ORIGINAL ARTICLE
ALLERGY

Effect of fexofenadine hydrochloride on allergic rhinitis aggravated by air pollutants

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ABSTRACT In recent decades, seasonal allergic rhinitis (SAR) prevalence has increased and recent studies have shown that air pollutants, such as diesel exhaust particles (DEP), can increase inflammatory and allergic biomarkers. The aim of this study was to investigate the effects of DEP on SAR symptoms induced by ragweed and to evaluate the efficacy and safety of fexofenadine HCl 180 mg *versus* placebo.

This phase 3, single-centre, sequential, parallel-group, double-blind, randomised study (NCT03664882) was conducted in an environmental exposure unit (EEU) during sequential exposures: Period 1 (ragweed pollen alone), Period 2 (ragweed pollen+DEP), and Period 3 (ragweed pollen+DEP+single-dose fexofenadine HCl 180 mg or placebo). Efficacy and safety were evaluated in Period 3. Primary endpoints were the area under the curve (AUC) of total nasal symptom score (TNSS) from baseline to hour 12 (AUC_{0-12}) during Period 1 and Period 2; and the AUC of the TNSS from hour 2 to 12 (AUC_{2-12}) during Period 3.

251 out of 257 evaluable subjects were included in the modified intent-to-treat population. Least squares mean difference (95% CI) for TNSS Log AUC_{0-12} in Period 2 *versus* Period 1 was 0.13 (0.081–0.182; p<0.0001). Least squares mean difference in TNSS Log AUC_{2-12} for fexofenadine HCl *versus* placebo during Period 3 was −0.24 (−0.425–−0.047; p=0.0148). One fexofenadine HCl-related adverse event was observed.

SAR symptoms evoked by ragweed were aggravated by DEP. Fexofenadine HCl 180 mg was effective in relieving pollen-induced, air pollution-aggravated allergic rhinitis symptoms.

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This is the first randomised, double-blind, large study to demonstrate the beneficial effect of a histamine H1-receptor antagonist by reducing ragweed pollen-induced seasonal allergic rhinitis symptoms aggravated by controlled exposure to air pollutants https://bit.ly/3oauMFu

Cite this article as: Ellis AK, Murrieta-Aguttes M, Furey S, *et al.* Effect of fexofenadine hydrochloride on allergic rhinitis aggravated by air pollutants. *ERJ Open Res* 2021; 7: 00806-2020 [https://doi.org/10.1183/23120541.00806-2020].

This article has supplementary material available from openres.ersjournals.com

This study is registered at www.clinicaltrials.gov with identifier number NCT03664882. Qualified researchers may request access to patient-level data and related documents (including, *e.g.*, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications). Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies and process for requesting access can be found at www.clinicalstudydatarequest.com.

Received: 30 Oct 2020 | Accepted: 18 Jan 2021

Introduction

Seasonal allergic rhinitis (SAR) is caused by a type I immunoglobulin (Ig)E-mediated hypersensitivity reaction to allergens, such as pollens (*e.g.* ragweed), which provokes characteristic symptoms including sneezing, rhinorrhoea, nasal obstruction, itching of the throat and nose, and watery eyes [1]. Worldwide, allergic rhinitis affects between 10 and 30% of the population and an overall increase in prevalence has been shown in recent studies [2]. Epidemiological studies have identified environmental risk factors, such as air pollutant exposure and climate change, as potentially associated with this trend [3, 4].

Diesel exhaust particles (DEP) comprise a carbon core with adsorbed organic compounds [5, 6]; their small size and large surface area allow them to infiltrate airway epithelial cells, leading to inflammation and cytotoxicity [7]. Of note, DEP have been implicated in exacerbating long-distance spread of viral infection, for example during the coronavirus disease 2019 pandemic [8]. Additionally, they can interact with allergens to enhance allergen-induced responses, up to 50-times more than allergens alone [9].

Fexofenadine hydrochloride (HCl) is a second-generation, selective histamine H1-receptor antagonist, approved to relieve SAR symptoms in adults and children [10], and is marketed in approximately 100 countries worldwide, including the USA, Japan and Europe. Depending on the country, the approved single daily dose is either 120 mg or 180 mg (Allegra/Telfast; Sanofi, Paris, France) [11, 12].

This study (NCT03664882) was a prospective, sequential and parallel-group, double-blind, single-dose, placebo-controlled, randomised clinical investigation of the effects of DEP on SAR ragweed-induced symptoms and evaluating the efficacy and safety of fexofenadine HCl 180 mg *versus* placebo in alleviating such pollution-aggravated symptoms.

