Amlitelimab reduces serum IL-13 in a Phase 2a clinical trial in atopic dermatitis without impacting T-cell expansion in a T-cell recall assay

Stephan Weidinger[1], Michael Cork[2], Adam Reich[3], Thomas Bieber[4], Davide Lucchesi[5], Natalie Rynkiewicz[6], Richard C A Sainson[7*], Ron Chen[7*], Francesca Prandi[5], Cassandra van Krinks[5], Marisa Stebegg[8], and Ben Porter-Brown[5]

[1]Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany; [2]Sheffield Dermatology Research, IICD, University of Sheffield, Sheffield, United Kingdom; [3]Department of Dermatology, University of Rzeszow, Rzeszow, Poland; [4]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany; [5]Sanofi, Cambridge, United Kingdom; [6]Sanofi, Australia; [7]Kymab (a Sanofi Company), Cambridge, United Kingdom; [8]Sanofi, Frankfurt, Germany; *Formerly Kymab Ltd (a Sanofi Company)

This study was funded by Kymab Ltd, A Sanofi Company

Disclosures: S Weidinger: AbbVie, Almirall, Galderma, Janssen, Kymab Ltd, LEO Pharma, Lilly, Pfizer, Regeneron, Sanofi; **M Cork:** Astellas, Atopix, Boots, Dermavant, Galapagos, Galderma, Hyphens, Johnson & Johnson, Kymab Ltd, LEO Pharma, L'Oréal/La Roche-Posay, Menlo Therapeutics, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron, Sanofi; **A Reich:** AbbVie, Bioderma, Celgene, Chema Elektromet, Drug Delivery Solutions Ltd., Eli Lilly, Galderma, Genentech, Janssen, Kymab Ltd, LEO Pharma, Medac, Menlo Therapeutics, MetrioPharm, MSD, Novartis, Pfizer, Pierre-Fabre, Sandoz, Trevi; **T Bieber:** AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, ASLAN Pharma, Bayer Health, BioVerSys, Boehringer Ingelheim, Bristol Myers Squibb, Domain Therapeutics, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, IQVIA, Janssen, Kirin, Kymab Ltd, LEO Pharma, LG Chem, Lilly, L'Oréal, MenloTx, Novartis, OM-Pharma, Pfizer, Pierre Fabre, Sanofi/Regeneron, UCB; **D Luchessi, N Rynkiewicz, F Prandi, C van Krinks, M Stebegg, B Porter-Brown:** Employees of Kymab Ltd/Sanofi and may be Sanofi; stockholders; **RCA Sainson, R Chen:** None

Medical writing assistance, funded by Sanofi, was provided by Cam Hubert, PhD, and Heather Shawcross, PhD, of Fishawack Communications Ltd., part of Fishawack Health

Poster at the Revolutionizing Atopic Dermatitis Virtual Conference | Dec 11, 2022

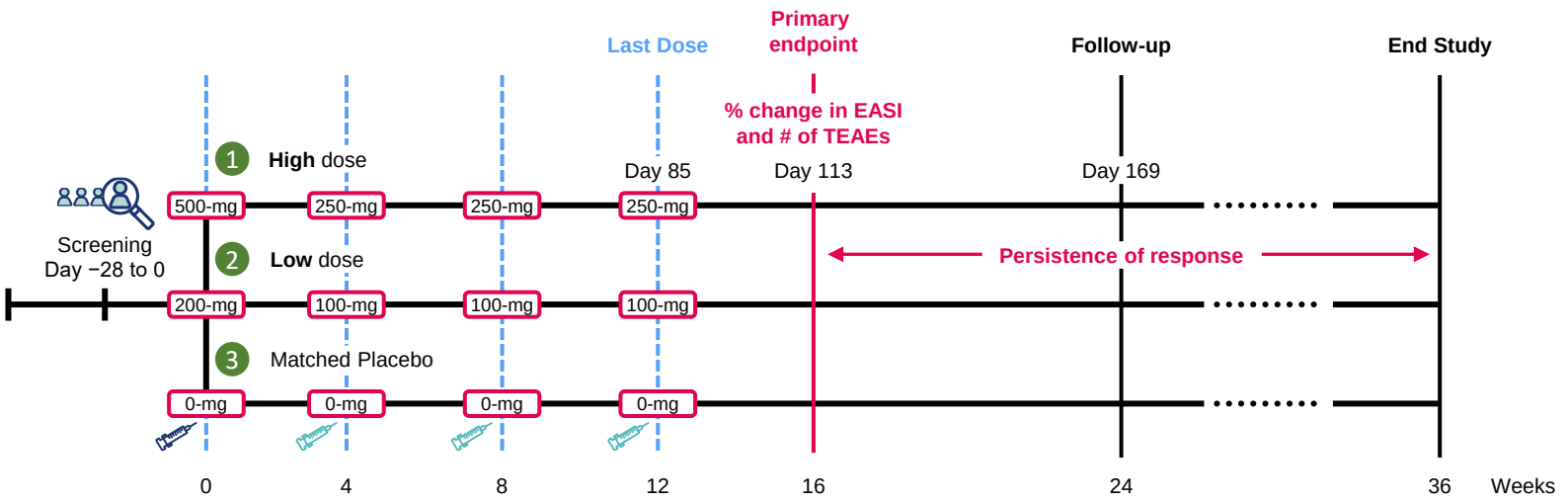
Methods: Impact of amlitelimab OX40L blockade on IL-13 in a pre-clinical T-cell recall assay and a Phase 2a AD clinical trial

