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ORIGINAL PAPER

Durable improvements in atopic dermatitis in the head and neck and across other anatomic regions with rocatinlimab

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Abstract

In a randomized phase 2b trial (NCT03703102) for adult patients with moderate-to-severe atopic dermatitis (AD), treatment with the T cell rebalancing anti-OX40 receptor antibody rocatinlimab (AMG 451/KHK4083) led to significant improvements in clinical measurements versus placebo including whole-body Eczema Area and Severity Index (EASI) score. AD manifestations can impact variable anatomic regions, and involvement of the head and neck, a sensitive, hard-to-treat area, can negatively impact quality of life. In this post hoc analysis, we investigated response to rocatinlimab treatment across anatomic regions, including the head and neck. Least squares mean change from baseline to Week 56 in EASI score was analyzed by anatomic region (head and neck, trunk, upper extremities, or lower extremities) for patients with baseline moderate-to-severe AD in the respective anatomic region, using mixed models for repeated measures. Rocatinlimab groups were compared with placebo at Week 16. The proportion of patients achieving at least 75% reduction from baseline in EASI (EASI-75) was calculated. Probability of relapsing in EASI-75 during the off-treatment follow-up period (Weeks 36–56) was estimated using a Kaplan – Meier approach. At Week 16, decrease from baseline in mean EASI score was greater with all rocatinlimab regimens versus placebo across all anatomic regions for patients with baseline moderate-to-severe AD in the respective region (all $P < 0.001$). EASI scores continued to improve on treatment after Week 16 and were maintained during the off-treatment period across all regions. Among patients with baseline moderate-to-severe AD in the head and neck (n = 219; rocatinlimab, n = 174; placebo, n = 45), mean difference (rocatinlimab vs placebo) at Week 16 in LS mean percent change in head and neck EASI score ranged from − 30.4% to − 42.6% across treatment regimens. In patients who received rocatinlimab from the start of the trial, 47% − 71% achieved EASI-75 in the head and neck at Week 36. Among EASI-75 responders at Week 36, the probability of relapsing in EASI-75 in any region was low (< 25% in the head and neck) 20 weeks after treatment discontinuation until Week 56.

Rocatinlimab treatment led to durable improvements in AD across multiple anatomic regions, including the sensitive head and neck region.

Keywords Atopic dermatitis · Rocatinlimab · Efficacy · Durability

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with heterogenous presentation, in which the morphology and distribution of lesions can vary across anatomic regions [19]. In order to diagnose patients and guide treatment decisions, clinical measures of disease activity must incorporate different features of AD [5]. For example, the Eczema Area and Severity Index (EASI) score measures the severity and extent of lesions across anatomic regions, namely the head and neck, trunk, upper extremities, and lower extremities [5, 26]. It measures the intensity of four common eczema signs: erythema, excoriation, induration (or edema/papulation), and lichenification [26]. Despite the extensive treatment guidelines and multitude of scores attempting to capture AD heterogeneity, disease management is challenging and should consider the variability of AD symptoms and treatment response across anatomic regions [5].

Treatment is particularly challenging for sensitive areas such as the head, face, and neck, which are often exposed to environmental triggers [14, 19, 27, 33]. Up to 72% of patients have AD on the head, face, and/or neck, depending on geographical and demographic factors [40]. AD in the head and neck was shown to have a greater impact on patient's quality of life (QoL) compared with AD in other anatomic regions [31]. Sensitive areas with thin skin, such as the face, may be more susceptible to the side effects of standard local anti-inflammatory treatments such as topical corticosteroids (e.g., skin atrophy causing a burning sensation, telangiectasia, perioral dermatitis) [1, 14].

New therapeutic options for patients with moderate-to-severe AD have been approved in recent years, targeting type 2 inflammatory pathways that are frequently upregulated in patients with AD [15, 16, 18, 34–37]. These therapeutic options include Janus kinase (JAK) inhibitors such as baricitinib, upadacitinib, and abrocitinib, and biologics such as tralokinumab, lebrikizumab, and dupilumab [15, 16, 34–37]. Of note, de novo appearance of head and neck dermatitis has been reported following interleukin-4 (IL-4) and interleukin-13 (IL-13) inhibition with dupilumab, which has been recognized as a distinct adverse event (termed dupilumab-associated head and neck dermatitis [DAHND]) [3, 20, 28, 39]. While the mechanisms driving DAHND are not fully understood, biopsy analyses revealed upregulated type 22-associated inflammation in the new lesions [3]. These findings might be relevant for guiding new treatment approaches for AD [3].

The immune pathophysiology of AD is largely driven by an influx of activated T cells with release of proinflammatory cytokines [13, 17]. Disease presentation results from effector T cells, which drive the Th2 pathway and other pro-inflammatory pathways, while memory T cells contribute to the persistent/chronic nature of disease [13, 17]. Given the central role that pathogenic T cells play in AD [13], rebalancing both the number and activity of these cells could offer a durable approach to treating the disease. An emerging therapeutic target is OX40, a co-stimulatory receptor that is transiently expressed on both effector and memory T cells upon activation, which contributes to T helper (Th) 2 type as well as Th1, Th17 and Th22 type responses and other inflammatory responses [13, 29]. The OX40 receptor binds to its ligand, OX40L (expressed on activated antigen-presenting cells), and promotes the survival of pathogenic effector T cells and the expansion of effector memory T cells [29] making the OX40 receptor an attractive drug target in AD [13].

Rocatinlimab (AMG 451/KHK4083) is a T cell rebalancing therapy that inhibits and reduces the number of pathogenic T cells by targeting the OX40 receptor [30]. Notably, rocatinlimab inhibits not only type 2 inflammatory pathways but also Th1, Th17, and Th22 signaling, which play an important role in the pathogenesis of AD [17, 21]. Given the aforementioned association between DAHND and Th22 inflammation following IL-4 inhibition, the reduction of Th22 markers observed following rocatinlimab treatment could suggest a low risk of new head and neck dermatitis [3, 17, 21].

In a phase 2b trial in adults with moderate-to-severe AD, treatment with rocatinlimab versus placebo led to greater improvement in clinical measures, including whole-body EASI score at Week 16 (primary endpoint), while maintaining a favorable safety profile [21]. Improvements were sustained in most patients after treatment discontinuation, supporting the potential remittive effect of targeting the OX40 receptor [21]. However, the efficacy of rocatinlimab across anatomic regions, and in hard-to-treat regions such as the head and neck, has not yet been investigated. This post hoc analysis of the phase 2b study investigated the efficacy of rocatinlimab across different anatomic regions, particularly in the head and neck, in adult patients with moderate-to-severe AD.

