



An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study

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Summary

Background OX40 is crucial for T-cell differentiation and memory induction. The anti-OX40 antibody, rocatinlimab inhibits the OX40 pathway. We evaluated the efficacy and safety of rocatinlimab in adults with moderate-to-severe atopic dermatitis.

Methods This multicentre, double-blind, placebo-controlled phase 2b study was done at 65 secondary and tertiary sites in the USA, Canada, Japan, and Germany. Eligible patients were adults (aged 18 years or older) with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria or local diagnostic criteria) with moderate-to-severe disease activity, as defined by an Eczema Area and Severity Index (EASI) score of 16 or more, validated Investigator's Global Assessment for Atopic Dermatitis score of 3 (moderate) or 4 (severe), and affected body surface area 10% or higher at both screening and baseline, with documented history (within 1 year) of inadequate response to topical medications or if topical treatments were medically inadvisable. Patients were randomly assigned (1:1:1:1) to receive subcutaneous rocatinlimab every 4 weeks (150 mg or 600 mg) or every 2 weeks (300 mg or 600 mg) or subcutaneous placebo up to week 18, with an 18-week active-treatment extension and 20-week follow-up. Percentage change from baseline in EASI score was assessed as the primary endpoint at week 16 and during the active extension and follow-up in all randomly assigned patients exposed to study drug with a post-baseline EASI score at week 16 or earlier according to the group they were randomly assigned to. Safety was assessed in all randomly assigned patients exposed to study drug; patients were analysed according to the group they were randomly assigned to. The study is registered with ClinicalTrials.gov, NCT03703102.

Findings Between Oct 22, 2018, and Oct 21, 2019, 274 patients (114 [42%] women, 160 [58%] men; mean age 38·0 years [SD 14·5]) were randomly assigned to one of the rocatinlimab groups (217 [79%] patients) or to the placebo group (57 [21%] patients). Compared with placebo (−15·0 [95% CI −28·6 to −1·4]), significant least-squares mean percent reductions in EASI score at week 16 were observed in all rocatinlimab groups (rocatinlimab 150 mg every 4 weeks −48·3 [−62·2 to −34·0], $p=0·0003$; rocatinlimab 600 mg every 4 weeks −49·7 [−64·3 to −35·2], $p=0·0002$; rocatinlimab 300 mg every 2 weeks −61·1 [−75·2 to −47·0], $p<0·0001$; and rocatinlimab 600 mg every 2 weeks −57·4 [−71·3 to −43·4], $p<0·0001$). The most common adverse events during the double-blind period in patients receiving rocatinlimab (adverse events $\geq 5\%$ of patients in the total rocatinlimab group and more common than the placebo group) were pyrexia (36 [17%] patients), nasopharyngitis (30 [14%] patients), chills (24 [11%] patients), headache (19 [9%] patients), aphthous ulcer (15 [7%] patients), and nausea (13 [6%] patients). There were no deaths.

Interpretation Patients treated with rocatinlimab had progressive improvements in atopic dermatitis, which was maintained in most patients after treatment discontinuation. Treatment was well tolerated.

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Introduction

Despite advances in new treatments of atopic dermatitis targeting the interleukin (IL)-4–IL-13 pathway and the Janus kinase pathways, a substantial number of patients do not respond adequately or cannot tolerate treatments.^{1–3} Therefore, an unmet need remains for safe and effective treatments for moderate-to-severe atopic dermatitis. T helper 2 (Th2) cell responses are considered a predominant inflammatory pathway in atopic dermatitis.^{4,5} Activated Th2 cells release IL-4, IL-13, IL-31,

or thymus-regulated and activation-regulated chemokine (TARC; CCL17), which contribute to chronic itch and skin barrier dysfunction.^{4,6} These atopic dermatitis-associated cytokines and chemokines might function as biomarkers for disease severity.^{4,6} The OX40–OX40 ligand axis plays a crucial role in long-lasting T-cell responses^{7,8} and the pathogenesis of atopic dermatitis.⁹ OX40 is highly expressed in skin lesions in atopic dermatitis.¹⁰ Its expression pattern is unique, increasing transiently only with antigen-specific major

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Research in context

Evidence before this study

There remains an unmet need for treatment of moderate-to-severe atopic dermatitis, particularly for treatments with disease-modifying effects. OX40 is a key regulator of T-cell proliferation and memory formation, which is only expressed on activated T cells. Additionally, OX40 is expressed in a wide variety of T-cell subsets, making it of great therapeutic interest for treating inflammatory conditions, such as atopic dermatitis. We searched PubMed from inception of the database to July 7, 2022, with the search terms “(KHK4083 OR AMG 451) AND atopic dermatitis”. No language restrictions were used. We found one phase 1, single-centre, open-label study that investigated three doses of the anti-OX40 antibody KHK4083 (now rocatinlimab) for 4 weeks in a cohort of 22 Japanese patients with moderate-to-severe atopic dermatitis (NCT03096223). Three repeated intravenous infusions of rocatinlimab had an acceptable safety profile in this study. A trend of improvements in clinical efficacy measures, including Eczema Area and Severity Index and Investigator Global Assessment, was seen over 22 weeks of the study. Treatment with rocatinlimab was also associated with a trend of decrease in thymus-regulated and activation-regulated chemokine (TARC) and interleukin (IL)-22.

Added value of this study

The randomised, double-blind, placebo-controlled design of this phase 2 study provides an assessment of the efficacy and

safety of different doses of rocatinlimab versus placebo for the treatment of moderate-to-severe atopic dermatitis over 56 weeks. This study includes a much larger and more diverse patient population than the previous study. We recruited 274 patients globally from North America, Europe, and Japan. The primary endpoint was reported with all active rocatinlimab doses versus placebo at week 16, and all active dose cohorts continued improving after week 16. Most patients maintained the response for at least 20 weeks off-treatment, potentially indicating rocatinlimab as a novel disease-modifying therapy. The clinical data were supported by established atopic dermatitis biomarker data, including decreased TARC, IL-22, and IgE. The study also showed an acceptable long-term safety profile.

Implications of all the available evidence

The results of this study support rocatinlimab as a safe and effective treatment for moderate-to-severe atopic dermatitis, highlighting the importance of the OX40 pathway in atopic dermatitis pathogenesis and as a potential novel treatment target. Additional clinical studies of rocatinlimab are needed to assess long-term safety and efficacy and to evaluate in a larger patient population.

histocompatibility complex-induced T-cell receptor activation.^{8,11} Therefore, blocking the OX40 pathway potentially inhibits antigen-specific T cells involved in atopic dermatitis without generalised immunosuppression.^{8,9,11} Furthermore, the OX40 pathway plays a unique role in differentiating activated effector T cells into memory T cells, suggesting a potential for long-term effects on immune function.⁸

Rocatinlimab (previously KHK4083) is an anti-OX40 monoclonal antibody that inhibits and reduces the number of activated OX40-expressing T cells.¹² It is a human, non-fucosylated, IgG1 antibody that induces antibody-dependent cellular cytotoxicity, thus potentially targeting pathogenic cells. Here we present the results of a phase 2b study evaluating the efficacy and safety of rocatinlimab in patients with moderate-to-severe atopic dermatitis.

