

Efficacy and safety of switching from dupilumab to upadacitinib versus continuous upadacitinib in moderate-to-severe atopic dermatitis: results from an open-label extension of the phase 3, randomized, controlled trial (Heads Up)

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Supplemental Table I. Demographics and baseline disease characteristics among those patients who entered the open-label extension study

Characteristic	DUPI → UPA N = 245	UPA → UPA N = 239
Sex, n (%)		
Female	105 (42.9)	107 (44.8)
Male	140 (57.1)	132 (55.2)
Age, y, mean (SD)	35.6 (13.2)	36.4 (14.6)
Age group, n (%)		
<40 years	169 (69.0)	156 (65.3)
≥40 to < 65 years	68 (27.8)	72 (30.1)
≥65 years	8 (3.3)	11 (4.6)
Weight (kg), mean (SD)	75.3 (18.8)	78.8 (21.7)
Disease duration since diagnosis, (y), mean (SD)	24.9 (13.6)	23.8 (14.9)
Previous systemic treatment, n (%)	128 (52.2)*	130 (54.4)†
EASI, mean (SD)		
Heads Up	28.8 (11.1)	30.5 (12.3)
OLE	3.3 (4.2)	2.6 (4.3)
BSA in percentage, mean (SD)		
Heads Up	45.1 (22.2)	47.4 (23.4)
OLE	7.1 (10.0)	5.3 (9.1)
vIGA-AD (Heads Up), n (%)		
3 (moderate)	120 (49.0)	120 (50.2)
4 (severe)	125 (51.0)	119 (49.8)
Worst Pruritus NRS (weekly average), mean (SD)		
Heads Up	7.6 (1.6)	7.4 (1.6)
OLE	3.0 (2.4)	2.2 (2.6)

BMI, Body mass index; *BSA*, body surface area; *DUPI*, dupilumab; *EASI*, Eczema Area and Severity Index; *NRS*, numerical rating scale; *OLE*, open-label extension; *UPA*, upadacitinib; *vIGA-AD*, validated Investigator Global Assessment for Atopic Dermatitis.

*At baseline of Heads Up, 175 (50.9%) of the 344 patients randomized to dupilumab had received previous systemic treatment.

†At baseline of Heads Up, 178 (51.1%) of the 348 patients randomized to upadacitinib had received previous systemic treatment.

Supplemental Table II. Overview of treatment-emergent adverse events with upadacitinib 30 mg through week 40 (week 16 of the OLE study) among those patients who entered the OLE study

Event (E/100PY)	N = 484 PY = 383.9
AE*	1528 (398.0)
Serious AE	20 (5.2)
AE leading to discontinuation of study drug	17 (4.4)
AE leading to death [†]	1 (0.3) [‡]

AE, Adverse event; OLE, open-label extension; PY, patient years.

*Defined as any treatment-emergent adverse events that begin or worsen in severity after initiation of upadacitinib during Heads Up study or the OLE study through 30 days following the last dose of upadacitinib.

[†]As assessed by the investigator.

[‡]Bone tuberculosis deemed to have no reasonable possibility of being related to study drug in a 69-year-old female patient with no significant risk factors other than a history of missionary work.

Supplemental Table III. Serious adverse events during the 24-week double-blinded period of Heads Up and 16 weeks of the open-label extension study

System order class Serious adverse events (E/100PY)	Heads Up		Upadacitinib exposure during Heads Up and the open-label extension study
	DUPI n = 344 PY = 151.0	UPA n = 348 PY = 154.8	N = 484 PY = 383.9
Any serious adverse event	9 (6.0)	21 (13.6)	20 (5.2)
Blood and lymphatic system disorders			
Lymphopenia	0	1 (0.6)	0
Neutropenia	0	1 (0.6)	0
Eye disorders			
Glaucoma	0	1 (0.6)	1 (0.3)
Gastrointestinal disorders			
Incarcerated umbilical hernia	1 (0.7)	0	0
Pancreatitis	0	0	1 (0.3)
Immune system disorders			
Food allergy	0	1 (0.6)	1 (0.3)
Type I hypersensitivity	1 (0.7)	0	0
Infections and infestations			
Beta hemolytic streptococcal infection	0	1 (0.6)	0
Bone tuberculosis	0	0	1 (0.3)
Bullous impetigo	0	0	1 (0.3)
Cellulitis	1 (0.7)	0	0
COVID-19 pneumonia	0	0	2 (0.5)
Eczema herpeticum	0	0	2 (0.5)
Erysipelas	1 (0.7)	0	0
Herpes simplex	0	1 (0.6)	0
Influenza	0	1 (0.6)	0

