]	71/257 (27.6) [22.2, 33.1][a]	105/257 (41.0) [34.9, 47.0][a]	14/261 (5.4) [2.6, 8.1]
POEM ≥4 improvement	177/237 (74.5) [68.9, 80.1][a]	192/238 (80.7) [75.7, 85.7][a]	52/238 (21.8) [16.5, 27.1]	169/236 (71.6) [65.9, 77.4][a]	201/239 (84.1) [79.5, 88.7][a]	69/234 (29.5) [23.6, 35.3]	207/258 (80.4) [75.5, 85.2][a]	217/257 (84.6) [80.1, 89.0][a]	100/262 (38.1) [32.2, 43.9]
ADerm-IS Sleep domain ≥12-point change from baseline	108/189 (57.1) [50.1, 64.2][a]	123/186 (66.1) [59.3, 72.9][a]	25/189 (13.2) [8.4, 18.1]	100/195 (51.3) [44.3, 58.3][a]	125/202 (61.9) [55.2, 68.6][a]	26/209 (12.4) [8.0, 16.9]	129/202 (63.9) [57.2, 70.5][a]	160/217 (73.7) [67.9, 79.6][a]	46/202 (22.8) [17.0, 28.6]
HADS-A <8 and HADS-D <8[d]	55/123 (44.7) [35.9, 53.5][a]	61/123 (49.5) [40.6, 58.3][a]	18/108 (16.7) [9.6, 23.7]	57/122 (46.7) [37.9, 55.6][a]	75/130 (57.6) [49.1, 66.1][a]	16/127 (12.6) [6.8, 18.4]	61/140 (43.4) [35.1, 51.7][b]	68/138 (49.3) [40.9, 57.6][a]	36/128 (28.3) [20.5, 36.1]

ADerm-IS, Atopic Dermatitis Impact Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; HADS-D, Hospital Anxiety and Depression Scale – Depression; NRS, numerical rating scale; PBO, placebo; POEM, Patient Oriented Eczema Measure; UPA, upadacitinib; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

[a] $P < .001$ for upadacitinib vs placebo.

[b] $P < .01$.

[c] For patients with DLQI >1 at baseline.

[d] For patients with HADS-A or HADS-D ≥8 at baseline.

