P 6685

Efficacy and Safety of Single Agent Rezpegaldesleukin, A Selective Regulatory T-Cell-Inducing Interleukin-2 Conjugate, in the Treatment of Atopic Dermatitis: Final Results from a Randomized Phase 1b Study

Jonathan Silverberg[1], David Rosmarin[2], Raj Chovatiya[3], Stephen Schleicher[4], Leon Kircik[5,6], Timothy Rodgers[7], Sohail Chaudhry[8], Christie Fanton[8], Danni Yu[8], Yi Liu[8], Brian Kotzin[8], Mary Tagliaferri[8], Carsten Schmitz[9], Ajay Nirula[9], Jonathan Zalevsky[8]

[1] Department Of Dermatology, George Washington University School Of Medicine, Washington, DC, United States; [2] Indiana University School of Medicine, Indianapolis, IN, United States; [3] Feinberg School Of Medicine, Northwestern University, Chicago, IL, United States; [4] DermDox Centers for Dermatology, Sugarloaf, PA, United States; [5] Icans School of Medicine at Mt. Sinai, New York, NY, United States; [6] Skin Sciences, PLLC, Louisville, KY, United States; [7] Rodgers Dermatology, Frisco, TX, United States; [8] Nektar Therapeutics, San Francisco, CA, United States; [9] Eli Lilly and Company, Indianapolis, IN, United States.

Presenter and Conflicts

Jonathan Silverberg, MD, PhD, MPH

- Professor of Dermatology at The George Washington University School of Medicine and Health Sciences
- Director of Clinical Research and Contact Dermatitis

Conflict of Interest Disclosures:

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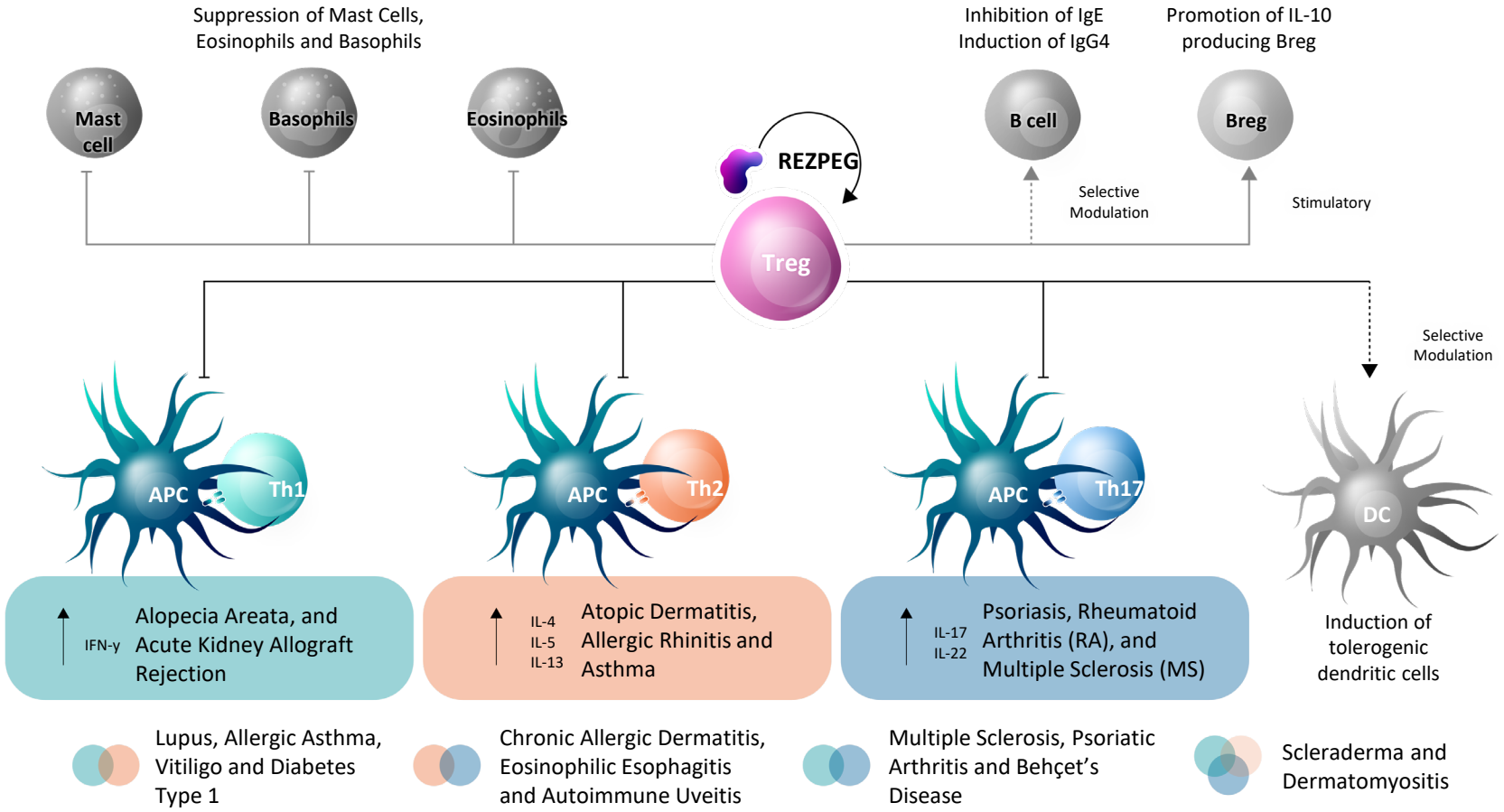
Why We Need Additional Therapies for Atopic Dermatitis

- Majority of patients do not achieve adequate disease control by the end of the induction period[1]
- Currently available systemic therapies may be limited by their safety profile:
  - Biologics (like dupilumab, tralokinumab, etc) are associated with conjunctivitis, facial erythema*, arthralgia*,[2]
  - JAK inhibitors (like abrocitinib, baricitnib, upadacitinib) carry multiple black box warnings[3]
- Even patients with a favorable response experience loss of disease control following cessation of therapy[4-5]
- The limited armamentarium of approved drugs with an adequate benefit–risk ratio represent major challenges in the field[6]
- New strategies aimed at inducing deep and potentially therapy-free remission are needed[7]

* Reported with dupilumab; **Sources:** [1]Silverberg JI, et al. *Dermatol Ther (Heidelb)* (2022) 5:1181-1196; [2]Torres T, et al. *J Dermatolog Treat* (2022) 33(5): 2554-2559; [3]Mikhaylov D, et al. *Ann Allergy, Asthma, Immuno* (2023) 130(5) 577-592; [4]Gooderham et al. *JAMA Derm* (2019) 155(12): 137101379; [5]Blauvelt et al. *Am J Clin Dermatol*. (2022) 23(3): 365-383; [6]Bieber T. *Nature Reviews Drug Discovery* (2022) 21: 21–40; [7]Bieber T. *Nature Reviews Drug Discovery* (2023) 22: 662–680.

Role of Regulatory T Cells in Autoimmune Disease



Regulatory T cells (Tregs) are indispensable for immune homoeostasis and for the prevention of autoimmune diseases.[1]

Rezpegaldesleukin (REZPEG)