Materials and methods

Study design and participants

The phase 2b study design, patient flow diagram, and methods have been described previously (NCT03703102) [21]. In brief, patients were randomized (1:1:1:1:1) to receive subcutaneous rocatinlimab 150 mg every 4 weeks (Q4W), rocatinlimab 600 mg Q4W, rocatinlimab 300 mg every 2 weeks (Q2W), rocatinlimab 600 mg Q2W, or placebo. All patients applied an investigator-approved topical emollient twice daily from 1 week before baseline until at least Week 36. Topical corticosteroids and immunosuppressives or systemic treatment

Table 1 Demographics and baseline characteristics for the full analysis set and the subgroups of patients with baseline moderate-to-severe AD per anatomic region

	Rocatinlimab 150 mg Q4W	Rocatinlimab 600 mg Q4W	Rocatinlimab 300 mg Q2W	Rocatinlimab 600 mg Q2W	Placebo
Full analysis set (N = 267)					
N	52	52	52	54	57
Age, mean (SD)	37.2 (13.8)	39.1 (14.6)	37.2 (14.4)	37.3 (16.3)	38.7 (14.4)
Sex, male, n (%)	37 (71.2)	30 (57.7)	30 (57.7)	30 (55.6)	31 (54.4)
Race, n (%)					
Asian: Japanese	29 (55.8)	27 (51.9)	31 (59.6)	30 (55.6)	30 (52.6)
Asian: Other	6 (11.5)	4 (7.7)	4 (7.7)	3 (5.6)	7 (12.3)
Black or African American	3 (5.8)	1 (1.9)	2 (3.8)	1 (1.9)	6 (10.5)
White	13 (25.0)	20 (38.5)	15 (28.8)	20 (37.0)	14 (24.6)
Other	1 (1.9)	0	0	0	0
EASI score, mean (SD)					
Whole body	33.2 (13.1)	32.5 (12.8)	31.6 (12.5)	31.1 (11.8)	29.2 (13.3)
Head and neck[a,b]	3.4 (1.8)	3.3 (1.6)	3.0 (2.0)	3.3 (1.5)	2.8 (1.6)
Trunk[a,b]	10.4 (4.7)	10.1 (4.5)	10.6 (4.6)	10.7 (4.5)	8.9 (5.0)
Upper extremities[a,b]	7.0 (2.8)	7.1 (2.9)	6.8 (3.2)	6.1 (2.7)	6.7 (3.1)
Lower extremities[a,b]	12.4 (6.5)	12.0 (6.4)	11.0 (6.0)	11.0 (6.1)	10.6 (6.4)
Subgroup with moderate-to-severe AD in the head and neck (N = 219)[c]					
N	47	46	36	45	45
Age, mean (SD)	36.4 (13.2)	38.2 (14.4)	36.1 (13.2)	35.3 (14.6)	37.2 (13.8)
Sex, male, n (%)	34 (72.3)	27 (58.7)	21 (58.3)	24 (53.3)	25 (55.6)
Race, n (%)					
Asian: Japanese	28 (59.6)	25 (54.3)	26 (72.2)	28 (62.2)	26 (57.8)
Asian: Other	6 (12.8)	4 (8.7)	4 (11.1)	3 (6.7)	7 (15.6)
Black or African American	2 (4.3)	1 (2.2)	0	0	4 (8.9)
White	11 (23.4)	16 (34.8)	6 (16.7)	14 (31.1)	8 (17.8)
Other	0	0	0	0	0
EASI score in the head and neck, mean (SD)[a]	3.7 (1.6)	3.6 (1.4)	4.0 (1.7)	3.7 (1.2)	3.4 (1.2)
Subgroup with moderate-to-severe AD in the trunk (N = 237)[c]					
N	46	48	46	51	46
Age, mean (SD)	37.7 (13.5)	39.7 (14.5)	37.8 (14.3)	37.4 (16.6)	37.0 (13.9)
Sex, male, n (%)	34 (73.9)	29 (60.4)	30 (65.2)	30 (58.8)	28 (60.9)
Race, n (%)					
Asian: Japanese	27 (58.7)	27 (56.3)	29 (63.0)	30 (58.8)	28 (60.9)
Asian: Other	6 (13.0)	4 (8.3)	4 (8.7)	3 (5.9)	6 (13.0)
Black or African American	2 (4.3)	0	2 (4.3)	1 (2.0)	4 (8.7)
White	11 (23.9)	17 (35.4)	11 (23.9)	17 (33.3)	8 (17.4)
Other	0	0	0	0	0
EASI score in the trunk, mean (SD)[a]	11.4 (4.0)	10.7 (4.2)	11.5 (4.0)	11.2 (4.1)	10.4 (4.4)
Subgroup with moderate-to-severe AD in the upper extremities (N = 242)[c]					
N	49	50	46	46	51
Age, mean (SD)	37.7 (14.0)	38.2 (14.1)	38.5 (14.6)	36.5 (14.5)	38.1 (14.0)
Sex, male, n (%)	34 (69.4)	30 (60.0)	26 (56.5)	25 (54.3)	27 (52.9)
Race, n (%)					
Asian: Japanese	26 (53.1)	27 (54.0)	27 (58.7)	26 (56.5)	28 (54.9)
Asian: Other	6 (12.2)	4 (8.0)	3 (6.5)	2 (4.3)	7 (13.7)
Black or African American	3 (6.1)	1 (2.0)	2 (4.3)	1 (2.2)	5 (9.8)
White	13 (26.5)	18 (36.0)	14 (30.4)	17 (37.0)	11 (21.6)
Other	1 (2.0)	0	0	0	0

Table 1 (continued)

	Rocatinlimab 150 mg Q4W	Rocatinlimab 600 mg Q4W	Rocatinlimab 300 mg Q2W	Rocatinlimab 600 mg Q2W	Placebo
EASI score in the upper extremities, mean (SD)[a]	7.2 (2.7)	7.3 (2.8)	7.4 (2.9)	6.8 (2.2)	7.2 (2.9)
Subgroup with moderate-to-severe AD in the lower extremities (N = 212)[c]					
N	43	45	40	42	42
Age, mean (SD)	36.0 (13.6)	39.0 (14.6)	38.2 (15.3)	36.5 (13.4)	40.6 (15.0)
Sex, male, n (%)	30 (69.8)	28 (62.2)	25 (62.5)	25 (59.5)	25 (59.5)
Race, n (%)					
Asian: Japanese	23 (53.5)	26 (57.8)	22 (55.0)	26 (61.9)	23 (54.8)
Asian: Other	6 (14.0)	4 (8.9)	3 (7.5)	2 (4.8)	3 (7.1)
Black or African American	2 (4.7)	0	2 (5.0)	1 (2.4)	6 (14.3)
White	11 (25.6)	15 (33.3)	13 (32.5)	13 (31.0)	10 (23.8)
Other	1 (2.3)	0	0	0	0
EASI score in the lower extremities, mean (SD)[a]	14.1 (5.8)	13.1 (6.2)	13.3 (4.7)	13.1 (5.1)	12.9 (5.8)

[a]EASI score for each anatomic region was weighted for the corresponding BSA percentage, i.e., corrected by the coefficient 0.1 for head and neck, 0.2 for upper extremities, 0.3 for trunk, and 0.4 for lower extremities

[b]In the full analysis set, some treatment groups had minimum EASI scores of zero at baseline in the head and neck, trunk, upper extremities, and lower extremities

[c]Moderate-to-severe AD for each anatomic region was defined based on EASI ≥ 16 weighted for the BSA percentage of each region, i.e., corrected by the coefficient 0.1 for head and neck, 0.2 for upper extremities, 0.3 for trunk, and 0.4 for lower extremities

AD atopic dermatitis, *BSA* body surface area, *EASI* Eczema Area and Severity Index, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation

for AD were prohibited from baseline until the end of study. The study consisted of three periods: a double-blind period (Weeks 0–18), during which patients received one of the above rocatinlimab dose regimens or placebo; an active-treatment extension period (Weeks 18–36), during which patients initially randomized to receive rocatinlimab continued to receive the same dose while patients randomized to receive placebo switched to rocatinlimab 600 mg Q2W; and an off-treatment follow-up period (Weeks 36–56). Patients who received rescue treatment during off-treatment follow-up were kept on study and observed until study end (Week 56), but additional efficacy assessments were omitted.

