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Efficacy and Safety of Dupilumab Maintained in Adults ≥ 60 Years of Age with Moderate-to-Severe Atopic Dermatitis: Analysis of Pooled Data from Four Randomized Clinical Trials

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Abstract

Background Adults aged ≥ 60 years are often underrepresented in atopic dermatitis (AD) clinical trials; age-related comorbidities may impact treatment efficacy and safety.

Objective The aim was to report dupilumab efficacy and safety in patients aged ≥ 60 years with moderate-to-severe AD.

Methods Data were pooled from four randomized, placebo-controlled dupilumab trials of patients with moderate-to-severe AD (LIBERTY AD SOLO 1 and 2, LIBERTY AD CAFÉ, and LIBERTY AD CHRONOS) and stratified by age (< 60 [$N = 2261$] and ≥ 60 [$N = 183$] years). Patients received dupilumab 300 mg every week (qw) or every 2 weeks (q2w), or placebo with/without topical corticosteroids. Post hoc efficacy at week 16 was examined using broad categorical and continuous assessments of skin lesions, symptoms, biomarkers, and quality of life. Safety was also assessed.

Results In the ≥ 60 -year-old group at week 16, a greater proportion of dupilumab-treated patients achieved an Investigator's Global Assessment score of 0/1 (q2w: 44.4%; qw: 39.7%) and 75% improvement in Eczema Area and Severity Index (63.0%; 61.6%) versus placebo (7.1% and 14.3%, respectively; $P < 0.0001$). Type 2 inflammation biomarkers (immunoglobulin E and thymus and activation-regulated chemokine) were also significantly reduced in dupilumab- versus placebo-treated patients ($P < 0.01$). Results were similar in the < 60 -year-old group. The exposure-adjusted incidences of adverse events in dupilumab-treated patients were generally similar to those receiving placebo, with numerically fewer treatment-emergent adverse events in the dupilumab-treated ≥ 60 -year-old group versus placebo.

Limitations There were fewer patients in the ≥ 60 -year-old group; post hoc analyses.

Conclusion Dupilumab improved AD signs and symptoms in patients aged ≥ 60 years; results were comparable to those in patients aged < 60 years. Safety was consistent with the known dupilumab safety profile.

Trial Registration ClinicalTrials.gov: NCT02277743, NCT02277769, NCT02755649, NCT02260986.

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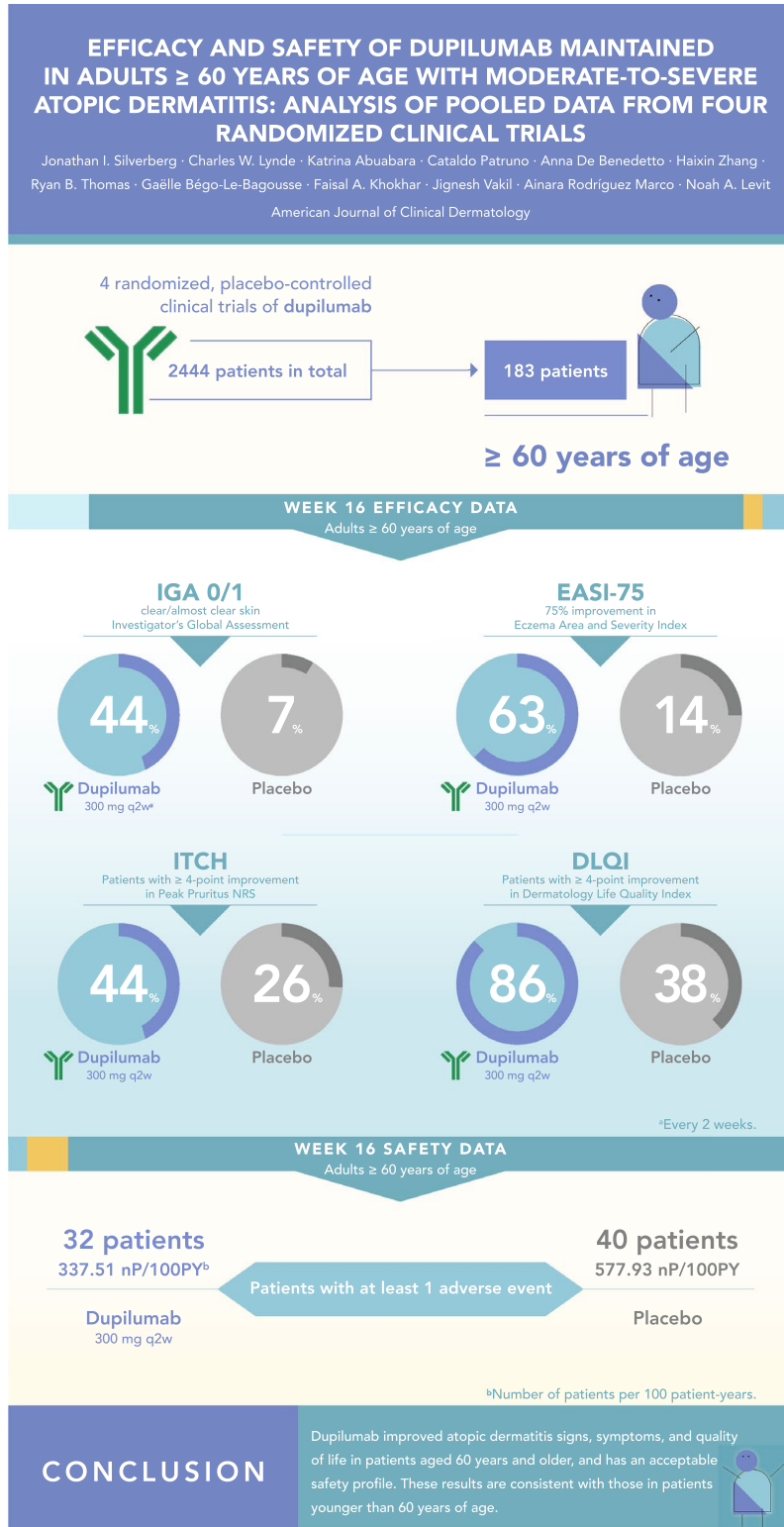
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Graphical abstract



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Key Points

Dupilumab, with or without topical corticosteroids, improved atopic dermatitis (AD) signs, symptoms, and quality of life in adults \geq 60 years of age.

Dupilumab efficacy in patients \geq 60 years of age was generally consistent with that seen in patients $<$ 60 years of age; safety findings were consistent with the known dupilumab safety profile.

In both age groups, dupilumab significantly reduced the AD biomarkers thymus and activation-regulated chemokine and immunoglobulin E compared with placebo.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that impacts around 10% of the population worldwide and may be more common than previously thought in older adults [1–5]; the prevalence of AD in older adults was found to be similar to or higher than that in younger adults [1, 2].

Safety is an important consideration for AD treatment in older adults due to the increased burden of medical comorbidities, age-related changes in drug metabolism, and risks associated with polypharmacy [5]. Treatment options without broad immunosuppressing action are important in older adults, due to heightened age-related considerations. For more elderly patients who may be less independent, options for long-term therapy that do not require frequent laboratory monitoring may be an important practical consideration.

