Efficacy and Safety of Rezpegaldesleukin, A Selective Regulatory T-Cell-Inducing Interleukin-2 Conjugate, in the Treatment of Atopic Dermatitis: Final Results from the 16-Week Induction of a Randomized Phase 2b Study (REZOLVE-AD)

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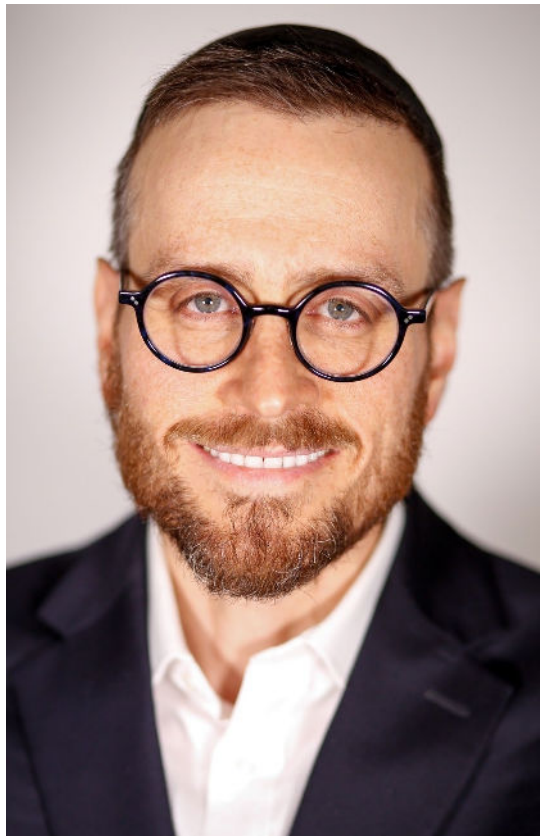
Presenter and Conflicts



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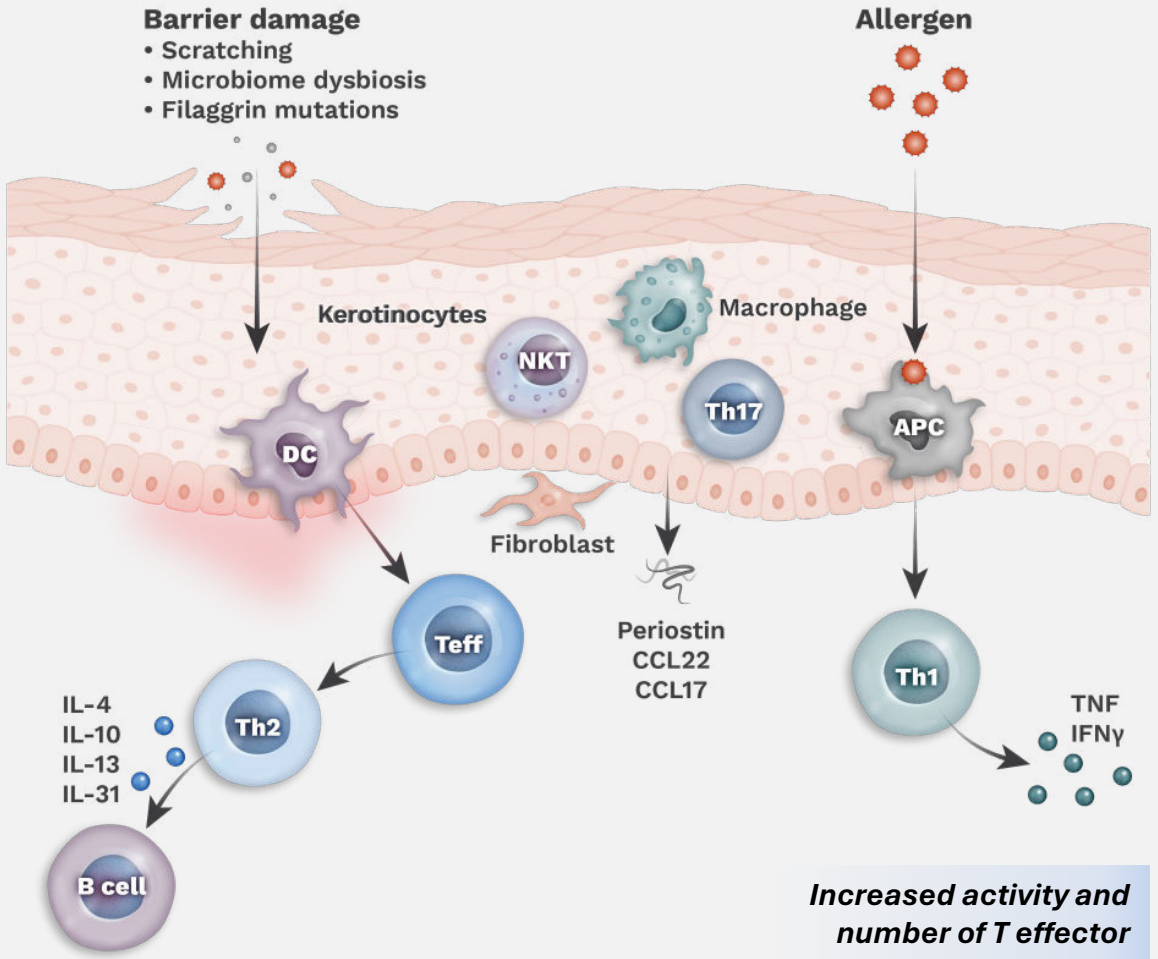
Conflict of Interest Disclosures:

Speaker, advisory board member, consultant and/or received institutional grants from Abbvie, Alamar, Aldena, Amgen, AObiome, Arcutis, Arena, Asana, Aslan, BioMX, Biosion, Bodewell, Boehringer-Ingelheim, Bristol Myers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Nektar, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sanofi-Genzyme, Shaperon, TARGET-RWE, Union, UpToDate

Rezpegaldesleukin (Rezpeg) is a potential first-in-class regulatory T cell mechanism to restore balance in the immune system

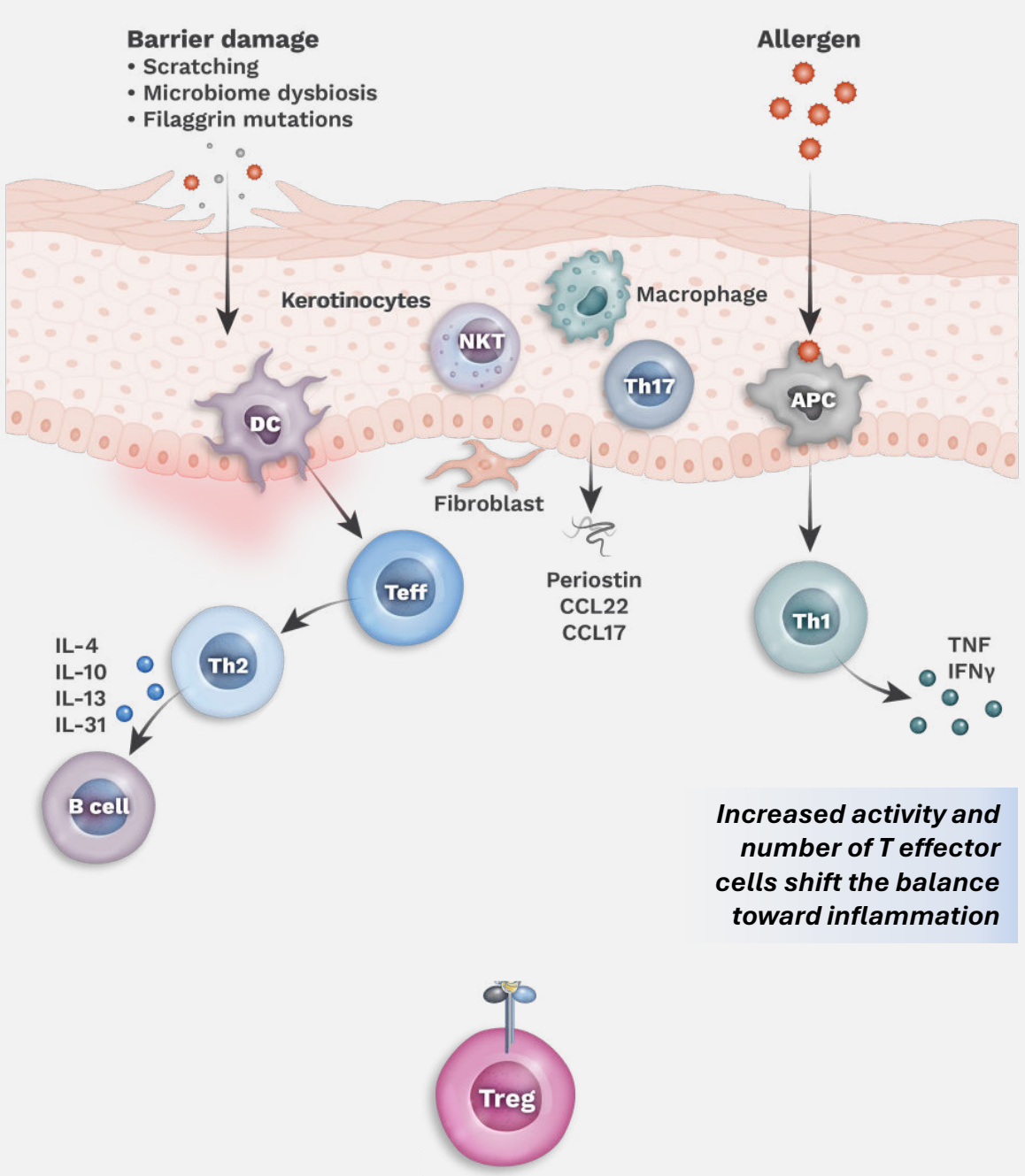
- **AD is driven by imbalance in heterogeneous inflammatory T cell subsets,** including T effector cells, that drive inflammation and disease pathology in the skin



