Rezpegaldesleukin, Novel Treg-Inducing Therapy, Demonstrates Efficacy in Atopic Dermatitis and Asthma in Phase 2b Trial

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Presenter and Conflicts

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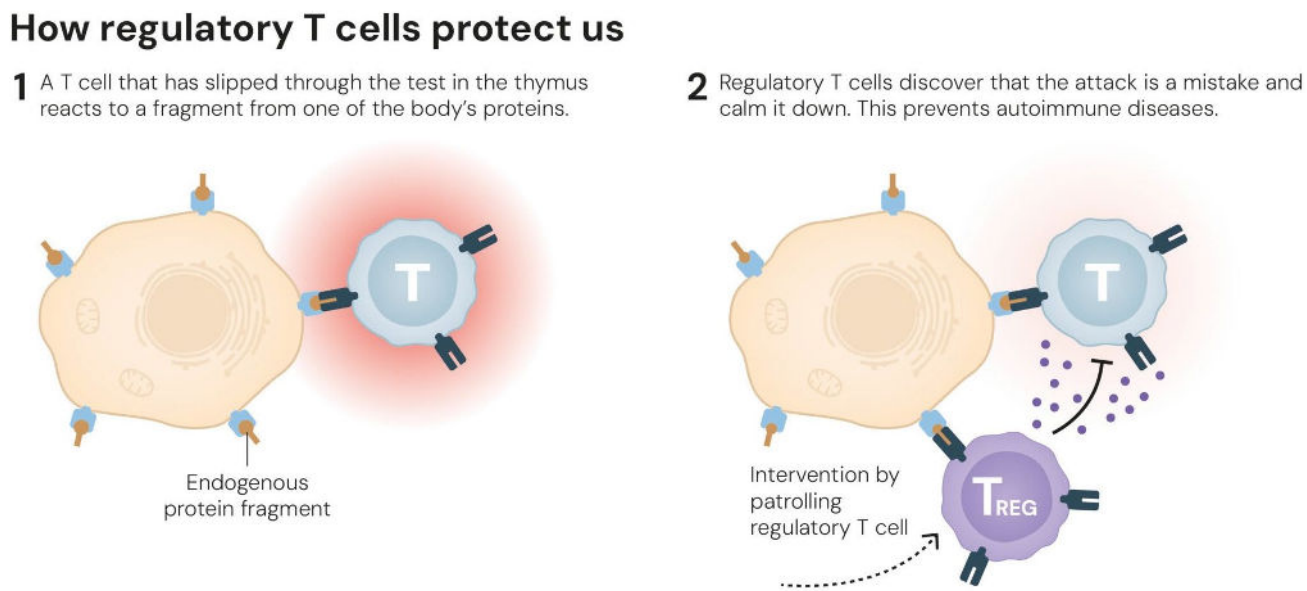
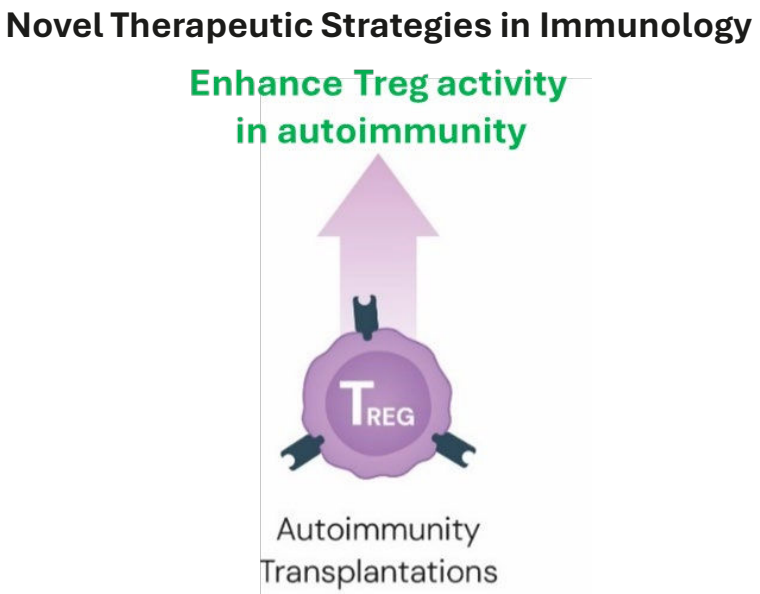
- Consultant: Arcutis Biotherapeutics, Nektar Therapeutics and Palvella Therapeutics
- Advisory Board: Arcutis Biotherapeutics and Incyte Corp.
- Scientific Advisory Board: Palvella Therapeutics

Regulatory T Cells and Peripheral Immune Tolerance: “Immune System’s Security Guards”

Discovery Served as Basis for 2025 Nobel Prize in Physiology and Medicine and MOA Represents a Novel Therapeutic Target