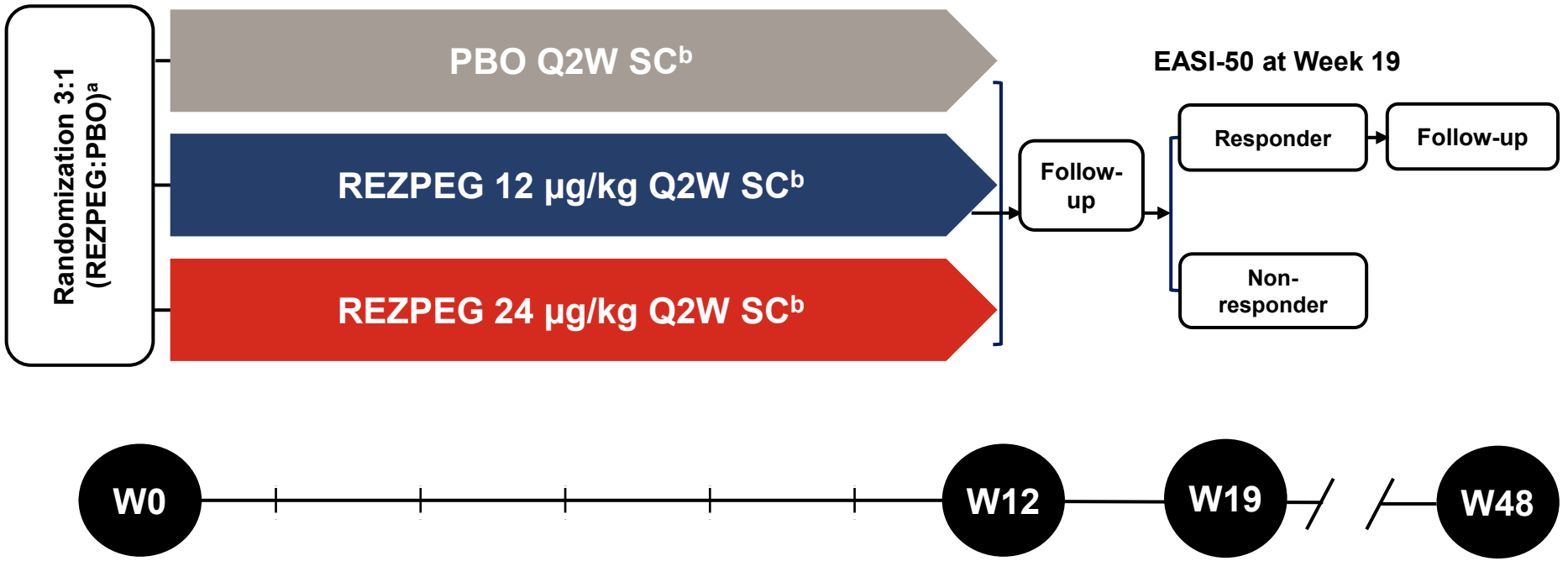
- Polymer conjugated recombinant human Interleukin-2 (rhIL-2)[2]
- Administered as an active drug, with pegylation conferring high selectivity for Tregs without activation of effector T-cells (Tcons)[2-3]
- Enhancing Treg function is a novel therapeutic strategy for restoring immunological homeostasis[2-3]
- Nearly 600 healthy volunteers and patients have been administered REZPEG to-date across 9 studies
- REZPEG results in dose-dependent, selective, and up-to 17-fold increase in CD25^{bright} Tregs over baseline that is sustained for 20–30 days[3]

Sources: [1] Lykhopiy V, et al. *Genes Immun.* (2023) Epub ahead of print; [2] Dixit N, et al. *J Transl Autoimmun*. (2021) 4:100103; [3] Fanton C, et al. *J Transl Autoimmun*. (2022) 5:100152.

REZPEG Phase 1b, Double-Blind, Placebo-Controlled Study of Patients With Atopic Dermatitis (NCT04081350)

Key Eligibility Criteria

- Aged 18-70 years
- Moderate-to-severe AD involving ≥10% body surface area in the affected skin
- History of inadequate response or intolerance to topical medications
- vIGA-AD™ ≥3
- Eczema Area and Severity Index (EASI) ≥16



Efficacy:

- Change from baseline in EASI
- Proportion of patients who achieved EASI-75
- Proportion of patients who achieved vIGA-AD of 0 (clear) or 1 (almost clear)
- Proportion of patients who achieved ≥4-point improvement in Itch Numeric Rating Scale (NRS)

Rescue Therapy: Topical corticosteroids and calcitonin inhibitors were permitted as rescue therapy for atopic dermatitis on or after day 21.

Source: Schleicher et. al.: "*Efficacy and Safety of a Selective Regulatory T-Cell Inducing IL-2 Conjugate (LY3471851) in the Treatment of Atopic Dermatitis: A Phase 1 Randomised Study*"

[a] Full study design is not shown; the REZPEG 10 µg/kg cohort is not included in this analysis

[b] Total of 7 doses/patient; *EASI-50=50% improvement from baseline in Eczema Area and Severity Index; PBO=placebo; Q2W=once every 2 weeks; SC=subcutaneous; W=Week*

Study Demographics of Patients in Phase 1b Trial in Atopic Dermatitis

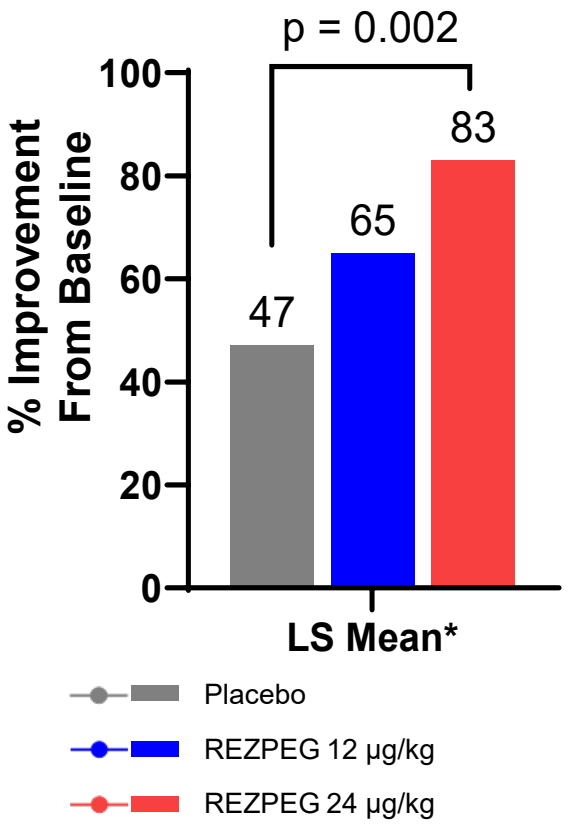
Characteristic	PBO (n=10)	REZPEG 12 µg/kg (n=16)	REZPEG 24 µg/kg (n=17)
Mean age, years (SD)	42.5 (19.8)	47.9 (17.5)	37.5 (16.4)
Sex, n (%)			
Female	6 (60.0%)	11 (68.8%)	7 (41.2%)
Male	4 (40.0%)	5 (31.3%)	10 (58.8%)
Race, n (%)			
White	6 (60.0%)	11 (68.8%)	14 (82.4%)
Black or African American	3 (30.0%)	3 (18.8%)	3 (17.6%)
Asian	1 (10.0%)	2 (12.5%)	0
Ethnicity, n (%)			
Hispanic or Latino	0	3 (18.8%)	7 (41.2%)
Not Hispanic or Latino	10 (100.0%)	13 (81.3%)	10 (58.8%)
Mean EASI score (SD)	23.7 (7.1)	23.5 (11.2)	21.9 (5.1)
Mean BSA score (SD)	39.0 (21.6)	33.8 (20.1)	33.5 (15.8)
vIGA score, n (%)			
3 (moderate)	5 (50.0%)	9 (56.3%)	11 (64.7%)
4 (severe)	5 (50.0%)	7 (43.8%)	6 (35.3%)
Mean Itch NRS score (SD)	8.5 (1.3)	7.8 (2.1)	7.4 (2.5)
Mean DLQI score (SD)	13.0 (5.9)	12.4 (6.7)	11.3 (7.2)
Mean POEM score (SD)	21.2 (5.7)	20.0 (5.2)	19.6 (7.0)

