# 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

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## Summary

**Background** Rezpegaldesleukin is an interleukin-2 receptor agonist that selectively expands and enhances the function of regulatory T cells (Tregs), offering a novel therapeutic approach for autoimmune and inflammatory diseases such as atopic dermatitis. We aimed to compare the efficacy and safety analyses of rezpegaldesleukin with placebo in adults with moderate-to-severe atopic dermatitis naive to biological treatments.

**Methods** REZOLVE-AD was a phase 2b, randomised, double-blind, placebo-controlled study conducted in 107 community research centres or hospitals in ten countries (Australia, Bulgaria, Canada, Croatia, Czechia, Germany, Hungary, Poland, Spain, and the USA). Eligible patients were adults (aged 18 years or older) with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria) diagnosed at least 12 months before enrolment, with moderate-to-severe disease activity defined by an Eczema Area and Severity Index (EASI) score of at least 16·0, validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of at least 3 (moderate), and at least 10% affected body surface area. Patients were randomly allocated (3:3:3:2) to receive subcutaneous rezpegaldesleukin 24 µg/kg or rezpegaldesleukin 18 µg/kg every 2 weeks, rezpegaldesleukin 24 µg/kg every 4 weeks, or placebo for 16 weeks during the induction period. Randomisation was done by an independent vendor using Randomisation and Trial Supply Management methodology via an interactive response system and was stratified by baseline disease severity (vIGA-AD 3 [moderate] *vs* 4 [severe]) and geographical region (North America *vs* rest of world). All patients, investigators, and those assessing outcomes were masked to treatment assignment. Outcomes for the induction period were assessed through week 16 and are included in this report. The primary endpoint was percentage change from baseline in EASI score at week 16. Efficacy and safety analyses were conducted in all randomly assigned patients exposed to study treatment, excluding those enrolled at two sites closed due to Good Clinical Practice non-compliance, both of which received notification of closure approximately 300 days before database lock. All missing data were imputed with multiple imputation. The trial was registered with ClinicalTrials.gov (NCT06136741).

**Findings** 398 patients were enrolled between Nov 15, 2023, and Jan 9, 2025. A total of 393 patients were analysed (104 in the rezpegaldesleukin 24 µg/kg every 2 weeks group, 106 in the rezpegaldesleukin 18 µg/kg every 2 weeks group, 110 in the rezpegaldesleukin 24 µg/kg every 4 weeks group, and 73 in the placebo group); 203 (52%) patients were female and 190 (48%) were male. All three rezpegaldesleukin groups met the primary endpoint. Rezpegaldesleukin showed dose-dependent improvements compared with placebo in mean percentage change in EASI from baseline at week 16: –61% (SE 3·8) for rezpegaldesleukin 24 µg/kg every 2 weeks, –58% (3·8) for rezpegaldesleukin 18 µg/kg every 2 weeks, and –53% (3·7) for rezpegaldesleukin 24 µg/kg every 4 weeks versus –31% (4·5) for placebo. Treatment differences versus placebo were –30 percentage points (95% CI –41·3 to –18·0; p<0·0001) for rezpegaldesleukin 24 µg/kg every 2 weeks, –27 percentage points (–38·5 to –15·7; p<0·0001) for rezpegaldesleukin 18 µg/kg every 2 weeks, and –22 percentage points (–33·3 to –10·3; p=0·0002) for rezpegaldesleukin 24 µg/kg every 4 weeks. Treatment-emergent adverse events observed in at least 5% of rezpegaldesleukin-treated patients (n=320) and greater than placebo (n=73) included injection-site reaction (223 [70%] *vs* three [4%]), eosinophilia (25 [8%] *vs* two [3%]), pyrexia (20 [6%] *vs* two [3%]), headache (20 [6%] *vs* three [4%]), upper respiratory tract infections (19 [6%] *vs* four [5%]), and arthralgia (16 [5%] *vs* one [1%]). Nearly all (>99%) injection-site reactions were mild to moderate in severity and resolved. There was no evidence of an increased risk of serious or severe adverse events, and no deaths were reported during the induction period.

**Interpretation** Over the 16-week induction period, rezpegaldesleukin treatment resulted in significant and clinically meaningful improvements across multiple clinical endpoints, including the primary endpoint of EASI percentage change from baseline, in comparison with placebo. Rezpegaldesleukin had a clinically favourable adverse event

Published **Online** August 21, 2026 https://doi.org/10.1016/S0140-6736(26)01143-8

See **Online/Comment** https://doi.org/10.1016/S0140-6736(26)01242-0

*Listed in appendix 1 (pp 4–10)

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See Online for appendix 1

**profile in adult patients with moderate-to-severe atopic dermatitis, supporting its further development as a novel Treg-enhancing biological treatment.**

**Funding** Nektar Therapeutics.



## Introduction

Atopic dermatitis is a common, chronic, inflammatory skin disease characterised by recurrent, localised eczema accompanied by intense itch.[1,2] As measured by disability-adjusted life years, the disease is ranked first among all skin diseases globally,[3] and substantially impairs quality of life for patients and their families, including effects on lifestyle (51%), activities (43%), and social interaction (39%).[4] Various factors have been implicated in the persistent inflammation associated with atopic dermatitis, including a complex interaction of genetics, environment, skin barrier dysfunction, and dysregulation of effector T helper (Th) type 2 cells.[5] Despite therapeutic advances, there remains an unmet need for efficacious, safe, and durable treatment options for atopic dermatitis management.

Regulatory T cells (Tregs) hold a pivotal role in orchestrating immune homoeostasis through their ability to modulate the activity of Th1, Th2, and Th17 T-cell effector subsets.[6] A disruption of the normal homoeostasis of functional Tregs relative to conventional T cells (Tcons) occurs in many autoimmune and inflammatory diseases, including atopic dermatitis.[7] Interleukin-2 (IL-2) is a pleiotropic cytokine that serves as an essential growth factor for Tregs at physiological quantities and induces Tcon responses at supra-physiological concentrations.[8] Previous studies showed that low doses of IL-2 can reverse the deficiency of Tregs

### Research in context

#### Evidence before this study

Atopic dermatitis remains challenging to treat despite advances in systemic biological or immunosuppressive therapies targeting dysregulated pathways, including interleukin (IL)-4, IL-13, IL-31, Janus kinase, and OX40. Due to unpredictable or incomplete responses, adverse events, and chronic relapse, there remains an unmet need for efficacious and durable treatment options, with good adverse event profiles, for the management of atopic dermatitis. A disruption of the normal balance of functional regulatory T cells (Tregs) relative to conventional T cells (Tcons) is shared by many autoimmune and inflammatory diseases, including atopic dermatitis. IL-2 plays an essential role in Treg proliferation and survival, with low-dose IL-2 shown to partly rescue Treg function and provide clinical benefit in multiple autoimmune diseases. To date, more than 30 different autoimmune and inflammatory diseases have been treated with low-dose IL-2 therapy in pilot studies and clinical trials, supporting the development of therapeutic agents that restore the homoeostatic balance between Tregs and Tcons. Low-dose IL-2, however, has restricted therapeutic practicality, with shortcomings including a narrow therapeutic window and short half-life, requiring frequent dosing and the potential to induce Tcons. Before the start of this study, we searched ClinicalTrials.gov and PubMed for randomised, blinded clinical trials published in English between database inception and May 15, 2023, using keywords "atopic dermatitis" and "regulatory T cells" or "interleukin-2". Previous phase 1b studies of the IL-2 receptor agonist rezpegaldesleukin for the treatment of atopic dermatitis showed favourable data for safety and efficacy endpoints.

#### Added value of this study

To the best of our knowledge, this is the first report of a phase 2 clinical trial evaluating a first-in-class IL-2 receptor agonist with preferential activity for Tregs for the treatment of moderate-to-severe atopic dermatitis. The primary endpoint of mean percentage change in Eczema Area and Severity Index (EASI) at week 16 was met with all rezpegaldesleukin dosing regimens (rezpegaldesleukin 24 µg/kg every 2 weeks, rezpegaldesleukin 18 µg/kg every 2 weeks, and rezpegaldesleukin 24 µg/kg every 4 weeks). All key secondary endpoints of disease reduction were also met in the rezpegaldesleukin 24 µg/kg every 2 weeks group, including EASI reduced by at least 75% relative to baseline score, validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1, EASI reduced by at least 90% relative to baseline score, itch Numerical Rating Scale, and body surface area involvement. No new safety signals were identified.