Impact of amlitelimab on IL-13 in a pre-clinical T-cell recall assay

- **Objective:** To test whether amlitelimab can modify T-cell proliferation and IL-13 production by human PBMCs in response to a recall antigen
- **Recall antigen:** CMVpp65 protein (induces OX40 expression in culture[1]; CMV-specific immune cells detected in 50−60% of UK adults[2,3])
- PBMCs (5 donors) were simultaneously treated with 15 µg/mL CMVpp65 and amlitelimab or isotype at 2.5 µg/mL, 250 µg/mL, and 25 µg/mL (in triplicate)
  - Day 1: CMV-dependent upregulation of OX40/OX40L confirmed by flow cytometry in all donors
  - Days 3 and 6: IL-13 assessed using Olink's 96plex inflammation panel (25 µg/mL antibody)
  - Day 6: T-cell phenotypes and proliferation assessed by flow cytometry (all concentrations)

Impact of amlitelimab on IL-13 in patients with AD

- A Phase 2a, randomized, placebo-controlled study (NCT03754309) assessed adults with moderate-to-severe AD* for ≥1 year at baseline (Week 0)[4,5]
- Serum was collected at baseline, Week 4, Week 16, and at Weeks 24 and 36 for 'responders'†. IL-13 levels measured by ultrasensitive single molecule array (Simoa)[6]
- Safety follow-up until Week 36[4,5]
  - Disease severity was measured with EASI, SCORAD, and vIGA at each visit up to Week 16, and at Weeks 24 and 36 in patients who responded at Week 16 (vIGA 0 or 1)



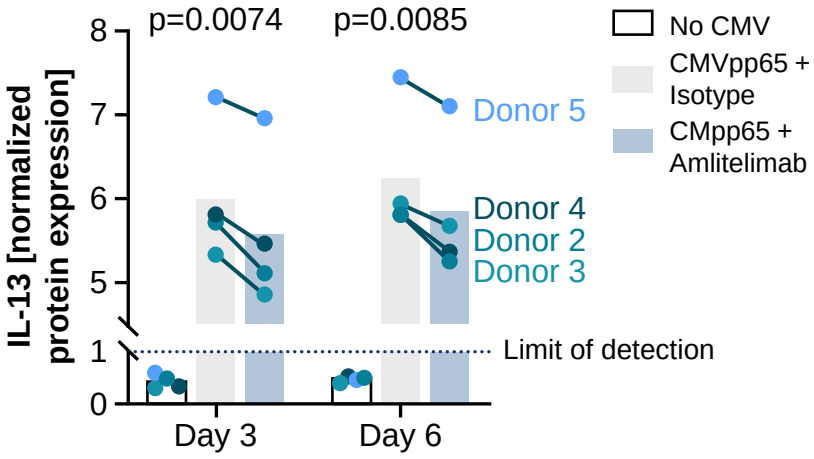
*EASI ≥16; vIGA 3 or 4; and inadequate response or intolerance to topical treatments prior to baseline; †Patients achieving clear or almost clear skin; vIGA score 0 or 1.
AD, atopic dermatitis; CMV, cytomegalovirus; EASI, Eczema Area and Severity Index; IL, interleukin; OX40L, OX40 ligand; PBMC, peripheral blood mononuclear cells; SCORAD, SCORing of Atopic Dermatitis; vIGA, validated Investigator Global Assessment.
1. Zaunders JJ, et al. J Immunol. 2009;183:2827-36. 2. NHS Blood and Transplant. 2018. https://nhsbtdbe.blob.core.windows.net/umbraco-assetscorp/14652/blc7071.pdf. 3. Vyse AJ, et al. Epidemiol Infect. 2009;137:526-33. 4. Weidinger S, et al. Presented at the European Academy of Dermatology and Venereology (EADV) Virtual Congress 2021 (abstract 2729). 5. Weidinger S, et al. Presented at the 4th Annual Revolutionizing Atopic Dermatitis Conference (RAD) 2022 (abstract 203). 6. Weidinger S, et al. Presented at the American Academy of Dermatology (AAD) 2022 Annual Meeting (abstract 34312).

