Safety and Efficacy of Upadacitinib for Atopic Dermatitis in Japan: 2-Year Interim Results From the Phase 3 Rising Up Study

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SUPPLEMENTARY MATERIALS

Table S1 Patient demographics and baseline characteristics among adolescents

Characteristic	Upadacitinib 15 mg[a] (*N* = 10)	Upadacitinib 30 mg[a] (*N* = 10)	Placebo[a] (*N* = 9)
Age, years, mean (SD)	15.4 (1.9)	16.3 (1.5)	14.9 (1.6)
Sex, *n* (%)			
Female	3 (30.0)	2 (20.0)	2 (22.2)
Male	7 (70.0)	8 (80.0)	7 (77.8)
Weight, kg, mean (SD)	51.3 (7.2)	60.7 (12.9)	58.8 (10.8)
Affected BSA, %, mean (SD)	64.7 (21.5)	65.4 (25.2)	57.5 (26.3)
Disease duration since diagnosis, years, mean (SD)	10.4 (5.1)	12.0 (4.6)	9.5 (5.1)
vIGA-AD, *n* (%)			
Moderate (score of < 4)	6 (60.0)	6 (60.0)	5 (55.6)
Severe (score of 4)	4 (40.0)	4 (40.0)	4 (44.4)
EASI, mean (SD)	34.6 (13.4)	37.0 (14.7)	32.3 (16.0)
WP-NRS, mean (SD)	6.7 (1.4)	5.9 (1.1)	6.4 (1.6)
hsCRP, mg/L, mean (SD)	1.7 (2.9)	0.9 (0.9)	5.1 (13.1)

BSA, body surface area; EASI, Eczema Area and Severity Index; hsCRP, high-sensitivity C-reactive protein; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS, Worst Pruritus Numerical Rating Scale

[a]All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion

Table S2 Exposure-adjusted event rates through 52 weeks and 112 weeks in the Rising Up study

	Week 52		Week 112	
Events (E/100 PY)	**Upadacitinib 15 mg[a] (*N* = 133; PY = 151.2)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 149.7)**	**Upadacitinib 15 mg[a] (*N* = 133; PY = 289.4)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 287.7)**
Overview				
Any AE	339 (224.2)	386 (257.8)	563 (194.5)	594 (206.4)
AE with reasonable possibility of being drug related	90 (59.5)	108 (72.1)	146 (50.4)	155 (53.9)
Severe AE	10 (6.6)	12 (8.0)	20 (6.9)	19 (6.6)
Serious AE	6 (4.0)	5 (3.3)	17 (5.9)	11 (3.8)
AE leading to discontinuation of study drug	4 (2.6)	3 (2.0)	7 (2.4)	5 (1.7)
Deaths	0	0	0	0
Most common AEs[b]				
Acne	29 (19.2)	46 (30.7)	39 (13.5)	58 (20.2)
Nasopharyngitis	44 (29.1)	59 (39.4)	51 (17.6)	65 (22.6)
Herpes zoster	7 (4.6)	19 (12.7)	18 (6.2)	33 (11.5)
Pyrexia	8 (5.3)	7 (4.7)	14 (4.8)	17 (5.9)

Table S2 Exposure-adjusted event rates through 52 weeks and 112 weeks in the Rising Up study