Pelvic abscess	0	1 (0.6)	0
Pneumonia	0	1 (0.6)	1 (0.3)
Sepsis	0	1 (0.6)	0
Staphylococcal infection	0	1 (0.6)	0
Urinary tract infection	0	1 (0.6)	0
Injury, poisoning and procedural complications			
Foot fracture	0	0	1 (0.3)
Joint injury	0	1 (0.6)	1 (0.3)
Pelvic fracture	1 (0.7)	0	0
Investigations			
Blood creatine phosphokinase increased	1 (0.7)	0	0
Hemoglobin decreased	0	0	1 (0.3)
Metabolism and nutrition disorders			
Hyperglycemia	0	1 (0.6)	0
Musculoskeletal and connective tissue disorders			
Bursitis	2 (1.3)	0	0
Neoplasm benign, malignant, and unspecified (including cysts and polyps)			
Invasive ductal breast carcinoma	0	1 (0.6)	0
Parathyroid tumor benign	0	1 (0.6)	1 (0.3)
Uterine leiomyoma	0	0	1 (0.3)
Nervous system disorders			
Headache	0	0	1 (0.3)
Psychiatric disorders			
Intentional self-injury	0	1 (0.6)	1 (0.3)
Renal and urinary disorders			
Acute kidney injury	0	1 (0.6)	0
Reproductive system and breast disorders			
Endometriosis	0	0	1 (1.3)
Respiratory, thoracic, and mediastinal disorders			

Asthma	1 (0.7)	0	0
Skin and subcutaneous tissue disorders			
Dermatitis atopic	0	1 (0.6)	0
Eczema	0	1 (0.6)	0
Surgical and medical procedures			
Abortion induced	0	1 (0.6)	1 (0.3)
Vascular disorders			
Essential hypertension	0	0	1 (0.3)

DUPI, Dupilumab; *PY*, patient-years; *UPA*, upadacitinib.

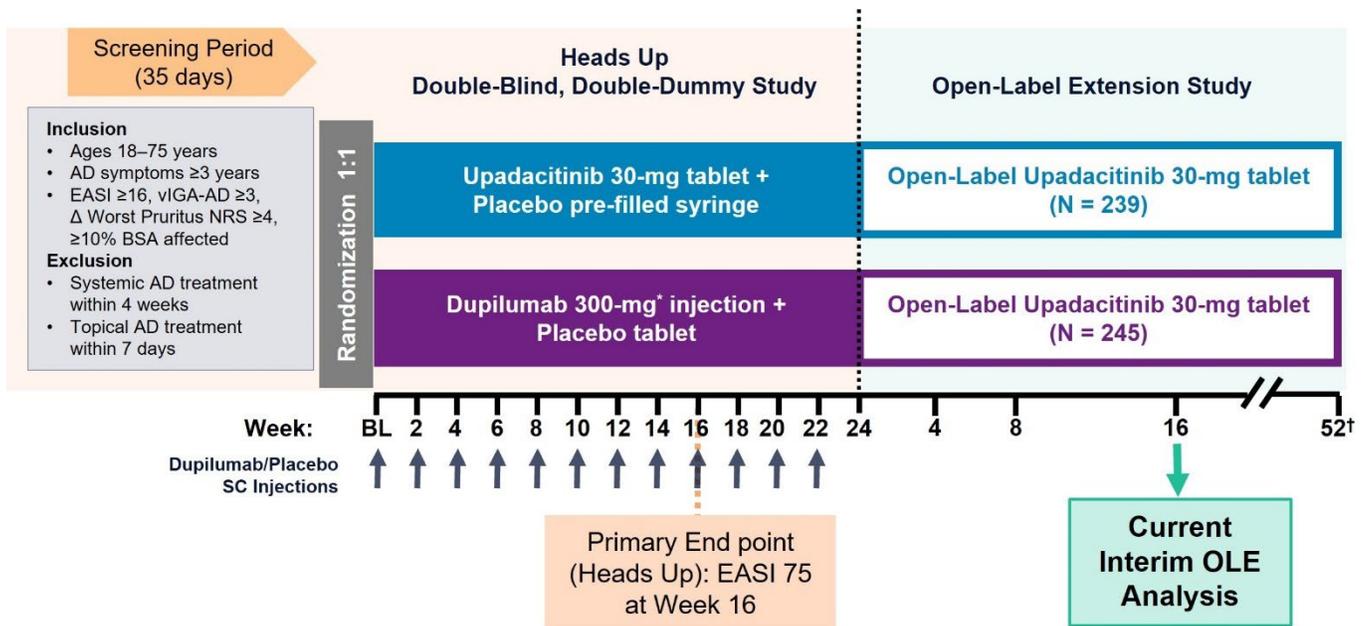
Supplemental Table IV. Treatment-emergent adverse events of special interest with upadacitinib 30 mg through week 40 (week 16 of the OLE study) among those patients who entered the OLE