#### Implications of all the available evidence

Results from the induction treatment period of this study support and extend the findings from the phase 1b study in patients with atopic dermatitis, showing a favourable adverse event profile and robust efficacy across both physician-assessed and patient-reported endpoints. The combination of consistent efficacy and absence of new safety concerns establishes a positive benefit–risk profile, particularly for patients with few treatment options or tolerability challenges with existing therapies, and supports advancement to phase 3 development. Importantly, this is the first large trial to show modulation of Tregs with clinical benefit, highlighting rezpegaldesleukin's clinical potential as a key target in the treatment paradigm for atopic dermatitis.

and enhance their growth and survival, leading to improved disease outcomes.[9] Low-dose IL-2, however, has little therapeutic practicality, with shortcomings including a narrow therapeutic window and short half-life, requiring more frequent dosing that could result in Tcon induction.[10]

Rezpegaldesleukin (NKTR-358) is a novel IL-2 receptor agonist with stable, covalently attached polyethylene glycol moieties designed to enhance Treg responses with minimal effects on Tcons.[11] Compared with recombinant human IL-2, rezpegaldesleukin shows prolonged systemic exposure and provides longer-term, selective activation and proliferative expansion of Tregs.[12] In a multicentre, randomised, phase 1b trial in adult patients with moderate-to-severe atopic dermatitis, rezpegaldesleukin treatment resulted in significant improvements in Eczema Area and Severity Index (EASI) scores in comparison with placebo after 12 weeks of treatment. Among patients treated with rezpegaldesleukin who had a 75% or greater improvement in EASI score from baseline until the end of treatment at week 12, 71% maintained their response through 36 weeks after treatment discontinuation.[13] These findings validated a key role for rezpegaldesleukin in Treg restoration and underscored the importance of additional studies. Here, we report the outcomes from the placebo-controlled 16-week induction treatment period of a phase 2b trial of rezpegaldesleukin monotherapy (REZOLVE-AD) with the aim to compare the efficacy and safety of rezpegaldesleukin with placebo in adults with moderate-to-severe atopic dermatitis who are naive to biological treatment.

## Methods

### Study design

This randomised, double-blind, multicentre, placebo-controlled, dose-ranging, phase 2b trial (REZOLVE-AD) was conducted across 107 sites in ten countries (Australia, Bulgaria, Canada, Croatia, Czechia, Germany, Hungary, Poland, Spain, and the USA) to evaluate the efficacy and safety of rezpegaldesleukin induction and maintenance dosing regimens in adult patients with atopic dermatitis. The study design included an initial 16-week induction period, followed by 36-week maintenance and 52-week off-treatment follow-up periods (appendix 1 p 17); only the data from the 16-week induction period are presented here. The study design was based on the available clinical safety, efficacy, pharmacokinetic, and pharmacodynamic data from the rezpegaldesleukin phase 1b and phase 2 studies in healthy volunteers and patients,[12–14] as well as previous clinical trials of systemic therapies in atopic dermatitis.[15] The study protocol is available online (appendix 2).

The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. Study protocols were approved by the relevant institutional review board or independent ethics committee and regulatory health authorities in accordance with local regulations before trial commencement. Ethics approval was provided by Advarra (approval number Pro00072492). There was no patient or public involvement in the study design, conduct, or reporting. The trial was registered with ClinicalTrials.gov (NCT06136741) and EudraCT (2023-507456-69-00).

### Participants

Adults (aged ≥18 years) were eligible for participation if they had moderate-to-severe atopic dermatitis with a baseline EASI score of at least 16·0 points, a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of at least 3, an affected body surface area (BSA) involvement of at least 10·0% at screening and randomisation, and chronic atopic dermatitis for at least 12 months with inadequate response or intolerance to topical therapy. Patients were excluded if they had received previous treatment with a systemic biological therapy or an oral Janus kinase inhibitor. Additional methods and eligibility criteria are provided in the trial protocol (appendix 2 pp 75–84). Patients were recruited through competitive enrolment. Sex at birth was self-reported with the options of male, female, undifferentiated, or unknown. Race and ethnicity data were self-reported. All patients provided written informed consent.

### Randomisation and masking

At the baseline visit, we randomly assigned eligible patients in a 3:3:3:2 ratio to receive either rezpegaldesleukin 24 µg/kg every 2 weeks, rezpegaldesleukin 18 µg/kg every 2 weeks, rezpegaldesleukin 24 µg/kg every 4 weeks, or placebo every 2 weeks. Randomisation was done with a Randomisation and Trial Supply Management (RTSM) methodology via an Interactive Response Technology (IRT) system managed by a third-party independent vendor. The randomisation sequence was generated by an independent project team using a block size of 11. The system stratified patients by baseline disease severity, as measured by vIGA-AD (3 [moderate] *vs* 4 [severe]), and by geographic region (North America *vs* rest of world). The team responsible for sequence generation and the RTSM/IRT vendor were not involved in patient enrolment, clinical management, outcome assessment, or data analysis. All patients, investigators, site staff, and individuals assessing outcomes remained masked to each patient's assigned study intervention. The schedule, labelling, presentation, and volume of injection for active rezpegaldesleukin and placebo were identical. The designated sponsor study team was unmasked at the primary database lock after the completion of the 16-week induction period.

See Online for appendix 2

### Procedures

Patients received rezpegaldesleukin or placebo (0·9% sodium chloride for injection), administered by site staff masked to allocation, subcutaneously for

16 weeks during the induction period. Patients assigned to the rezpegaldesleukin 24 µg/kg every 4 weeks group were administered placebo on weeks 2, 6, 10, and 14 to match the induction dosing schedule of the rezpegaldesleukin 24 µg/kg every 2 weeks group. Background therapy consisted of at least one emollient used once daily throughout the study.

At study initiation, the use of topical treatments (mid-potency or low-potency topical corticosteroid or topical calcineurin inhibitor) was permitted as rescue therapy only between the week 4 and week 14 visits. The protocol was later amended to allow topical corticosteroid or topical calcineurin inhibitor as rescue therapy only between days 1 and 14 of the induction period. The use of systemic treatments for atopic dermatitis was prohibited through week 16; rezpegaldesleukin was discontinued if systemic rescue therapy was used.

We assessed efficacy, patient-reported outcomes, and safety every 2 weeks at study visits from week 0 through week 16. Blood for pharmacokinetic, pharmacodynamic, and biomarker analyses was sampled approximately every 2–4 weeks; additional details are provided in appendix 1 (pp 12–13). The protocol provides the full schedule of assessments.

### Outcomes

The primary endpoint was the investigator-assessed mean percentage change from baseline in EASI score (range 0–72, with higher values indicating a greater severity and extent of disease) at week 16. 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.[16]

Secondary outcomes included the proportion of patients at week 16 with a vIGA-AD score of 0 or 1 (range, 0 [clear skin] to 4 [severe disease], with the score describing the overall appearance of atopic dermatitis lesions at a given timepoint)[17] and at least a 2-point reduction from baseline, EASI reduction from baseline of at least 75% (EASI-75), EASI reduction from baseline of at least 90% (EASI-90), EASI reduction from baseline of at least 50% (EASI-50), improvement of at least 4 points from baseline in the subset of patients with at least a 4-point itch Numerical Rating Scale (NRS) score at baseline (range, 0 [no itch] to 10 [worst itch imaginable], with values describing the worst itch in the past 24 h),[18] and mean percentage change from baseline at week 16 in BSA involvement. These outcomes were also assessed in a subset of patients with a baseline EASI of at least 18, but are not included in this Article because the results were generally similar. Rezpegaldesleukin plasma concentrations were assessed at various timepoints throughout the study. Although the secondary endpoint of SCORing Atopic Dermatitis Index (SCORAD) showed efficacy results consistent with the overall treatment effect, these data are not presented in this Article, as SCORAD will not be included as an endpoint in the phase 3 development programme. Exploratory assessments included Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), Atopic Dermatitis Control Tool (ADCT), Atopic Dermatitis Sleep Scale (ADSS), and skin pain NRS, and are described in appendix 1 (pp 11–12).

The overall safety and tolerability of rezpegaldesleukin was measured by the incidence of treatment-emergent adverse events and serious adverse events.

### Statistical analysis

We estimated that a sample size of 108 patients in each rezpegaldesleukin group and 72 patients in the placebo group based on a 0·05 significance level in a two-sample Z test would provide the trial with more than 98% power to detect an improvement of 26% in the percentage change in EASI from baseline to week 16 in the rezpegaldesleukin group, assuming 38% reduction of EASI in the placebo group with common SD of 43%. The assumptions on the placebo group and SD were estimated on the basis of data from previously reported trials.[19,20] No dropout rate was assumed in the sample size calculation as missing data were imputed.

