Amlitelimab Reduces Th2-, Th1-, and Th17/22-Related Cytokines and Chemokines in Adults With Moderate-to-Severe Atopic Dermatitis: Results From an Exploratory Analysis of the Phase 2b STREAM-AD Study

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Key Conclusions

1. Amlitelimab **previously demonstrated improvements in clinical features of AD** in STREAM-AD, **with associated reductions in AD-related biomarkers**[1]
2. In addition, **amlitelimab significantly reduced numerous plasma proteins associated with Th2, Th1, and Th17/22 inflammation at Week 16** in adults with moderate-to-severe AD
3. Data further support that OX40L blockade is a relevant target for treating Th2, Th1, and Th17/22 inflammation in AD

Introduction

- Amlitelimab (SAR445229, KY1005), a fully human, nondepleting monoclonal antibody, binds OX40 ligand (OX40L) on antigen-presenting cells, preventing OX40L-OX40 interaction on activated T cells[1,2]
- In the STREAM-AD Phase 2b trial, amlitelimab demonstrated clinically meaningful improvements in atopic dermatitis (AD) lesions, pruritus, quality of life, and overall symptoms in adults with moderate-to-severe AD at Week 24[3,4]
- Reductions in key AD-related plasma and cutaneous biomarkers were also observed (eg, IL-31, IL-13, eosinophils, TARC/CCL17, IL-17A)[3,4]

Objective

- Evaluate the effect of amlitelimab on additional plasma Th2-, Th1-, and Th17/Th22-associated cytokines and chemokines in the STREAM-AD Phase 2b trial

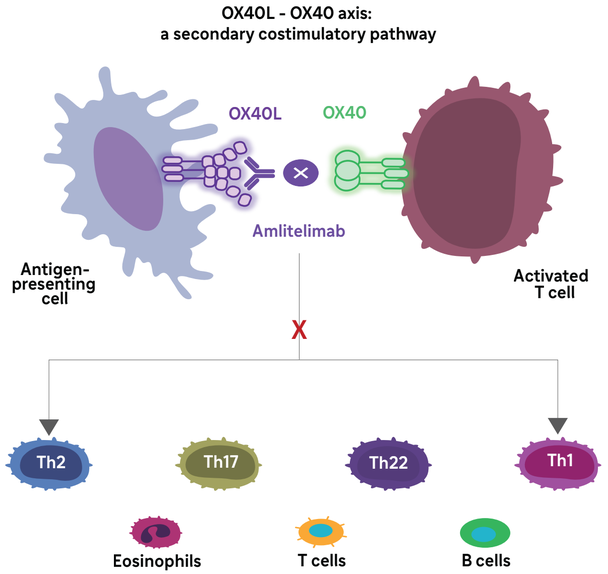
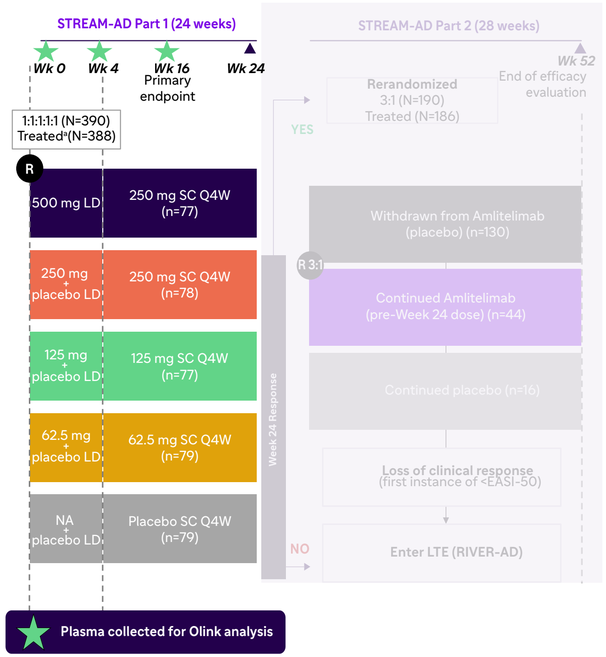


Figure adapted from Fu Y, et al. *Acta Pharm Sin B*. 2020;10(3):414-433; and Haddad EB, et al. *Dermatol Ther (Heidelb)*. 2022;12(7):1501-1533.

Methods

Study design of STREAM-AD (NCT05131477)



Analysis

- Changes in preselected cytokines and chemokines from baseline (Week 0) to Week 16 were evaluated utilizing an exploratory protein multiplex panel (Olink® Explore 384 Inflammation I, Olink Proteomics) on plasma from patients with AD treated with amlitelimab (n=300) vs placebo (n=76) in Part 1
- Olink protein levels are expressed in Normalized Protein eXpression (NPX) units, using a log2 scale
  - 1 NPX difference corresponds to 2x difference in protein concentration
  - Change from baseline was calculated by subtracting the baseline NPX from the NPX at each time point, resulting in the log2 fold change from baseline (NPX log2FC)

Results

Amlitelimab reduced plasma proteins associated with Th2 inflammation from baseline to Week 16

