

Multi-omic profiling identifies early molecular responses to rezpegaldesleukin, a novel regulatory T cell-inducing therapy, in atopic dermatitis

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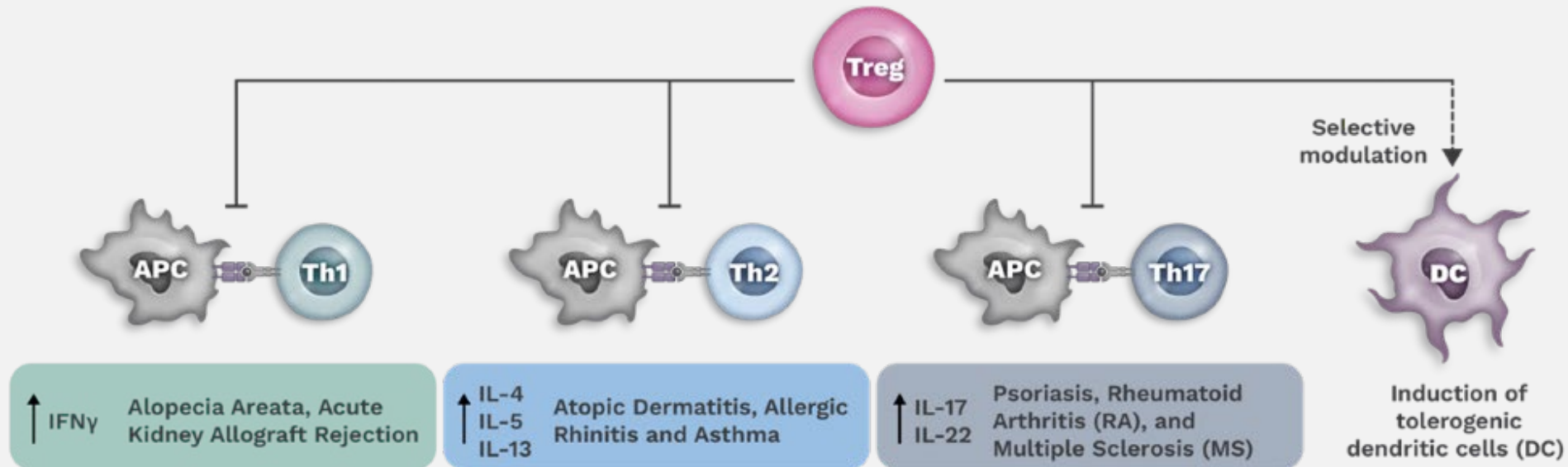
Disclosures and Acknowledgements

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by T-cell-mediated immune dysregulation and multiple associated comorbidities, with substantial impact on patients' quality of life.

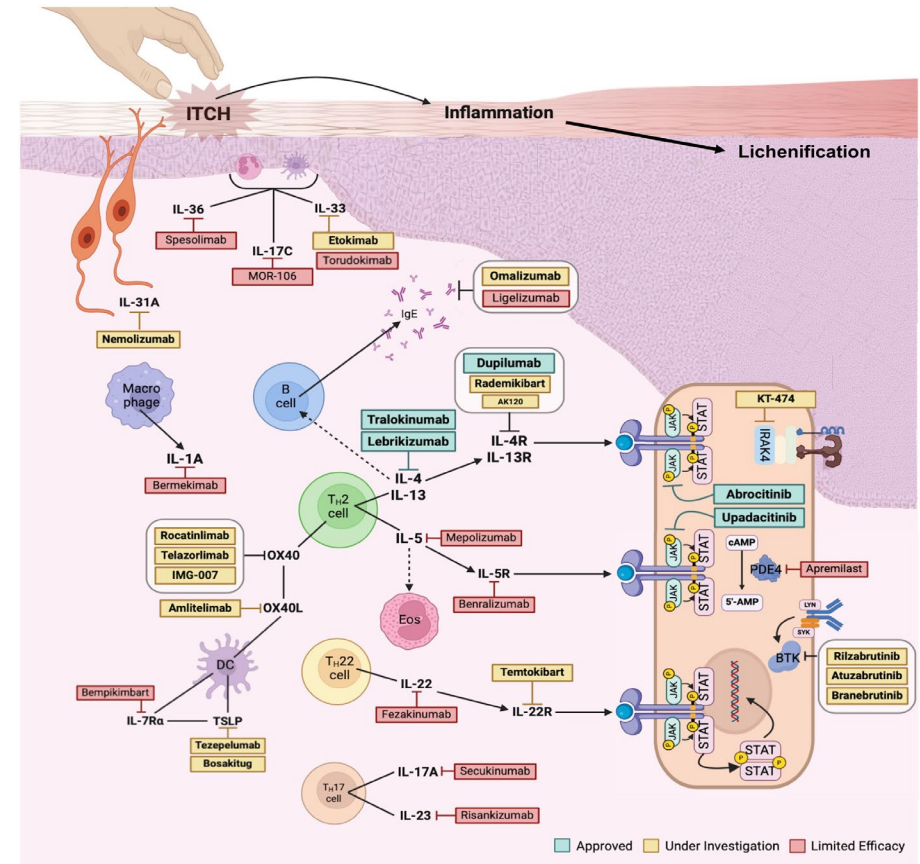
Rezpegaldesleukin (REZPEG) is an IL-2 receptor (IL-2R) pathway agonist designed to stimulate the expansion and function of regulatory T cells (Tregs).