Events (E/100PY)	N = 484 PY = 383.9
Serious infections	7 (1.8)
Opportunistic infections (excluding TB and herpes zoster)	6 (1.6)
Malignancy*	0
Lymphoma	0
Hepatic disorder	24 (6.3)
Adjudicated gastrointestinal perforations	0
Anemia	10 (2.6)
Neutropenia	14 (3.6)
Lymphopenia	3 (0.8)
Herpes zoster	25 (6.5)
Creatine phosphokinase elevation	69 (18.0)
Renal dysfunction	0
Active TB	1 (0.3)
Adjudicated MACE	0
Adjudicated VTE	0

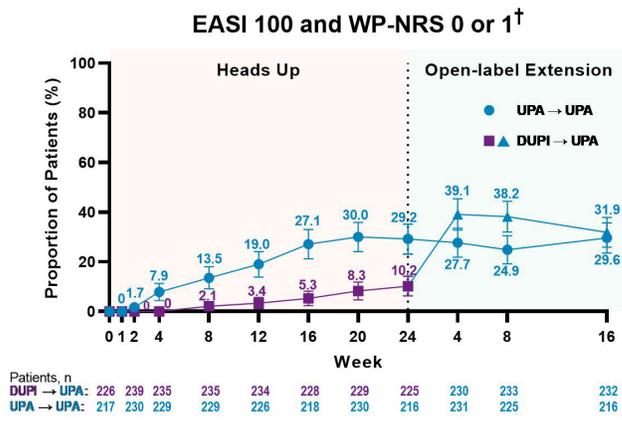
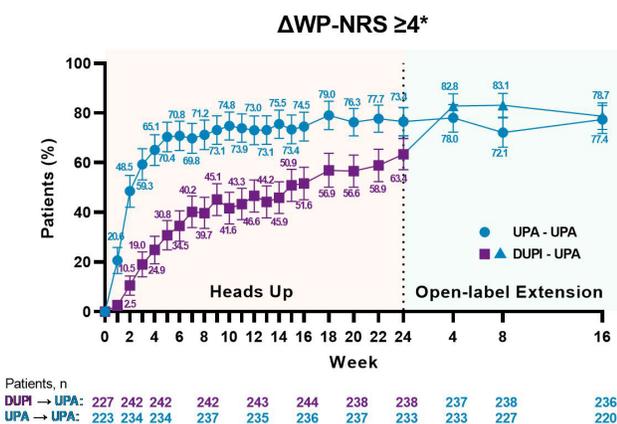
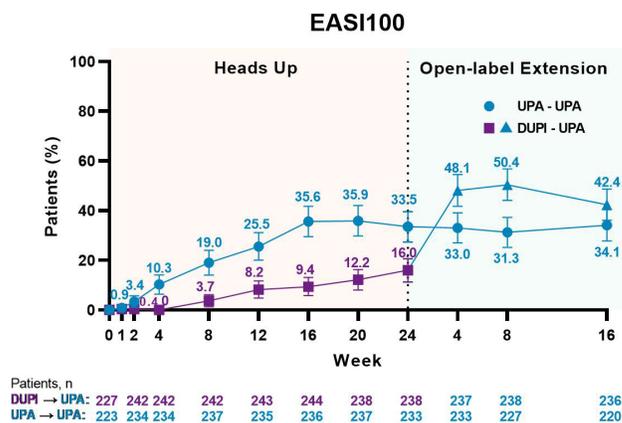
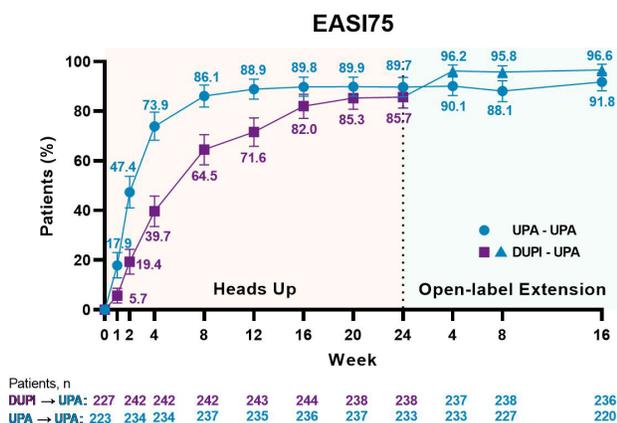
MACE, Major adverse cardiovascular event; OLE, open-label extension; PY, patient years; TB, tuberculosis; VTE, venous thromboembolic event.

*Includes nonmelanoma skin cancer.