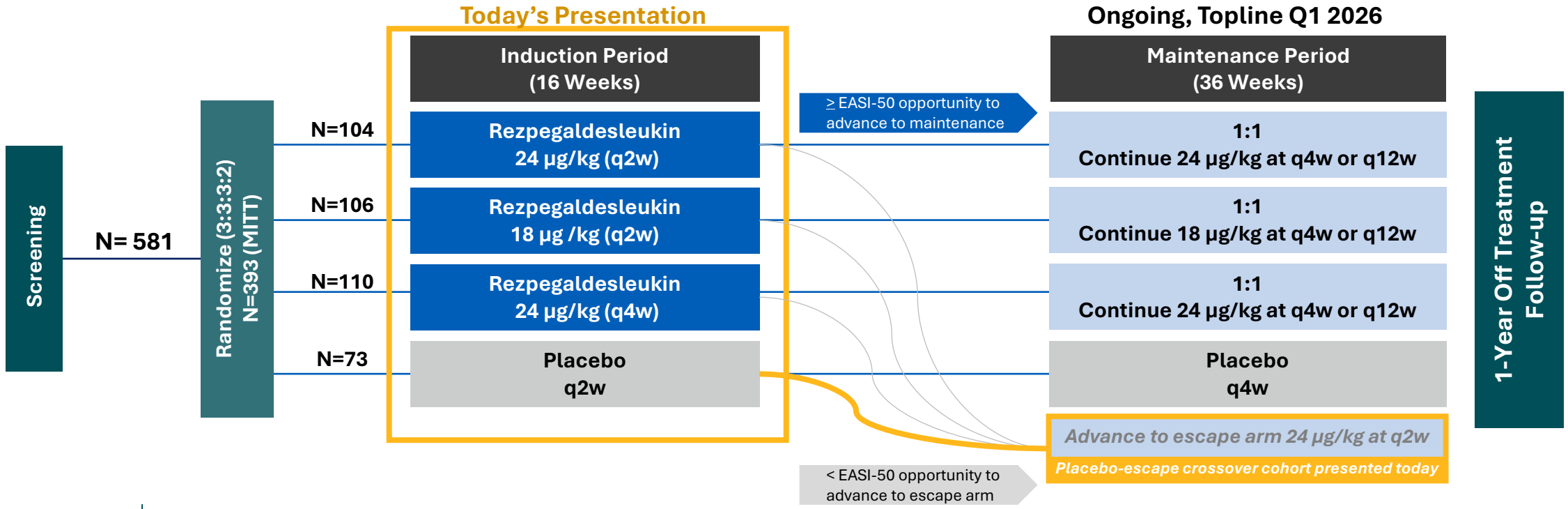


- In a landmark 1995 study, Dr. Sakaguchi and colleagues showed that IL-2 receptor alpha chain expressing $CD4^+$ T lymphocytes possessed immune regulatory functions
- Rezpegaldesleukin is an IL-2 receptor agonist that:
  - *In vivo* selectively expands and enhances the function of regulatory T cells (Tregs)
  - Demonstrated efficacy in patients with moderate to severe atopic dermatitis

https://www.nobelprize.org/prizes/medicine/2025/popular-information/, accessed 16Oct2025, citing Silverberg, *et al. Nature Comm* (2024) 15:9230; Fanton *et al. J. Translational Autoimmunity* (2022) 5:100152.

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-naive
- Failure of prior therapy, including TCS of medium or higher potency, within last 6 months

Primary Endpoints:

Mean % EASI improvement at Week 16

Key Secondary Endpoints:

- vIGA-AD of 0 or 1 with ≥ 2-point reduction from baseline
- EASI-75, EASI-90
- Itch NRS (≥ 4-point reduction) in patients with baseline score ≥ 4

Exploratory Endpoints at Week 16:

- Change in ACQ-5 score in patients with self-reported asthma comorbidity with assessment values at baseline and Week 16

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

REZOLVE-AD: Baseline Demographics

- **Atopic Dermatitis and Asthma:** Both are common atopic diseases characterized by immune dysregulation and allergic inflammation.[1]
- **Epidemiological Evidence:** Approximately 25% of patients with atopic dermatitis also have asthma, with higher risk observed in children.[2]

	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%)
ACQ-5*				
n	19 (26.0%)	27 (26.0%)	25 (23.6%)	28 (25.5%)
≥0.5, n	8 (11.0%)	12 (11.5%)	16 (15.1%)	17 (15.5%)
≥1.5, n	2 (2.7%)	8 (7.7%)	8 (7.5%)	7 (6.4%)

* Patients with baseline and Week 16 assessments

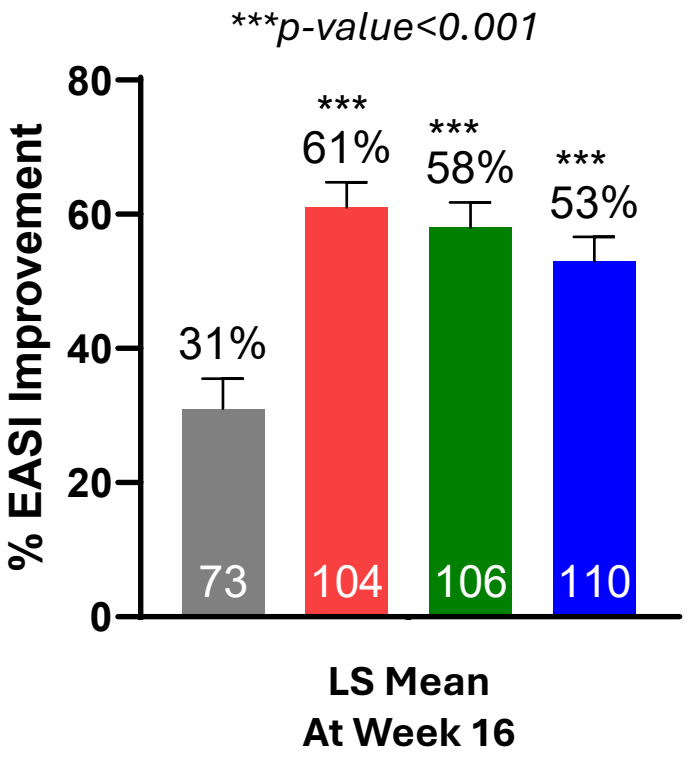
The ACQ-5, or Asthma Control Questionnaire-5, is a standardized five question tool to evaluate the frequency and severity of asthma symptoms, use of rescue medication, and overall control over the past week. The ACQ-5 is widely used by clinicians to monitor asthma management and adjust treatment plans accordingly, providing a quick and reliable measure of disease control.

[1]Spergel, J. M., & Paller, A. S. (2003) *The Journal of Allergy and Clinical Immunology,* 112(6), S118-S124; [2]Williams, H. C., et al. (2004). British Journal of Dermatology, 150(2), 211-219.