Eligible patients were aged ≥ 18 years, with confirmed AD (American Academy of Dermatology Consensus Criteria or local diagnostic criteria), with moderate-to-severe disease activity (EASI ≥ 16; validated Investigator's Global Assessment for Atopic Dermatitis score of 3 [moderate] or 4 [severe]; affected body surface area [BSA] ≥ 10% at both screening and baseline), who showed inadequate response to topical medications or for whom topical treatments were medically inadvisable. Full inclusion/exclusion criteria were previously published [21].

The primary efficacy endpoint was percent change from baseline to Week 16 in whole-body EASI score (range 0–72; higher scores indicate greater severity and extent of AD) [21]. The primary endpoint was analyzed in the full analysis set (all randomly assigned patients exposed to rocatinlimab or placebo with a post-baseline EASI score at Week 16 or earlier) [21].

Post hoc analyses

We analyzed percent change from baseline to Week 16 in EASI score for each anatomic region (head and neck, trunk, upper extremities, and lower extremities) in the subgroup of patients with moderate-to-severe AD at baseline in the respective region (patients with baseline head and neck EASI ≥ 1.6, trunk EASI ≥ 4.8, upper extremities EASI ≥ 3.2, or lower extremities EASI ≥ 6.4, respectively); moderate-to-severe AD for each anatomic region was defined based on EASI ≥ 16 weighted for the BSA percentage of each region (i.e., corrected by the coefficient 0.1 for head and neck, 0.3 for trunk, 0.2 for upper extremities, and 0.4 for lower extremities). Change from baseline in EASI scores per anatomic region were calculated for all data collection timepoints up to Week 56. To evaluate the EASI score changes over time per anatomic region in all patients, irrespective of baseline EASI score per anatomic region, change from baseline in EASI score was also analyzed in the full analysis set.

Change from baseline in EASI components (erythema, excoriation, induration, and lichenification) was calculated for all timepoints up to Week 56. This analysis was performed per anatomic region for the subgroup of patients with moderate-to-severe AD at baseline in the respective region.

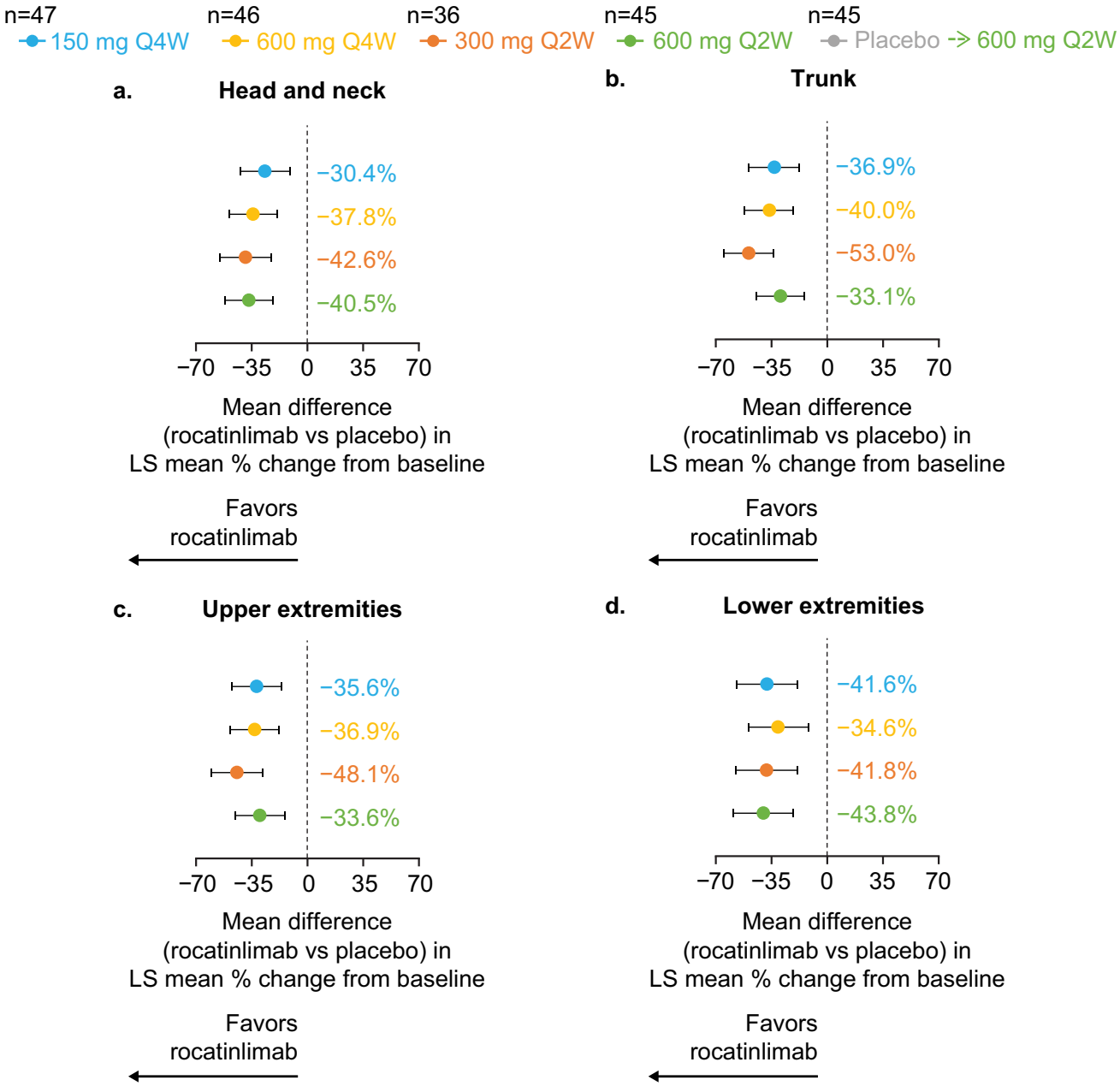

Fig. 1 Mean difference (rocatinlimab vs placebo) in LS mean % change from baseline to Week 16 in each anatomic region in patients with moderate-to-severe AD at baseline in each region. **a** head and neck, **b** trunk, **c** upper extremities, and **d** lower extremities. *AD* atopic dermatitis, *LS* least squares, *Q2W* every 2 weeks, *Q4W* every 4 weeks

Post hoc responder analyses included the proportion of patients achieving at least 50%, 75%, and 90% reductions from baseline in EASI score (EASI-50, -75, and -90 respectively) at Weeks 16, 24, 36, and 56; time to relapse in EASI-75 during the off-treatment follow-up period among EASI-75 responders at Week 36 (time in weeks from Week 36 to loss of EASI-75); and the probability of relapsing on EASI-75 after Week 36 among EASI-75 responders at Week 36, per anatomic region, from the subgroups of patients with moderate-to-severe AD at baseline in the respective anatomic region.