Results: Sustained reduction of serum IL-13 with amlitelimab in the T-cell recall assay and Phase 2a clinical trial

- **T-cell recall assay:** Amlitelimab inhibited IL-13 production at Days 3 and 6 in response to CMVpp65 without negatively impacting (OX40^{high}) CD4 T-cell expansion (data not shown), suggesting that OX40-OX40L blockade exerted an inhibitory effect on IL-13 production in this T-cell recall assay
- **Phase 2a study:** Amlitelimab provided 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[1]
  - Reduced baseline IL-13 serum levels shown with amlitelimab were sustained through 36 weeks, and significant correlation between IL-13 and severity of disease at baseline was noted as measured by EASI and SCORAD (data not shown)

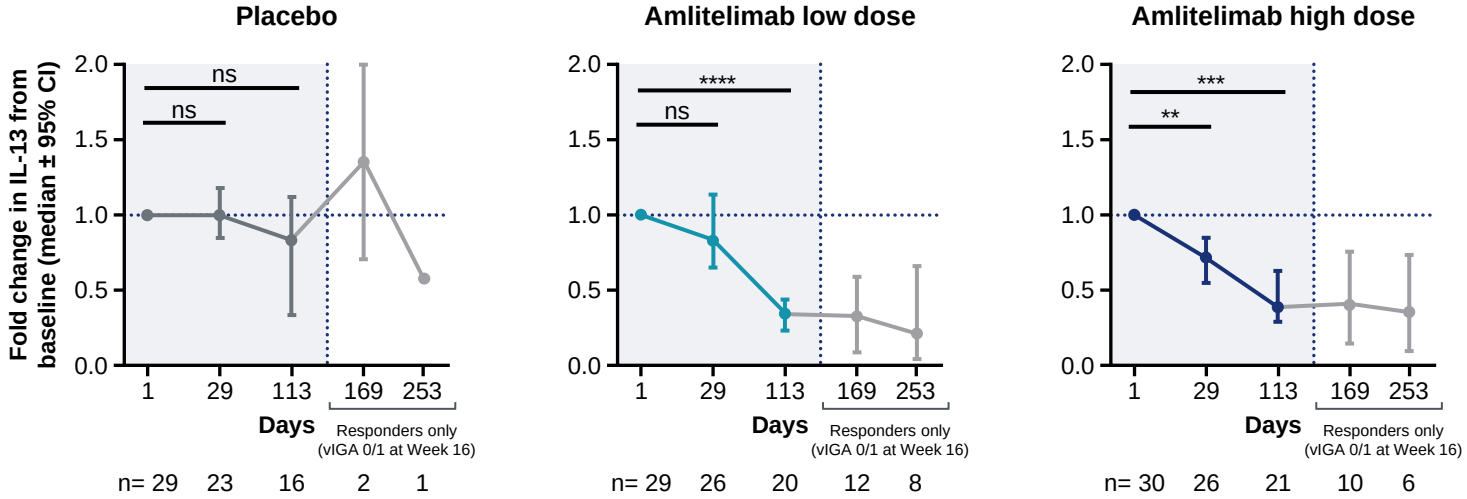
Amlitelimab reduced IL-13 levels in a T-cell recall assay[2*]