Methods

Study design and participants

This phase 2b, multicentre, randomised, double-blind, parallel-group study was done at 65 sites (19 secondary centres, 46 tertiary centres) in the USA (17 centres), Canada (seven centres), Japan (31 centres), and Germany (ten centres). Eligible patients were adults (aged 18 years or older) with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria or local

diagnostic criteria) with moderate-to-severe disease activity, defined by an Eczema Area and Severity Index (EASI) of score 16 or more, validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) score of 3 (moderate) or 4 (severe); and affected body surface area 10% or higher at both screening and baseline, with documented history (within 1 year) of inadequate response to topical medications or if topical treatments were medically inadvisable.

Patients with history of clinically significant illness; laboratory abnormalities; history of at least three systemic infections requiring systemic (excluding oral) treatment within 1 year; or active infection requiring systemic treatment within 4 weeks or superficial skin infections within 2 weeks (protocol) were excluded. Laboratory abnormalities were defined as serum creatinine concentration more than 1.5 mg/dL; alanine aminotransferase or aspartate aminotransferase concentration 2.5 times or higher than the upper limit of normal; and neutrophil count of less than 1.5×10^3 per μL ; and other laboratory abnormalities that were not prespecified in the protocol that might affect the completion or evaluation of the study, as judged by the investigator.

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 principal investigator and sub-investigators were responsible for

For the protocol see
https://clinicaltrials.gov/ProvidedDocs/02/NCT03703102/Prot_SAP_000.pdf

conducting the study in full accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. All patients provided written informed consent before participating.

Randomisation and masking

Patients were randomly assigned (1:1:1:1:1) to receive double-blind subcutaneous rocatinlimab 150 mg every 4 weeks, 600 mg every 4 weeks, 300 mg every 2 weeks, 600 mg every 2 weeks, or subcutaneous placebo for 18 weeks. Randomisation was done centrally using an interactive web response system with a minimisation algorithm based on the Pollock and Simon method, and stratified according to disease severity (moderate [vIGA-AD 3] or severe [vIGA-AD 4]) at baseline, region (Japan *vs* rest of world), and previous use of biologic treatments. Patients, investigator, sponsor, and all study site personnel were masked to treatment assignment with the exception of monitors responsible for drug storage and preparation and safety personnel.

Procedures

After a screening period of 2 to 6 weeks, patients received subcutaneous rocatinlimab or placebo for 18 weeks. At week 18, patients entered an active-treatment extension (week 18 to week 36, with the last injection at week 34). During the active-treatment extension, patients initially randomly assigned to receive rocatinlimab continued to receive the same dose and patients initially randomly assigned to receive placebo received rocatinlimab 600 mg every 2 weeks. The double-blind period and active-treatment extension were followed by a 20-week off-treatment follow-up (weeks 36–56). Patients were followed up every 4 weeks during the follow-up period. The schedule of assessments for each treatment period and the follow-up period can be found in the protocol on pages 63–68. Patients remained masked until week 56.

Alongside the study regimen, patients applied an investigator-approved topical emollient (appendix p 7) twice daily from 1 week before baseline until at least week 36. Topical corticosteroids and immunosuppressives or systemic treatment for atopic dermatitis were prohibited from week 1 before the baseline visit until the end of study. Patients who initiated rescue treatment for exacerbation of atopic dermatitis at any time until week 36 or who had unchanged or worsened vIGA-AD scores at week 26 compared with baseline were withdrawn and underwent end-of-study assessments. Data obtained after initiation of rescue treatment were considered missing data. 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.

Outcomes

The primary efficacy endpoint was percent change from baseline to week 16 in EASI score (range 0–72; higher

scores indicating greater severity and extent of atopic dermatitis).¹³ Disease severity measures and patient-reported outcomes were assessed as secondary endpoints at each scheduled visit from weeks 1 to 56.

Secondary disease severity endpoints were 50%, 75%, or 90% reductions from baseline in EASI score (EASI-50, EASI-75, or EASI-90); change from baseline in EASI score; vIGA-AD score of 0 (clear) or 1 (almost clear) and at least 2-point reduction from baseline (range 0–4 [higher score indicates more severe disease]);¹⁴ and percent change from baseline in SCORing Atopic Dermatitis (SCORAD; range 0–103 [higher score indicates greater disease extent and intensity]).¹⁵ Prespecified patient-reported outcomes were change from baseline in percent body surface area affected; change from baseline in Dermatology Life Quality Index (DLQI; range 0–30 [higher scores indicating greater effect on quality of life]);¹⁶ percent change from baseline in pruritus numerical rating scale (NRS) score (range 0–10 [higher scores indicate more severe itch]; and percent change from baseline in sleep disturbance NRS score (range 0–10 [with higher scores indicating worse sleep]).¹⁷ The prespecified outcomes of a 4-point improvement or greater from baseline in pruritus NRS,¹⁸ evaluated at each timepoint, and time to relapse for EASI-75 (defined as days from week 36 to loss of EASI-75), evaluated during follow-up, are also reported.

Safety was evaluated up to week 56 based on adverse events, laboratory values, vital signs, and standard 12-lead electrocardiogram (ECG).

Prespecified exploratory endpoints for biomarkers associated with atopic dermatitis disease activity were assessed until week 56. Assessments included analysis of serum concentrations of inflammatory and disease markers (TARC [CCL17], IgE, IL-22, and lactate dehydrogenase).

Statistical analysis

Assuming a mean percent change in EASI at week 16 of –60% in rocatinlimab groups (–35% in the placebo group), and a common standard deviation of 40% based on published studies,^{2,12,13,19} a sample size of 42 patients per group was required to obtain a statistically significant difference in the primary endpoint with a two-sided significance level of 5% and power more than 80%. A target sample size of 50 patients per group was selected to account for fluctuations in group allocation.

Efficacy was analysed in the full analysis set (all randomly assigned patients exposed to study drug with a post-baseline EASI score at week 16 or earlier). Safety and pharmacodynamics were evaluated in the safety population (all randomly assigned patients exposed to study drug; patients were analysed according to the randomly assigned group).

