

5th Inflammatory Skin Disease Summit

The Translational Revolution

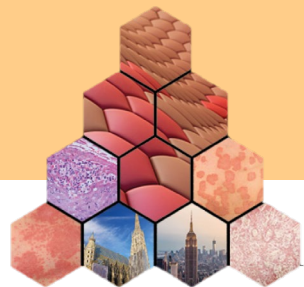
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Treatment with the Oral CCR4 Antagonist RPT193 Results in Meaningful Changes in Cutaneous Biomarkers Detected by Transcriptomic Profiling of Tape-Strips

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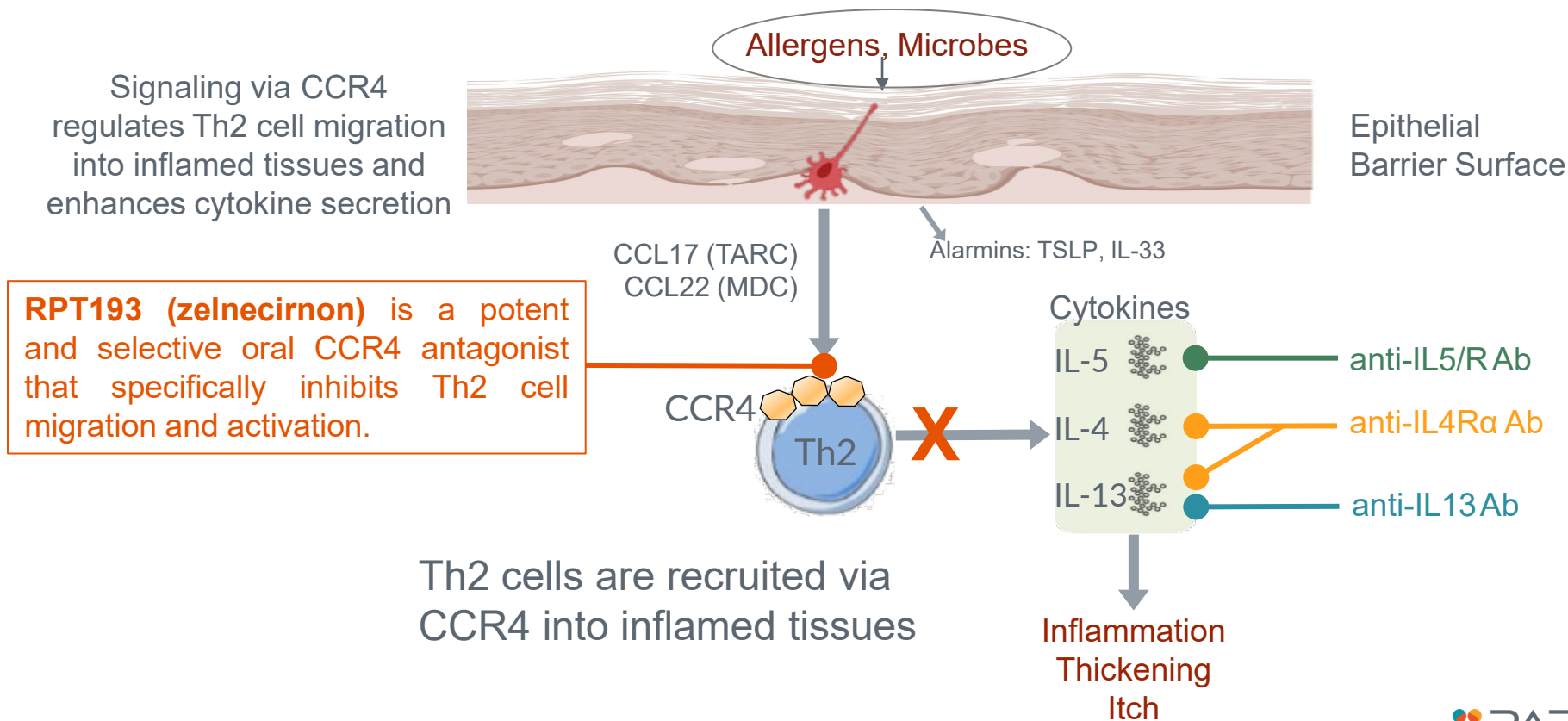
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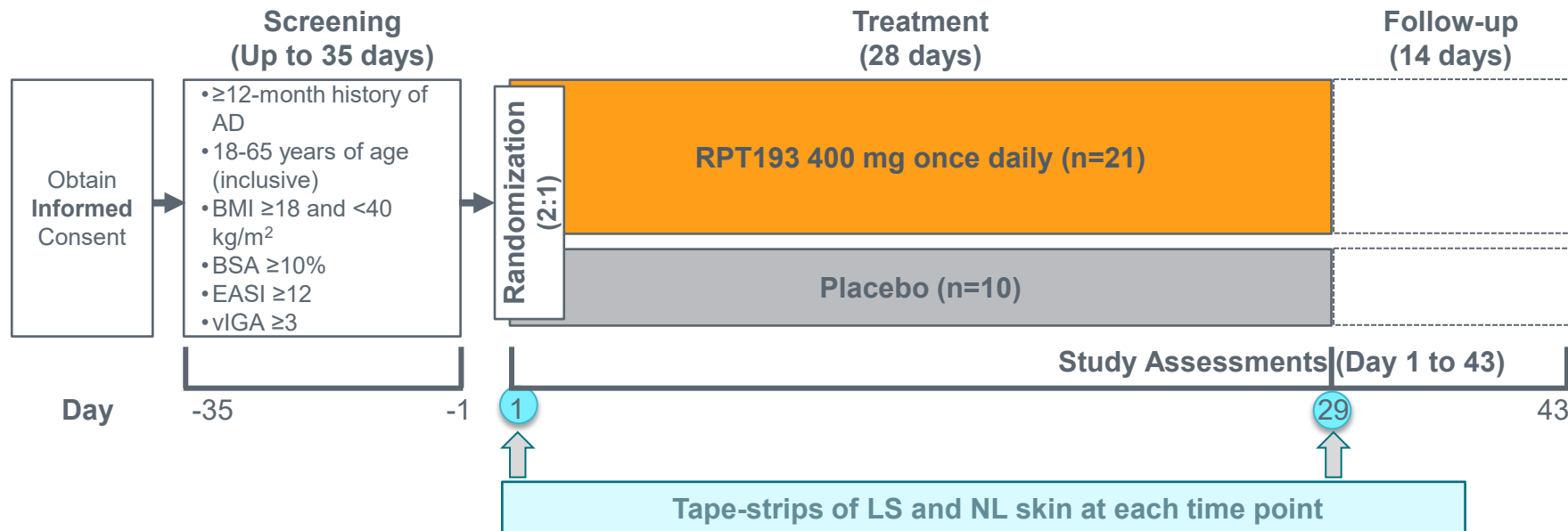
No COIs to disclose