AD is a clinically heterogeneous disorder with phenotypic and endotypic shifts observed across age groups and disease chronicity [5–9]. In infants, exudative lesions and erythema predominate and tend to be localized to the cheeks, forehead, scalp, and extensor areas of the extremities. During childhood, subacute and chronic lesions with scaling and lichenification begin to appear, with prominent involvement of the flexural extremities [8, 10]. In adolescents and adults, erythematous and edematous papules and plaques with variable scaling, excoriation, oozing/crusting, and lichenification are typically located on the head, neck, and flexural areas [8, 10]. In older adults with AD, localized disease of the head/neck and hands/feet, and relatively less involvement of the flexural areas of arms and

legs, is typical, but lesions may affect any skin site [8, 11, 12]. Rates of some distinct lesional morphologies were reported to be at least twofold higher in adults, including erythrodermic AD, papular/lichenoid eczematous dermatitis, nummular eczema, and AD complicated by prurigo nodularis [13].

Dupilumab, a fully human VelocImmune[®]-derived [14, 15] monoclonal antibody that blocks the shared receptor subunit for interleukin (IL)-4 and IL-13, is approved for patients with type 2 inflammatory diseases, including AD, asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis [16, 17]. In phase III clinical trials, dupilumab improved AD signs and symptoms, improved quality of life, and had an acceptable safety profile across age groups [18–24]. Similar to clinical trials for other AD treatments, older adults are underrepresented in adult dupilumab clinical trials [25, 26]. Here, we pooled data from four adult dupilumab clinical trials and stratified patients by age ($<$ 60 and \geq 60 years of age) to examine the efficacy and safety of dupilumab, with or without topical corticosteroids (TCS), in patients \geq 60 years of age. We further describe baseline levels and changes in immunoglobulin E (IgE) and serum thymus and activation-regulated chemokine (TARC), which serve as markers of systemic type 2 inflammation, known to correlate with AD severity [27–29].

2 Methods

2.1 Study Design, Patients, and Treatment

This was a pooled analysis of four phase III, randomized, multicenter, double-blinded, placebo-controlled, parallel-group trials of dupilumab in adults with moderate-to-severe AD (LIBERTY AD SOLO 1 [NCT02277743]; LIBERTY AD SOLO 2 [NCT02277769]; LIBERTY AD CAFÉ [NCT02755649]; and LIBERTY AD CHRONOS [NCT02260986]). Detailed study designs are reported in previous publications [18–20]. Briefly, SOLO 1 and SOLO 2 were 16-week monotherapy trials of identical design, conducted independently and in parallel at study sites across North America, Europe, and Asia. The studies enrolled adults with moderate-to-severe AD with a history of inadequate response to topical treatments, or for whom such therapies were medically inadvisable. Patients were randomized 1:1:1 to receive subcutaneous (SC) dupilumab 300 mg every week (qw), 300 mg every 2 weeks (q2w), or placebo. Concomitant TCS were not permitted, but patients could use topical therapies as rescue treatment. In the United States, the primary endpoint was the proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1 with a \geq 2-point reduction from baseline. In Europe, there were two primary co-endpoints: an IGA score of 0 or

Table 1 Baseline demographics and clinical characteristics

	Age \geq 60 years				Age < 60 years			
	Placebo qw (n = 56)	Dupilumab 300 mg q2w (n = 54)	Dupilumab 300 mg qw (n = 73)	Total (N = 183)	Placebo qw (n = 827)	Dupilumab 300 mg q2w (n = 616)	Dupilumab 300 mg qw (n = 818)	Total (N = 2261)
Baseline characteristics								
Age, median (Q1–Q3), years	65.0 (63.0–69.0)	66.0 (63.0–72.0)	64.0 (62.0–68.0)	65.0 (62.0–69.0)	35.0 (25.0–45.0)	35.0 (26.0–45.0)	34.0 (25.0–45.0)	35.0 (25.0–45.0)
Male sex, n (%)	31 (55.4)	33 (61.1)	45 (61.6)	109 (59.6)	480 (58.0)	361 (58.6)	493 (60.3)	1334 (59.0)
Race, n (%)								
White	53 (94.6)	48 (88.9)	69 (94.5)	170 (92.9)	561 (67.8)	450 (73.1)	561 (68.6)	1572 (69.5)
Black/African American	1 (1.8)	3 (5.6)	3 (4.1)	7 (3.8)	54 (6.5)	22 (3.6)	47 (5.7)	123 (5.4)
Asian	2 (3.6)	3 (5.6)	1 (1.4)	6 (3.3)	189 (22.9)	126 (20.5)	186 (22.7)	501 (22.2)
American Indian or Alaska Native	0	0	0	0	0	1 (0.2)	0	1 (0)
Native Hawaiian or other Pacific Islander	0	0	0	0	1 (0.1)	1 (0.2)	2 (0.2)	4 (0.2)
Other	0	0	0	0	15 (1.8)	9 (1.5)	18 (2.2)	42 (1.9)
Not reported	0	0	0	0	7(0.8)	7 (1.1)	4 (0.5)	18 (0.8)
Clinical characteristics								
Duration of AD, median (Q1–Q3), years	40.0 (7.5–62.0)	51.0 (20.0–62.0)	41.5 (14.0–60.5)	45.0 (11.0–61.0)	27.0 (19.0–38.0)	26.0 (18.0–37.0)	26.0 (18.0–38.0)	26.0 (18.0–38.0)
BSA % affected by AD, median (Q1–Q3)	48.3 (36.0–70.0)	56.3 (38.0–72.0)	52.0 (38.0–67.1)	52.0 (37.0–69.0)	55.0 (38.0–74.5)	54.0 (39.0–71.0)	53.0 (37.0–70.5)	54.0 (38.0–72.3)
EASI score, median (Q1–Q3)	27.8 (21.6–43.2)	29.9 (21.4–40.1)	29.3 (24.3–39.3)	29.4 (22.0–40.4)	30.8 (22.6–41.9)	30.2 (22.4–40.4)	29.4 (21.8–40.9)	30.0 (22.2–41.0)
IGA score, n (%)								
4	29 (51.8)	30 (55.6)	41 (56.2)	100 (54.6)	395 (47.8)	296 (48.1)	376 (46.0)	1067 (47.2)
3	27 (48.2)	24 (44.4)	32 (43.8)	83 (45.4)	431 (52.1)	320 (51.9)	441 (53.9)	1192 (52.7)
Peak Pruritus NRS, median (Q1–Q3)	8.0 (5.8–9.0)	8.0 (6.6–9.0)	7.9 (5.6–8.9)	8.0 (6.0–9.0)	7.6 (6.2–8.6)	7.6 (6.1–8.6)	7.4 (6.0–8.6)	7.6 (6.1–8.6)
SCORAD—total score, median (Q1–Q3)	66.4 (58.6–78.1)	66.8 (60.0–78.3)	69.8 (56.5–75.8)	68.1 (58.5–76.7)	66.4 (57.3–77.3)	67.4 (57.5–77.2)	66.0 (56.5–76.5)	66.5 (57.1–76.9)
POEM, median (Q1–Q3)	21.0 (14.0–23.5)	20.0 (14.0–24.0)	20.0 (16.0–24.0)	20.0 (15.0–24.0)	21.0 (16.0–25.0)	21.0 (16.0–25.0)	21.0 (16.0–26.0)	21.0 (16.0–25.0)
DLQI score, median (Q1–Q3)	11.5 (6.5–18.0)	12.0 (8.0–19.0)	11.0 (7.0–17.0)	12.0 (7.0–18.0)	14.0 (9.0–21.0)	14.0 (9.0–21.0)	14.0 (9.0–21.0)	14.0 (9.0–21.0)

