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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Silverberg JI, Rosmarin D, Bieber T, et al. Rezpegaldesleukin treatment of moderate-to-severe atopic dermatitis (REZOLVE-AD): final results from the 16-week induction period of an international, double-blind, placebo-controlled, randomised phase 2b study. *Lancet* 2026; published online Aug 21. https://doi.org/10.1016/S0140-6736(26)01143-8.

Supplementary Appendix

Supplement to: Silverberg JI, Rosmarin D, Bieber T, et al. Rezpegaldesleukin treatment of moderate-to-severe atopic dermatitis (REZOLVE-AD): final results from the 16-week induction period of an international, double-blind, placebo-controlled, randomised phase 2b study.

This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Methods

Exploratory Assessments

The Dermatology Life Quality Index (DLQI) is a patient-reported, 10-item, quality of life questionnaire that covers 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment). The recall period of the scale is over the last week. Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (or "not relevant") responses scored as 0. Scores range from 0 to 30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related quality of life,[1] and a 4-point reduction from baseline is considered as the minimal clinically important difference threshold.[2]

The Patient-Oriented Ezema Measure (POEM) is a patient-reported 7-item scale that assesses disease severity in adults. Patients respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping or oozing, cracking, flaking, and dryness or roughness) over the past week. Response categories include "no days," "1-2 days," "3-4 days," "5-6 days," and "every day" with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity.[3] A 4-point reduction from baseline in POEM score is the threshold applied for the response analysis.

The Atopic Dermatitis Control Tool (ADCT) is a patient-reported tool that evaluates 6 symptoms and effects associated with AD over the past week: overall severity of symptoms, days with intense episodes of itching, intensity of bother, problem with sleep, impact on daily activities, and impact on mood or emotions. Each of the 6 ADCT items has a score range from 0 (no problem) to 4 (worst), rating the severity of each concept. A score of ≥7 points was derived as the threshold to identify patients "not in control." The threshold for meaningful within-person change was estimated to be 5 points.[4, 5]

The Atopic Dermatitis Sleep Scale (ADSS) is a patient-reported questionnaire developed to assess the impact of itch on sleep, including difficulty falling asleep, frequency of waking,

and difficulty getting back to sleep in the past night. Patients rate their difficulty falling asleep in Item 1 using a 5-point Likert-type scale. Response options include “not at all,” “a little bit,” “somewhat,” “quite a bit,” and “very difficult,” with corresponding scores of 0, 1, 2, 3, and 4, respectively.[6] The estimated threshold for a meaningful within-person reduction in ADSS Item 1 was approximately 1.25 points.[7]

The Skin Pain Numerical Rating Scale (NRS) is a patient-reported, 11-point scale anchored at 0 and 10, with 0 representing “no pain” and 10 representing “worst pain imaginable.” Overall severity of a patient’s skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.[7, 8] A 4-point reduction from baseline in Pain NRS is considered meaningful.[7]

Schedule of Assessments

Patients were instructed to complete Itch NRS, Pain NRS, and ADSS dairies daily. Diary entries were aggregated on a weekly basis for analysis. The average of all available scores from the 7 days preceding (but not including) each visit day was used, provided that at least 3 days of data were reported; otherwise, the assessment for that visit was considered missing.

In addition, patients completed the DLQI, POEM, and ADCT questionnaires on site during scheduled visits. Following the patient-reported assessments, clinicians performed the EASI, vIGA-AD, and BSA evaluations.

Pharmacokinetics and Pharmacodynamics

REZPEG was measured in human plasma samples with a validated sandwich enzyme-linked immunosorbent assay (ELISA) and detected at a minimum required dilution of 1:100. Capture of REZPEG was achieved by coating with two capture reagents: a custom product-specific mouse anti-human IL-2 antibody and an anti-human IL-2 antibody (MabTech). Detection was achieved by using a biotin-conjugated anti-polyethylene glycol (PEG)

antibody (Abcam) as secondary, followed with streptavidin-conjugated horseradish peroxidase and color produced with 3,3',5,5'-tetramethylbenzidine (TMB). The lower limit of quantitation (LLOQ) was 2.0 ng/mL. Accuracy and precision were ±20% over the quantitative range and ±25% at the LLOQ and upper limit of quantitation. Concentrations were reported as IL-2 protein equivalents. Pharmacokinetic concentration data were analysed using SAS Version 9·4.

For flow cytometry of peripheral whole blood samples, fluorescent antibodies against CD45, CD3, CD4, CD25, and FoxP3 were obtained from BioLegend (San Diego, CA) or BD Biosciences (San Jose, CA). Flow cytometry samples were analysed using a Fortessa X-20 (Becton Dickinson) and instrument settings were set with machine software in conjunction with calibration beads. Data were acquired using BD FACSDiva software (San Jose, CA) and processed using De Novo FCS Express Flow Clinical Edition (Pasadena, CA). $CD25^{bright}$ Tregs were defined as CD45+ CD3+ CD4+ CD25++ FoxP3+. Immunophenotyping results were enumerated as relative percentage (%) values for each phenotype. Positive Treg populations were identified based on fluorescence minus one control. To ensure comparability across longitudinal samples, the baseline $CD25^{bright}$ Treg gate was set at approximately 0·5% (0·4–0·6%) of CD4 + T cells for each individual, and this gate position was maintained across the individual's timepoints. The gating strategy for the CD25+ Treg population is based on that previously described in Silverberg 2024.[9]

Biomarkers

Protein biomarkers were measured in serum purified from peripheral whole blood using commercially available assays by Rules Based Medicine, an IQVIA Business (Austin, TX). Interleukin-19 (IL-19) was measured using the single-molecule array (SiMoA®) singleplex platform and thymus and activation-regulated chemokine (TARC)/CCL17, macrophage-derived chemokine (MDC)/CCL22, and Periostin were measured using the Luminex multi-analyte profile (MAP) platform.

Statistical Analyses

The primary estimand of interest for the primary endpoint was a hybrid estimand for the question: what is the difference in mean EASI percentage change from baseline in the target population between treatment conditions, (i.e., REZPEG vs placebo), after completing 16 weeks of treatment when using rescue medication outside protocol specifications or treatment discontinuation due to lack of efficacy is informative about the outcome (ie, no clinical benefit or treatment failure), if all patients continue with treatment except those who discontinue due to lack of efficacy?

The primary estimands for efficacy endpoints in the Induction Period were described by the following attributes:

A. Population: Adult patients with moderate-to-severe AD defined through appropriate inclusion and exclusion criteria.

B. Treatment: Rezpegaldesleukin (REZPEG) 24 µg/kg every two weeks (q2w), REZPEG 24 µg/kg every four weeks (q4w), REZPEG 18 µg/kg q2w, and placebo.

C. Endpoint: Applied to the primary, secondary and important exploratory efficacy endpoints

D. The following were considered as the intercurrent events (ICEs) in the study:

a. Use of rescue medication after randomization outside specifications per the protocol version patients were enrolled under or discontinuation of treatment due to lack of efficacy prior to Week 16

b. Early discontinuation of study treatment due to reasons other than lack of efficacy prior to Week 16

The ICEs were accounted as:

- Patients who used rescue medications outside specifications per the protocol version they were enrolled under or who discontinued due to lack of efficacy prior to the Week 16 study treatment (REZPEG or placebo) were

considered as treatment failures after the ICEs. A composite strategy was used.

- For patients who discontinued treatment due to reasons other than lack of efficacy prior to Week 16, it was of interest to estimate what the treatment effect would have been if all patients had continued with the study treatment. Therefore, a hypothetical strategy was used for these types of ICEs.

E. Population-level summary: Difference between treatment conditions in means of percentage change from baseline, means of change from baseline, or response proportions.