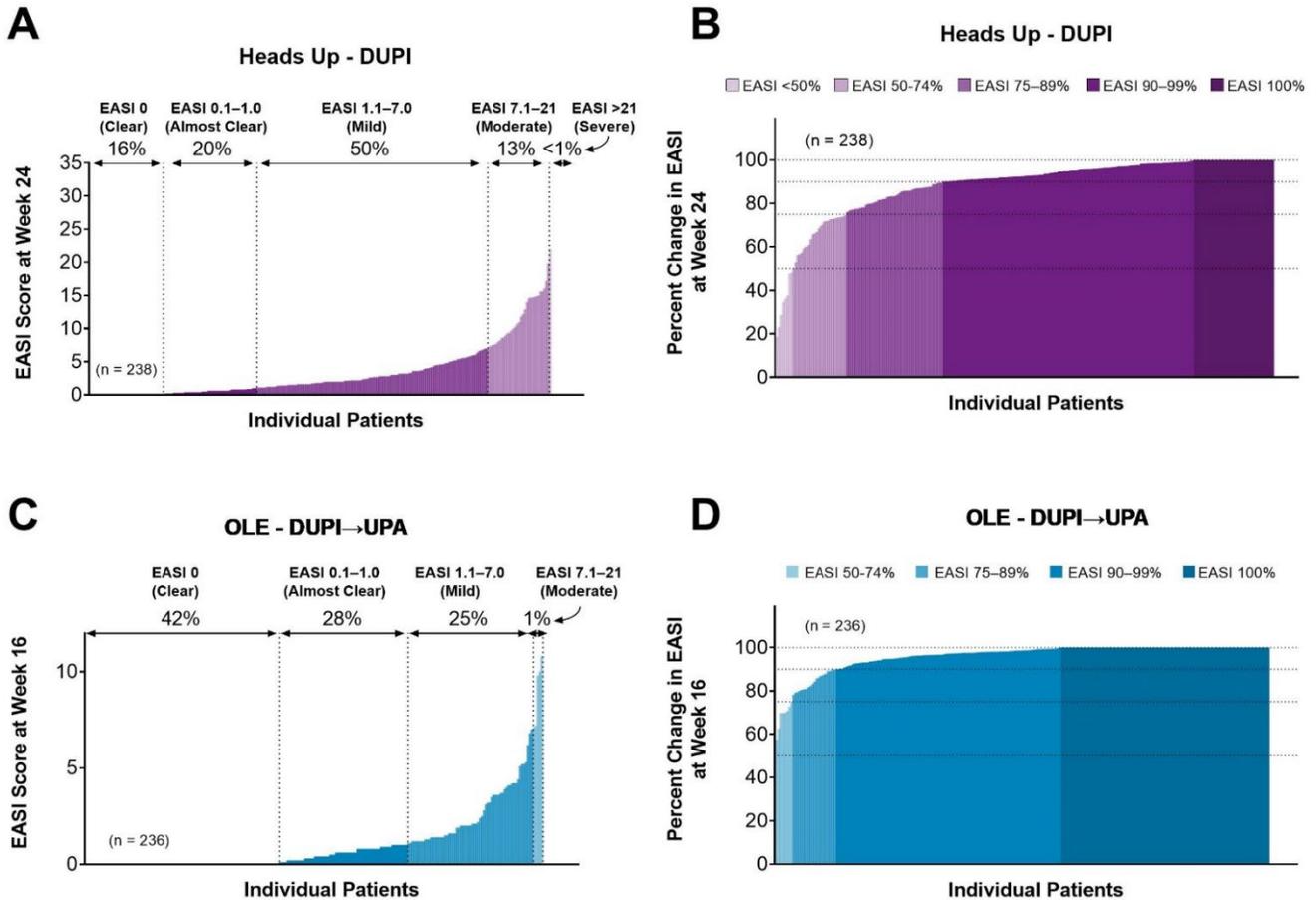
Supplemental Fig 1. Study design of Heads Up and the open-label extension. *Dupilumab 300 mg SC injection administered every other week starting at the week 2 visit and until the week 22 visit, after an initial 600 mg SC injection loading at the baseline visit. † Consists of 132 weeks in some countries. *AD*, Atopic dermatitis; *BL*, baseline; *BSA*, body surface area; *EASI*, Eczema Area and Severity Index; *NRS*, Numerical Rating Scale; *OLE*, open-label extension; *SC*, subcutaneous; *vIGA-AD*, validated Investigator Global Assessment for Atopic Dermatitis.