AD atopic dermatitis, BSA body surface area, DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, IGA Investigator's Global Assessment, NRS Numerical Rating Scale, POEM Patient-Oriented Eczema Measure, Q quartile, q2w every 2 weeks, qw every week, SCORAD SCORING Atopic Dermatitis

1 with a \geq 2-point reduction from baseline, and the proportion of patients achieving a 75% improvement in the Eczema Area and Severity Index (EASI-75). CHRONOS was a 52-week trial conducted at approximately 161 study sites across North America, Europe, and Asia. The study enrolled adults with moderate-to-severe AD with a history of inadequate response to TCS. Patients were randomized 3:1:3 to receive SC dupilumab 300 mg qw, 300 mg q2w, or placebo with concomitant TCS (or topical calcineurin inhibitors [TCI] if TCS were inadvisable). Coprimary endpoints were the proportion of patients achieving an IGA of

score 0/1 with a \geq 2-point reduction and the proportion of patients achieving EASI-75. CAFÉ was a 16-week trial conducted in ten European countries. The study enrolled adults with moderate-to-severe AD who had a history of inadequate response or intolerance to the widely used immunosuppressant cyclosporine A (CsA), or for whom CsA was medically inadvisable. Patients were randomized 1:1:1 to receive SC dupilumab 300 mg qw, 300 mg q2w, or placebo with concomitant TCS. The primary endpoint was the proportion of patients achieving EASI-75.

2.2 Ethics

All studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and local applicable regulatory requirements, including institutional review board approval. All patients provided written informed consent prior to participation.

2.3 Outcomes Assessed in this Analysis

Efficacy was assessed by the proportion of patients achieving an IGA score of 0/1 with a ≥ 2-point reduction from baseline, and the proportion of patients achieving EASI-75. Additional outcomes included the following: least squares (LS) mean change in EASI, LS mean change in Peak Pruritus Numerical Rating Scale (NRS), the proportion of patients achieving a ≥ 4-point improvement in Peak Pruritus

NRS, the proportion of patients achieving a 4-point reduction in Dermatology Life Quality Index (DLQI), the proportion of patients achieving a 4-point reduction in Patient-Oriented Eczema Measure (POEM), LS mean change in SCORing Atopic Dermatitis (SCORAD), LS mean change in SCORAD Sleep Visual Analog Scale (VAS), and LS mean change in EuroQol 5-dimension questionnaire (EQ-5D) pain/discomfort. IgE and TARC biomarkers were also assessed based on the LS mean change in total IgE, the percentage change in total IgE, the LS mean change in TARC, and the percentage change in TARC.

Safety outcomes were assessed over the 16-week treatment period and included the following: prevalence of treatment-emergent adverse events (TEAEs), drug-related TEAEs, TEAEs leading to permanent drug discontinuation, maximum TEAE intensity, death, serious TEAEs, drug-related serious TEAEs, and serious TEAEs leading to permanent drug discontinuation. According to the European

Table 2 Baseline type 2 biomarkers and history of atopic comorbidities

	Age ≥ 60 years				Age < 60 years			
	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	Total	Placebo qw	Dupilumab 300 mg q2w	Dupilumab 300 mg qw	Total
Laboratory characteristics								
Total IgE (IU/mL), median (IQR), <i>n</i>	1665.5 (196.0–6559.0), <i>n</i> = 56	1364.5 (71.0–7360.0), <i>n</i> = 54	837.0 (123.0–6711.0), <i>n</i> = 73	1172.0 (123.0–7338.0) ^a , <i>N</i> = 183	3561.0 (595.0–10,000.0), <i>n</i> = 823	3187.5 (625.5–10,000.0), <i>n</i> = 616	2825.0 (548.0–10,000.0), <i>n</i> = 817	3136.0 (582.0–10,000.0) ^a , <i>N</i> = 2256
TARC (pg/mL), median (IQR), <i>n</i>	2629.1 (874.5–9151.5), <i>n</i> = 56	2871.5 (936.0–8054.0), <i>n</i> = 54	2273.0 (899.7–6655.0), <i>n</i> = 73	2602.1 (899.7–7355.0), <i>N</i> = 183	2258.7 (915.0–6722.8), <i>n</i> = 821	2295.5 (903.0–7011.8), <i>n</i> = 614	1943.3 (823.0–5928.0), <i>n</i> = 813	2143.3 (883.3–6584.5), <i>N</i> = 2248
History of atopic comorbidities, <i>n</i> (%)	<i>n</i> = 56	<i>n</i> = 55	<i>n</i> = 72	<i>N</i> = 183	<i>n</i> = 823	<i>n</i> = 627	<i>n</i> = 808	<i>N</i> = 2258
Asthma	17 (30.4)	17 (30.9)	24 (33.3)	58 (31.7)	330 (40.1)	268 (42.7)	312 (38.6)	910 (40.3)
Allergies ^b	36 (64.3)	28 (50.9)	45 (62.5)	109 (59.6)	516 (62.7)	406 (64.8)	533 (66.0)	1455 (64.4)
Allergic rhinitis	22 (39.3)	24 (43.6)	26 (36.1)	72 (39.3)	386 (46.9)	315 (50.2)	397 (49.1)	1098 (48.6)
Food allergy	15 (26.8)	10 (18.2)	23 (31.9)	48 (26.2)	293 (35.6)	254 (40.5)	313 (38.7)	860 (38.1)
Allergic conjunctivitis	11 (19.6)	14 (25.5)	15 (20.8)	40 (21.9)	235 (28.6)	184 (29.3)	218 (27.0)	637 (28.2)
Hives	8 (14.3)	8 (14.5)	10 (13.9)	26 (14.2)	95 (11.5)	86 (13.7)	100 (12.4)	281 (12.4)
Chronic rhinosinusitis	3 (5.4)	6 (10.9)	5 (6.9)	14 (7.7)	54 (6.6)	33 (5.3)	45 (5.6)	132 (5.8)
Nasal polyps	2 (3.6)	0	3 (4.2)	5 (2.7)	18 (2.2)	13 (2.1)	22 (2.7)	53 (2.3)
Eosinophilic esophagitis	0	1 (1.8)	0	1 (0.5)	3 (0.4)	6 (1.0)	1 (0.1)	10 (0.4)

IgE immunoglobulin E, IU international units, IQR interquartile range, mL milliliter, pg picograms, q2w every 2 weeks, qw every week, TARC thymus and activation-regulated chemokine

^aSignificant differences in total IgE (IU/mL) were observed between the ≥ 60 and < 60 groups ($P = 0.0013$)