SD: Standard deviation

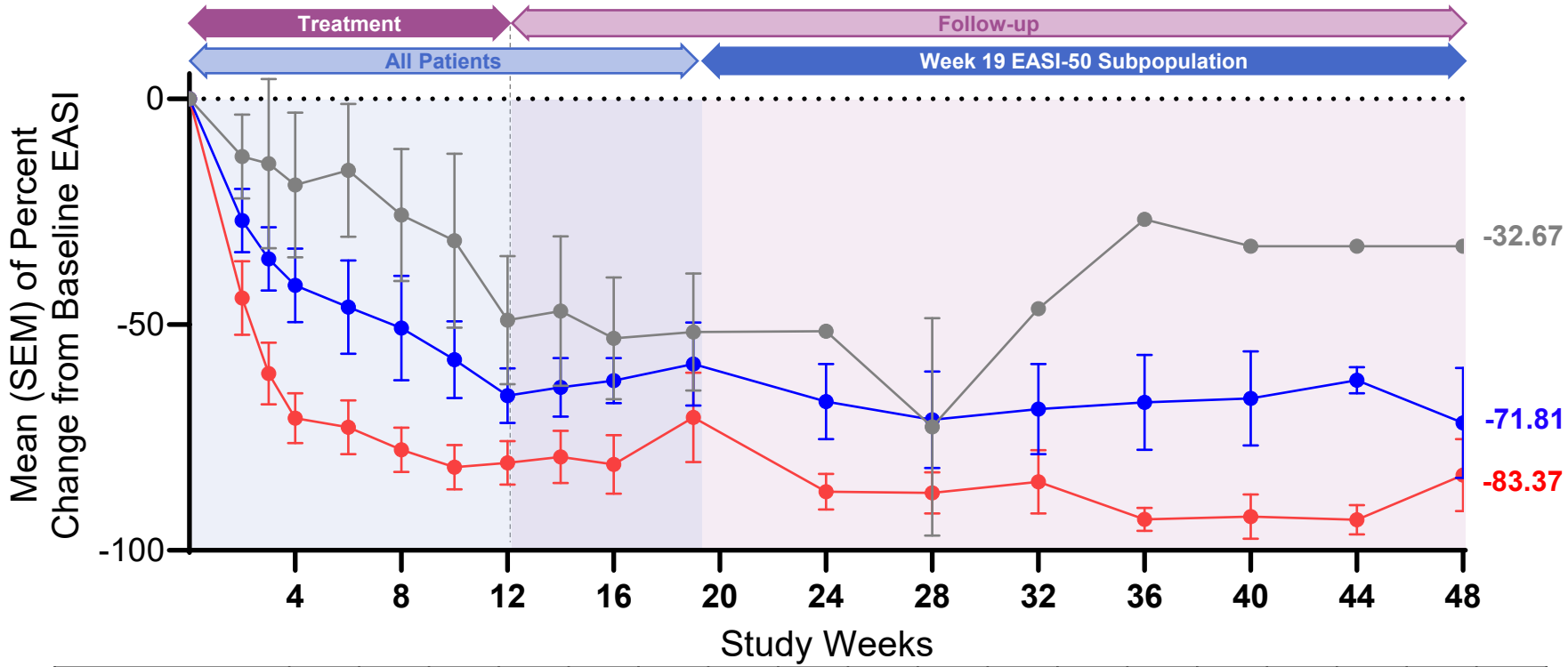
Phase 1b Study of REZPEG in Atopic Dermatitis

Percent Change From Baseline for EASI Score (Observed)

EASI Improvement at Week 12



Percent Reduction from Baseline EASI



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	10	8	6	8	6	8	5	7	5	5	6	1	2	1	1	1	1	1
REZPEG 12 µg/kg, n	16	16	15	15	14	14	12	12	12	12	12	7	5	5	5	4	3	4
REZPEG 24 µg/kg, n	17	16	16	15	15	14	13	12	13	13	13	8	9	9	7	7	7	7

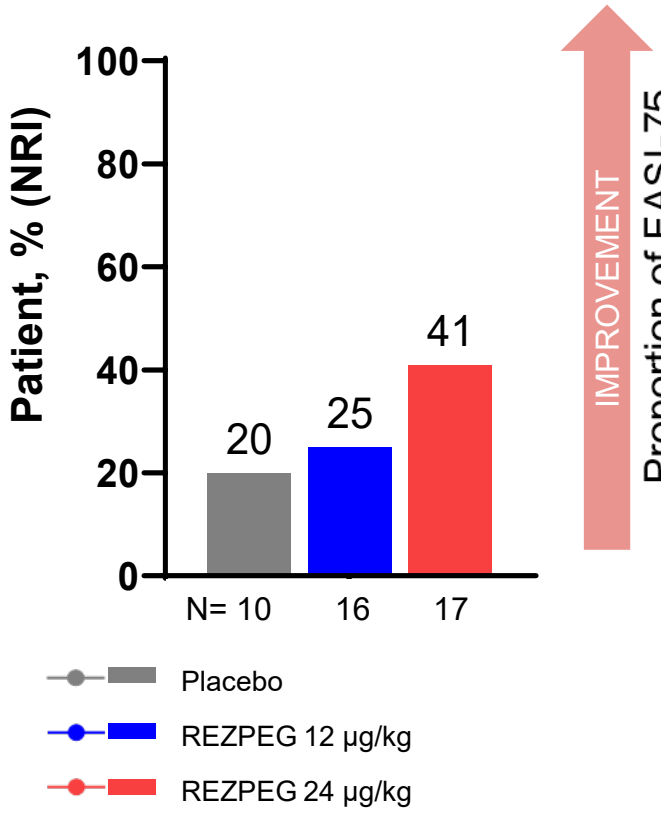
n = number of participants who were evaluated at each defined timepoint

SEM: Standard error of the mean; continuous endpoint using observed data; *EASI Improvement results are least squares (LS) mean percent change from baseline obtained from Mixed Model for Repeated Measures (MMRM) as specified in the statistical analysis plan (SAP) defined in the protocol (generated by independent statistical audit firm)

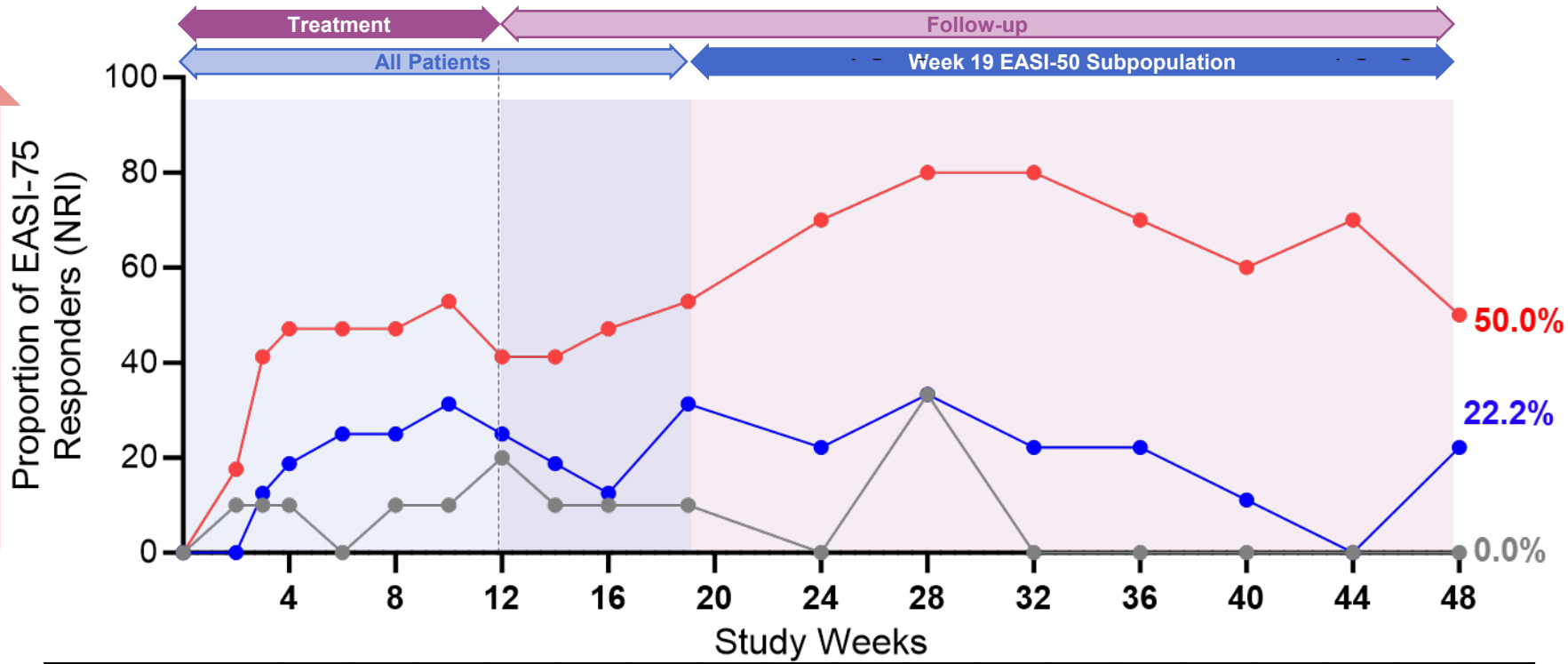
EASI-75 (EASI Score Decreased by at Least 75%)