Atopic dermatitis is a complex disease with multiple underlying immune pathways



Disease heterogeneity necessitates treatment heterogeneity

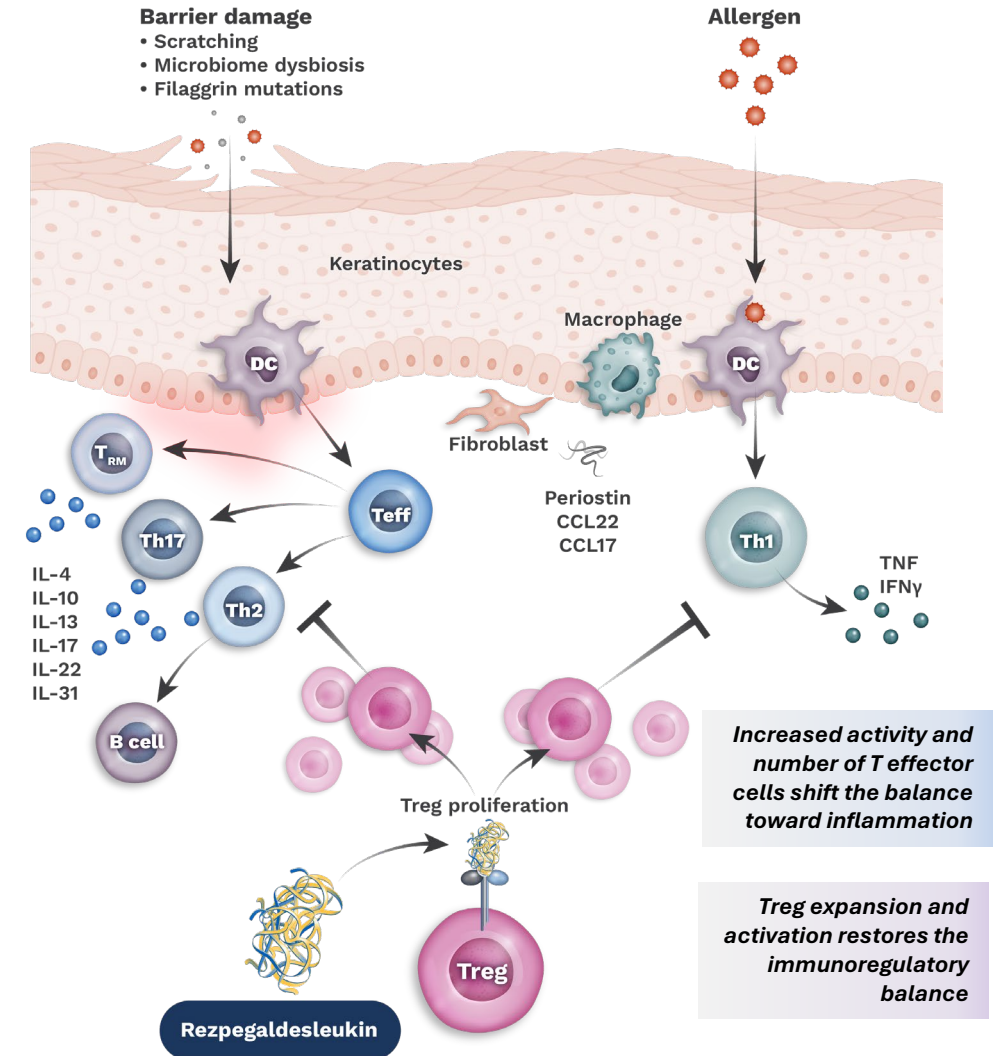


Adapted from Liu D, Patel D, Lau M, Largent J, Hu BD, He H, et al. A translational approach to improve therapeutics in atopic dermatitis and beyond. The Journal of Immunology. 2025;214(9):2165-79.

Rezpeg targets Tregs that are impaired in AD

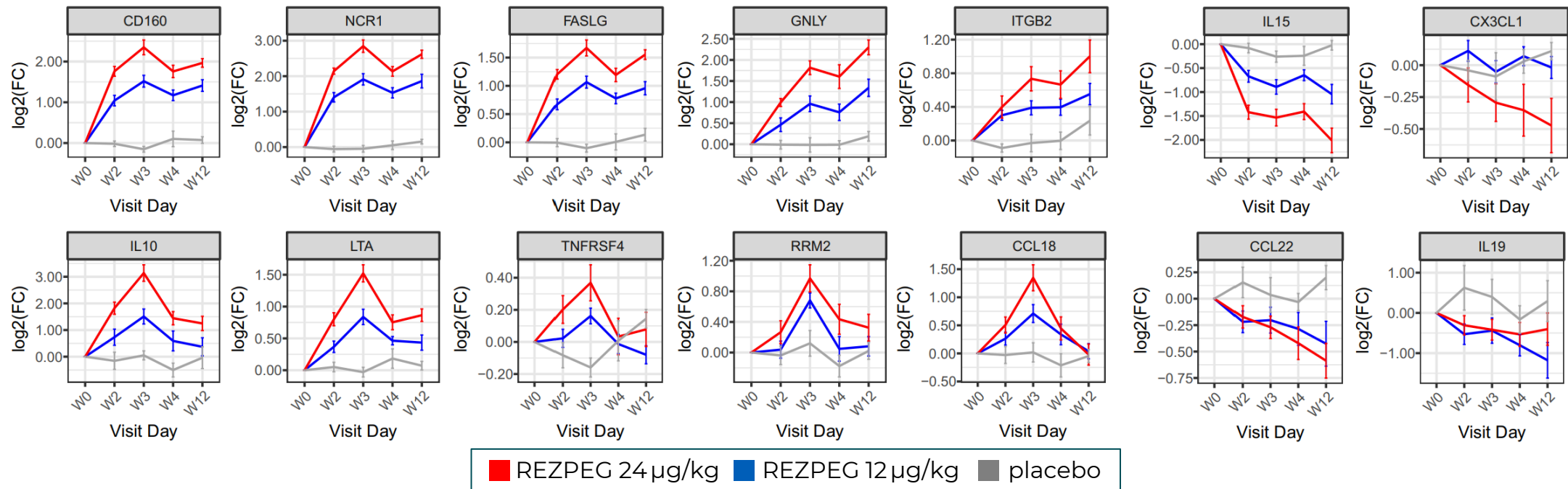
REZPEG utilizes the approved recombinant human IL-2 (rhIL-2) aldesleukin sequence with stable, covalently attached polyethylene glycol (PEG) moieties, extending the half-life and conferring a selectivity for regulatory T cells (Treg) stimulation.

By targeting receptors on Tregs, **REZPEG stimulates proliferation** of these cells, including FOXP3⁺ Tregs, and works as a **master immune-modulator** upstream of the pro-inflammatory cytokine pathways.



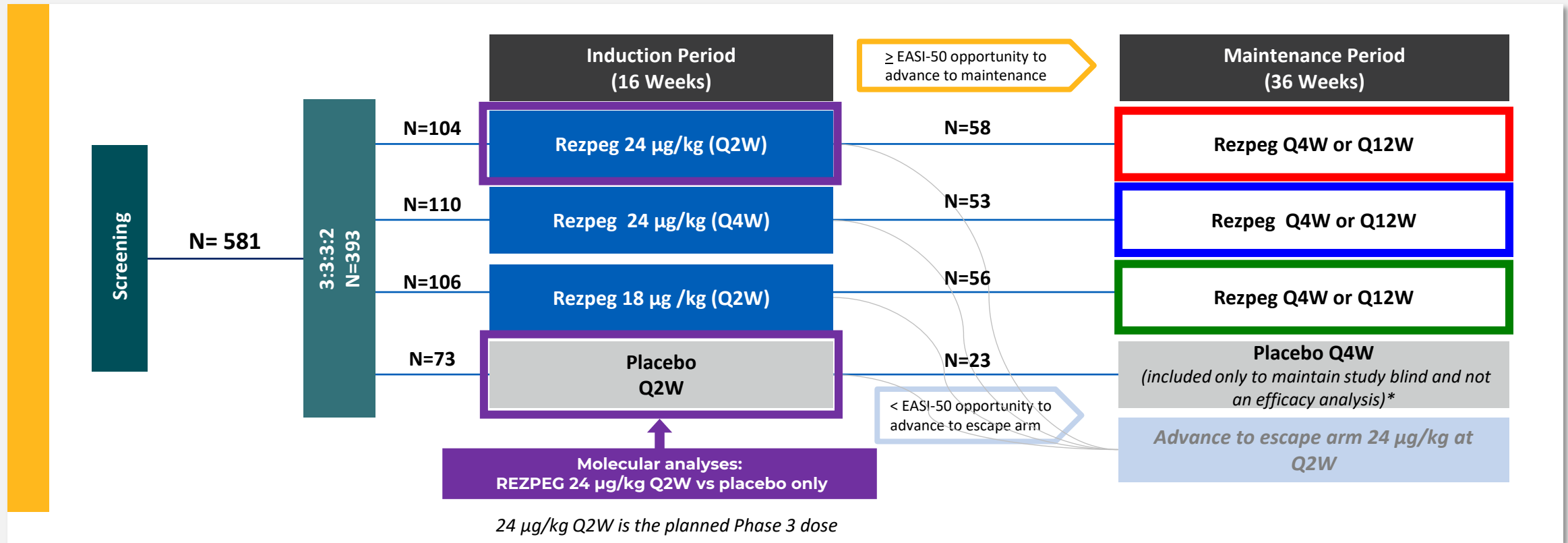
Molecular findings from phase 1b trial

The protein expression profiles of serum biomarkers exhibited **dose- and time-dependency of REZPEG administration** over the 12-week induction period