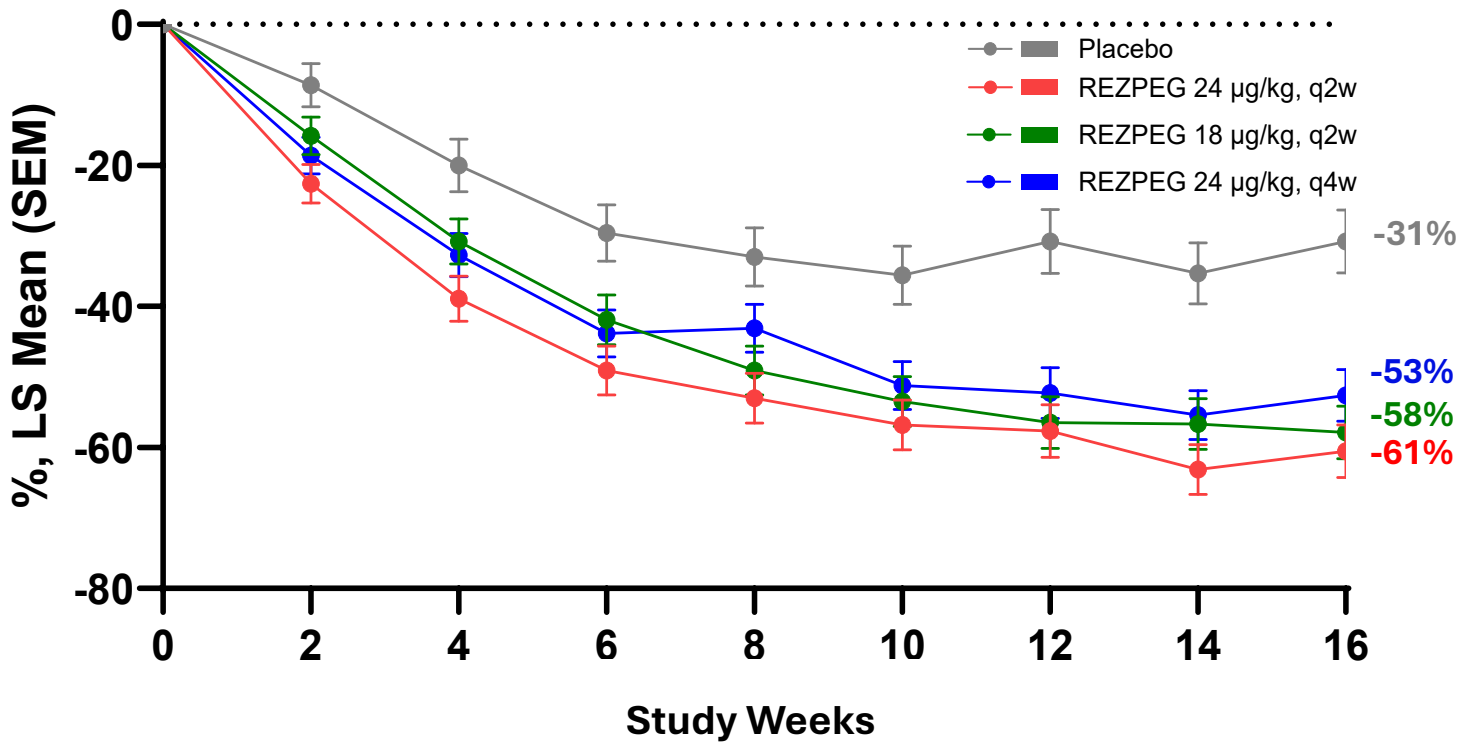
Dose Dependent Percent EASI Reduction

Clear Separation from Placebo at All Timepoints for Study Treatment Arms

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



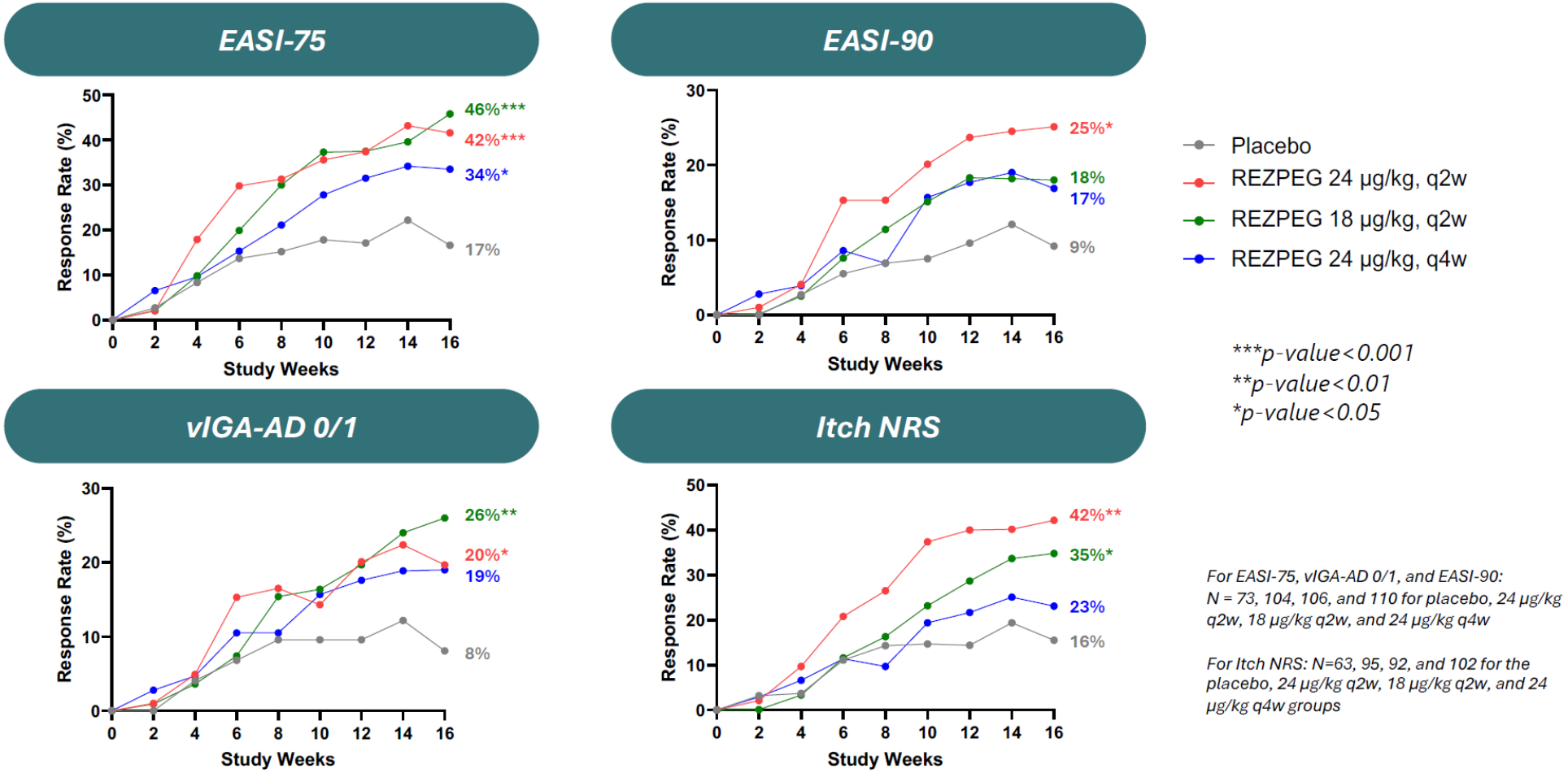
% EASI Reduction from Baseline (Primary Estimand)



