New Insights Into Neuronal Itch Mechanisms by Targeting IL-13Rα1 With Eblasakimab

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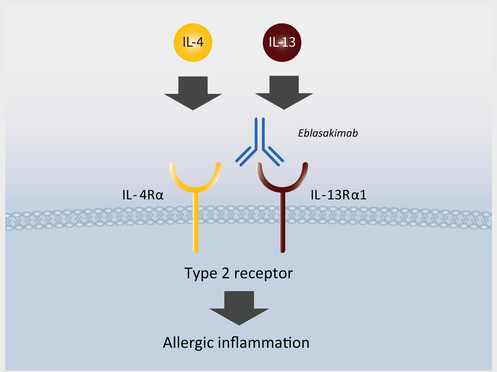
INTRODUCTION

- Chronic itch is a cardinal feature of multiple type-2 inflammation-associated skin disorders such as atopic dermatitis (AD)[1,2]
- Itch signaling in AD has been recently postulated to be amplified by inflammatory cytokines present in the skin, which exacerbate immune responses, disrupt the skin barrier, and drive disease pathology[1-4]
- Recently, it has been shown that interleukin-13 (IL-13) acts as a neuronal enhancer for a multitude of different itch pathways in human neurons[5]
- A prior murine study established that interleukin-4 (IL-4) and IL-13 do not induce itch but rather sensitize neuronal itch responses[2]; additionally, the study showed a direct effect of IL-4 in human sensory neurons[2]
- Eblasakimab, a first-in-class, fully human monoclonal antibody under investigation for the treatment of moderate-to-severe AD, binds the human IL-13 receptor α1 subunit (IL-13Rα1) with high affinity and blocks the signaling of IL-4 and IL-13 through the type 2 receptor (**Figure 1**)
- Type 2 receptors are expressed on a range of immune and non-immune cells, including sensory neurons[2,4]
- In a Phase 1b clinical trial (N≈50), eblasakimab demonstrated statistically significant improvements versus placebo across a range of endpoints, with no emerging safety concerns in participants with moderate-to-severe AD[6]

Figure 1. Eblasakimab Mechanism of Action



Eblasakimab binds to and blocks the IL-13 receptor α1 subunit (IL-13Rα1), one of the type 2 receptor components, thereby preventing signaling through both IL-4 and IL-13, key drivers of allergic inflammation in atopic dermatitis.
IL-4, interleukin-4; IL-4Rα, interleukin-4 receptor α; IL-13, interleukin-13; IL-13Rα1, interleukin-13 receptor α1 subunit

OBJECTIVE

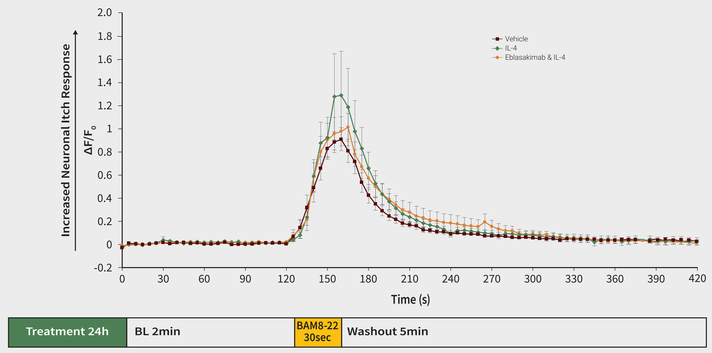
- To determine the impact of targeting the IL-13Rα1 receptor with eblasakimab on neuronal itch responses