Silverberg JI, Rosmarin D, Chovatiya R, Bieber T, Schleicher S, Beck L, et al. The regulatory T cell-selective interleukin-2 receptor agonist rezpegaldesleukin in the treatment of inflammatory skin diseases: two randomized, double-blind, placebo-controlled phase 1b trials. *Nat Commun.* 2024;15(1):9230.

Phase 2b trial explored efficacy and safety of REZPEG in subjects with moderate-to-severe AD



Primary Endpoint: Mean percent change in **EASI** from baseline at Week 16

Exploratory Endpoint: Mean percent change from baseline in pharmacodynamic biomarkers

Study methods and objectives

- Tape strips collected from lesional skin and blood samples of patients from the molecular cohort treated with the planned Ph3 dose (24µg/kg, q2w) **REZPEG (n=59)** or **placebo (n=41)**.
- mRNA was extracted from tape strips and analyzed with **RNA sequencing** with differential expression defined as fold change/FCH>1.5 and p<0.05.
- **Proteomic validation** using tape strips and serum was performed using Olink® Target 96 multiplex platform, with differential expression defined as FCH>1.3 and p<0.05.
- Statistical and correlation analysis with clinical severity scores was performed using Spearman correlations.

Objectives:

- To further **characterize the molecular mechanism of action** of REZPEG
- To evaluate **the effect of REZPEG on AD biomarkers** in both blood samples and tape strips, a non-invasive skin sampling approach to evaluate treatment response

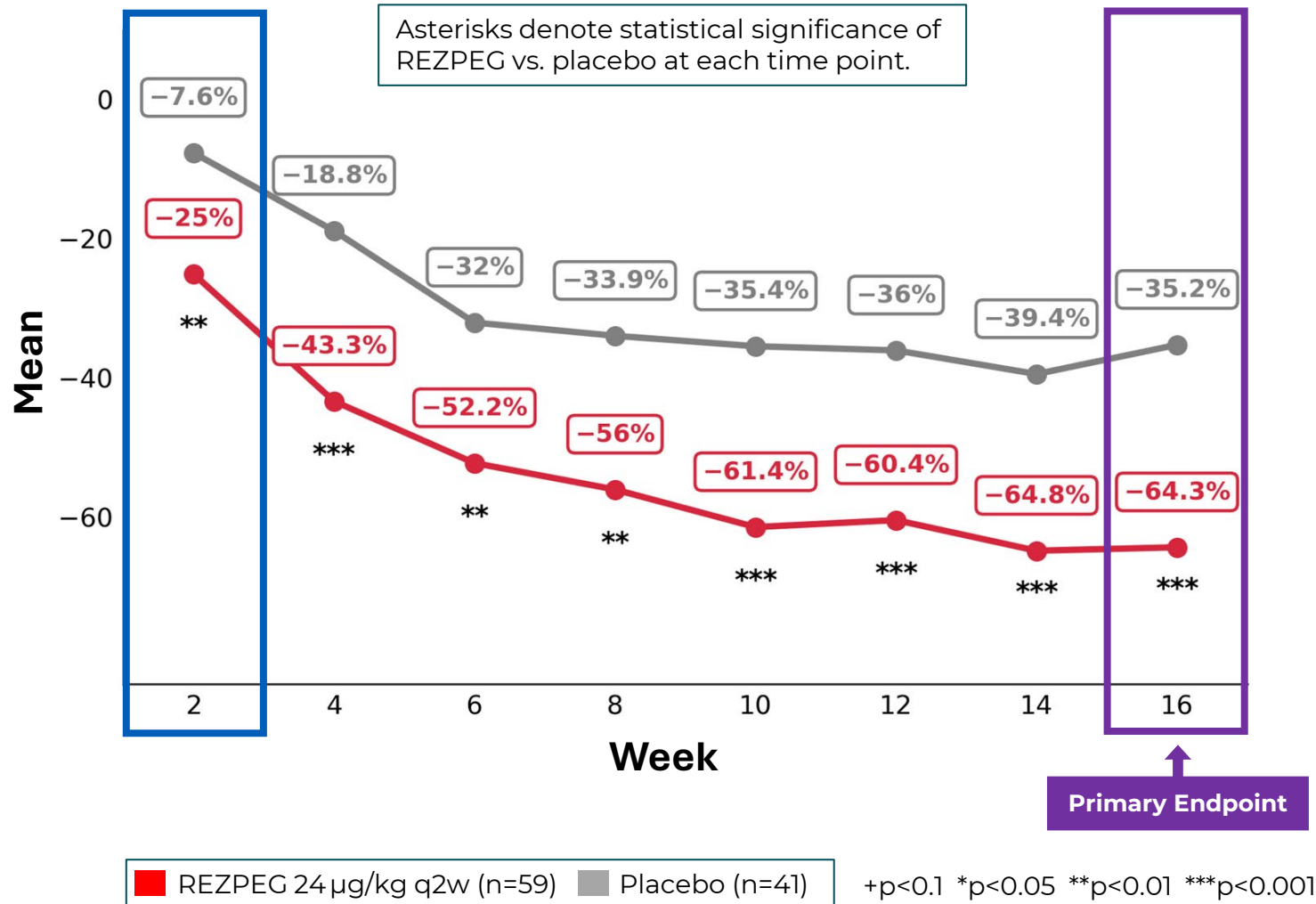
Tape strips: demographics & baseline disease characteristics

**No significant differences
were observed between
treatment groups**

† p value between Rezpeg and placebo patients
Wilcoxon rank-sum test and Fisher's exact test, where appropriate