Statistical analysis

Least squares (LS) mean and 95% confidence intervals for percentage change from baseline in EASI score and EASI components for the whole body and/or each anatomic region were compared in the rocatinlimab versus placebo groups using mixed models for repeated measures. These models

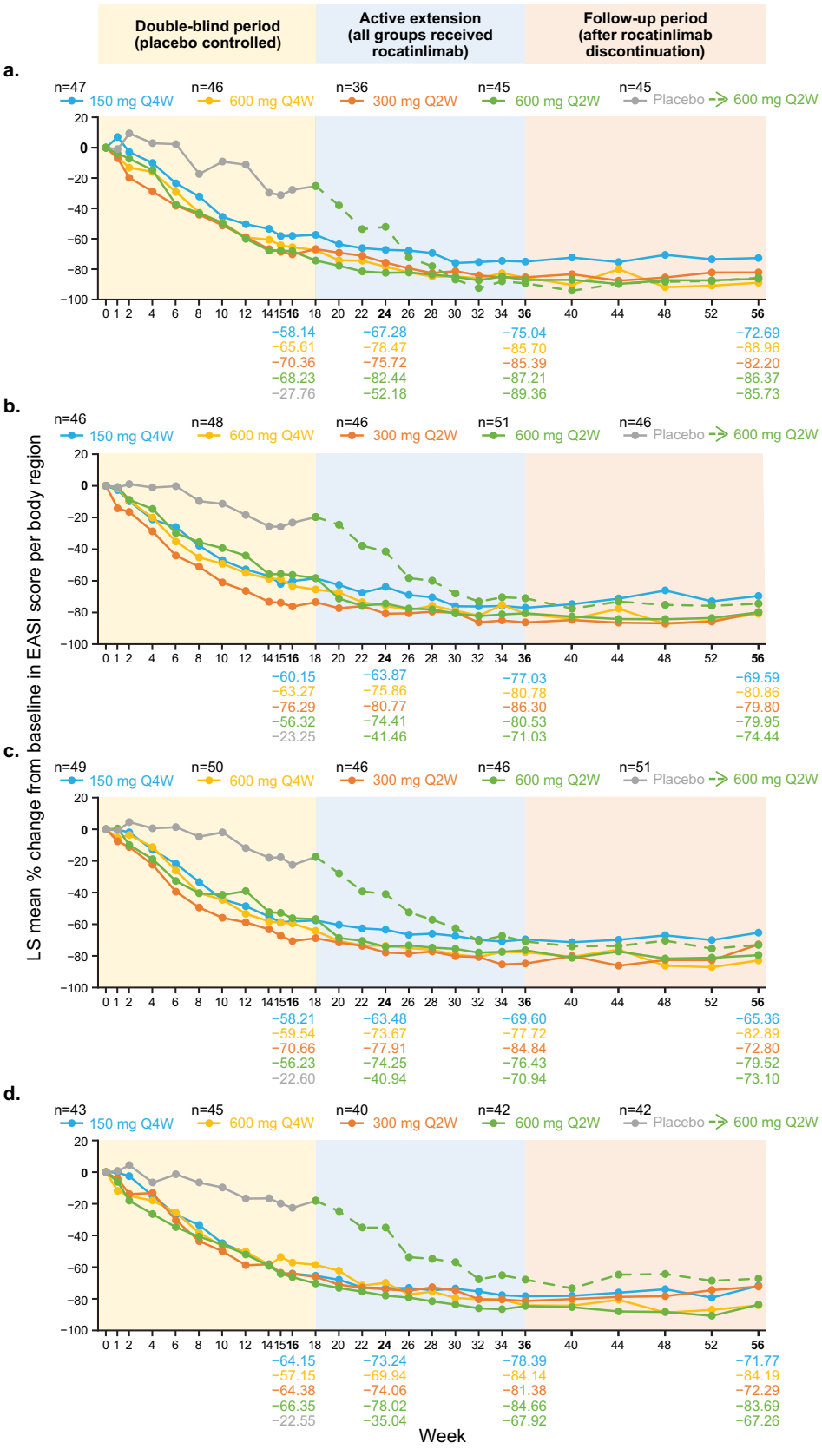

Fig. 2 LS mean % change (baseline to end of trial) in EASI score in each anatomic region in patients with moderate-to-severe AD at baseline in each region. **a** head and neck, **b** trunk, **c** upper extremities, and **d** lower extremities. *AD* atopic dermatitis, *EASI* Eczema Area and Severity Index, *LS* least squares, *Q2W* every 2 weeks, *Q4W* every 4 weeks

used restricted maximum likelihood estimation and included subject as a random effect; fixed effects included treatment, visit, and interaction of treatment with visit; covariates included baseline severity of AD (Investigator's Global Assessment Scale = 3/4), region (Japan/Rest of World), previous use of biological products for AD (yes/no), and baseline EASI score.

For the responder analyses, the probabilities of achieving EASI-50, -75, and -90 were compared between rocatinlimab groups and the placebo group using a Fisher's exact test. Time to relapse in EASI-75 and probability of relapsing in EASI-75 were estimated using the Kaplan–Meier approach. For this analysis, patients who discontinued during the follow-up period were censored at their last EASI evaluation, as described in the phase 2b study [21].

P-values were calculated for exploratory purposes and no adjustment of multiplicity were applied. All analyses were performed with SAS software (version 9.3 or higher SAS Institute Inc., Cary, NC, USA).

Results

Population, demographics, and baseline EASI scores across anatomic regions

Of the 274 patients participating in the phase 2b study, 267 comprised the full analysis set of the primary study [21] and this post hoc analysis. These patients were randomly assigned to rocatinlimab 150 mg Q4W (n = 52), 600 mg Q4W (n = 52), 300 mg Q2W (n = 52), 600 mg Q2W (n = 54), or placebo (n = 57) [21].

Demographics and baseline EASI scores per anatomic region and treatment group are summarized in Table 1 for the full analysis set and for the subgroups of patients with baseline moderate-to-severe AD per anatomic region. At baseline, > 75% of patients had moderate-to-severe AD in each anatomic region (head and neck: n = 219, 79.9%; trunk: n = 237, 86.5%; upper extremities: n = 242, 88.3%; lower extremities: n = 212, 77.4%). For patients with moderate-to-severe AD in each anatomic region, mean ± standard deviation scores for the four EASI components (erythema, excoriation, induration, and lichenification) were similar across anatomic regions. Within each anatomic region, erythema scores were generally highest and excoriation scores were generally the lowest (Table S1).