Proportion of EASI-75 Responders

EASI-75 Responders at Week 12



Proportion of EASI-75 Responders



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	N=10	1	1	1	0	1	1	2	1	1	1	0	1	0	0	0	0	0
REZPEG 12 µg/kg, n	N=16	0	2	3	4	4	5	4	3	2	5	2	3	2	2	1	0	2
REZPEG 24 µg/kg, n	N=17	3	7	8	8	8	9	7	7	8	9	7	8	8	7	6	7	5

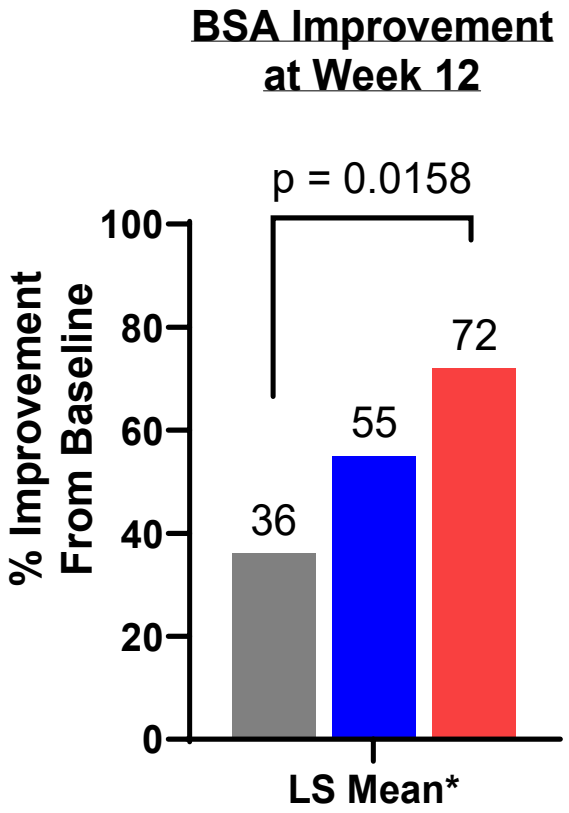
n = number of participants who achieved a response at each defined timepoint

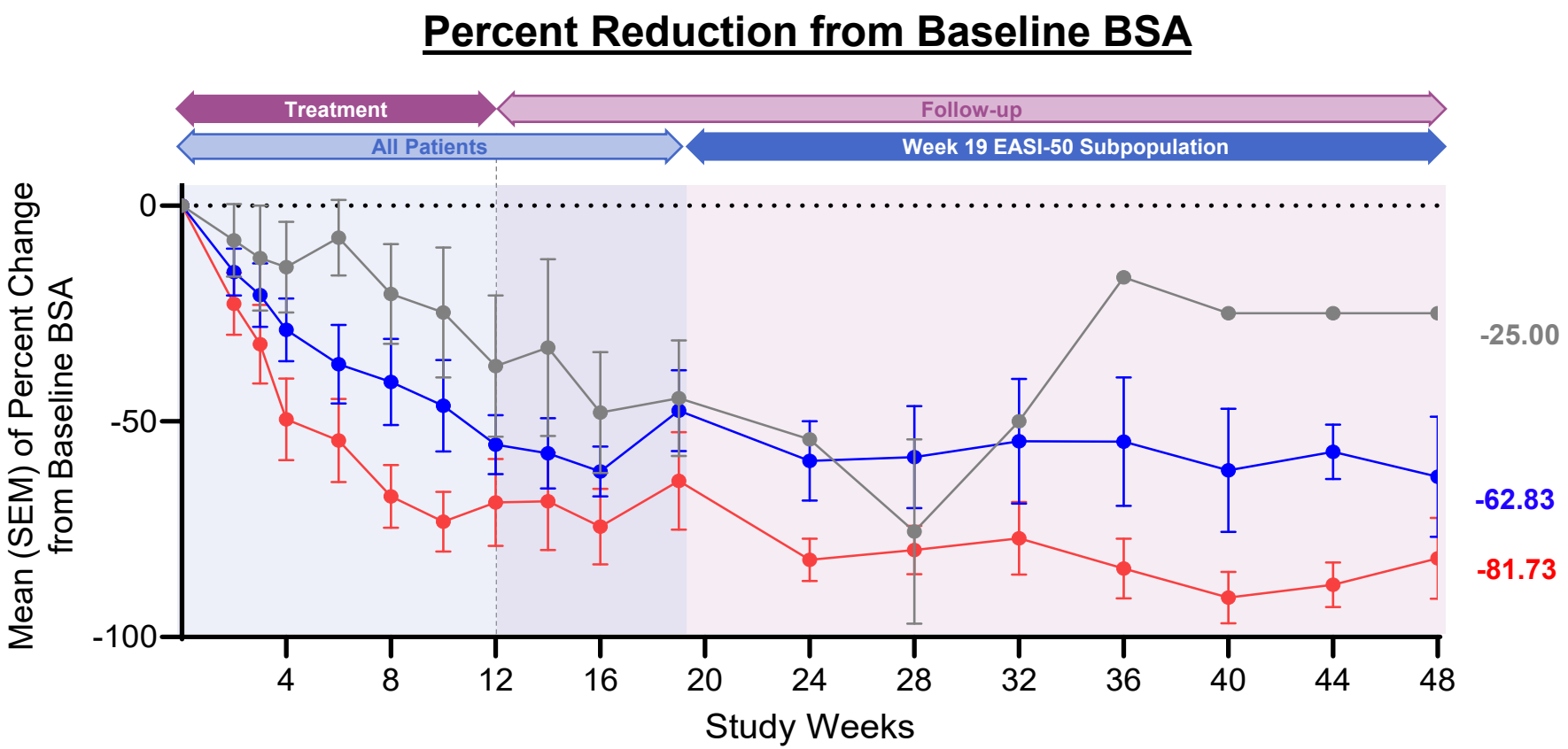
The EASI-50 response was (PBO, 12 µg/kg, 24 µg/kg): 30%, 69%, 71% at Week 12 and 0%, 33% and 70% at Week 48, respectively.

Patients were followed until Week 19 (10, 16, and 17 pts in the PBO, 12 µg/kg and 24 µg/kg groups), and those with ≥EASI-50 response at Week 19 (3, 9, and 10 pts in the PBO, 12 µg/kg and 24 µg/kg groups) were followed until Week 48 or until EASI-25 response criteria were no longer met; patients who were not EASI-50 responders at week 19 were excluded from the denominator for visits after week 19; NRI: non-responder imputation

BSA (Body Surface Area)

Percent Change From Baseline for BSA (Observed)





Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, N	10	8	6	8	6	8	5	7	5	5	6	1	2	1	1	1	1	1
REZPEG 12 µg/kg, N	16	16	15	15	14	14	12	12	12	12	12	7	5	5	5	4	3	4
REZPEG 24 µg/kg, N	17	16	16	15	15	14	13	12	13	13	13	8	9	9	7	7	7	7

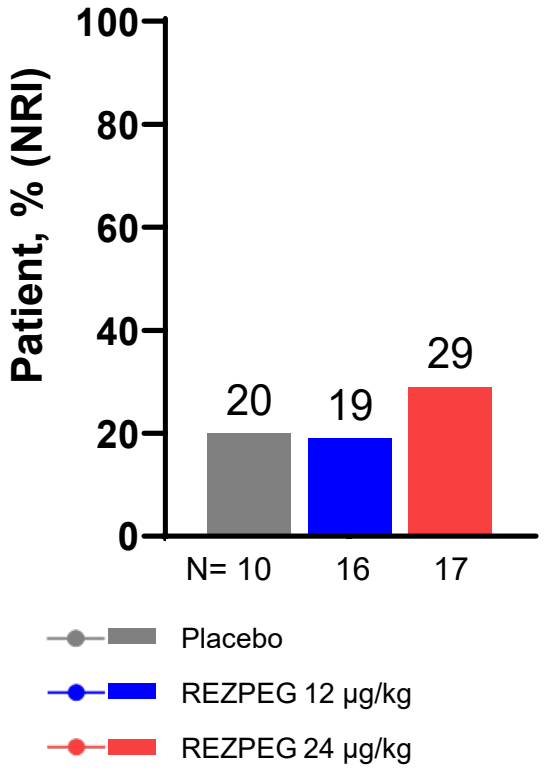
N = number of participants who were evaluated at each defined timepoint