Figure 1. Heatmap of log2 fold change (FC) from baseline to Week 16 of Th2-associated cytokines/chemokines

Amlitelimab	Placebo	Cytokine/ Chemokine
- 0.034	0.016	CCL11
- 0.406**	- 0.093	CCL13
- 0.981**	- 0.179	TARC/CCL17
- 0.492**	- 0.252	CCL22
- 0.128	- 0.1	CCL24
- 0.629**	- 0.207	CCL26
- 0.427**	- 0.216	CCL7
- 0.144	0.29	IL -10
- 0.501**	- 0.129	IL -13
- 0.196**	- 0.07	IL -24

log2FC

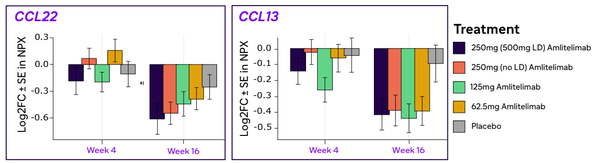
Key: Increased expression / Decreased expression

Log2FC	FC
1	2
0.5	~1.4
0	1
-0.5	~0.7
-1	0.5

Preselected list of cytokines and chemokines of interest, displaying the mean fold change (log2FC) for amlitelimab and the placebo group with FDR-adjusted P-values: *P<0.05; **P<0.01 from baseline.

- Treatment with amlitelimab reduced plasma cytokines and chemokines associated with Th2 inflammation, including CCL13, TARC/CCL17, CCL22, CCL26, CCL7, IL-13, and IL-24 (P<0.01 for all) from baseline to Week 16 (**Figure 1**)
  - Many of these play a role in recruitment and/or activation of inflammatory immune cells
- Reductions in Th2-inflammation-associated proteins were observed at Week 16 across all doses for CCL22 and CCL13 (**Figure 2**)

Figure 2. Reduction in CCL22 and CCL13 at Week 4 and Week 16 by treatment group



Th2-associated

Amlitelimab reduced plasma proteins associated with Th1 and Th17/22 inflammation from baseline to Week 16

Figure 3. Heatmap of log2 fold change (FC) from baseline to Week 16 of Th1- and Th17/22-associated cytokines/chemokines

Th1			Th17/22		
Amlitelimab	Placebo	Cytokine/ Chemokine	Amlitelimab	Placebo	Cytokine/ Chemokine
-0.173**	-0.057	CCL23	-0.328**	0.035	CCL20
-0.119	-0.129	CXCL1	-0.465**	0.137	IL -17A
-0.247**	-0.035	CXCL10	-0.334**	0.087	IL -17C
-0.235**	-0.165	CXCL8	-0.07	-0.013	IL -17F
-0.242**	-0.081	CXCL9	-0.511**	-0.039	IL -32
-0.08	0.207	IFNG	-0.29*	0.037	IL -6
-0.197**	0.114	IL-12B			
0.01	0.083	IL-15			
-0.241**	-0.085	IL-18			
-0.168**	-0.197	IL-1B			
-0.216**	0.072	TNF			

log2FC

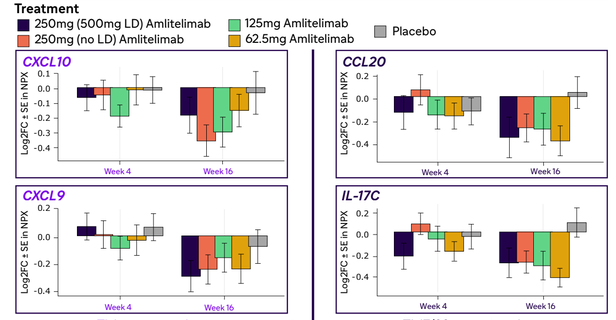
Key: Increased expression / Decreased expression

Log2FC	FC
1	2
0.5	~1.4
0	1
-0.5	~0.7
-1	0.5

Preselected list of cytokines and chemokines of interest, displaying the mean fold change (log2FC) for amlitelimab and the placebo group with FDR-adjusted P-values: *P<0.05; **P<0.01 from baseline.

- Amlitelimab treatment reduced markers of Th1- and Th17/22-related inflammation (**Figure 3**)
- Reductions in Th1- and Th17/22-inflammation-associated proteins were observed at Week 16 across all doses (**Figure 4**)

Figure 4. Reduction in CXCL10, CXCL9, CCL20, and IL-17C at Week 4 and Week 16 by treatment group



Th1-associated | Th17/22-associated

AD, atopic dermatitis; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; EASI, Eczema Area and Severity Index; FC, fold change; FDR, false discovery rate; IFNG, interferon gamma; IL, interleukin; LD, loading dose; LTE, long-term extension; NA, not applicable; NPX, Normalized Protein expression; OX40L, OX40 ligand; Q4W, every 4 weeks; R, randomization; SC, subcutaneous; SE, standard error; TARC, thymus- and activation-regulated chemokine; Th, helper T cell; TNF, tumor necrosis factor; Wk, week.

Disclaimers
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