The primary endpoint was evaluated by analysis of covariance with treatment, baseline EASI score, and stratification factors as covariates (two-sided 5% significance level). To maintain overall type I error rate, a closed test procedure was done using the following sequence: 600 mg

See Online for appendix

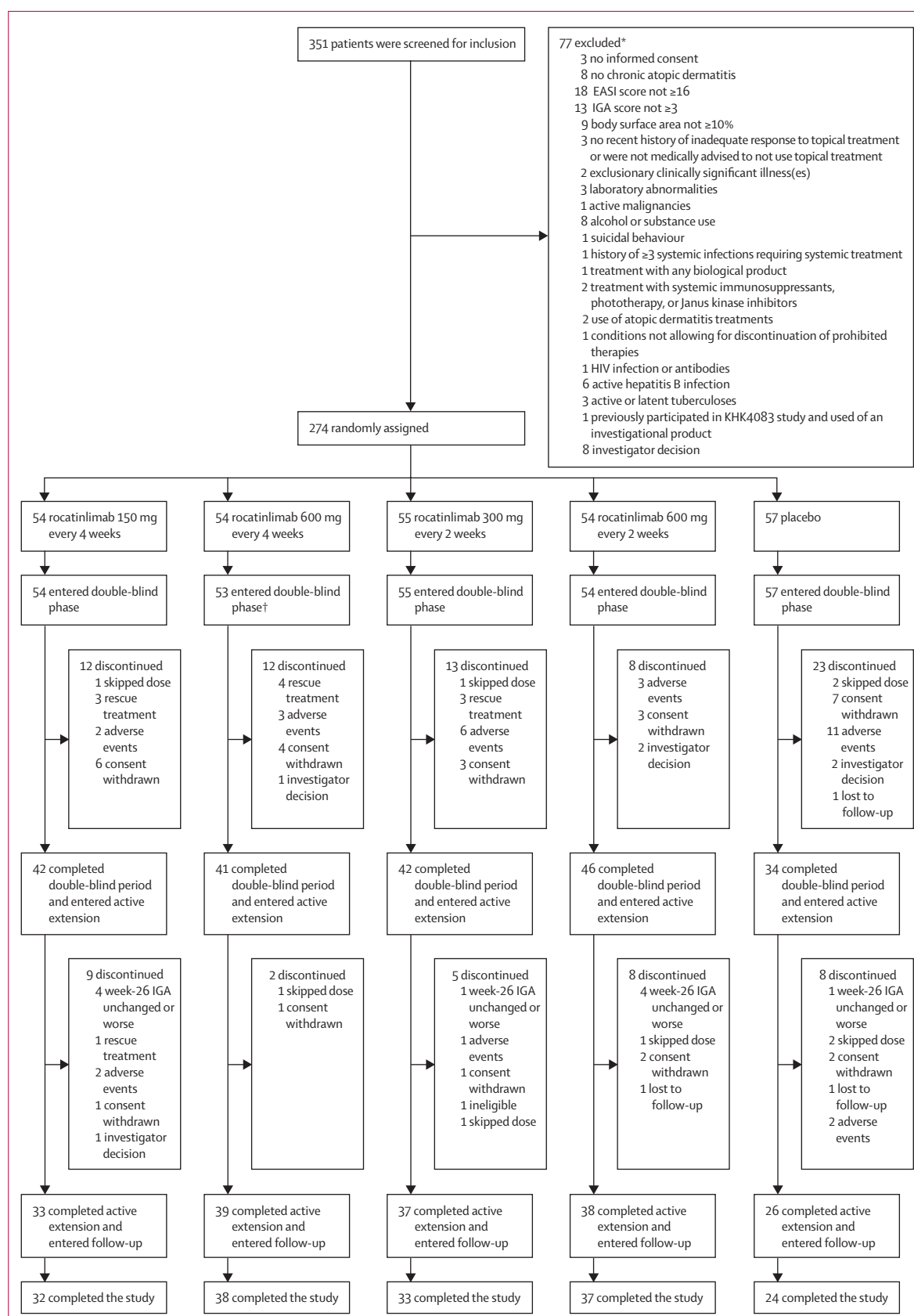


Figure 1: Trial profile
EASI=Eczema Area and Severity Index.
IGA=Investigator's Global Assessment. *Some individuals are included in more than one category. †One patient withdrew informed consent and did not enter the double-blind period.

every 2 weeks versus placebo, 300 mg every 2 weeks versus placebo, 600 mg every 4 weeks versus placebo, and 150 mg every 4 weeks versus placebo. Missing data for continuous variables were imputed using the last observation carried forward method and dichotomous endpoints were summarised using non-responder imputation. Sensitivity analyses are described in the appendix (p 6).

Other continuous endpoints were analysed by analysis of covariance using last-observation-carried-forward imputation without multiplicity adjustment. Categorical endpoints were summarised descriptively using non-responder imputation without multiplicity adjustment and exact 95% CIs for the difference between the placebo group and each rocatinlimab group were calculated.

Of the patients with EASI-75 at week 36, time to relapse of EASI-75 (defined as days from week 36 to loss of EASI-75) was evaluated, and probability of not relapsing for EASI-75 was estimated using the Kaplan-Meier method. Patients who used rescue treatment (mostly topical corticosteroids) during the follow-up period while maintaining EASI-75 response were not considered as having relapsed; they were censored at their last EASI evaluation visit date. Patients who completed the study or

discontinued during the follow-up period were censored at the visit date of their last EASI evaluation before that event.

Analyses were done with SAS software (version 9.3). The study is registered with ClinicalTrials.gov, NCT03703102.

Role of the funding source

The funder was involved in study design, data analysis, data interpretation, and writing of the report, but not data collection.

Results

Between Sept 22, 2018, and Nov 12, 2020, 274 patients (114 [42%] women, 160 [58%] men; mean age 38.0 years [SD 14.5]) were randomly assigned to one of five active-treatment groups or placebo; 273 patients received study treatment (safety population), 205 completed the double-blind period, and 164 completed the 56-week study (figure 1).

Demographics and baseline disease characteristics for the full analysis set are reported in table 1. Mean disease duration was 16.2 years (SD 14.9) and 147 (55%) patients had vIGA-AD score of 3 at baseline. Mean EASI score was 31.5 (SD 12.7), SCORAD score was 68.3 (13.8), and