The Primary Estimand analysis for % EASI improvement uses a mixed model for repeated measures (MMRM). Data after use of rescue therapy outside protocol specifications or discontinued treatment due to lack of efficacy were imputed using baseline observation carry forward (BLOCF); data after patients who discontinued due to other reasons were set to missing and all missing data are imputed using the multiple imputation method.

Fast Onset of Action Across All Key Secondary Endpoints

EASI-75, EASI-90, vIGA-AD 0/1, and Itch NRS (≥ 4-point Reduction) Responses Seen Early and Sustained Throughout



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

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

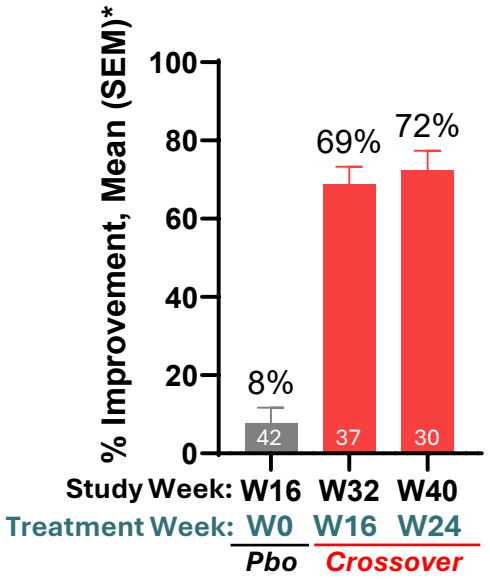
For Itch NRS: N=63, 95, 92, and 102 for the placebo, 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w groups

The Primary Estimand analysis for binary endpoints use logistic regressions. Data after use of rescue therapy outside protocol specifications or discontinued treatment due to lack of efficacy were imputed as non-responders; data after patients who discontinued due to other reasons were set to missing and all missing data are imputed using the multiple imputation method.

Crossover from Placebo to Rezpegaldesleukin at Study Week 16

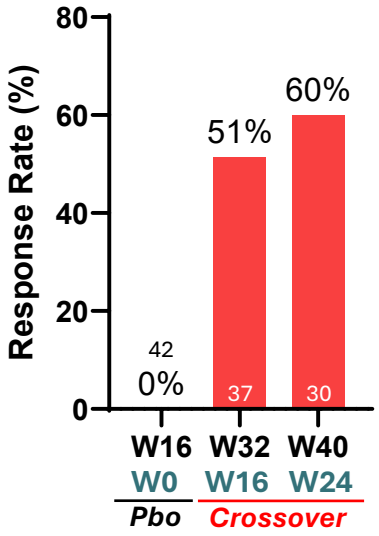
Deepening of Responses in Crossover Arm Support 24-Week Induction and Dose of 24 µg/kg q2w for Phase 3 Program

Mean EASI % Change

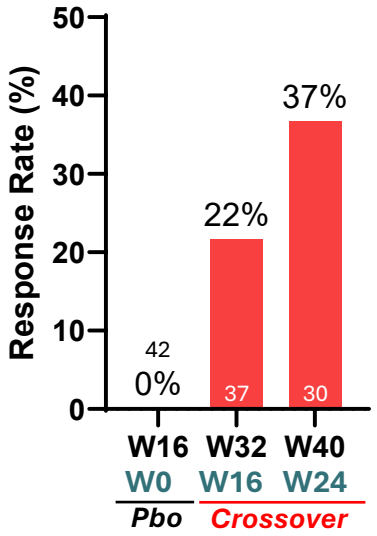


*Mean change from baseline at Week 16/24 post-induction phase of study for patients randomized to placebo and who are EASI<50 at the end of 16-week induction.