Increased activity and number of T effector cells shift the balance toward inflammation

Rezpegaldesleukin (Rezpeg) is a potential first-in-class regulatory T cell mechanism to restore balance in the immune system

- **AD is driven by imbalance in heterogeneous inflammatory T cell subsets,** including T effector cells, that drive inflammation and disease pathology in the skin
- **Tregs play a central role in controlling AD** by dampening inflammatory cytokines and overactive T cells[1]

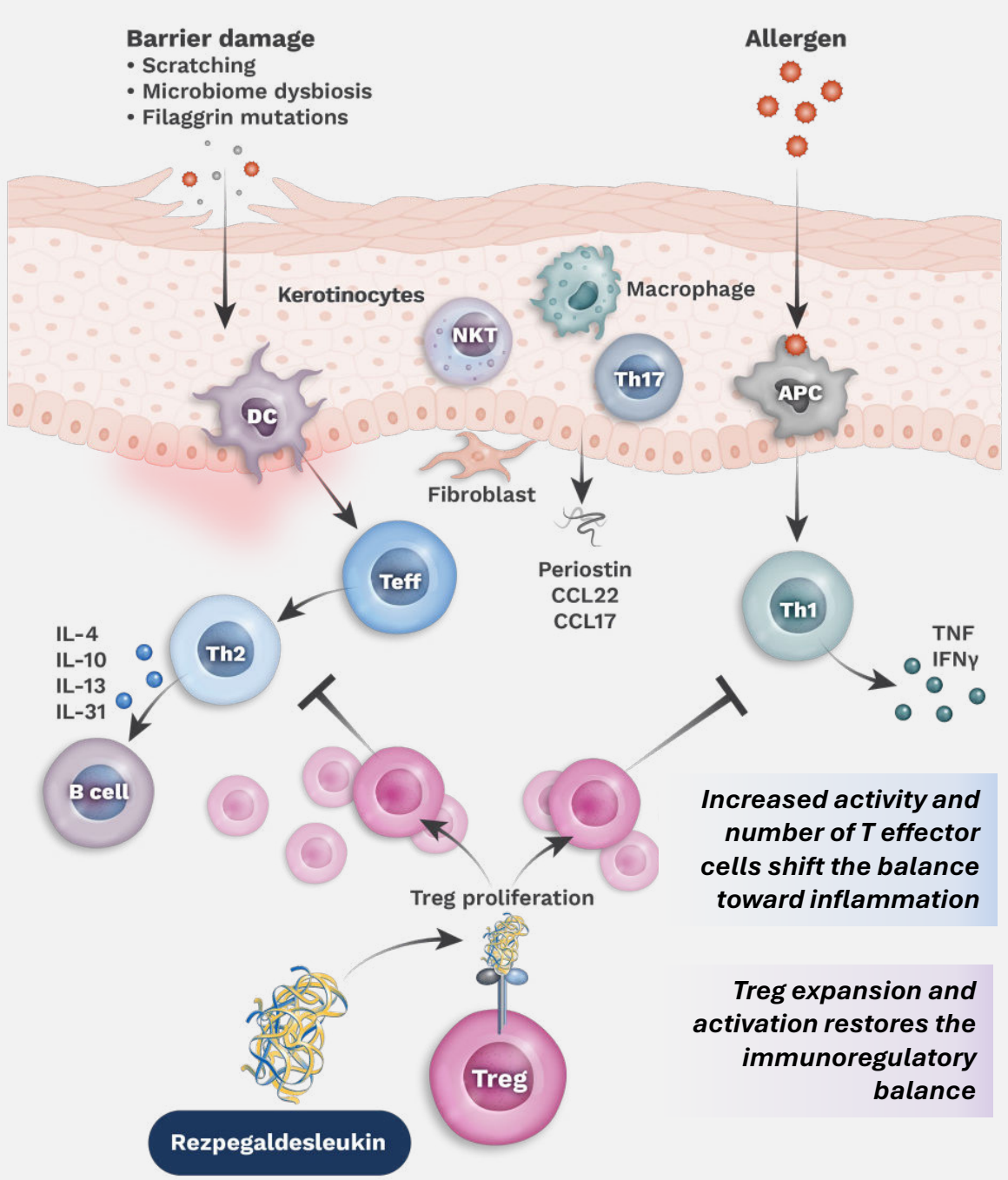


Increased activity and number of T effector cells shift the balance toward inflammation

Sources: 1. Silverberg et al. 2024 Nature Communications, 15:9230

Rezpegaldesleukin (Rezpeg) is a potential first-in-class regulatory T cell mechanism to restore balance in the immune system

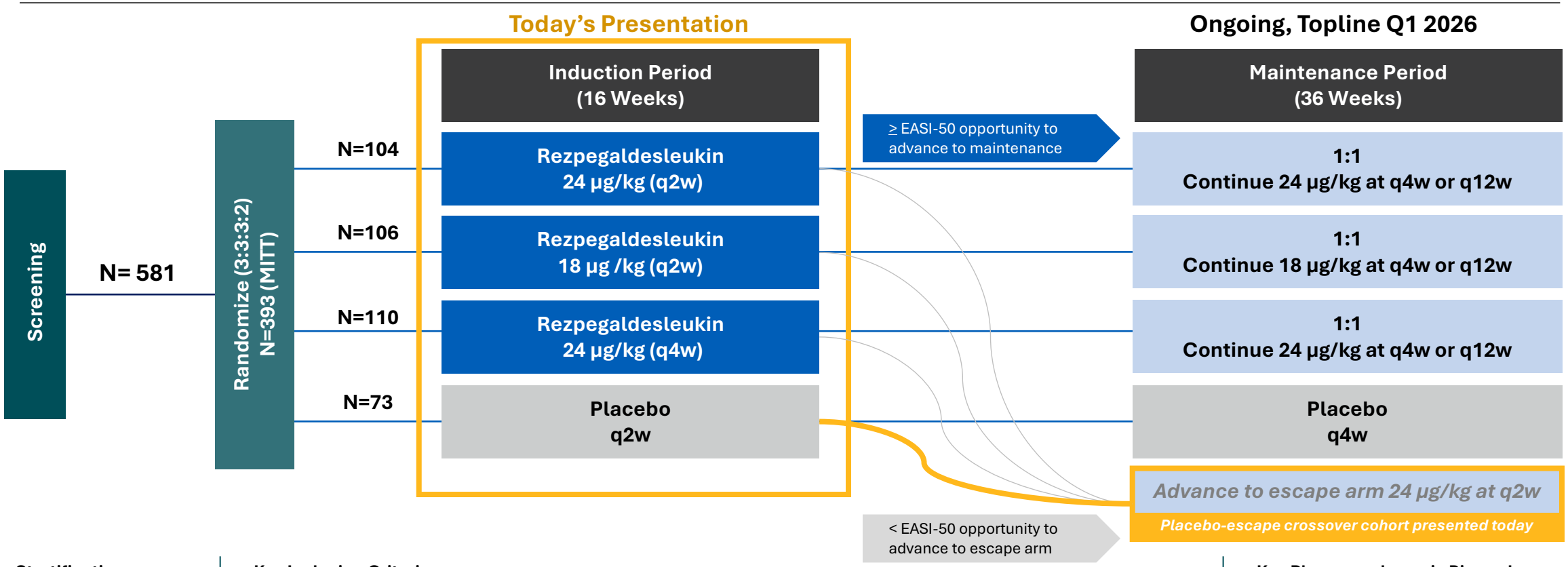
- **Tregs play a central role in controlling AD** by dampening inflammatory cytokines and overactive T cells[1]
- **Rezpeg** is a potential T-cell balancing therapy that acts on IL2 receptors and has been shown to[2,3]:
  - **Proliferate** regulatory T cells
  - **Restore** their functionality, reducing proinflammatory cytokines
  - **Offer potential long-term control** of overactive immune responses
- **Granted Fast Track designation in Feb 2025** for treatment of adult and pediatric patients ≥12 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable



Sources: 1. Silverberg et al. 2024 Nature Communications, 15:9230; 2. Fanton et al. 2022 J. Translational Autoimmunity, 5:100152; 3. Dixit et al. 2021 J Translational Autoimmunity, 4:100103

REZOLVE-AD: Phase 2b Trial Design

Patients with Moderate-to-Severe Atopic Dermatitis



Stratification

- ✓ Geographic region
- ✓ Disease severity by vIGA-AD

Key Inclusion Criteria:

- ✓ Age: ≥18 years
- ✓ Moderate/severe AD diagnosis for ≥ 12 months
  - EASI ≥ 16
  - vIGA-AD of 3 or 4
  - BSA ≥ 10%
- ✓ Biologic-naive (no prior biologic systemic therapy) and systemic JAKi-naïve
- ✓ Failure of prior therapy, including TCS of medium or higher potency, within last 6 months

Key Pharmacodynamic Biomarkers:

- T regulatory cell
- TARC/CC17
- Periostin
- MDC/CCL22
- IL-19

MITT is defined as patients who were randomized and received at least one dose of study treatment or placebo.