	Week 52		Week 112	
Events (E/100 PY)	**Upadacitinib 15 mg[a] (*N* = 133; PY = 151.2)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 149.7)**	**Upadacitinib 15 mg[a] (*N* = 133; PY = 289.4)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 287.7)**
Dermatitis atopic	7 (4.6)	6 (4.0)	17 (5.9)	10 (3.5)
Skin papilloma	6 (4.0)	1 (0.7)	16 (5.5)	7 (2.4)
Folliculitis	11 (7.3)	4 (2.7)	17 (5.9)	7 (2.4)
Oral herpes	5 (3.3)	9 (6.0)	16 (5.5)	11 (3.8)
Blood CPK increased	3 (2.0)	6 (4.0)	6 (2.1)	13 (4.5)
Herpes simplex	14 (9.3)	7 (4.7)	23 (7.9)	11 (3.8)
Influenza	6 (4.0)	11 (7.3)	7 (2.4)	11 (3.8)
Eczema herpeticum	9 (6.0)	3 (2.0)	15 (5.2)	6 (2.1)
ALT increased	4 (2.6)	6 (4.0)	8 (2.8)	10 (3.5)
Headache	5 (3.3)	4 (2.7)	10 (3.5)	9 (3.1)
Tinea pedis	2 (1.3)	5 (3.3)	2 (0.7)	11 (3.8)
Gastroenteritis	3 (2.0)	3 (2.0)	8 (2.8)	5 (1.7)
Arthralgia	1 (0.7)	12 (8.0)	1 (0.3)	13 (4.5)

Table S2 Exposure-adjusted event rates through 52 weeks and 112 weeks in the Rising Up study

	Week 52		Week 112	
Events (E/100 PY)	**Upadacitinib 15 mg[a] (*N* = 133; PY = 151.2)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 149.7)**	**Upadacitinib 15 mg[a] (*N* = 133; PY = 289.4)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 287.7)**
Dental caries	2 (1.3)	2 (1.3)	7 (2.4)	4 (1.4)
Furuncle	6 (4.0)	3 (2.0)	8 (2.8)	4 (1.4)
Asthma	2 (1.3)	8 (5.3)	1 (0.3)	9 (3.1)

AE, adverse event; ALT, alanine aminotransferase; CPK, creatine phosphokinase; E/100 PY, events per 100 patient-years; PY, patient years

[a]All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion

[b]Most common AEs are defined as those occurring in > 5% of patients in either group

Table S3 Short- and long-term safety of upadacitinib among adolescents in the Rising Up study

Parameter	Week 16, *n* (%)			Week 112; *n*/PY (*n*/100 PY)	
	Upadacitinib 15 mg +TCS (*N* = 10)	Upadacitinib 30 mg +TCS (*N* = 10)	Placebo +TCS (*N* = 9)	Upadacitinib 15 mg[a] (*N* = 14)	Upadacitinib 30 mg[a] (*N* = 14)
Overview					
Any AE	9 (90.0)	8 (80.0)	6 (66.7)	13/8.3 (155.8)	12/4.6 (260.9)
AE with reasonable possibility of being drug related	2 (20.0)	1 (10.0)	1 (11.1)	8/19.9 (40.2)	6/21.4 (28.1)
Severe AE	0	1 (10.0)	0	2/28.3 (7.1)	1/24.9 (4.0)
Serious AE	0	0	0	3/28.0 (10.7)[b]	0/27.2
AE leading to discontinuation of study drug	0	0	0	1/30.8 (3.2)	1/27.1 (3.7)
Deaths	0	0	0	0/31.1	0/27.2
Most common AEs[c]					
Acne	3 (30.0)	3 (30.0)	1 (11.1)	6/20.6 (29.2)	7/13.7 (51.2)
Nasopharyngitis	1 (10.0)	1 (10.0)	3 (33.3)	4/24.5 (16.4)	7/18.3 (38.2)
Influenza	1 (10.0)	1 (10.0)	0	2/27.0 (7.4)	2/23.2 (8.6)
Upper RTI	3 (30.0)	1 (10.0)	0	3/24.1 (12.4)	1/24.7 (4.0)

Table S3 Short- and long-term safety of upadacitinib among adolescents in the Rising Up study