	REZPEG (24 ug/kg q2w) n=59	Placebo (q2w) n=41	p-value†
Age (years) <i>Mean (SD)</i>	36.6 (13.5)	37.1 (13.8)	0.87
Sex <i>Female</i> <i>Male</i>	28 (47%) 31 (53%)	20 (49%) 21 (51%)	>0.99
Race <i>White</i> <i>Asian</i> <i>Black or African American</i> <i>Other/Unknown</i>	47 (80%) 6 (10%) 5 (8%) 1 (2%)	31 (76%) 7 (17%) 1 (2%) 2 (5%)	0.39
Ethnicity <i>Not Hispanic or Latino</i> <i>Hispanic or Latino</i> <i>Not Reported</i>	57 (97%) 2 (3%) 0 (0%)	36 (88%) 4 (10%) 1 (2%)	0.14
EASI <i>Mean (SD)</i>	26.56 (10.16)	25.1 (9.49)	0.47
BSA <i>Mean (SD)</i>	40.29 (19.13)	37.22 (20.24)	0.44
IGA <i>Moderate (3)</i> <i>Severe (4)</i>	38 (64%) 21 (36%)	26 (63%) 15 (37%)	0.92
NRS-Itch <i>Mean (SD)</i>	6.53 (2.02)	6.22 (2.37)	0.49

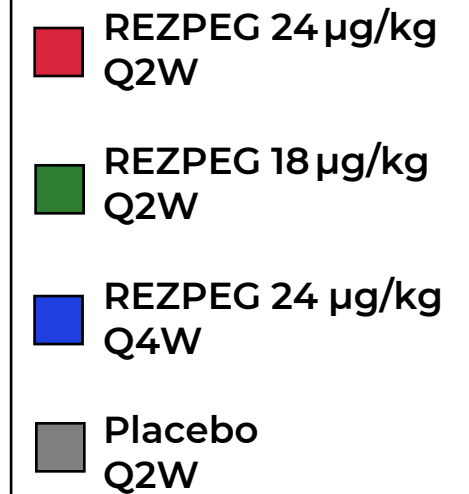
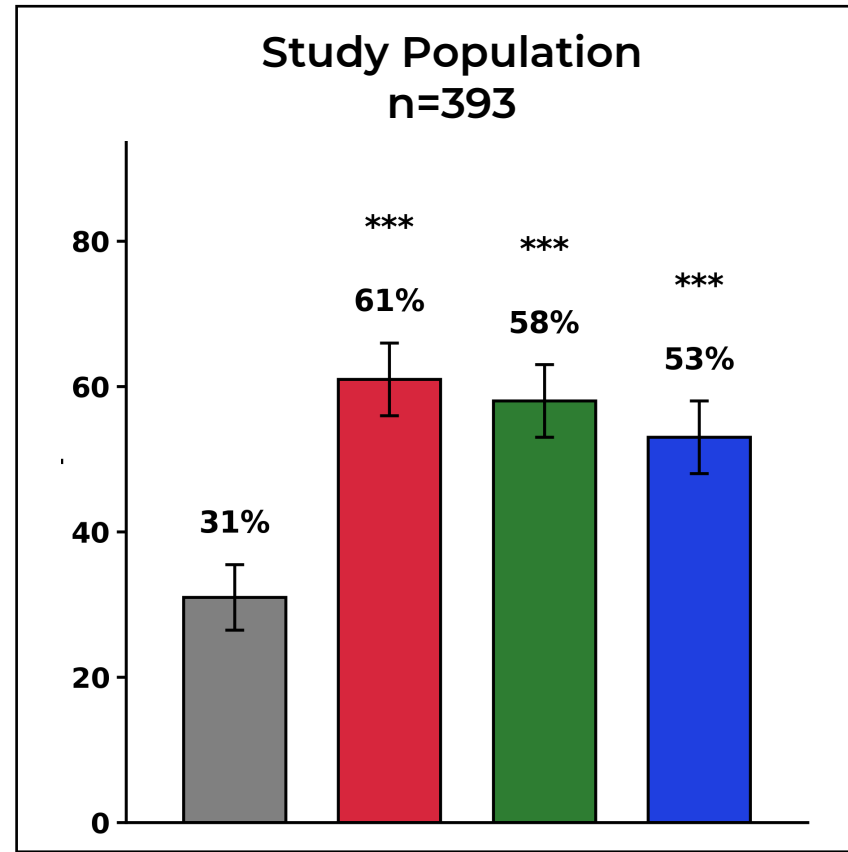
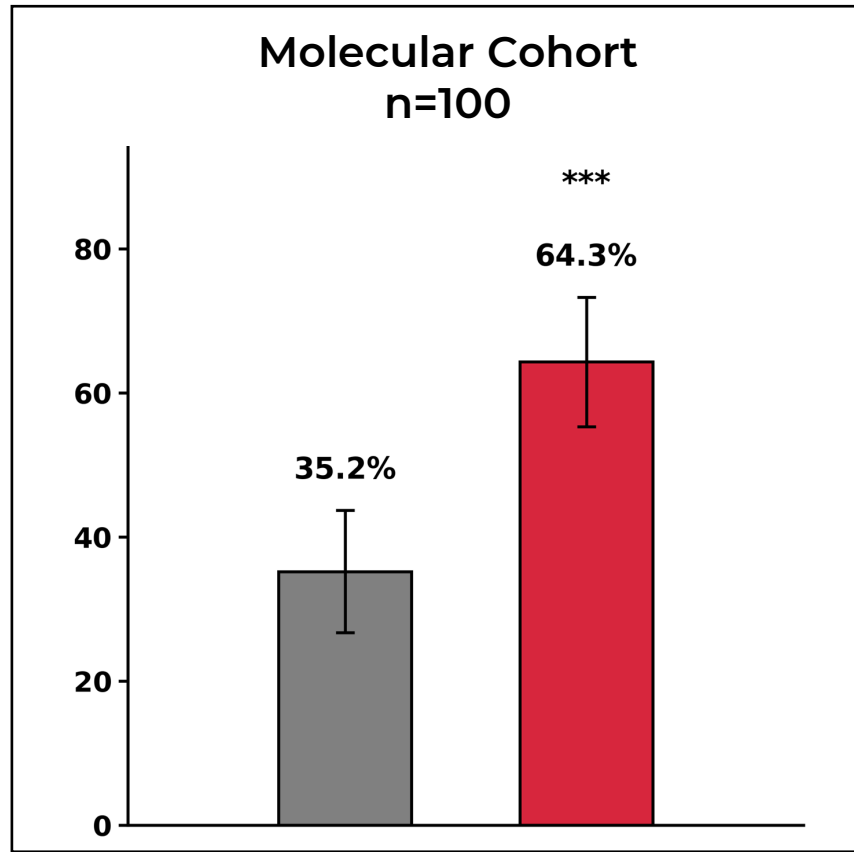
REZPEG produced rapid and clinically meaningful improvement in the molecular cohort



- REZPEG-treated patients achieved a **significantly greater** improvement in EASI at **week 16**, and as early as **week 2**.
- 42% of patients achieved EASI-75 and 75% achieved EASI-50 at week 16.
- 32% of patients achieved a ≥ 2 -pt improvement in IGA at week 16.

Improvement in the molecular cohort demonstrated consistency with overall phase 2b study population

Primary Endpoint: Mean Percent Change in EASI at Week 16



Asterisks denote statistical significance of REZPEG vs. placebo at each time point.