REZOLVE-AD: Phase 2b Trial Design

Primary and Secondary Endpoints, Use of Rescue Therapy and Statistical Analysis Methods

Primary Endpoint:
- Mean % EASI improvement at Week 16

Key Secondary Endpoints at Week 16:
- vIGA-AD of 0 or 1 with ≥ 2-point reduction from baseline (vIGA-AD 0/1)
- EASI-75, -90, -50
- Itch NRS, Pain NRS, DLQI response defined as ≥ 4-point reduction from baseline
- ADCT response defined as ≥ 5-point reduction from baseline
- ADSS Q1 response defined as ≥ 1.25-point reduction in weekly average score from baseline
- Mean % Body Surface Area (BSA) improvement

- **Primary Estimand Analysis:** MITT patients who used rescue therapy outside protocol specifications or who discontinued treatment due to lack of efficacy were considered **NONRESPONDERS** (using baseline observation carry forward (BLOCF) for continuous endpoints, and non responder imputation for binary endpoints), regardless of observed clinical response; data after patients who discontinued due to other reasons are set to missing and all missing data are imputed using the multiple imputation method.
- **As Observed Analysis:** Data for patients escaped at Week 16 from placebo in Induction with ongoing open label REZPEG 24 µg/kg q2w treatment are summarized using observed data.

Statistical Analysis Methods
- The Primary Estimand analysis for continuous endpoints of % EASI improvement and % BSA improvement use a mixed model for repeated measures (MMRM) to estimate the treatment difference between dose arms and placebo
- The Primary Estimand analysis for binary endpoints (vIGA-AD 0/1, EASI-75, EASI-90, EASI-50, Itch NRS, Pain NRS, DLQI, ADCT, ADSS Q1 response) use a logistic regression model to estimate the treatment difference between dose arms and placebo

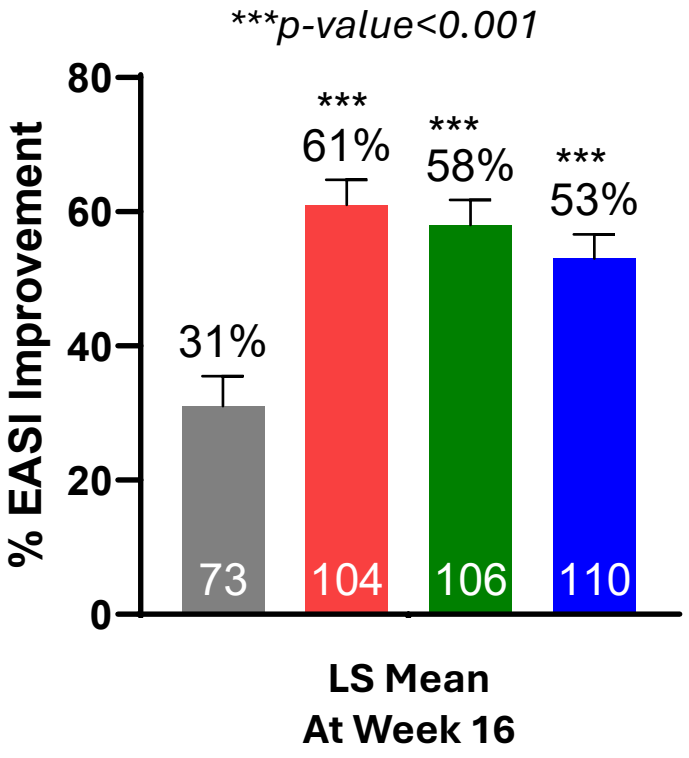
EASI: Eczema Area and Severity Index; vIGA-AD: Validated Investigators Global Assessment for Atopic Dermatitis; NRS: Numerical Rating Scale; DLQI: Dermatology Life Quality Index; ADCT: Atopic Dermatitis Control Tool; ADSS: Atopic Dermatitis Sleep Scale

REZOLVE-AD: Baseline Demographics

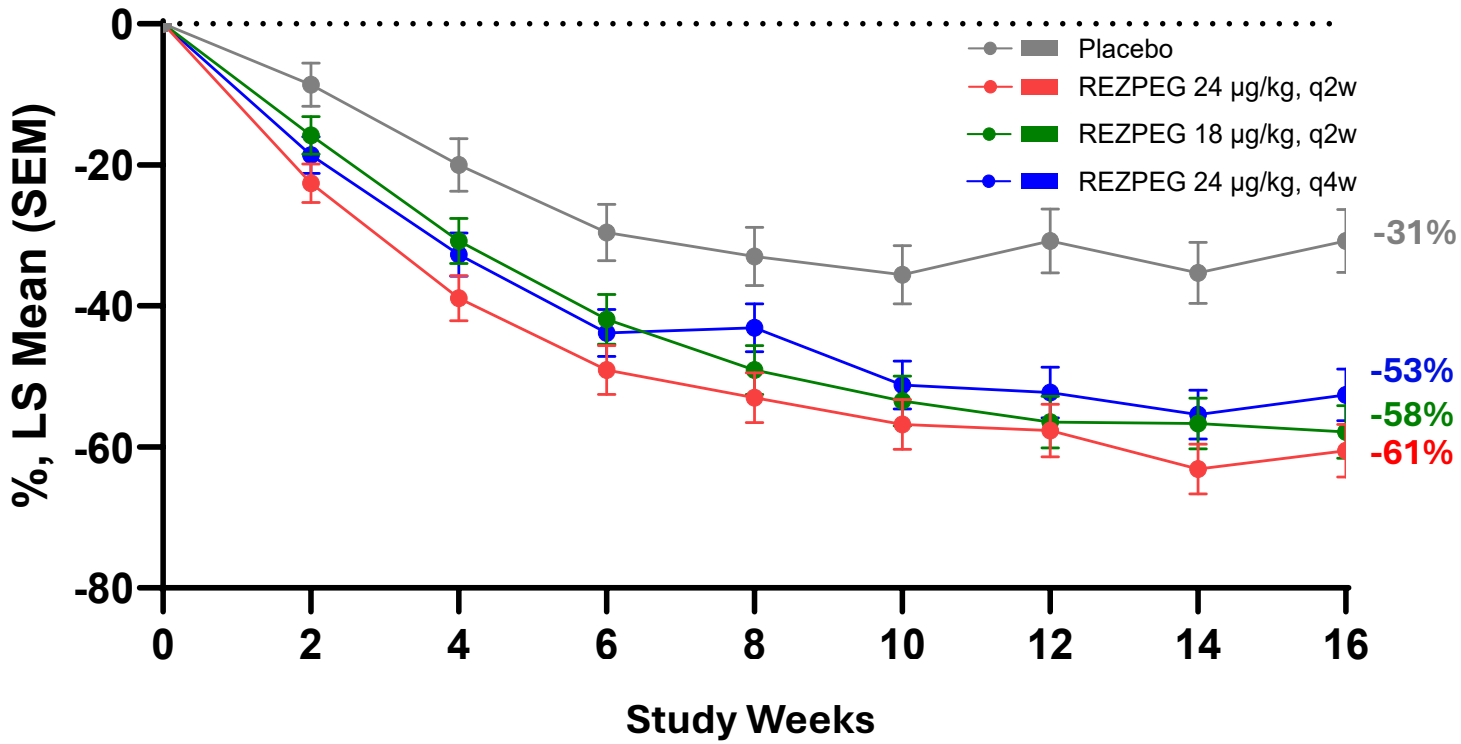
	Placebo q2w (N = 73)	Rezpeg 24 µg/kg q2w (N = 104)	Rezpeg 18 µg/kg q2w (N = 106)	Rezpeg 24 µg/kg q4w (N = 110)
Age, Mean (SD)	37.9 (14.39)	38.0 (13.73)	36.3 (15.41)	36.5 (14.30)
Sex, Female, n (%)	35 (47.9%)	49 (47.1%)	56 (52.8%)	63 (57.3%)
Race, White, n (%)	58 (79.5%)	87 (83.7%)	90 (84.9%)	96 (87.3%)
Region, North America (US/Canada)	21 (28.8%)	27 (26.0%)	29 (27.4%)	31 (28.2%)
vIGA-AD: 4-Severe, n (%)	22 (30.1%)	33 (31.7%)	36 (34.0%)	35 (31.8%)
EASI:				
Mean (SD)	25.2 (8.57)	25.4 (9.14)	27.2 (10.40)	26.1 (10.45)
≥21, n (%)	44 (60.3%)	60 (57.7%)	63 (59.4%)	66 (60.0%)
BSA (%), Mean (SD)	38.2 (19.7)	39.3 (18.8)	40.7 (20.9)	39.6 (20.6)
Itch NRS score				
Mean (SD)	6.3 (2.2)	6.8 (2.0)	6.7 (1.9)	7.1 (1.8)
≥4, n (%)	63 (86.3%)	95 (91.3%)	92 (86.8%)	102 (92.7%)
Pain NRS score				
Mean (SD)	5.4 (2.6)	5.9 (2.5)	5.9 (2.5)	6.2 (2.4)
≥4, n (%)	50 (68.5%)	84 (80.8%)	82 (77.4%)	90 (81.8%)
DLQI score				
Mean (SD)	13.4 (7.1)	14.5 (7.2)	13.8 (7.3)	15.9 (7.1)
≥4, n (%)	65 (89.0%)	100 (96.2%)	102 (96.2%)	107 (97.3%)
ADCT score				
Mean (SD)	14.5 (5.7)	15.4 (4.9)	15.5 (5.3)	16.3 (5.0)
≥5, n (%)	67 (91.8%)	101 (97.1%)	104 (98.1%)	107 (97.3%)
ADSS Q1 score				
Mean (SD)	1.8 (1.2)	1.9 (1.1)	2.0 (1.2)	2.1 (1.0)
≥1.25, n (%)	45 (61.6%)	71 (68.3%)	70 (66.0%)	85 (77.3%)