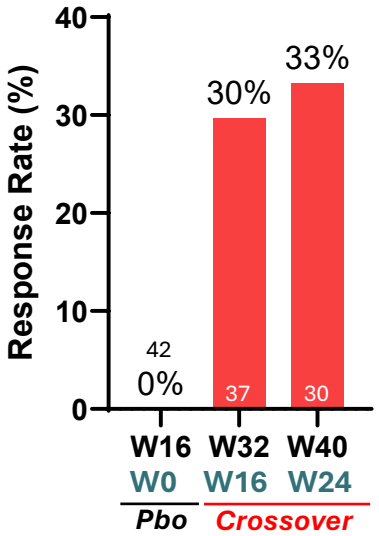
EASI-75



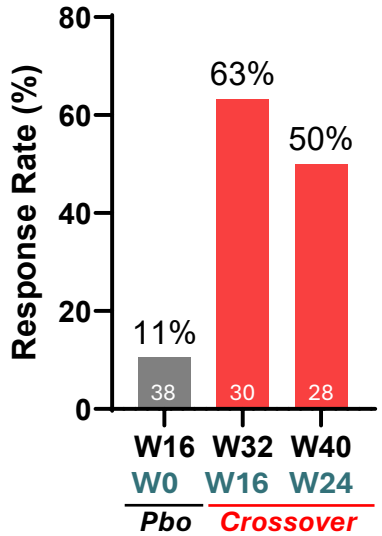
EASI-90



vIGA-AD 0/1



Itch NRS

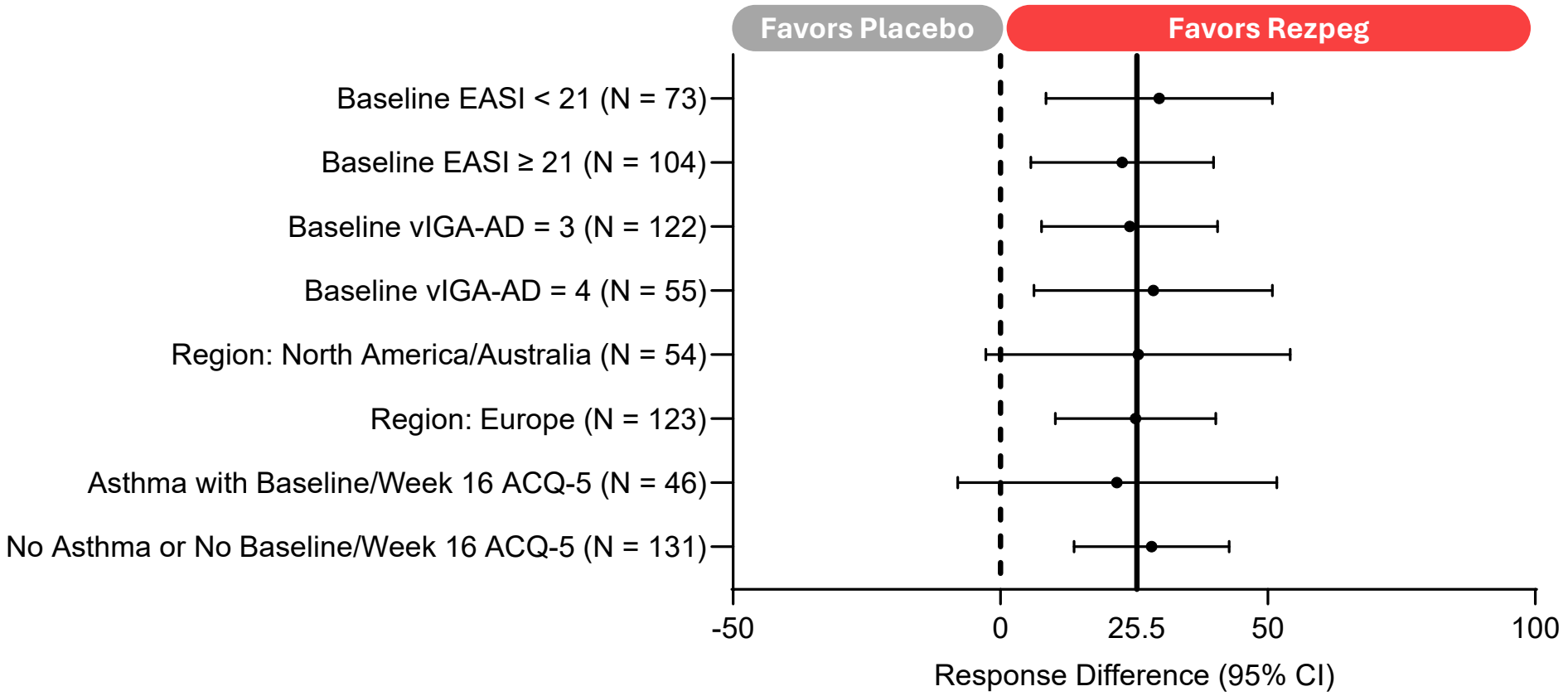


Interim analysis (15Oct2025 data cut), dosing up to study week 52 is ongoing.

As of 15Oct2025 data cut, 7 patients have discontinued up to week 24 (patient decision most common reason) and 1 patient has not yet reached week 24. Note 4 patients have missing data at week 24 but are ongoing and have data at later timepoints. The analysis of Mean EASI % Change for the crossover patients uses descriptive summary measures on observed data. The analysis of binary endpoints (EASI-75, EASI-90, vIGA-AD 0/1, and Itch NRS response) for the crossover patients uses descriptive summaries and number of patients with observed data as denominator.