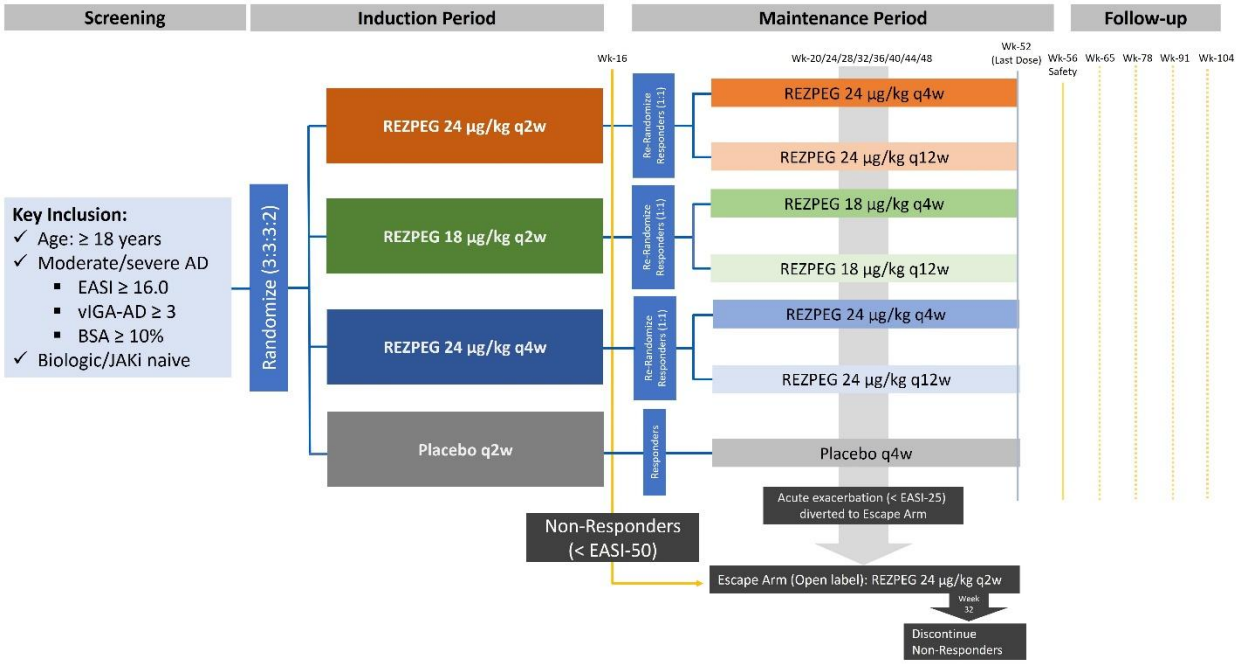
In the estimation of the primary estimand, we imputed data subsequent to the use of rescue medication, or treatment discontinuation due to lack of efficacy with baseline values for continuous endpoint and non-response for binary endpoint. Data after treatment discontinuation due to other reasons were treated as missing data, and all missing data were imputed with multiple imputation (MI). The imputation was conducted within treatment arms and repeated 50 times with the use of the PROC MI procedure in SAS. For all binary endpoints, logistic regression with treatment group, baseline value, and randomization stratification factors as covariates were used. The differences in response rates were based on Mantel-Haenszel method and adjusted by the stratification factors: disease severity measured by vIGA-AD (score of 3 [moderate] versus 4 [severe]) and region (North America versus rest of world). The analysis on continuous endpoints were based on mixed models for repeated measures (MMRM) with baseline value, randomization stratification factors, treatment group, visit, and treatment-by-visit interaction as factors. The differences in least square (LS) means between each REZPEG dosing regimen and placebo were derived from the MMRM models.

The supportive estimands applied the treatment policy strategy for the ICE of treatment discontinuation due to reasons other than lack of efficacy and all observed data after this

type of ICE were included in the analyses (Table S6). The strategy for the other ICEs (ie, use of rescue medication or treatment discontinuation due to lack of efficacy) and analyses methods remained the same as the primary estimands.

To assess the robustness of the primary analysis results, a prespecified sensitivity analysis was conducted on the primary endpoint of EASI percentage change where MMRM was directly performed without the imputation of missing data (Table S3).

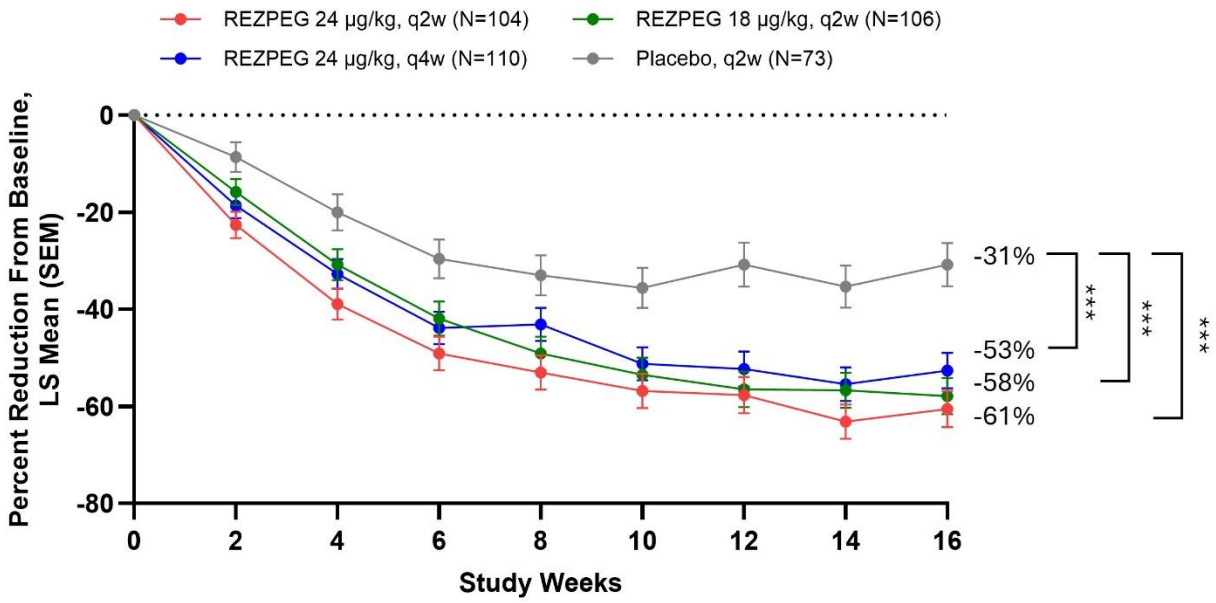
Figure S1. REZOLVE-AD Study Design



AD=atopic dermatitis. BSA=body surface area. EASI=Eczema Area and Severity Index. EASI-XX=Eczema Area and Severity Index reduced by at least XX% relative to baseline score. JAKi=Janus kinase inhibitor. q12w=every 12 weeks. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. vIGA-AD=Validated Global Assessment for Atopic Dermatitis. Wk=week.