+p<0.1 *p<0.05 **p<0.01 ***p<0.001

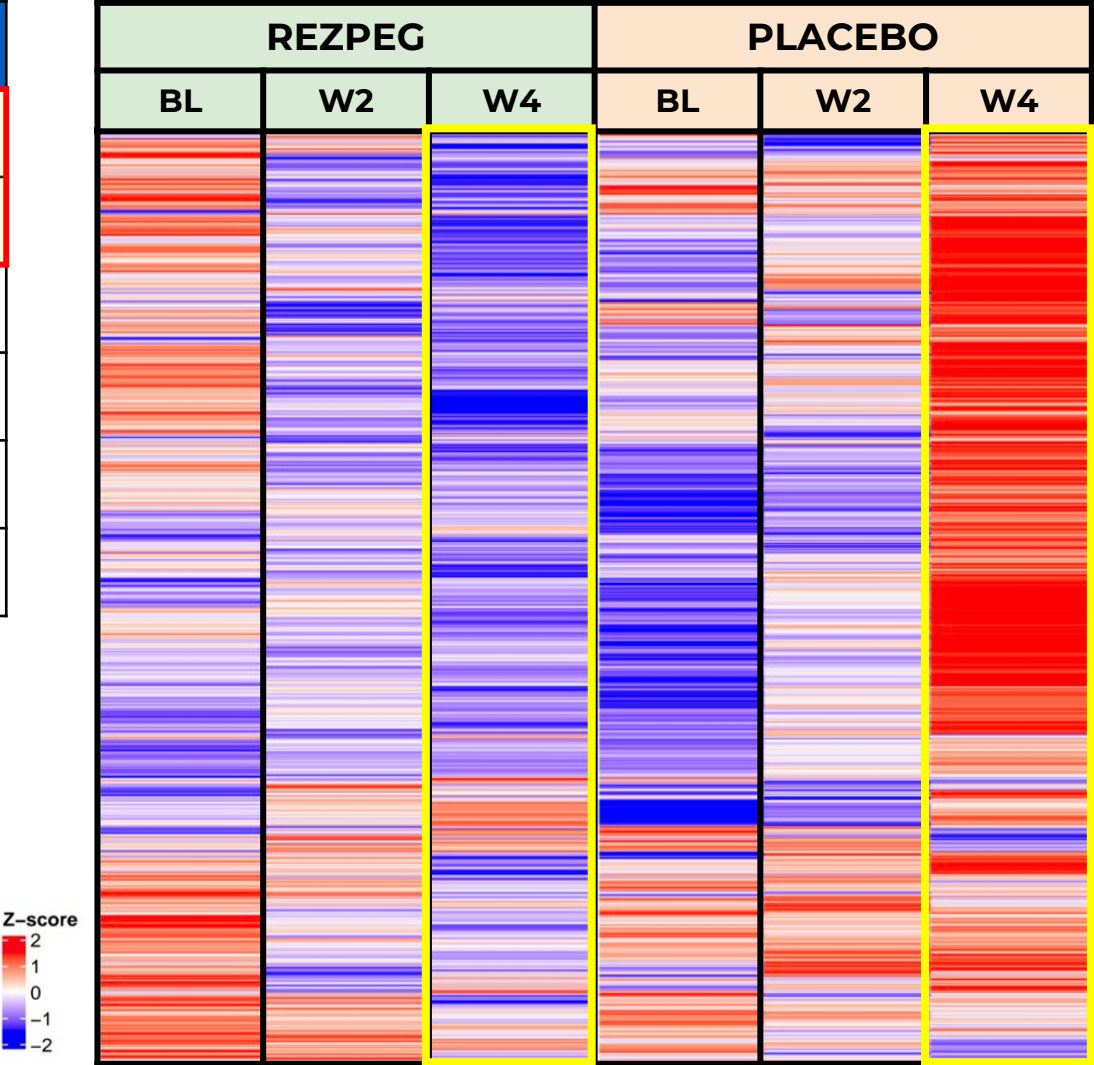
REZPEG induced rapid, broad transcriptomic modulation in lesional skin

 FCH >1.5, p<0.05	Up	Down
REZPEG W4 vs Baseline	180	388
REZPEG W2 vs Baseline	165	212
Placebo W4 vs Baseline	372	16
Placebo W2 vs Baseline	176	99
REZPEG vs PBO W4 vs BL	74	614
REZPEG vs PBO W2 vs BL	95	257

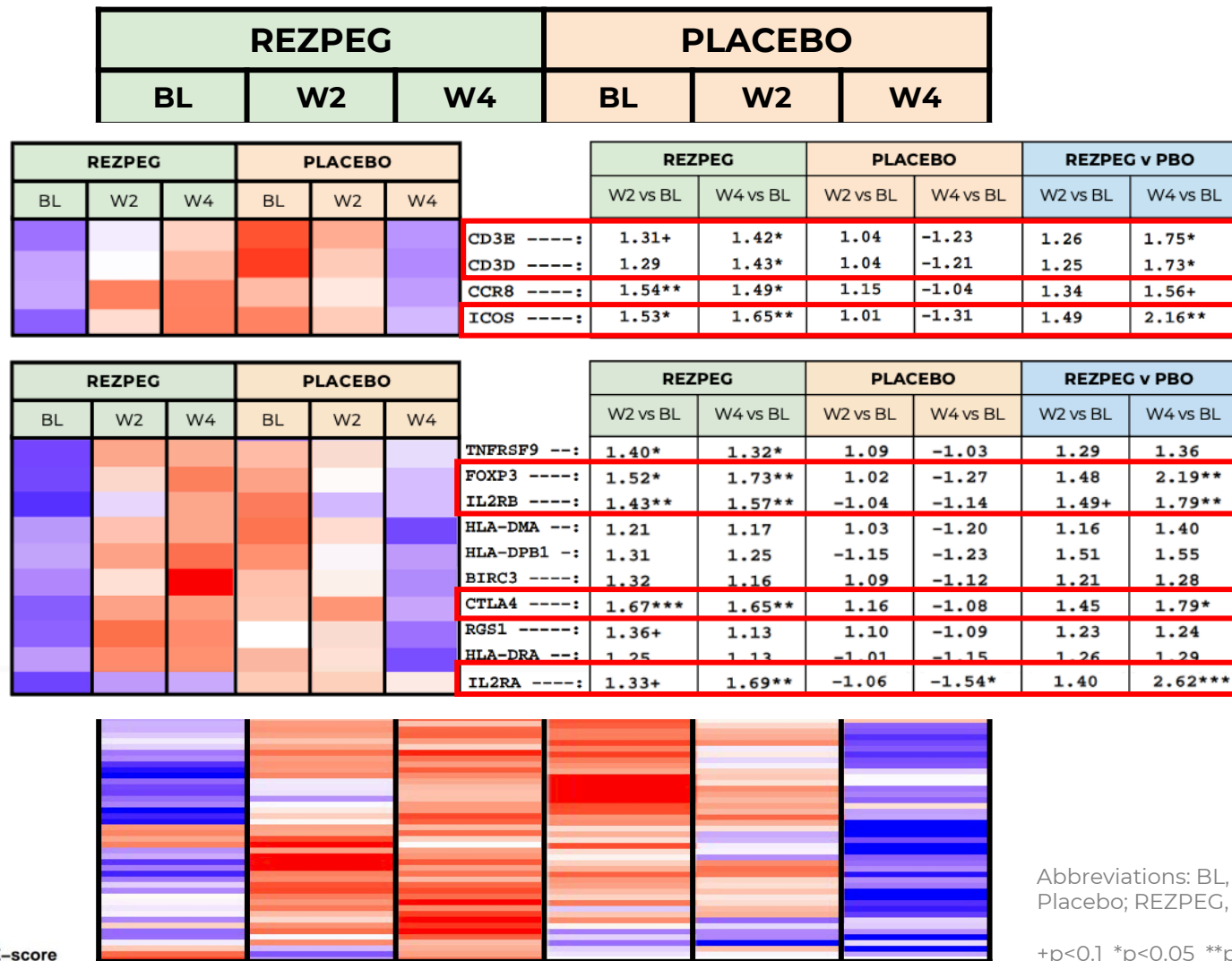
Z-scores reflect relative gene expression across samples, with red indicating higher relative expression and blue indicating lower relative expression.