^bAllergies other than food

Table 3 Efficacy outcomes at week 16

	Age ≥ 60 years			Age < 60 years		
	Placebo qw (n = 56)	Dupilumab 300 mg q2w (n = 54)	Dupilumab 300 mg qw (n = 73)	Placebo qw (n = 827)	Dupilumab 300 mg q2w (n = 616)	Dupilumab 300 mg qw (n = 818)
Patients achieving IGA 0/1 and ≥ 2-point improvement from baseline, n (%)	4 (7.1)	24 (44.4) < 0.0001	29 (39.7) < 0.0001	100 (12.1)	233 (37.8) < 0.0001	325 (39.7) < 0.0001
Patients achieving EASI-75, n (%)	8 (14.3)	34 (63.0) < 0.0001	45 (61.6) < 0.0001	183 (22.1)	340 (55.2) < 0.0001	494 (60.4) < 0.0001
EASI, LS mean change (SE)	- 10.15 (1.742)	- 24.77 (1.805) < 0.0001	- 23.89 (1.530) < 0.0001	- 10.09 (0.436)	- 23.47 (0.495) < 0.0001	- 23.27 (0.436) < 0.0001
Peak Pruritus NRS, LS mean change (SE)	- 1.65 (0.337)	- 3.80 (0.345) < 0.0001	- 3.96 (0.292) < 0.0001	- 1.53 (0.079)	- 3.64 (0.091) < 0.0001	- 3.64 (0.080) < 0.0001
Patients achieving ≥ 4-point improvement in Peak Pruritus NRS, n/N1 (%)	12/47 (25.5)	23/52 (44.2) 0.0096	38/65 (58.5) 0.0003	128/776 (16.5)	262/582 (45.0) < 0.0001	353/753 (46.9) < 0.0001
Patients achieving ≥ 4-point improvement in DLQI, n/N1 (%)	19/50 (38.0)	43/50 (86.0) < 0.0001	50/70 (71.4) 0.0004	382/783 (48.8)	465/579 (80.3) < 0.0001	623/783 (79.6) < 0.0001
Patients achieving ≥ 4-point improvement in POEM, n/N1 (%)	24/56 (42.9)	42/53 (79.2) < 0.0001	60/73 (82.2) < 0.0001	343/820 (41.8)	495/614 (80.6) < 0.0001	656/815 (80.5) < 0.0001
SCORAD, LS mean change (SE)	- 14.83 (2.560)	- 42.21 (2.668) < 0.0001	- 40.35 (2.232) < 0.0001	- 14.84 (0.686)	- 37.78 (0.782) < 0.0001	- 37.14 (0.687) < 0.0001
SCORAD Sleep VAS, LS mean change (SE)	- 1.28 (0.354)	- 3.80 (0.369) < 0.0001	- 3.74 (0.306) < 0.0001	- 1.16 (0.095)	- 3.45 (0.108) < 0.0001	- 3.39 (0.095) < 0.0001
EQ-5D pain/discomfort, LS mean change (SE)	- 0.15 (0.071)	- 0.54 (0.073) 0.0001	- 0.56 (0.062) < 0.0001	- 0.21 (0.020)	- 0.57 (0.022) < 0.0001	- 0.57 (0.020) < 0.0001
Total IgE (IU/mL), LS mean change (SE)	208.60 (429.161)	- 1833.37 (400.539) 0.0005	- 1655.52 (340.953) 0.0006	213.63 (121.010)	- 2635.17 (127.014) < 0.0001	- 2375.93 (112.642) < 0.0001
Total IgE (IU/mL), median (Q1-Q3)	2161.5 (273.0-8445.0)	731.5 (46.7-3102.0)	652.5 (67.1-3809.5)	3966.0 (616.0-10000.0)	1632.0 (284.0-4923.0)	1320.5 (283.5-4308.5)
TARC (pg/mL), LS mean change (SE)	956.05 (1564.354)	- 5770.96 (1489.830) 0.0018	- 5671.11 (1249.615) 0.0009	- 1071.60 (210.011)	- 5569.19 (232.172) < 0.0001	- 5370.59 (203.903) < 0.0001
TARC (pg/mL), median (Q1-Q3)	1118.3 (669.0-3882.0)	422.2 (215.5-657.7)	393.6 (279.7-696.0)	1385.0 (648.0-3527.0)	407.0 (263.1-698.0)	391.0 (246.5-633.5)

DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, EASI-75 75% decrease in EASI, EQ-5D EuroQol – 5 Dimension, IGA Investigator's Global Assessment, IgE Immunoglobulin E, IU international units, LS least squares, mL milliliter, NRS Numerical Rating Scale, N1, number of patients with baseline NRS score ≥ 3, pg picograms, POEM Patient-Oriented Eczema Measure, Q quartile, q2w every 2 weeks, qw every week, SCORAD SCORing Atopic Dermatitis, SE standard error, TARC thymus and activation-regulated chemokine, VAS visual analog scale

Patients' Academy for Therapeutic Innovation (EUPATI) [30], an adverse event is defined as any undesirable event occurring after a participant officially consents to take part in a trial (and could occur before treatment begins). The most common TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) were also reported.

2.4 Statistical Analysis

Efficacy analyses were performed using the full analysis set (all randomized patients), while safety analyses were performed using the safety analysis set (all patients who received at least one dose of study drug). All analyses included data up to week 16. This post hoc, subgroup analysis stratified patients by age (< 60 and ≥ 60 years of age); only descriptive comparisons were made between the age groups. All P values were two-sided. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

3 Results

3.1 Patients

A total of 2444 patients were included in this analysis, of whom 183 were ≥ 60 years of age and 2261 were < 60 years

of age. Among patients ≥ 60 years of age, 56 received placebo, 54 received dupilumab 300 mg q2w, and 73 received dupilumab 300 mg qw. Among patients < 60 years of age, 827 received placebo, 616 received dupilumab 300 mg q2w, and 818 received dupilumab 300 mg qw. The median age (interquartile range [IQR]) of patients in the ≥ 60 age group was 65 (62.0–69.0), while the median age of patients in the < 60 age group was 35 (25.0–45.0) years (Table 1). TCS use differed across the adult studies. Most patients included in this analysis were taken from the SOLO pooled monotherapy studies, where topical therapy use was an exclusion criterion at baseline. Among the ≥ 60 -year-old group included in this analysis, monotherapy patients from SOLO comprised 57.1% of the placebo group (32/56), 72.2% of the dupilumab 300 mg q2w group (39/54), and 53.4% of the dupilumab 300 mg qw group (39/73), with similar proportions for the < 60 -year-old group (placebo: 51.8%, 428/827; dupilumab 300 mg q2w: 67.9%, 418/616; dupilumab 300 mg qw: 51.7%, 423/818). The remaining patients were from CHRONOS and CAFÉ, where concomitant low/medium-potency TCS use were required. For all studies, high-/ultra-potent TCS constituted rescue medication for the purposes of the binary efficacy endpoints, after which patients were classified as non-responders from the time of rescue and not included in the endpoint analyses, and any further data were set to missing.

With the exception of age, baseline demographics and disease characteristics were generally similar across treatment and age groups (Table 1). However, a greater proportion of patients in the ≥ 60 age group were White (92.9%)