RPT193 (zelnecirnon) Targets Th2 Cells: Key Drivers of Inflammation in Atopic Dermatitis, Asthma, and Other Diseases





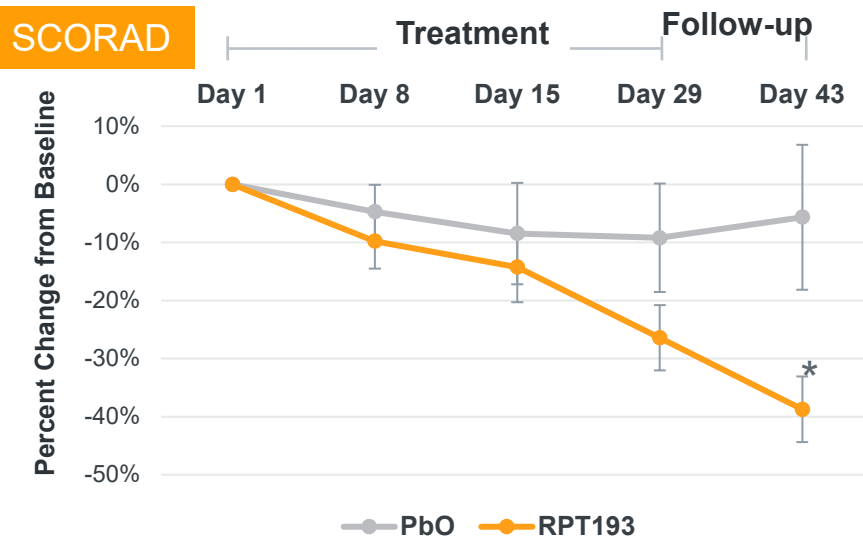
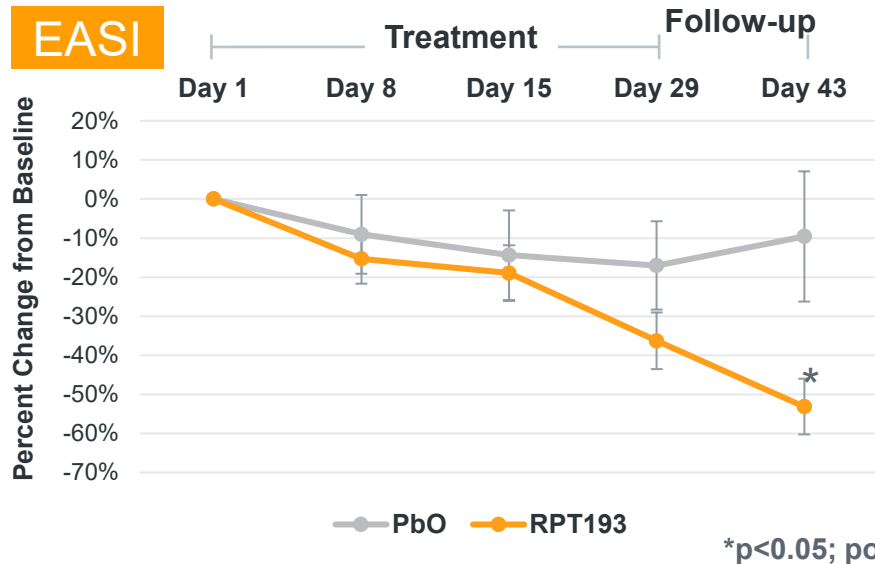
Phase 1b Trial Explored RPT193 Activity in Subjects with Moderate-to-Severe Atopic Dermatitis



- Phase 1b trial part of a broader study including healthy volunteers to investigate single and multiple doses of RPT193
- Double-blind, randomized, monotherapy study
- Primary and secondary endpoints were safety and PK
 - Trial was not powered for clinical endpoints (EASI and SCORAD were exploratory endpoints)
- In addition to tape-strips, skin biopsies, plasma and whole-blood biomarker assessments were performed (data not shown)



RPT193: Previously Reported Phase 1b Data



RPT193 demonstrated improvement compared to placebo in EASI and SCORAD at Day 29 with further deepening of response at Day 43

Once-daily, oral RPT193 was well tolerated after 28 days of dosing



Aims

- To further characterize the molecular mechanism of action of RPT193
- This study on the MOA aimed to evaluate the effect of RPT193 on AD biomarkers using tape-strips, a novel, noninvasive skin sampling approach to evaluate treatment response



-
- Skin Biomarker Analysis**
- Lesional
- Nonlesional
- Placebo
- RPT193
- LS NL
- D1 D29 D1 D29 D1 D29 D1 D29
- RNA-sequencing transcriptomic analysis**