SEM: Standard error of the mean; continuous endpoint using observed data; *BSA Improvement results are least squares (LS) mean percent change from baseline obtained from Mixed Model for Repeated Measures (MMRM) as specified in the statistical analysis plan (SAP) defined in the protocol

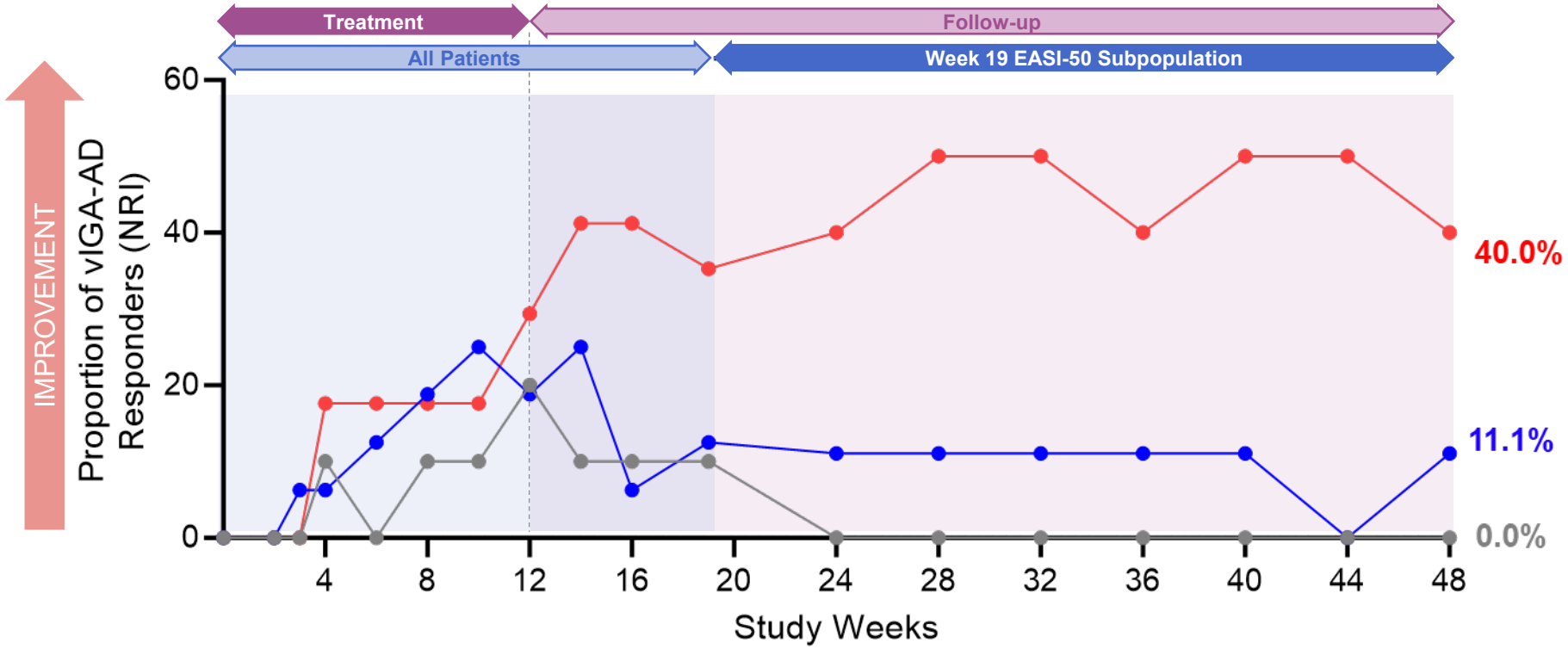
vIGA-AD (Validated Investigator Global Assessment)

Proportion of vIGA-AD Responders; Responder defined as a score of 0 or 1 and at least a 2-point reduction from baseline

vIGA-AD Responders at Week 12



Proportion of vIGA-AD Responders



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	N=10	0	0	1	0	1	1	2	1	1	1	0	0	0	0	0	0	0
REZPEG 12 µg/kg, n	N=16	0	1	1	1	2	3	3	3	1	2	1	1	1	1	1	0	1
REZPEG 24 µg/kg, n	N=17	0	0	2	2	2	3	5	7	7	6	4	5	5	4	5	5	4

n = number of participants who achieved a vIGA response at each defined timepoint

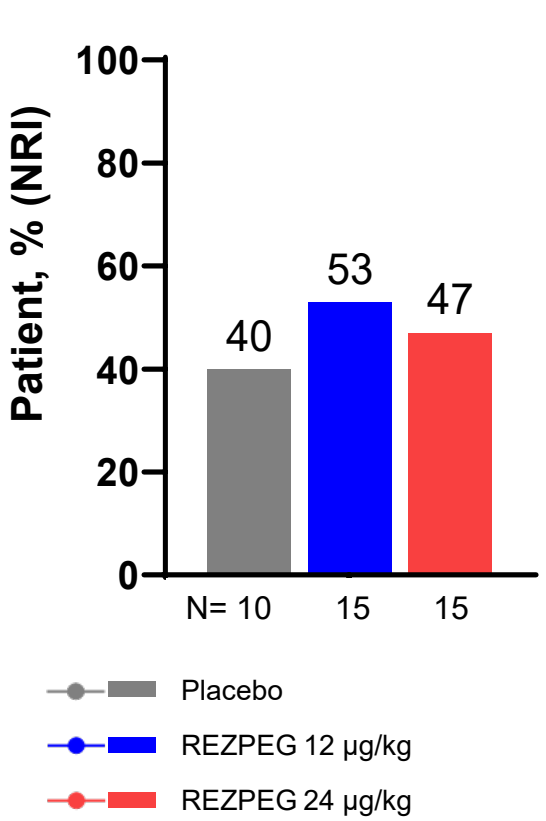
The EASI-90 response was (PBO, 12 µg/kg, 24 µg/kg): 20%, 13%, 24% Week 12 and 0%, 11% and 40% Week 48, respectively.

Patients were followed until Week 19 (10, 16, and 17 pts in the PBO, 12 µg/kg and 24 µg/kg groups), and those with ≥EASI-50 response at Week 19 (3, 9, and 10 pts in the PBO, 12 µg/kg and 24 µg/kg groups) were followed until Week 48 or until EASI-25 response criteria were no longer met; patients who were not EASI-50 responders at week 19 were excluded from the denominator for visits after week 19; NRI: non-responder imputation

