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# Treatment with the oral CCR4 antagonist RPT193 results in meaningful changes in cutaneous biomarkers detected by transcriptomic profiling of tape-strips

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## INTRODUCTION

- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by cytokine activation and barrier dysfunction driven by Th2 inflammation.
- RPT193 is an oral CCR4 antagonist, inhibiting the migration and subsequent activation of Th2 T-cells.
- Here, we present biomarker data collected during a double-blinded phase 1b study evaluating the safety and efficacy of RPT193 as monotherapy.

## OBJECTIVE

- **To further characterize the mechanism of action of RPT193**
- **To assess changes in the skin transcription profile using tape-strips in RPT193- or placebo-treated AD subjects**

## METHODS

### Study Design

Using tape-strips, we analyzed the effect of RPT193 on skin biomarkers in 30 subjects with moderate-to-severe AD subjects receiving either RPT193 400mg once daily (n=20) or placebo (n=10) for 4 weeks. Tape-strips were collected from lesional and non-lesional skin at baseline and on day 29 and analyzed with RNA-seq.

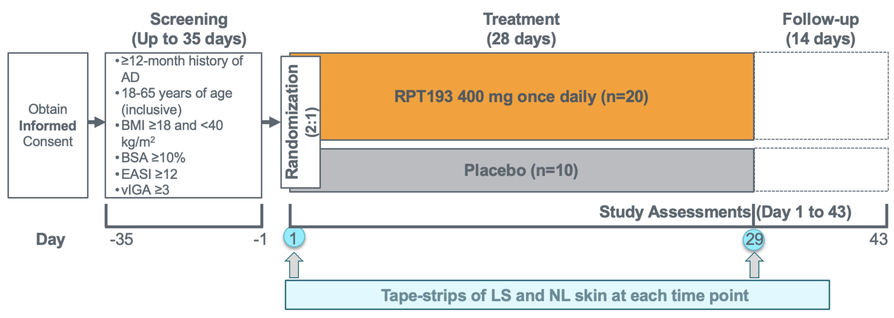
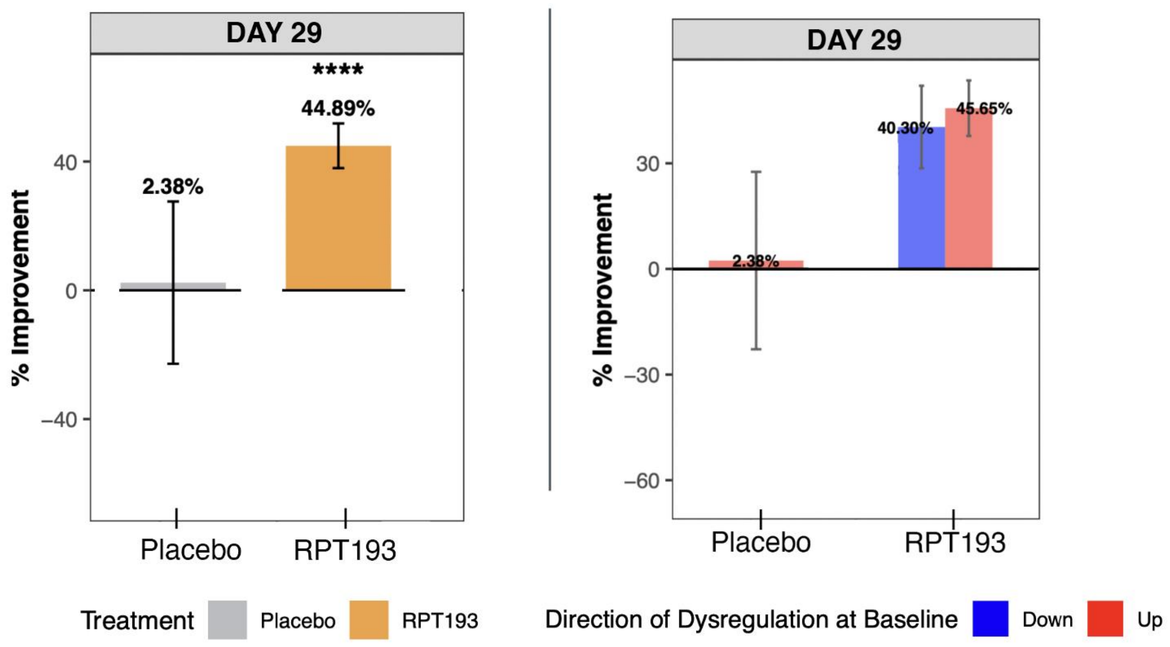



**Figure 1. Study design**

Significance was defined using criteria of |fold change|>2 and p<0.05. Biomarker changes were correlated with improvements in clinical severity and itch (EASI, SCORAD, NRS).