Efficacy analyses were based on the modified intention-to-treat (mITT) population that consisted of all randomly assigned patients who received at least one dose of study drug (excluding three patients enrolled at two sites closed due to non-compliance with Good Clinical Practice (GCP); the sites received early closure notification 292 days and 333 days before database lock, respectively). All continuous endpoints, including the primary endpoint of EASI percentage change from baseline and BSA involvement, were analysed with mixed models for repeated measures, including baseline value, randomisation stratification factors, treatment group, visit, and treatment-by-visit interaction as factors. All binary endpoints were analysed with logistic regression using treatment group, baseline value, and randomisation stratification factors as covariates and Mantel–Haenszel differences in response rates adjusted for stratification factors. In the estimation of the primary estimand, data collected after the use of rescue medication or discontinuation of treatment due to a lack of efficacy were imputed as non-responders for binary endpoints and as baseline values for continuous endpoints. Data collected after patients discontinued due to reasons other than a lack of efficacy were regarded as missing. All missing data were imputed with multiple imputation. The imputation was conducted within treatment groups and repeated 50 times with the use of the PROC MI procedure in SAS. Additional details are provided in appendix 1 (p 15).

Prespecified subgroup analyses for endpoints under the primary estimand at week 16 were conducted for the baseline vIGA-AD (3 *vs* 4) subgroups with sample sizes greater than 20. Post-hoc subgroup analyses were done for patients with and without injection-site reactions and

the subgroup of patients with baseline itch NRS of at least 7.

As a phase 2 study, no multiplicity adjustments were made for the hypothesis testing in the primary and secondary endpoints and no confirmatory inferences were made regarding the secondary endpoints. All reported p values were two-sided and confidence intervals are presented as two-sided 95% CIs. SAS version 9.4 was used for all analyses.

Safety analyses were conducted in the safety population that comprised all randomly assigned patients who received at least one dose of study drug (excluding three patients enrolled at two sites closed due to GCP non-compliance) using descriptive statistics, such as number of observations and percentages summarised by treatment group. All adverse events were coded according to the Medical Dictionary for Regulatory Activities version 26.0 and summarised by system organ class, preferred term, severity, and relationship to the study intervention by treatment group.

Additional details of the statistical analyses, including descriptions of the primary and supportive estimands and sensitivity analyses, are provided in appendix 1 (pp 14–16).

### Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

## Results

Of 581 patients assessed for eligibility, 398 patients were enrolled between Nov 15, 2023, and Jan 9, 2025 (figure 1). Two patients did not receive study treatment and three patients from GCP non-compliant sites were excluded from the analysis, leaving a final mITT analysis population of 393 patients. 104 patients received rezpegaldesleukin 24 µg/kg every 2 weeks, 106 patients received rezpegaldesleukin 18 µg/kg every 2 weeks, 110 patients received rezpegaldesleukin 24 µg/kg every 4 weeks, and 73 patients received placebo. Treatment

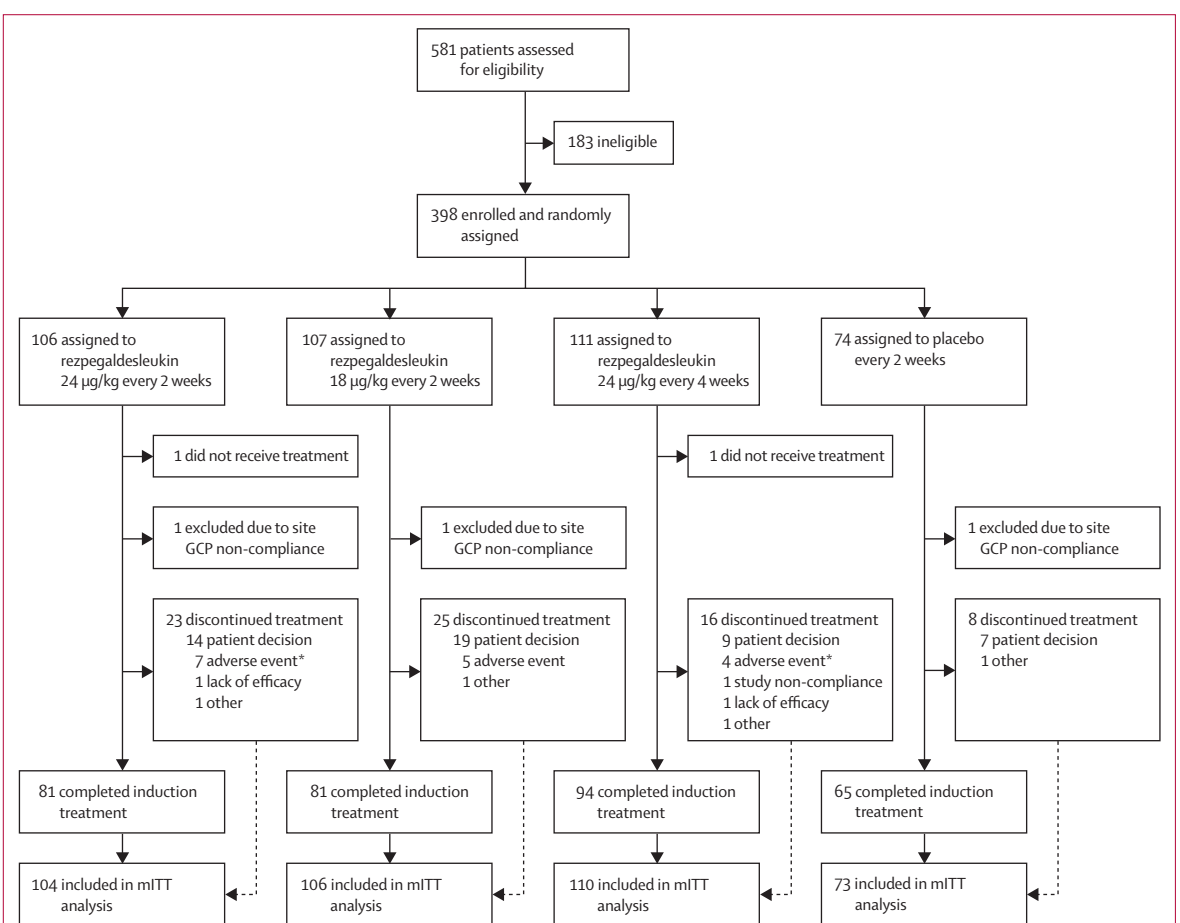


***Figure 1:*** **Trial profile for the 16-week induction period**

Two clinical sites were closed early for serious GCP non-compliance (ie, lack of principal investigator oversight potentially impacting patient care and safety); they were reported to their respective Independent Review Boards and the US Food and Drug Administration. GCP=Good Clinical Practice. mITT=modified intention-to-treat. *Excludes one patient who discontinued treatment due to adverse event during the induction period after completing induction treatment.