eTable 2. Summary of Treatment-Emergent Adverse Events in Adults Through Week 16

	Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
Adverse events	**Measure Up 1 (n = 239)**	**Measure Up 2 (n = 243)**	**AD Up (n = 261)**	**Measure Up 1 (n = 243)**	**Measure Up 2 (n = 247)**	**AD Up (n = 260)**	**Measure Up 1 (n = 241)**	**Measure Up 2 (n = 242)**	**AD Up (n = 264)**
All TEAEs, n (%)	150 (62.8)	145 (59.7)	173 (66.3)	175 (72.0)	155 (62.8)	184 (70.8)	148 (61.4)	128 (52.9)	173 (65.5)
Drug-related AEs[a]	72 (30.1)	75 (30.9)	101 (38.7)	105 (43.2)	84 (34.0)	114 (43.8)	49 (20.3)	51 (21.1)	60 (22.7)
Severe AEs	11 (4.6)	9 (3.7)	13 (5.0)	21 (8.6)	11 (4.5)	10 (3.8)	13 (5.4)	10 (4.1)	15 (5.7)
Serious AEs	5 (2.1)	3 (1.2)	7 (2.7)	8 (3.3)	7 (2.8)	4 (1.5)	7 (2.9)	6 (2.5)	9 (3.4)
Drug-related serious AEs[a]	1 (0.4)	2 (0.8)	4 (1.5)	1 (0.4)	2 (0.8)	0	2 (0.8)	0	1 (0.4)
AEs leading to discontinuation	4 (1.7)	9 (3.7)	3 (1.1)	11 (4.5)	7 (2.8)	4 (1.5)	11 (4.6)	11 (4.5)	6 (2.3)
Most commonly reported AEs[b], n (%)									
Acne	13 (5.4)	31 (12.8)	25 (9.6)	40 (16.5)	38 (15.4)	36 (13.8)	6 (2.5)	5 (2.1)	6 (2.3)
Headache	12 (5.0)	17 (7.0)	11 (4.2)	16 (6.6)	16 (6.5)	11 (4.2)	10 (4.1)	10 (4.1)	12 (4.5)
Upper respiratory tract infection	20 (8.4)	13 (5.3)	20 (7.7)	31 (12.8)	14 (5.7)	19 (7.3)	17 (7.1)	11 (4.5)	21 (8.0)
CPK elevation	12 (5.0)	8 (3.3)	12 (4.6)	11 (4.5)	10 (4.0)	16 (6.2)	5 (2.1)	4 (1.7)	7 (2.7)
Nasopharyngitis	19 (7.9)	14 (5.8)	31 (11.9)	28 (11.5)	18 (7.3)	37 (14.2)	15 (6.2)	11 (4.5)	31 (11.7)
Atopic dermatitis	8 (3.3)	7 (2.9)	8 (3.1)	4 (1.6)	2 (0.8)	2 (0.8)	24 (10.0)	19 (7.9)	18 (6.8)
Oral herpes	5 (2.1)	7 (2.9)	9 (3.4)	12 (4.9)	10 (4.0)	22 (8.5)	3 (1.2)	1 (0.4)	5 (1.9)
AEs of special interest, n (%)									
Serious infection	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.8)	2 (0.8)	0	0	1 (0.4)	3 (1.1)
Opportunistic infection[c]	0	3 (1.2)	3 (1.1)	3 (1.2)	0	4 (1.5)	4 (1.7)	0	0
Herpes zoster	4 (1.7)	6 (2.5)	3 (1.1)	4 (1.6)	3 (1.2)	4 (1.5)	0	2 (0.8)	3 (1.1)
Active tuberculosis	0	0	0	0	0	0	0	0	0
Malignancy	1 (0.4)	2 (0.8)	0	2 (0.8)	2 (0.8)	2 (0.8)	0	0	0

NMSC	1 (0.4)	2 (0.8)	0	0	1 (0.4)	1 (0.4)	0	0	0
Malignancy, excluding NMSC	0	0	0	2 (0.8)	1 (0.4)	1 (0.4)	0	0	0
Lymphoma	0	0	0	0	1 (0.4)	0	0	0	0
Hepatic disorder	2 (0.8)	2 (0.8)	4 (1.5)	8 (3.3)	4 (1.6)	3 (1.2)	2 (0.8)	4 (1.7)	5 (1.9)
Adjudicated gastrointestinal perforation	0	0	0	0	0	0	0	0	0
Anemia	0	2 (0.8)	0	5 (2.1)	4 (1.6)	3 (1.2)	1 (0.4)	2 (0.8)	1 (0.4)
Neutropenia	4 (1.7)	0	2 (0.8)	12 (4.9)	4 (1.6)	2 (0.8)	1 (0.4)	1 (0.4)	0
Lymphopenia	1 (0.4)	0	0	2 (0.8)	1 (0.4)	0	2 (0.8)	0	1 (0.4)
CPK elevation	12 (5.0)	8 (3.3)	12 (4.6)	11 (4.5)	10 (4.0)	16 (6.2)	5 (2.1)	4 (1.7)	7 (2.7)
Renal dysfunction	0	0	1 (0.4)	0	0	0	0	0	0
Adjudicated VTE	0	0	0	0	0	0	0	1 (0.4)	0

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; NMSC, nonmelanoma skin cancer; TEAE, treatment-emergent adverse events; VTE, venous thromboembolic event.

[a]As assessed by investigator.

[b]AEs reported for ≥5% of patients in any treatment group.