	Week 16, *n* (%)			Week 112; *n*/PY (*n*/100 PY)	
Parameter	**Upadacitinib 15 mg +TCS (*N* = 10)**	**Upadacitinib 30 mg +TCS (*N* = 10)**	**Placebo +TCS (*N* = 9)**	**Upadacitinib 15 mg[a] (*N* = 14)**	**Upadacitinib 30 mg[a] (*N* = 14)**
Anemia	0	0	0	3/28.0 (10.7)	0/27.2
Asthma	0	1 (10.0)	0	1/29.2 (3.4)	2/23.5 (8.5)
Blood CPK increased	1 (10.0)	0	0	2/27.2 (7.4)	1/26.8 (3.7)
Headache	0	0	0	1/30.2 (3.3)	2/25.6 (7.8)
Otitis externa	0	0	0	2/28.5 (7.0)	1/26.2 (3.8)
Pharyngitis	0	1 (10.0)	0	1/29.7 (3.4)	2/23.8 (8.4)
Pyrexia	1 (10.0)	1 (10.0)	0	2/27.5 (7.3)	1/24.9 (4.0)
Skin papilloma	0	0	0	1/30.8 (3.2)	2/25.9 (7.7)
Enterocolitis	0	0	0	0/31.1	2/25.3 (7.9)
Gastroenteritis	0	0	1 (11.1)	2/30.2 (6.6)	0/27.2
Hepatic function abnormal	0	0	0	2/30.2 (6.6)	0/27.2
Herpes zoster	0	0	0	0/31.1	2/26.3 (7.6)
Impetigo	0	0	0	2/30.0 (6.7)	0/27.2

Table S3 Short- and long-term safety of upadacitinib among adolescents in the Rising Up study

	Week 16, *n* (%)			Week 112; *n*/PY (*n*/100 PY)	
Parameter	**Upadacitinib 15 mg +TCS (*N* = 10)**	**Upadacitinib 30 mg +TCS (*N* = 10)**	**Placebo +TCS (*N* = 9)**	**Upadacitinib 15 mg[a] (*N* = 14)**	**Upadacitinib 30 mg[a] (*N* = 14)**

AE, adverse event; CPK, creatine phosphokinase; n/100 PY, number of patients with at least one event per 100 patient-years; n/PY, number of patients with at least one event divided by the total patient years for patients at risk of an event; RTI, respiratory tract infection; TCS, topical corticosteroids; UPA, upadacitinib

[a]After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion

[b]Serious AEs included appendicitis (possibly related to study drug), concussion due to accident (unrelated to study drug), and irritable bowel syndrome (unrelated to study drug)

[c]Most common AEs are defined as those occurring in ≥ two patients in either adolescent treatment group at week 112

Table S4 Exposure-adjusted event rates for AESIs through 52 weeks and 112 weeks in the Rising Up study

	Week 52		Week 112	
AESI, events (E/100 PY)	**Upadacitinib 15 mg[a] (*N* = 133; PY = 151.2)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 149.7)**	**Upadacitinib 15 mg[a] (*N* = 133; PY = 289.4)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 287.7)**
Serious infections	4 (2.6)	4 (2.7)	6 (2.1)	4 (1.4)
Opportunistic infection excluding TB and herpes zoster	10 (6.6)	3 (2.0)	16 (5.5)	7 (2.4)
Malignancy	0	0	1 (0.3)	0
NMSC	0	0	0	0
Malignancy excluding NMSC	0	0	1 (0.3)	0
Lymphoma	0	1 (0.7)	0	1 (0.3)
Hepatic disorder	8 (5.3)	11 (7.3)	18 (6.2)	19 (6.6)
Gastrointestinal perforation	0	0	0	0
Anemia	4 (2.6)	7 (4.7)	5 (1.7)	9 (3.1)
Neutropenia	2 (1.3)	8 (5.3)	2 (0.7)	12 (4.2)
Lymphopenia	0	1 (0.7)	0	2 (0.7)
Herpes zoster	8 (5.3)	21 (14.0)	21 (7.3)	37 (12.9)
CPK elevation	3 (2.0)	6 (4.0)	6 (2.1)	13 (4.5)

Table S4 Exposure-adjusted event rates for AESIs through 52 weeks and 112 weeks in the Rising Up study