	Rocatinlimab 150 mg every 4 weeks group (n=52)	Rocatinlimab 600 mg every 4 weeks group (n=52)	Rocatinlimab 300 mg every 2 weeks group (n=52)	Rocatinlimab 600 mg every 2 weeks group (n=54)	Placebo group (n=57)	Full analysis set (n=267)
Age, years	37.2 (13.8)	39.1 (14.6)	37.2 (14.4)	37.3 (16.3)	38.7 (14.4)	37.9 (14.7)
Sex						
Men	37 (71%)	30 (58%)	30 (58%)	30 (56%)	31 (54%)	158 (59%)
Women	15 (29%)	22 (42%)	22 (42%)	24 (44%)	26 (46%)	109 (41%)
Race						
Asian	35 (67%)	31 (60%)	35 (67%)	33 (61%)	37 (65%)	171 (64%)
Black or African American	3 (6%)	1 (2%)	2 (4%)	1 (2%)	6 (11%)	13 (5%)
White	13 (25%)	20 (39%)	15 (29%)	20 (37%)	14 (25%)	82 (31%)
Other	1 (2%)	0	0	0	0	1 (<1%)
BMI at screening, kg/m ²	24.9 (4.9)	24.7 (5.7)	26.9 (7.4)	25.2 (6.5)	24.3 (5.2)	25.2 (6.0)
Asthma	13 (25%)	17 (33%)	11 (21%)	12 (22%)	15 (26%)	68 (26%)
Allergic rhinitis	4 (8%)	5 (10%)	3 (6%)	5 (9%)	6 (11%)	23 (9%)
Time from diagnosis of atopic dermatitis to random assignment, * years	18.9 (16.2)	16.1 (15.5)	15.0 (12.5)	15.2 (13.1)	15.8 (17.0)	16.2 (14.9)
Severity of atopic dermatitis—Investigator's Global Assessment for Atopic Dermatitis						
3	29 (56%)	28 (54%)	30 (58%)	29 (54%)	31 (54%)	147 (55%)
4	23 (44%)	24 (46%)	22 (42%)	25 (46%)	26 (46%)	120 (44%)
Pruritus numerical rating scale score	7.7 (1.6)	7.7 (2.1)	7.3 (1.6)	7.6 (1.9)	7.2 (2.3)	7.5 (1.9)
Sleep disturbance numerical rating scale score	5.9 (2.6)	5.5 (3.1)	5.0 (2.9)	5.9 (2.7)	5.0 (3.1)	5.5 (2.9)
Eczema Area and Severity Index score	33.2 (13.1)	32.5 (12.8)	31.6 (12.5)	31.1 (11.8)	29.2 (13.3)	31.5 (12.7)
SCORing Atopic Dermatitis score	68.7 (12.8)	69.8 (13.5)	68.2 (14.4)	68.8 (14.4)	66.4 (14.1)	68.3 (13.8)
Percent body surface area	59.5% (24.0)	58.8% (25.4)	55.7% (20.9)	55.3% (23.4)	54.3% (23.5)	56.7% (23.4)
Previous use of biological products for treatment of atopic dermatitis	7 (14%)	5 (10%)	8 (15%)	8 (15%)	9 (16%)	37 (14%)
Data are n (%) or mean (SD). Data are presented from the full analysis set, which included patients who received at least one dose of study drug with evaluable Eczema Area and Severity Index score at week 16; 267 (97%) of 274 randomly assigned patients were included in the full analysis set. *On the basis of documented diagnosis of atopic dermatitis.						
Table 1: Baseline demographics and disease characteristics						

	Rocatinlimab 150 mg every 4 weeks group (n=52)	Rocatinlimab 600 mg every 4 weeks group (n=52)	Rocatinlimab 300 mg every 2 weeks group (n=52)	Rocatinlimab 600 mg every 2 weeks group (n=54)	Placebo group (n=57)
Primary endpoint					
Percent change from baseline in EASI, least-squares mean	-48.3 (-62.2 to -34.0)	-49.7 (-64.3 to -35.2)	-61.1 (-75.2 to -47.0)	-57.4 (-71.3 to -43.4)	-15.0 (-28.6 to -1.4)
Treatment difference	-33.3 (-51.3 to -15.3)	-34.7 (-52.7 to -16.8)	-46.1 (-64.0 to -28.2)	-42.3 (-60.0 to -24.7)	..
p value versus placebo	0.0003	0.0002	<0.0001	<0.0001	..
Secondary endpoints					
EASI-50*	30 (58%; 43.2 to 71.3)	31 (60%; 45.1 to 73.0)	36 (69%; 54.9 to 81.3)	35 (65%; 50.6 to 77.3)	17 (30%; 18.4 to 43.4)
Treatment difference	27.9 (9.0 to 45.1)	29.8 (10.9 to 46.9)	39.4 (21.0 to 55.8)	35.0 (16.4 to 51.7)	..
EASI-75*	23 (44%; 30.5 to 58.7)	21 (40%; 27.0 to 54.9)	28 (54%; 39.5 to 67.8)	21 (39%; 25.9 to 53.1)	6 (11%; 4.0 to 21.5)
Treatment difference	33.7 (15.1 to 50.5)	29.9 (11.1 to 46.9)	43.3 (25.3 to 59.2)	28.4 (10.0 to 45.7)	..
EASI-90*	10 (19%; 9.6 to 32.5)	6 (12%; 4.4 to 23.4)	19 (37%; 23.6 to 51.0)	10 (19%; 9.3 to 31.4)	2 (4%; 0.4 to 12.1)
Treatment difference	15.7 (-3.2 to 33.8)	8.0 (-11.0 to 26.4)	33.0 (14.5 to 49.8)	15.0 (-4.1 to 33.0)	..
Investigator's Global Assessment for Atopic Dermatitis 0 or 1 and 2 point or greater improvement*	10 (19%; 9.6 to 32.5)	8 (15%; 6.9 to 28.1)	16 (31%; 18.7 to 45.1)	10 (19%; 9.3 to 31.4)	1 (2%; 0.04 to 9.4)
Treatment difference	17.5 (-1.5 to 35.5)	13.6 (-5.4 to 31.8)	29.0 (10.5 to 46.2)	16.8 (-2.3 to 34.6)	..
Percent change from baseline in SCORing Atopic Dermatitis, least squares mean (95% CI)	-34.9 (-45.2 to -24.5)	-35.1 (-45.5 to -24.7)	-46.7 (-56.8 to -36.6)	-40.8 (-50.7 to -30.8)	-11.9 (-21.6 to -2.2)
Treatment difference	-23.0 (-35.8 to -10.1)	-23.2 (-36.0 to -10.4)	-34.8 (-47.5 to -22.1)	-28.9 (-41.5 to -16.3)	..
Change from baseline in percent body surface area, least squares mean (95% CI)	-22.9 (-30.3 to -15.4)	-21.5 (-29.1 to -13.9)	-27.9 (-35.3 to -20.5)	-25.0 (-32.3 to -17.8)	-7.9 (-15.0 to -0.8)
Treatment difference	-15.0 (-24.3 to -5.6)	-13.6 (-23.0 to -4.3)	-20.1 (-29.4 to -10.7)	-17.2 (-26.4 to -8.0)	..
Percent change from baseline in pruritus numerical rating scale, least squares mean (95% CI)	-25.6 (-39.5 to -11.7)	-34.4 (-48.6 to -20.2)	-48.0 (-61.7 to -34.3)	-36.8 (-50.4 to -23.3)	-6.2 (-19.4 to 7.0)
Treatment difference	-19.4 (-36.8 to -2.0)	-28.2 (-45.6 to -10.8)	-41.8 (-59.2 to -24.5)	-30.7 (-47.9 to -13.4)	..
Change from baseline in sleep disturbance numerical rating scale, least squares mean (95% CI)	-1.1 (-2.0 to -0.2)	-1.9 (-2.9 to -1.0)	-2.6 (-3.5 to -1.7)	-2.0 (-2.9 to -1.1)	-0.01 (-0.9 to 0.9)
Treatment difference	-1.1 (-2.2 to 0.1)	-1.9 (-3.1 to -0.8)	-2.6 (-3.7 to -1.4)	-2.0 (-3.1 to -0.9)	..
Change from baseline in Dermatology Life Quality Index, least squares mean (95% CI)	-2.6 (-4.7 to -0.4)	-4.7 (-6.9 to -2.4)	-6.3 (-8.4 to -4.2)	-4.9 (-7.0 to -2.8)	0.2 (-1.9 to 2.3)
Treatment difference	-2.8 (-5.4 to -0.1)	-4.9 (-7.6 to -2.2)	-6.5 (-9.1 to -3.8)	-5.1 (-7.8 to -2.5)	..
Post-hoc outcomes					
Pruritus numerical rating scale 4-point improvement or greater	19 (37%; 23.6 to 51.0)	24 (46%; 32.2 to 60.5)	29 (56%; 41.3 to 69.5)	24 (44%; 30.9 to 58.6)	11 (19%; 10.1 to 31.9)
Treatment difference	17.2 (-1.7 to 35.3)	26.9 (8.2 to 44.3)	36.5 (18.1 to 53.0)	25.2 (6.6 to 42.5)	..

