EA DV CONGRESS
BERLIN 11-14 OCTOBER 2023
EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

Abstract N°: 324

Neuromodulation beyond itch is blocked by targeting IL-13Rα1 with eblasakimab

Yannick Miron[1], Paul E Miller[1], Carl Firth[2], Ferda Cevikbas*[2]

[1]AnaBios Corporation, San Diego, United States, [2]ASLAN Pharmaceuticals, San Mateo, United States

Introduction & Objectives:

Interleukin-4 (IL-4) and IL-13 are cytokines known to drive inflammation and play a role in atopic dermatitis (AD) pathogenesis. Both enhance neuronal itch via the Type 2 receptor. Eblasakimab, a high affinity IgG4 monoclonal antibody, which binds IL-13Ra1 and blocks signaling of IL-4 and IL-13 via the Type 2 receptor, is being developed for the treatment of moderate-to-severe AD. This study evaluated 1) whether IL-4 and IL-13 exert redundant or distinct functions in human sensory neurons, and whether eblasakimab can 2) attenuate cytokine-enhanced neuronal responses to itch and 3) reduce spontaneous neuronal activity.

Materials & Methods:

Human dorsal root ganglia neurons were treated with IL-4, IL-13, or their combination with or without eblasakimab and subsequently either challenged with pruritogens (BAM8-22 [bovine adrenal medulla 8–22 peptide] and PAMP-20 [pro-adrenomedullin peptide 1-20]) or tested for spontaneous neuronal activity. Neuronal responses to pruritogens and spontaneous neuronal activity were measured via live-cell calcium imaging.

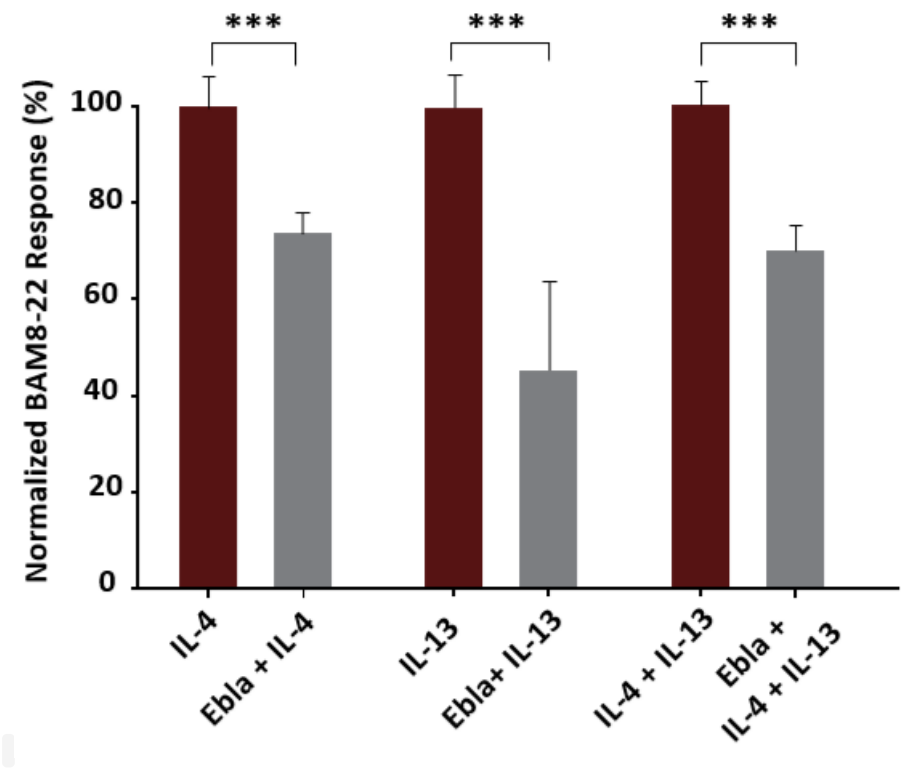
Results:

Treatment with IL-4, IL-13, and their combination enhanced neuronal responses to BAM8-22. Only IL-13 treatment increased neuronal responses to PAMP-20 by amplifying activity of the itch-specific receptor MRGPRX2 (Mas-related G-protein coupled receptor X2). This suggests a novel neuroimmune pathway besides the receptor's mast cell specific function. Eblasakimab significantly reduced cytokine-enhanced itch responses to both pruritogens ($p<0.0001$, BAM8-22; $p<0.05$, PAMP-20; Figures 1 and 2). Spontaneous neuronal activity was not impacted by IL-13 treatment (data not shown) but was increased with IL-4 treatment ($p<0.05$ vs vehicle), which was also effectively reduced by eblasakimab ($p<0.05$; Figure 3).

