Treatment with amlitelimab – a novel non-depleting, non-cytotoxic, anti-OX40-ligand monoclonal antibody – reduces IL-22 serum levels in a Phase 2a randomized, placebo-controlled trial in patients with moderate-to-severe atopic dermatitis

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Methods: A Phase 2a, randomized, placebo-controlled trial of amlitelimab in patients with moderate-to-severe AD

Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (NCT03754309)^1,2

• Adults with moderate-to-severe AD for ≥1 year at baseline (Week 0), defined as^1,2:
  - EASI ≥16; vIGA 3/4; and inadequate response or intolerance to topical treatments prior to baseline
• IL-22 serum levels measured with ultrasensitive single molecule array (Simoa)
• Serum collected at baseline, Week 4, and Week 16
  - Further serum collection at Weeks 24 and 36 in patients who responded at Week 16 (vIGA 0/1)
• All patients: safety follow-up visits until Week 36^1,2
  - Responders at Week 16 (vIGA 0/1) assessed for durability of response up to Week 36
  - Disease severity measured with EASI, SCORAD, and vIGA at each visit up to Week 16, and at Weeks 24 and 36 in responders at Week 16 (vIGA 0/1)

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IL, interleukin; SCORAD, SCORing of Atopic Dermatitis; TEAE, treatment-emergent adverse event; vIGA, validated Investigator Global Assessment.

Results: Significant and sustained reduction of serum IL-22 in patients receiving amlitelimab

- In the Phase 2a study, patients receiving amlitelimab demonstrated clinically meaningful improvements in mean percentage change in EASI from baseline to Week 16 versus placebo, alongside significant improvements at all time points in responders (patients achieving clear or almost clear skin; vIGA score 0 or 1) from baseline to Week 16.
- Mean change in EASI from baseline at Week 16 was −89.37% for amlitelimab low dose (p=0.009) and −69.97% for amlitelimab high dose (p=0.072) versus −49.37% for placebo.
- IL-22 baseline serum levels did not differ between responders and non-responders (data not shown) and were shown to correlate with EASI scores.
  - IL-22 reduction in responders was persistent in the follow-up period, suggesting that effect on IL-22 is long-lasting.

Baseline correlation between EASI and IL-22 serum levels

- Significant correlation of IL-22 levels with severity of disease at baseline, as measured by EASI (figure below) and SCORAD (graph not shown; r=0.3616, p<0.0011).

Circulating IL-22 over time

- Significant decrease in IL-22 serum levels in patients treated with amlitelimab, but not placebo, at Week 16. Decrease was maintained until Week 36 in responders to amlitelimab (vIGA 0 or 1 at Week 16), but not to placebo.
- The sustained reduction in IL-22 serum levels in amlitelimab-treated patients was treatment-dependent and strongly indicates that amlitelimab effectively targets immune dysregulation in AD.

*Linear regression and correlation analysis with r coefficients and p-values based on Spearman correlations (n=78). Repeated measures two-way ANOVA plus Tukey’s multiple comparison test on fold changes in IL-22 compared to baseline for patients with complete dataset at Week 16 (placebo, n=16; amlitelimab low dose, n=20; and amlitelimab high dose, n=22). ns, p>0.05; **** p<0.0001.

AD, atopic dermatitis; ANOVA, analysis of variance; CI, confidence interval; EASI, Eczema Area and Severity Index; IL, interleukin; ns, not significant; SCORAD, SCORing of Atopic Dermatitis; vIGA, validated Investigator Global Assessment.
Concluding remarks

- In a Phase 2a study, amlitelimab treatment not only induced significant improvements in signs and symptoms of AD\(^1\), but also significantly reduced serum levels of IL-22, a T\(_{H22}\) cell-associated cytokine involved in the underlying immunopathogenesis of AD
  - IL-22 baseline levels significantly correlated with clinical disease severity, suggesting IL-22 as a potential disease biomarker
  - Amlitelimab, but not placebo, reduced IL-22 serum levels at Week 16
  - The amlitelimab-induced reduction in IL-22 serum levels was maintained up to Week 36 in responders (vIGA 0/1 at Week 16)

- The findings of this exploratory analysis:
  - Suggest that OX40L blockade on APCs represents a promising novel approach in the treatment of AD by effectively targeting underlying T-cell immune dysregulation
  - Support the hypothesis that targeting OX40L on APCs modulates not only the Type 2 response, but also other T-cell pathways, including T\(_{H22}\)

- A Phase 2b study is now underway (STREAM-AD; NCT05131477)

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