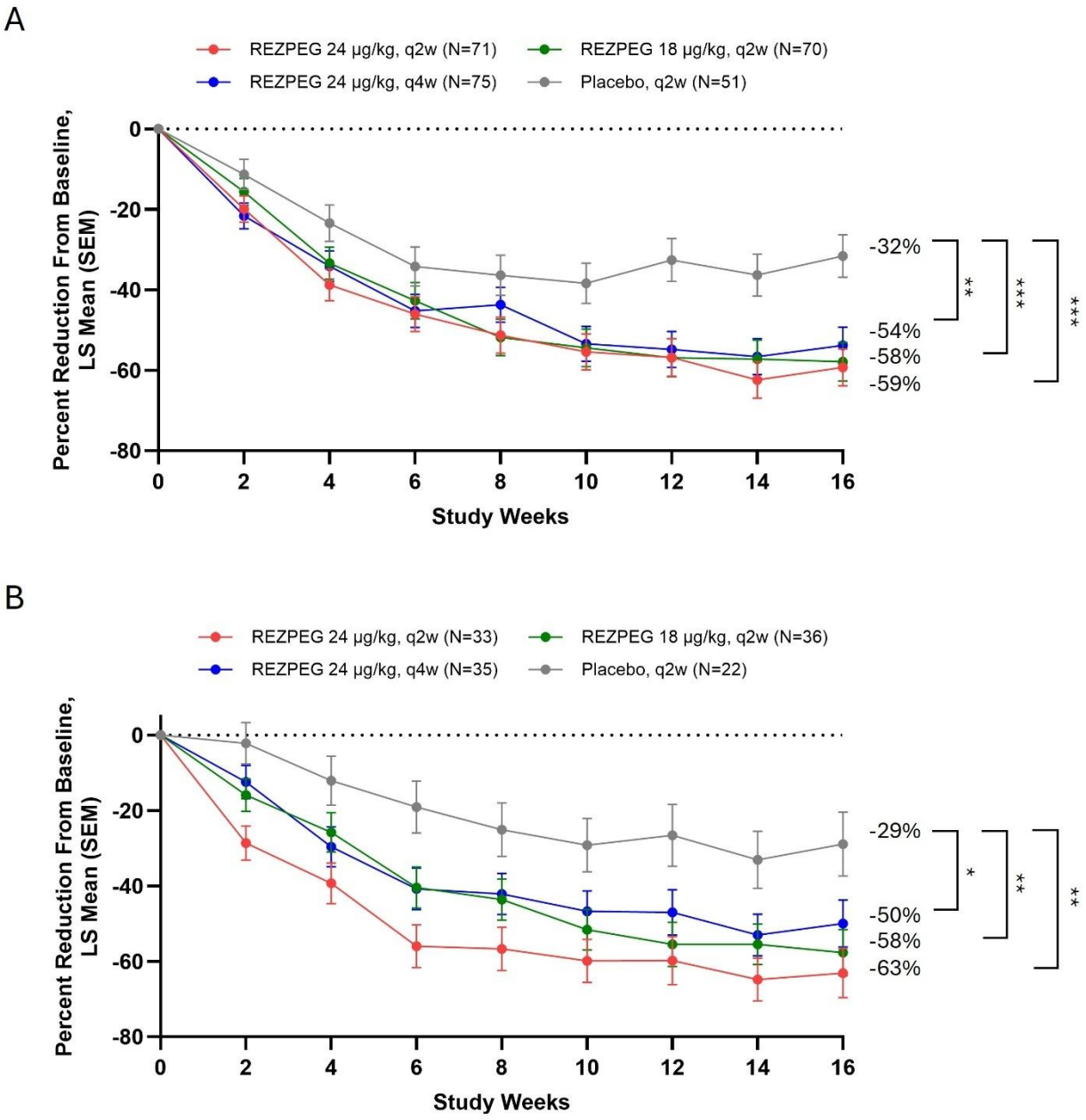
Note: Only data from the 16-week induction period are presented in this article.

Figure S2. Time Course for EASI Percentage Reduction from Baseline (mITT Population)



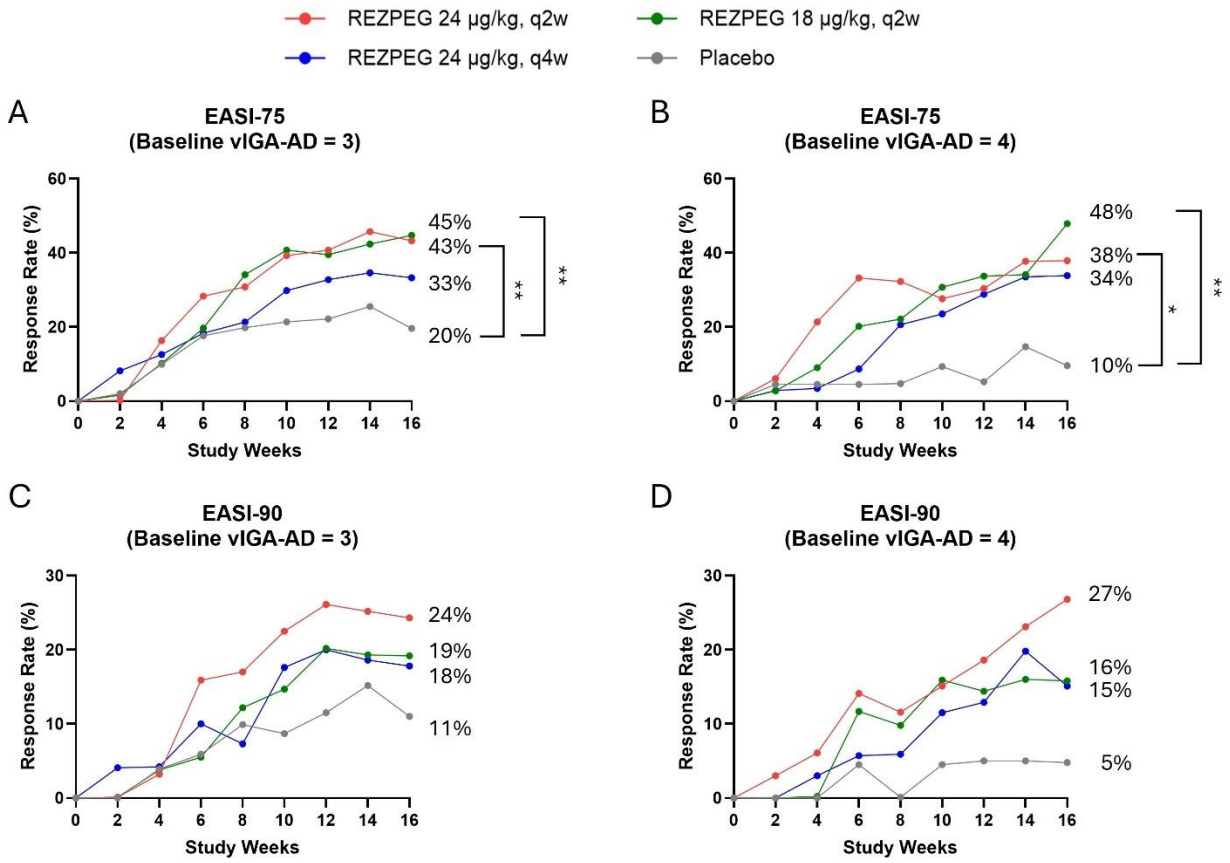
Data include the integrated estimates from 50 datasets in which missing values were imputed with the multiple imputation method. The primary estimand applied a hybrid approach of having a composite strategy for the use of rescue mediations outside of protocol specifications and end of treatment due to lack of efficacy, and a hypothetical strategy for end of treatment due to other reasons. Efficacy analyses were based on a modified intent-to-treat population of all randomized patients who received at least one dose of study drug that excluded data for three patients from GCP noncompliant sites. EASI=Eczema Area and Severity Index. GCP=Good Clinical Practice. LS=least square. mITT=modified intent-to-treat. q2w=every 2 weeks. q4w= every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean. *** indicates p<0.001.

Figure S3. EASI Percentage Reduction from Baseline in the Subpopulations of Patients with Baseline vIGA-AD of 3 or 4