Methods

Study population

Eligible subjects were aged 18–65 years with a 2-year history of SAR provoked by ragweed; a positive skin prick test to ragweed (defined as a wheal diameter ⩾3 mm larger than the control one); a self-reported history of SAR symptoms aggravated by pollen or air pollutants exposure; and at least one documented total nasal symptom score (TNSS) ⩾3 during the first 3 h of pollen exposure in Period 1. At the investigator's discretion, subjects who had significant allergy to perennial allergens that could not be avoided during the study were excluded. Other major exclusion criteria are listed in the Supplementary Material. Regulatory approval was obtained from Health Canada and ethical clearance was provided by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB). The trial was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and all applicable regulations. Written informed consent was obtained prior to study enrolment.

Study design

This phase 3, single-centre (Kingston Health Sciences Centre, KGH Site, ON, Canada), sequential and parallel-group, double-blind, single-dose, placebo-controlled, randomised study evaluated the efficacy and safety of fexofenadine HCl 180 mg, compared with placebo. The study was conducted outside of the typical ragweed pollen season in the locale of the environmental exposure unit (EEU). Details of the EEU methodology are available in the Supplementary Material. Figure 1 schematically depicts the study design.

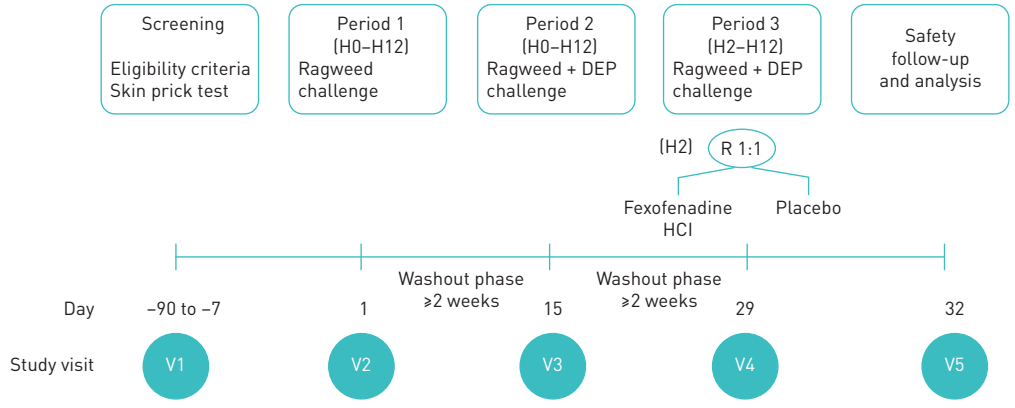

FIGURE 1 Schematic of study design. DEP: diesel exhaust particles; H: hour; V: visit. Note: visit 5 on day 32 could be accomplished *via* a telephone contact.

At Visit 1, ragweed sensitivity was determined *via* skin testing. Additionally, skin prick tests were performed to assess sensitivity to other common allergens (dog, cat, *Alternaria*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass, trees). During Visit 2 (Period 1), eligible subjects were exposed to ragweed pollen alone in the EEU and TNSS was self-assessed every 30 min during the first 3 h of exposure (in the EEU). Subjects were then discharged and recorded hourly TNSS scores for the following 9 h; those who reported at least one TNSS score of ⩾3 during the first 3 h of Visit 2 were eligible for Visit 3 (Period 2). In Period 2 eligible subjects were exposed to ragweed+DEP in the EEU for 3 h and then discharged. The timing of TNSS assessments was identical to that in Period 1. At Visit 4 (Period 3) subjects were randomised 1:1 to receive either fexofenadine HCl 180 mg or placebo. Subjects were exposed to ragweed+DEP for 3 h and study medication was administered at hour 2. TNSS was rated every 30 min during the first 3 h of ragweed+DEP exposure and then hourly up to hour 12. Each challenge period was separated by at least a two-week washout. Diary collection and safety follow-up occurred during Visit 5.

Outcomes

The primary objective was to demonstrate the aggravation of the SAR symptoms caused by DEP exposure. The second primary objective was to evaluate the efficacy of fexofenadine HCl in alleviating symptoms aggravated by DEP presence. The first primary endpoint was the area under the curve (AUC) for TNSS from baseline (hour 0) to hour 12 (TNSS $AUC_{0–12}$) in Periods 1 and 2. Tested sequentially, the second primary endpoint was AUC for TNSS during Period 3 from time of study medication administration (hour 2) to hour 12 (TNSS $AUC_{2–12}$). Of note, the primary and second primary endpoints were independent and therefore not comparable. Secondary efficacy endpoints in Period 3 were sequentially evaluated as follows: Total symptom score (TSS) $AUC_{2–12}$; each individual symptom score $AUC_{2–12}$; TSS and individual symptom score by time point from hour 2 to hour 12. All adverse events were recorded.

Subjects scored allergic rhinitis symptom severity on a diary card using a 0–3 scale adapted from US Food and Drug Administration (FDA)-recommended definitions (0: none, symptom is completely absent; 1: mild, symptom is present, but not bothersome; 2: moderate, symptom is bothersome, but tolerable; and 3: severe, symptom is hard to tolerate, I would like to have a treatment) [13, 14].