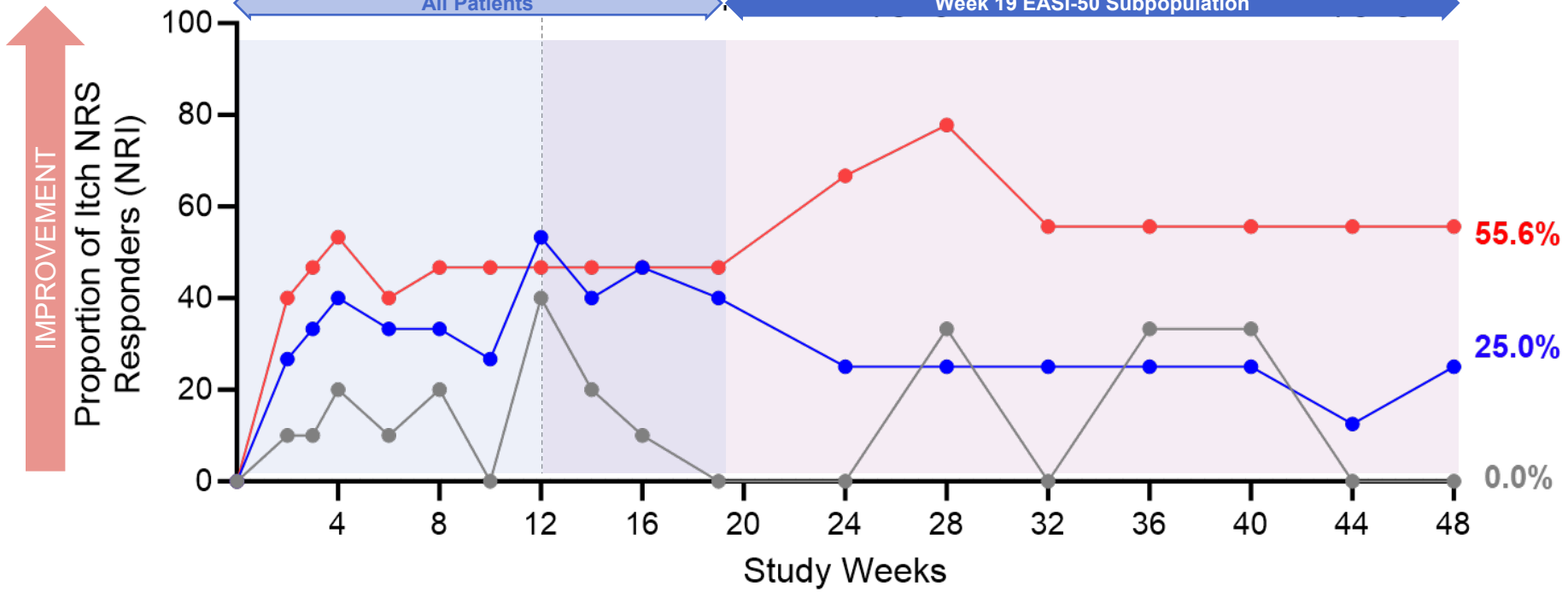
Itch NRS (Numeric Rating Scale)

Proportion of Itch NRS Responders; Responder defined as greater than or equal to a 4-point reduction from baseline – ***Only patients with a baseline score of 4 points or greater included***

Itch NRS Responders at Week 12



Proportion of Itch NRS Responders



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	N=10	1	1	2	1	2	0	4	2	1	0	0	1	0	1	1	0	0
REZPEG 12 µg/kg, n	N=15	4	5	6	5	5	4	8	6	7	6	2	2	2	2	2	1	2
REZPEG 24 µg/kg, n	N=15	6	7	8	6	7	7	7	7	7	7	6	7	5	5	5	5	5

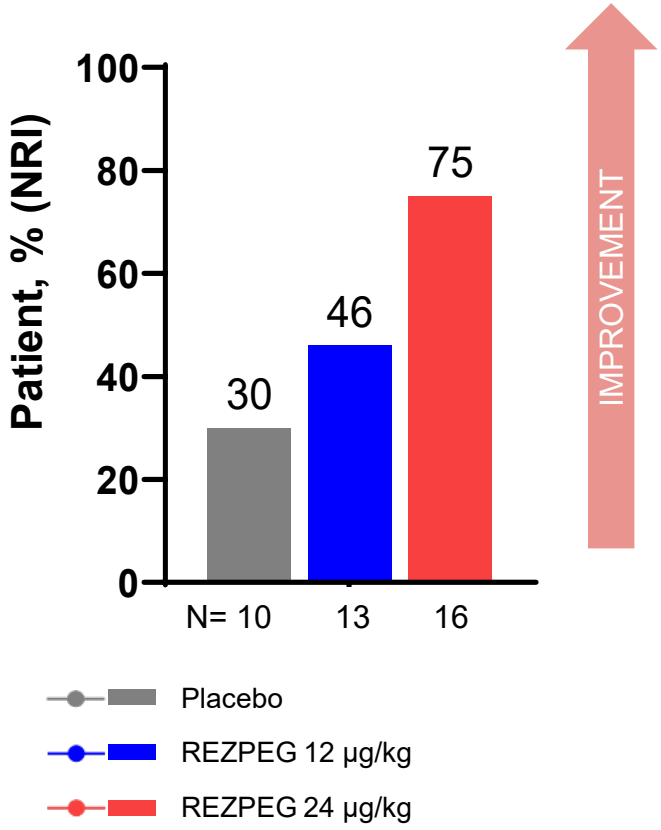
n = number of participants who achieved a Itch NRS response at each defined timepoint

Patients were followed until Week 19 (10, 15, and 15 pts in the PBO, 12 µg/kg and 24 µg/kg groups), and those with ≥EASI-50 response at Week 19 (3, 8, and 9 pts in the PBO, 12 µg/kg and 24 µg/kg groups) were followed until Week 48 or until EASI-25 response criteria were no longer met; patients who were not EASI-50 responders at week 19 were excluded from the denominator for visits after week 19; NRI: non-responder imputation

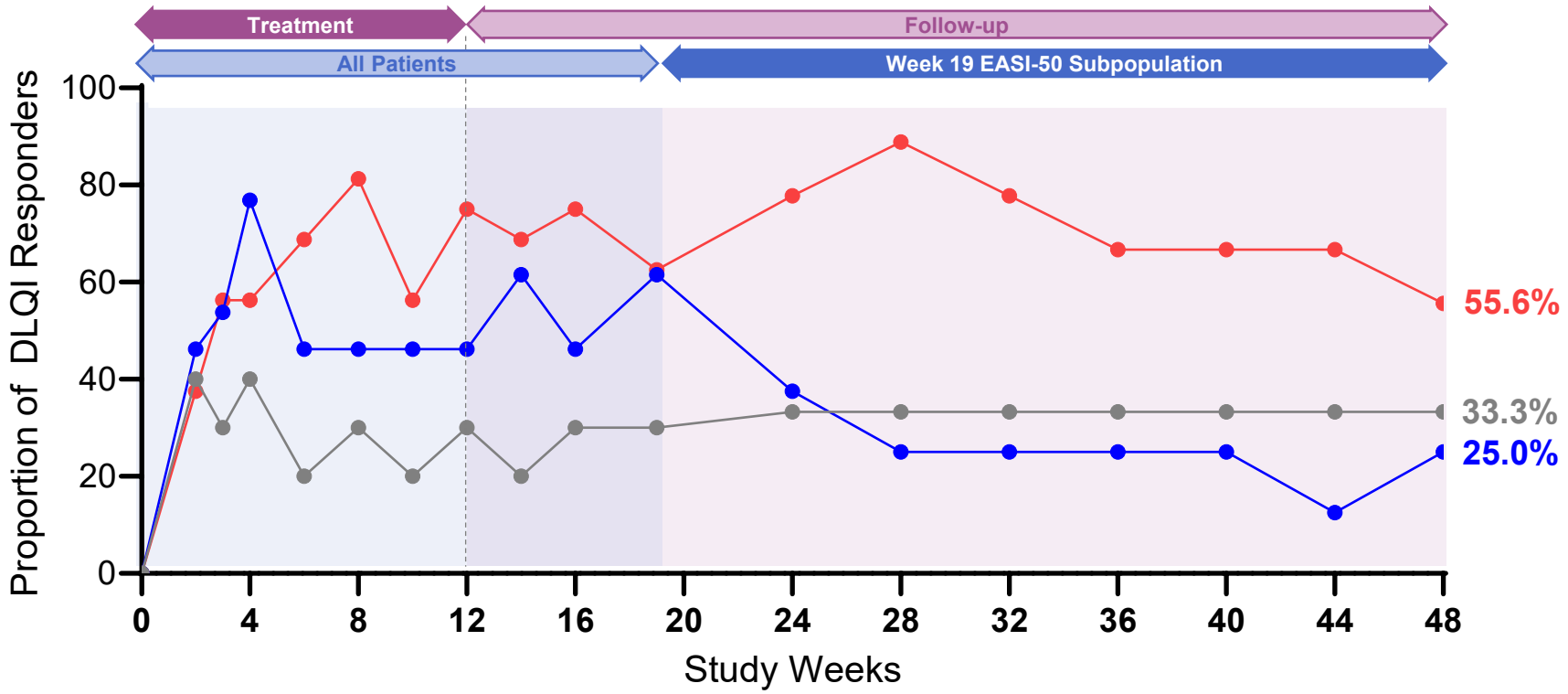
DLQI (Daily Life Quality Index)

DLQI Responders; Responder defined as greater than or equal to a 4-point reduction from baseline – ***Only patients with a baseline score of 4 points or greater included***