Abbreviations: BL, baseline; FCH, fold change; PBO, Placebo; REZPEG, Rezpegaldesleukin; W, week.

+p<0.1 *p<0.05 **p<0.01 ***p<0.001



REZPEG increased Treg-associated and regulatory gene expression as early as week 2

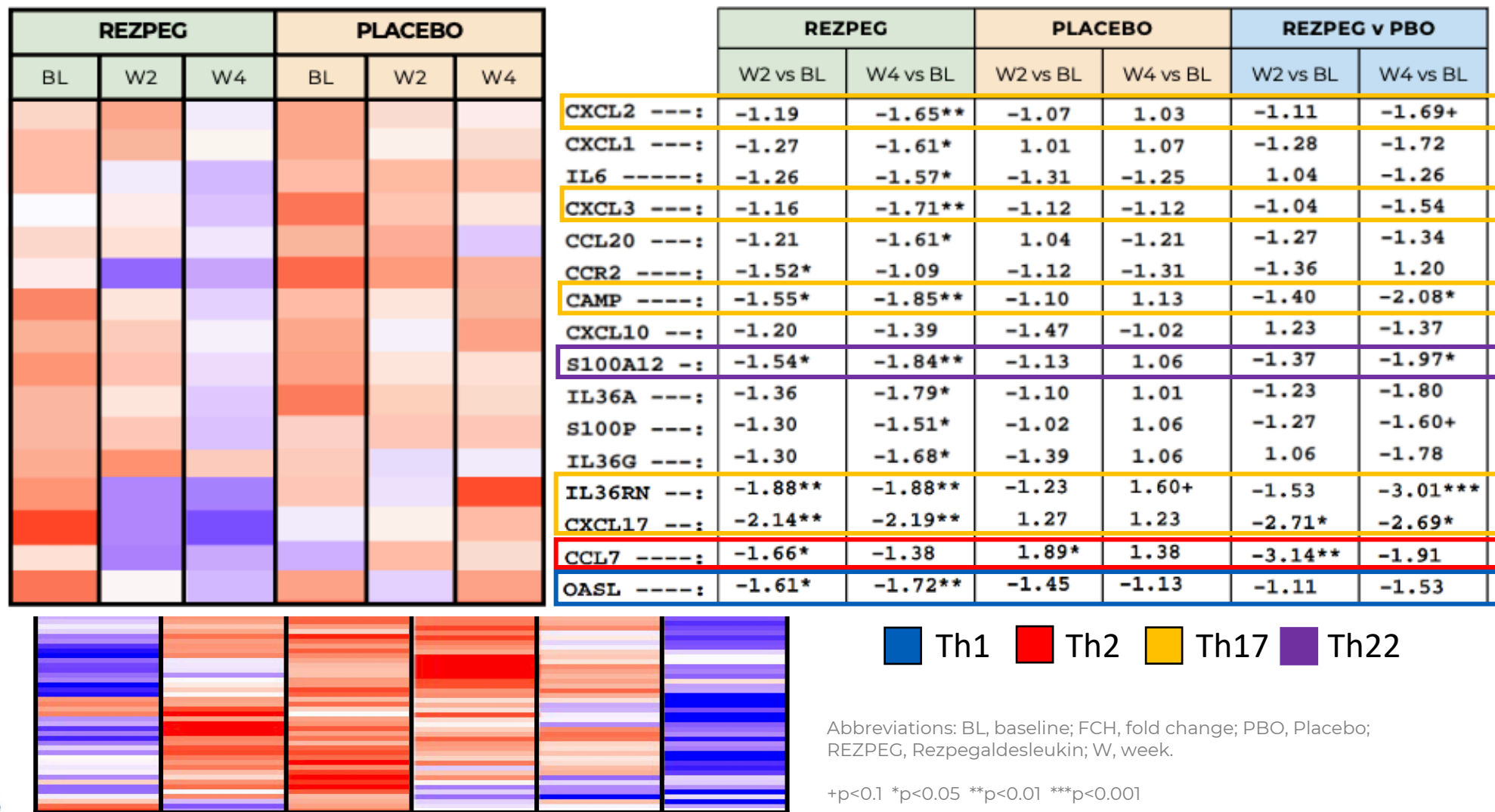


- REZPEG induced early upregulation of T-cell biomarkers, including **CD3D**, **CD3E**, **ICOS**.
- FOXP3** and **IL2RA**, hallmark genes identifying Tregs, increased with REZPEG treatment by week 2.
- These changes highlight early expansion and activation of regulatory T-cell programs.

Abbreviations: BL, baseline; FCH, fold change; PBO, Placebo; REZPEG, Repegaldesleukin; W, week.

+p<0.1 *p<0.05 **p<0.01 ***p<0.001

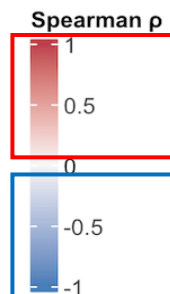
REZPEG drives **early changes** in immune pathways of implicated in AD



Independent RNA and protein analyses confirmed coordinated molecular effects of Rezpeg by week 4