Eight symptoms were rated: rhinorrhoea, sneezing, nasal itching, nasal congestion, itchy eyes, watery eyes, red or burning eyes and itching of the ears or palate or throat. TNSS was calculated as the sum of rhinorrhoea, sneezing and nasal itching scores [13]. TSS was calculated as the sum of all eight symptoms.

The safety analysis defined pre-treatment adverse events as those that developed, worsened, or became serious from the signed informed consent date up to study drug administration. Treatment-emergent adverse events (TEAE) were any adverse events recorded from study drug intake up to three following days.

Randomisation and masking

Evaluable subjects completing Period 1 and 2 and returning for Period 3 were randomly assigned 1:1 to fexofenadine HCl or placebo according to a double-blind, permuted block schedule prepared by Sanofi. Fexofenadine HCl 180 mg and matching film-coated placebo tablets were individually packaged by pharmacy personnel otherwise not involved with the study. This enabled subjects and all study personnel to be blinded to treatment assignment.

Statistical analysis

The evaluable population, the population analysed for the first primary endpoint, comprised all subjects who participated in Periods 1 and 2; had a TNSS recorded at hour 0; and at ⩾1 subsequent time points for both periods. The intent-to-treat (ITT) population consisted of all subjects randomised during Period 3. The modified ITT (mITT) population comprised all subjects receiving study medication who recorded TNSS at hour 2 (before study drug intake) and at ⩾1 subsequent time points. The second primary endpoint and all efficacy secondary endpoints were analysed using the mITT population. The safety population included all randomised subjects who received study medication.

Assuming an effect size of 0.25 for the aggravation of SAR symptoms in the presence of DEP, 260 evaluable subjects were required to provide 98% power for the first primary endpoint. Assuming 23% of subjects would be deemed ineligible or non-evaluable, approximately 340 subjects were needed to qualify for Visit 2 (Period 1). An mITT population of approximately 240 subjects was required to detect an effect size of 0.37 for fexofenadine HCl 180 mg with 81% power for the second primary endpoint. A 0.5 change in TNSS when four individual symptoms (rhinorrhoea, nasal congestion, nasal itching and sneezing) are measured is commonly defined as the minimum clinically important difference [15]. Because fexofenadine HCl lacks α-adrenergic vasoconstrictor activity, nasal congestion was not a TNSS score component; therefore, in this analysis an adjusted difference of 0.65 was deemed clinically important (rather than 0.5).

A hierarchical procedure was used to control for type I error and handle multiple comparisons (details available in the Supplementary Material). The first sequential primary analysis, TNSS (AUC_{0-12}) compared between Periods 1 and 2, employed a two-sided test controlled for a 5% type I error rate using a mixed model for repeated measures (MMRM). The MMRM was adjusted for baseline TNSS (measured at hour 0) and pollen counts (at subject level) for Periods 1 and 2, with period as a fixed categorical effect. The second primary analysis, TNSS (AUC_{2-12}) in Period 3 compared between treatment groups, employed a two-sided test controlled for a 5% type I error rate using an analysis of covariance (ANCOVA) with treatment group as a fixed categorical effect and baseline TNSS (measured at hour 2) as covariate. If required, log transformation of the primary endpoints was performed to improve normality of the distributions. All secondary efficacy endpoints based on AUC_{2-12} were analysed using an ANCOVA with treatment group as fixed categorical effect and the respective baseline score (hour 2) as covariate. TNSS, TSS, and individual symptom score analysis at each time point used a MMRM, with treatment group, time point, and treatment-group-by-time-point interaction as fixed effects and the respective baseline score (hour 2) as covariate. Secondary endpoints were analysed sequentially to maintain a 5% type I error. The safety analysis was descriptive and conducted on the safety population.

Results

Disposition and demographic characteristics

Overall, 375 subjects were screened, and 266 (70.9%) met the eligibility criteria, of which 257 (96.6%) were included in the evaluable population (figure 2). The first subject was enrolled in November 2018 and the last subject completed the study in January 2019. Five eligible subjects discontinued before entering Period 2. Four subjects were excluded from the evaluable population due to the absence of baseline TNSS in Period 1 or Period 2, leaving 257 subjects. In total, 13 eligible subjects discontinued the study before entering Period 3 due to: scheduling conflicts (five), adverse events (two), meeting an exclusion criterion (two), withdrawal of consent (one), poor compliance to protocol (one), EEU challenge intolerance (one) and withdrawal from study (one). Of the 253 subjects in Period 3, 127 were randomised to fexofenadine HCl 180 mg and 126 to placebo. The ITT and safety populations consisted of 253 subjects, and the mITT population of 251 subjects due to missing baseline TNSS scores for two individuals. Baseline demographics and characteristics for the ITT and mITT populations are shown in table 1, respectively. Mean±SE age was 40.8 (0.78) and 40.7 (0.79) years in the evaluable and mITT populations, respectively. In both populations, the majority of subjects were female and non-smokers. The mean±SD values of common perennial allergens using the skin prick test were all significantly lower compared to ragweed in