Data are n (%; 95% CI) or point estimate (95% CI), unless otherwise stated. Continuous endpoints were analysed by an analysis of covariance model, including treatment assignment, EASI score at baseline, severity of atopic dermatitis at baseline (validated Investigator's Global Assessment for Atopic Dermatitis 3-4), region (Japan vs rest of world), and previous use of biological products for the treatment of atopic dermatitis at baseline (yes vs no) as covariates. Missing data of the endpoint at week 16 were imputed by the last observation carried forward method, and a closed testing procedure was applied for adjustment of multiplicity. EASI=Eczema Area and Severity Index. *Exact 95% CIs for the difference between the placebo group and each rocatinlimab group were calculated; widths of the intervals have not been adjusted for multiplicity and therefore inferences drawn might not be reproducible.

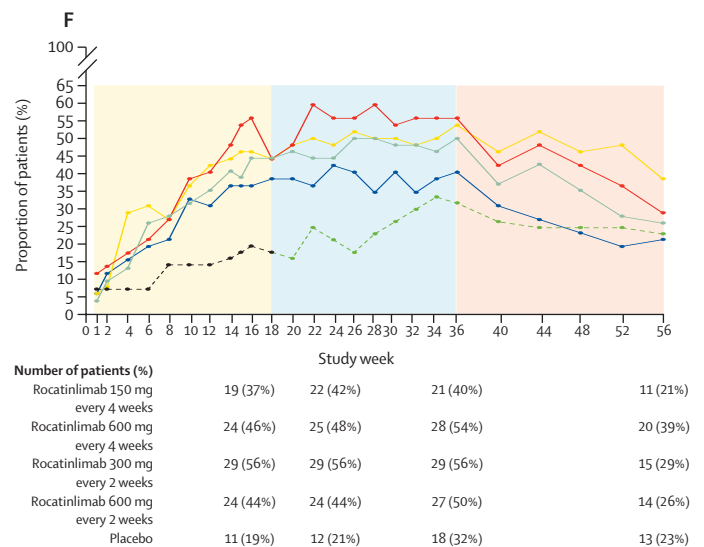
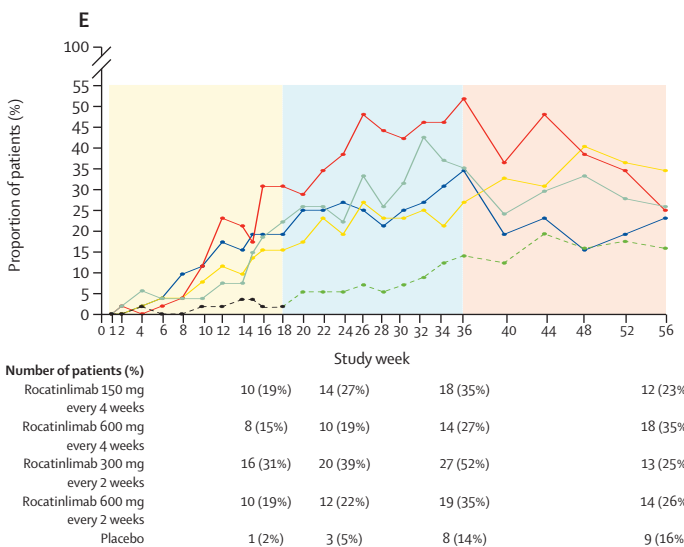
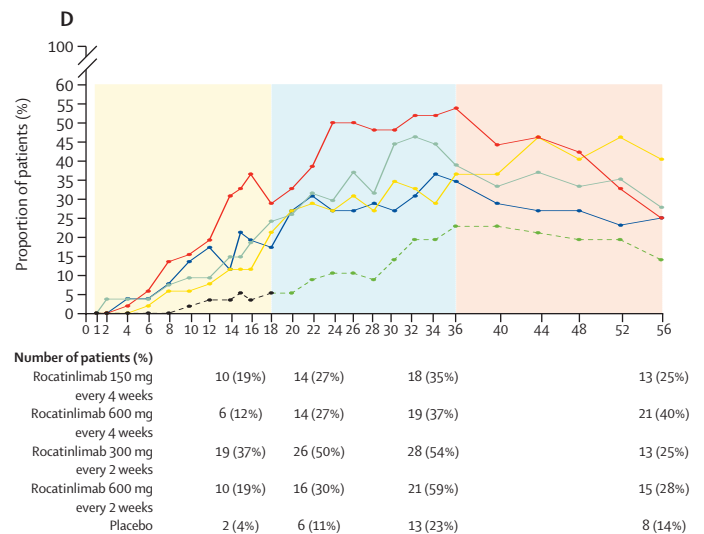
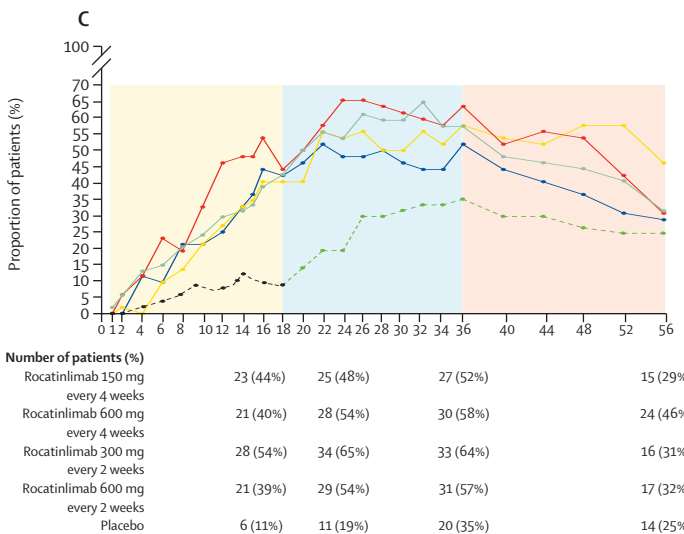
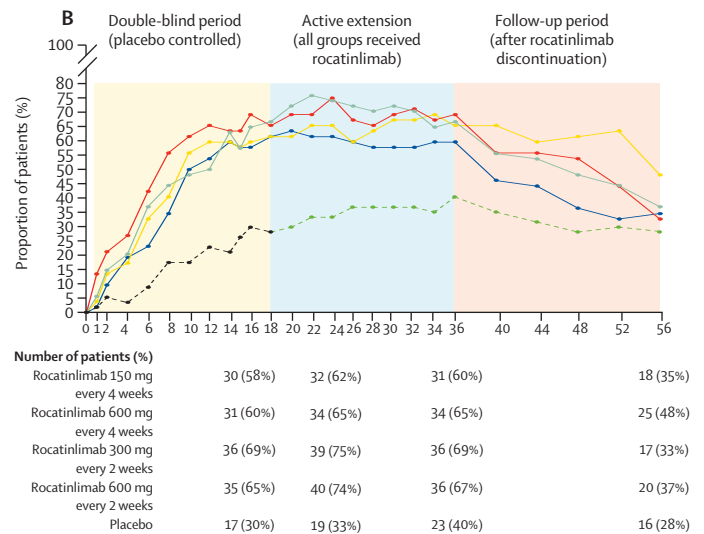
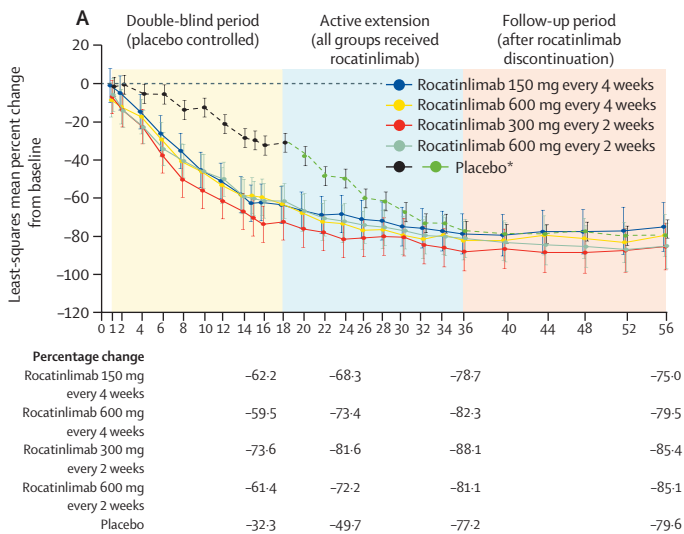
Table 2: Efficacy results at week 16