Improvement in EASI scores across anatomic regions over time with rocatinlimab

In the subgroups, as defined in the Methods, at baseline in each anatomic region, patients treated with rocatinlimab showed greater EASI improvement (LS mean percentage change from baseline) compared with placebo at Week 16 for the head and neck, trunk, upper extremities, and lower extremities (Fig. 1; Tables S2–S5). Among patients with baseline moderate-to-severe AD in the head and neck (rocatinlimab, n = 174; placebo, n = 45), mean difference (rocatinlimab vs placebo) at Week 16 in LS mean percent change in head and neck EASI score ranged from − 30.4% to − 42.6% across treatment regimens. Improvements from baseline in mean EASI scores across anatomic regions were visible from the second week of treatment, depending on the rocatinlimab dosing regimen, compared with placebo (Fig. 2; Tables S2–S5). Similar results were seen in the full analysis data set (Fig. S1 and S2; Tables S6–S9).

Mean EASI score continued to decrease relative to baseline in all anatomic regions during the active-treatment extension period when all patients received rocatinlimab (Weeks 18–36). By Week 36, patients who switched from placebo to rocatinlimab 600 mg Q2W also showed reductions in EASI scores (Fig. 2 and S2; Tables S2–S5). EASI score reductions were maintained for all treatment groups across all anatomic regions at Week 56 (off-treatment follow-up period up).

Improvement in EASI components across anatomic regions over time with rocatinlimab

For patients with moderate-to-severe AD, scores for all four EASI components (erythema, excoriation, induration, lichenification) improved with any rocatinlimab dosing regimen versus placebo at Week 16 in the head and neck, trunk, upper extremities, and lower extremities (Tables S6–S9). Generally, improvements between components were similar across anatomic regions.

Improvements in EASI components with rocatinlimab treatment continued to increase from Week 16 until Week 36 and were generally maintained during the off-treatment follow-up period between Weeks 36 and 56 (Fig. 3 and Fig. S3–S5). At Week 56, the greatest LS mean change from baseline across treatment groups was seen for lichenification in the head and neck, trunk, and upper extremities, and for excoriation in the lower extremities.

Proportion of patients achieving EASI-75 and probability of relapsing across anatomic regions

Of patients with moderate-to-severe AD in the head and neck at baseline, significantly more patients achieved EASI-50, EASI-75, or EASI-90 in this anatomic region by Week 16 with rocatinlimab (any dosage) compared with placebo (EASI-50: rocatinlimab 51% − 73% vs placebo 29%, all $P < 0.05$, Fig. S6a; EASI-75: rocatinlimab 45% − 53% vs placebo 11%, all $P < 0.001$, Fig. 4a; EASI-90: rocatinlimab 24% − 28% vs placebo 2%, all $P < 0.01$, Fig. S7a). Similar results were seen at Week 16 in the trunk, upper extremities,

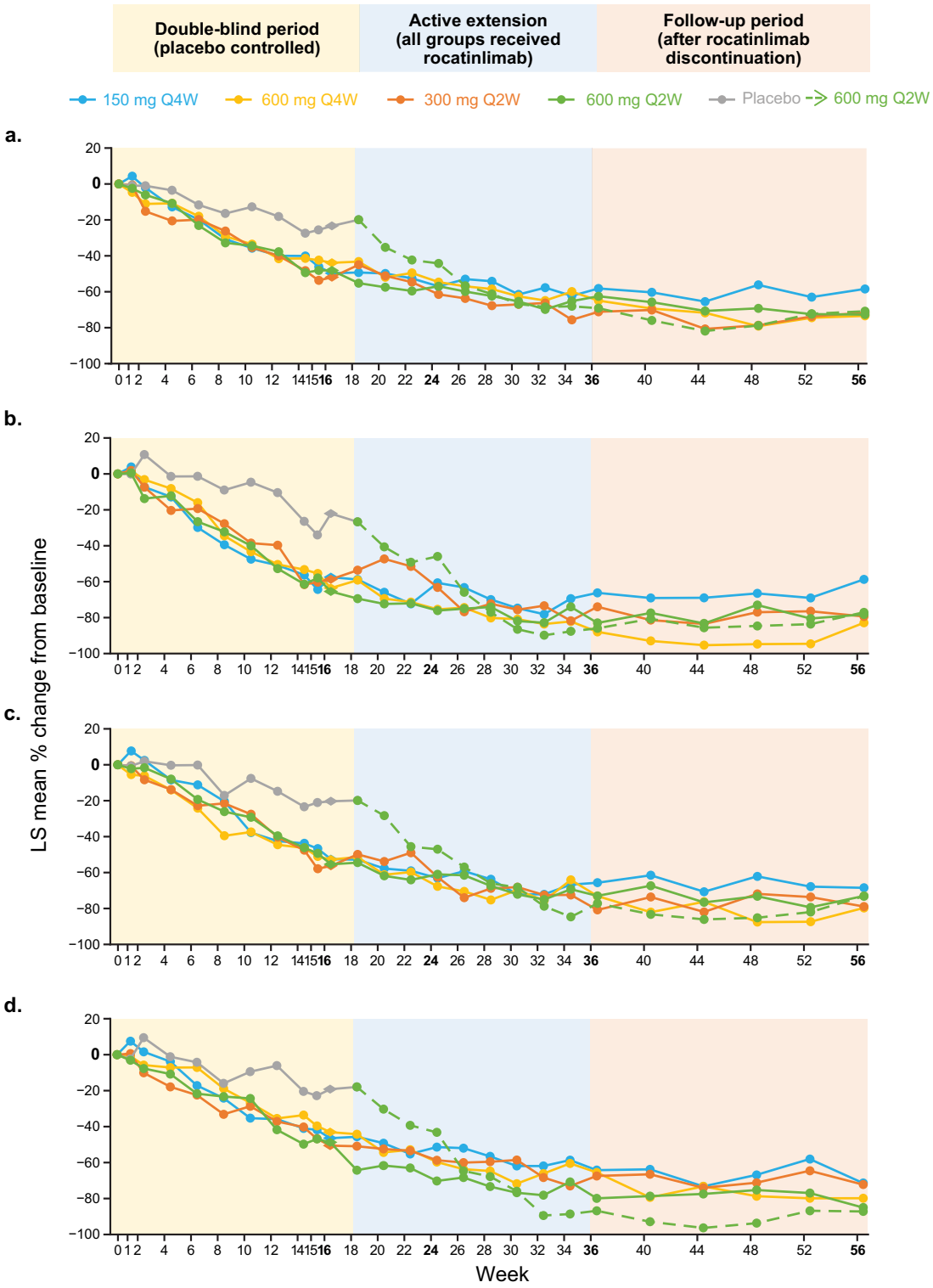

Fig. 3 EASI component scores in the head and neck over time (n = 219). LS mean % change from baseline in head and neck EASI component scores for patients with baseline moderate-to-severe AD in the head and neck for **a** erythema, **b** excoriation, **c** induration, **d** lichenification. *AD*, atopic dermatitis, *EASI*, Eczema Area and Severity Index, *LS*, least squares, *Q2W*, every 2 weeks, *Q4W*, every 4 weeks