	Week 52		Week 112	
AESI, events (E/100 PY)	**Upadacitinib 15 mg[a] (*N* = 133; PY = 151.2)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 149.7)**	**Upadacitinib 15 mg[a] (*N* = 133; PY = 289.4)**	**Upadacitinib 30 mg[a] (*N* = 136; PY = 287.7)**
Renal dysfunction	0	0	0	0
Active TB	0	0	0	0
Adjudicated MACE[b]	1 (0.7)	0	1 (0.3)	0
Adjudicated VTE[c]	0	0	0	0

AESI, adverse event of special interest; MACE, major adverse cardiovascular event, E/100 PY, events per 100 patient-years; NMSC, non-melanoma skin cancer; TB, tuberculosis; VTE, venous thromboembolic events

[a]All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion

[b]MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

[c]VTE is defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal)

Table S5 Short-term incidence and long-term exposure-adjusted incidence rates for AESIs among adolescents in the Rising Up study

	Week 16, *n* (%)			Week 112; *n*/PY (*n*/100 PY)	
Parameter	**Upadacitinib 15 mg + TCS (*N* = 10)**	**Upadacitinib 30 mg + TCS (*N* = 10)**	**Placebo + TCS (*N* = 9)**	**Upadacitinib 15 mg[a] (*N* = 14)**	**Upadacitinib 30 mg[a] (*N* = 14)**
Serious infections	0	0	0	1/29.6 (3.4)	0/27.2
Opportunistic infection excluding TB and herpes zoster	1 (10.0)	0	0	1/30.8 (3.2)	0/27.2
Malignancy	0	0	0	0/31.1	0/27.2
NMSC	0	0	0	0/31.1	0/27.2
Malignancy excluding NMSC	0	0	0	0/31.1	0/27.2
Lymphoma	0	0	0	0/31.1	1/27.1 (3.7)
Hepatic disorder	0	0	0	3/29.5 (10.2)	1/26.1 (3.8)
Gastrointestinal perforation	0	0	0	0/31.1	0/27.2
Anemia	0	0	0	3/28.0 (10.7)	0/27.2
Neutropenia	0	0	0	0/31.1	1/26.1 (3.8)
Lymphopenia	0	0	0	0/31.1	0/27.2
Herpes zoster	0	0	0	0/31.1	2/26.3 (7.6)
CPK elevation	1 (10.0)	0	0	2/27.2 (7.4)	1/26.8 (3.7)

Table S5 Short-term incidence and long-term exposure-adjusted incidence rates for AESIs among adolescents in the Rising Up study

	Week 16, *n* (%)			Week 112; *n*/PY (*n*/100 PY)	
Parameter	**Upadacitinib 15 mg + TCS (*N* = 10)**	**Upadacitinib 30 mg + TCS (*N* = 10)**	**Placebo + TCS (*N* = 9)**	**Upadacitinib 15 mg[a] (*N* = 14)**	**Upadacitinib 30 mg[a] (*N* = 14)**
Renal dysfunction	0	0	0	0/31.1	0/27.2
Active TB	0	0	0	0/31.1	0/27.2
Adjudicated MACE	0	0	0	0/31.1	0/27.2
Adjudicated VTE	0	0	0	0/31.1	0/27.2

AESI, adverse event of special interest; MACE, major adverse cardiovascular event, n/100 PY, number of patients with at least one event per 100 patient-years; n/PY, number of patients with at least one event divided by the total patient years for patients at risk of an event; NMSC, non-melanoma skin cancer; TB, tuberculosis; TCS, topical corticosteroids; VTE, venous thromboembolic events

[a]After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion

Table 6 Institutional review boards and ethics committees for the Rising Up study