Dose Dependent % EASI Reduction, Clear Separation from Placebo at All Timepoints for Study Treatment Arms

All dose arms met primary endpoint with statistical significance p-value <0.001



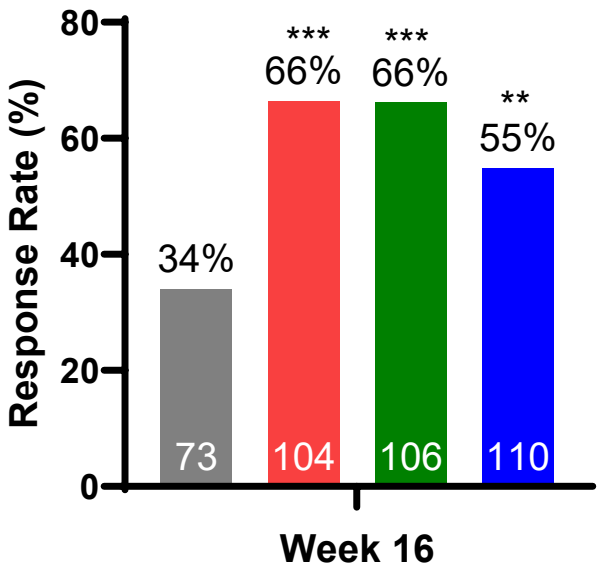
% EASI Reduction from Baseline (Primary Estimand)



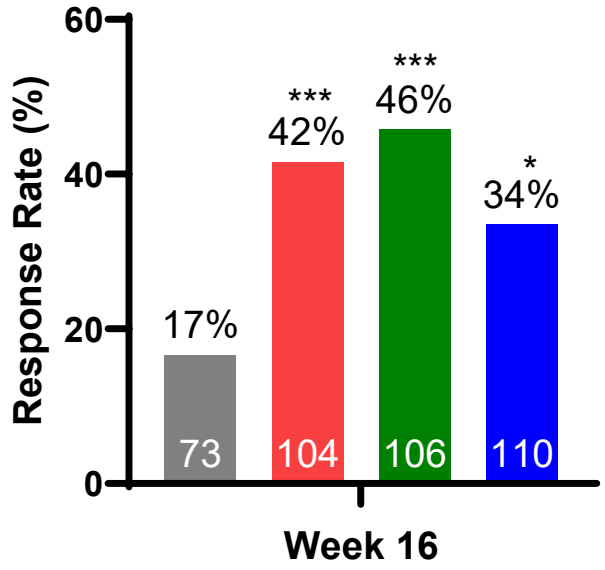
High Dose Met All Key Secondary Endpoints

Multiple endpoints met for 2 additional dose arms

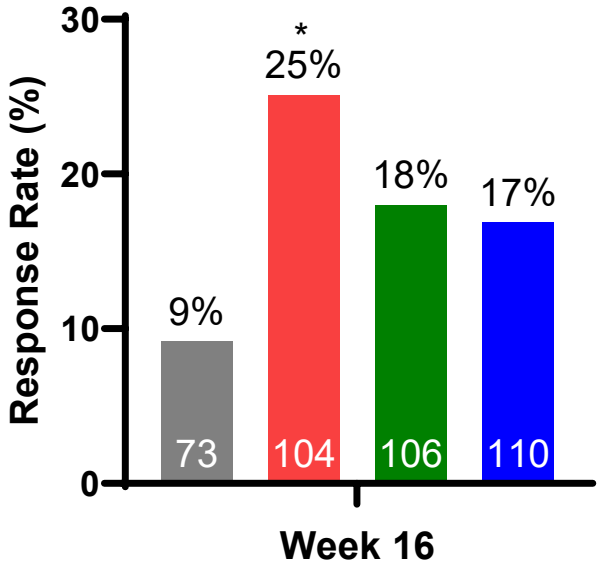
EASI-50



EASI-75



EASI-90



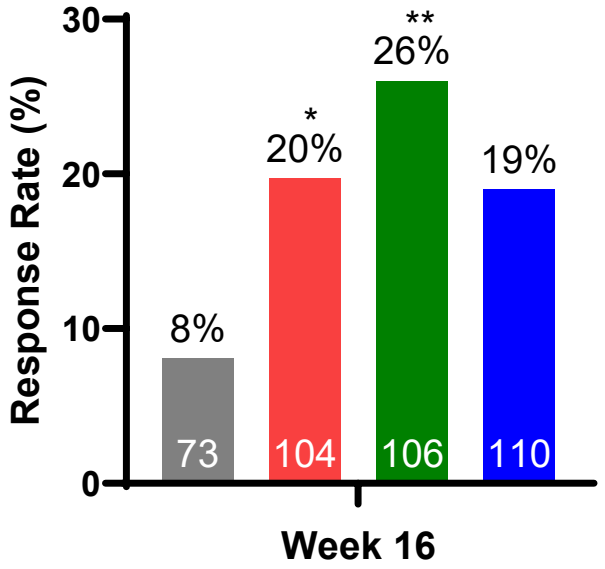
****p-value<0.001*
***p-value<0.01*
**p-value<0.05*

- Placebo
- REZPEG 24 µg/kg, q2w
- REZPEG 18 µg/kg, q2w
- REZPEG 24 µg/kg, q4w

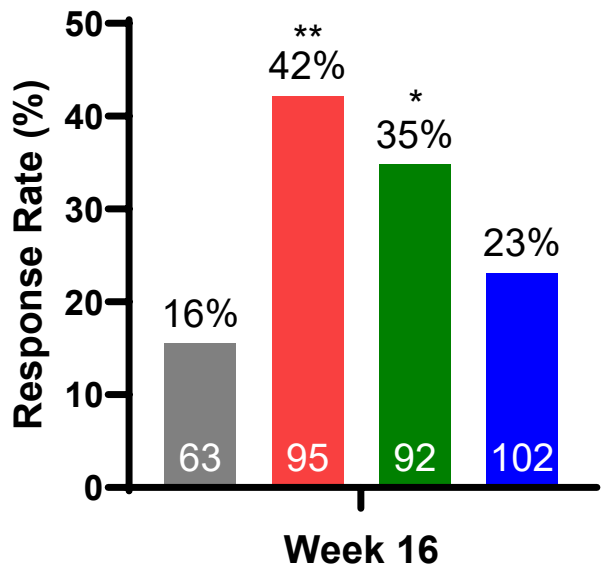
High Dose Met All Key Secondary Endpoints

Multiple endpoints met for 2 additional dose arms

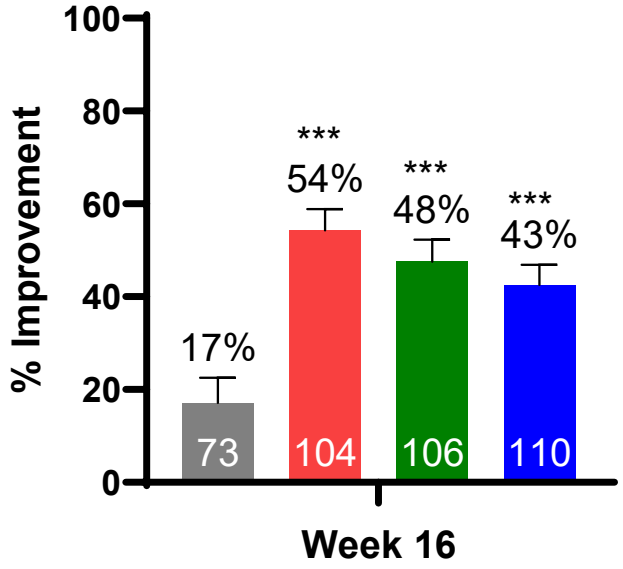
vIGA-AD 0/1
(≥ 2-point reduction)



Itch NRS
(≥ 4-point reduction)



BSA
(% Improvement)



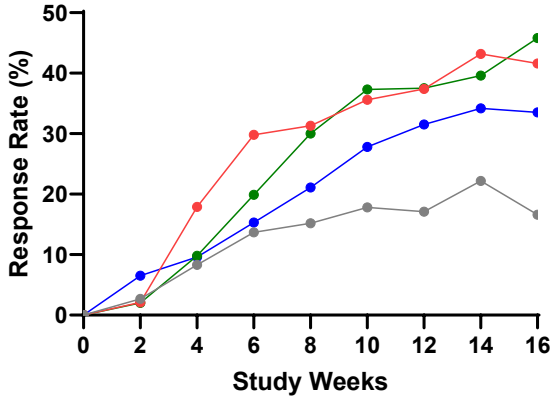
****p-value<0.001*
***p-value<0.01*
**p-value<0.05*