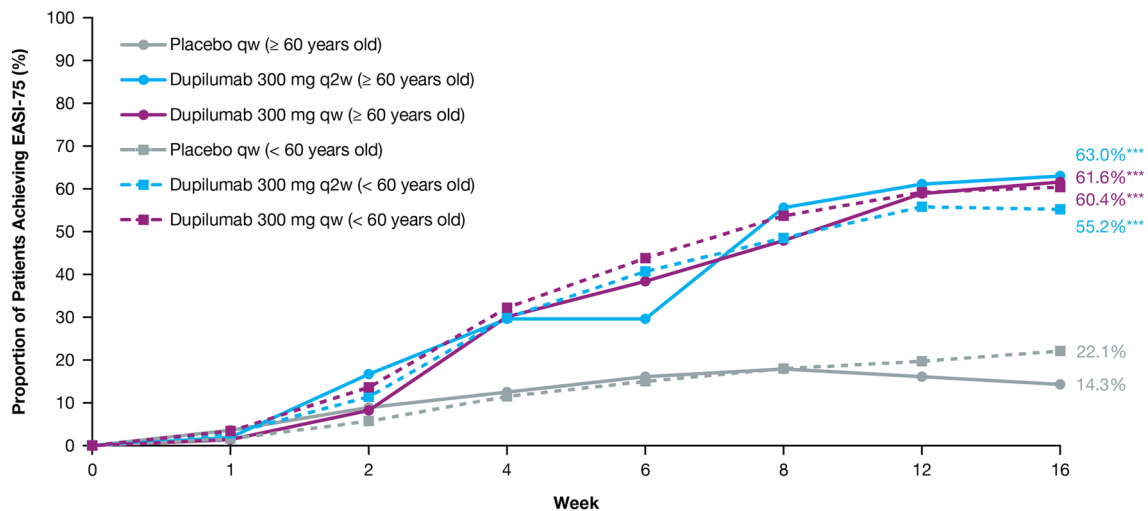


Fig. 1 Proportion (%) of patients achieving EASI-75. A higher proportion of patients aged < 60 years treated with dupilumab 300 mg qw achieved EASI-75 at week 1 vs placebo ($P < 0.05$), and a higher proportion of patients aged < 60 years treated with dupilumab 300 mg qw or q2w achieved EASI-75 from week 2 through week 16 vs placebo ($P < 0.0001$). A higher proportion of patients aged ≥ 60 years treated with dupilumab 300 mg qw or q2w achieved EASI-75

from week 4 vs placebo ($P < 0.05$), week 8 vs placebo (dupilumab qw, $P < 0.001$; dupilumab q2w, $P < 0.0001$), and from week 12 through week 16 vs placebo ($P < 0.0001$ for dupilumab qw and q2w). EASI Eczema Area and Severity Index, EASI-75 75% decrease in EASI, q2w every 2 weeks, qw every week. * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$

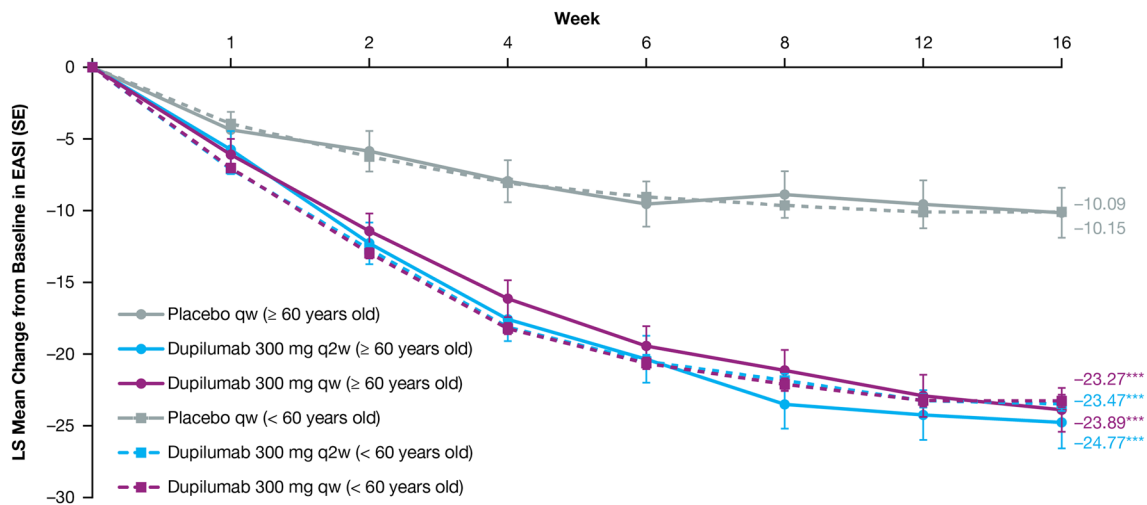


Fig. 2 LS mean change from baseline in EASI. Patients aged < 60 years treated with dupilumab 300 mg qw or q2w showed a greater LS mean change from baseline in EASI from week 1 through week 16 vs placebo ($P < 0.0001$). Patients aged ≥ 60 years treated with dupilumab 300 mg qw or q2w showed a greater LS mean change

from baseline in EASI from week 2 vs placebo ($P < 0.05$), and from week 4 through week 16 ($P < 0.0001$). EASI Eczema Area and Severity Index, LS least squares, q2w every 2 weeks, qw every week. * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$

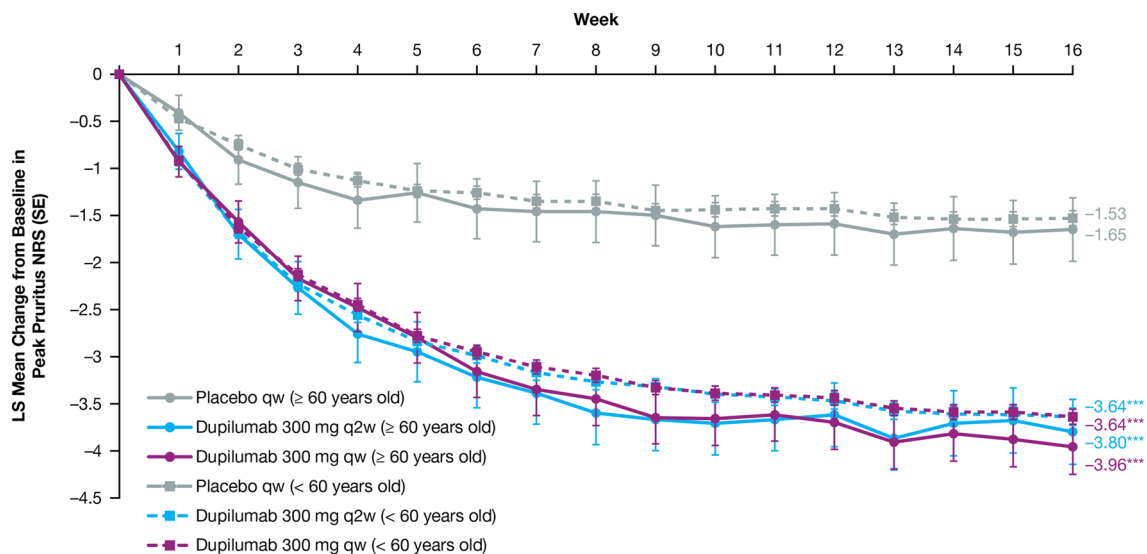


Fig. 3 LS mean change from baseline in Peak Pruritus NRS. Patients aged < 60 years treated with dupilumab 300 mg qw or q2w achieved a greater LS mean change from baseline in Peak Pruritus NRS from week 1 through week 16 vs placebo ($P < 0.0001$). Patients aged ≥ 60 years treated with dupilumab 300 mg qw achieved a greater LS mean

change from baseline in Peak Pruritus NRS at week 1 vs placebo ($P < 0.05$), with dupilumab 300 mg qw or q2w from week 2 vs placebo ($P < 0.05$), and from week 5 through week 16 ($P < 0.0001$). LS least squares, NRS Numerical Rating Scale, q2w every 2 weeks, qw every week. * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$

compared with the < 60 age group (69.5%), while a greater proportion of patients in the < 60 age group were Asian compared with the ≥ 60 age group (22.2% vs 3.3%). At least half of the participants in the ≥ 60 age group appeared to have teen- or adult-onset AD (with a median AD duration [IQR] of 45.0 [11.0–61.0] years). Reported history of atopic comorbidities was also similar across age and treatment

groups, with numerically higher rates of asthma, allergies, allergic rhinitis, food allergy, and allergic conjunctivitis in the < 60 age group (Table 2). Baseline values of total IgE among patients ≥ 60 years of age were lower in all treatment groups compared with patients < 60 years of age ($P = 0.0013$), while TARC values were generally similar across both treatment and age groups ($P = 0.8029$) (Table 2; Fig.