Patient Demographics

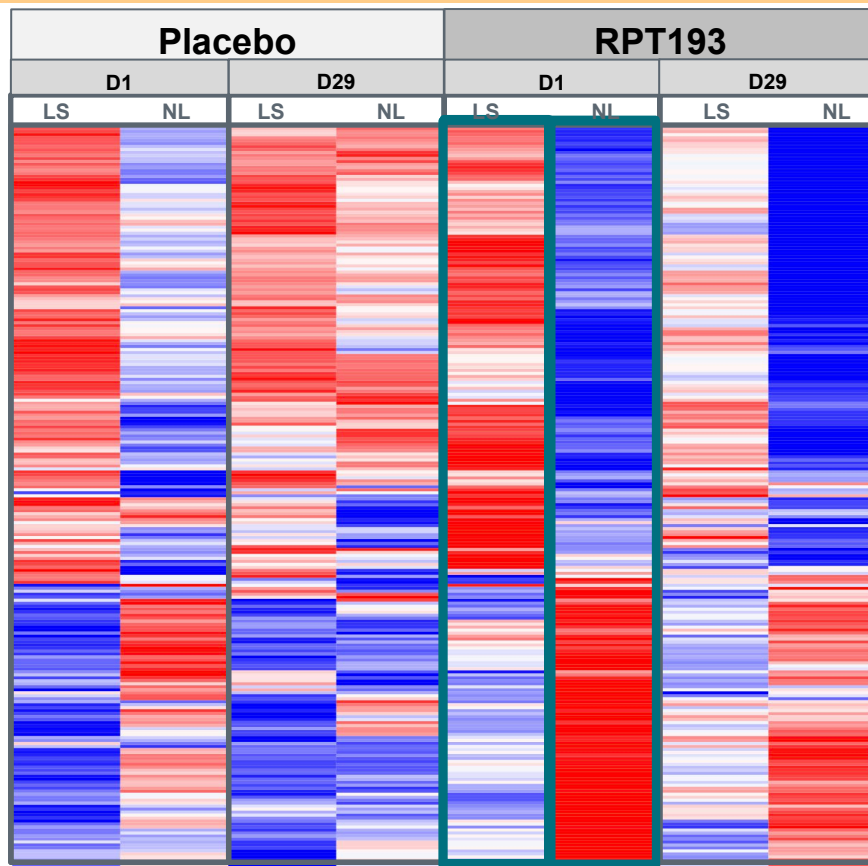
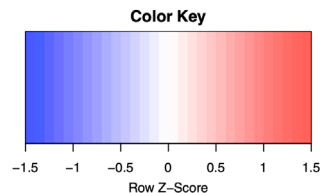
Patient characteristics
are balanced between
treatment arms

	Placebo n = 10		RPT193 n = 20		p-value
Age (years)					0.42
Mean (Standard Deviation)	35.8 (14.8)		40.5 (13.6)		
Range	22-64		19-63		
Sex	n	%	n	%	0.44
Male	6	60%	8	40.0%	
Female	4	40%	12	60.0%	
Race	n	%	n	%	0.61
Black	5	50.0%	7	35.0%	
White	5	50.0%	11	55.0%	
Asian	0	0%	2	10%	
IGA					0.75
Mean (Standard Deviation)	3.2 (0.4)		3.2 (0.4)		
Range	3-4		3-4		
EASI					0.39
Mean (Standard Deviation)	21.1 (9.4)		18.2 (5.7)		
Range	13.6-45.5		12-30		
BSA					0.84
Mean (Standard Deviation)	24.5 (15.1)		23.4 (11.7)		
Range	10-61		11-55		
NRS					0.62
Mean (Standard Deviation)	7.3 (2.1)		6.9 (2)		
Range	3-10		3-10		
SCORAD					0.95
Mean (Standard Deviation)	56.6 (12.4)		56.9 (11.9)		
Range	41-81.4		36.6-82.4		
POEM					0.34
Mean (Standard Deviation)	20.2 (6.3)		17.8 (6.7)		
Range	9-28		3-28		
DLQI					0.88
Mean (Standard Deviation)	12.5 (6.4)		12.9 (8.1)		
Range	2-24		2-29		