- Placebo
- REZPEG 24 µg/kg, q2w
- REZPEG 18 µg/kg, q2w
- REZPEG 24 µg/kg, q4w

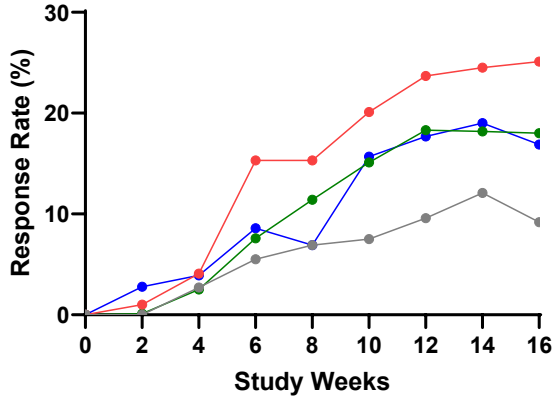
Sample size for Itch NRS response is based on patients with baseline Itch NRS ≥ 4

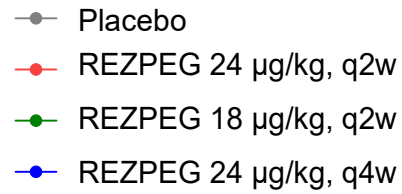
Fast Onset of Action Across All Key Secondary Endpoints

EASI-75

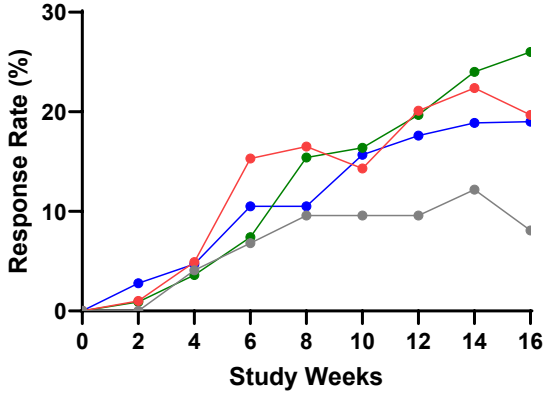


EASI-90

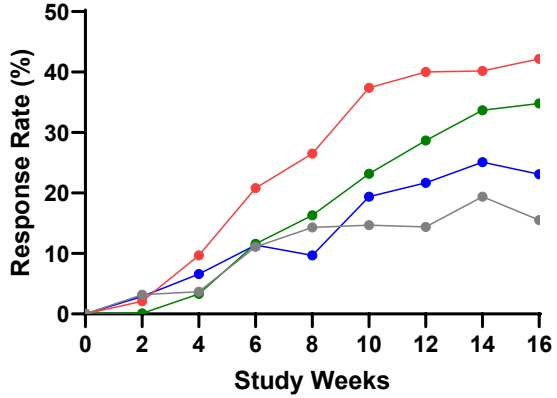




vIGA-AD 0/1



Itch NRS
(≥ 4-point reduction)

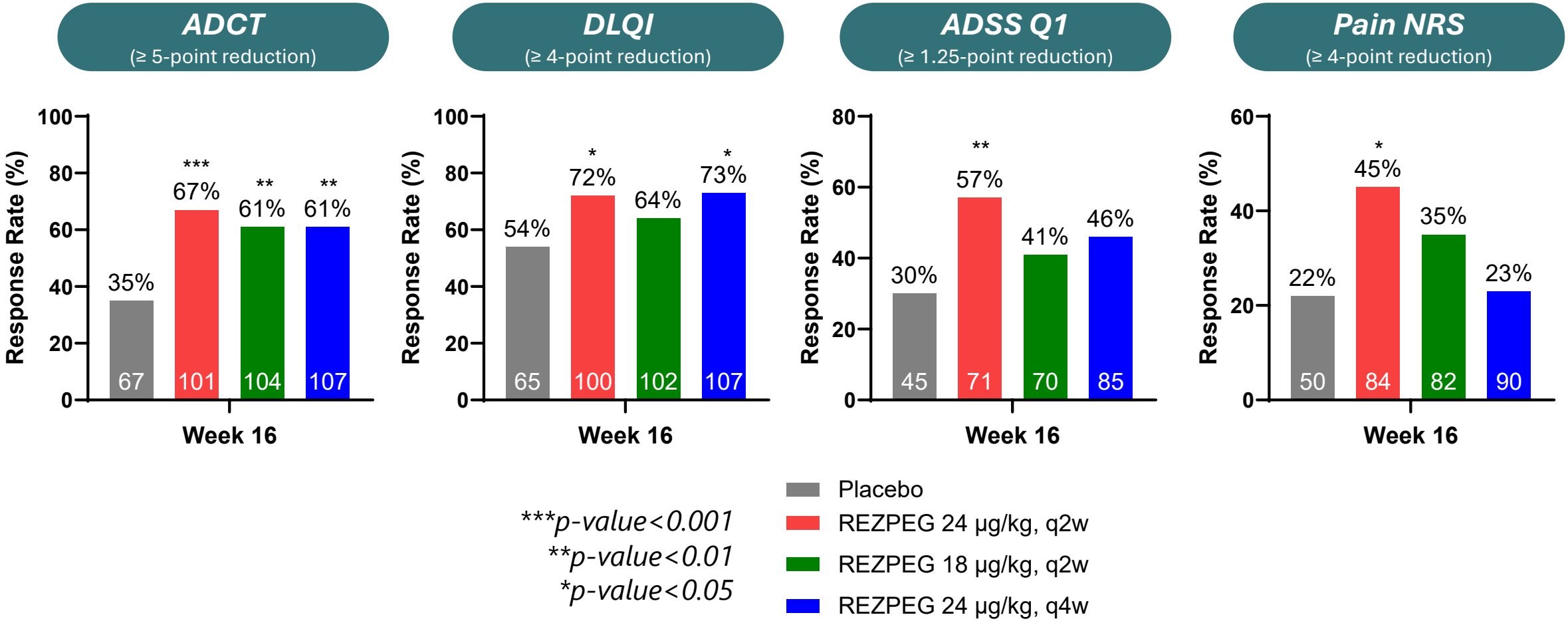


For EASI-75, vIGA-AD 0/1, and EASI-90: N = 73, 104, 106, and 110 for placebo, 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w

For Itch NRS: N=63, 95, 92, and 102 for the placebo, 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w groups

High Dose Met All Key Patient-Reported Outcomes

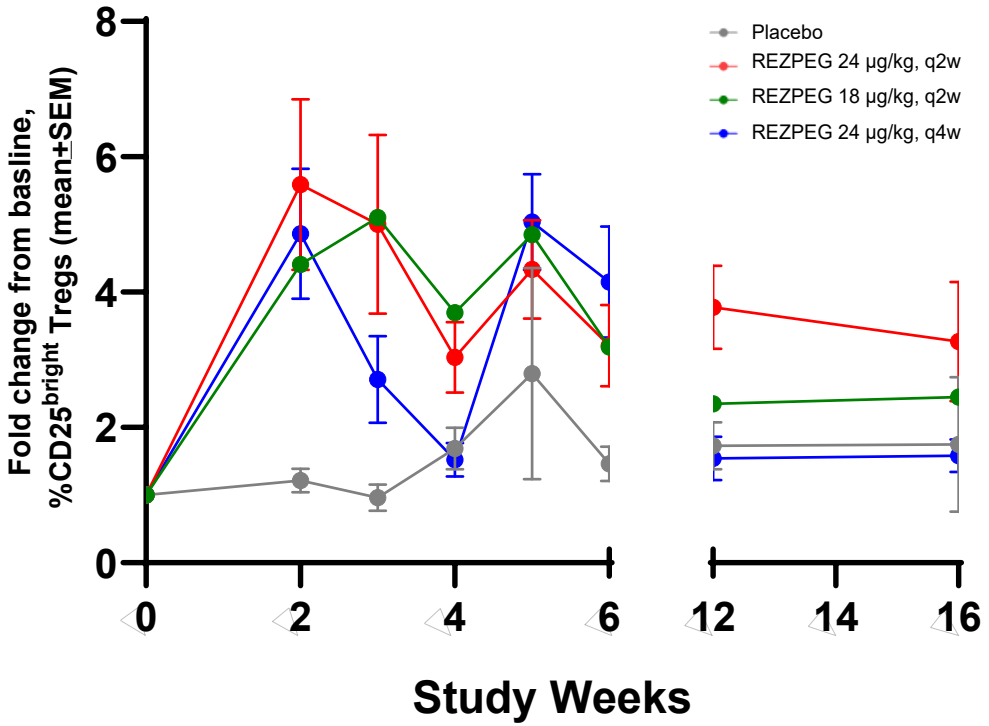
Multiple endpoints met in 2 additional dose arms



Sample size for ADCT response is based on patients with baseline ADCT ≥ 5; Sample size for DLQI response is based on patients with baseline DLQI ≥ 4;
Sample size for ADSS Q1 response is based on patients with baseline ADSS Q1 ≥ 1.25; Sample size for Pain NRS response is based on patients with baseline Pain NRS ≥ 4