## RESULTS

At baseline, 4,446 genes (1,452 up; 2,994 down) were differentially expressed between lesional and non-lesional skin across treatment arms. By Day 29, RPT193 improved expression of a subset of 174 immune genes by 45%, compared to 2.38% with placebo.




Relative to baseline, RPT193 significantly decreased expression of many key AD-related biomarkers in lesional and/or non-lesional skin by 4 weeks, including those related to Th1 (*IL2*, *IL2RA*, *IL12RB2*), Th2 (*CCR4*, *IL13*, *IL31*), and Th17/22 (*PI3*, *IL22*, *IL32*, *IL36A*, *S100A9*, *S100A12*).

**Figure 2. percentage improvement of the AD immune transcriptome in treatment and placebo group. Improvement is measured toward non-lesional tissue at baseline.**
Black = comparison of mean % Improvement to 0. + : p<0.1, * : p<0.05 ** : p<0.01

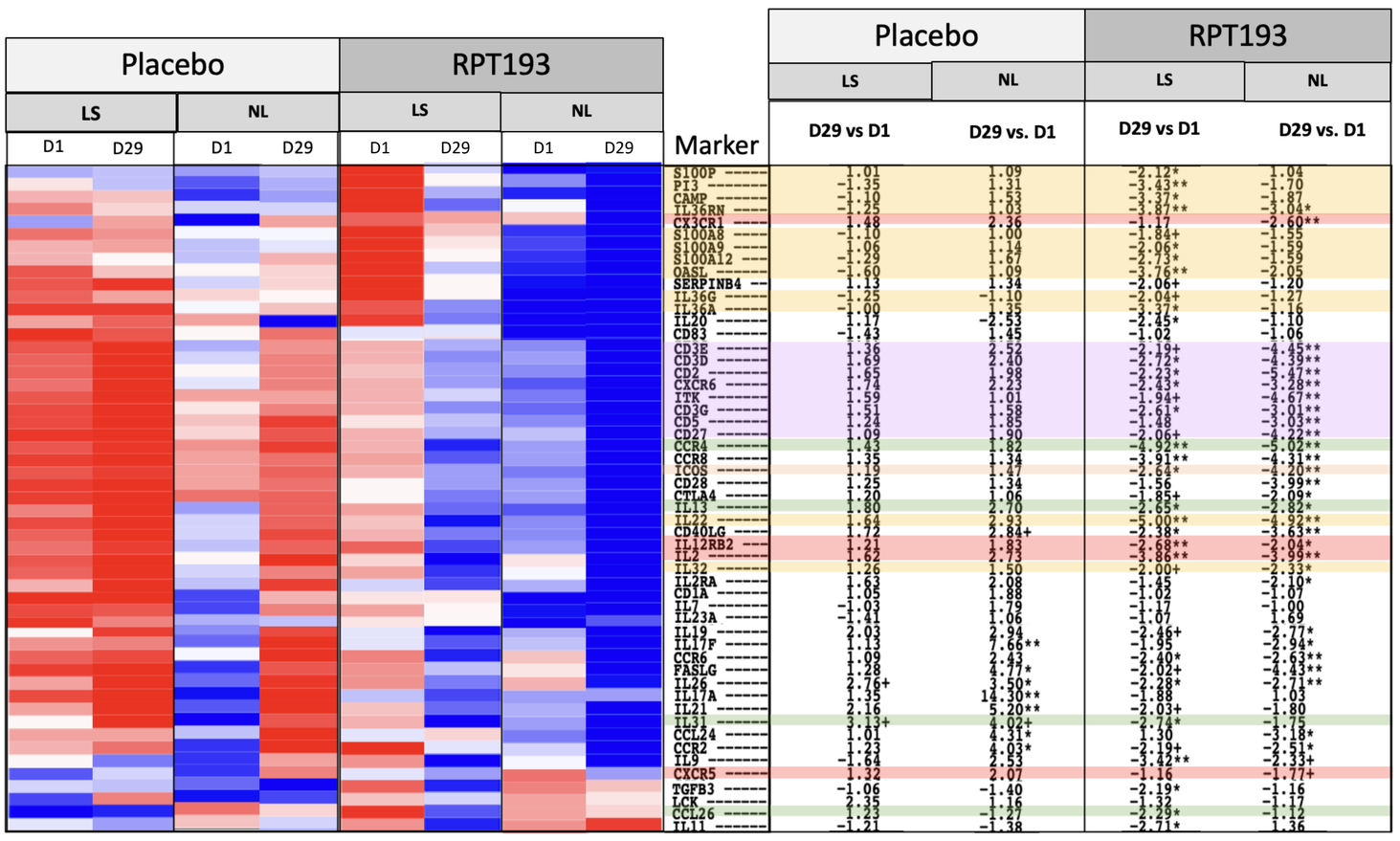



**Figure 3. Immune heatmap.** Comparisons of Change from Baseline (Day 1). LS, lesional; NL, non lesional. + : p<0.1 * : p<0.05 ** : p<0.01

EASI, SCORAD, and itch scoring (NRS) correlated significantly and positively with skin biomarkers central to AD disease. Changes in the tape-strip-derived AD transcriptome correlated significantly with corresponding skin biopsy data (data not shown).

**EASI score**

| | Spearman R | p-value |
|---|---|---|
| SGMS2 | 0.62 | 0.001 |
| SPHK2 | 0.58 | 0.003 |
| SPTLC2 | 0.57 | 0.004 |
| **S100A7A** | **0.53** | **0.008** |
| **SERPINB4** | **0.53** | **0.008** |