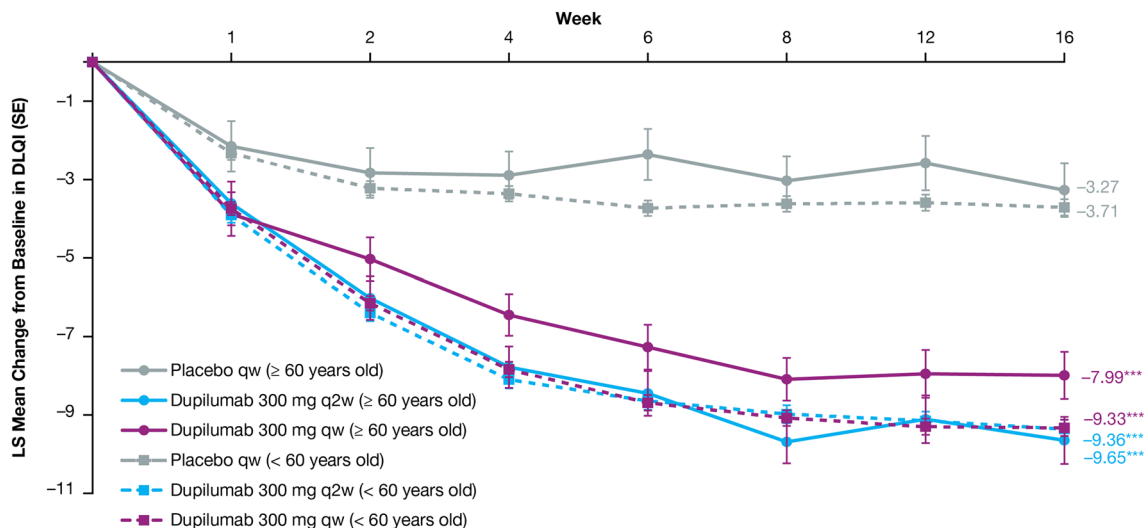


Fig. 4 LS mean change from baseline in DLQI. Patients aged < 60 years treated with dupilumab 300 mg qw or q2w achieved a greater LS mean change from baseline in DLQI from week 1 through week 16 vs placebo ($P < 0.0001$). Patients aged ≥ 60 years treated with dupilumab 300 mg qw showed a greater LS mean change from base-

line in DLQI at week 1 vs placebo ($P < 0.05$), with dupilumab q2w from week 2 vs placebo ($P < 0.001$), and with dupilumab qw or q2w from week 4 through week 16 ($P < 0.0001$). *DLQI* Dermatology Life Quality Index, *LS* least squares, *q2w* every 2 weeks, *qw* every week. * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$

S1, Online Resource, see the electronic supplementary material).

3.2 Efficacy

Dupilumab rapidly and significantly improved AD signs and symptoms compared with placebo, with comparable efficacy across age groups (Table 3). In the ≥ 60 age group, the proportion of patients achieving an IGA score of 0 or 1 (and a ≥ 2 -point reduction from baseline) was greater in those treated with dupilumab (q2w: 44.4%, qw: 39.7%) than in those given placebo (7.1%; $P < 0.0001$ for both comparisons) at week 16. The proportion of patients achieving EASI-75 in the ≥ 60 age group was also greater in dupilumab-treated patients (q2w: 63.0%, qw: 61.6%) compared with those administered placebo (14.3%; $P < 0.0001$ for both comparisons), with significantly more patients who received dupilumab versus placebo achieving EASI-75 as early as week 4 for both doses ($P < 0.05$, Fig. 1). Similar effects were observed at week 16 in the < 60 age group for both IGA 0/1 (q2w: 37.8%, qw: 39.7%, placebo: 12.1%; $P < 0.0001$ for both comparisons) and EASI-75 (q2w: 55.2%, qw: 60.4%, placebo: 22.1%; $P < 0.0001$ for both comparisons) (Table 3, Fig. 1). At baseline, mean EASI scores were similar across treatment and age groups (Table 1) and decreased significantly from week 4 through week 16 among dupilumab-treated (qw and q2w) patients compared with placebo-treated patients in both age groups ($P < 0.0001$ for all comparisons) (Table 3, Fig. 2). The same was observed in both age groups for the LS mean change from baseline in Peak Pruritus NRS from week 5

through week 16 ($P < 0.0001$) (Fig. 3), and LS mean change from baseline in DLQI from week 4 through week 16 ($P < 0.0001$) (Fig. 4). Dupilumab also significantly improved several other clinical outcomes compared with placebo in both age groups, including the proportion of patients achieving a ≥ 4 -point improvement in Peak Pruritus NRS, the proportion of patients achieving a ≥ 4 -point improvement in POEM, LS mean change in SCORAD, LS mean change in SCORAD Sleep VAS, and LS mean change in EQ-5D pain/discomfort (Table 3).

Dupilumab impacted levels of serum T helper 2 (T_H2) cell biomarkers TARC and IgE (Table 3). Among patients ≥ 60 years of age, the LS mean change (standard deviation [SD]) in total IgE at week 16 was significantly greater in patients receiving dupilumab q2w (-1833.37 [400.539]) and qw (-1655.52 [340.953]) compared with placebo (208.60 [429.161]; $P = 0.0005$ and $P = 0.0006$, respectively; Table 3). Similar results were shown in patients < 60 years of age, with a significantly greater LS mean change in total IgE with dupilumab treatment in this age group (q2w: -2635.17 [127.014], qw: -2375.93 [112.642]) compared with placebo (213.63 [121.010]; $P < 0.0001$ for both comparisons). The LS mean change in TARC at week 16 in patients ≥ 60 years of age was also significantly greater in those receiving dupilumab q2w (-5770.96 [1489.830]) or qw (-5671.11 [1249.615]) compared with placebo (956.05 [1564.354]; $P = 0.0018$ and $P = 0.0009$, respectively, Table 3). Again, results were similar for patients < 60 years of age, with a greater LS

Table 4 Exposure-adjusted safety outcomes during the 16-week treatment period per 100 PY by the safety analysis set