| | Rezpegaldesleukin 24 µg/kg every 2 weeks (n=104) | Rezpegaldesleukin 18 µg/kg every 2 weeks (n=106) | Rezpegaldesleukin 24 µg/kg every 4 weeks (n=110) | Rezpegaldesleukin overall (n=320) | Placebo every 2 weeks (n=73) | Total (N=393) |
|---|---|---|---|---|---|---|
| Age, years | 38·0 (13·7) | 36·3 (15·4) | 36·5 (14·3) | 36·9 (14·5) | 37·9 (14·4) | 37·1 (14·4) |
| Sex | | | | | | |
| Female | 49 (47%) | 56 (53%) | 63 (57%) | 168 (53%) | 35 (48%) | 203 (52%) |
| Male | 55 (53%) | 50 (47%) | 47 (43%) | 152 (48%) | 38 (52%) | 190 (48%) |
| Race | | | | | | |
| White | 87 (84%) | 90 (85%) | 96 (87%) | 273 (85%) | 58 (79%) | 331 (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 | 6 (6%) | 7 (7%) | 11 (10%) | 24 (8%) | 8 (11%) | 32 (8%) |
| Not Hispanic or Latino | 98 (94%) | 98 (92%) | 99 (90%) | 295 (92%) | 64 (88%) | 359 (91%) |
| Not reported or unknown | 0 | 1 (1%) | 0 | 1 (<1%) | 1 (1%) | 2 (1%) |
| Weight, kg | 80·5 (19·1) | 77·3 (19·6) | 73·3 (15·6) | 76·9 (18·3) | 79·4 (21·1) | 77·4 (18·9) |
| BMI, kg/m² | 27·1 (6·0) | 26·7 (5·9) | 25·4 (4·7) | 26·4 (5·6) | 26·9 (6·3) | 26·5 (5·7) |
| Region | | | | | | |
| North America | 27 (26%) | 29 (27%) | 31 (28%) | 87 (27%) | 21 (29%) | 108 (27%) |
| Rest of the world | 77 (74%) | 77 (73%) | 79 (72%) | 233 (73%) | 52 (71%) | 285 (73%) |
| Age at onset, years | 14·4 (18·1) | 15·7 (19·6) | 17·6 (19·9) | 15·9 (19·2) | 15·9 (19·3) | 15·9 (19·2) |
| Duration since onset, years | 23·9 (15·2) | 21·0 (14·5) | 19·2 (14·1) | 21·3 (14·7) | 22·3 (15·7) | 21·5 (14·9) |
| vIGA-AD* | | | | | | |
| 3 | 71 (68%) | 70 (66%) | 75 (68%) | 216 (68%) | 51 (70%) | 267 (68%) |
| 4 | 33 (32%) | 36 (34%) | 35 (32%) | 104 (33%) | 22 (30%) | 126 (32%) |
| EASI total score† | 25·4 (9·14) | 27·2 (10·40) | 26·1 (10·45) | 26·2 (10·02) | 25·2 (8·57) | 26·0 (9·77) |
| <21 | 44 (42%) | 43 (41%) | 44 (40%) | 131 (41%) | 29 (40%) | 160 (41%) |
| ≥21 | 60 (58%) | 63 (59%) | 66 (60%) | 189 (59%) | 44 (60%) | 233 (59%) |
| BSA‡ | 39% (18·83) | 41% (20·85) | 40% (20·62) | 40% (20·08) | 38% (19·73) | 40% (20·00) |
| Itch NRS score§ | 6·8 (1·96) | 6·7 (1·90) | 7·1 (1·77) | 6·9 (1·88) | 6·3 (2·21) | 6·8 (1·95) |
| n | 104 | 106 | 109 | 319 | 72 | 391 |
| <4 | 9 (9%) | 14 (13%) | 7 (6%) | 30 (9%) | 9 (12%) | 39 (10%) |
| ≥4 | 95 (91%) | 92 (87%) | 102 (93%) | 289 (90%) | 63 (86%) | 352 (90%) |
| Pain NRS¶ | 5·9 (2·54) | 5·9 (2·53) | 6·2 (2·35) | 6·0 (2·47) | 5·4 (2·64) | 5·9 (2·51) |
| n | 104 | 106 | 109 | 319 | 72 | 391 |
| <4 | 20 (19%) | 24 (23%) | 19 (17%) | 63 (20%) | 22 (30%) | 85 (22%) |
| ≥4 | 84 (81%) | 82 (77%) | 90 (82%) | 256 (80%) | 50 (68%) | 306 (78%) |
| ADSS item 1‖ | 1·9 (1·14) | 2·0 (1·15) | 2·1 (1·02) | 2·0 (1·10) | 1·8 (1·17) | 2·0 (1·12) |
| n | 104 | 106 | 109 | 319 | 72 | 391 |
| <1·25 | 33 (32%) | 36 (34%) | 24 (22%) | 93 (29%) | 27 (37%) | 120 (31%) |
| ≥1·25 | 71 (68%) | 70 (66%) | 85 (77%) | 226 (71%) | 45 (62%) | 271 (69%) |
| DLQI** | 14·5 (7·18) | 13·8 (7·25) | 15·9 (7·12) | 14·7 (7·21) | 13·4 (7·07) | 14·5 (7·20) |
| <4 | 4 (4%) | 4 (4%) | 3 (3%) | 11 (3%) | 8 (11%) | 19 (5%) |
| ≥4 | 100 (96%) | 102 (96%) | 107 (97%) | 309 (97%) | 65 (89%) | 374 (95%) |
| POEM†† | 19·3 (5·87) | 19·7 (5·71) | 20·8 (5·41) | 20·0 (5·68) | 18·7 (6·22) | 19·7 (5·80) |
| <4 | 2 (2%) | 0 | 0 | 2 (1%) | 1 (1%) | 3 (1%) |
| ≥4 | 102 (98%) | 106 (100%) | 110 (100%) | 318 (99%) | 72 (99%) | 390 (99%) |

(Table 1 continues on next page)

| | Rezpegaldesleukin 24 µg/kg every 2 weeks (n=104) | Rezpegaldesleukin 18 µg/kg every 2 weeks (n=106) | Rezpegaldesleukin 24 µg/kg every 4 weeks (n=110) | Rezpegaldesleukin overall (n=320) | Placebo every 2 weeks (n=73) | Total (N=393) |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| ADCT‡‡ | 15·4 (4·94) | 15·5 (5·27) | 16·3 (4·95) | 15·8 (5·06) | 14·5 (5·67) | 15·5 (5·19) |
| n | 103 | 106 | 109 | 318 | 72 | 390 |
| <5 | 2 (2%) | 2 (2%) | 2 (2%) | 6 (2%) | 5 (7%) | 11 (3%) |
| ≥5 | 101 (97%) | 104 (98%) | 107 (97%) | 312 (98%) | 67 (92%) | 379 (96%) |
| At least one previous atopic dermatitis treatment | 104 (100%) | 106 (100%) | 110 (100%) | 320 (100%) | 73 (100%) | 393 (100%) |
| Topical treatment | 99 (95%) | 105 (99%) | 109 (99%) | 313 (98%) | 73 (100%) | 386 (98%) |
| Systemic treatment | 64 (62%) | 65 (61%) | 59 (54%) | 188 (59%) | 47 (64%) | 235 (60%) |

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. ADCT=Atopic Dermatitis Control Tool. ADSS=Atopic Dermatitis Sleep Scale. BSA=body surface area. DLQI=Dermatology Life Quality Index. EASI=Eczema Area and Severity Index. IGA=Investigator Global Assessment. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. vIGA-AD=validated Investigator Global Assessment for Atopic Dermatitis. *vIGA-AD describes the overall appearance of atopic dermatitis 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 ≥3. †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. ‡BSA estimates the extent of disease or skin involvement with respect to atopic dermatitis and is expressed as a percentage of total body surface. §Itch NRS describes the worst level of itch in the past 24 h; scores range from 0 (no itch) to 10 (worst itch imaginable). ¶Skin pain NRS describes the worst level of skin pain in the past 24 h; scores range from 0 (no pain) to 10 (worst pain imaginable). ||ADSS item 1 assesses the impact of itch on difficulty falling asleep; scores range from 0 (not at all) to 5 (very difficult). **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. ††POEM assesses the frequency of seven 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. ‡‡ADCT evaluates six symptoms and effects associated with atopic dermatitis over the past week; scores for each item range from 0 (no problem) to 4 (worst).

***Table 1:*** **Demographics and baseline disease characteristics (modified intention-to-treat population)**

completion rates ranged from 76% to 85% in the rezpegaldesleukin groups and 89% in the placebo group. Important protocol deviations consisted of intercurrent events due to rescue medication use (appendix 1 p 28). There were no key eligibility violations or dosing errors.

Patient demographics and baseline disease characteristics of the mITT population are shown in table 1. Mean age was 37·1 years (SD 14·4), 203 (52%) were female, and 190 (48%) were male. Overall, 331 (84%) patients were White, 36 (9%) were Asian, and 17 (4%) were Black or African American. Demographics and baseline disease characteristics in the ITT population that included all randomly assigned patients were similar to those of the mITT population (appendix 1 pp 29–31). No meaningful differences in demographic and baseline characteristics were observed between patients who had week 16 missing data versus those who did not.

The primary efficacy endpoint was met, with patients in all rezpegaldesleukin groups showing a significantly greater and dose-dependent reduction in mean EASI percentage change from baseline compared with the placebo group at week 16. The mean EASI percentage change from baseline at week 16 was –61% (SE 3·8) with rezpegaldesleukin 24 µg/kg every 2 weeks, –58% (3·8) with rezpegaldesleukin 18 µg/kg every 2 weeks, and –53% (3·7) with rezpegaldesleukin 24 µg/kg every 4 weeks compared with –31% (4·5) in the placebo group, reflecting treatment differences compared with placebo of –30 percentage points (95% CI –41·3 to –18·0; p<0·0001) for rezpegaldesleukin 24 µg/kg every 2 weeks, –27 percentage points (–38·5 to –15·7; p<0·0001) for rezpegaldesleukin 18 µg/kg every 2 weeks, and –22 percentage points (–33·3 to –10·3; p=0·0002) for rezpegaldesleukin 24 µg/kg every 4 weeks (table 2).