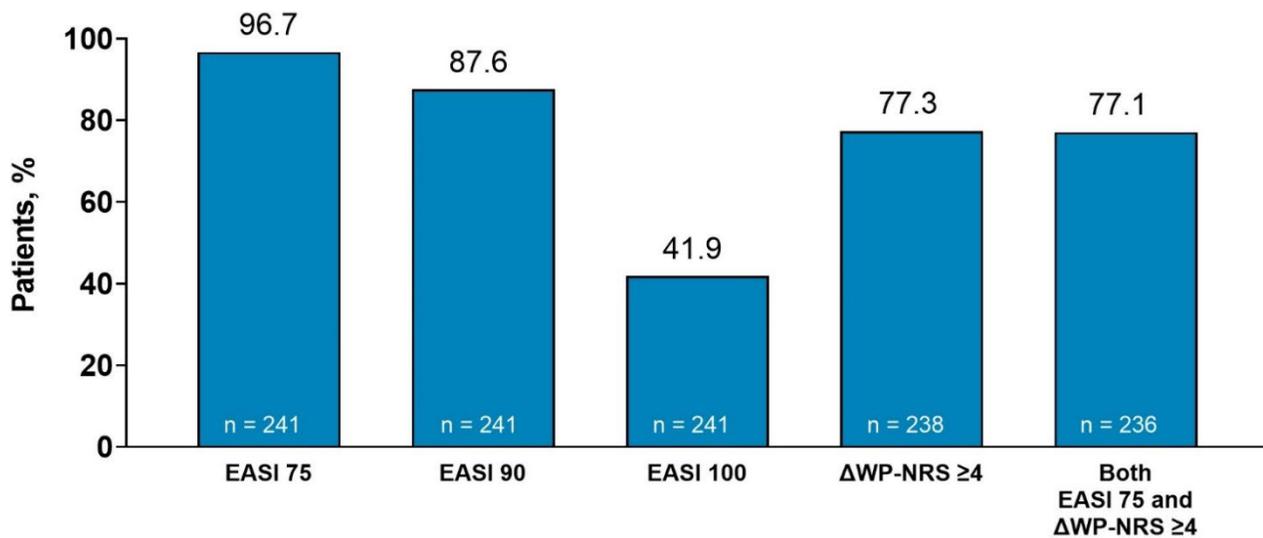
Supplemental Fig 2. Achievement of **A**, EASI75; **B**, EASI100; **C**, Δ WP-NRS ≥ 4 from baseline; and **D**, concurrent EASI100 and WP-NRS 0 or 1 over time during Heads Up and the open-label extension (OC). *Assessed in patients with baseline WP-NRS >1. Error bars indicate 95% confidence interval. *DUPI*, Dupilumab; *EASI75*, at least a 75% improvement from baseline in Eczema Area and Severity Index; *EASI100*, a 100% improvement from baseline in EASI; *OC*, observed case; *OLE*, open-label extension; *UPA*, upadacitinib; *WP-NRS*, Worst Pruritus-Numerical Rating Scale.