- CMVpp65 recall treatment **consistently induced IL-13 secretion** into the cell culture supernatant in all 5 donors
- IL-13 levels were **significantly reduced by amlitelimab** compared to the isotype control



Circulating IL-13 over time[3†]

- The **sustained reduction‡ in IL-13 serum levels** in amlitelimab-treated patients was **treatment dependent** and **strongly indicates that amlitelimab effectively targets immune dysregulation in AD.** This was in line with the **observed reduction in IL-13 production** in a **preclinical T-cell recall model**



*IL-13 levels in cell culture supernatants were measured by semiquantitative Olink technology on Days 3 and 6. Results from 4 donors. No CMV (open bar) – untreated control (no CMVpp65 or antibody treatment); CMVpp65 + Isotype (grey bar) – peripheral blood mononuclear cells treated with CMVpp65 and 25 µg/mL IgG4PE isotype control; CMVpp65 + amlitelimab (blue bar) – peripheral blood mononuclear cells treated with CMVpp65 and 25 µg/mL amlitelimab. Each condition was set up in duplicates or triplicates. Each dot represents the mean of an individual donor. Paired samples are connected by lines (except for "no CMV" control). P values are based on two-way repeated-measures ANOVA and Šídák's multiple comparisons test for difference between amlitelimab vs isotype control treatment at each time point. †Repeated-measures two-way ANOVA plus Tukey's multiple comparison test on fold changes in IL-13 compared to baseline (Day 1) for patients with complete dataset at Day 113 (placebo, n=15; amlitelimab low dose, n=20; and amlitelimab high dose, n=20). ns, p>0.05; ** p<0.01; *** p<0.001; **** p<0.0001.
‡Decrease maintained in all patients, except for one patient treated with amlitelimab low dose whose IL-13 levels increased at Day 169 versus baseline.
AD, atopic dermatitis; ANOVA, analysis of variance; CI, confidence interval; CMV, cytomegalovirus; EASI, Eczema Area and Severity Index; IL, interleukin; ns, not significant; OX40^{high}, expressing high levels of OX40; OX40L, OX40 ligand; SCORAD, SCORing of Atopic Dermatitis.

1. Weidinger S, et al. Presented at the 4th Annual Revolutionizing Atopic Dermatitis Conference (RAD) 2022 (abstract 203); 2. Weidinger S, et al. Presented at the 12th International Symposium on Atopic Dermatitis (ISAD) 2022 (oral presentation 34); 3. Weidinger S, et al. Presented at the American Academy of Dermatology (AAD) 2022 Annual Meeting (abstract 33781).

Concluding remarks

IL-13 production and T-cell expansion in a T-cell recall assay

- Amlitelimab treatment significantly reduced IL-13 levels in cell culture supernatants compared with isotype control, suggesting OX40-OX40L blockade exerts an inhibitory effect on IL-13 production in response to recall antigen
- Amlitelimab treatment did not significantly impact $CD4^+$ T-cell expansion at all tested concentrations
- These results indicate that amlitelimab can effectively inhibit IL-13 production without negatively impacting T-cell expansion

Serum IL-13 in a Phase 2a trial in AD

- Amlitelimab induced clinically meaningful improvements for patients with AD[1] and significantly reduced serum levels of IL-13, a cytokine involved in the underlying immunopathogenesis of AD
- IL-13 baseline levels significantly correlated with clinical disease severity, suggesting IL-13 as a disease biomarker
- A Phase 2b study is now underway (STREAM-AD; NCT05131477)

- Thus, OX40L blockade on APCs represents a promising novel approach for AD treatment by effectively targeting underlying T-cell immune dysregulation without the need for T-cell depletion

AD, atopic dermatitis; APCs, antigen-presenting cells; IL, interleukin; OX40L, OX40Ligand; TH, T-helper.

1. Weidinger S, et al. Presented at the 4th Annual Revolutionizing Atopic Dermatitis Conference (RAD) 2022 (abstract 203).