EASI-75 Response for Rezpegaldesleukin 24 µg/kg q2w vs. Placebo

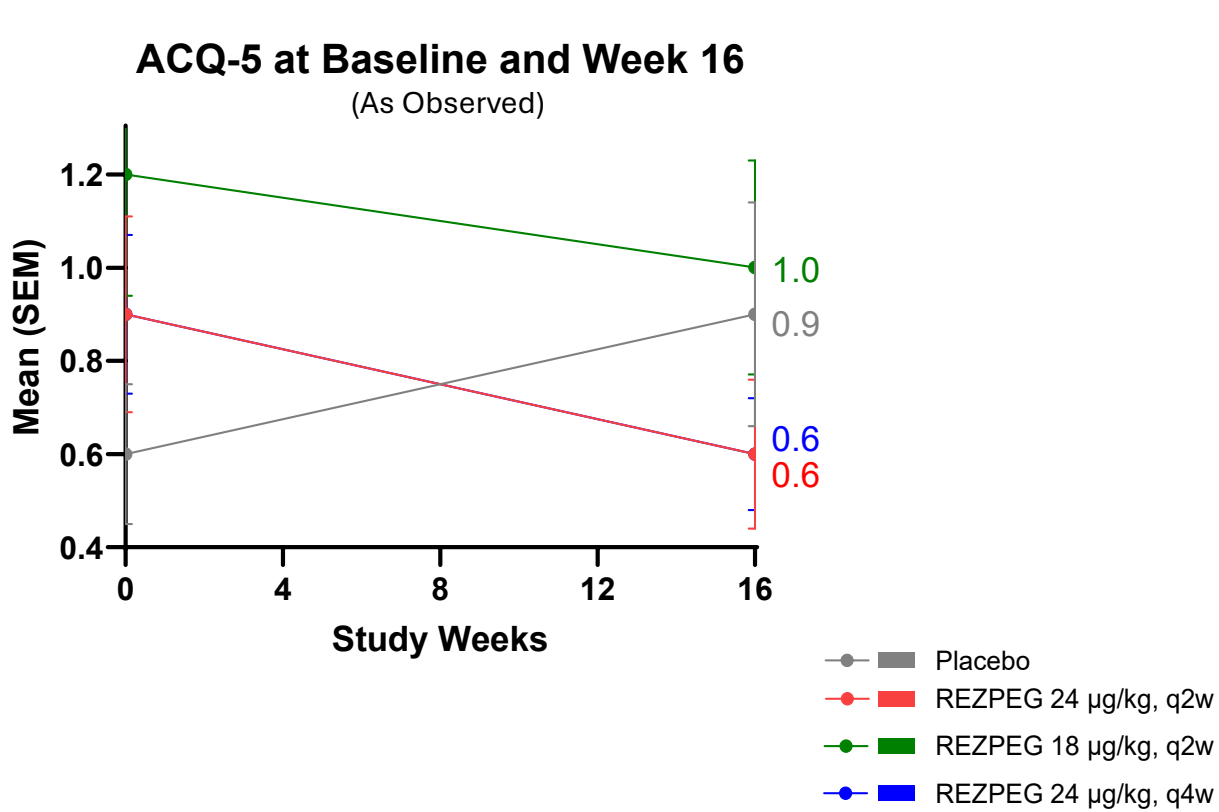
Consistent Treatment Effect Observed Across Baseline Severity of Disease, Geographical Region and Comorbidity of Asthma

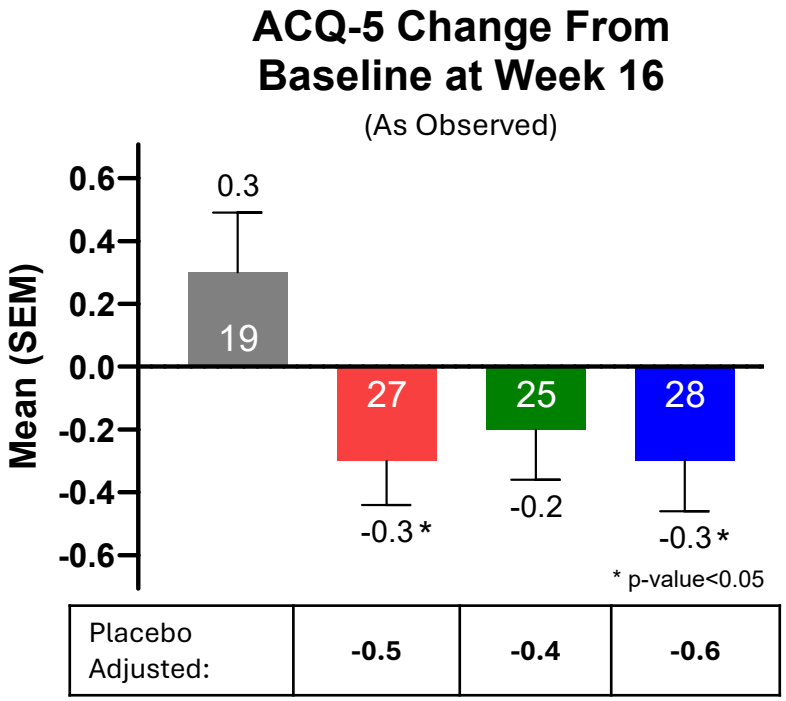


The Primary Estimand analysis for binary endpoints use logistic regressions. Data after use of rescue therapy outside protocol specifications or discontinued treatment due to lack of efficacy were imputed as non-responders; data after patients who discontinued due to other reasons were set to missing and all missing data are imputed using the multiple imputation method.