Dose-dependent improvements were observed in secondary endpoints including EASI-50, EASI-75, EASI-90, vIGA-AD, and itch NRS responses among patients receiving rezpegaldesleukin, relative to placebo (table 2). As early as week 4 (after two doses) or week 6 (after three doses), a greater proportion (ranging from up to 1.4-fold to 2.9-fold) of patients in the rezpegaldesleukin 24 µg/kg every 2 weeks group had EASI-75, EASI-90, vIGA-AD, and itch NRS responses compared with the other treatment groups (figure 2). By week 16, 26 (25%) patients in the rezpegaldesleukin 24 µg/kg every 2 weeks group had an EASI-90 response compared with seven (9%) in the placebo group (treatment difference *vs* placebo 16 percentage points, p=0·011). Similarly, week 16 EASI-75 response rates in the rezpegaldesleukin 24 µg/kg every 2 weeks group were greater than those in the placebo group (42% [43 of 104] *vs* 17% [12 of 73]; treatment differences *vs* placebo 26 percentage points, p=0·0008), as were EASI-50 response rates (66% [69 of 104] *vs* 34% [25 of 73]; treatment differences *vs* placebo 32 percentage points, p<0·0001; table 2). Although the placebo EASI-75 and EASI-90 response rates were lower in patients with baseline severe disease (vIGA-AD score of 4), rezpegaldesleukin treatment resulted in similar

| | Rezpegaldesleukin 24 µg/kg every 2 weeks (n=104) | Rezpegaldesleukin 18 µg/kg every 2 weeks (n=106) | Rezpegaldesleukin 24 µg/kg every 4 weeks (n=110) | Placebo every 2 weeks (n=73) |
|---|---|---|---|---|
| **Primary endpoint** | | | | |
| EASI percentage change from baseline* | −61% (3·8) | −58% (3·8) | −53% (3·7) | −31% (4·5) |
| Treatment difference | −30% (−41·3 to −18·0) | −27% (−38·5 to −15·7) | −22% (−33·3 to −10·3) | .. |
| p value | <0·0001 | <0·0001 | 0·0002 | .. |
| **Secondary endpoints** | | | | |
| EASI-50 response | 69 (66%) | 70 (66%) | 60 (55%) | 25 (34%) |
| Treatment difference† | 32% (17·6 to 47·3) | 32% (17·4 to 47·1) | 21% (6·2 to 35·6) | .. |
| p value | <0·0001 | <0·0001 | 0·0086 | .. |
| EASI-75 response | 43 (42%) | 49 (46%) | 37 (34%) | 12 (17%) |
| Treatment difference† | 26% (12·2 to 38·8) | 30% (16·4 to 43·0) | 17% (4·3 to 29·9) | .. |
| p value | 0·0008 | 0·0001 | 0·015 | .. |
| EASI-90 response | 26 (25%) | 19 (18%) | 19 (17%) | 7 (9%) |
| Treatment difference† | 16% (5·4 to 27·5) | 9% (−1·4 to 19·8) | 8% (−1·7 to 17·7) | .. |
| p value | 0·011 | 0·093 | 0·14 | .. |
| vIGA-AD response‡§ | 20 (20%) | 28 (26%) | 21 (19%) | 6 (8%) |
| Treatment difference† | 12% (1·2 to 22·2) | 18% (7·1 to 29·2) | 11% (1·2 to 20·9) | .. |
| p value | 0·047 | 0·0054 | 0·053 | .. |
| Itch NRS response¶‖** | 40 (42%) | 32 (35%) | 24 (23%) | 10 (16%) |
| Treatment difference† | 27% (12·4 to 40·7) | 20% (5·4 to 33·6) | 7% (−5·1 to 19·8) | .. |
| p value | 0·0011 | 0·014 | 0·42 | .. |
| BSA percentage change from baseline†† | −54% (4·6) | −48% (4·8) | −43% (4·4) | −17% (5·4) |
| Treatment difference | −37% (−51·3 to −23·1) | −30% (−44·4 to −16·5) | −25% (−39·1 to −11·8) | .. |
| p value | <0·0001 | <0·0001 | 0·0003 | .. |

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. EASI=Eczema Area and Severity Index. EASI-50=reduction in EASI score by at least 50% relative to baseline score. EASI-75=reduction in EASI score by at least 75% relative to baseline score. EASI-90=reduction in EASI score by at least 90% relative to baseline score. NRS=Numerical Rating Scale. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. *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. †Mantel–Haenszel treatment differences in response rates were adjusted for stratification factors. ‡vIGA-AD describes the overall appearance of atopic dermatitis lesions at a given timepoint; scores range from 0 (clear skin) to 4 (severe disease). §vIGA-AD response was defined as a score of 0 (clear) or 1 (almost clear) and ≥2-point reduction from baseline. ¶Itch NRS describes the worst level of itch in the past 24 h; scores range from 0 (no itch) to 10 (worst itch imaginable). ‖Patients evaluable for the corresponding endpoint requiring baseline itch NRS score ≥4 were n=95 for the rezpegaldesleukin 24 µg/kg every 2 weeks group, n=92 for the rezpegaldesleukin 18 µg/kg every 2 weeks group, n=102 for the rezpegaldesleukin 24 µg/kg every 4 weeks group, and n=63 for the placebo group. **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. ††BSA estimates the extent of disease or skin involvement with respect to atopic dermatitis and is expressed as a percentage of total body surface.

***Table 2:*** **Week 16 efficacy outcomes (modified intention-to-treat population)**

response rates in both populations of patients with baseline moderate (vIGA-AD score of 3) and severe disease (appendix 1 p 20).

Among patients with a baseline itch NRS score of at least 4, week 16 responses were observed in 40 (42%) of 95 patients in the rezpegaldesleukin 24 µg/kg every 2 weeks group compared with ten (16%) of 63 patients in the placebo group (treatment difference *vs* placebo 27 percentage points, p=0·0011) and in 32 (35%) of 92 patients in the rezpegaldesleukin 18 µg/kg every 2 weeks group (treatment difference *vs* placebo 20 percentage points, p=0·014; table 2). For patients characterised with severe itch (itch NRS ≥7) at baseline, itch NRS response rates were seen in 29 (54%) of 54 patients in the rezpegaldesleukin 24 µg/kg every 2 weeks group and 26 (49%) of 53 patients in the rezpegaldesleukin 18 µg/kg every 2 weeks group, compared with nine (24%) of 36 patients in the placebo group (appendix 1 p 21), reflecting a greater itch response rate in this subpopulation of patients compared with those in the mITT population (table 2).

Similar to improvements in EASI, patients in all rezpegaldesleukin groups showed a greater reduction in mean BSA score from baseline than in the placebo group, beginning as early as week 4, with increasing improvement through week 16 (appendix 1 p 22). Week 16 treatment differences compared with placebo in mean BSA percentage change from baseline were −37 percentage points (−51·3 to −23·1; p<0·0001) with rezpegaldesleukin 24 µg/kg every 2 weeks group, −30 percentage points (−44·4 to −16·5; p<0·0001) with rezpegaldesleukin 18 µg/kg every 2 weeks, and

