EPS-3903 is a Potent and Selective Oral STAT6 Inhibitor That Blocks Th2 Inflammation in a House Dust Mite-Induced Asthma Mouse Model

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BACKGROUND

- Asthma is a complex respiratory disease characterized by airway hyperresponsiveness and inflammation.
- An IL-4/IL-13 signaling-mediated Th2 immune response is the determinant driver of allergic asthma. Dupilumab, an injectable monoclonal antibody that blocks human IL-4Rα, has been approved to treat moderate-to-severe asthma.
- House dust mite (HDM) is a clinically relevant allergen that induces allergic responses in 85% of asthmatic individuals.[1] The HDM asthma mouse model[2] is commonly used to evaluate allergic asthma therapeutics. Dupilumab has been shown to effectively attenuate HDM-induced asthma pathology in IL-4/IL-4Rα humanized mice[3].
- STAT6 is a transcription factor that mediates IL-4/IL-13 signaling and is central to Th2 inflammation (**Figure 1**). STAT6 activation results in lung inflammation and tissue remodeling via regulation of Th2 cell differentiation, eosinophilic recruitment and epithelial mucus production. STAT6 genetic loss-of-function protects against Th2 inflammation associated asthma in humans[4].
- EPS-3903 is a selective and potent, orally bioavailable allosteric small molecule inhibitor of STAT6 with the potential to treat a wide range of allergic diseases, including asthma and atopic dermatitis[5,6].

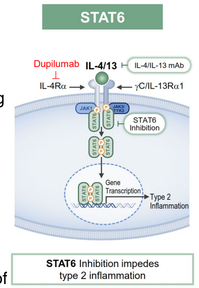

Figure 1. STAT6 is the key transcription factor mediating Th2 inflammation

METHODS

- *In vitro* inhibitory potency against mouse STAT6 phosphorylation (pSTAT6) and TARC secretion was assessed in primary mouse splenocytes with mouse IL-4 (mIL-4) stimulation.
- *In vitro* potency against IL-4-induced pSTAT6 nuclear translocation in human alveolar cells (A549) and IL-13-induced periostin secretion in human bronchial smooth muscle cells was evaluated.
- pSTAT6 and TARC levels were quantified by MSD. Total STAT6 (tSTAT6) was quantified by alphaLISA. pSTAT6 nuclear translocation was determined by pSTAT6 nuclear staining. Periostin secretion was detected by ELISA.
- An *in vivo* asthma mouse model was established in IL-4/IL-4Rα humanized mice with an HDM challenge, 3 times per week.EPS-3903 was given orally to the mice once daily for 28 days. Dupilumab and the isotype IgG4 control were injected subcutaneously, twice per week. Mice were euthanized on Day 28.
- BALF was harvested for leukocyte and eosinophil quantification by flow cytometry. BALF supernatants and lung tissues were used for Th2 biomarker measurement (TARC, eotaxin) by MSD. Serum IgE was assessed by ELISA. Histologic scoring was done by hematoxylin and eosin (H&E) and PAS staining. Lung *muc5ac* gene expression was measured by real-time PCR. Lung RNAseq was analyzed with RStudio.

RESULTS

EPS-3903 is a Potent STAT6 Inhibitor *In Vitro*

Stimulator	Assay	Cell Type	EPS-3903 EC_{50} (nM)
mIL-4	Mouse pSTAT6	Primary Mouse Splenocytes	9
mIL-4	Mouse TARC	Primary Mouse Splenocytes	4
hIL-4	Human pSTAT6 Nuclear Translocation	Human Alveolar Epithelial Cell Line (A549)	14
hIL-13	Human Periostin	Human Bronchial Smooth Muscle Cells (BSMCs)	3

Table 1. Potency of EPS-3903 *in vitro*. Potency of EPS-3903 against IL4-stimulated pSTAT6 and TARC secretion was evaluated in mouse splenocytes. Inhibition of pSTAT6 nuclear translocation was evaluated in A549 cells. Inhibition of IL13-stimulated periostin secretion was evaluated in BSMCs. EC_{50}: half-maximal effective concentration. TARC: thymus and activation-regulated chemokine.

EPS-3903 Blocks HDM-Induced Lung STAT6 Phosphorylation in an Asthma Mouse Model

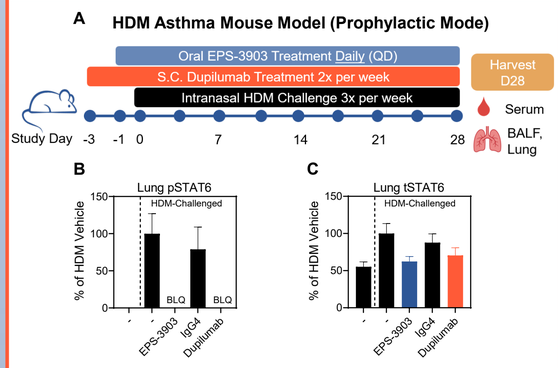

Figure 2. Lung Target Engagement of EPS-3903 in HDM Asthma Model. (A) Study design of HDM-induced asthma mouse model. S.C.: subcutaneous. QD: once daily. (B) Lung pSTAT6 and total STAT6 (tSTAT6) were measured in lung lysates from HDM-treated mice. Data are normalized to HDM-treated vehicle. * p<0.05 vs corresponding vehicle.