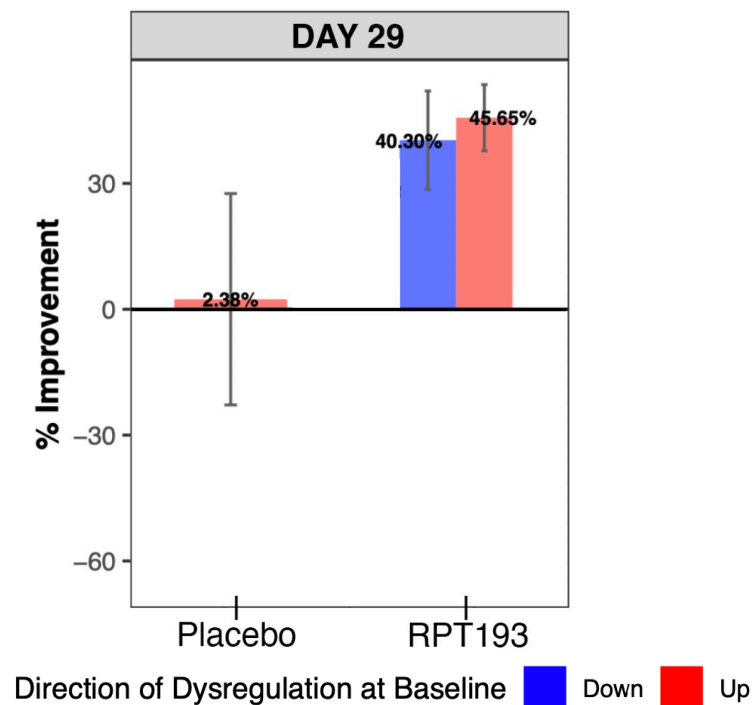
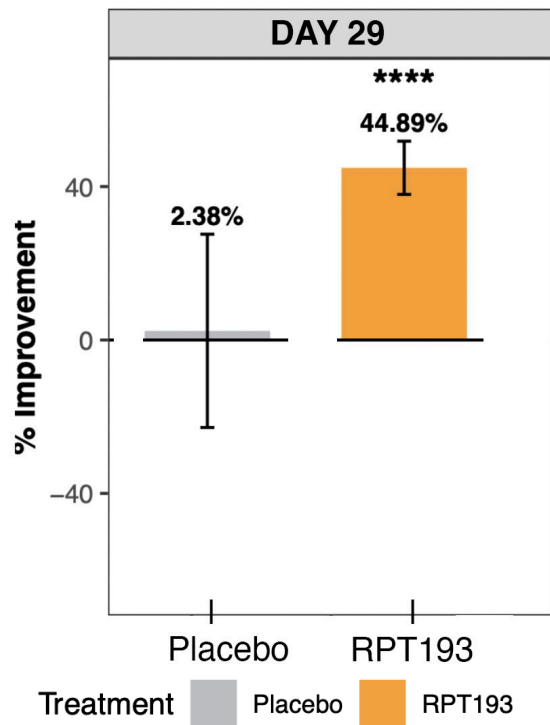
RPT193 Modulates the Lesional AD Transcriptome Towards a Non-Lesional Phenotype ($|FCH| > 2$, $p < 0.05$)

Lesional vs. Non-Lesional				
RPT193	LS vs. NL	Day vs. Baseline	Up	Down
		Day 1	989	2412
		Day 29	810	3773
Placebo	LS vs. NL	Day 1	463	582
		Day 29	428	513





RPT193 Induces Improvement of the Dysregulation Seen in the AD Immune Transcriptome



