**Bifidobacterium breve** MRx-4DP0004 protects against airway inflammation in a severe asthma model by suppressing both neutrophil and eosinophil lung infiltration

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## Background
- Asthma is a phenotypically heterogeneous disease characterized by recurrent, reversible airway obstruction and increased bronchial hyper-responsiveness.
- In severe asthma (SA), airway inflammation can be predominantly eosinophilic, neutrophilic, or mixed. Only a limited number of drug candidates are in development to address this unmet clinical need.
- MRx-4DP0004 is a commensal *Bifidobacterium breve* strain isolated from the microbiome of a healthy human infant.
- The strain was tested prophylactically and therapeutically by oral gavage in a house dust mite mouse model of severe asthma (Raftis et al., 2018).

## Study design
**Daily oral dosing with vehicle or MRx0004**

- **Prophylactic dosing D-14 until D18**
- **Therapeutic dosing D7 until D18**

Preclinical model of severe asthma delivers a disease phenotype with elevated neutrophilic and eosinophilic lung infiltration, lung histopathology and a mixed Th1/Th17 cytokine profile. 5 animals/group (3 for baseline). HDM = house dust mite, CFA = complete Freund’s adjuvant, stats = ANOVA followed by Tukey’s post test.

## Prophylactic dosing reduces lung infiltrates
- **MRx-4DP0004 treatment significantly reduces total cell number in the lung, lung infiltrating neutrophils, and lymphocyte numbers in the lung**

## Reduction of neutrophil and eosinophil lung infiltrate associated with lung inflammatory scores

- **Histopathological analysis of lungs of mice exposed to HDM, and treated with MRx-4DP0004, anti-IL-17 or vehicle, with samples collected 24 h after final exposure**
- (a) Representative images (original magnification x250) for histopathology scoring; (b) immuno-labelled CD4+ cells (green), double-labelled with DAPI (blue); (c) mean inflammatory scores. Capped bars illustrate the maximum and minimum data points within each treatment group. *p < 0.05, **p < 0.01, ***p < 0.001 between treatment groups.

## Conclusions
- MRx-4DP0004 was tested prophylactically and therapeutically by oral gavage in a house dust mite mouse model of severe asthma.
- We have demonstrated that treatment with MRx-4DP0004, a microbiota-derived bacterial strain, can reduce both neutrophilic and eosinophilic infiltration in lung bronchoalveolar lavage fluid in a severe asthma model.
- Peribroncholar and perivascular immunopathology was also reduced. MRx-4DP0004 increased lung CD4+CD44+ cells and CD4+FoxP3+ cells and decreased activated CD11b+ dendritic cells. Cytokine analysis of lung tissue revealed reductions of pro-inflammatory cytokines and chemokines involved in neutrophil migration.
- In comparison, anti-IL-17 antibody treatment effectively reduced neutrophilic infiltration and increased CD4+FoxP3+ cells, but it induced lung eosinophilia and did not decrease histopathology scores.
- Further mechanistic studies are underway to clarify the effect of MRx-4DP0004 on host immunity and identify the mediators of it’s effect on the gut-lung axis.
- MRx-4DP0004 is a promising next-generation drug for management of severe asthma.
- A first-in-man clinical trial is planned in asthma for the second half of 2018.