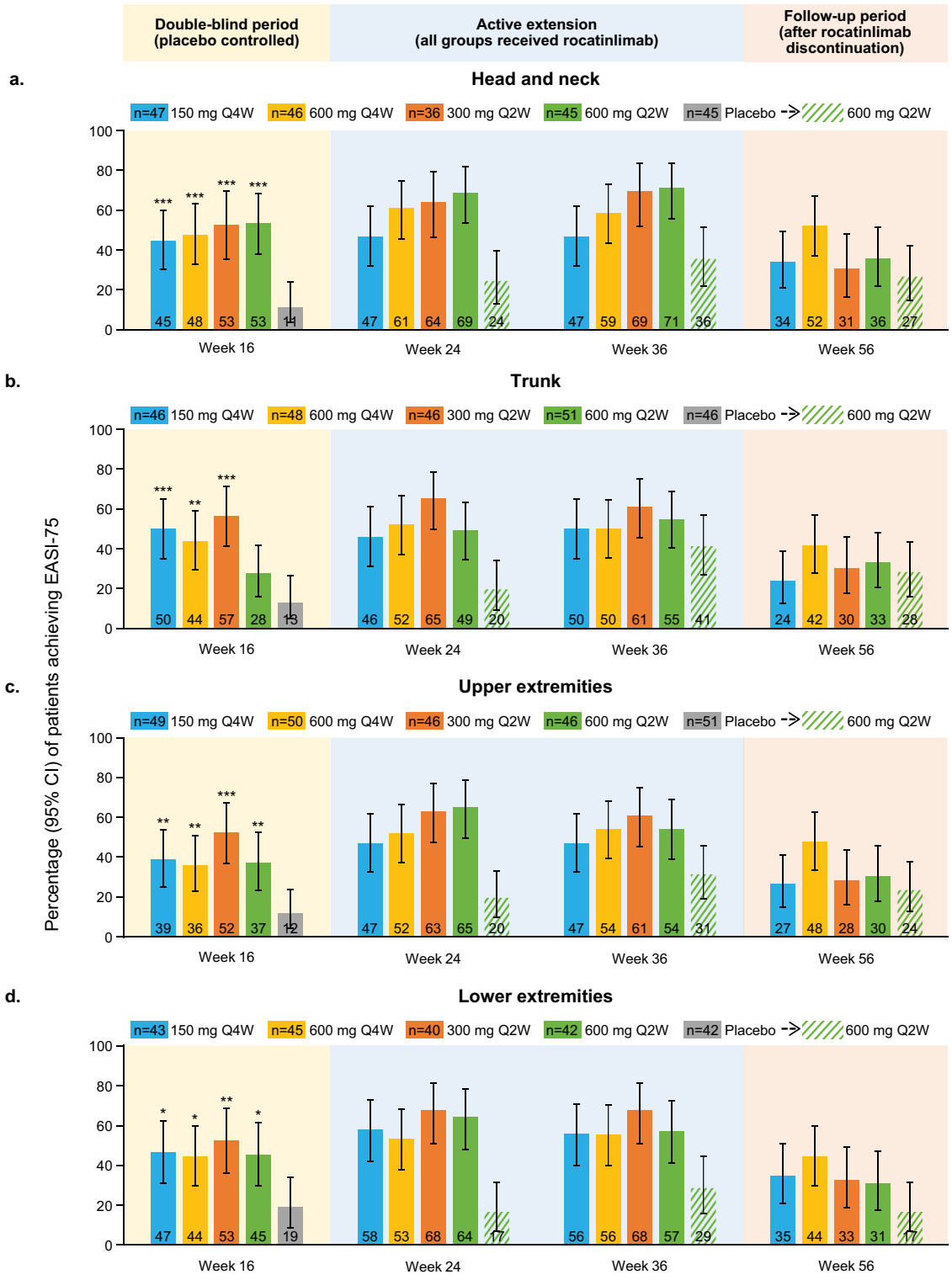

Fig. 4 Proportion of patients with EASI-75 by anatomic region in the subgroup of patients with moderate-to-severe AD at baseline in each anatomic region. Percentage (95% CI) of patients achieving EASI-75 in the **a** head and neck, **b** trunk, **c** upper extremities, and **d** lower extremities. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. *AD* atopic dermatitis, *CI* confidence interval, *EASI* Eczema Area and Severity Index, *Q2W* every 2 weeks, *Q4W* every 4 weeks

and lower extremities, except for the trunk in patients receiving 600 mg Q2W (Fig. S6b–d; Fig. 4b–d; Fig. S7b–d).

The percentage of patients achieving EASI-75 generally increased from Week 16 to Week 36 across most treatment groups and all anatomic regions, including for patients who switched from placebo to rocatinlimab 600 mg Q2W during the active-treatment extension period (Fig. 4). Most patients who achieved EASI-50, EASI-75, or EASI-90 at Week 36 maintained responses across all anatomic regions during the off-treatment follow-up period (Fig. 4; Fig. S6 and S7).

Of the patients who achieved EASI-75 at Week 36, the probabilities of relapsing in EASI-75 by Week 56 ranged from 0 to 23% across dosage groups in the head and neck, 0–29% in the trunk, 8–6% in the upper extremities, and 6–33% in the lower extremities (Fig. 5; Table S10).

Discussion

In this post hoc analysis of a phase 2b trial, we investigated the efficacy of rocatinlimab across anatomic regions, with a focus on the sensitive, hard-to-treat head and neck. Patients with moderate-to-severe AD receiving rocatinlimab showed progressive and durable improvements in EASI scores across all anatomic regions, including the head and neck, as well as the trunk, upper extremities, and lower extremities. All rocatinlimab dosing regimens compared with placebo led to significant improvements in EASI scores at Week 16 in patients with moderate-to-severe baseline involvement in the corresponding region. Improvements in EASI score across anatomic regions were maintained in the absence of topical corticosteroids in most patients up to 20 weeks after rocatinlimab discontinuation, suggesting that OX40 receptor blockade with rocatinlimab may rebalance pathogenic T cell responses and have long-term effects on disease activity in the head and neck and across other anatomic regions in patients with AD. Clinical studies and real-world evidence in moderate-to-severe AD have shown that JAK inhibitors and IL4/13 inhibitors were less effective in treating the head and neck compared with lower and upper limbs, particularly in reducing erythema and edema, highlighting the unmet need for new treatment options for these patients [22–25, 38].