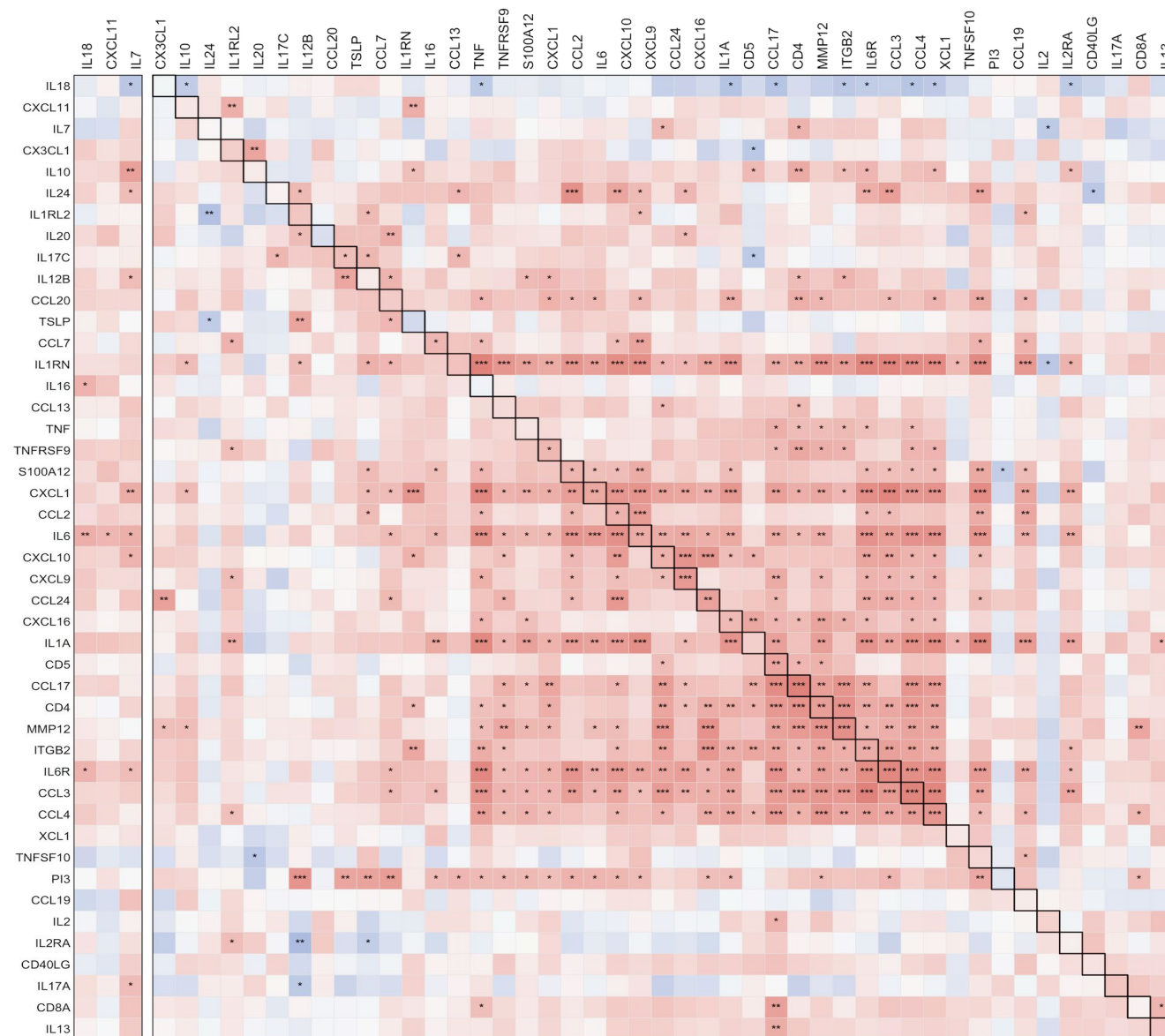
Positive correlations

Negative correlations



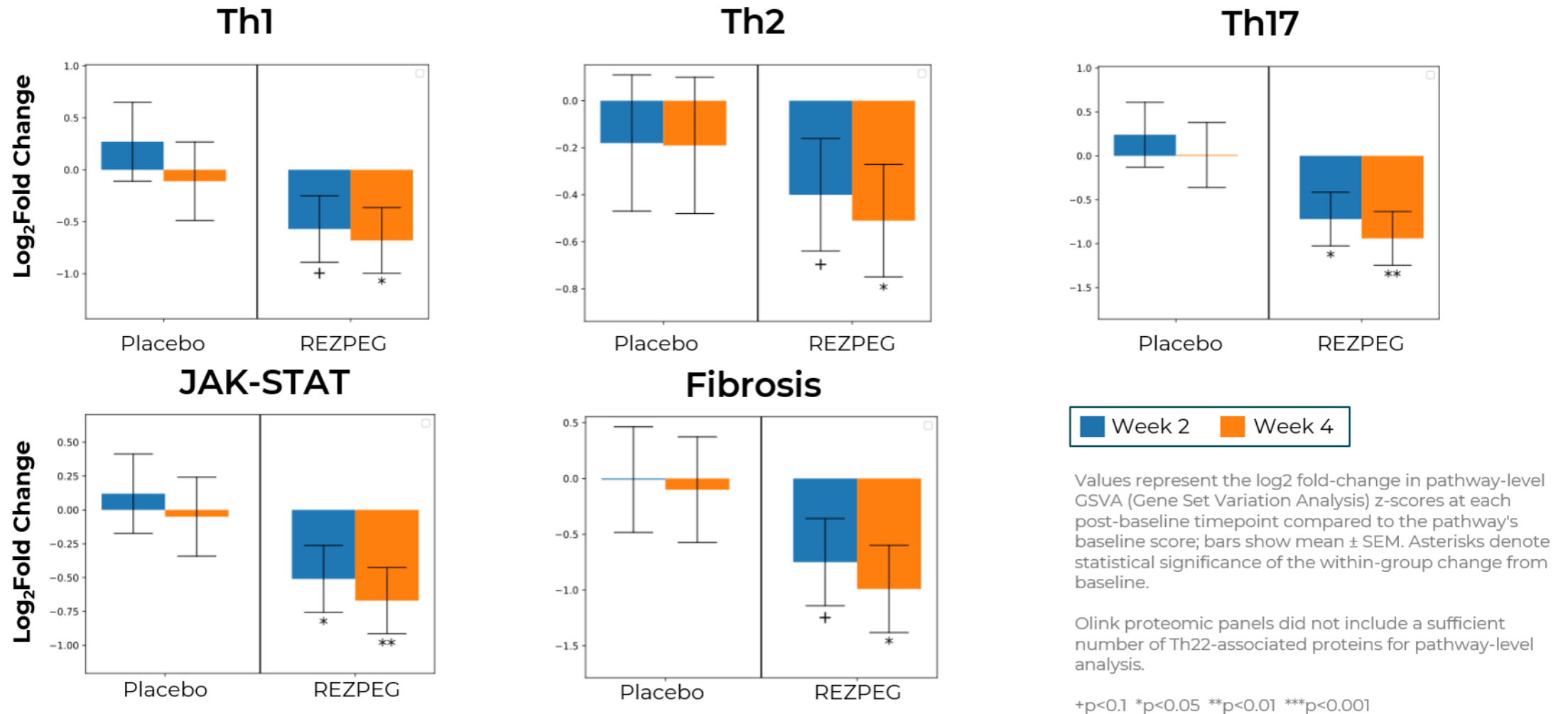
+ : $p < 0.1$ * : $p < 0.05$ ** : $p < 0.01$ *** : $p < 0.001$