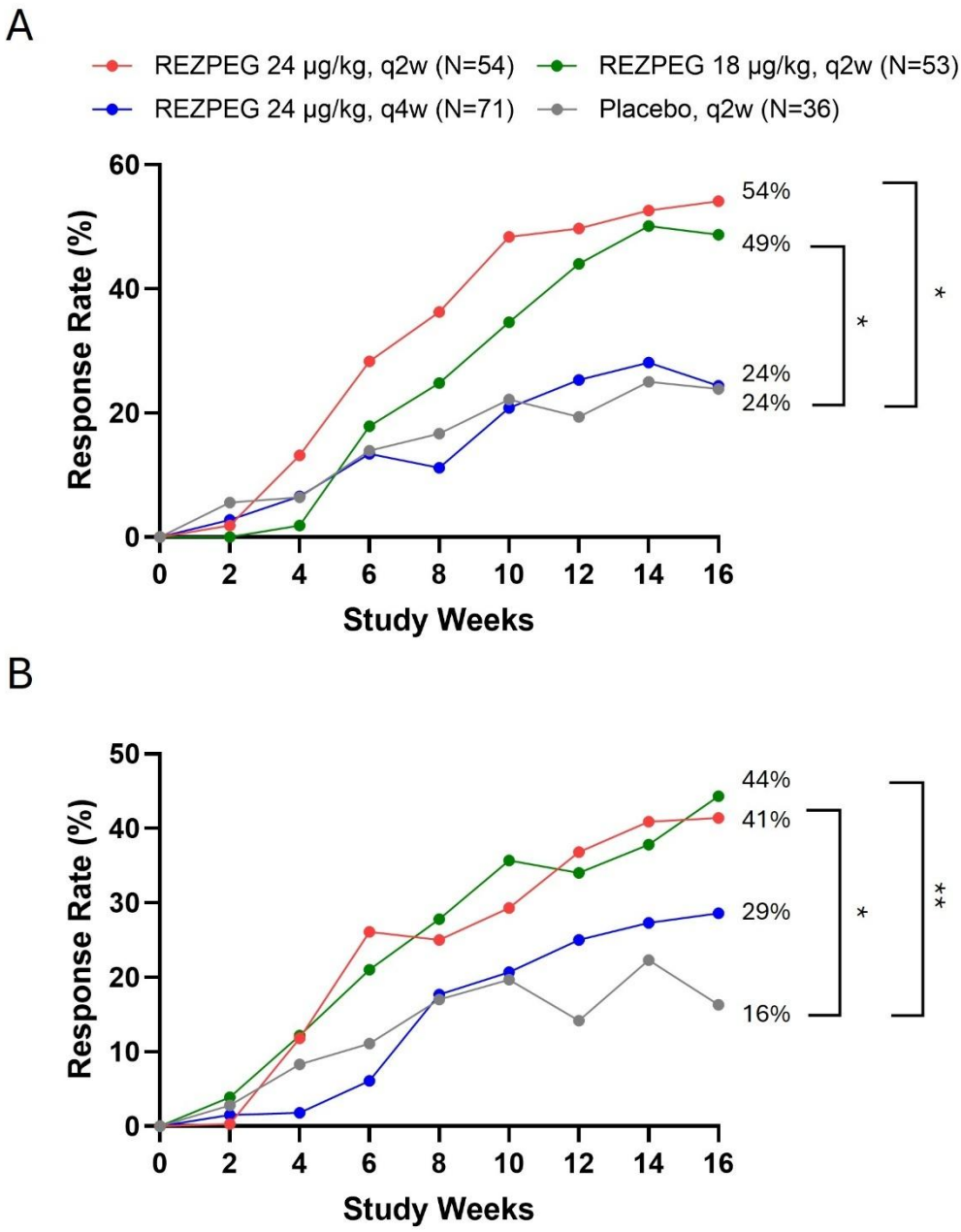
(A) Time course for EASI percentage reduction from baseline in the subpopulation of patients with baseline vIGA-AD of 3 and (B) baseline vIGA-AD of 4. EASI=Eczema Area and Severity Index. LS=least square. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$.

Figure S4. EASI-75 and EASI-90 Response Rates in the Subpopulations of Patients with Baseline vIGA-AD of 3 or 4



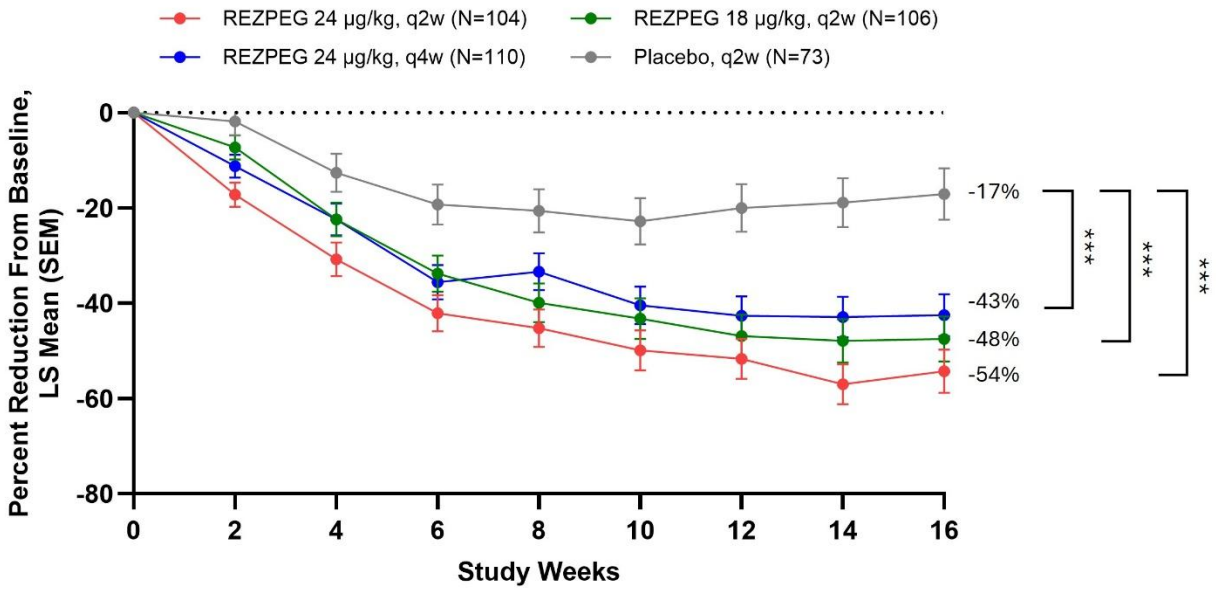
EASI-75 and EASI-90 response over time for the subpopulation of patients with baseline vIGA-AD of 3 (Panels A and C, respectively), and baseline vIGA-AD of 4 (Panels B and D, respectively). For patients with baseline vIGA-AD of 3: n=51, 71, 70, and 75 for placebo, REZPEG 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w, respectively. For patients with baseline vIGA-AD of 4: n=22, 33, 36, and 35 for placebo, REZPEG 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w, respectively. EASI=Eczema Area and Severity Index. EASI-XX=Eczema Area and Severity Index reduced by at least XX% relative to baseline score. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. * indicates $p<0.05$, ** indicates $p<0.01$.

Figure S5. Itch NRS and EASI-75 Response Rates in the Subpopulation of Patients with Baseline Itch NRS ≥7



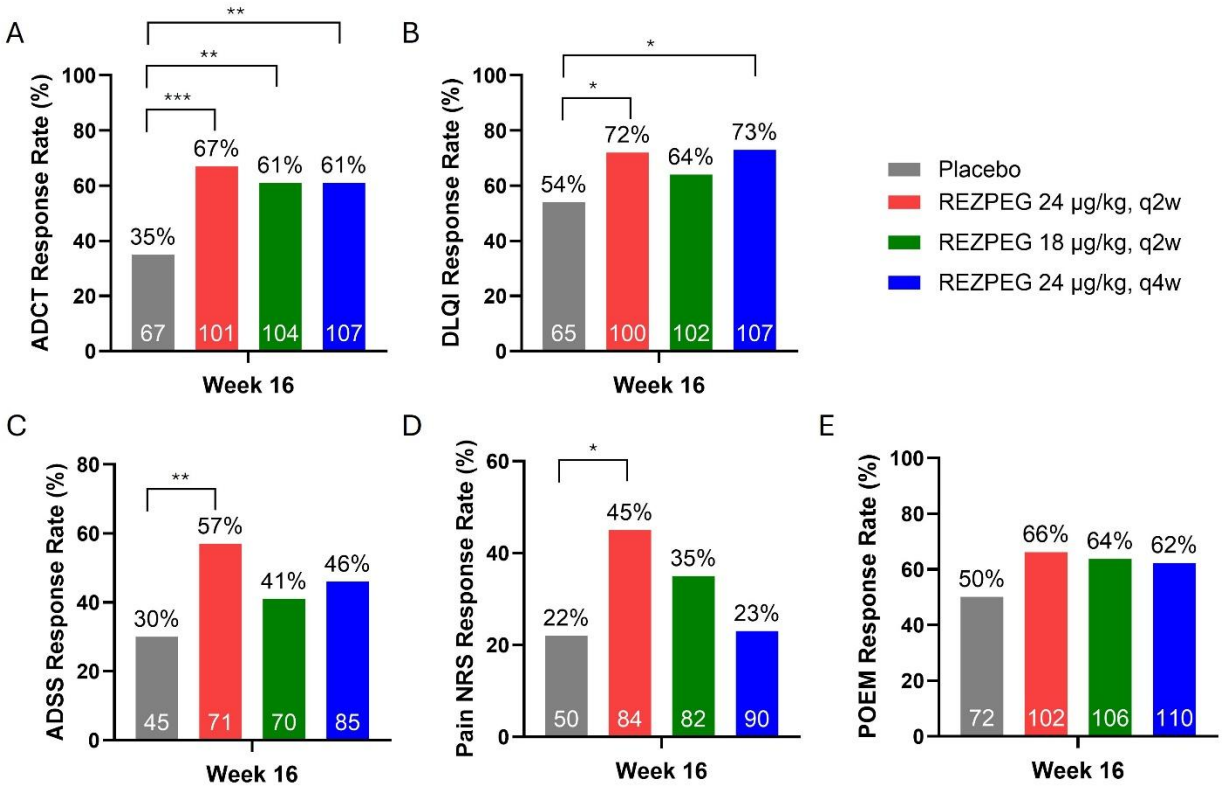
(A) Itch NRS and (B) EASI-75 response over time for the subpopulation of patients with baseline Itch NRS ≥7. EASI=Eczema Area and Severity Index. EASI-XX=Eczema Area and Severity Index reduced by at least XX% relative to baseline score. NRS=Numerical Rating Scale. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. * indicates $p<0.05$.

