Long-term Treatment with Tralokinumab Normalizes the Molecular Gene Signature of Atopic Dermatitis

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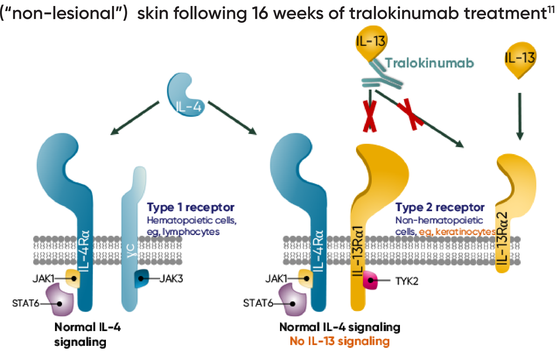
Introduction

- Interleukin (IL)-13 is a key driver of the skin inflammation and barrier abnormalities in atopic dermatitis (AD)[1–4]
- Tralokinumab binds to IL-13 with high affinity, preventing receptor interaction and IL-13 signaling[5–7]
- Tralokinumab demonstrated efficacy and safety for AD treatment in pivotal Phase 3 trials at Week 16[8,9]
  - High levels of EASI-75 and IGA 0/1 responses were sustained through 2 years of continued treatment[10]
- Key biomarkers in skin lesions showed shifts in inflammatory mediators and skin barrier markers towards those of uninvolved ("non-lesional") skin following 16 weeks of tralokinumab treatment[11]



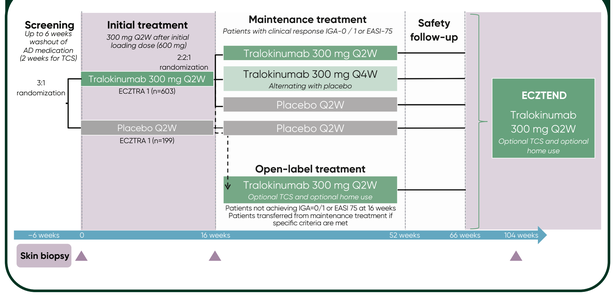
Objective

- To investigate the long-term impact of IL-13 neutralization on skin biomarkers following 2 years of tralokinumab treatment in a subset of patients with moderate-to-severe AD in the Phase 3 ECZTRA 1 trial (NCT03131648) and the long-term extension ECZTEND trial (NCT03587805)

Methods

- Skin biopsy samples from 13 tralokinumab-treated subjects were collected from lesional (baseline, Week 16, and Week 104) and non-lesional skin (baseline and Week 104) **(Figure 1)**
- Gene expression levels of biomarkers related to inflammation and skin barrier integrity were assessed by RNA sequencing
- Treatment differences were estimated by linear mixed effect models with treatment and time as fixed effects and random effects for each patient

Figure 1. ECZTRA 1 trial design and skin biopsy sampling schedule



Abbreviations: γc, common gamma chain; AD, atopic dermatitis; BL, baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FCH, fold-change; FDR, false discovery rate; IGA, Investigator's Global Assessment IL, interleukin; JAK, Janus kinase; NRS, numerical range scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; STAT, signal transducer and activator of transcription; TCS, topical corticosteroid TYK, tyrosine kinase.

Results

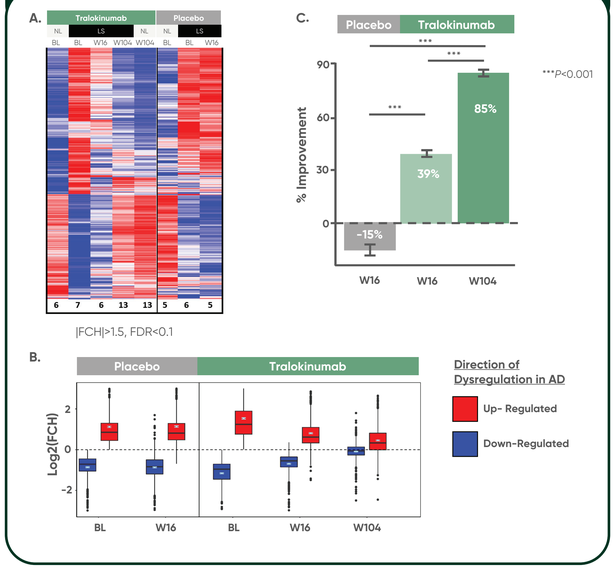
- Baseline characteristics were similar between the biopsy subgroup and all patients in ECZTRA 1 **(Table 1)**
- Continued tralokinumab treatment led to a shift towards a non-lesional profile over 2 years **(Figure 2)**

Table 1. Baseline demographics and clinical characteristics for randomized subjects in parent study (ECZTRA 1) and in the biopsy biomarker subgroup