Conclusion:

These results reveal that IL-4 and IL-13 exert nonredundant neuronal function in enhancing itch and inducing spontaneous neuronal activity. They also demonstrate the ability of eblasakimab to block these cytokine-mediated effects. Together, these data provide a mechanistic basis for the reduction of itch observed in moderate-to-severe AD patients treated with eblasakimab in a phase 1b clinical trial.

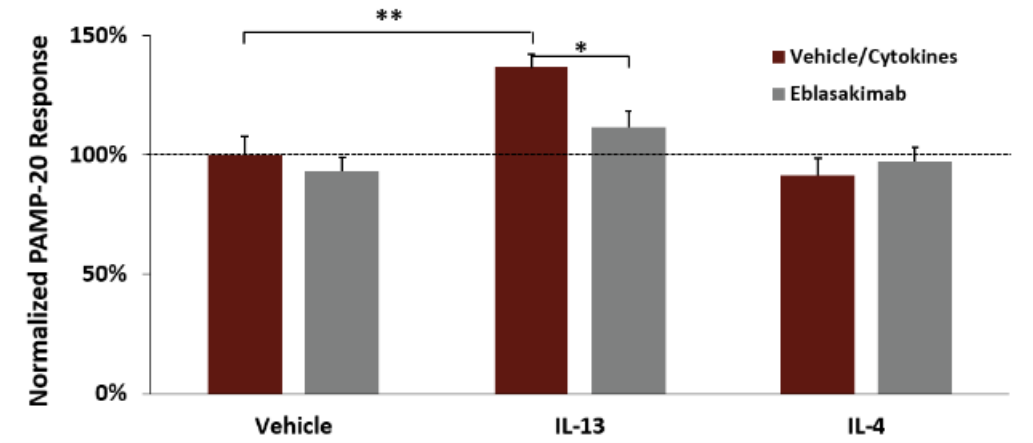
Figure 1. Neuronal Responses to BAM8-22 in the Presence of Cytokines and Eblasakimab



BAM8-22, bovine adrenal medulla 8–22 peptide; ebla, eblasakimab.

***p<0.0001. Error bars indicate standard error of mean.

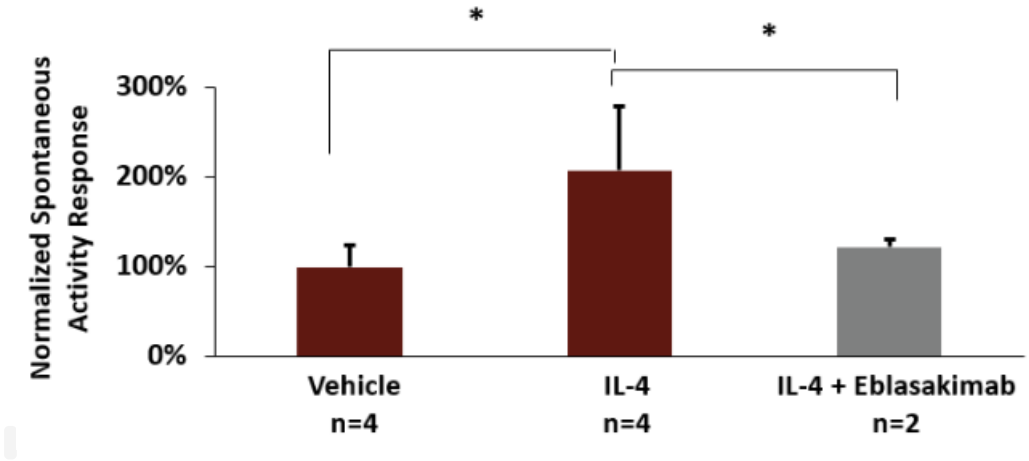
Figure 2. Neuronal Responses to PAMP-20 in the Presence of Cytokines and Eblasakimab



PAMP-20, pro-adrenomedullin peptide 1-20.

*p<0.05, **p<0.01. Error bars indicate standard error of mean. **

Figure 3. Summary Of Spontaneous Neuronal Activity Induced by IL-4 With and Without Eblasakimab



*p<0.05. Error bars indicate standard error of mean.