KEY RESULTS: EBLASAKIMAB SIGNIFICANTLY REDUCED CYTOKINE-ENHANCED NEURONAL ITCH RESPONSES

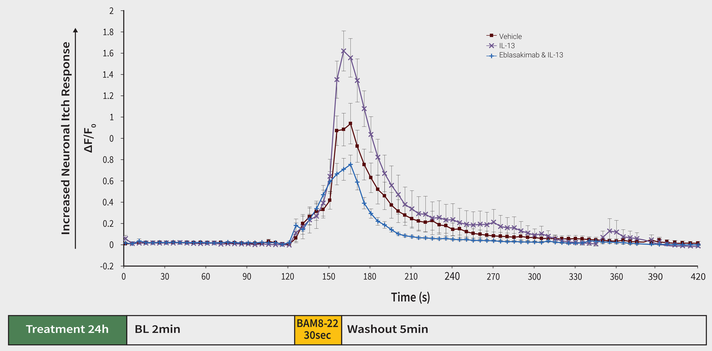
- Incubation of human sensory neurons with IL-4, IL-13, and IL-4 + IL-13 combined elicited an enhanced pruritic neuronal effect profile in response to the pruritogen BAM8-22 (**Figure 2A-C**)
  - Eblasakimab attenuated the IL-4- and IL-13-driven enhanced responses (**Figure 2A-C**)
  - Simultaneous application of both IL-4+IL-13 produced no obvious synergy or combined additive enhancer effects on pruritic pathways (**Figure 2A-C**)
- Quantification of relative neuronal response showed eblasakimab significantly reduced neuronal responses to IL-4, IL-13, and their combination by an average of up to 40% ($p<0.0001$) (**Figure 3A**), with some responses demonstrating inhibition up to 100% (**Figure 2B, C**)
- Eblasakimab treatment in the presence of cytokines reduced pruritic neuronal responses below vehicle conditions (**Figure 3B**)

Figure 2. Representative Time Courses of Neuronal Responses

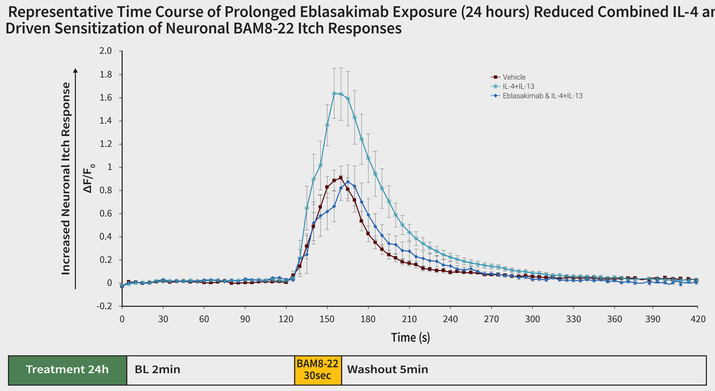
A. Representative Time Course of Prolonged Eblasakimab Exposure (24 hours) Reduced IL-4-Driven Sensitization of Neuronal BAM8-22 Itch Responses



B Representative Time Course of Prolonged Eblasakimab Exposure (24 hours) Reduced IL-13-Driven Sensitization of Neuronal BAM8-22 Itch Responses



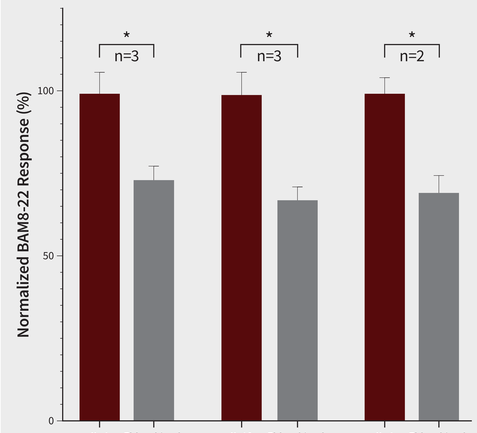
C. Representative Time Course of Prolonged Eblasakimab Exposure (24 hours) Reduced Combined IL-4 and IL-13-Driven Sensitization of Neuronal BAM8-22 Itch Responses



BL, baseline measurement; h, hours; IL-4, interleukin-4; IL-13, interleukin-13; sec, seconds
Error bars indicate standard error of mean

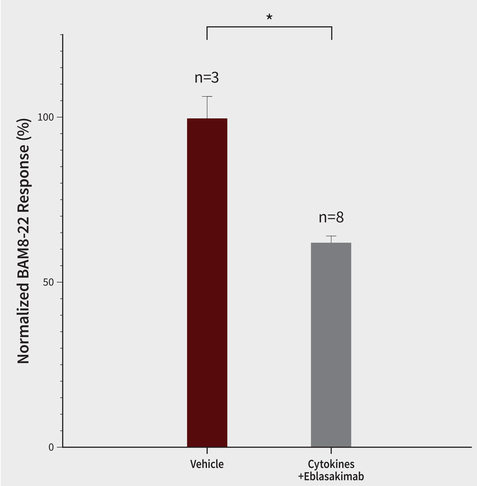
Figure 3. Eblasakimab Significantly Reduced Cytokine-Enhanced Neuronal Itch Responses