Durable improvements in EASI score were observed for all anatomic regions, and these sustained responses were numerically highest in the head and neck. For patients with moderate-to-severe AD in each anatomic region who achieved EASI-75 at Week 36 in the respective region, the probability of losing EASI-75 by Week 56 was lowest in the head and neck compared with other regions, with 77% – 100% of patients maintaining EASI-75 in the head and neck up to the end of the trial. Of note, the probability of not relapsing on EASI-75 also remained high in the trunk (71–100%), upper extremities (64–92%), and lower extremities (67–94%). Similar durability of response in the head and neck was seen with EASI-90; 24–28% of patients attained EASI-90 response in the head and neck at Week 16 with rocatinlimab versus 2% with placebo, and response rates continued to increase across treatment regimens (36–58%) at Week 36, and were generally maintained (23%–48%) at Week 56 (20 weeks after treatment discontinuation). Other targeted therapies have also shown efficacy across anatomic domains, including lebrikizumab and dupilumab [4, 32]; however, some patients have reported DAHND [3, 27], highlighting the need for additional AD treatment options. As head and neck AD may impact QoL more significantly than AD in other anatomic regions [31], the improvements in head and neck disease seen in this post hoc analysis could be linked to the improvements in QoL with rocatinlimab treatment observed in the phase 2b study [21].

In addition to durability of response, the rapid onset of response is of interest to patients and their physicians and may impact patients' QoL [2]. Rapid improvement in visually prominent areas, including the head and neck and upper extremities, may provide benefit for patients beyond symptomatic improvement, as feeling comfortable in public correlates with QoL [2]. In particular, women living with AD rate being able to "get better skin quickly" as an important feature of AD treatment [2]. Here, relative to placebo, EASI scores were improved in these prominent areas after 1 rocatinlimab dose (2 or 4 weeks after treatment initiation, depending on the dosing regimen).

EASI components (erythema, edema, excoriation, and lichenification) represent different clinical manifestations with each component contributing to the heterogeneous nature of AD [26]. Erythema shows skin redness due to increased blood flow to superficial capillaries, while edema represents clinical signs of acute spongiosis and inflammation; excoriations are physical evidence of pruritus from scratching or rubbing and lichenification manifests a leathery thickening of the epidermis due to prolonged scratching or rubbing in chronic disease [26]. As aforementioned, currently available treatments are less effective in reducing erythema and edema scores for treating AD in the head and neck versus other body regions, and treatment outcomes may vary according to different EASI components [22]. However, these EASI components have received less attention in the investigation of treatment response than total EASI scores. In addition, recommended treatments and therapeutic response in patients with AD can vary according to the affected region and lesion morphology [5, 19]. To date, The prevalence of AD manifestations differs across anatomic region; for example, erythematosus plaques may be more common in the head and neck than lichenified plaques [19]. This is supported by our analyses of patients with moderate-to-severe AD in the head and neck, in whom erythema scores

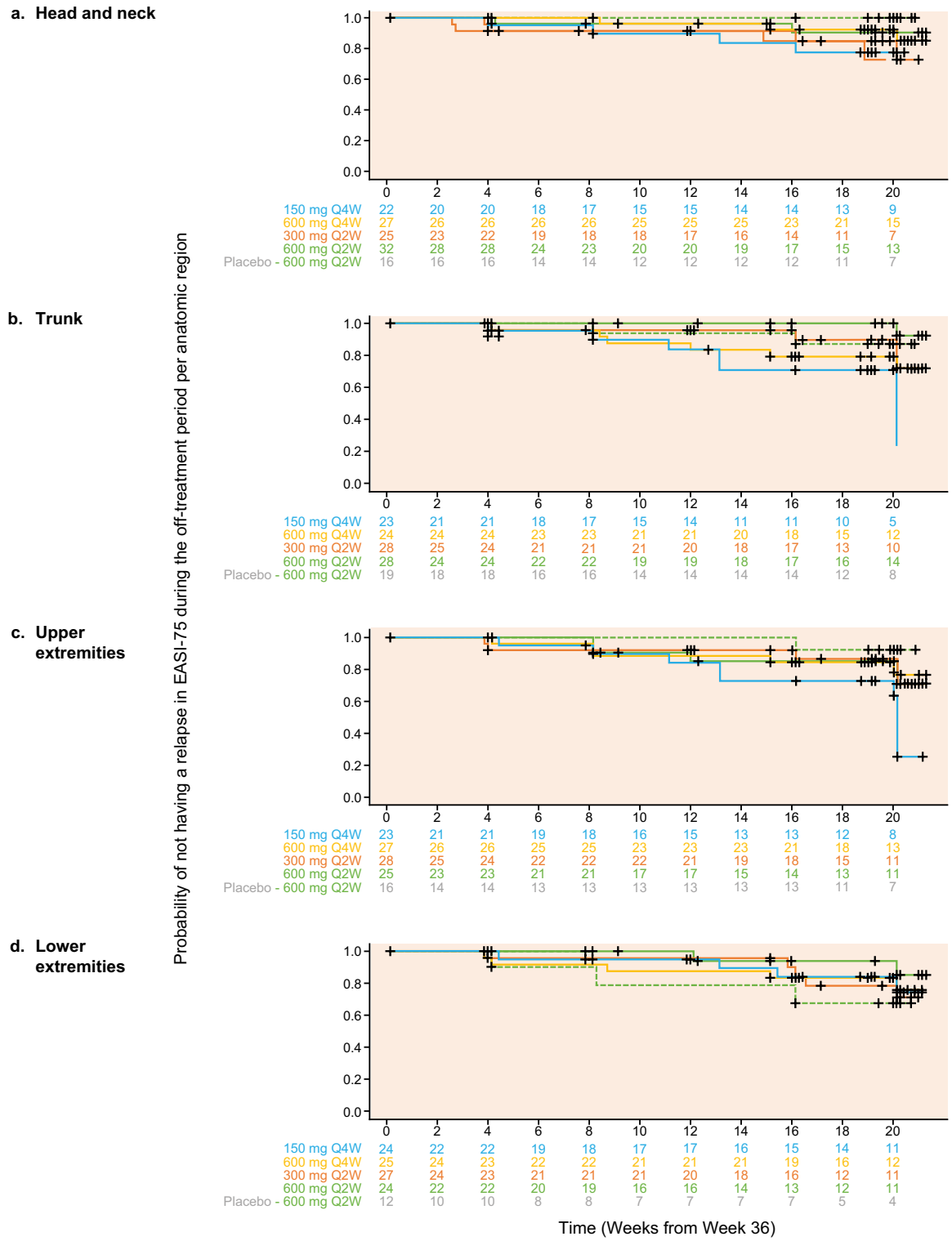

Fig. 5 Probability of not relapsing in EASI-75 among EASI-75 responders at Week 36 across anatomic regions for patients with baseline moderate-to-severe AD at baseline in the corresponding region. Probability of not relapsing (loss of EASI-75 response) during the off-treatment (Weeks 36–56) in the **a** head and neck, **b** trunk, **c** upper extremities, and **d** lower extremities. *AD* atopic dermatitis, *EASI* Eczema Area and Severity Index, *Q2W* every 2 weeks, Q4W every 4 weeks

were numerically higher than lichenification scores. Furthermore, treatment response durability may differ between these manifestations, as some are associated with acute AD (e.g., erythema; Fig. 3 and S3–S5), while others are associated with chronic disease (e.g., lichenification; Fig. 3 and S3–S5) [19]. In our study, treatment with rocatinlimab led to sustained improvements in all EASI components across anatomic regions. These improvements were seen from Week 2, depending on the rocatinlimab dosing regimen, and responses were generally maintained throughout the 20-week off-treatment period. While all components generally improved to a similar extent throughout the trial at Week 56, lichenification showed the greatest improvement in the head and neck, trunk, and upper extremities, and excoriation in the lower extremities. To our knowledge, the association between individual EASI components and disease severity, disease prognosis, and QoL have not been formally assessed, and would be of value to understand how treatment response impacts individual AD signs.