ACQ-5 Response in Patients with Self-Reported Asthma History

Improvement in ACQ-5 Scores From Baseline to Week 16 in Rezpegaldesleukin Treated Patients with Asthma Comorbidity





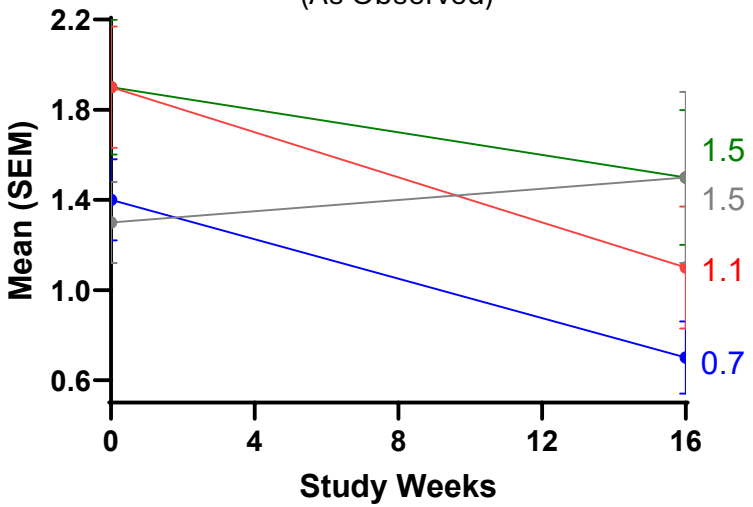
Only patients with both Baseline and Week 16 ACQ-5 data are included. The analysis for ACQ-5 data uses descriptive summary measures on observed data. P-value for change from baseline is from two-sample t-test.

Patients with Self-Reported Asthma History and Baseline ACQ-5 ≥0.5

Improvement in ACQ-5 From Baseline to Week 16 in Rezpegaldesleukin Treated Patients with Baseline ACQ-5 Score ≥ 0.5

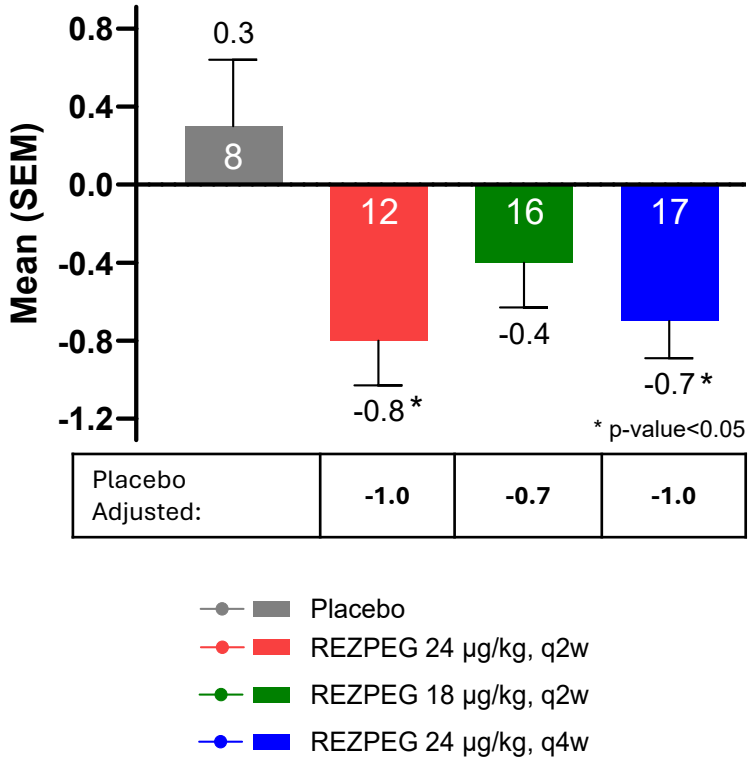
ACQ-5 at Baseline and Week 16

(As Observed)



ACQ-5 Change From Baseline at Week 16

(As Observed)

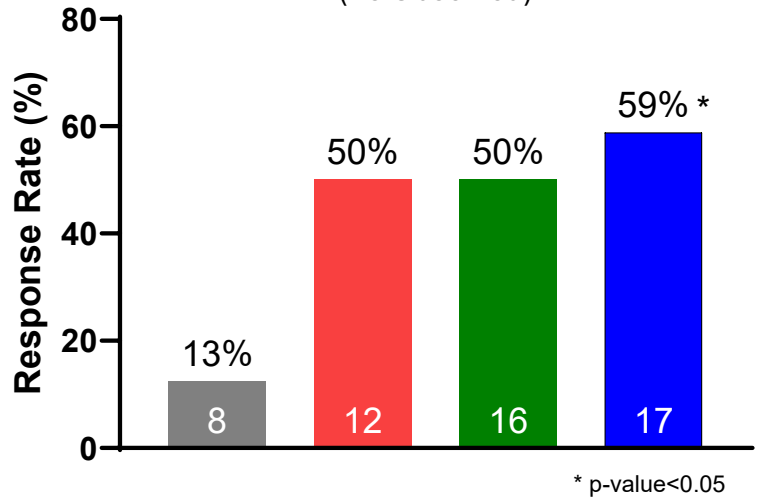


Placebo Adjusted:	-1.0	-0.7	-1.0

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

Proportion of Patients with ACQ-5 Improvement of ≥ 0.5 at Week 16

(As Observed)



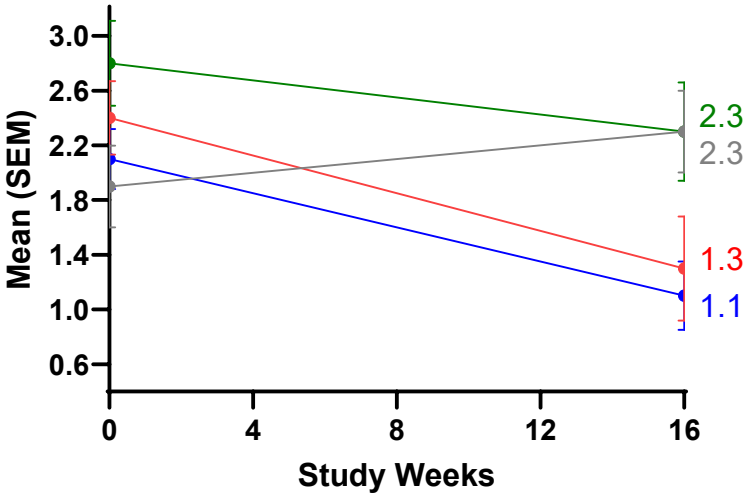
Only patients with both Baseline and Week 16 ACQ-5 data and baseline ACQ-5 ≥ 0.5 are included. The analysis for ACQ-5 data uses descriptive summary measures on observed data. P-value for change from baseline is from two-sample t-test and p-value for response is from Cochran-Mantel-Haenszel test.