Figure S6. Time Course for BSA Percentage Reduction From Baseline (mITT Population)



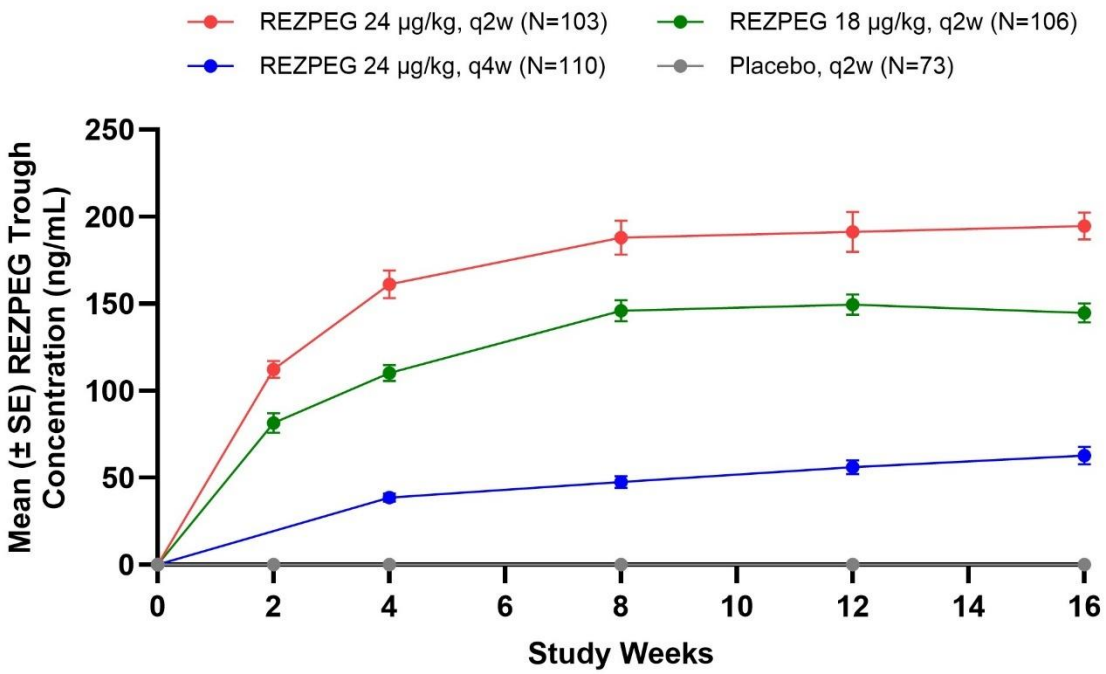
BSA=body surface area. LS=least square. mITT=modified intent-to-treat. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean. *** indicates p<0.001.

Figure S7. Week 16 Exploratory Efficacy



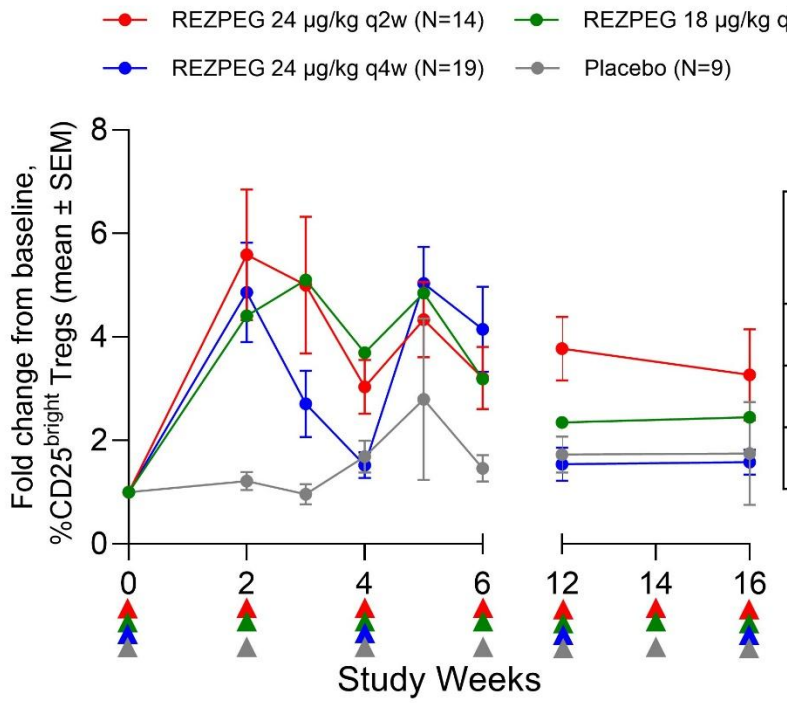
Percentage of patients with (A) ADCT, (B) DLQI, (C) ADSS, (D) Pain NRS, and (E) POEM responses at Week 16. ADCT response was defined as a ≥5-point change from baseline in ADCT score (range, 0 to 24, with higher scores indicating greater severity) in the subpopulation of patients with baseline ADCT ≥5. DLQI response was defined as a ≥4-point reduction from baseline in the DLQI score (range, 0 to 30, with higher scores indicating greater impairment of quality of life) in the subpopulation of patients with baseline DLQI ≥4. ADSS response was defined as ≥1.25-point reduction from baseline in ADSS Item 1 score (range, 0 to 4, with higher scores indicating worse sleep impact) in the subpopulation of patients with baseline ADSS Item 1 ≥1.25. Pain NRS response was defined as ≥4-point reduction from baseline in Pain NRS score (range, 0 to 10, with higher scores indicating greater severity) in the subpopulation of patients with baseline Pain NRS ≥4. POEM response was defined as a ≥4-point reduction from baseline in POEM (range, 0 to 28, with higher total scores indicating greater disease severity) in the subpopulation of patients with baseline POEM ≥4. The number of patients analysed in each group is indicated in the numbers at the base of each bar; numerical response rates are shown above each bar. ADCT=Atopic Dermatitis Control Tool. ADSS=Atopic Dermatitis Sleep Scale. DLQI=Dermatology Life Quality Index. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$.

Figure S8. Mean (± SE) REZPEG Trough Concentrations Over Time for the Induction Period (PK Population)



The PK population included all patients who were randomised to treatment, received at least one dose of REZPEG, and had available and applicable PK data. Week 2 PK data for the 24 µg/kg q4w arm was available but not included since it was not a trough datapoint of the q4w dosing schedule. PK samples collected according to the protocol-defined dosing and sampling schedule were included in the summary statistics. PK=pharmacokinetic. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SE=standard error.