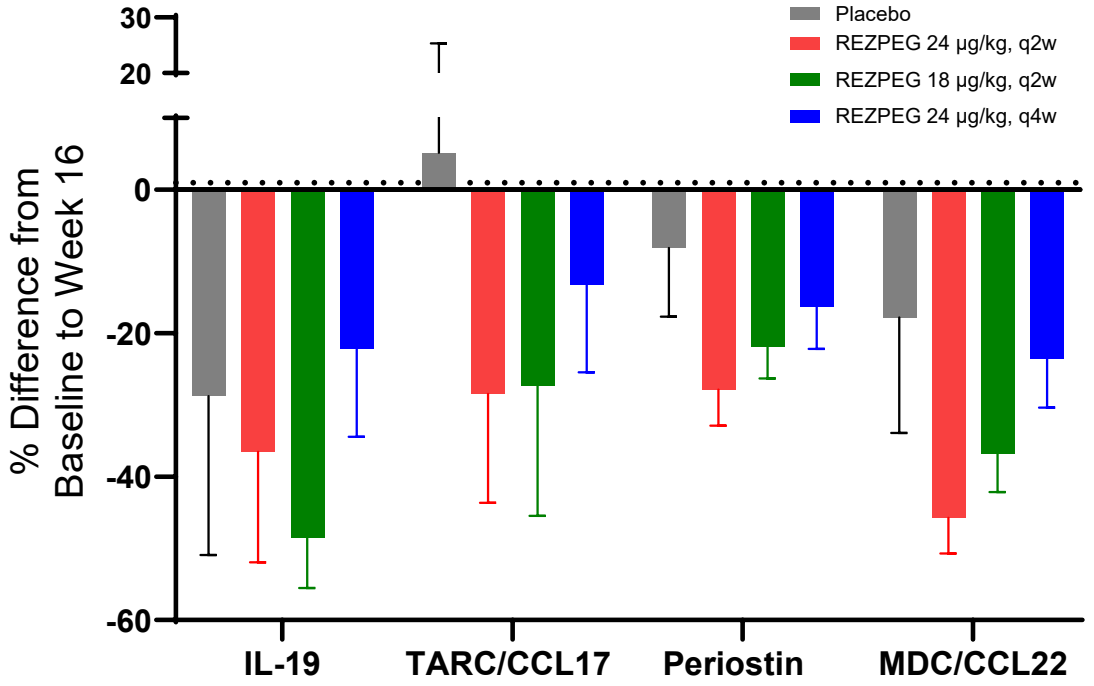
Dose Dependent Increase in Tregs and Reduction in Th2 Inflammation

Up to 6-fold increase in T-reg consistent with prior studies of REZPEG. Tregs elevated above baseline over entire dose interval on q2w schedule



▲ Administration q4w dosed on w0, w4, w8, w12, and w16

Dose dependent reduction in TARC/CCL17, Periostin, MDC/CCL22, and IL-19*

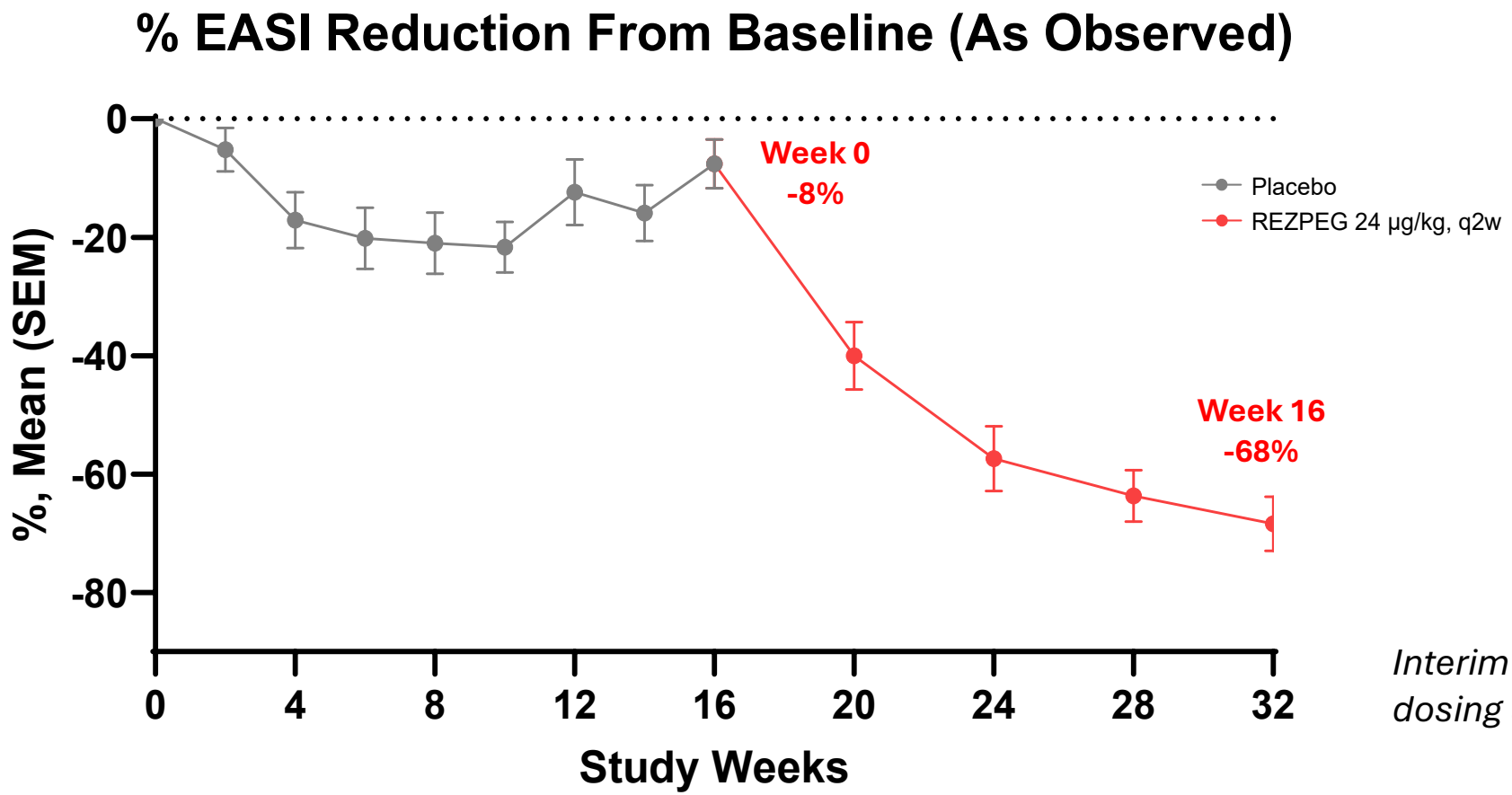


Patients with baseline values >ULN included in the analysis

* Key markers associated with atopic dermatitis: 2021 Renert-Yuval et. al. https://doi.org/10.1016/j.jaci.2021.01.013; 2019 Konrad et. al. https://rdcu.be/eq5C3

Crossover from Placebo to Rezpegaldesleukin at Study Week 16

Rapid efficacy observed through 16 weeks of dosing at 24 µg/kg q2w in the open label escape arm

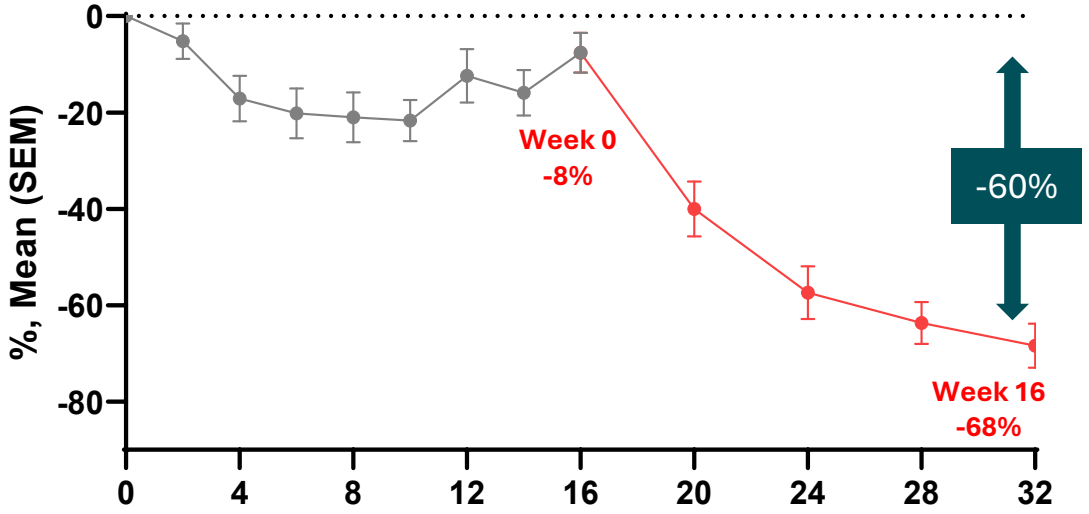


Interim analysis (18Aug2025 data cut), dosing up to study week 52 is ongoing.