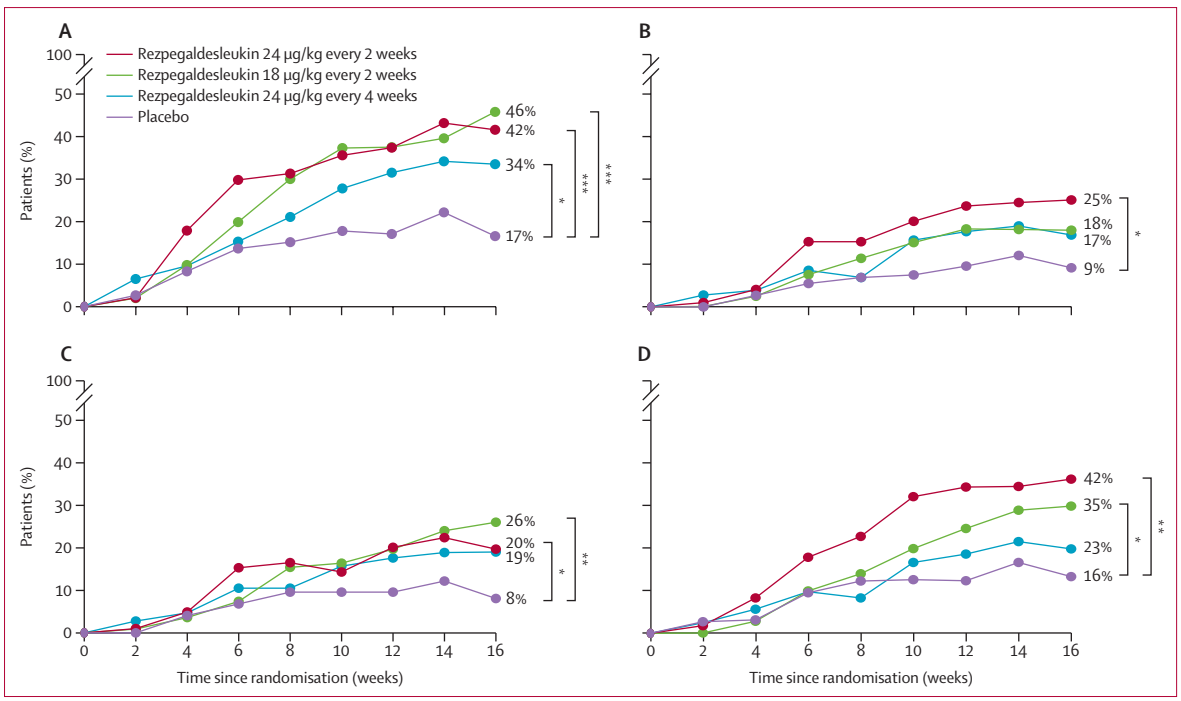


***Figure 2:*** **Responses over time for key secondary outcomes (modified intention-to-treat population)**
(A) EASI-75 response. (B) EASI-90 response. (C) vIGA-AD response (defined as a score of 0 [clear] or 1 [almost clear] with a reduction from baseline of ≥2 points). (D) Itch NRS response (defined as a ≥ 4-point improvement from baseline in Itch NRS [scores ranging from 0 to 10]) in patients with baseline itch NRS score ≥4. For EASI-75, EASI-90, and vIGA-AD: placebo (n=73), rezpegaldesleukin 24 µg/kg every 2 weeks (n=104), rezpegaldesleukin 18 µg/kg every 2 weeks (n=106), and rezpegaldesleukin 24 µg/kg every 4 weeks (n=110). For Itch NRS: placebo (n=63), rezpegaldesleukin 24 µg/kg every 2 weeks (n=95), rezpegaldesleukin 18 µg/kg every 2 weeks (n=92), and rezpegaldesleukin 24 µg/kg every 4 weeks (n=102). EASI=Eczema Area and Severity Index (range 0–72, with higher scores indicating greater severity). EASI-75=reduction in EASI score by at least 75% relative to baseline score. EASI-90=reduction in EASI score by at least 90% relative to baseline score. NRS=Numerical Rating Scale. vIGA-AD=validated Investigator Global Assessment for Atopic Dermatitis (range from 0 to 4). *p<0·05, **p<0·01, ***p<0·001.

–25 percentage points (–39·1 to –11·8; p=0·0003) with the rezpegaldesleukin 24 µg/kg every 4 weeks group (table 2). Significant improvement in EASI percentage change from baseline between the rezpegaldesleukin 24 µg/kg groups relative to the placebo group was present from week 2 and persisted to week 16, with greater separation over time (appendix 1 p 18). Notably, patients with baseline severe disease (vIGA-AD score of 4) had similar improvements in EASI to those who were baseline moderate (vIGA-AD score of 3; appendix 1 p 19). Subgroup analyses based on geographical region were similar to the overall population results and were not included here. Placebo-adjusted differences in mean EASI percentage change from baseline at week 16 for patients with baseline severe disease were –34 percentage points (–55·5 to –13·0; p=0·0016) with rezpegaldesleukin 24 µg/kg every 2 weeks, –29 percentage points (–49·3 to –8·4; p=0·0058) with rezpegaldesleukin 18 µg/kg every 2 weeks, and –21 percentage points (–41·7 to –0·7; p=0·043) with rezpegaldesleukin 24 µg/kg every 4 weeks; and for patients with baseline moderate disease were –28 percentage points (–41·6 to –13·8; p<0·0001) with rezpegaldesleukin 24 µg/kg every 2 weeks, –26 percentage points (–40·2 to –12·4; p=0·0002) with rezpegaldesleukin 18 µg/kg every 2 weeks, and –22 percentage points (–36·1 to –8·3; p=0·0017) with rezpegaldesleukin 24 µg/kg every 4 weeks.

Rezpegaldesleukin improved patient-reported exploratory outcomes (appendix 1 p 23). The highest week 16 response rates were observed in the rezpegaldesleukin 24 µg/kg every 2 weeks group relative to placebo for ADCT (67% of patients *vs* 35% of patients), DLQI (72% *vs* 54%), ADSS Item 1 (57% *vs* 30%), skin pain NRS (45% *vs* 22%), and POEM (66% *vs* 50%).

After subcutaneous administration of rezpegaldesleukin, mean trough plasma concentrations showed a stable plateau at week 8 after the first dose (appendix 1 p 24). Mean steady-state values displayed dose proportional increases across the rezpegaldesleukin treatment regimens. As predicted based on previous studies,[13,14] the highest dose exposure was observed in the rezpegaldesleukin 24 µg/kg every 2 weeks group, followed by the rezpegaldesleukin 18 µg/kg every 2 weeks group, and finally the rezpegaldesleukin 24 µg/kg every 4 weeks group.

A dose-dependent increase in Tregs was observed in rezpegaldesleukin-treated cohorts during the 16-week induction period, with up to a six-fold increase from baseline in $CD25^{bright}$ Tregs (appendix 1 p 25). Patients

| | Rezpegaldesleukin 24 µg/kg every 2 weeks (n=104) | Rezpegaldesleukin 18 µg/kg every 2 weeks (n=106) | Rezpegaldesleukin 24 µg/kg every 4 weeks (n=110) | Rezpegaldesleukin overall (n=320) | Placebo every 2 weeks (n=73) |
|---|---|---|---|---|---|
| At least one treatment-emergent adverse event | 89 (86%) | 78 (74%) | 90 (82%) | 257 (80%) | 42 (58%) |
| At least one treatment-emergent adverse event (excluding injection-site reactions) | 69 (66%) | 60 (57%) | 64 (58%) | 193 (60%) | 42 (58%) |
| At least one serious treatment-emergent adverse event | 1 (1%) | 4 (4%) | 0 | 5 (2%) | 0 |
| At least one severe treatment-emergent adverse event | 3 (3%) | 6 (6%) | 1 (1%) | 10 (3%) | 1 (1%) |
| At least one treatment-emergent adverse event leading to death | 0 | 0 | 0 | 0 | 0 |
| At least one treatment-emergent adverse event leading to discontinuation of treatment | 8 (8%) | 5 (5%) | 5 (5%) | 18 (6%) | 0 |
| Treatment-emergent adverse events reported in ≥5% of patients in any group by system organ class and preferred term | | | | | |
| General disorders and administration-site conditions | 80 (77%) | 67 (63%) | 78 (71%) | 225 (70%) | 7 (10%) |
| Injection-site reaction (at least one event) | 79 (76%) | 66 (62%) | 78 (71%) | 223 (70%) | 3 (4%) |
| Patients with ≤2 injection-site reactions | 54 (52%) | 68 (64%) | 68 (62%) | 190 (59%) | 73 (100%) |
| Pyrexia | 11 (11%) | 5 (5%) | 4 (4%) | 20 (6%) | 2 (3%) |
| Infections and infestations | 29 (28%) | 39 (37%) | 32 (29%) | 100 (31%) | 25 (34%) |
| Nasopharyngitis | 10 (10%) | 14 (13%) | 14 (13%) | 38 (12%) | 10 (14%) |
| Upper respiratory tract infection | 7 (7%) | 8 (8%) | 4 (4%) | 19 (6%) | 4 (5%) |
| Blood and lymphatic system disorders | 29 (28%) | 6 (6%) | 11 (10%) | 46 (14%) | 3 (4%) |
| Eosinophilia | 17 (16%) | 4 (4%) | 4 (4%) | 25 (8%) | 2 (3%) |
| Lymphadenopathy | 7 (7%) | 1 (1%) | 3 (3%) | 11 (3%) | 0 |
| Musculoskeletal and connective tissue disorders | 19 (18%) | 5 (5%) | 11 (10%) | 35 (11%) | 3 (4%) |
| Arthralgia | 10 (10%) | 2 (2%) | 4 (4%) | 16 (5%) | 1 (1%) |
| Skin and subcutaneous tissue disorders | 12 (12%) | 10 (9%) | 13 (12%) | 35 (11%) | 8 (11%) |
| Dermatitis atopic | 2 (2%) | 5 (5%) | 6 (5%) | 13 (4%) | 7 (10%) |
| Nervous system disorders | 10 (10%) | 10 (9%) | 9 (8%) | 29 (9%) | 6 (8%) |
| Headache | 8 (8%) | 6 (6%) | 6 (5%) | 20 (6%) | 3 (4%) |
| Gastrointestinal disorders | 8 (8%) | 7 (7%) | 11 (10%) | 26 (8%) | 3 (4%) |
| Respiratory, thoracic, and mediastinal disorders | 6 (6%) | 5 (5%) | 5 (5%) | 16 (5%) | 1 (1%) |
| Investigations | 6 (6%) | 4 (4%) | 3 (3%) | 13 (4%) | 1 (1%) |

Data are number of patients (%). Preferred terms were coded based on the Medical Dictionary for Regulatory Activities version 26.0. The safety population comprised patients who were randomly assigned and received at least one dose of rezpegaldesleukin or placebo, excluding patients enrolled at two sites that were closed due to non-compliance with Good Clinical Practice. No serious or severe adverse events were reported at either of these sites.