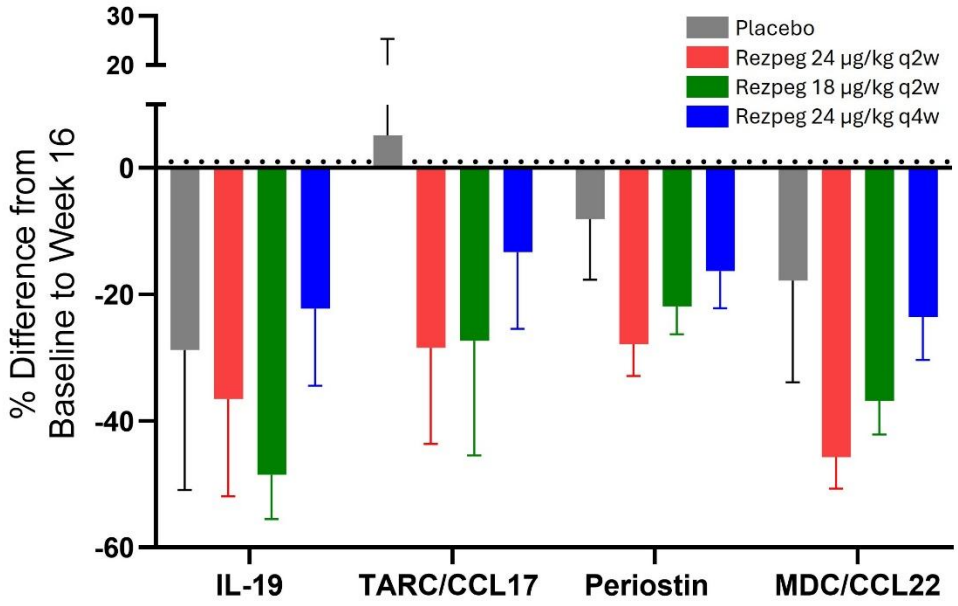
Figure S9. Fold Change from Baseline in CD25^{bright} Regulatory T Cells



Cohort	1st Peak (W2-3)	2nd Peak (W5)	Trough (W16)
	%CD25^{bright} Treg mean fold change from baseline (W0)		
24 µg/kg q2w	5.6	4.3	3.3
18 µg/kg q2w	5	4.9	2.5
24 µg/kg q4w	4.9	5	1.6

Dosing time points indicated by triangles, with colors corresponding to dosing arms. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean. Tregs=regulatory T cells. W=week.

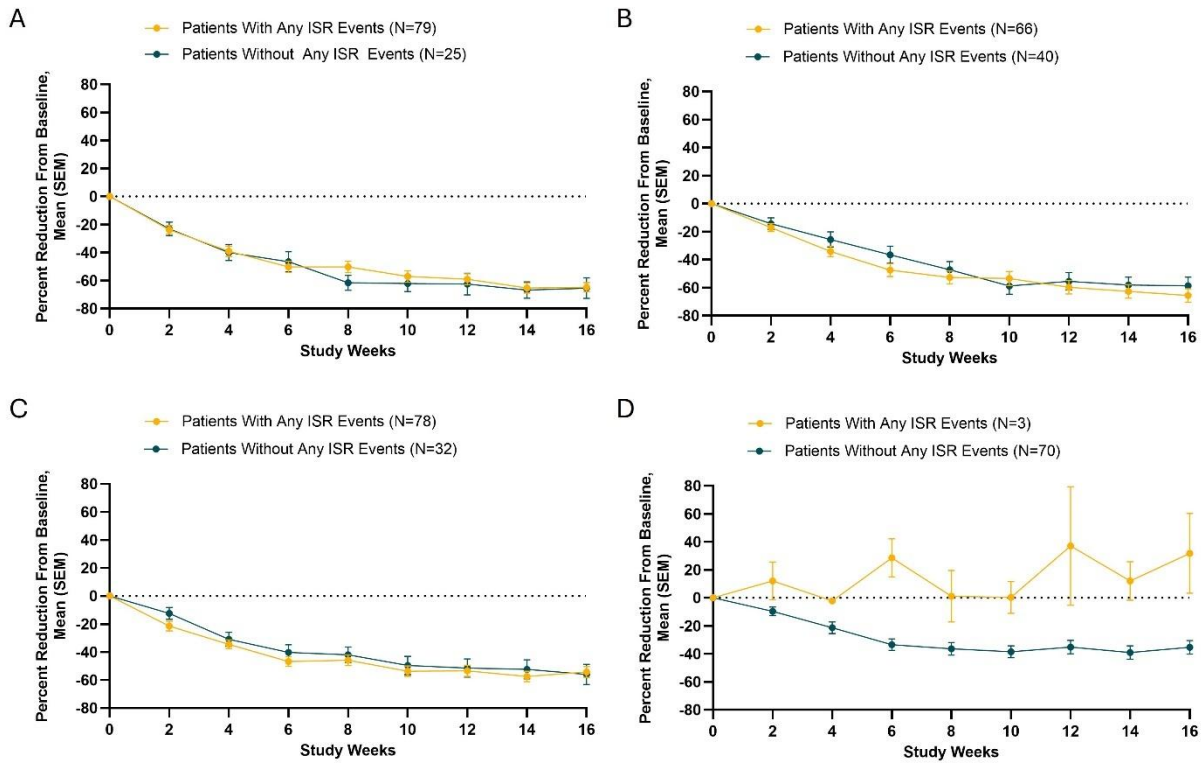
Figure S10. Atopic Dermatitis Biomarkers



Study Arm	IL-19 (>51 pg/mL)	TARC/ CCL17 (>0.94 ng/mL)	Periostin (>322 ng/mL)	MDC/ CCL22 (>839 pg/mL)
Placebo	14	29	21	21
24 µg/kg, q2W	25	35	29	28
18 µg/kg, q2W	23	34	29	28
24 µg/kg, q4W	28	34	32	27

REZPEG induced reductions in 4 key biomarkers associated with AD[10] observed in patients with baseline levels above the upper limit seen in healthy subjects. Data are provided as mean ± SEM. The normal ranges of TARC/CCL17, MDC/CCL22, and periostin were provided by Rules Based Medicine, based on their analysis of 100 normal healthy volunteers. The normal range of IL-19 was derived from Konrad 2019.[11] The number of patients analysed in each treatment group are indicated in the table below the figure. Only patients with baseline values above the upper limit of normal for each biomarker were included in the analysis. AD=atopic dermatitis. CCL=C-C motif chemokine ligand. IL-19=interleukin-19. MDC=macrophage-derived chemokine. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean. TARC=thymus and activation-regulated chemokine.

Figure S11. Time Course for EASI Percentage Reduction from Baseline for the Subpopulations of Patients With and Without ISR Events



Mean percentage reduction in EASI from baseline by patients with or without any ISR events based on observed data regardless of rescue medication use and treatment discontinuation reasons for the (A) REZPEG 24 µg/kg q2w arm, (B) REZPEG 18 µg/kg q2w arm, (C) REZPEG 24 µg/kg q4w arm, and (D) Placebo arm. EASI=Eczema Area and Severity Index. ISR=injection site reaction. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SEM=standard error of the mean.

Table S1. Summary of Important Protocol Deviations for the Induction Period (mITT Population)

	REZPEG 24 µg/kg q2w (n=104)	**REZPEG 18 µg/kg q2w (n=106)**	**REZPEG 24 µg/kg q4w (n=110)**	**REZPEG Overall (n=320)**	**Placebo q2w (n=73)**	**Total (n=393)**
Patients with at least one important protocol deviation	4 (4%)	4 (4%)	1 (1%)	9 (3%)	2 (3%)	11 (3%)
ICE due to rescue medication	4 (4%)	4 (4%)	1 (1%)	9 (3%)	2 (3%)	11 (3%)
Key eligibility violations	0	0	0	0	0	0
Dosing error	0	0	0	0	0	0

Data are number of patients (%). ICE=intercurrent event. mITT=modified intent-to-treat. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin.