[c]Opportunistic infections excluding tuberculosis and herpes zoster (all opportunistic infections were cases of eczema herpeticum).

eTable 3. Treatment-emergent Severe Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation of Study Drug in Adolescents Through Week 16

	Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
System Organ Class Preferred Term[a]	Measure Up 1 (n = 63)	Measure Up 2 (n = 58)	AD Up (n = 60)	Measure Up 1 (n = 58)	Measure Up 2 (n = 62)	AD Up (n = 60)	Measure Up 1 (n = 58)	Measure Up 2 (n = 60)	AD Up (n = 62)
Any Severe AEs, n (%)	6 (10)	3 (5)	4 (7)	1 (2)	3 (5)	0	3 (5)	2 (3)	0
Blood and lymphatic system disorders, n (%)									
Neutropenia	0	0	0	0	1 (2)	0	0	0	0
Gastrointestinal disorders, n (%)									
Dental caries	1 (2)	0	0	0	0	0	0	0	0
Hepatobiliary disorders, n (%)									
Hepatic functional abnormal	0	0	1 (2)	0	0	0	0	0	0
Infections and infestations, n (%)									
Cellulitis	0	0	0	0	0	0	0	1 (2)	0
Impetigo	1 (2)	0	0	0	0	0	0	0	0
Subcutaneous abscess	0	0	0	0	0	0	0	1 (2)	0
Injury, poisoning and procedural complications, n (%)									
Ligament rupture	0	0	1 (2)	0	0	0	0	0	0
Investigations, n (%)									
Blood CPK increased	2 (3)	2 (3)	1 (2)	1 (2)	2 (3)	0	1 (2)	0	0
Nervous system disorders, n (%)									
Headache	1 (2)	0	0	0	0	0	0	0	0
Psychiatric disorders, n (%)									
Suicide attempt[b]	0	1 (2)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders, n (%)									
Dermatitis atopic	0	1 (2)	1 (2)	0	0	0	1 (2)	1 (2)	0
Eczema	1 (1.6)	0	0	0	0	0	0	0	0

Any Serious AEs, (n (%)	1 (2)	2 (3)	1 (2)	0	0	0	1 (2)	3 (5)	0
Infections and infestations, n (%)									
Cellulitis	0	0	0	0	0	0	0	1 (2)	0
Impetigo	1 (2)	0	0	0	0	0	0	0	0
Subcutaneous abscess	0	0	0	0	0	0	0	1 (2)	0
Injury, poisoning and procedural complications, n (%)									
Ligament rupture	0	0	1 (1.7)	0	0	0	0	0	0
Nervous system disorders, n (%)									
Migraine	0	0	0	0	0	0	0	1 (2)	0
Psychiatric disorders, n (%)									
Suicide attempt[b]	0	1 (2)	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders, n (%)									
Pneumomediastinum	0	1 (2)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders, n (%)									
Dermatitis atopic	0	1 (2)	0	0	0	0	1 (2)	1 (2)	0
Eczema	0	0	0	0	0	0	0	0	0
Any AE Leading to Discontinuation, n (%)	0	2 (3)	1 (2)	1 (2)	0	0	1 (2)	1 (2)	1 (2)
Hepatobiliary disorders, n (%)									
Hepatic function abnormal	0	0	1 (2)	0	0	0	0	0	0
Immune system disorders, n (%)									
Drug hypersensitivity	0	0	0	0	0	0	1 (2)	0	0
Respiratory, thoracic and mediastinal disorders, n (%)									
Asthma	0	1 (2)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders, n (%)									
Acne	0	0	0	1 (1.6)	0	0	0	0	0
Dermatitis atopic	0	0	0	0	0	0	0	1 (2)	1 (2)
Pruritus	0	1 (2)	0	0	0	0	0	0	0

Abbreviation: AE, adverse event; CPK, creatinine phosphokinase.

[a]Patients counted once for each preferred term, regardless of the number of events they may have had.