Total PY	Age ≥ 60 years				Age < 60 years							
	Placebo qw [n = 56]	Dupilumab 300 mg q2w [n = 55]	Dupilumab 300 mg qw [n = 72]	Placebo qw [n = 823]	Dupilumab 300 mg q2w [n = 627]	Dupilumab 300 mg qw [n = 808]	nE (nE/100 PY)	nP/PY (nP/100 PY)	nE (nE/100 PY)	nP/PY (nP/100 PY)		
Any TEAE	154 (952.40)	87 (525.93)	147 (678.35)	1701 (686.93)	563/120.6 (466.89)	447/90.3 (494.75)	1794 (737.71)	560/120.8 (463.47)	1318 (692.10)	447/90.3 (494.75)	1794 (737.71)	560/120.8 (463.47)
Any drug-related TEAE	22 (136.06)	12/13.0 (92.31)	37 (170.74)	330 (133.27)	164/212.1 (77.32)	183/151.3 (120.97)	605 (248.78)	240/193.2 (124.23)	397 (208.47)	183/151.3 (120.97)	605 (248.78)	240/193.2 (124.23)
Any TEAE causing permanent discontinuation of study drug	0	3 (18.14)	4 (18.46)	32 (12.92)	3/21.4 (14.01)	23/245.2 (9.38)	6 (3.15)	14/241.9 (5.79)	6 (3.15)	5/189.9 (2.63)	18 (7.40)	14/241.9 (5.79)
Maximum intensity for any TEAE												
Mild	96 (593.70)	43 (259.94)	94 (433.78)	1060 (428.07)	186/208.4 (89.25)	214/144.2 (148.39)	1328 (546.09)	255/190.8 (133.66)	935 (490.98)	214/144.2 (148.39)	1328 (546.09)	255/190.8 (133.66)
Moderate	49 (303.04)	25/9.8 (253.93)	50 (230.73)	565 (228.17)	34/14.2 (239.42)	200/144.5 (138.39)	431 (177.23)	260/182.9 (142.18)	354 (185.89)	200/144.5 (138.39)	431 (177.23)	260/182.9 (142.18)
Severe	9 (55.66)	6/15.0 (40.09)	3 (13.84)	76 (30.69)	2/21.2 (9.44)	33/182.5 (18.08)	35 (14.39)	45/233.5 (19.27)	29 (15.23)	33/182.5 (18.08)	35 (14.39)	45/233.5 (19.27)
Any death	0	0	0	0	0	0	1 (0.41)	1/243.2 (0.41)	0	0	1 (0.41)	1/243.2 (0.41)
Any serious TEAE	4 (24.74)	2/15.7 (12.77)	6 (27.69)	41 (16.56)	3/21.1 (14.19)	14/188.1 (7.45)	14 (5.76)	13/241.8 (5.38)	15 (7.88)	14/188.1 (7.45)	14 (5.76)	13/241.8 (5.38)
Any drug-related serious TEAE	0	0	0	6 (2.42)	0	6/246.6 (2.43)	4 (1.64)	4/242.8 (1.65)	3 (1.58)	6/246.6 (2.43)	4 (1.64)	4/242.8 (1.65)
Most common TEAEs by PT (≥ 5% of patients)												
Dermatitis atopic	22 (136.06)	17/12.7 (133.71)	5 (23.07)	320 (129.23)	233/202.2 (115.25)	71/178.9 (39.68)	113 (46.47)	89/228.9 (38.87)	86 (45.16)	71/178.9 (39.68)	113 (46.47)	89/228.9 (38.87)
Nasopharyngitis	3 (18.55)	3/15.6 (19.29)	11 (50.76)	101 (40.79)	87/233.6 (37.24)	76/178.3 (42.63)	108 (44.41)	92/228.0 (40.35)	91 (47.79)	76/178.3 (42.63)	108 (44.41)	92/228.0 (40.35)
Injection-site reaction	3 (18.55)	3/15.3 (19.58)	4 (18.46)	79 (31.90)	43/238.3 (18.04)	63/177.0 (35.59)	105 (43.18)	62/229.7 (26.99)	145 (76.14)	63/177.0 (35.59)	105 (43.18)	62/229.7 (26.99)
Headache	3 (18.55)	3/15.5 (19.33)	4 (18.46)	66 (26.65)	2/21.1 (9.49)	46/238.5 (19.28)	86 (45.16)	62/229.7 (26.99)	86 (45.16)	53/177.7 (29.83)	105 (43.18)	62/229.7 (26.99)
Conjunctivitis	0	0	7 (32.30)	8 (3.23)	5/20.8 (24.01)	32/185.1 (17.28)	22 (9.05)	22/239.7 (9.18)	37 (19.43)	32/185.1 (17.28)	22 (9.05)	22/239.7 (9.18)
Conjunctivitis allergic	0 ^a	2 (12.09) ^a	3 (13.84) ^a	22 (8.88)	3/21.2 (14.16)	20/243.7 (8.21)	43 (16.86)	36/237.5 (15.16)	43 (22.58)	35/184.7 (18.95)	41 (16.86)	36/237.5 (15.16)
Upper respiratory tract infection	6 (37.11)	4/15.3 (26.09)	4 (18.46)	32 (12.92) ^a	4/20.8 (19.20)	27/242.2 (11.15)	46 (18.92) ^a	40/236.6 (16.90)	26 (13.65) ^a	20/187.2 (10.69)	46 (18.92) ^a	40/236.6 (16.90)
Arthralgia	5 (30.92)	3/15.8 (18.97)	1 (4.61)	17 (6.87) ^a	1/21.7 (4.62)	16/244.4 (6.55)	9 (3.70) ^a	7/242.0 (2.89)	16 (8.40) ^a	13/188.0 (6.92)	9 (3.70) ^a	7/242.0 (2.89)

mean change in TARC with dupilumab treatment (q2w: -5569.19 [232.172], qw: -5370.59 [203.903]) versus placebo (-1071.60 [210.011]; $P < 0.0001$ for both comparisons). TARC decreased rapidly with dupilumab treatment (with significant differences observed vs placebo by week 2 for both age groups and dose regimens) and then plateaued for the remainder of the treatment period (Fig. S2, Online Resource, see the electronic supplementary material), while IgE decreased steadily throughout the course of dupilumab treatment (Fig. S3, Online Resource). TARC and IgE values among patients receiving placebo remained steady across the treatment period, with little change from baseline.

3.3 Safety

The exposure-adjusted incidence of TEAEs were similar across treatment groups for patients < 60 years of age. For patients ≥ 60 years of age, there were numerically fewer TEAEs per 100 patient years (PY) in the dupilumab groups compared with the placebo group (Table 4). Most TEAEs were of mild-to-moderate severity, with a greater exposure-adjusted incidence of severe TEAEs in the placebo arms compared with the dupilumab arms in both age groups. In the ≥ 60 age group, the number of patients [nP] with a severe event per 100 PY was 40.09 in the placebo arm versus 12.54 nP/100 PY and 9.44 nP/100 PY in patients treated with dupilumab q2w and qw, respectively. In patients < 60 years of age, 31.25 nP/100 PY were reported in the placebo arm, and 18.08 nP/100 PY and 19.27 nP/100 PY among patients treated with dupilumab q2w and qw, respectively. The incidence of TEAEs leading to drug discontinuation was low, but slightly more common among dupilumab-treated patients ≥ 60 years of age (12.21 nP/100 PY and 14.01 nP/100 PY for q2w and qw, respectively) compared with patients < 60 years of age (2.63 nP/100 PY and 5.79 nP/100 PY). No deaths occurred in the ≥ 60 age group, while one death occurred in the < 60 age group but was deemed unrelated to the study drug [19].

The most common TEAEs ($\geq 5\%$ incidence) in the ≥ 60 age group were AD in the placebo and q2w dupilumab groups (133.71 nP/100 PY and 74.67 nP/100 PY, respectively) and injection-site reactions in the qw dupilumab group (50.74 nP/100 PY) (Table 4). Exposure-adjusted incidence rates of common TEAEs were generally comparable across age groups, or higher in the < 60 age group, with the exceptions of AD, arthralgia, and urinary tract infection in the q2w dupilumab arm and conjunctivitis and urinary tract infection in the qw dupilumab arm, which were higher in the ≥ 60 age group. Within both age groups, patients treated with placebo experienced higher rates of AD, while dupilumab-treated patients (qw) were more likely to experience injection-site reactions (Table 4). Serious TEAEs were

rare in both age groups, with no drug-related serious TEAEs reported in the ≥ 60 age group. In the < 60 age group, the only two serious TEAEs occurring were AD (placebo: 3.25 nP/100 PY; q2w: 1.58 nP/100 PY; qw: 0.82 nP/100 PY) and suicidal ideation (placebo: 1.21 nP/100 PY; q2w: 0 nP/100 PY; qw: 0 nP/100 PY). The overall safety data for these studies have been published previously [18–20].