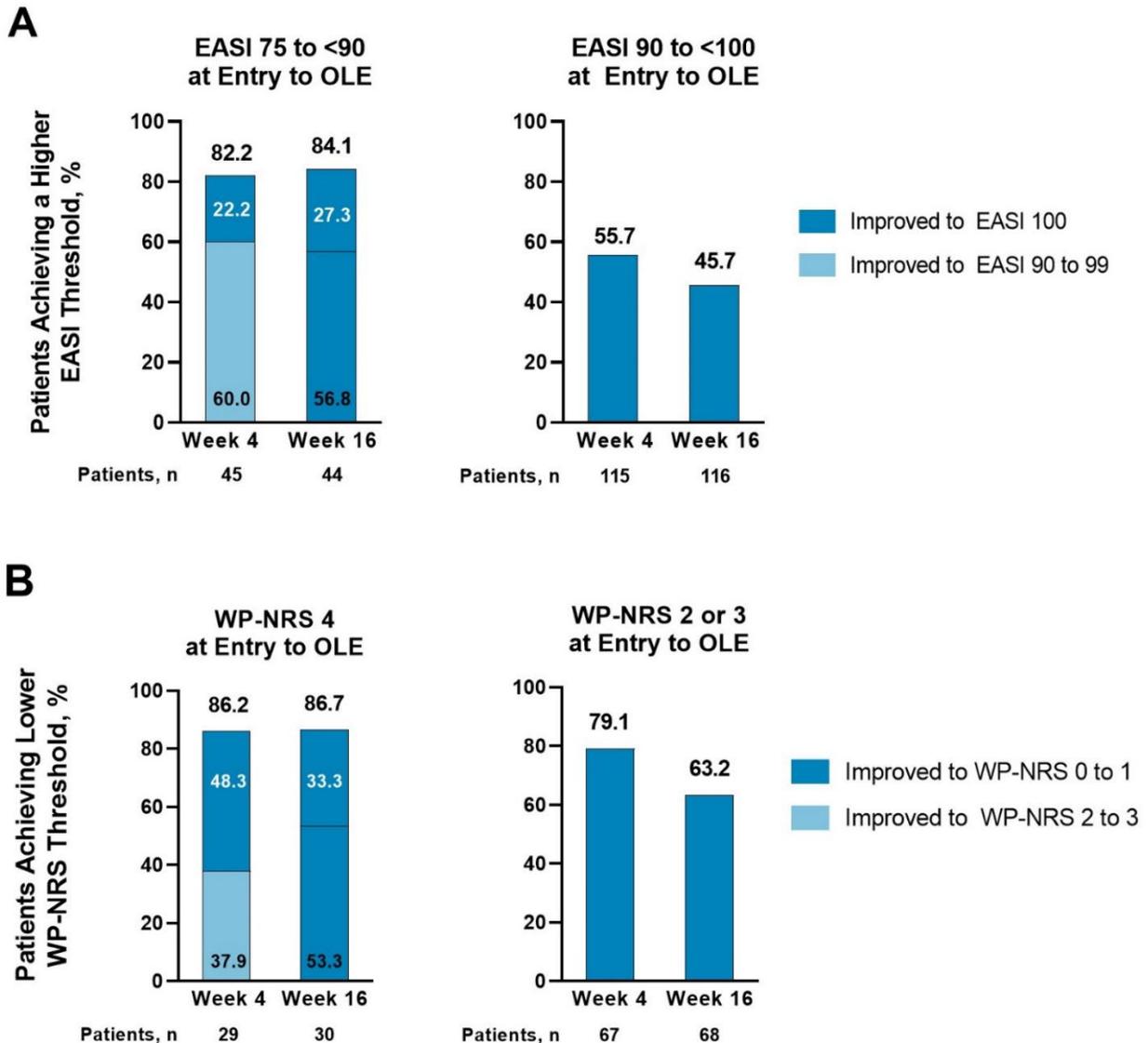
Supplemental Fig 3. A and B, Distribution of EASI and percent change in EASI from baseline after 24 weeks of dupilumab during Heads Up. **C and D**, After 16 weeks of upadacitinib during the open-label extension among patients who switched to upadacitinib (OC). *DUPI*, Dupilumab; *EASI*, Eczema Area and Severity Index; *OC*, observed case; *OLE*, open-label extension; *UPA*, upadacitinib. Dotted lines in panel **B** and **D** represent 50, 75, 90, and 100% change in EASI.



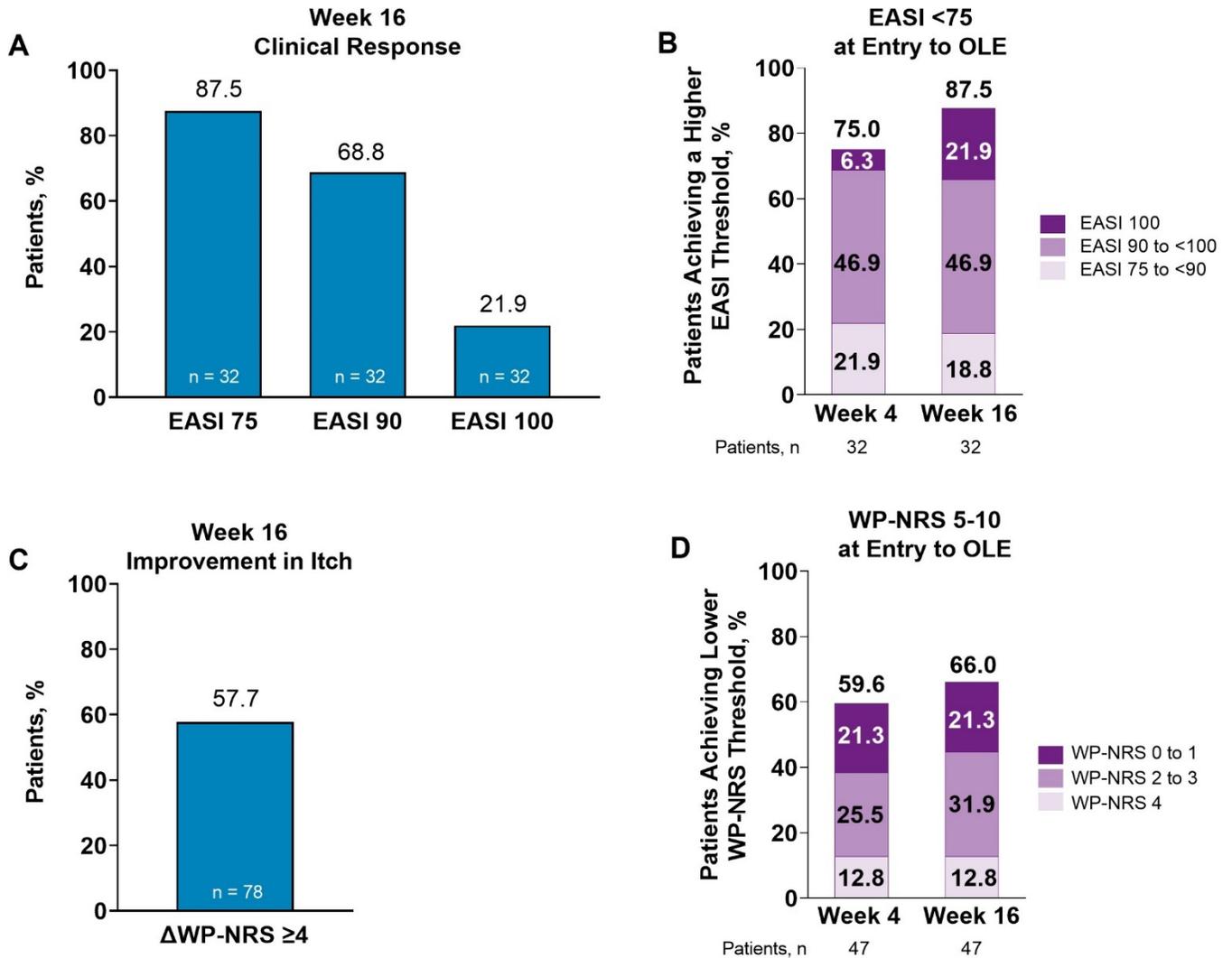
Supplemental Fig 4. Achievement of efficacy end points at week 16 of the open-label extension among patients who received dupilumab during Heads Up and switched to upadacitinib (LOCF). *EASI75*, At least a 75% improvement from baseline in Eczema Area and Severity Index; *EASI90*, at least a 90% improvement from baseline in EASI; *EASI100*, a 100% improvement from baseline in EASI; *LOCF*, last observation carried forward; *WP-NRS*, Worst Pruritus-Numerical Rating Scale.