IRB/IEC Name	City	State/Province, Country
Nihon University Hospitals' Joint Institutional Review Board	Itabashi-Ku	Tokyo, Japan
Kansai Rosai Hospital IRB	Amagasaki-shi	Hyogo, Japan
Toyama Prefectural Central Hospital Institutional Review Board	Toyama-shi	Toyama, Japan
Nihonbashi Sakura Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Tokyo Rosai Hospital IRB	Ohta-ku	Tokyo, Japan
Nihonbashi Sakura Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Tokyo Eki Center Building Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Asahikawa Medical University Hospital Institutional Review Board	Asahikawa-shi	Hokkaido, Japan
Fukuyama City Hospital IRB	Fukuyama-shi	Hiroshima, Japan
Nakameguro Atlas Clinic IRB	Meguro-ku	Tokyo, Japan
Japan Conference of Clinical Research	Toshima-ku	Tokyo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Central Japan International Medical Center IRB	Minokamo-shi	Gifu, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nakameguro Atlas Clinic IRB	Meguro-ku	Tokyo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan

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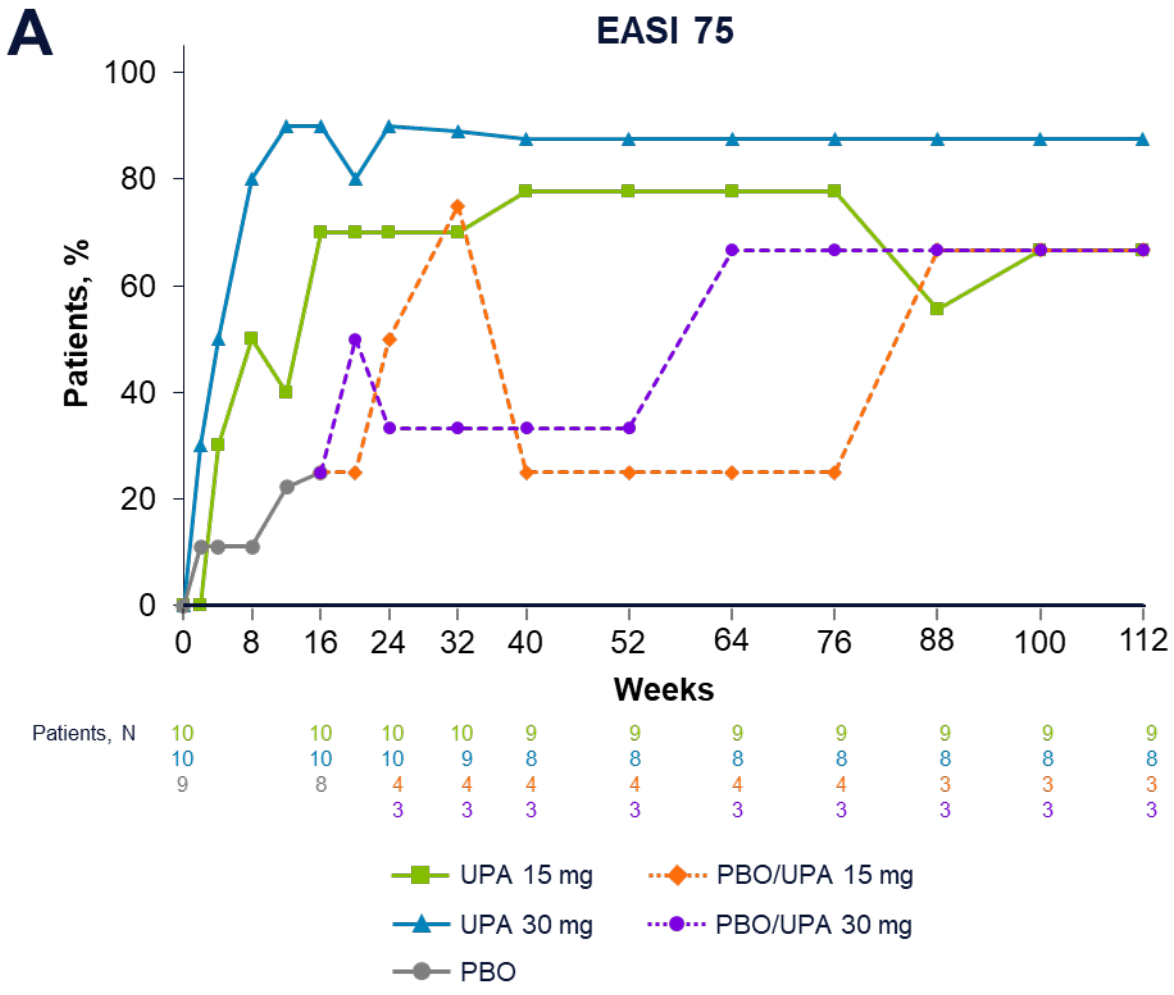
IRB/IEC Name	City	State/Province, Country
Hyogo Prefectural Amagasaki General Medical Center IRB	Amagasaki-shi	Hyogo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Tokai University Hospital–Isehara Campus	Isehara-Shi	Kanagawa, Japan
Nihonbashi Sakura Clinic Institution Review Borad	Chuo-ku	Tokyo, Japan
Nakameguro Atlas Clinic IRB	Meguro-ku	Tokyo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nihonbashi Sakura Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Ichinomiya Municipal Hospital Institutional Review Board	Ichinomiya-shi	Aichi, Japan
Tokyo Eki Center Building Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nagoya City University Institutional Review Board	Nagoya-shi	Aichi, Japan
Gunma University Hospital Institutional Review Board	Maebashi-shi	Gunma, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nippon Medical School Musashi Kosugi Hospital Institutional Review Board	Kawasaki-shi	Kanagawa, Japan
Kiryu Kosei General Hospital Institutional Review Board	KIRYU-SHI	Gunma, Japan
Kobe University Hospital Institutional Review Board	Kobe-shi	Hyogo, Japan