4 Discussion

Dupilumab improved AD signs, symptoms, and quality of life in adults ≥ 60 years of age with moderate-to-severe AD. Dupilumab efficacy and safety in patients ≥ 60 years of age were generally consistent with those in patients < 60 years of age, who constituted most of the adult clinical study population, and therefore contributed most to the overall dupilumab efficacy and safety profile. These findings support prior studies demonstrating that dupilumab improves AD signs and symptoms; safety findings were consistent with the known dupilumab safety profile [31–33]. In both age groups, severe TEAEs and TEAEs leading to treatment discontinuation were uncommon.

The complex pathophysiology of AD is influenced by genetic, immunologic, and environmental factors that lead to a dysfunctional skin barrier and polarized inflammatory response, characterized by marked type 2 inflammation. Activation of additional T_H cell subsets, including $T_H1/T_H17/T_H22$, was also described in AD; for example, increased T_H1 cells were associated with chronic lesions in adults [7, 34]. Further research is warranted to better understand AD phenotype–endotype correlations and the clinical relevance of different immune profiles and barrier abnormalities across age groups. Despite this differential expression of other T_H cell pathways, the shared molecular signature of AD across ages is T_H2 skewed. Clinical severity scores significantly correlate with T_H2 -related markers in all age groups [6, 34]. Here, we find elevated levels of total IgE and TARC (two markers of type 2 inflammation) in adult patients with AD. However, compared with adults < 60 years of age at baseline, we find lower levels of total IgE in adults ≥ 60 years of age. This is consistent with findings from Zhou et al., 2019, who found an inverse relationship between IgE levels and age in adults [7]. Zhou et al. also found lower TARC levels in older adults compared with younger adults, whereas we found TARC levels to be comparable between age groups. In both age groups, dupilumab treatment (q2w or qw) significantly reduced levels of IgE and TARC compared with placebo. These data suggest that dupilumab reduces type 2 inflammation in adults regardless of age.

AD treatment options in older adults can be limited due to medical comorbidities, age-related changes in drug

metabolism, and risks associated with polypharmacy [5]. Moreover, most AD studies and treatment guidelines typically do not include patients \geq 60 years of age as a separate group from adults $<$ 60 years of age [25, 26, 35]. Despite limited AD treatment guidelines for older adults, a scoping review of International Eczema Council (IEC) councilors and associates showed dupilumab was the most commonly preferred first-line systemic treatment for special patient populations, including patients over the age of 65 years [36].

Strengths of this study include the pooling of data across four clinical trials, thus allowing for assessment of dupilumab efficacy and safety in adults \geq 60 years of age, a group that is underrepresented in clinical trials of AD treatments, including dupilumab. Limitations include the smaller sample size in the \geq 60 age group compared with the $<$ 60 age group, the lack of statistical comparisons across different age groups (statistical comparisons presented here only compare dupilumab against placebo within each age group, except for baseline TARC and IgE levels), the post hoc nature of the analyses, the fact that the study does not account for chronicity of disease within age groups, the failure to evaluate different clinical phenotypes in each age group, and the relatively short 16-week study duration. Another limitation in this study is that most patients in the \geq 60 age group were 60–70 years of age, which limits the generalizability of these findings—future studies should explore dupilumab's safety in patients 70 years and older. Finally, the age threshold defining older patients from younger patients is largely arbitrary, and it is not known if results would differ substantially if the threshold was moved. Sample size considerations additionally limited analyses with thresholds set higher than age 60.

5 Conclusions

Dupilumab, with or without TCS, improves AD signs and symptoms with an acceptable safety profile in patients \geq 60 years of age with moderate-to-severe AD. Dupilumab efficacy and safety profiles in patients \geq 60 years of age are also generally consistent with those in patients $<$ 60 years of age.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40257-022-00754-4>.

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Declarations

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Conflict of interest Jonathan I. Silverberg is an investigator for AbbVie, Celgene, Lilly, GSK, Incyte, LEO Pharma, Realm Therapeutics, Regeneron Pharmaceuticals Inc. and Roche; a consultant for AbbVie, Anacor Pharmaceuticals, Lilly, Galderma, GSK, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, MedImmune, Menlo Therapeutics, Pfizer, Procter & Gamble, Realm Therapeutics, and Regeneron Pharmaceuticals Inc.; and a speaker for Regeneron Pharmaceuticals Inc. and Sanofi. Charles W. Lynde is an advisor, consultant, and speaker for AbbVie, Altius Pharmaceuticals, Amgen, Aralez Pharmaceuticals, Arcutis Biotherapeutics, Bausch Health, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Cipher Pharmaceuticals, Dermavant, Lilly, Fresenius Kabi, Galderma, GSK, Innovaderm, Intega Skin Sciences, Janssen, Kyowa Kirin, La Roche-Posay, LEO Pharma, L'Oréal, Medexus Pharmaceuticals, Merck Group, Pfizer, Procter & Gamble, PEDIAPHARM, Regeneron Pharmaceuticals Inc., Roche, Sanofi, Sentrex Health Solutions, Teva, Tribute Pharmaceuticals, UCB, Valeant, and Viatrix. Katrina Abuabara has received personal fees from TARGET-DERM and is an investigator for Pfizer and L'Oréal. Cataldo Patrino is an investigator, speaker, consultant, and advisory board member for AbbVie, Amgen, Lilly, LEO Pharma, Novartis, Pfizer, Pierre Fabre, and Sanofi. Anna De Benedetto is a consultant for dMed and Incyte; has received grant support or clinical trial support from Dermira, Kiniksa Pharmaceuticals, Novartis, and Pfizer. Ryan B. Thomas, Faisal A. Khokhar, and Noah A. Levit are employees and shareholders of Regeneron Pharmaceuticals Inc. Haixin Zhang was an employee of Regeneron Pharmaceuticals Inc., and may have held stock/stock options in Regeneron Pharmaceuticals Inc. Ainara Rodríguez Marco and Gaëlle Bégo-Le-Bagousse are employees of Sanofi, and may hold stock and/or stock options in the company. Jignesh Vakil was an employee of Sanofi at the time of the study, may have held stock and/or stock options in Sanofi, and is currently an employee at Moderna.

Ethics approval This study was conducted in accordance with ethical standards of the responsible committees and the Declaration of Helsinki and with the International Conference on Harmonisation guidelines for Good Clinical Practice. The trial was overseen by an independent data and safety monitoring board. The protocol was reviewed and approved by institutional review boards/ethics committees at all centers.

Consent to participate Written informed consent was obtained from all patients or their proxies.

Consent for publication Not applicable as no personal patient-related data were used.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Noah A. Levit, Ainara Rodríguez Marco, and Haixin Zhang. The first draft of the manuscript was written by medical writer Sandra Dedrick, Ph.D., of Excerpta Medica, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material Qualified researchers may request access to study documents (including the clinical study report, study

protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this article. Individual anonymized participant data will be considered for sharing once the indication is approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org>.

Code availability Not applicable.

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