Table S2. Summary of Demographics and Baseline Disease Characteristics (ITT Population)

	REZPEG 24 µg/kg q2w (n=106)	**REZPEG 18 µg/kg q2w (n=107)**	**REZPEG 24 µg/kg q4w (n=111)**	**REZPEG Overall (n=324)**	**Placebo q2w (n=74)**	**Total (n=398)**
Age, years	37·8 (13·7)	36·2 (15·4)	36·5 (14·3)	36·8 (14·4)	38·0 (14·4)	37·1 (14·4)
Sex						
Female	50 (47%)	56 (52%)	63 (57%)	169 (52%)	36 (49%)	205 (52%)
Male	56 (53%)	51 (48%)	48 (43%)	155 (48%)	38 (51%)	193 (49%)
Race						
White	89 (84%)	91 (85%)	97 (87%)	277 (86%)	59 (80%)	336 (84%)
Black or African American	7 (7%)	3 (3%)	5 (5%)	15 (5%)	2 (3%)	17 (4%)
Asian	9 (9%)	11 (10%)	7 (6%)	27 (8%)	9 (12%)	36 (9%)
American Indian or Alaska Native	0	1 (1%)	0	1 (<1%)	0	1 (<1%)
Native Hawaiian or other Pacific Islander	0	0	1 (1%)	1 (<1%)	2 (3%)	3 (1%)
Other	1 (1%)	0	0	1 (<1%)	0	1 (<1%)
Not reported or unknown	0	1 (1%)	1 (1%)	2 (1%)	2 (3%)	4 (1%)
Ethnicity						
Hispanic or Latino	7 (7%)	7 (7%)	11 (10%)	25 (8%)	8 (11%)	33 (8%)
Not Hispanic or Latino	99 (93%)	99 (93%)	100 (90%)	298 (92%)	65 (88%)	363 (91%)
Not reported or unknown	0	1 (1%)	0	1 (<1%)	1 (1%)	2 (1%)
Weight, kg	80·7 (19·3)	77·4 (19·5)	73·6 (15·8)	77·2 (18·4)	79·3 (20·9)	77·6 (18·9)
BMI, kg/m^2	27·2 (6·0)	26·7 (5·8)	25·5 (4·8)	26·5 (5·6)	27·0 (6·3)	26·6 (5·7)
Region						
North America	28 (26%)	30 (28%)	32 (29%)	90 (28%)	22 (30%)	112 (28%)

	REZPEG 24 µg/kg q2w (n=106)	REZPEG 18 µg/kg q2w (n=107)	REZPEG 24 µg/kg q4w (n=111)	REZPEG Overall (n=324)	Placebo q2w (n=74)	Total (n=398)
Rest of the world	78 (74%)	77 (72%)	79 (71%)	234 (72%)	52 (70%)	286 (72%)
Age at onset, years	14·3 (18·0)	15·5 (19·6)	17·8 (19·9)	15·9 (19·2)	16·3 (19·6)	16·0 (19·2)
Duration since onset, years	23·8 (15·2)	21·0 (14·5)	19·1 (14·1)	21·3 (14·7)	22·0 (15·8)	21·4 (14·9)
vIGA-AD[a]						
3	73 (69%)	70 (65%)	76 (69%)	219 (68%)	51 (69%)	270 (68%)
4	33 (31%)	37 (35%)	35 (32%)	105 (32%)	23 (31%)	128 (32%)
EASI total score[b]	25·4 (9·12)	27·2 (10·36)	26·1 (10·41)	26·2 (9·98)	25·2 (8·51)	26·0 (9·73)
<21	45 (43%)	43 (40%)	44 (40%)	132 (41%)	29 (39%)	161 (41%)
≥21	61 (58%)	64 (60%)	67 (60%)	192 (59%)	45 (61%)	237 (60%)
BSA[c]	39·1 (18·69)	40·6 (20·76)	39·6 (20·52)	39·8 (19·97)	38·3 (19·62)	39·5 (19·89)
Itch NRS score[d]	6·8 (1·98)	6·7 (1·90)	7·1 (1·77)	6·9 (1·88)	6·4 (2·22)	6·8 (1·96)
n	105	107	109	321	73	394
<4	9 (8%)	14 (13%)	7 (6%)	30 (9%)	9 (12%)	39 (10%)
≥4	96 (91%)	93 (87%)	102 (92%)	291 (90%)	64 (86%)	355 (89%)
Pain NRS[e]	5·9 (2·56)	5·9 (2·52)	6·2 (2·35)	6·0 (2·47)	5·4 (2·67)	5·9 (2·52)
n	105	107	109	321	73	394
<4	20 (19%)	24 (22%)	19 (17%)	63 (19%)	22 (30%)	85 (21%)
≥4	85 (80%)	83 (78%)	90 (81%)	258 (80%)	51 (69%)	309 (78%)
ADSS Item 1[f]	1·9 (1·15)	2·0 (1·14)	2·1 (1·02)	2·0 (1·11)	1·8 (1·19)	2·0 (1·12)
n	105	107	109	321	73	394
<1·25	33 (31%)	36 (34%)	24 (22%)	93 (29%)	27 (36%)	120 (30%)
≥1·25	72 (68%)	71 (66%)	85 (77%)	228 (70%)	46 (62%)	274 (69%)

	REZPEG 24 µg/kg q2w (n=106)	REZPEG 18 µg/kg q2w (n=107)	REZPEG 24 µg/kg q4w (n=111)	REZPEG Overall (n=324)	Placebo q2w (n=74)	Total (n=398)
DLQI[g]	14·6 (7·24)	13·8 (7·22)	15·8 (7·14)	14·8 (7·22)	13·5 (7·13)	14·5 (7·21)
<4	4 (4%)	4 (4%)	3 (3%)	11 (3%)	8 (11%)	19 (5%)
≥4	102 (96%)	103 (96%)	108 (97%)	313 (97%)	66 (89%)	379 (95%)
POEM[h]	19·4 (5·88)	19·8 (5·74)	20·9 (5·43)	20·0 (5·70)	18·7 (6·21)	19·8 (5·81)
<4	2 (2%)	0	0	2 (1%)	1 (1%)	3 (1%)
≥4	104 (98%)	107 (100%)	111 (100%)	322 (99%)	73 (99%)	395 (99%)
ADCT[i]	15·6 (4·97)	15·5 (5·27)	16·3 (4·92)	15·8 (5·06)	14·6 (5·72)	15·6 (5·20)
n	105	107	110	322	73	395
<5	2 (2%)	2 (2%)	2 (2%)	6 (2%)	5 (7%)	11 (3%)
≥5	103 (97%)	105 (98%)	108 (97%)	316 (98%)	68 (92%)	384 (97%)

Data are n (%) or mean (SD). Percentages are based on the total number of patients in each column and do not always add to 100% because of rounding. Analyses were based on the intent-to-treat population that included all randomised patients. AD=atopic dermatitis. ADCT=Atopic Dermatitis Control Tool. AD=atopic dermatitis. ADSS=Atopic Dermatitis Sleep Scale. BMI=body mass index. BSA=body surface area. DLQI=Dermatology Life Quality Index. EASI=Eczema Area and Severity Index. GCP=Good Clinical Practice. ITT= intent-to-treat. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SD=standard deviation. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. [a] vIGA-AD describes the overall appearance of AD lesions at a given timepoint; scores range from 0 (clear skin) to 4 (severe disease). To be eligible for enrolment, patients were required to have an IGA score of ≥3. [b] EASI assesses four signs of disease (erythema, induration or papulation, excoriation, and lichenification) across four body regions (head/neck, trunk, upper and lower extremities) and extent of skin involvement in each region; scores range from 0 to 72 with higher values indicating a greater severity and extent of disease. [c] BSA estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. [d] Itch NRS describes the worst level of itch in the past 24 hours; scores range from 0 (no itch) to 10 (worst itch imaginable). [e] Skin Pain NRS describes the worst level of skin pain in the past 24 hours; scores ranging from 0 (no pain) to 10 (worst pain imaginable). [f] ADSS Item 1 assesses the impact of itch on difficulty falling asleep; scores range from 0 (not at all) to 5 (very difficult). [g] DLQI is a ten-item quality of life questionnaire that covers six domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment). Scores range from 0 to 30 with higher scores indicating greater impairment of quality of life. [h] POEM assesses the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping or oozing, cracking, flaking, and dryness or roughness) over the past week. Scores range from 0 to 28, with higher total scores indicating greater disease severity. [i] ADCT evaluates six symptoms and effects associated with AD over the past week; scores for each item range from 0 (no problem) to 4 (worst).