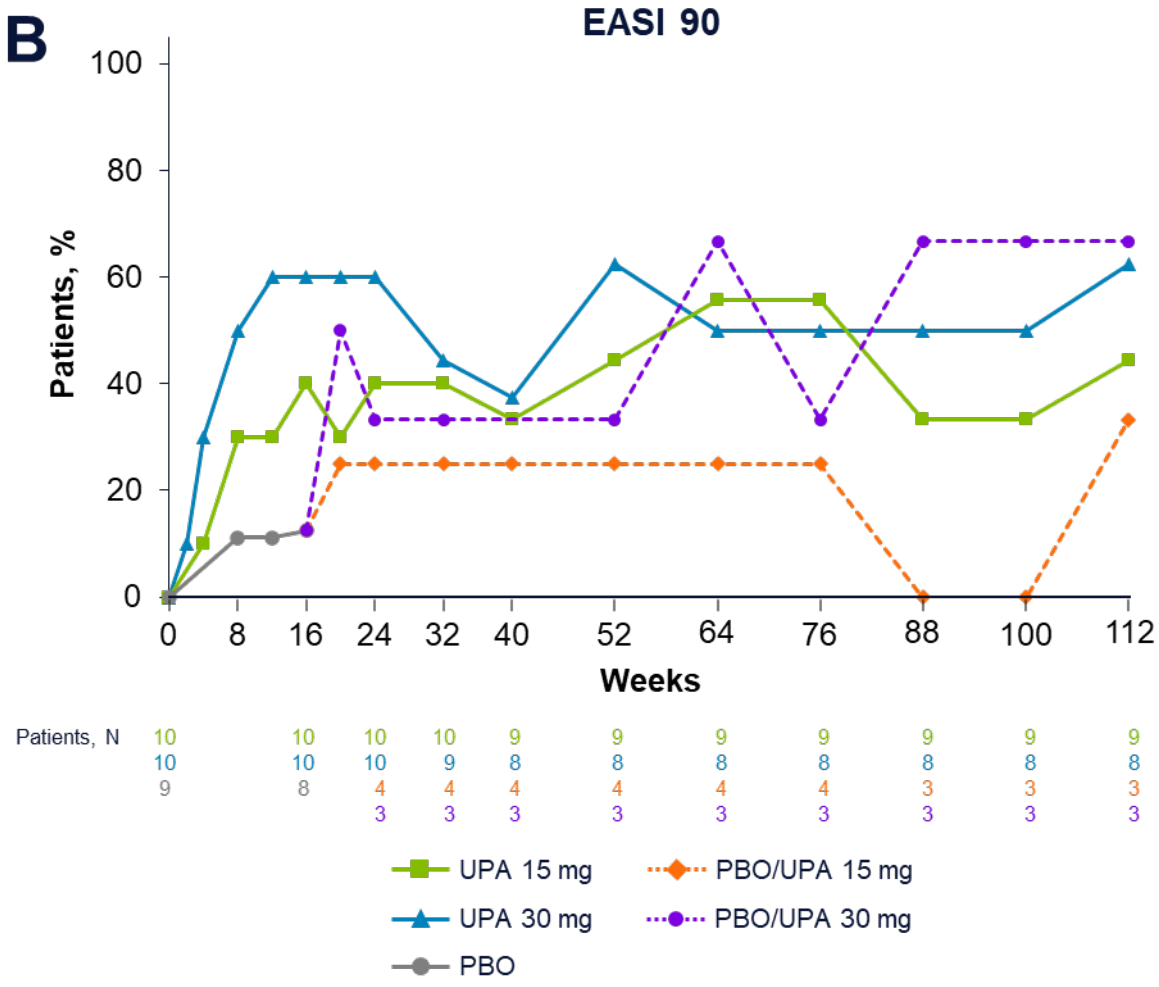
Table 6 Institutional review boards and ethics committees for the Rising Up study