[b]Female patient with low self-esteem had a suicide attempt deemed by the investigator to have no reasonable possibility of being related to study drug.

eTable4. Characterization of Acne Adverse Events in Adolescents[a]

Parameter	Patients, n (%)		
	Upadacitinib 15 mg (n = 181)	Upadacitinib 30 mg (n = 180)	Placebo (n = 180)
Any acne AE, n (%)	23 (12.7)	28 (15.6)	4 (2.2)
Predisposing factors, n (%)	n = 23	n = 28	n = 4
Medical history of acne	9 (39.1)	4 (14.3)	4 (100)
Family history of acne	11 (47.8)	12 (42.9)	2 (50.0)
Concomitant medication associated with acne	0	0	0
Other predisposing factors for acne	5 (21.7)	11 (39.3)	1 (25.0)
Discontinuation of study due to acne AE, n (%)	0	1 (0.6)	0
Recurrence of acne AE, n (%)	1 (0.6)	1 (0.6)	0
Time to onset of first acne event, median (range), days	48.0 (11, 103) (n = 23)	47.5 (1, 102) (n = 28)	41.5 (8, 96) (n = 4)
Duration of first acne event, median (range), days	128 (17, 902) (n = 9)	152 (23, 746) (n = 15)	337 (21, 653) (n = 2)
Medications used to treat acne, n (%)	n = 23	n = 28	n = 4
None	5 (21.7)	11 (39.3)	1 (25.0)
Topical	12 (52.2)	13 (46.4)	3 (75.0)
Oral[b]	2 (8.7)	0	0
Missing	6 (26.1)	4 (14.3)	0
Areas of acne involvement[c], n (%)	n = 23	n = 28	n = 4
Face	22 (95.7)	27 (96.4)	4 (100)
Trunk	13 (56.5)	10 (35.7)	1 (25.0)
Extremities	0	0	0
Morphology of acne[c], n (%)	n = 23	n = 28	n = 4
Inflammatory papules	19 (82.6)	22 (78.6)	4 (100)
Comedones	12 (52.2)	16 (57.1)	3 (75.0)
Pustules	9 (39.1)	7 (25.0)	1 (25.0)
Scarring	4 (17.4)	1 (3.6)	0
Inflammatory nodules and cysts	0	0	0

Abbreviation: AE, adverse event.

[a]Acne adverse events refer to investigator identified events from Measure Up 1, Measure Up 2, and AD Up.

[b]Included retinoid (1 patient) and tetracycline (1 patient).

[c]Percentages calculated out of the number of patients experiencing acne, not the total population.

eTable 5. Grade 3 or 4 Laboratory Elevations in Adolescents During the Double-blind Period

		Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
Laboratory parameter	**Grade**	**Measure Up 1 (n = 63)**	**Measure Up 2 (n = 58)**	**AD Up (n = 60)**	**Measure Up 1 (n = 58)**	**Measure Up 2 (n = 62)**	**AD Up (n = 60)**	**Measure Up 1 (n =58)**	**Measure Up 2 (n = 60)**	**AD Up (n = 62)**
Hemoglobin, n/N (%)	3	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
Lymphocytes, n/N (%)	3	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
Neutrophils, n/N (%)	3	0	1/58 (2)	0	2/58 (3)	1/62 (2)	3/60 (5)	0	0	0
	4	0	0	0	0	0	0	0	0	0
ALT, n/N (%)	3	0	0	1/60 (2)	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
AST, n/N (%)	3	0	1/58 (2)	0	0	1/62 (2)	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
Creatinine, n/N (%)	3	0	0	0	0	0	0	0	0	0
	4	0	0	1/60 (2)	0	0	0	0	0	0
CPK, n/N (%)	3	0	2/58 (3)	0	3/58 (5)	2/62 (3)	1/60 (2)	1/58 (2)	0	0
	4	2/63 (3)	2/58 (3)	1/60 (2)	1/58 (2)	1/62 (12)	2/60 (3)	0	1/59 (2)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; CTCAE, NCI Common Terminology Criteria for Adverse Events.
Measured laboratory values must be worse than baseline in terms of CTCAE toxicity grade. Toxicity grading was based on NCI CTCAE criteria v4.03.