Table S3. Sensitivity Analyses for the Primary Endpoint of Percentage Change from Baseline in EASI at Week 16 Without Multiple Imputation

The primary endpoint in the mITT patients				
	REZPEG 24 µg/kg q2w (n=104)	**REZPEG 18 µg/kg q2w (n=106)**	**REZPEG 24 µg/kg q4w (n=110)**	**Placebo q2w (n=73)**
EASI percentage change from baseline[a]	-60% (3·7)	-58% (3·7)	-52% (3·6)	-31% (4·3)
Treatment difference	-29% (-40·4, -18·1)	-27% (-38·4, -16·0)	-21% (-32·2, -10·2)	—
p value	<0.0001	<0.0001	0.0002	—
The primary endpoint in the mITT patients and the patients enrolled at the non-GCP sites who received at least one dose of study treatment				
	REZPEG 24 µg/kg q2w (n=105)	**REZPEG 18 µg/kg q2w (n=107)**	**REZPEG 24 µg/kg q4w (n=110)**	**Placebo q2w (n=74)**
EASI percentage change from baseline[a]	-60% (3·7)	-58% (3·7)	-52% (3·6)	-30% (4·2)
Treatment difference	-30% (-40·9, -18·7)	-28% (-39·1, -17·0)	-22% (-32·7, -10·9)	—
p value	<0.0001	<0.0001	0.0001	—

Data are LS mean (SE) or adjusted percentage difference (95% CI) versus placebo; p values are also shown. CI=confidence interval. EASI=Eczema Area and Severity Index. EASI-XX=Eczema Area and Severity Index reduced by at least XX% relative to baseline score. LS=least square. mITT=modified intent-to-treat. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SE=standard error. [a] EASI assesses four signs of disease (erythema, induration or papulation, excoriation, and lichenification) across four body regions (head/neck, trunk, upper and lower extremities) and extent of skin involvement in each region; scores range from 0 to 72 with higher values indicating a greater severity and extent of disease.

Table S4. Rescue Medication Use and Intercurrent Events in the Induction Period (mITT Population)

	REZPEG 24 µg/kg q2w (n=104)	REZPEG 18 µg/kg q2w (n=106)	REZPEG 24 µg/kg q4w (n=110)	REZPEG Overall (n=320)	Placebo q2w (n=73)
Patients with at least one rescue medication	9 (9%)	7 (7%)	12 (11%)	28 (9%)	16 (22%)
Topical treatment	9 (9%)	7 (7%)	12 (11%)	28 (9%)	16 (22%)
Topical corticosteroid	8 (8%)	7 (7%)	12 (11%)	27 (8%)	16 (22%)
Low/mid potency	7 (7%)	7 (7%)	11 (10%)	25 (8%)	16 (22%)
High potency	1 (1%)	2 (2%)	1 (1%)	4 (1%)	0
Topical calcineurin inhibitor	5 (5%)	1 (1%)	3 (3%)	9 (3%)	3 (4%)
Topical JAK inhibitor	0	0	0	0	0
Systemic treatment	0	2 (2%)	0	2 (1%)	0
Antihistamines	0	1 (1%)	0	1 (<1%)	0
Systemic corticosteroid	0	1 (1%)	0	1 (<1%)	0
Biologics or oral JAK inhibitor	0	0	0	0	0
Intercurrent events[a]					
Patients with early treatment discontinuation due to lack of efficacy	1 (1%)	0	1 (1%)	2 (1%)	0
Patients using rescue medication outside specifications per the protocol version	4 (4%)	4 (4%)	1 (1%)	9 (3%)	2 (3%)

Data are number of patients (%). JAK=Janus kinase. mITT=modified intent-to-treat. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin.

[a] Efficacy data after these intercurrent events were imputed as baseline for continuous endpoints and as non-responder for binary endpoints.

Table S5. Severity of Injection Site Reactions

ISRs reported at the event level	REZPEG 24 µg/kg q2w (n=104)	REZPEG 18 µg/kg q2w (n=106)	REZPEG 24 µg/kg q4w (n=110)	REZPEG Overall (n=320)	Placebo q2w (n=73)
Proportion of mild events	66%	71%	70%	68%	100%
Proportion of moderate events	34%	29%	30%	31%	0
Proportion of severe events	1%	<1%	0	<1%	0

Data are % of all ISR events. ISR=injection site reaction. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin.

Table S6. Supportive Analyses of Week 16 Efficacy Outcomes (mITT Population)

Statistic	REZPEG 24 µg/kg q2w (n=104)	REZPEG 18 µg/kg q2w (n=106)	REZPEG 24 µg/kg q4w (n=110)	Placebo q2w (n=73)
Primary endpoint				
EASI percentage change from baseline[a]	-60% (3·7)	-58% (3·7)	-52% (3·5)	-31%(4·3)
Treatment difference	-29% (-40·4, -18·4)	-26% (-37·6, -15·3)	-21% (-31·7, -10·0)	—
p value	<0·0001	<0·0001	0·0002	—
Secondary endpoints				
EASI-50 response	69 (66%)	70 (66%)	60 (54%)	25 (34%)
Treatment difference[b]	32% (17·7, 47·0)	33% (17·7, 47·2)	21% (6·2, 35·1)	—
p value	<0·0001	<0·0001	0·0084	—
EASI-75 response	42 (41%)	47 (44%)	36 (33%)	12 (16%)
Treatment difference[b]	25% (11·9. 38·2)	29% (15·6, 41·6)	17% (4·3, 29·0)	—
p value	0·0009	0·0002	0·014	—
EASI-90 response	25 (24%)	18 (17%)	18 (17%)	7 (9%)
Treatment difference[b]	15% (4·6, 26·2)	9% (-1·6, 18·9)	8% (-1·6, 17·0)	—
p value	0·014	0·11	0·15	—
vIGA-AD Response[c,d]	21 (20%)	27 (25%)	20 (19%)	6 (8%)
Treatment difference[b]	13% (2·5, 23·1)	18% (6·7, 28·7)	11% (1·1, 20·7)	—
p value	0·033	0·0065	0·055	—
Itch NRS response[e,f,g]	39 (41%)	31 (34%)	23 (23%)	10 (15%)
Treatment difference[b]	25% (11·3, 39·0)	19% (5·4, 33·0)	8% (-4·8, 19·9)	—
p value	0·0015	0·014	0·40	—
BSA percentage change from baseline[h]	-54% (4·4)	-48% (4·7)	-43% (4·2)	-17% (5·0)
Treatment difference	-36·9 (-49·9, -23·9)	-30·9 (-44·5, -17·3)	-25·6 (-38·5, -12·8)	—
p value	<0·0001	<0·0001	<0·0001	—

Data are least squares mean (SE), n (%), or adjusted percentage difference (95% CI) versus placebo. Response rates were estimated using multiple imputation. The number of responders was then calculated by multiplying the estimated response rate (using the unrounded value) by the number of participants in the analysis population and rounding to the nearest whole number. As a result, the reported responder counts and rounded responses may not always align exactly when the response rate is recalculated from the displayed responder count. BSA=body surface area. CI=confidence interval. EASI=Eczema Area and Severity Index. EASI-XX=Eczema Area and Severity Index reduced by at least XX% relative to baseline score. mITT=modified intent-to-treat. NRS=Numerical Rating Scale. q2w=every 2 weeks. q4w=every 4 weeks. REZPEG=rezpegaldesleukin. SE=standard error. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. [a] EASI assesses four signs of disease (erythema, oedema or papulation, excoriation, and lichenification) across four body regions (head or neck, trunk, upper and lower extremities) and extent of skin involvement in each region; scores range from 0 to 72 with higher values indicating a greater severity and extent of disease. [b] Mantel-Haenszel treatment differences in response rates were adjusted for stratification factors. [c] vIGA-AD describes the overall appearance of AD lesions at a given timepoint; scores range from 0 (clear skin) to 4 (severe disease). [d] vIGA-AD response was defined as a score of 0 (clear) or 1 (almost clear) and ≥2-point reduction from baseline. [e] Itch NRS describes the worst level of itch in the past 24 hours; scores range from 0 (no itch) to 10 (worst itch imaginable). [f] Patients evaluable for the corresponding endpoint requiring baseline Itch NRS score ≥4 were n=95, n=92, n=102,

and n=63 for the REZPEG 24 µg/kg q2w, 18 µg/kg q2w, 24 µg/kg q4w, and placebo groups, respectively. [g] Itch NRS response was defined as ≥4-point improvement from baseline in Itch NRS in the subset of patients with ≥4-point Itch NRS at baseline. [h] BSA estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface.

Supplementary References

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