affected body surface area percentage was 56.7% (23.4). Overall, 37 (14%) patients had received previous biologic treatment (table 1).

The least-squares mean percent change in EASI score from baseline to week 16 was significantly greater for patients in all rocatinlimab dose groups (rocatinlimab 150 mg every 4 weeks -48.3% [95% CI -62.2 to -34.0], $p=0.0003$; rocatinlimab 600 mg every 4 weeks -49.7% [-64.3 to -35.2], $p=0.0002$; rocatinlimab 300 mg every 2 weeks -61.1% [-75.2 to -47.0], $p<0.0001$; rocatinlimab 600 mg every 2 weeks -57.4% [-71.3 to -43.4], $p<0.0001$) than those receiving placebo (-15.0% [-28.6 to -1.4]; table 2). Conclusions from the sensitivity

Figure 2: Efficacy assessments over time

(A) Least-squares mean percent change in EASI score. (B) EASI-50 response. (C) EASI-75 response. (D) EASI-90 response. (E) Validated Investigator's Global Assessment for Atopic Dermatitis score of 0 or 1 with a reduction of 2 or more points from baseline. (F) 4-point pruritus numerical rating scale improvement or more. Efficacy assessments were analysed in the full analysis set. For percent change from baseline in EASI score, error bars are 95% CI. A mixed-effects model with repeated measures was used for least-squares mean percent change in EASI score. EASI-75, EASI-90, and assessments of validated Investigator's Global Assessment for Atopic Dermatitis score of 0 or 1 or reduction of 2 or more points from baseline were summarised using non-responder imputation. EASI=Eczema Area and Severity Index. EASI-50=50% reductions from baseline in EASI score. EASI-75=75% reductions from baseline in EASI score. EASI-90=90% reductions from baseline in EASI score. *Patients in the placebo group received 600 mg rocatinlimab from week 18 to week 56.



analysis were consistent with the primary analysis although reported treatment effects were smaller (appendix p 10).

At week 16, numerically higher proportions of patients in the rocatinlimab groups versus placebo had EASI-50, EASI-75, and EASI-90, and had a vIGA-AD score of 0 or 1 (table 2). Numerically greater improvements in skin involvement as measured by mean change from baseline in affected body surface area were also seen in all rocatinlimab groups versus the placebo group (table 2). The proportion of patients who had a 4-point improvement or greater from baseline in pruritus NRS score at week 16 was higher across all rocatinlimab groups compared with placebo (table 2). Similarly, a difference was also seen in mean percent change from baseline in pruritus NRS score at week 16 between the rocatinlimab groups and the placebo group (table 2). Patients in the rocatinlimab group had a decrease in sleep disturbances, whereas patients in the placebo group had no change (table 2). Numerically greater improvements were also seen in overall disease severity and quality of life at week 16 with rocatinlimab versus placebo, as measured by SCORAD and DLQI (table 2). For each outcome, numerically greater improvements were observed at week 16 for patients in the rocatinlimab 300 mg every 2 weeks group compared with all other dose groups (table 2).

Improvements in disease severity and pruritus NRS response observed at week 16 continued in all rocatinlimab groups throughout the active extension period to week 36 (figure 2). During the off-treatment follow-up period, improvements in disease severity measures and patient-reported outcomes largely remained within the ranges observed in the active extension, which continued until week 56 (figure 2; appendix pp 11–14).

EASI-75 response rates were maintained in most patients during off-drug follow-up (weeks 36 to 56; figure 3). During follow-up, 37 (26%) patients received rescue treatment (mostly topical corticosteroids) despite maintaining EASI-75 response (not considered relapsed), and were censored at the date of their last EASI evaluation. Of the patients with EASI-75 at week 36, the probabilities of not relapsing for EASI-75 at week 56 ranged from 73% to 96% across rocatinlimab groups (figure 3).