RNA Seq - Tape Strips

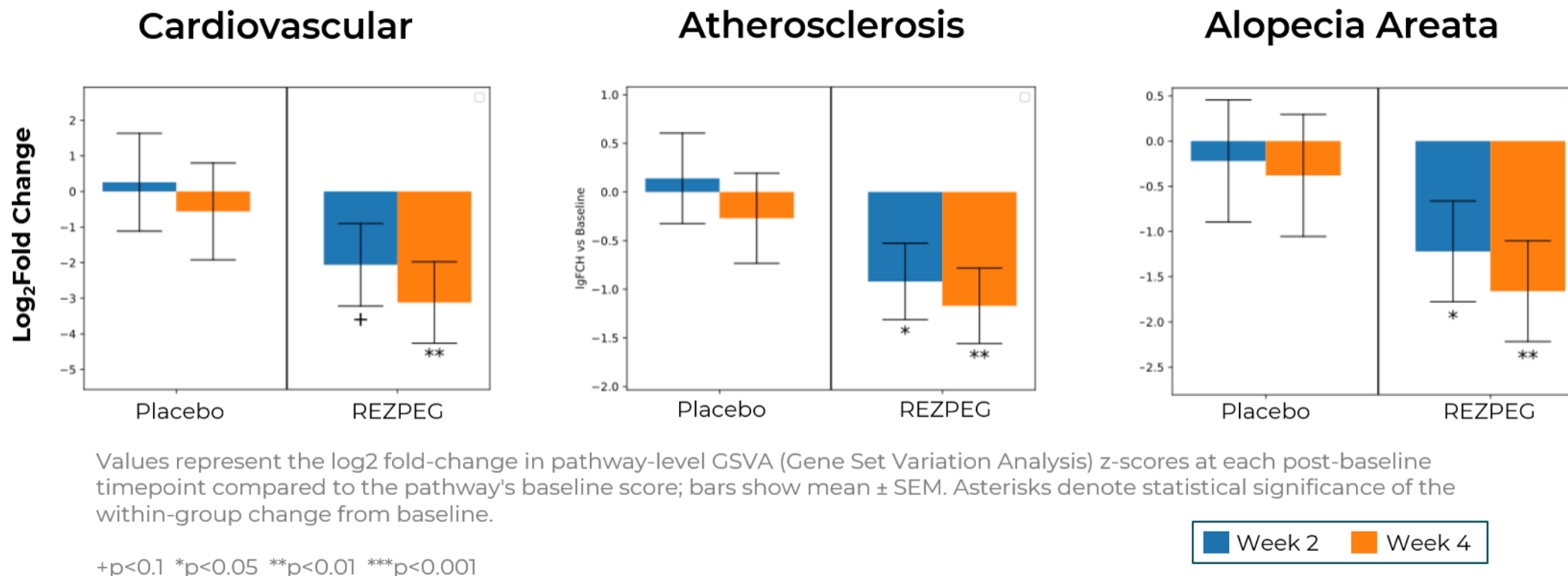


Protein - Tape Strips

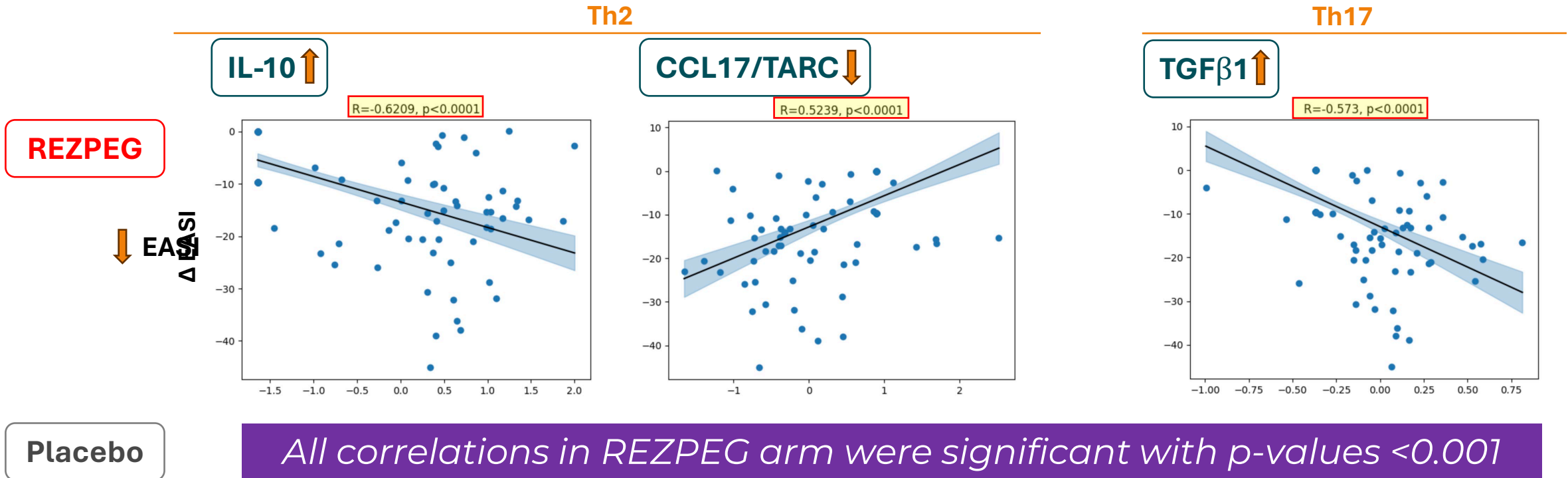
Tape-strip proteomics reveal significant modulation of key immune pathways by week 4



Tape-strip proteomics demonstrate early improvement of validated systemic and cutaneous disease pathways



Early serum biomarker changes associated with improvement in EASI at week 16



- Increases in IL-10 and TGFβ1 expression were associated with greater reductions in EASI at week 16.
- Reduction in CCL17/TARC expression was also associated with greater clinical improvement at week 16.

Conclusion

- REZPEG induced **rapid Treg-associated molecular changes**, with concurrent modulation of the complex immune dysregulation underlying AD.
- Transcriptomic and proteomic analyses demonstrated **systemic and cutaneous normalization** across multiple immune pathways, including Th1, Th2, Th17, and JAK-STAT signaling.
- Molecular effects extended **beyond canonical AD pathways**, including modulation of an alopecia areata-associated signature.
- **Early serum biomarker changes were associated with subsequent EASI improvement**, linking early molecular effects with later clinical response.

These findings support REZPEG as a Treg-directed approach to heterogeneous inflammatory diseases, as demonstrated in AD, through early modulation of dysregulated immune pathways.

If you're interested in learning more about REZPEG...

Rezpegaldesleukin Provides Durable and Deepening Improvements in the Signs and Symptoms of Atopic Dermatitis with Monthly and Quarterly Dosing: Results from the Phase 2b REZOLVE-AD Maintenance Part of Study

Presenter: Dr. Thomas Bieber

Presentation Date and Time: Thursday, October 1st 10:25 – 10:35 CEST

Location: Hall N

Rezpegaldesleukin, a Novel Regulatory T Cell-Inducing Biologic, Demonstrates Efficacy and Safety in Severe-to-Very-Severe Alopecia Areata: 52-Week Results from the Phase 2b REZOLVE-AA Study

Presenter: Dr. David Rosmarin

Presentation Date and Time: Thursday, October 1st 16:30 – 16:40 CEST

Location: Hall N



Thank you!