| UGCG | 0.49 | 0.014 |
| **S100A7** | **0.49** | **0.015** |
| **DEFB4A** | **0.49** | **0.016** |
| TGM3 | 0.48 | 0.018 |
| GBA | 0.47 | 0.021 |
| CNFN | 0.47 | 0.022 |
| SPRR2D | 0.46 | 0.023 |
| **IL22** | **0.46** | **0.024** |
| SAMD8 | 0.45 | 0.027 |
| **S100A9** | **0.44** | **0.031** |
| EREG | 0.44 | 0.033 |
| KRT79 | 0.43 | 0.036 |
| SPRR2G | 0.42 | 0.041 |
| PLA2G4D | 0.42 | 0.041 |
| GM2A | 0.41 | 0.047 |
| **S100A8** | **0.41** | **0.048** |
| ALOX12B | 0.41 | 0.048 |
| **LCN2** | **0.41** | **0.049** |
| **SPRR1A** | **0.40** | **0.051** |
| IL36A | 0.36 | 0.080 |
| IL7 | 0.36 | 0.082 |
| **KRT1** | 0.35 | 0.089 |

**SCORAD**

| | Spearman R | p-value |
|---|---|---|
| UGCG | 0.52 | 0.010 |
| TGM3 | 0.52 | 0.010 |
| **PPL** | 0.51 | 0.012 |
| **CNFN** | 0.50 | 0.014 |
| SPHK2 | 0.48 | 0.018 |
| **KRT2** | 0.46 | 0.023 |
| **KRT79** | 0.46 | 0.024 |
| **EREG** | 0.46 | 0.025 |
| SGPP2 | 0.45 | 0.028 |
| **IL17C** | **0.45** | **0.029** |
| **CCL25** | **0.45** | **0.029** |
| CERS3 | 0.45 | 0.030 |
| **S100A7A** | **0.44** | **0.032** |
| GBA | 0.44 | 0.033 |
| **KRT1** | 0.44 | 0.034 |
| SPRR1A | 0.43 | 0.035 |
| **IL1RL2** | **0.41** | **0.048** |
| TGM1 | 0.41 | 0.049 |
| **KRT23** | 0.41 | 0.051 |
| ALOX12B | 0.40 | 0.055 |
| **DEFB4A** | 0.40 | 0.055 |
| **IL36RN** | 0.39 | 0.057 |
| **S100A14** | 0.39 | 0.063 |
| **SERPINB4** | 0.39 | 0.063 |
| **S100A9** | 0.36 | 0.083 |
| **S100A7** | 0.35 | 0.091 |