IRB/IEC Name	City	State/Province, Country
Yokohama Rosai Hospital Institutional Review Board	Yokhama-shi	Kanagawa, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nagasaki University Hospital Institutional Review Board	Nagasaki-shi	Nagasaki, Japan
Tokyo Allergy and Respiratory Disease Research Institute IRB	Taito-ku	Tokyo, Japan
Shizuoka General Hospital Institutional Review Board	Shizuoka shi	Shizuoka, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Hokkaido P.W.F.A.C Sapporo-Kosei General Hospital Institutional Review Board	Sapporo-shi	Hokkaido, Japan
Tokyo Eki Center Building Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Nihonbashi Sakura Clinic Institutional Review Board	Chuo-ku	Tokyo, Japan
Joint Institutional Review Board	Kochi-shi	Kochi, Japan
Nagaoka Red Cross Hospital Institutional Review Board	Nagaoka-shi	Niigata, Japan

IEC, international ethics committee; IRB, institutional review board

Fig. S1 Adolescents achieving EASI 75 and EASI 90 from baseline to week 112. Data are presented as observed cases with no imputation for missing data. All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion. EASI 75/90, ≥ 75%/≥ 90% improvement in Eczema Area Severity Index; PBO, placebo; UPA, upadacitinib




B
EASI 90
Patients, %
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60
40
20
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8
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Patients, N
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9 8 4 3
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9 8 3 3
UPA 15 mg
UPA 30 mg
PBO
PBO/UPA 15 mg
PBO/UPA 30 mg

Fig. 2 Adolescents achieving vIGA-AD 0/1[a] from baseline to week 112. Data are presented as observed cases with no imputation for missing data. All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion. [a]Patients achieving vIGA-AD 0/1 with at least two grades of reduction from baseline. AD, atopic dermatitis; PBO, placebo; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator Global Assessment for AD score of clear or almost clear.