***Table 3:*** **Summary of treatment-emergent adverse events during the induction period (safety population)**

showed increases in %CD25$^{bright}$ Tregs from baseline of 5·6-fold for the rezpegaldesleukin 24 µg/kg every 2 weeks group, 5·0-fold for the rezpegaldesleukin 18 µg/kg every 2 weeks group, and 4·9-fold for the rezpegaldesleukin 24 µg/kg every 4 weeks group at the first peak between weeks 2 and 3. Tregs remained elevated in both cohorts receiving rezpegaldesleukin every 2 weeks, at weeks 12 and 16 trough collections, showing a 3·3-fold increase from baseline at week 16 for the rezpegaldesleukin 24 µg/kg every 2 weeks group and a 2·5-fold increase for the rezpegaldesleukin 18 µg/kg every 2 weeks group. The regimens with rezpegaldesleukin every 2 weeks maintained blood Treg elevations over the entire 16-week induction treatment period, whereas with the rezpegaldesleukin every 4 weeks dosing regimen, Tregs returned to baseline at the end of each 4-week dosing interval.

At week 16, rezpegaldesleukin dose-dependently reduced concentrations of the key atopic dermatitis biomarkers thymus and activation-regulated chemokine (CCL17), periostin, macrophage-derived chemokine (CCL22), and IL-19 in the subset of patients with baseline protein values above the upper limit of the normal range (appendix 1 p 26). The greatest magnitude of response was observed in the rezpegaldesleukin every 2 weeks dosing regimens.

More patients in the placebo group than in the rezpegaldesleukin overall group (16 [22%] of 73 patients *vs* 28 [9%] of 320 patients) received rescue therapy (eg, topical or systemic corticosteroids, topical calcineurin inhibitor, or systemic antihistamines; appendix 1 p 33).

257 (80%) of 320 patients receiving rezpegaldesleukin and 42 (58%) of 73 patients receiving placebo had at least one treatment-emergent adverse event during the

induction period (table 3). Severe treatment-emergent adverse events were observed in ten (3%) patients in the rezpegaldesleukin overall group and one (1%) patient in the placebo group. 18 (6%) rezpegaldesleukin-treated patients discontinued treatment due to treatment-emergent adverse events; treatment-emergent adverse events that led to treatment discontinuation in more than one patient were arthralgia in three (0·9%) patients, and dyspnoea, hypersensitivity, local injection-site reaction, and urticaria, each in two (0·6%) patients. Serious adverse events were observed in five (2%) patients in the rezpegaldesleukin overall group, with no events occurring in more than one patient. Treatment-related serious adverse events included tonsillitis and drug hypersensitivity. No deaths occurred during the induction period.

The most frequent treatment-emergent adverse event was injection-site reaction, reported in 223 (70%) of 320 patients in the rezpegaldesleukin overall group and three (4%) of 73 patients receiving placebo (table 3). Most (>99%) injection-site reactions were of mild or moderate severity (appendix 1 p 34) and 190 (59%) patients receiving rezpegaldesleukin reported two or fewer injection-site reactions (table 3). Additionally, nearly all (>99%) injection-site reactions resolved; the median time to resolution was 7 days (IQR 4–9). Two (0·6%) patients in the rezpegaldesleukin overall group discontinued treatment due to injection-site reactions over the 16-week induction period. Importantly, there was no observed difference in EASI percentage change from baseline in any rezpegaldesleukin treatment group based on injection-site reactions (appendix 1 p 27). Treatment-emergent adverse events excluding injection-site reactions were reported in 193 (60%) patients receiving rezpegaldesleukin and 42 (58%) 73 patients receiving placebo.

Supportive estimands that applied the treatment policy strategy for the intercurrent event of treatment discontinuation due to reasons other than a lack of efficacy showed similar results to the primary estimands (appendix 1 p 35). Prespecified sensitivity analyses without multiple imputation and post-hoc sensitivity analyses that included the three patients originally excluded from the primary analysis due to site GCP non-compliance (appendix 1 p 32) were similar to the primary analysis.

## Discussion

The REZOLVE-AD phase 2b trial evaluated the efficacy and safety of rezpegaldesleukin monotherapy administered every 2 weeks or every 4 weeks in adults with moderate-to-severe atopic dermatitis. After 16 weeks of treatment, patients receiving rezpegaldesleukin had significant improvements with respect to the primary endpoint of mean percentage change in EASI from baseline. Analysis of secondary endpoints suggested greater improvements among patients receiving rezpegaldesleukin than in those receiving placebo. These results show a rapid onset of action in multiple domains of the disease, including skin clearance and itch resolution, and support the findings from the phase 1b trial of rezpegaldesleukin (NCT04081350).[13]

Placebo-adjusted differences in EASI percentage improvement from baseline with rezpegaldesleukin 24 µg/kg every 2 weeks were similar to those reported in phase 2b trials for other biological treatments at similar timepoints.[20–24] Similar observations were applicable to EASI-75 and vIGA-AD comparisons. Due to inherent differences in study designs, trial centres, and patient populations, cross-trial comparisons should be interpreted carefully. Rezpegaldesleukin was equally efficacious in moderate and severe subpopulations, and showed a rapid, dose-dependent itch NRS response as early as week 4 after only two doses, a response that became even more pronounced at week 16, especially in the subset of patients with severe itch (baseline itch NRS score ≥7). This outcome is important because itch is a major contributor to the reduced quality of life in patients with atopic dermatitis.[4]

Improvements in efficacy were accompanied by dose-dependent increases in activated Tregs and were consistent with previously observed data with rezpegaldesleukin.[13,14] A dose–response relationship is especially meaningful in atopic dermatitis because it shows that greater pathway modulation translates into greater clinical effect, supporting both mechanism validation and dose selection. The results from this trial, corroborated by biomarker evidence of rezpegaldesleukin's mechanistic activity,[13] support a central role of Treg imbalance in the pathogenesis of atopic dermatitis[25] and IL-2 receptor agonism as an important therapeutic target. To the best of our knowledge, this study is the first large trial to show modulation of Tregs, the discovery of which was recognised by the 2025 Nobel Prize in Physiology or Medicine,[26] as a novel mechanism for immunoregulation of chronic inflammatory disease. These findings provide additional in vivo context for better understanding the systemic effects of rezpegaldesleukin and the role of Tregs in the setting of infection—specifically, whether they promote pathogen persistence or confer host protection. In this study and previous rezpegaldesleukin studies, comprising approximately 1000 participants in total, Treg expansion through rezpegaldesleukin-mediated IL-2 receptor agonism was not associated with an increased risk for viral or bacterial infections.[27] Although future studies are required, these data support a protective role for Tregs in limiting tissue damage. Whereas current therapeutic strategies largely focus on inhibiting cytokines and effector T-cell activity to suppress inflammatory responses, Treg-directed agonism could offer an alternative approach in atopic dermatitis. By resolving inflammation through the restoration of immune homoeostasis, this strategy represents a disease-modifying potential without broad

immunosuppression or evidence of increased infection risk that has historically restricted the use of many effective therapies.