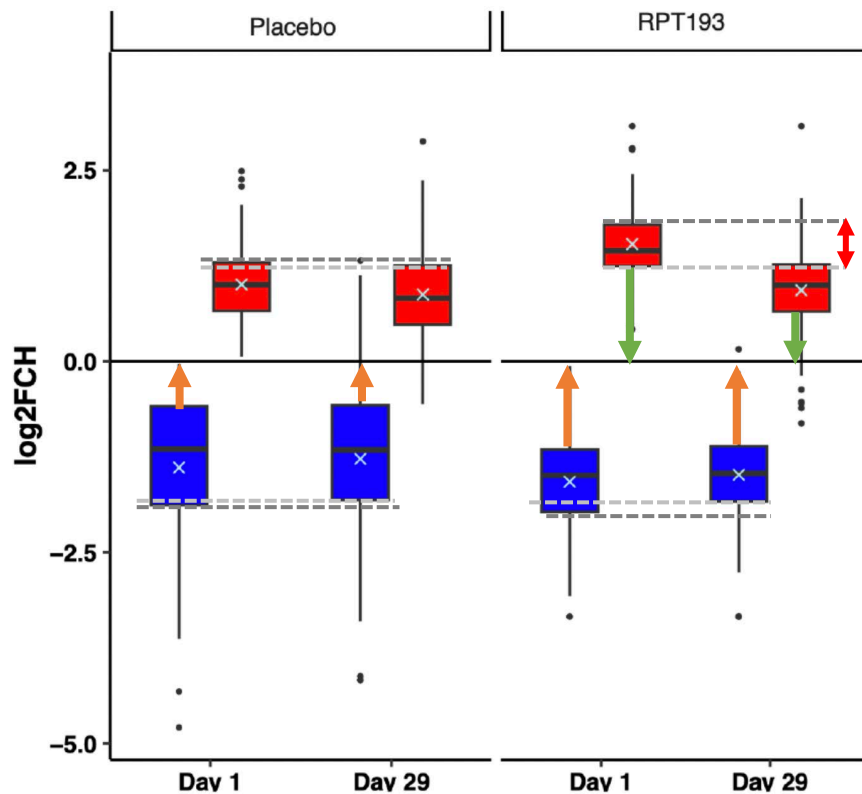
* : $p < 0.05$ ** : $p < 0.01$ *** : $p < 0.001$ **** : $p < 0.0001$

Black = comparison of mean % Improvement to 0

No significant differences in mean improvement between placebo and RPT193 at any time point




RPT193 Reduces Dysregulation of the Lesional Immune Transcriptome Towards that of Non-Lesional Tissue



Mean dysregulation of upregulated genes attenuated more with RPT193 at Day 29

--- Day 1/Baseline
--- Day 29

Direction of Dysregulation at Baseline  Down  Up

Key AD Immune Pathways are Significantly Modulated with RPT193: Th2

Placebo				RPT193				Marker	Placebo		RPT193	
LS		NL		LS		NL			LS	NL	LS	NL
D1	D29	D1	D29	D1	D29	D1	D29		D29 vs D1	D29 vs D1	D29 vs D1	D29 vs D1
								CCL22 ---	-1.43	1.34	1.04	-1.21
								TNFRSF4 ---	-1.06	1.38	-1.48	-1.41
								CCL17 ---	1.12	2.21	-1.31	-1.12
								CCL13 ---	-1.13	3.52+	-1.01	-1.41
								IL10 ----	1.26	2.45	-2.06+	-2.07+
								IL13 ----	1.80	2.70	-2.65*	-2.82*
								CCR4 ----	1.43	1.82	-4.92**	-5.02**
								CCL24 ---	1.01	4.31*	1.30	-3.18*
								IL4R ----	-1.04	1.89+	-1.40	-1.16
								CCR5 ----	1.30	1.95	-1.28	-1.01
								IL7R ----	1.81	1.06	1.29	-1.17
								IL31 ----	3.13+	4.02+	-2.74*	-1.75
								TNFSF4 --	-1.36	1.50	1.97+	1.10
								IL5 ----	1.26	1.38	2.07+	-1.62
								STAT6 ---	1.05	-1.39	1.21	1.21
								IL33 ----	1.50	1.01	-1.29	-1.34
								CCL7 ----	-1.17	2.36	-1.81	-1.77
								IL9 ----	-1.64	2.53	-3.42**	-2.33+
								IL4 ----	1.26	2.40	1.30	-1.84
								CCL26 ---	1.23	-1.27	-2.29*	-1.12
								CCR3 ----	-1.23	-1.35	-1.39	-1.35
								TSLP ----	-1.13	1.44	-1.40	-2.16*
								IL25 ----	-1.35	1.31	-1.65+	-2.06*
								CCL11 ---	1.02	-1.10	-1.17	-2.00*