DLQI Responders at Week 12



Proportion of DLQI Responders



Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	N=10	4	3	4	2	3	2	3	2	3	3	1	1	1	1	1	1	1
REZPEG 12 µg/kg, n	N=13	6	7	10	6	6	6	6	8	6	8	3	2	2	2	2	1	2
REZPEG 24 µg/kg, n	N=16	6	9	9	11	13	9	12	11	12	10	7	8	7	6	6	6	5

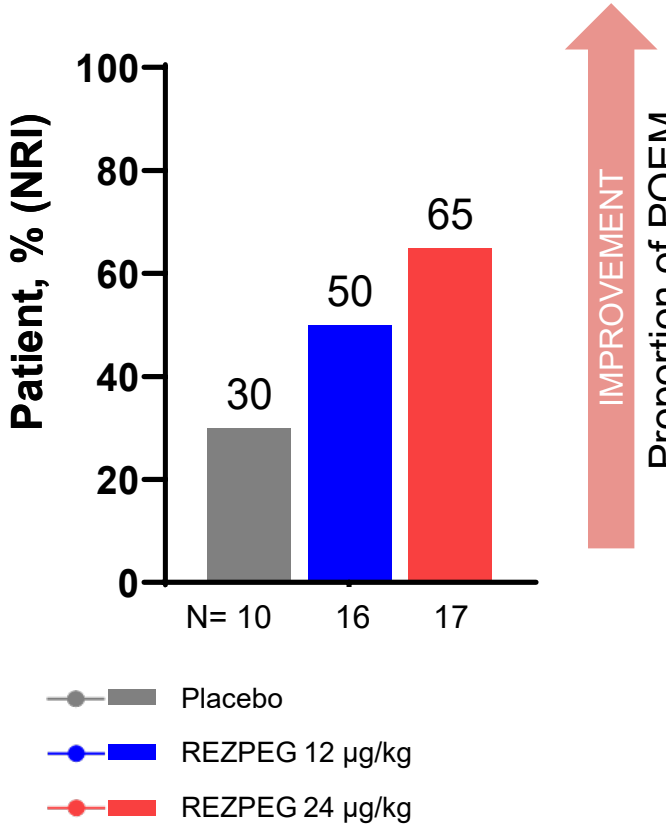
n = number of participants who achieved a DLQI response at each defined timepoint

Patients were followed until Week 19 (10, 13, and 16 pts in the PBO, 12 µg/kg and 24 µg/kg groups), and those with ≥EASI-50 response at Week 19 (3, 8, and 9 pts in the PBO, 12 µg/kg and 24 µg/kg groups) were followed until Week 48 or until EASI-25 response criteria were no longer met; patients who were not EASI-50 responders at week 19 were excluded from the denominator for visits after week 19; NRI: non-responder imputation

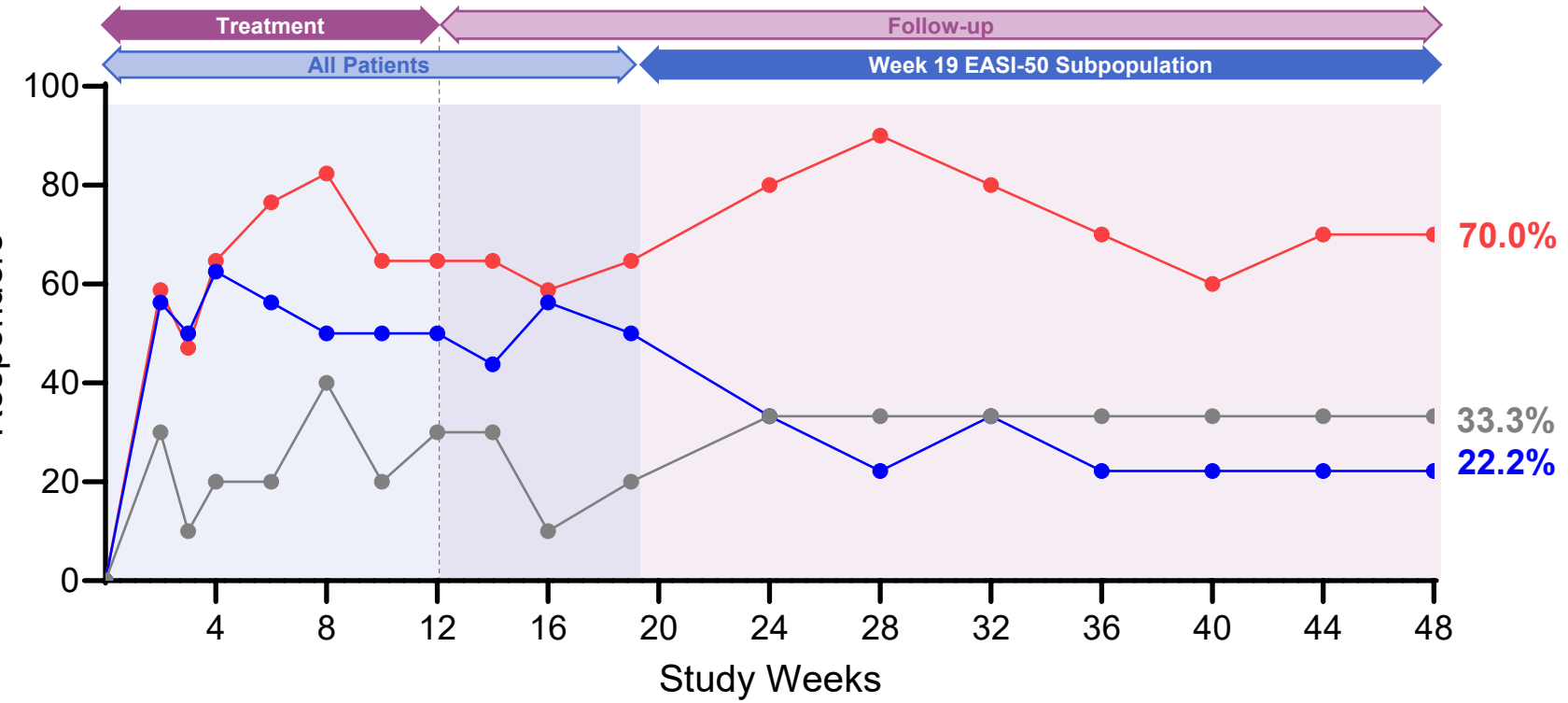
POEM (Patient Oriented Eczema Measure)

POEM Responders; Responder defined as greater than or equal to a 4-point reduction from baseline – ***Only patients with a baseline score of 4 points or greater included***

POEM Responders at Week 12



Proportion of POEM Responders



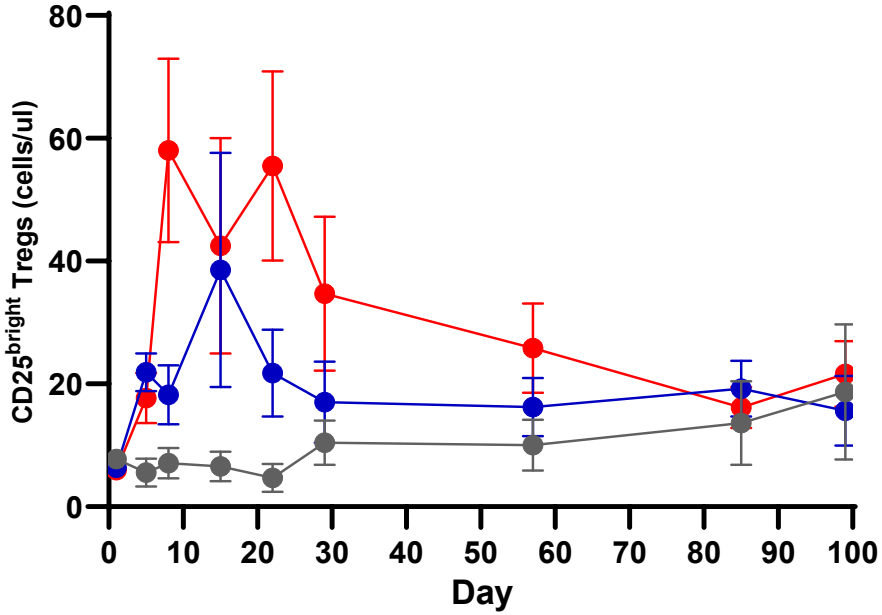
Weeks	0	2	3	4	6	8	10	12	14	16	19	24	28	32	36	40	44	48
PBO, n	N=10	3	1	2	2	4	2	3	3	1	2	1	1	1	1	1	1	1
REZPEG 12 µg/kg, n	N=16	9	8	10	9	8	8	8	7	9	8	3	2	3	2	2	2	2
REZPEG 24 µg/kg, n	N=17	10	8	11	13	14	11	11	11	10	11	8	9	8	7	6	7	7