A limitation of this study was the inability to localize AD in specific subregions within each of the four anatomic regions that comprise the EASI score and the results cannot be generalized to specific subregions (e.g., the study result may be not generalizable to show the treatment efficacy in sensitive disease areas such as AD in the face as part of the head and neck or in the hands as part of the upper extremities). EASI scores per individual anatomic regions are not validated scales for AD. Further analyses will be conducted on data from the ongoing phase 3 trials [6–12].

To conclude, rocatinlimab, a T cell rebalancing anti-OX40 receptor monoclonal antibody [30], improved disease activity across multiple anatomic regions in patients with moderate-to-severe AD. Rocatinlimab's unique mechanism of action offers the potential to achieve rapid, durable treatment responses across anatomic regions, including the head and neck, while maintaining a favorable safety profile.

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Data availability Data included in this manuscript can be available upon request from the corresponding author.

Declarations

Conflicts of interests EG-Y received grants/contracts from Amgen, Aslan, Boehringer Ingelheim, Bristol Meyers Squibb, Cara Therapeutics, GSK, Incyte, Kyowa Kirin, Leo Pharma, Pfizer, RAPT, Sanofi, and UCB; received consulting fees from AbbVie, Almirall, Amgen, AnaptysBio, Apogee Therapeutics, Apollo Therapeutics Limited, Artax Biopharma Inc., AstraZeneca, Bristol Meyers Squibb, Boehringer Ingelheim, Cara Therapeutics, Centrexion Therapeutics Corporation, Concert, Connect Biopharm, Eli Lilly, Enveda Biosciences, Escient Pharmaceuticals Inc., Fairmount Funds Management LLC, FL2022-001 Inc., Galderma, Gate Bio, Google Ventures, GSK Immunology, Horizon Therapeutics USA Inc., Incyte, Inmagene, Janssen Biotech, Japan Tobacco, Jasper Therapeutics, Kyowa Kirin, Leo Pharma, Merck, Nektar Therapeutics, Novartis Pharmaceuticals Corporation, NUMAB Therapeutics AG, OrbiMed Advisors LLC, OTSUKA, Pfizer, Pharmaxis Ltd, Pioneering Medicine VII Inc., Proteologix US Inc., RAPT, Regeneron Pharmaceuticals, RibonTherapeutics Inc., Sanofi, SATO, Schrödinger Inc., Sun Pharma Advanced Research Company, Teva Branded Pharmaceutical Products R&D Inc., and UCB; EE is an employee of Kyowa Kirin; HM is an employee of Kyowa Kirin; TA is an employee and stock holder of Kyowa Kirin; ADI received consulting fees from AbbVie, Arena, Benevolent AI, Eli Lilly, Leo Pharma, Novartis, Pfizer, Regeneron, and Sanofi; received payment/honoraria from AbbVie, Eli Lilly, Janssen, Leo Pharma, Regeneron, and Sanofi; has patents pending with J & J, and Regeneron; has leadership/fiduciary roles in International Eczema Council; MJC received research grants from Hyphens Pharma, J & J, Leo Pharma, L'Oréal, Perrigo (ACO Nordic), and Sanofi Genzyme; received consulting fees and payment/honoraria from, and participated in Data Safety Monitoring/Advisory Board for Hyphens Pharma, J & J, Leo Pharma, L'Oréal, Perrigo (ACO Nordic), Regeneron, and Sanofi Genzyme + Kymab (subsid); is a voluntary Medical Advisor for the National Eczema Society (UK); KK received research grants/contracts from AbbVie, Astellas Kyowa Kirin, Jansen Biotech, Maruho, P&G Japan, Taiho, Tanabe Mitsubishi, Toray and Torii; received consulting fees from Eli Lilly, Maruho, and Leo Pharma; received honoraria from Bristol Myers Squibb, Leo Pharma, Maruho, Sanofi, Taiho, and Torii; CC was an employee of Kyowa Kirin at the time the study was conducted; ES received grants/contracts from AbbVie, Acrotech, Amgen, Arcutis, ASLAN, Castle, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Kirin, National Jewish Health, Leo Pharma, Pfizer, Regeneron, Sanofi, Target, and VeriSkin; received consulting fees from AbbVie, Advances in Cosmetic Medical Derm Hawaii LLC, Amgen, AOBiome LLC, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharma, Boehringer Ingelheim USA Inc., Boston Consulting Group, Bristol Myers Squibb, Collective Acumen LLC, CorEvitas, Dermira, Eli Lilly, Evelo Biosciences, Evidera, ExcerptaMedica, FIDE, Forte Bio RX, Galderma, GSK, Gilead Sciences, Inc., Impetus Healthcare, Incyte, Innovaderm Reche, Janssen, J & J, Kyowa Kirin Pharmaceutical Development, Leo Pharma, Medscape LLC, Merck, MauiDerm, MLG Operating, MJH holding, Pfizer, Physicians World LLC, PRImE, Recludix Pharma, Regeneron, Revolutionizing Atopic Dermatitis Inc., Roivant, Sanofi-Genzyme, Trevi Therapeutics, Valeant, Vindico Medical education, and WebMD; received payment/honoraria from AbbVie, Advances in Cosmetic Medical Derm Hawaii LLC, Amgen, AOBiome LLC, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharma, Boehringer Ingelheim USA, Inc., Boston Consulting Group, Bristol Myers Squibb, Collective Acumen LLC, CorEvitas, Dermira, Eli Lilly, Evelo Biosciences, Evidera, ExcerptaMedica, FIDE, Forte Bio RX, Galderma, GSK, Gilead Sciences Inc., Impetus Healthcare, Incyte, Innovaderm Reche, Janssen, J & J, Kyowa Kirin Pharmaceutical Development, Leo Pharma, Medscape LLC, Merck, MauiDerm, MLG Operating, MJH holding, Pfizer, Physicians World LLC, PRImE, Recludix Pharma, Regeneron, Revolutionizing Atopic Dermatitis Inc., Roivant, Sanofi-Genzyme, Trevi therapeutics, Valeant, Vindico

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Ethical approval The study protocol was approved by the Institutional Review Board or Independent Ethics Committee and regulatory health authorities in accordance with local regulations before study commencement. The study was conducted in full accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. All patients provided written informed consent before participating in the trial.

Informed consent All patients provided written informed consent before participating in the trial.

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