Safety data for rezpegaldesleukin for the 16-week induction period were consistent with the previously observed and reported safety profile.[12–14,27] As with previous rezpegaldesleukin studies, a transient dose-dependent increase in constitutional treatment-emergent adverse events was observed that is consistent with rezpegaldesleukin's mechanism of action as a cytokine agonist.[14] Serious and severe adverse events were rare for patients exposed to rezpegaldesleukin, as was discontinuation due to adverse events, and were within the ranges reported in the treatment groups of other contemporary phase 2b studies for approved and late-stage biological treatments.[19–24] Therapeutics that are approved or in development for atopic dermatitis pose increased risks of conjunctivitis, oral ulcers, or infections,[22,28,29] but no evidence for an increased risk of infection with rezpegaldesleukin was observed in this study. The most frequently observed treatment-emergent adverse event was injection-site reaction; most were mild or moderate in severity, self-resolving, and did not lead to treatment discontinuation. The majority of patients reported two or fewer injection-site reactions and there was no observed difference in efficacy based on EASI mean percentage change from baseline in rezpegaldesleukin-treated patients with or without injection-site reactions. Across multiple indications, injection-site reactions are frequently reported in studies of low-dose IL-2 administered subcutaneously.[30]

The data reported here are from the 16-week induction period of the trial; additional data from the maintenance period and the subsequent 52-week off-treatment follow-up period will be informative. In this study, the inclusion of only biological treatment-naive, adult patients, with most being White, might limit the ability to generalise the results to the overall population with atopic dermatitis. Observed efficacy rates in the placebo group were similar to those observed in other trials.[31] The REZOLVE-AD study was not designed to detect statistically significant differences in efficacy endpoints between rezpegaldesleukin treatment groups; any differences observed between rezpegaldesleukin doses should be interpreted according to the limitations of the analysis. With respect to the 12 physician-assessed and patient-reported efficacy endpoints presented here, ten (83%) of these favoured the rezpegaldesleukin 24 µg/kg every 2 weeks regimen over the rezpegaldesleukin 18 µg/kg every 2 weeks dosing regimen. Therefore, based on Treg pharmacodynamic data, efficacy measures at week 16, time to response by week 4, and overall risk–benefit assessments, the rezpegaldesleukin 24 µg/kg every 2 weeks dosing regimen will be pursued in subsequent phase 3 studies.

Atopic dermatitis is a broad indication, and for the many patients who do not derive benefit from existing therapies, a novel treatment option is much needed. Moreover, as more options with non-overlapping mechanisms become available, a higher proportion of patients receive care and, to this end, the standard of care is advanced. To our knowledge, this is the first large, placebo-controlled trial validating the immunomodulatory effect of Tregs, now 25 years after their discovery, with no evidence of immunosuppression. Compared with available therapies and those in late-stage development, rezpegaldesleukin has a rapid onset of efficacy with a differentiating safety profile.

#### Contributors

JIS, DR, TB, RC, MG, SC, ZHL, DY, YL, CF, BK, MT, and JZ conceptualised the study. DR, MG, SG, AR, DFM, JS, NS, IB, AT, PF-P, JSK, TM-V, TAP, AK, MBS, and VTL were investigators in the study. DY and YL conducted the statistical analysis. DY and YL directly accessed and verified the underlying data reported in the manuscript. All authors had full access to the study data, had a role in interpreting study data, provided input to the manuscript, and had final responsibility for the decision to submit for publication. All authors will ensure that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved, have reviewed the final version of the manuscript to be submitted, and agree with the content and submission.

#### Declaration of interests

JIS has served as a speaker, advisory board member, consultant and (or) received institutional grants from AbbVie, Alamar Biosciences, Aldena Therapeutics, Amgen, Abiomed, Arcutis Biotherapeutics, Arena Pharmaceuticals, Asana BioSciences, Aslan Pharmaceuticals, BioMX, Biosion, Bodewell, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant Sciences, Dermtech, Lilly, Galderma, GSK, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Nektar Therapeutics, Novartis, Optum, Pfizer, RAPT Therapeutics, Recludix Pharma, Regeneron Pharmaceuticals, Sanofi, Shaperon, Target PharmaSolutions, UNION Therapeutics, and UpToDate. DR has served as a speaker, advisory board member, consultant and (or) investigator for AbbVie, Abcuro, Ability Biologics, Almirall, AltruBio, Amgen, Arena Pharmaceuticals, Astria, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert Pharmaceuticals, CSL Behring, Dermavant Sciences, Dermira, Dualitas, Edesa Biotech, EMD Serono, Forte Biosciences, Galderma, Incyte, Inmagene, Janssen Pharmaceuticals, Kymera, Kyowa Kirin, Lilly, Merck, Nektar Therapeutics, Novartis, Pfizer, Phothera, RAPT Therapeutics, Recludix Pharma, Regeneron Pharmaceuticals, Revolo Biotherapeutics, Sanofi, Sun Pharma, Takeda, Triveni Bio, UCB, Viela Bio, and Zura Bio. TB has served as a speaker and (or) consultant for AbbVie, Aclaris, Almirall, AnaptysBio, Apogee, Aristea, Attovia, Belenos, Biocryst, Biogeneration, BioVerSys, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, BYOME Labs, Cantargia, CellDex, Choate, Dermavant, DirigentBio, Domain Therapeutics, EMD Serono, EngImmune, Ennovate, Evommune, Forbion, Formycon, Galderma, Gilead, GSK, ImageneBio, Janssen, Kyowa Kirin, Kymera, LEO Pharma, LG Chem, Lilly, Mabylon, MSD, Micreos, Nektar Therapeutics, Nextech, Novartis, Numab, Ornavi, Overtone, Pfizer, Pierre Fabre, Protagonist Tx, Samsung Bioepis, Sanofi/Regeneron, Scienta Lab, Serono, SwitchKine, TIRmed, Triton, Triveni, UCB, Union Therapeutics, UPStream Bio, WinWard, YUHAN, and Zurabio; he is founder and chairman of the board of Davos Biosciences within the international Kühne-Foundation, and founder and senior medical advisor of Bieber Dermatology Consulting. RC has served as a speaker, advisory board member, consultant, and (or) investigator for AbbVie, Acelyrin, Almirall, Alumis, Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics, Argenx, Astria Therapeutics, Avalere Health, Beiersdorf, BioCryst Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celldex Therapeutics, CLn Skin Care, Dermavant, DKSH, EMD Serono, Enveda Therapeutics, EPI Health, Formation Bio, Forte Biosciences, Galderma, Genentech, GSK, Incyte, ImageneBio, Immunocore, Indero, Johnson & Johnson, Kenvue, LEO Pharma, Lilly, L'Oréal, Nektar Therapeutics, Nia Health, Novan, Novartis, Opsidio, Organon, Pfizer, Propeller Bio, RAPT

Therapeutics, Regeneron, Sanofi, Sitryx, SUN Pharma, Takeda, TRex Bio, UCB, Zai Lab, ZenZema, and Zuellig Pharma. MG has served as a speaker, advisory board member, consultant, investigator, and (or) received institutional grants from AbbVie, Acelyrin, Amgen, AnaptysBio, Arcutis Biotherapeutics, Aristea Therapeutics, ASLAN Pharmaceuticals, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Celgene, Dermavant Sciences, Dermira, Lilly, Galderma Laboratories, ImageneBio, Janssen Pharmaceuticals, LEO Pharma, Medimmune, Meiji Seika Pharma, Moonlake, Nektar Therapeutics, Nimbus Therapeutics, Novartis Pharmaceuticals, Pfizer, Regeneron, Reistone Biopharma, Sanofi Genzyme, Sanofi/Regeneron, Sun Pharma, Takeda Pharmaceuticals, Tarsus, UCB, and Ventyx Biosciences. 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JSK has received grants to his institution related to this work from Nektar Therapeutics; grants to his institution unrelated to this work from AbbVie, Amicus, Amgen, Arcutis, Argenix, AstraZeneca, Biofrontera, Boehringer, Bristol Myers Squibb, Celldex, Chiesi, CSL, DFG/Fresenius, Dompé, Lilly, Exopharm, Galderma, Genentech, Incyte, InflaRx, Kiniksa, Merck, Mitsubishi, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB. TM-V has served as an investigator for Nektar Therapeutics; she has participated in conferences and research projects with Abbvie, Almirall, Incyte, LEO Pharma, Lilly, Novartis, Sanofi, Pfizer-Wyeth, and UCB Pharma, as well as with the Instituto de Salud Carlos III. 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JS, IB, AT, and TAP have served as clinical investigators and received institutional grants on the current study from Nektar Therapeutics. SC, ZHL, MH, DY, YL, CF, HL, BK, MT, and JZ serve as employees or consultants for and are stockholders at Nektar Therapeutics. MT has served as an advisory board member for ADARx Pharmaceuticals and Iambic Therapeutics. 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### Data sharing

Qualified science and medical researchers can request access to anonymised data sets from which results presented in this Article are derived. Data availability and supporting documents will begin 6 months after approval of the indication by a regulatory body and will end 5 years from publication of the article. Requests for access to the data can be made by sending an email together with a research proposal detailing planned analyses to StudyInquiry@nektar.com.

### Acknowledgments

The study was funded by Nektar Therapeutics. The authors would like to thank the patients for their participation in these studies, and the investigators and study staff at each participating site. Clinical operations support from Nektar Therapeutics was provided by Wang Waltz, Jenny Gilbert, and Charleen Jue, and data management support was provided by Connie Louie-Tse and Karyn Cassello. Medical writing and editorial assistance was provided by Jaime S Horton of CD Chunn & Associates and was funded by Nektar Therapeutics according to the Good Publication Practice guidelines.

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