	All randomized (N=802)	Biopsy subgroup (n=13)
Age, years		
Mean (SD)	38.8 (14.1)	45.4 (11.1)
Sex, n (%)		
Male	474 (59.1)	8 (61.5)
Female	328 (40.9)	5 (38.5)
Race n (%)		
White	564 (70.3)	11 (84.6)
Black	59 (7.4)	1 (7.7)
Asian	160 (20.0)	1 (7.7)
IGA n (%)		
n	802	13
Moderate Disease	391 (48.8)	10 (76.9)
Severe Disease	407 (50.7)	3 (23.1)
EASI		
Mean (SD), n	32.4 (13.8), 798	35.3 (15.5), 13
SCORAD		
Mean (SD), n	70.6 (12.9), 798	73.2 (15), 13
DLQI		
Mean (SD), n	16.9 (7.0), 785	17.4 (7), 12
Worst Daily Pruritus NRS (weekly average)		
Mean (SD), n	7.7 (1.4), 793	7.9 (1.4), 13

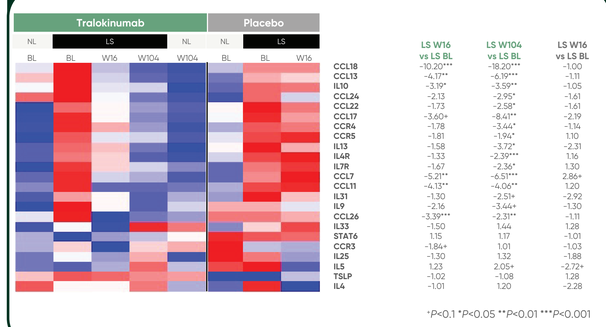
IGA, Investigator's Global Assessment; EASI, Eczema Area and Severity index; SCORAD, Scoring Atopic Dermatitis; DLQI, Dermatology Life Quality Index

Figure 2. Transcriptome analyses depicting **A.** Differentially expressed genes **B.** Direction of dysregulation in AD and **C.** Improvements towards non-lesional transcriptome profiles for tralokinumab and placebo groups



- Tralokinumab treatment modulated key immune pathways/markers over 2 years **(Figures 3-6)**

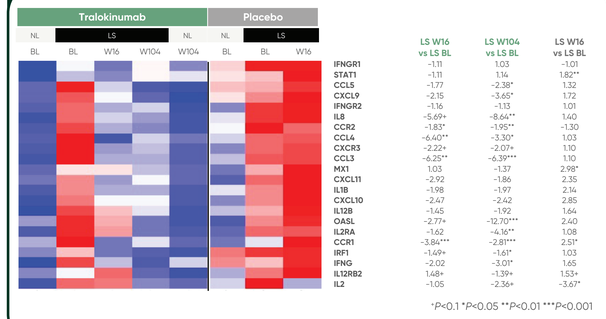
Figure 3. Tralokinumab treatment modulated Th2 pathways over two years



	LS W16 vs LS BL	LS W104 vs LS BL	LS W16 vs LS BL
CCL18	-10.20***	-18.20***	-1.00
CCL13	-4.17**	-6.19***	-1.11
IL10	-3.19*	-3.59**	-1.05
CCL24	-2.13	-2.95*	-1.61
CCL22	-1.73	-2.58*	-1.61
CCL17	-3.60+	-8.41**	-2.19
CCR4	-1.78	-3.44*	-1.14
CCR5	-1.81	-1.94*	1.10
IL13	-1.58	-3.72*	-2.31
IL4R	-1.33	-2.39***	1.16
IL7R	-1.67	-2.36*	1.30
CCL7	-5.21**	-6.51***	2.86+
CCL11	-4.13**	-4.06**	1.20
IL31	-1.30	-2.51+	-2.92
IL9	-2.16	-3.44+	-1.30
CCL26	-3.39***	-2.31*	-1.11
IL33	-1.50	1.44	1.28
STAT6	1.15	1.17	-1.01
CCR3	-1.84+	1.01	-1.03
IL25	-1.30	1.32	-1.88
IL5	1.23	2.05+	-2.72+
TSLP	-1.02	-1.08	1.28
IL4	-1.01	1.20	-2.28

*P<0.1 *P<0.05 **P<0.01 ***P<0.001

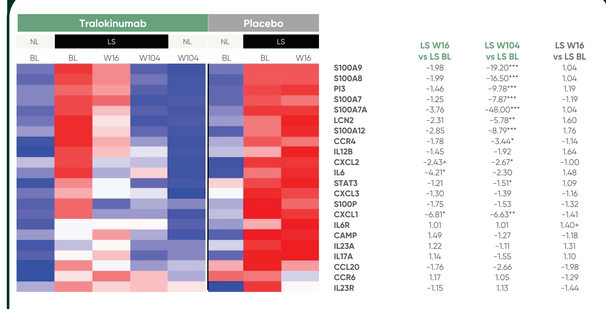
Figure 4. Tralokinumab treatment modulated Th1 pathways over two years