									Crossover				
Study Weeks	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**
Placebo, N	42	42	41	42	42	42	42	42	42	40	39	39	36

Crossover from Placebo to Rezpegaldesleukin at Week 16

Open label escape arm results for 24 µg/kg q2w are comparable to the blinded 16-week induction

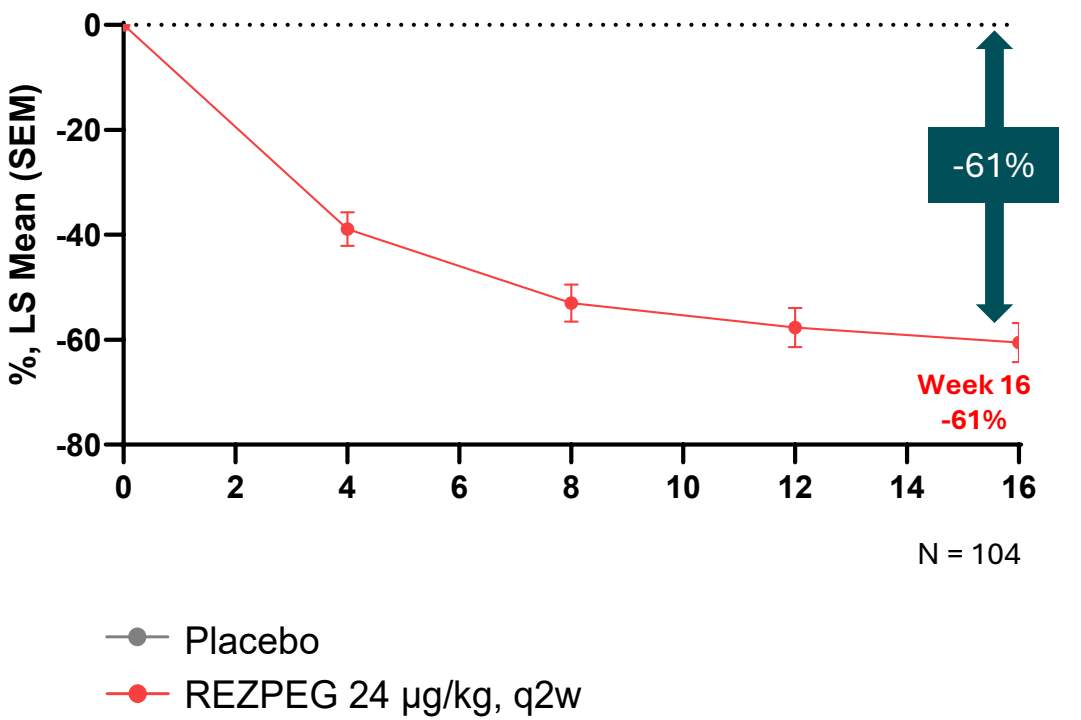


Crossover

Study Weeks	0	2	4	6	8	10	12	14	16	20	24	28	32
Placebo, N	42	42	41	42	42	42	42	42	42	40	39	39	36

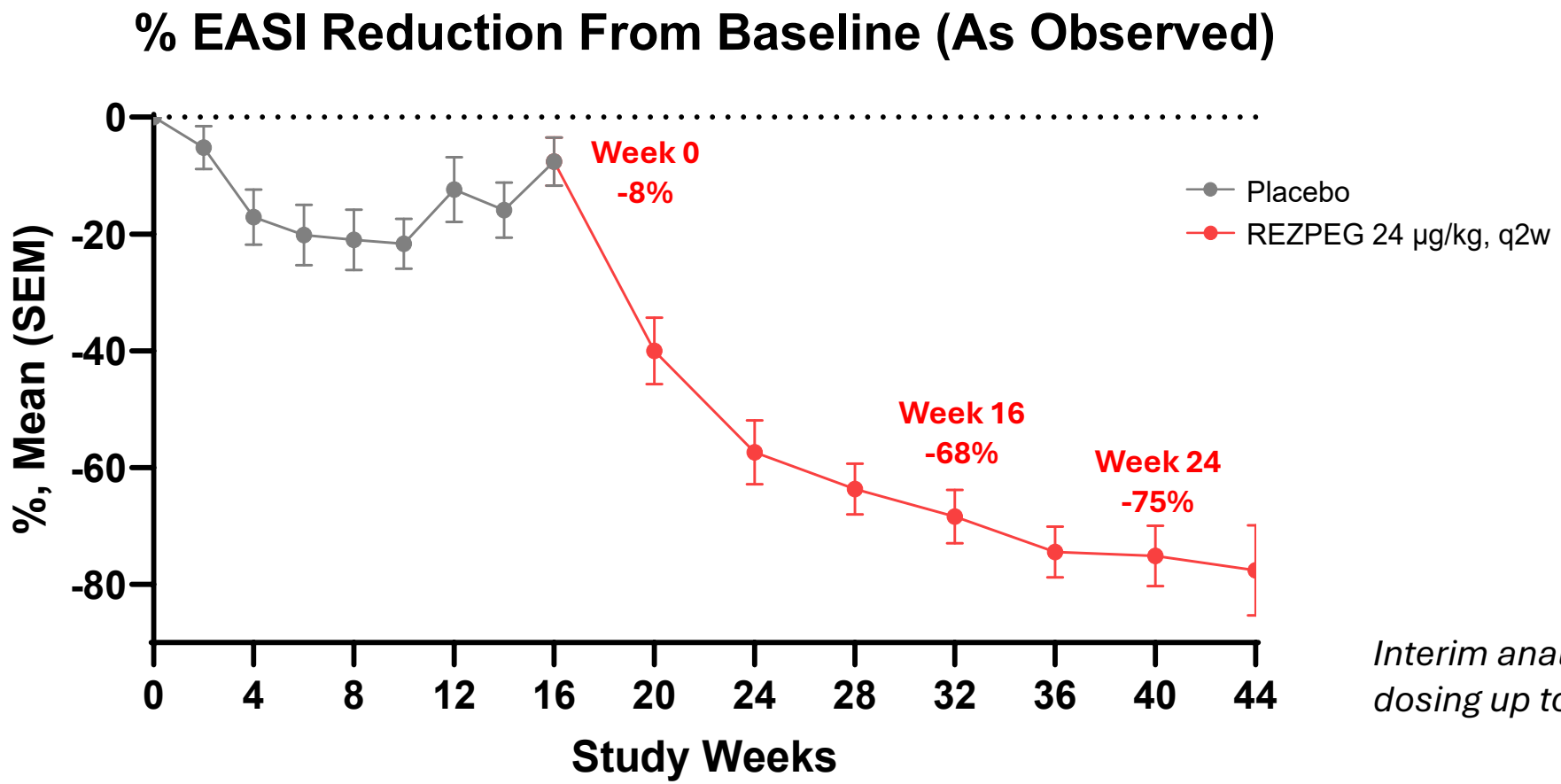
Interim analysis (18Aug2025 data cut), dosing up to study week 52 is ongoing.

For comparison



Crossover from Placebo to Rezpegaldesleukin at Week 16

Increased clinical benefit in EASI observed with extended dosing beyond 16 weeks of rezpegaldesleukin 24 µg/kg q2w



Interim analysis (18Aug2025 data cut), dosing up to study week 52 is ongoing.

