Supplementary Material

S1. Exclusion criteria

- A history of grade IV anaphylaxis (to any antigen).
- Asthma symptoms or exacerbations requiring regular inhaled steroids for ≥4 weeks in the past 12 months or any oral corticosteroid use/asthma-related hospitalisations.
- Chronic sinusitis.
- Recent (within 30 days) active or suspected systemic infection
- Immunodeficiency.
- Excluded medications included: beta-blockers; tricyclic antidepressants; monoamine oxidase inhibitors; antihistamines or intranasal/inhaled corticosteroids within 7 days of the subsequent EEU challenge; and before enrolment sodium cromoglycate in any form (14 days): systemic corticosteroids or a leukotriene antagonist (30 days); and omalizumab or dupilumab (6 months).
- Consumption of any citrus fruits (grapefruit, orange, etc.) or their juices within 5 days from the study entry.

S2. EEU methodology

The EEU is a specifically engineered room that enables controlled exposure to airborne pollen and DEP. Rotorod® sampling equipment and a microaethalometer measured and tracked ragweed and DEP levels, respectively. A custom-engineered computer delivery system dispersed both airborne compounds via a seated-height, airflow-regulated wall duct, floor-level wall vents, and directional fans.
Ragweed pollen was sourced in the USA (Greer Laboratories, Lenoir, NC), independently tested for fungal and bacterial contamination (Paracel Laboratories Ltd.), and approved for use by a toxicologist. DEP was sourced from NIST (National Institute of Standards & Technology) as “standard reference material 2975” and was supplied with a certificate of analysis and material safety data sheet. Further independent metals content and endotoxin testing was completed (Paracel Laboratories Ltd.) to verify suitability for use. The DEP was resuspended from bulk form using a custom aerosoliser. DEP output through the aerosoliser was adjusted via increasing or decreasing the measured airflow through the main portal while

monitoring the real-time 880nm, black carbon, channel output from the microaethelometer. This output was reflective of the average DEP room concentration. Taken from the NIST COA, subsamples of DEP taken from four separate bulk sources revealed that 50% of the volume was less than 19.4um in size and 10% was less than 5.3um.
Subjects were exposed to a mean target ragweed pollen concentration of 3500 ± 500 grains/m^3 and a mean target DEP concentration equivalent to 0.3 mg of DEP in 300 µL of saline during the three periods.

S3. Hierarchical test procedure

The following hierarchical procedure was used to control the type I error and handle multiple endpoints analysis.

Primary endpoints analysis

First, the first primary endpoint ($AUC_{0\text{-}12}$ of the TNSS compared between Period 1 and Period 2) was tested at a two-sided 5% type I error rate level. If the first primary analysis was significant, the second primary endpoint ($AUC_{2–12}$ of the TNSS in Period 3) was tested at the same two-sided 5% type I error rate level. If the results observed during this first primary analysis did not show that SAR symptoms were significantly aggravated in presence of pollutants, with a two-sided statistical significance of 5%, the analysis of the second primary efficacy endpoint and other secondary efficacy endpoints statistical analyses were planned to be descriptive only, without treatment group comparison.

Secondary endpoints analysis

The secondary efficacy endpoints analyses were planned to be descriptive only if the sequentially-tested comparison for the second primary efficacy endpoint was not significant at the 5%level. Secondary endpoints were analysed sequentially and upon the first non-significant endpoint analysis, all subsequent secondary endpoints were assessed using descriptive statistics. The sequence of testing was as follows:

- $AUC_{2–12}$ of the Total Symptom Score (TSS)
- $AUC_{2–12}$ of individual symptom scores.

    - The sequence of individual symptom analysis was: rhinorrhoea, sneezing, nasal itching, itchy eyes, watery eyes, red or burning eyes and itching of the ears or palate or throat, and nasal congestion.
- TNSS, followed by TSS and then individual symptom scores, each by time point.

Supplementary Table 1. Baseline results of the skin prick test (EP)

Allergen	EP (N=257)
Negative control	
Mean (SD)	0.5 (0.9)
Median	0
Q1;Q3	0.0;0.0
Ragweed	
Mean (SD)	12.4 (6.5)
Median	11.0
Q1;Q3	8.0;15.0
Dog	
Mean (SD)	0.9 (1.7)
Median	0.0
Q1;Q3	0.0;2.0
Cat	
Mean (SD)	3.4 (3.7)
Median	3.0
Q1;Q3	0.0;6.0
D. pteronyssinus	
Mean (SD)	5.2 (5.5)
Median	4.0
Q1;Q3	0.0;9.0
D. farinae	
Mean (SD)	4.8 (5.7)
Median	3.0

Q1;Q3	0.0;9.0
Alternaria	
Mean (SD)	1.8 (2.8)
Median	0.0
Q1;Q3	0.0;3.0
Grass	
Mean (SD)	7.8 (7.5)
Median	7.0
Q1;Q3	0.0;11.0
Trees	
Mean (SD)	5.6 (5.9)
Median	5.0
Q1;Q3	0.0;10.0

EP=evaluable population; SD=standard deviation.

Supplementary Table 2. Incidence of treatment-emergent adverse events by primary system organ class and preferred term (safety population)[a]

Primary system organ class (preferred term)	**Placebo, n (%) N=126**	**Fexofenadine HCl, n (%) N=127**
Any class	19 (15.1)	16 (12.6)
Infections and infestations	3 (2.4)	2 (1.6)
Upper respiratory tract infection	2 (1.6)	2 (1.6)
Gastroenteritis	1 (0.8)	0 (0.0)
Immune system disorders	7 (5.6)	6 (4.7)
Seasonal allergy	7 (5.6)	6 (4.7)
Nervous system disorders	2 (1.6)	2 (1.6)
Headache	1 (0.8)	2 (1.6)
Sinus headache	1 (0.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	5 (4.0)	2 (1.6)

Nasal dryness	0 (0.0)	2 (1.6)
Cough	1 (0.8)	0 (0.0)
Nasal congestion	1 (0.8)	0 (0.0)
Nasal pruritus	1 (0.8)	0 (0.0)
Rhinorrhoea	1 (0.8)	0 (0.0)
Sneezing	1 (0.8)	0 (0.0)
Upper-airway cough syndrome	1 (0.8)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	3 (2.4)
Dry mouth	0 (0.0)	1 (0.8)
Enlarged uvula	0 (0.0)	1 (0.8)
Nausea	0 (0.0)	1 (0.8)
Skin and subcutaneous tissue disorders	1 (0.8)	0 (0.0)
Pruritus	1 (0.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.8)	0 (0.0)
Back pain	1 (0.8)	0 (0.0)
General disorders and administration site conditions	1 (0.8)	0 (0.0)
Fatigue	1 (0.8)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.8)	1 (0.8)
Muscle strain	1 (0.8)	1 (0.8)

[a] Subjects may have experienced more than one type of AE with each primary system organ class during the study

HCl=hydrochloride