DISCLOSURE

All authors are employees of Enanta Pharmaceuticals, Inc. and received salary and stock compensation.

RESULTS

EPS-3903 Alleviates Th2 Inflammation with a Comparable Efficacy to Dupilumab Treatment

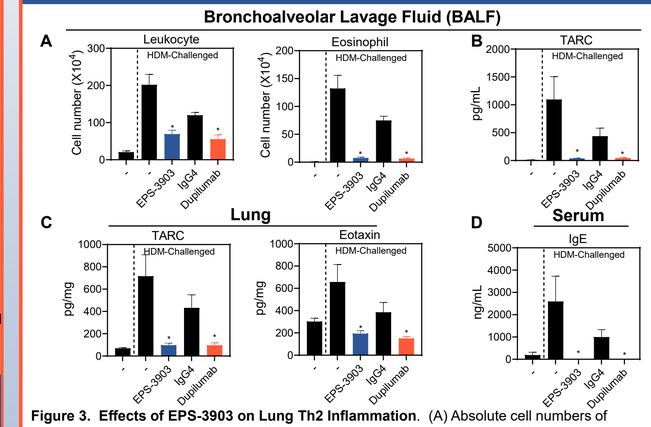

Figure 3. Effects of EPS-3903 on Lung Th2 Inflammation. (A) Absolute cell numbers of leukocytes and eosinophils in BALF. (B) TARC levels in BALF supernatants. (C) Lung Th2 inflammatory biomarkers: TARC and eotaxin. (D) Serum IgE. * p<0.05 vs corresponding vehicle.

EPS-3903 Improves Epithelial Histopathology with a Comparable Efficacy to Dupilumab Treatment

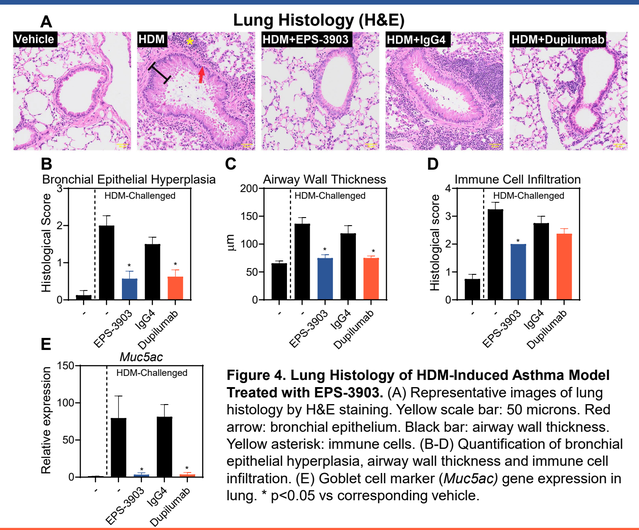

Figure 4. Lung Histology of HDM-Induced Asthma Model Treated with EPS-3903. (A) Representative images of lung histology by H&E staining. Yellow scale bar: 50 microns. Red arrow: bronchial epithelium. Black bar: airway wall thickness. Yellow asterisk: immune cells. (B-D) Quantification of bronchial epithelial hyperplasia, airway wall thickness and immune cell infiltration. (E) Goblet cell marker (*Muc5ac*) gene expression in lung. * p<0.05 vs corresponding vehicle.

RESULTS

EPS-3903 Recapitulates the Lung Transcriptomics Profile of Dupilumab

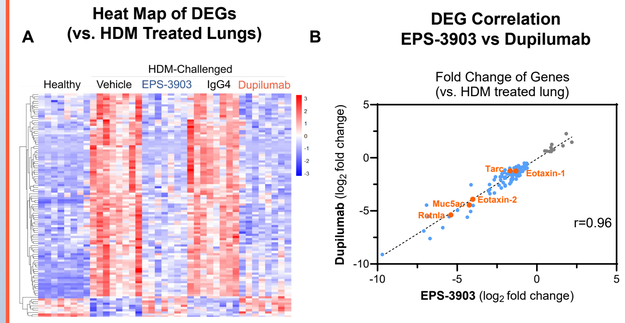

Figure 5. Lung RNAseq of HDM-induced Asthma Mouse Model Treated With EPS-3903 or Dupilumab. (A) Heatmap of differentially expressed genes (DEGs) in EPS-3903 and Dupilumab-treated lung versus HDM-vehicle control treatment, False Discovery Rate (FDR) <0.05; Data are presented as row Z-scores, upregulated (red), downregulated (blue). (B) Scatter plot correlation (log_2 fold change) of DEGs from EPS-3903 and dupilumab treatment. Th2 inflammation related genes are highlighted in orange.

CONCLUSIONS

- **Potency:** EPS-3903 is an oral small molecule allosteric STAT6 inhibitor with nanomolar potency across various cell types (lung epithelial, splenocytes).
- **Target Engagement:** EPS-3903 completely inhibits lung STAT6 activity without disrupting basal STAT6 levels in an HDM-induced asthma mouse model.
- **Preclinical Efficacy:** EPS-3903 alleviates Th2 inflammation and improves lung epithelial histopathology in an HDM asthma mouse model. EPS-3903 efficacy and lung transcriptomic profile were highly correlated with dupilumab treatment.

EPS-3903 may offer a dupilumab-like oral therapeutic option for treating allergic diseases including asthma and atopic dermatitis.

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