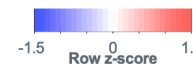
Comparisons of Change from Baseline (Day 1): + : p<0.1 * : p<0.05 ** : p<0.01



Key AD Immune Pathways are Significantly Modulated with RPT193: Th1

Placebo				RPT193				Marker	Placebo		RPT193	
LS		NL		LS		NL			LS	NL	LS	NL
D1	D29	D1	D29	D1	D29	D1	D29		D29 vs D1	D29 vs D1	D29 vs D1	D29 vs D1
								IL1B --	-1.39	2.87	-1.65	-1.20
								IRF1 --	-1.37	2.09	-1.31	1.09
								IFNGR2 .	-1.24	1.69+	1.01	1.04
								TNF ---	-1.17	1.41	-1.32	1.42
								MX1 ---	-1.25	-1.03	-1.48	-1.64
								OASL --	-1.60	1.09	-3.76**	-2.05
								CCR1 --	1.39	2.59	-1.63	-2.00
								CCR2 --	1.23	4.03*	-2.19+	-2.51*
								IFNG --	1.56	3.65+	-1.81	-1.36
								IL12RB2	1.21	1.83	-2.68**	-2.04*
								IL2RA -	1.63	2.08	-1.45	-2.10*
								IL2 ---	1.62	2.73	-3.86**	-3.99**
								IL12B -	-2.35	-1.19	1.94	1.33
								STAT1 -	-1.07	1.75	-1.10	1.19
								CXCL9 -	1.15	3.38	2.21	1.24
								IFNGR1 .	-1.07	1.10	1.18	1.19
								CXCL10 .	-1.00	1.17	-1.00	1.23
								CXCL11	1.45	-2.26	-1.09	1.34

Comparisons of Change from Baseline (Day 1): + : p<0.1 * : p<0.05 ** : p<0.01





Key AD Immune Pathways are Significantly Modulated with RPT193: Th17/Th22

Placebo				RPT193				Marker	Placebo		RPT193	
LS		NL		LS		NL			LS	NL	LS	NL
D1	D29	D1	D29	D1	D29	D1	D29		D29 vs D1	D29 vs D1	D29 vs D1	D29 vs D1
								S100A8 ----	-1.10	1.00	-1.84+	-1.55
								S100A9 ----	1.06	1.14	-2.06*	-1.59
								CAMP ----	-1.10	1.53	-3.37*	-1.87
								SERPINB4 --	1.13	1.34	-2.06+	-1.20
								CXCL1 ----	-1.59	1.80	-2.28+	-1.86
								CXCL2 ----	-1.75	1.82	-1.48	-1.17
								STAT3 ----	1.10	1.84+	-1.22	1.01
								SERPINB1 --	-1.06	2.34+	-1.30	-1.02
								IL17RA ----	-1.04	1.61	-1.28	1.09
								CCL20 ----	1.05	2.57	-1.68	1.56
								CXCL3 ----	-1.48	1.04	-1.72	1.30
								IL23A ----	-1.41	1.06	-1.07	1.69
								PI3 -----	-1.35	1.31	-3.43**	-1.70
								S100P ----	1.01	1.09	-2.12*	1.04
								S100A7 ----	-1.19	-2.26	-1.87+	1.20
								KRT1 ----	1.05	-3.67	-2.42	-1.29
								AHR ----	1.18	1.24	1.08	-1.17
								LOXL2 ----	1.30	2.16	-1.24	-1.10
								IL17A ----	1.35	14.30**	-1.88	1.03
								IL22 ----	1.64	2.93	-5.00**	-4.92**
								IL32 ----	1.26	1.50	-2.00+	-2.33*
								IL23R ----	1.59	1.49	-1.72	-2.01+
								IL17F ----	1.13	7.66**	-1.95	-2.94*
								CCR6 ----	1.09	2.43	-2.40*	-2.63**
								KRT10 ----	1.14	-8.37*	-1.93	-1.05
								FLG ----	-1.18	-2.86	-1.10	-1.31
								CALML5 ----	-1.25	-3.85*	-1.79	-1.13
								LCN2 ----	1.19	-3.59+	-1.83	1.12
								RORC ----	1.19	-1.74	1.32	-1.13