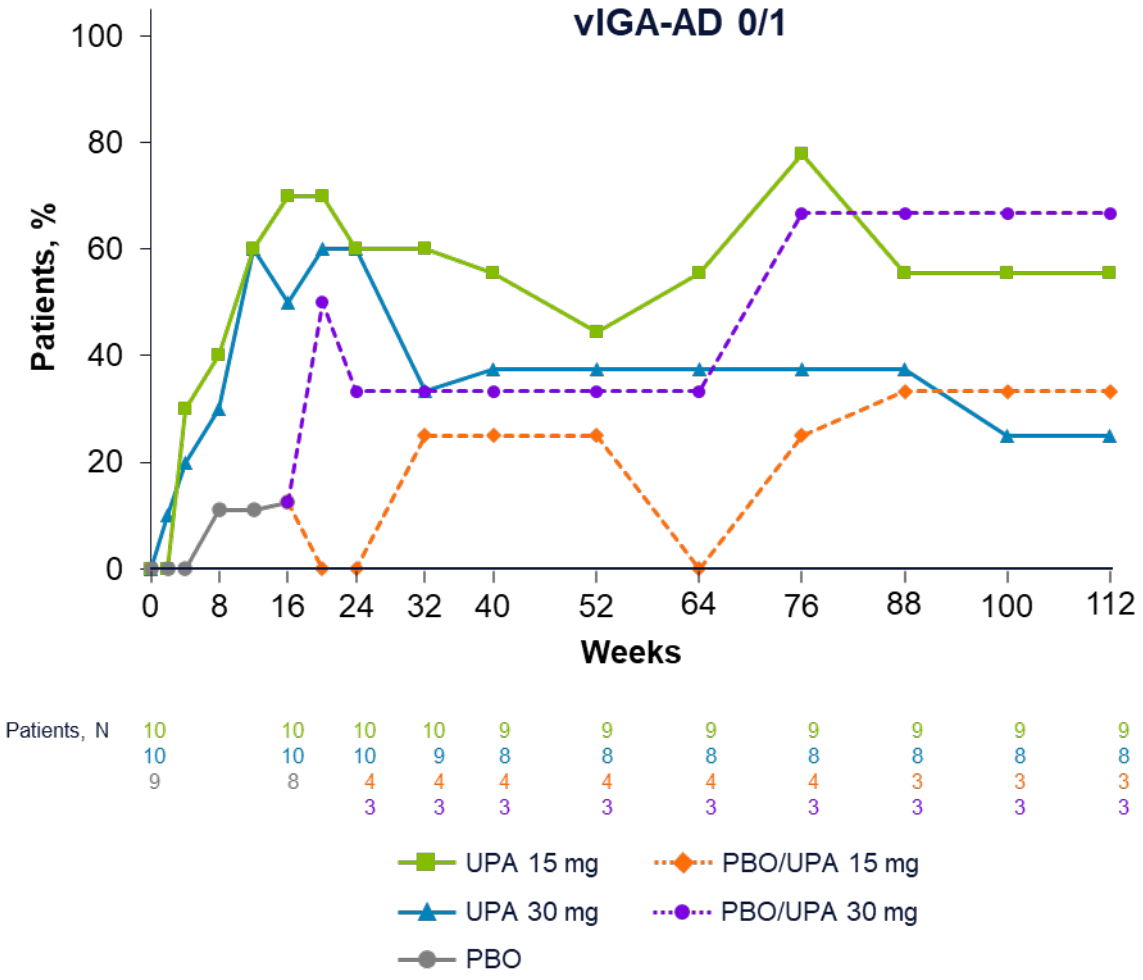

Fig. 3 Adolescents achieving WP-NRS ≥ 4-point improvement[a] from baseline to week 112. Data are presented as observed cases with no imputation for missing data. All patients received concomitant topical corticosteroids from baseline to week 16. After week 16, the use of concomitant topical corticosteroids was no longer required and was administered per investigator discretion. [a]Among patients with WP-NRS scores ≥ 4 at baseline. PBO, placebo; UPA, upadacitinib; WP-NRS, Worst Pruritus Numerical Rating Scale.