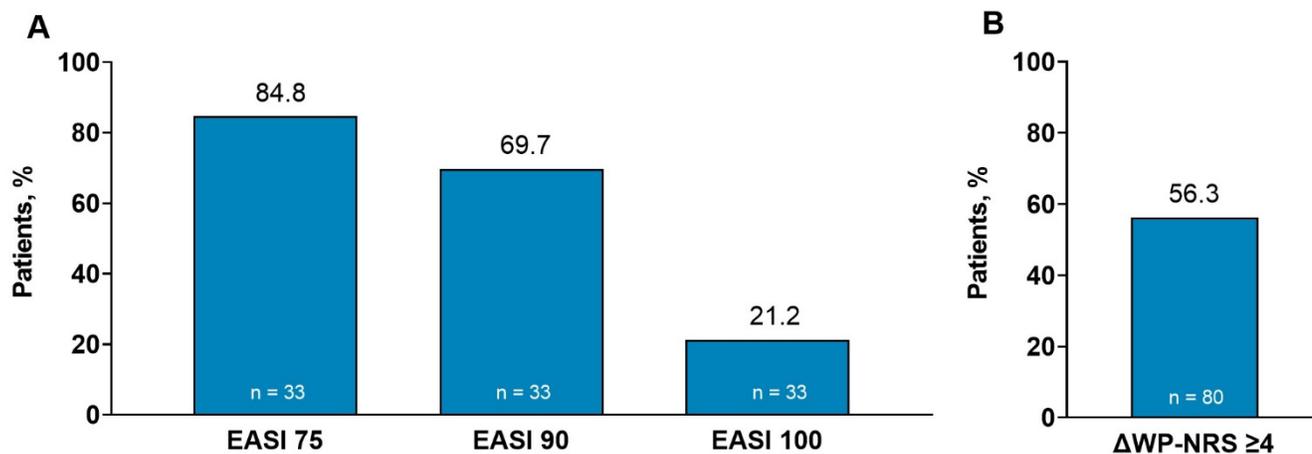
Supplemental Fig 5. Incremental improvement in clinical response and itch among patients with prior dupilumab response who switched to upadacitinib during the open-label extension and had achieved **A**, EASI75 .**B**, Had a WP-NRS score ≤ 4 after 24 weeks of dupilumab during Heads Up (OC). *DUPI*, Dupilumab; *EASI75*, at least a 75% improvement from baseline in Eczema Area and Severity Index; *EASI90*, at least a 90% improvement from baseline in EASI; *EASI100*, a 100% improvement from baseline in EASI; *ITT*, intent-to-treat population; *OC*, observed case; *OLE*, open-label extension; *UPA*, upadacitinib; *WP-NRS*, Worst Pruritus-Numerical Rating Scale.