Adverse events reported were generally similar between rocatinlimab groups (table 3). During the initial 18-week double-blind period, 175 (81%) patients across all of the rocatinlimab groups and 41 (72%) patients in the placebo group reported adverse events (table 3). The most frequent adverse events (occurring in $\geq 5\%$ of patients in the rocatinlimab groups and more common in the rocatinlimab group than the placebo group) in the pooled rocatinlimab groups were pyrexia, chills, headache, aphthous ulcer, and nausea (table 3). Pyrexia and chills (considered injection reactions by the investigators) were observed primarily after the first administration of rocatinlimab, were mild to

moderate in intensity, and did not result in treatment discontinuation.

The incidence of serious adverse events ranged from 2% to 6% in the rocatinlimab groups, and the incidence was 2% in the placebo group (table 3). One patient in the rocatinlimab 150 mg every 4 weeks group had a serious adverse event of anal abscess that was reported as related to study drug and led to treatment discontinuation. The event occurred following endoscopic mucosal resection due to polypectomy and a subsequent diagnosis of rectosigmoid cancer (stage 0), which was not evaluated as associated with rocatinlimab treatment because of risk factors such as smoking and alcohol consumption. No serious hypersensitivity reactions or deaths occurred. Adverse events leading to discontinuation of study treatment occurred in 19 (9%) patients in the pooled rocatinlimab group and 12 (21%) in the placebo group (table 3). There were no clinically significant changes in laboratory values, vital signs, or ECG findings (appendix p 6). Safety findings during the whole study period were consistent with the double-blind period (appendix p 6).

Rocatinlimab induced modulation of atopic dermatitis biomarkers (appendix pp 17–20). In the rocatinlimab groups, mean serum concentrations of TARC (CCL17), IgE, and IL-22 decreased over the double-blind period

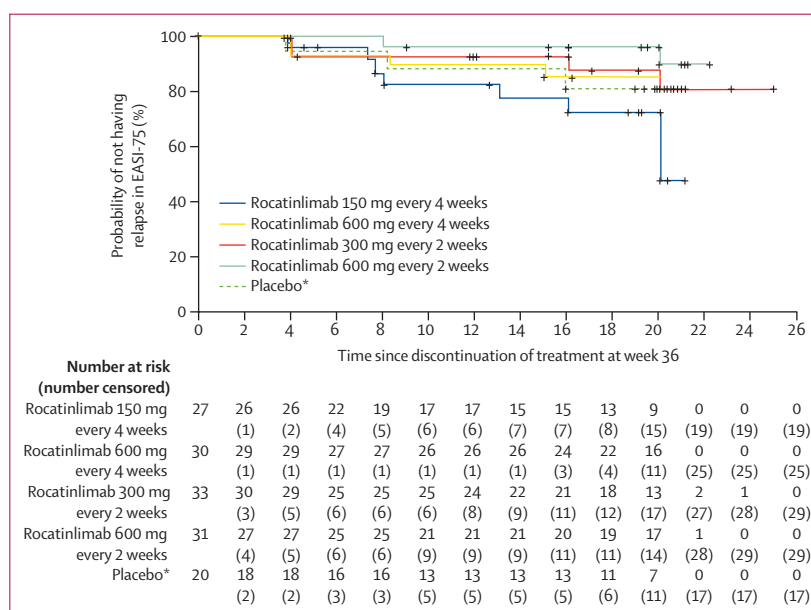


Figure 3: Durability of EASI-75 response after treatment discontinuation

Probability of not having relapse (defined as loss of EASI-75 response) during the off-drug follow-up period is shown for patients who achieved EASI-75 response at week 36 (last dose of rocatinlimab, week 34). Patients who received rescue treatment before the week 36 assessment discontinued study drug and underwent end-of-study assessment. 37 patients who received rescue treatment during the follow-up period while maintaining EASI-75 response (32 received topical corticosteroids; five received systemic therapy) were not considered as having relapsed. However, they were censored at the visit date of that EASI evaluation because efficacy assessments were omitted after initiation of rescue therapy. For patients who completed the study or discontinued the study during the follow-up period, data were censored at the visit date of their last EASI evaluation. EASI=Eczema Area and Severity Index. EASI-75=75% reductions from baseline in EASI score. *Patients in the placebo group received 600 mg every 2 weeks after week 18 throughout the treatment extension period until week 36.

	Rocatinlimab 150 mg every 4 weeks group (n=54)	Rocatinlimab 600 mg every 4 weeks group (n=53)	Rocatinlimab 300 mg every 2 weeks group (n=55)	Rocatinlimab 600 mg every 2 weeks group (n=54)	Rocatinlimab total (n=216)	Placebo (n=57)
Any adverse event	37 (69%)	45 (85%)	47 (86%)	46 (85%)	175 (81%)	41 (72%)
Serious adverse events	3 (6%)	1 (2%)	3 (6%)	1 (2%)	8 (4%)	1 (2%)
Adverse events leading to treatment discontinuation	5 (9%)	3 (6%)	7 (13%)	4 (7%)	19 (9%)	12 (21%)
All deaths	0	0	0	0	0	0
Adverse events with severity grade of 3 or greater	6 (11%)	1 (2%)	5 (9%)	4 (7%)	16 (7%)	2 (4%)
Adverse events in at least 5% of patients in the total rocatinlimab group and greater in the rocatinlimab group than the placebo group						
Pyrexia	7 (13%)	10 (19%)	9 (16%)	10 (19%)	36 (17%)	2 (4%)
Nasopharyngitis	8 (15%)	7 (13%)	7 (13%)	8 (15%)	30 (14%)	9 (16%)
Chills	2 (4%)	3 (6%)	7 (13%)	12 (22%)	24 (11%)	0
Headache	4 (7%)	6 (11%)	4 (7%)	5 (9%)	19 (9%)	1 (2%)
Aphthous ulcer	3 (6%)	8 (15%)	3 (6%)	1 (2%)	15 (7%)	0
Nausea	3 (6%)	2 (4%)	1 (2%)	7 (13%)	13 (6%)	1 (2%)

Data are n (%). Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0. Data are presented from the safety analysis set, which included patients who received at least one dose of rocatinlimab; 273 (97%) of 274 randomly assigned patients were included in the safety analysis set.

Table 3: Adverse events reported until week 18

to week 16, and remained reduced through the active extension and off-drug follow-up (week 56) in most groups (appendix pp 17–19). Lactate dehydrogenase concentration and mean eosinophil count, which exceeded the upper limit of normal at baseline, decreased gradually during the double-blind period, and remained reduced from baseline until week 56 (appendix p 20).