	LS W16 vs LS BL	LS W104 vs LS BL	LS W16 vs LS BL
IFNGR1	-1.11	1.03	-1.01
STAT1	-1.11	1.14	1.82**
CCL5	-1.77	-2.38*	1.32
CXCL9	-2.15	-3.65*	1.72
IFNGR2	-1.16	-1.13	1.01
IL8	-5.69+	-8.64**	1.40
CCR2	-1.83*	-1.95**	-1.30
CCL4	-6.40**	-3.30*	1.03
CXCR3	-2.22+	-2.07+	1.10
CCL3	-6.25**	-6.39***	1.10
MX1	1.03	-1.37	2.98*
CXCL11	-2.92	-1.86	2.35
IL1B	-1.98	-1.97	2.14
CXCL10	-2.47	-2.42	2.85
IL12B	-1.65	-1.92	1.64
OASL	-2.77+	-12.70***	2.40
IL2RA	-1.62	-4.16**	1.08
CCR1	-3.84***	-2.81***	2.51*
IRF1	-1.69+	-1.61*	1.03
IFNG	-2.02	-3.01*	1.65
IL12RB2	1.48+	-1.39+	1.53+
IL2	-1.05	-2.36+	-3.67*

*P<0.1 *P<0.05 **P<0.01 ***P<0.001

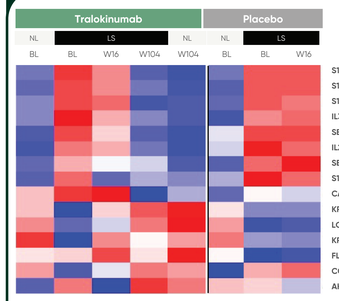
Figure 5. Tralokinumab treatment modulated Th17 pathways over two years



	LS W16 vs LS BL	LS W104 vs LS BL	LS W16 vs LS BL
S100A9	-1.98	-19.20***	1.04
S100A8	-1.99	-16.50***	1.04
PI3	-1.66	-9.78***	1.19
S100A7	-1.25	-7.87***	-1.19
S100A7A	-3.76	-48.00***	1.04
LCN2	-2.31	-5.78**	1.60
S100A12	-2.85	-8.79***	1.76
CCR4	-1.78	-3.44*	-1.14
IL12B	-1.45	-1.92	1.64
CXCL2	-2.43+	-2.67*	-1.00
IL6	-4.21*	-2.30	1.68
STAT3	-1.21	-1.51*	1.09
CXCL3	-1.30	-1.39	-1.16
S100P	-1.75	-1.53	-1.32
CXCL1	-6.81*	-6.63**	-1.41
IL6R	1.01	1.01	1.40+
CAMP	1.49	-1.27	-1.18
IL23A	1.22	-1.11	1.31
IL17A	1.14	-1.55	1.10
CCL20	-1.76	-2.66	-1.98
CCR6	1.17	1.05	-1.29
IL23R	-1.15	1.13	-1.44

*P<0.1 *P<0.05 **P<0.01 ***P<0.001

Figure 6. Tralokinumab treatment modulated Th22 pathways over two years



	LS W16 vs LS BL	LS W104 vs LS BL	LS W16 vs LS BL
S100A9	-1.98	-19.20***	1.04
S100A8	-1.99	-16.50***	1.04
S100A7	-1.25	-7.87***	-1.19
IL32	-1.38	-1.92*	1.06
SERPINB4	-6.52	-115.00***	1.09
IL22	-1.52	-8.86**	-1.77
SERPINB1	-1.27	-1.41	1.65+
S100P	-1.75	-1.53	-1.32
CALML5	1.08	-1.85**	-1.06
KRT10	1.55+	1.80**	1.01
LOR	1.40	2.32**	1.11
KRT1	1.51+	1.38	-1.02
FLG	1.25	-1.02	1.14
CCR10	1.17	1.36	1.07
AHR	-1.73**	1.08	-1.12

*P<0.1 *P<0.05 **P<0.01 ***P<0.001

- Long-term tralokinumab treatment led to downregulation of epidermal differentiation factor (EDC) and ceramide genes to levels comparable to non-lesional skin
- A strong shift was also observed in atherosclerosis signaling pathway genes after 2 years of tralokinumab treatment

Conclusions

- Two years of tralokinumab treatment shifted the transcriptomic profile of lesional skin towards that of non-lesional skin
  - The shift at 2 years was larger than that seen at Week 16
- At 2 years, tralokinumab treatment also modified the transcriptomic profile of non-lesional skin, improving subclinical disease seen at baseline in normal-appearing skin
- Shifts in cutaneous biomarker profile:
  - Highlight the role of IL-13 as a key driver of the AD molecular signature
  - Support the role of targeted biologic therapy for long-term AD management

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Disclosures

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