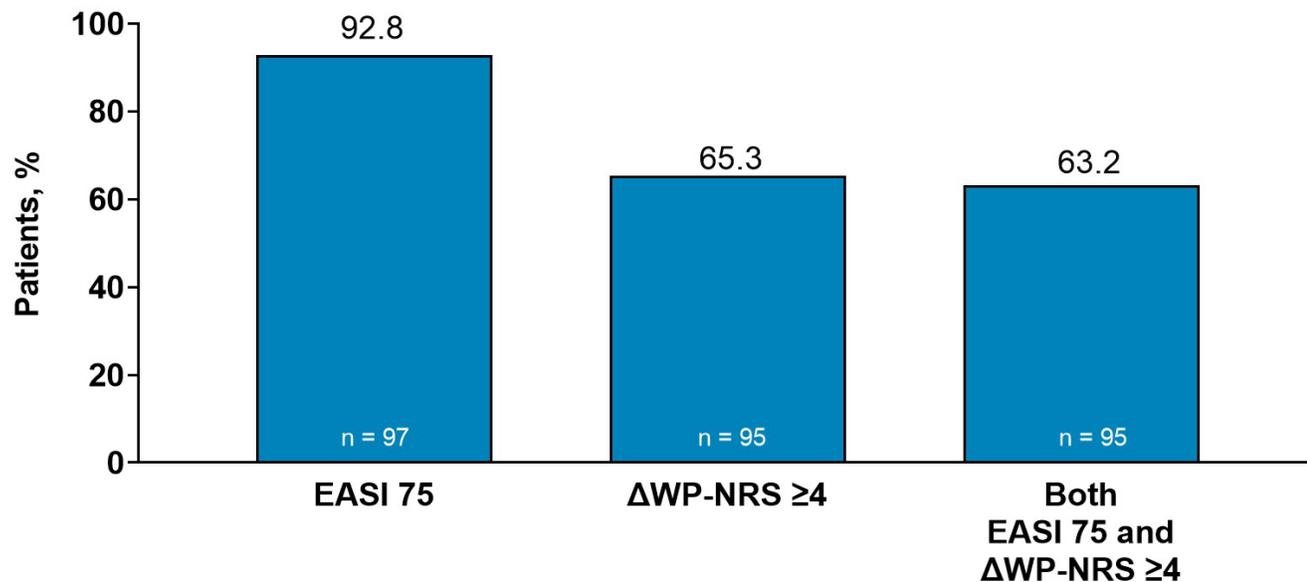
Supplemental Fig 6. Achievement in clinical response and improvement in itch with upadacitinib among patients with an inadequate response to prior dupilumab who **A** and **B**, did not achieve EASI75. **C**, Did not achieve Δ WP-NRS ≥ 4 from baseline. **D**, Had a WP-NRS score >4 after 24 weeks of dupilumab during Heads Up ($n = 47$) (OC). EASI75, at least a 75% improvement from baseline in Eczema Area and Severity Index; EASI90, at least a 90% improvement from baseline in EASI; EASI100, a 100% improvement from baseline in EASI; OC, observed cases; WP-NRS, Worst Pruritus-Numerical Rating Scale.



Supplemental Fig 7. Achievement in clinical response and improvement in itch at week 16 of upadacitinib among patients who **A**, Did not achieve EASI75. **B**, Did not achieve Δ WP-NRS ≥ 4 from baseline after 24 weeks of dupilumab during Heads Up (LOCF). *EASI75*, At least a 75% improvement from baseline in Eczema Area and Severity Index; *EASI90*, at least a 90% improvement from baseline in EASI; *EASI100*, a 100% improvement from baseline in EASI; *LOCF*, last observation carried forward; *WP-NRS*, Worst Pruritus-Numerical Rating Scale.



Supplemental Fig 8. Achievement of clinical response and improvement in itch at week 16 of upadacitinib among patients with an inadequate response to prior dupilumab (ie, did not achieve either EASI75 or Δ WP-NRS ≥ 4 from baseline) after 24 weeks of dupilumab during Heads Up (OC). EASI75, At least a 75% improvement from baseline in Eczema Area and Severity Index; OC, observed case; WP-NRS, Worst Pruritus-Numerical Rating Scale.



Supplemental Fig 9: Achievement of clinical response and improvement in itch at week 16 of upadacitinib among patients with an inadequate response to prior dupilumab (ie, did not achieve either EASI75 or Δ WP-NRS ≥ 4 from baseline) after 24 weeks of dupilumab during Heads Up (LOCF). EASI75, At least a 75% improvement from baseline in Eczema Area and Severity Index; LOCF, last observation carried forward; WP-NRS, Worst Pruritus-Numerical Rating Scale.