A. Effect of Eblasakimab Treatment on Cytokine Potentiation of Neuronal Response to BAM8-22



Average effect of eblasakimab + cytokine treated hDRG neuron responses versus their respective cytokine only responses. Cytokine treatment was normalized to 100% showing the inhibition of eblasakimab on the 2μM BAM8-22 response.
IL-4, interleukin-4; IL-13, interleukin-13
n, number of donors
* $p < 0.0001$ determined by ANOVA test

B. Summary of Vehicle and Cytokine + Eblasakimab Effects on Neuronal Response to BAM8-22



Combined average cytokines + eblasakimab treated hDRG neuron responses versus the untreated (vehicle) hDRG responses to 2μM BAM8-22.
n, number of donors
* $p < 0.0001$, determined by ANOVA test

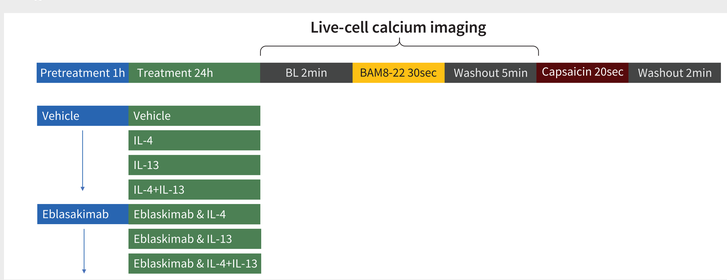
CONCLUSIONS & OUTLOOK

- Human sensory neurons pre-stimulated with IL-4, IL-13, and their combination showed enhanced neuronal itch effect profiles
  - Observed differences in the neuronal sensitization effects between IL-4 and IL-13 warrant further investigation
- Eblasakimab significantly reduced neuronal itch responses to IL-4, IL-13, and their combination
- Results suggest that both IL-4 and IL-13 cytokines may play a role in amplifying neuronal itch responses via type 2 IL-13Rα1 receptors
- The finding that eblasakimab treatment reduced pruritogenic neuronal responses sensitized by cytokines below vehicle controls suggests that IL-13Rα1 may play an additional role in neuro-immune modulation beyond the cytokine-related neuronal itch sensitization
  - Future studies could further investigate the molecular basis of the neuro-immune modulatory effects driven by eblasakimab's binding to neuronally expressed IL-13Rα1
- These results suggest a mechanistic basis for the improvement in pruritus observed with eblasakimab treatment in participants with moderate-to-severe AD in the Phase 1b clinical trial[6]
  - The observed dual inhibitory effects of IL-4 and IL-13 by targeting IL-13Rα1 with eblasakimab could possibly benefit other type-2 immune disorders in which neuronal sensitization might be part of the disease pathology

METHODS

- An *ex vivo* human neuronal model system was used to determine neuronal responses of human dorsal root ganglia (hDRG) neurons to itch signaling induced by the pruritogen BAM8-22 under various conditions (**Figure 4**)
- Neuronal responses were captured by live cell calcium imaging, with a minimum of 50 hDRG neurons used per assay
- All hDRG neurons used for this study were isolated from organ donors in the United States after obtaining informed consent in accordance with state and federal regulations, and the United Network for Organ Sharing policies[7]
- hDRG cells were loaded with Fluo-8-AM for 30 minutes and placed under the microscope to measure cytoplasmic calcium
- Images were acquired at 0.2 Hz and analyzed using MetaMorph software from Molecular Devices

Figure 4. Protocol Schematic



BL, baseline measurement; h, hours; IL-4, interleukin-4; IL-13, interleukin-13; sec, seconds
Compound concentrations used: eblasakimab, 500μg/mL; IL-4, 500nM; IL-13, 500nM; BAM8-22, 2μM; capsaicin, 200nM

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AUTHOR DISCLOSURES

Y. Miron and P. E. Miller are employees of AnaBios Corporation; C. Firth and F. Cevikbas are employees of ASLAN Pharmaceuticals.

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