ACQ-5 Response in Patients with Self-Reported *Uncontrolled* Asthma at Baseline

Improvement in ACQ-5 From Baseline to Week 16 in Rezpegaldesleukin Treated Patients with Baseline ACQ-5 Score ≥ 1.5

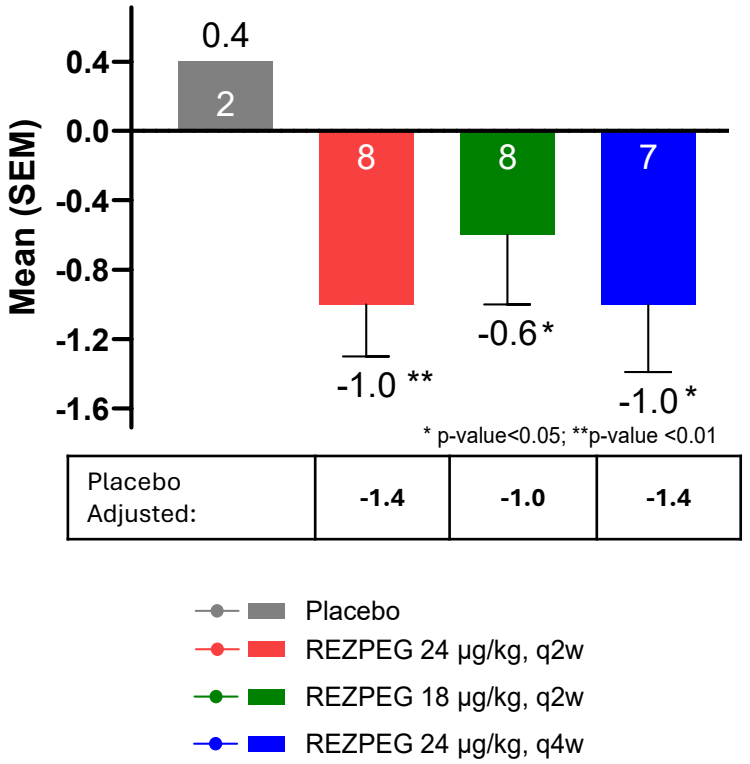
ACQ-5 at Baseline and Week 16

(As Observed)



ACQ-5 Change From Baseline at Week 16

(As Observed)

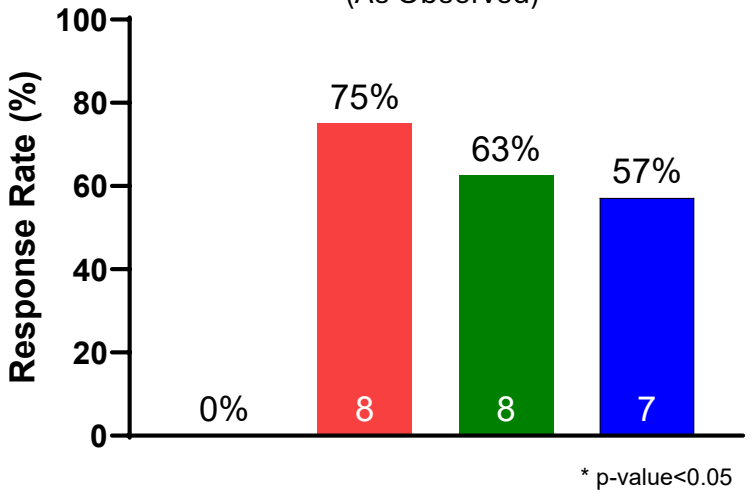


Placebo Adjusted:	-1.4	-1.0	-1.4

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

Proportion of Patients with ACQ-5 Improvement of ≥ 0.5 at Week 16

(As Observed)



Only patients with both Baseline and Week 16 ACQ-5 data and baseline ACQ-5 ≥ 1.5 are included. The analysis for ACQ-5 data uses descriptive summary measures on observed data. P-value for change from baseline is from two-sample t-test and p-value for response is from Cochran-Mantel-Haenszel test.

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%)
Proportion of patients with at least one Injection Site Reaction (ISR)	3 (4.1%)	79 (76.0%)	66 (62.3%)	78 (70.9%)	223 (69.7%)
Proportion of patients with ≤2 ISRs	73 (100.0%)	54 (51.9%)	68 (64.2%)	68 (61.8%)	190 (59.4%)
Injection site reaction (ISR) by Number of Events					
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%)

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

*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 ug/kg q2w) due to increased eosinophil count.

Summary

- Rezpegaldesleukin 24 µg/kg q2w demonstrated significant improvement compared to 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 ($p<0.05$)
  - Other dose levels demonstrated significant improvement in multiple endpoints
- Enhanced efficacy observed in the placebo-escape crossover cohort with 24 weeks of open-label treatment compared to 16 weeks of treatment
- Patients with a history of comorbidity of asthma reported improvement in self-reported asthma symptoms
- 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) (<1% discontinuations due to ISRs)
- First large study to validate the Treg mechanism of action and therapeutic potential of rezpegaldesleukin, an IL-2 agonist, in moderate-to-severe atopic dermatitis
- Pivotal Phase 3 planning for moderate-to-severe atopic dermatitis is underway, including assessing the treatment effect in patients with a comorbidity of asthma

Acknowledgements

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  - The investigators and their study teams
- This study was sponsored by Nektar Therapeutics

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