Comparisons of Change from Baseline (Day 1): + : $p < 0.1$ * : $p < 0.05$ ** : $p < 0.01$

Key Itch Markers are Significantly Modulated by Treatment

Placebo				RPT193					Placebo		RPT193	
LS		NL		LS		NL			LS	NL	LS	NL
D1	D29	D1	D29	D1	D29	D1	D29		D29 vs D1		D29 vs D1	
								S100A9	1.06	1.14	-2.06*	-1.59
								CXCL1	-1.59	1.80	-2.28+	-1.86
								JAK3	1.07	1.88	-2.02+	-2.56*
								S100P	1.01	1.09	-2.12*	1.04
								S100A7	-1.19	-2.26	-1.87+	1.20
								TAC1	1.08	-2.23	-4.50**	-1.03
								OSMR	-1.30	-2.29	-1.60	-1.03
								PIK3CA	-1.10	-1.57	1.48*	1.42+
								CTLA4	1.20	1.06	-1.85+	-2.09*
								IL13	1.80	2.70	-2.65*	-2.82*
								IL31	3.13+	4.02+	-2.74*	-1.75
								CALCA	1.08	1.21	1.04	-1.94+
								TLR3	1.05	1.56	1.80+	-1.34
								KLK7	-1.04	-3.47+	-3.72**	-1.56
								KLK6	1.36	-2.34	-3.83**	-1.05
								IL18	-1.00	-3.01*	-1.08	1.05
								POMC	-1.68	-4.21**	-1.55	-1.88+
								GRP	1.01	-1.32	1.13	-1.66*
								BDNF	-1.26	-1.22	-1.38	-1.76*
								IL31RA	1.10	1.10	1.50	-1.13
								F2RL3	-1.10	1.92	-1.44	1.10
								LPA	-1.11	1.41	-1.33	-1.33
								HTR7	-1.26	2.04	1.20	-1.61+
								OPRM1	1.15	1.80	1.12	-1.72*

Comparisons of Change from Baseline (Day 1): + : p<0.1 * : p<0.05 ** : p<0.01

Correlations between AD Biomarker and Disease Severity Score Changes in Lesional Skin

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

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

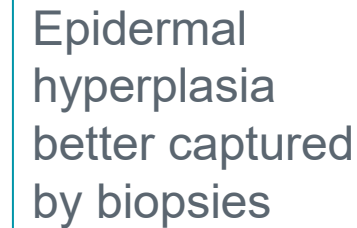
	Spearman R	p-value
CXCL10	-0.60	0.022
STAT6	-0.58	0.021
LPL	-0.46	0.018
CCL1	-0.45	0.016
IL5	-0.42	0.015
IFNA1	-0.40	0.014
FFAR2	-0.38	0.008
AGK	-0.37	0.008
CDH19	-0.37	0.004
PDE9A	-0.36	0.003
ANXA6	-0.35	0.001

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



Lipid changes better captured by tape-strips



Conclusions

- Data from the Phase 1b study in subjects with AD demonstrated clear benefit on all key exploratory endpoints including EASI and SCORAD
- RPT193 induces normalization of the AD immune transcriptome
- Normalization of the lesional immune transcriptome towards NL is greater with RPT193 than with placebo
- Significant improvements from baseline were seen in Th1-, Th2- and Th17/Th22-related genes with RPT193, but not with placebo
- Correlations of skin biomarkers central to AD disease with clinical end points highlight the utility of tape-strips
- Tape-strips captured changes in the MADAD transcriptome comparable to skin biopsy samples
- Tape-strips are a minimally invasive method that can accurately capture molecular changes with treatment over time, and may be a useful tool to objectively capture changes in skin biology