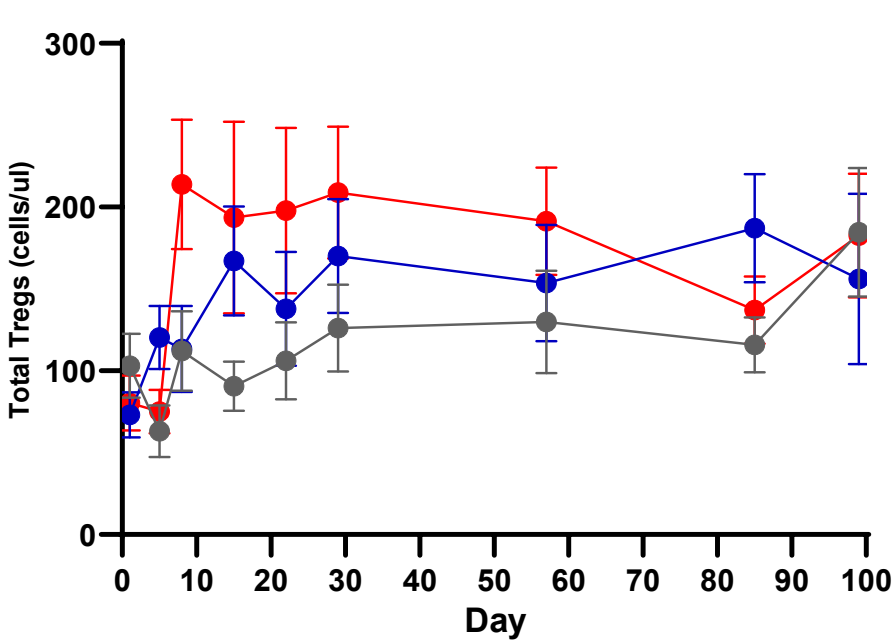
n = number of participants who achieved a POEM response at each defined timepoint

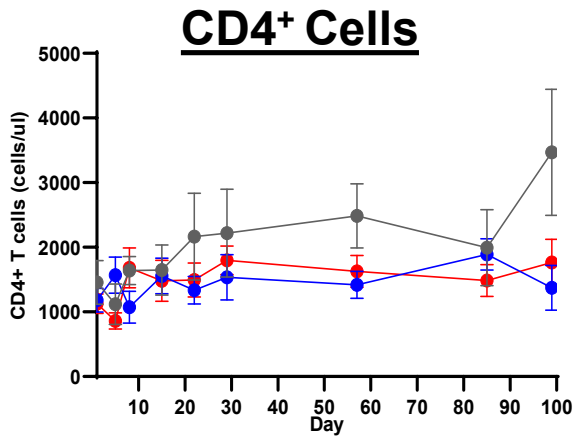
Patients were followed until Week 19 (10, 16, and 17 pts in the PBO, 12 µg/kg and 24 µg/kg groups), and those with ≥EASI-50 response at Week 19 (3, 9, and 10 pts in the PBO, 12 µg/kg and 24 µg/kg groups) were followed until Week 48 or until EASI-25 response criteria were no longer met; patients who were not EASI-50 responders at week 19 were excluded from the denominator for visits after week 19; NRI: non-responder imputation

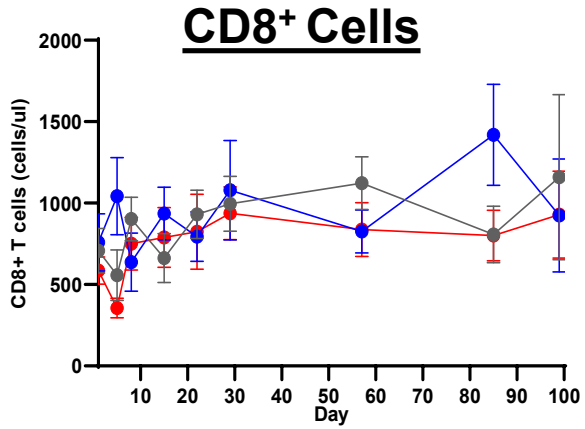
Phase 1b Study of REZPEG in Atopic Dermatitis

Pharmacodynamics









The peak increase in CD25^{bright} Treg number was 10-fold above baseline after the first and second doses in the 24 µg/kg group.

Day 7 and 21 values are inter-dose (peak) values and all others are pre-dose (troth) values.

Summary of Adverse Events Reported thru Week 48

Adverse Event	PBO (n=10)	REZPEG 12 µg/kg (n=16)	REZPEG 24 µg/kg (n=17)
Any Treatment Emergent Adverse Event (TEAE)	8 (80.0%)	10 (62.5%)	13 (76.5%)
TEAE in at least 5% of patients in the overall REZPEG group			
Infections and infestations	2 (20.0%)	7 (43.8%)	7 (41.2%)
Corona virus infection	0	2 (12.5%)	2 (11.8%)
Folliculitis	0	2 (12.5%)	0
Sinusitis	0	2 (12.5%)	0
Urinary tract infection	0	0	2 (11.8%)
Gastrointestinal disorders	3 (30.0%)	1 (6.3%)	3 (17.6%)
Nausea	0	1 (6%)	1 (6%)
General disorders and administration site conditions	1 (10.0%)	2 (12.5%)	2 (11.8%)
Pain	0	1 (6.3%)	1 (5.9%)
Investigations	0	0	4 (23.5%)
Nervous system disorders	0	2 (12.5%)	2 (11.8%)
Headache	0	2 (12.5%)	0
Blood and lymphatic system disorders	0	1 (6.3%)	1 (5.9%)
Eye disorders	0	2 (12.5%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (6.3%)	1 (5.9%)
Skin and subcutaneous tissue disorders	1 (10.0%)	1 (6.3%)	1 (5.9%)
Any Adverse Events Related to Study Drug	3 (30.0%)	2 (12.5%)	5 (29.4%)
Any Severe Adverse Events	3 (30.0%)	0	0
Any Serious Adverse Events	2 (20.0%)	0	0
Deaths	0	0	0
Any Adverse Events Leading to Discontinuation of Study	0	1 (6.3%)	3 (17.6%)
Injection site reactions	1 (10.0%)	12 (75.0%)	10 (58.8%)

AEs leading to study discontinuation were 1 pt each: mild headache & nausea (12 µg/kg), mild limb abscess at site distant from drug administration (24 µg/kg), moderate urticaria (24 µg/kg), moderate asymptomatic eosinophilia (24 µg/kg, protocol mandated)

- All TEAEs in study drug arms were mild to moderate in nature
- No severe or serious AEs observed in either REZPEG arms
- No reports of conjunctivitis
- Most common AEs were mild to moderate injection site reactions

No ADA (anti-REZPEG antibodies) detected

Summary

- First study to demonstrate the therapeutic potential of REZPEG, a selective regulatory T-cell enhancing IL-2 therapy, for patients with moderate-to-severe atopic dermatitis
- High dose REZPEG demonstrated significant improvement over placebo in:
  - EASI LS Mean Percent Change (p=0.002)
  - BSA LS Mean Percent Change (p=0.0158)
- Dose dependent trend favoring REZPEG observed for responder outcomes:
  - Investigator Assessed: EASI-75, vIGA-AD
  - Patient Reported: Itch NRS, POEM, DLQI
- REZPEG was well tolerated with only mild-moderate TEAE observed in study drug arms

Conclusion

- ***Remittive Potential:*** Majority of responders in high-dose REZPEG arm sustained their response through the 36-week extended follow-up period without additional therapy for AD

- ***Future Direction for REZPEG:***
  - Phase 2b study for moderate-to-severe AD in startup
    - TiP ePoster presented here at EADV – P0559
  - Phase 2b study for alopecia areata in development

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