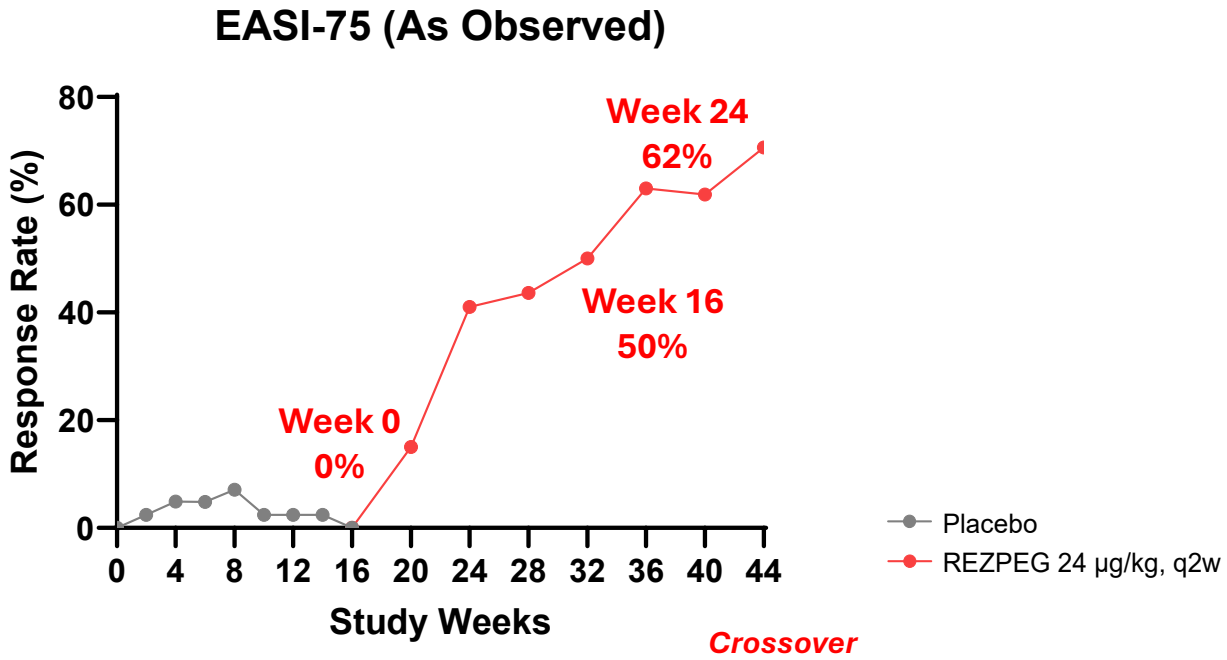
Crossover

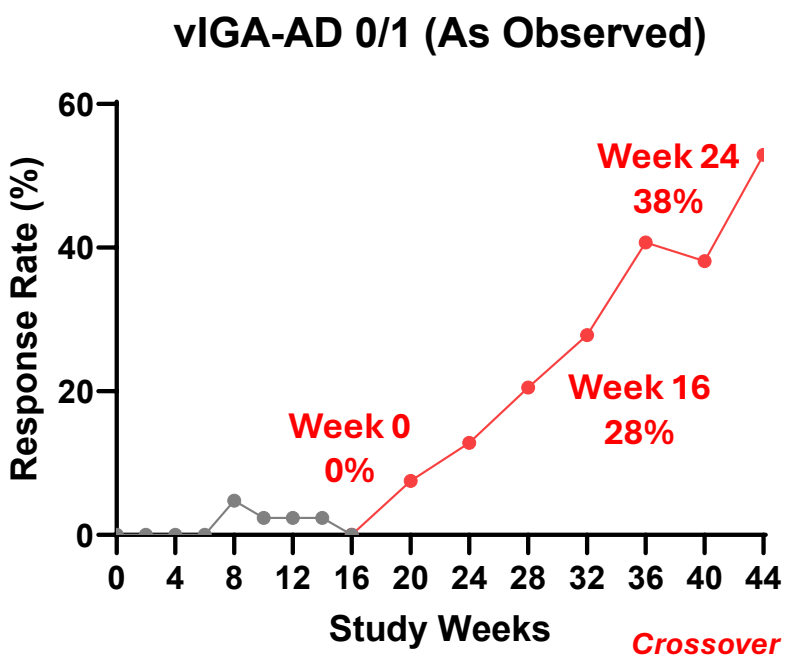
Study Weeks	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44
Placebo, N	42	42	41	42	42	42	42	42	42	40	39	39	36	27	21	17

As of 18Aug2025 data cut; 8 patients have discontinued up to week 44 (patient decision most common reason) and 16 patients have not yet reached week 44. Note 1 patient had missing data at week 44 but is ongoing and has data at later timepoints.

Crossover from Placebo to Rezpegaldesleukin at Week 16

Increased EASI-75 and vIGA-AD 0/1 efficacy observed with extended dosing beyond week 16





Study Weeks	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44
Responses, n	0	1	2	2	3	1	1	1	0	6	16	17	18	17	13	12
Placebo, N	42	42	41	42	42	42	42	42	42	40	39	39	36	27	21	17

Study Weeks	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44
Responses, n	0	0	0	0	2	1	1	1	0	3	5	8	10	11	8	9
Placebo, N	42	42	41	42	42	42	42	42	42	40	39	39	36	27	21	17

Interim analysis (18Aug2025 data cut), dosing up to study week 52 is ongoing.

As of 18Aug2025 data cut; 8 patients have discontinued up to week 44 (patient decision most common reason) and 16 patients have not yet reached week 44. Note 1 patient had missing data at week 44 but is ongoing with data at later timepoints.

Overall Summary of Treatment Emergent Adverse Events

16-Week Induction Period

	Placebo q2w N = 73	Rezpeg 24 µg/kg q2w N = 104	Rezpeg 18 µg/kg q2w N = 106	Rezpeg, 24 µg/kg q4w N = 110	Rezpeg Total N = 320
Patients With at Least One TEAE	42 (57.5%)	89 (85.6%)	78 (73.6%)	90 (81.8%)	257 (80.3%)
Patients With at Least One TEAE (Excluding ISRs)	42 (57.5%)	69 (66.3%)	60 (56.6%)	64 (58.2%)	193 (60.3%)
Patients With at Least One Serious TEAE	0	1 (1.0%)	4 (3.8%)	0	5 (1.6%)
Patients With at Least One Severe TEAE	1 (1.4%)	3 (2.9%)	6 (5.7%)	1 (0.9%)	10 (3.1%)
Patients With at Least One TEAE Leading to Death*	0	0	0	0	0
TEAEs by System Organ Class and Preferred Term Over ≥ 5% in Any Arm					
General disorders and administration site conditions	7 (9.6%)	80 (76.9%)	67 (63.2%)	78 (70.9%)	225 (70.3%)
Injection site reaction	3 (4.1%)	79 (76.0%)	66 (62.3%)	78 (70.9%)	223 (69.7%)
Proportion of ISR events-mild (%)	100%	65.5%	70.7%	69.9%	68.3%
Proportion of ISR events-moderate (%)	0%	33.9%	28.9%	30.1%	31.3%
Proportion of ISR events-severe (%)	0%	0.6%	0.4%	0%	0.4%
Pyrexia	2 (2.7%)	11 (10.6%)	5 (4.7%)	4 (3.6%)	20 (6.3%)
Infections and infestations	25 (34.2%)	29 (27.9%)	39 (36.8%)	32 (29.1%)	100 (31.3%)
Nasopharyngitis	10 (13.7%)	10 (9.6%)	14 (13.2%)	14 (12.7%)	38 (11.9%)
Upper respiratory tract infection	4 (5.5%)	7 (6.7%)	8 (7.5%)	4 (3.6%)	19 (5.9%)
Blood and lymphatic system disorders	3 (4.1%)	29 (27.9%)	6 (5.7%)	11 (10.0%)	46 (14.4%)
Eosinophilia**	2 (2.7%)	17 (16.3%)	4 (3.8%)	4 (3.6%)	25 (7.8%)
Lymphadenopathy	0	7 (6.7%)	1 (0.9%)	3 (2.7%)	11 (3.4%)
Musculoskeletal and connective tissue disorders	3 (4.1%)	19 (18.3%)	5 (4.7%)	11 (10.0%)	35 (10.9%)
Arthralgia	1 (1.4%)	10 (9.6%)	2 (1.9%)	4 (3.6%)	16 (5.0%)
Skin and subcutaneous tissue disorders	8 (11.0%)	12 (11.5%)	10 (9.4%)	13 (11.8%)	35 (10.9%)
Worsening atopic dermatitis	7 (9.6%)	2 (1.9%)	5 (4.7%)	6 (5.5%)	13 (4.1%)
Nervous system disorders	6 (8.2%)	10 (9.6%)	10 (9.4%)	9 (8.2%)	29 (9.1%)
Headache	3 (4.1%)	8 (7.7%)	6 (5.7%)	6 (5.5%)	20 (6.3%)
Gastrointestinal disorders	3 (4.1%)	8 (7.7%)	7 (6.6%)	11 (10.0%)	26 (8.1%)
Respiratory, thoracic and mediastinal disorders	1 (1.4%)	6 (5.8%)	5 (4.7%)	5 (4.5%)	16 (5.0%)
Investigations	1 (1.4%)	6 (5.8%)	4 (3.8%)	3 (2.7%)	13 (4.1%)

*Following 16-week induction, one death in a 38 y/o female occurred in the escape arm due to coronary thrombosis/heart failure. Patient had multiple, overlapping pre-existing cardiovascular risk factors. The death was assessed as unrelated to study treatment by the Sponsor Drug Safety Committee and independent external experts; **Eosinophilia was reported by the investigator based on the laboratory value being above the upper limit of normal. Only one patient discontinued in the study (at the mid-dose of 18 mg/kg q2w) due to increased eosinophil count.

Novel Mechanism of Action with Differentiated Safety Profile

16-Week Induction Period

No observed safety signal for:

- ❑ Conjunctivitis
- ❑ Facial swelling or erythema
- ❑ Oral (aphthous) ulcers
- ❑ Asthma
- ❑ Myocardial infarction
- ❑ Pulmonary embolus (PE)
- ❑ Deep venous thrombosis (DVT)
- ❑ Malignancy
- ❑ Depression / suicidality

No increased risk of conjunctivitis, oral ulcers, asthma, infections or MACE

Summary

- High dose rezpegaldesleukin demonstrated significant improvement over placebo during the 16-Week induction in:
  - Primary: EASI LS Mean Percent Change ($p<0.001$)
  - Key Secondary: EASI-75 ($p<0.001$), vIGA-AD 0/1 ($p<0.05$), Itch NRS ($p<0.01$), EASI-90 ($p<0.05$), BSA ($p<0.001$)
  - Additional PROs: ADCT response ($p<0.001$), DLQI response ($p<0.05$), ADSS Q1 response ($p<0.01$), Pain NRS response ($p<0.05$)
- Other dose levels demonstrated significant improvement in multiple endpoints
- Substantial improvement in primary and key secondary endpoints with 24-weeks of open label escape therapy, as compared to 16-weeks
- Safety consistent with previously-reported safety profile with no new safety concerns in study treatment arms
  - No increased risk of conjunctivitis, oral ulcers, or infections, including oral herpes
  - Most frequent AEs were mild injection site reactions (ISRs) that were self-resolving (<1% discontinuations due to ISRs)

Conclusions

- First large study to validate the Treg MOA and therapeutic potential of rezpegaldesleukin, an IL-2 agonist, in moderate-to-severe atopic dermatitis
- Upcoming data readouts from this ongoing AD study:
  - Maintenance data (comparing q4w vs. q12w regimens) is expected 1Q2026
  - 1-year off-treatment data is expected 1Q2027
- Additional data readouts from the rezpegaldesleukin clinical program:
  - Phase 2b 36-week treatment data in severe alopecia areata expected in December 2025
- **Next steps: Phase 3 planning for moderate to severe atopic dermatitis is underway**

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