Discussion

In this trial of patients with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, all dosing regimens of rocatinlimab produced greater improvement in EASI score, other clinical measures, and patient-reported outcomes compared with placebo. Although not powered for subgroup analyses, the largest improvements were observed with rocatinlimab 300 mg every 2 weeks based on all primary and secondary endpoints. Adverse events in the rocatinlimab groups were consistent with previous studies.^{12,20}

All rocatinlimab cohorts had significant changes in the primary endpoint and most cohorts showed significant changes in secondary endpoints versus placebo by week 16, and they continued to show progressive improvement in efficacy after week 16. By contrast, the maximum efficacy of dupilumab,²¹ oral Janus kinase inhibitors (including baricitinib and upadacitinib),^{22,23} and other approved systemic treatments for atopic dermatitis²⁴ were generally observed by week 16. This might reflect the unique mechanism of action of rocatinlimab, which inhibits Th2 T-cell activation and clonal expansion. Furthermore, OX40 is expressed on Th2 cells and other T-cell subsets that are upregulated in patients with atopic dermatitis, including Th1, Th17, and

Th22 cells,⁷ potentially explaining the progressive efficacy of rocatinlimab.

At week 36, an EASI-75 response was reported in 52–64% of patients randomly assigned to each rocatinlimab dose group. Similar rates of EASI-75 response were seen in trials of baricitinib, abrocitinib, and upadacitinib, but differences in study design and patient populations do not allow for direct comparisons.^{22,23,25} Patients with atopic dermatitis frequently have relapse, necessitating long-term treatment. In this study, most patients with an EASI-75 response ($\geq 70\%$ of patients in each rocatinlimab dose group) maintained responses for up to 20 weeks after treatment discontinuation. By contrast, other treatments for atopic dermatitis have not shown long durability of response off-treatment. In the SOLO-CONTINUE study,²¹ 30% of patients who had an EASI-75 response with dupilumab treatment and switched to placebo maintained EASI-75 response at week 36 compared with 72% of patients who continued taking dupilumab once a week or once every 2 weeks. Less frequent administration of dupilumab (every 4 weeks or every 8 weeks) also resulted in reduced efficacy in the SOLO-CONTINUE study.²¹ In the JADE REGIMEN trial,²⁶ 78% of patients who switched to placebo after a treatment response with abrocitinib (IGA 0/1 response with ≥ 2 grade improvement and EASI-75 response) were reported to have a flare at week 12.²⁶ Thus, the long off-treatment durability of response observed with rocatinlimab is unique among current atopic dermatitis therapies and might arise from its novel effect on activated OX40-positive T cells. The reduction of OX40-positive T cells by rocatinlimab could also contribute to the durability of response by potentially removing Ag-specific pathogenic T cells.²⁷ Thus, our data

suggest that rocatinlimab potentially has unique disease-modifying effects in atopic dermatitis which need to be explored in a phase 3 programme.

This study indicates the importance of the OX40 pathway in atopic dermatitis pathogenesis, and as a potential novel treatment target. Some study limitations should be noted. First, the sample size was relatively small, reflective of a phase 2b study. Second, the study population was largely Asian, potentially limiting interpretability for other racial groups. Third, there was no adjustment for multiplicity for secondary endpoints; therefore, p values could not be reported for those endpoints. No linear dose response was seen and this cannot be explained by differences in baseline characteristics, which were well balanced between cohorts. However, non-linear dose-response relationships have been seen with other monoclonal antibodies.^{28–31} Fourth, the 20-week follow-up period did not allow for investigation of the potential for longer durability of response. Finally, the study did not assess combination treatment of rocatinlimab with topical corticosteroids. Phase 3 studies that use larger study populations and combination therapy and have a longer follow-up are needed to address these limitations.

In conclusion, rocatinlimab, a monoclonal antibody that targets OX40-expressing T cells, showed greater improvements in disease severity compared with placebo in patients with atopic dermatitis over 16 weeks. Improvement increased progressively until end of treatment at week 36, with maintenance of EASI-75 response in most patients after discontinuation up to week 56.

Contributors

EG-Y, KR, ELS, KK, MF, and TM designed and planned the study. HM, EE, and TM contributed to data analysis. EG-Y, KR, ELS, KK, MF, and KI collected the data. EG-Y, KR, ELS, KK, MF, EE, TS, and TM interpreted the results. EG-Y, EE, TS, HM, and TM drafted the manuscript. EG-Y, KR, ELS, KK, MF, and KI critically reviewed the drafts. All authors gave final approval for submission. All authors had access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data, agree to be accountable for all aspects of the work, will ensure that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved, and have reviewed the final version of the manuscript to be submitted and agree with the content and submission.

Declaration of interests

EG-Y reports research funds (grants paid to the institution) from Amgen, AnaptysBio, Asana Biosciences, AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Celgene, Eli Lilly, Innovaderm, Kyowa Kirin, Leo Pharma, Novartis, Pfizer, and Regeneron Pharmaceuticals; served as a consultant for AbbVie, Almirall, Amgen, Arena, Asana Biosciences, Aslan Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Celgene, Connect Pharma, Eli Lilly, EMD Serono, Evidera, Galderma, Ichnos Sciences, Incyte, Janssen Biotech, Kyowa Kirin, Leo Pharma, Pandion Therapeutics, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Sanofi, SATO Pharmaceutical, Siolta Therapeutics, Target Pharma Solutions, UCB, and Ventyx Biosciences; reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, Aslan Pharma, Boston Consulting Group, Collective Acumen, Dermira, Eli Lilly, Evidera, Excerpta Medica, Forte Bio RX, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin Pharmaceutical Development, Leo Pharma, Medscape, Merck, Pfizer, Physicians World, Regeneron, Roivant, Sanofi-Genzyme, Trevi Therapeutics, Valeant, and WebMD; and reports grants from or serves as Principal Investigator for AbbVie, Amgen, Arcutis, Aslan, Castle Biosciences, CorEvitas,

Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Hakko Kirin, Leo Pharma, Pfizer, Regeneron, Sanofi, and TARGET-DERM. These potential conflicts of interest have been reviewed and managed by Oregon Health & Science University. KR served as an adviser or paid speaker for or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, Leo Pharma, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB and is a co-founder of Moonlake Immunotherapeutics. KK reports consulting fees or advisory board honoraria from Japan Tobacco, Kao, Leo Pharma, Chugai Pharmaceutical, Maruho, Pola Pharma, AbbVie, Eli Lilly, Sanofi, and Pfizer; and research grants from Leo Pharma, Japan Tobacco, P&G Japan, Eli Lilly Japan, Tanabe Mitsubishi, Ono Pharmaceutical, Kyowa Kirin, Pola Pharma, AbbVie, Sanofi, Kose, and Kyorin Pharmaceutical. KI reports lecture fees from AbbVie, Lilly, Sanofi, and Maruho. EE is an employee of Kyowa Kirin International. MF is a consultant for P&G Innovation GK. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this Article, after deidentification (text, tables, figures, and appendices) and the study protocol, reporting and analysis plan, dataset specifications, and clinical study report will be available to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Data will be available online beginning 3 months and ending 20 years after Article publication, marketing approval received in North America, Europe, and Japan, and completion of worldwide development programmes.

For the data see <https://vivli.org/ourmember/kyowa-kirin/>

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