**NRS SCORE**

| | Spearman R | p-value |
|---|---|---|
| TCHH | 0.55 | 0.005 |
| JAM2 | 0.53 | 0.007 |
| **IL4** | **0.46** | **0.025** |
| GJB5 | 0.45 | 0.026 |
| CSTA | 0.43 | 0.036 |
| **IL17C** | **0.41** | **0.049** |
| **CCR6** | **0.39** | **0.056** |
| **S100A14** | **0.39** | **0.059** |
| **CX3CR1** | **0.39** | **0.063** |
| KRT1 | 0.38 | 0.065 |
| TXLNA | 0.36 | 0.088 |
| EREG | 0.35 | 0.092 |

**EASI Score**

| | Spearman R | p-value |
|---|---|---|
| CXCL10 | -0.60 | 0.022 |
| STAT6 | -0.58 | 0.021 |
| **LPL** | **-0.46** | **0.018** |
| CCL1 | -0.45 | 0.016 |
| IL5 | -0.42 | 0.015 |
| IFNA1 | -0.40 | 0.014 |
| **FFAR2** | **-0.38** | **0.008** |
| **AGK** | **-0.37** | **0.008** |
| **CDH19** | **-0.37** | **0.004** |
| PDE9A | -0.36 | 0.003 |
| **ANXA6** | **-0.35** | **0.001** |

**SCORAD**

| | Spearman R | p-value |
|---|---|---|
| FABP4 | -0.51 | 0.084 |
| PSAP | -0.49 | 0.085 |
| LCK | -0.49 | 0.095 |
| IL12RB2 | -0.47 | 0.094 |
| PSORS1C2 | -0.45 | 0.092 |
| CDH5 | -0.43 | 0.088 |
| IFNG | -0.39 | 0.059 |
| FGF17 | -0.38 | 0.056 |
| IL2RA | -0.37 | 0.049 |
| CXCL13 | -0.36 | 0.026 |
| IL6R | -0.35 | 0.005 |

**NRS SCORE**

| | Spearman R | p-value |
|---|---|---|
| **LPL** | **-0.59** | **0.033** |
| CXCL10 | -0.53 | 0.032 |
| IL5 | -0.50 | 0.030 |
| STAT6 | -0.37 | 0.014 |
| IFNG | -0.46 | 0.029 |
| IFNA1 | -0.46 | 0.029 |
| CCL1 | -0.45 | 0.028 |
| **ANXA6** | **-0.43** | **0.025** |
| **CDH19** | **-0.42** | **0.024** |
| **APOL1** | **-0.39** | **0.023** |
| **PSAP** | **-0.38** | **0.018** |
| **ACLY** | **-0.36** | **0.012** |
| CD1B | -0.35 | 0.010 |

Gene grouping:
- Barrier-related
- Th2-related
- Th17/Th22-related
- Hyperplasia-related

**Figure 4. Spearman correlation of skin biomarkers with clinical scores.**

## CONCLUSIONS

**RPT193 induced significant changes in AD-related biomarkers in tape-stripped AD skin after 4 weeks of treatment. Transcriptional changes correlated with biopsy RNA-seq data (data not shown) and improved clinical metrics.**

These data suggest that RPT193 treatment improves the AD skin transcriptome, consistent with observed clinical efficacy and with decreases in CCR4 expression in the skin and on circulating Th2 cells. A phase 2 study investigating the safety and efficacy of RPT193 in patients with moderate-to-severe AD is ongoing (NCT05399368).

## REFERENCES

Bieber T et al. *Nat Rev Drug Discov.* 2022;22:21-40. Weidinger S et *Nat Rev Dis Primers.* 2018;4:1. Czarnowicki T et al. *J Allergy Clin Immunol.* 2019;143:1-11.