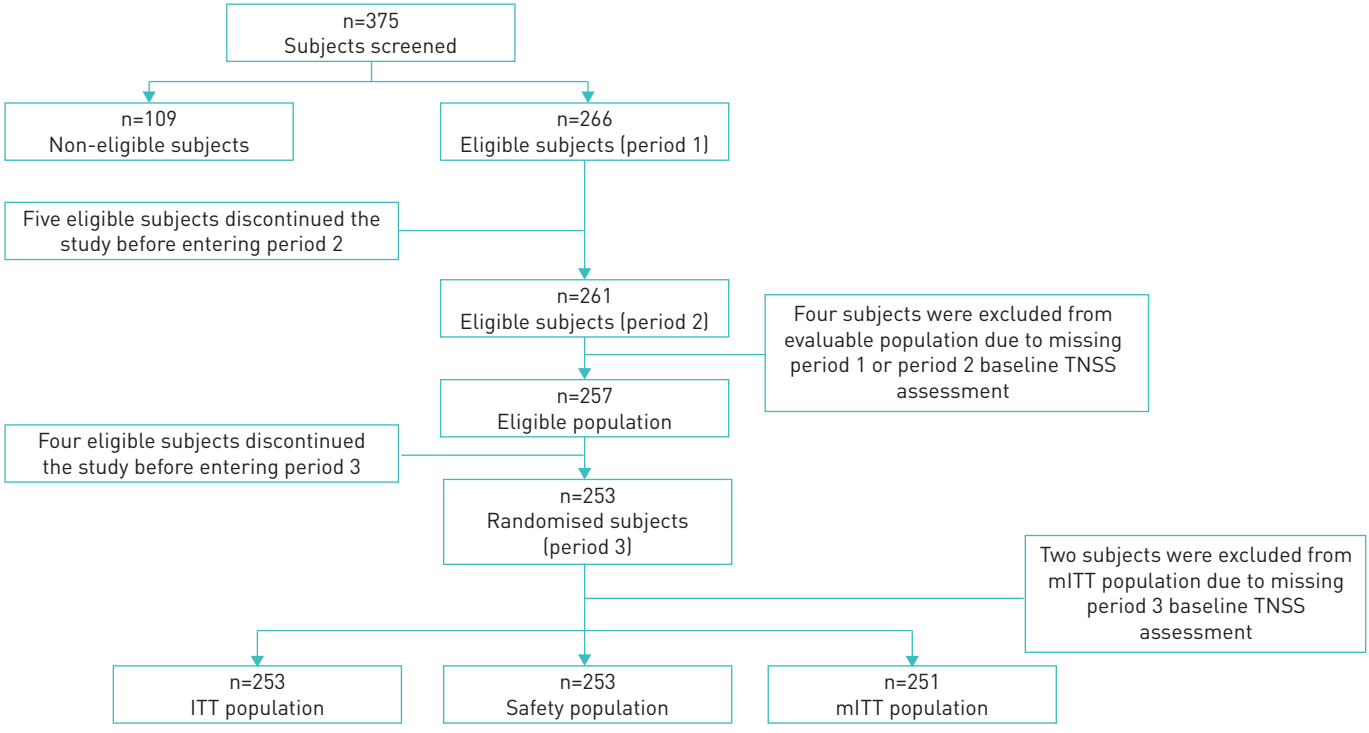

FIGURE 2 Subjects' disposition. TNSS: total nasal symptom score; ITT: intent-to-treat; mITT: modified intent-to-treat.

TABLE 1 Subject demographics and baseline characteristics

	Evaluable population	Modified intent-to-treat population		
		Placebo	Fexofenadine HCl 180 mg	All
Subjects	257	125	126	251
Age years	40.8±0.78	41.5±1.12	40.0±1.12	40.7±0.79
Sex				
Male	90 (35.0)	37 (29.6)	49 (38.9)	86 (34.3)
Female	167 (65.0)	88 (70.4)	77 (61.1)	165 (65.7)
Smoking status				
Never smoked	173 (67.3)	77 (61.6)	92 (73.0)	169 (67.3)
Quit smoking	52 (20.2)	30 (24.0)	22 (17.5)	52 (20.7)
Currently smokes	32 (12.5)	18 (14.4)	12 (9.5)	30 (12.0)
Allergic medical history				
Seasonal allergic rhinitis	257 (100.0)	125 (100.0)	126 (100.0)	251 (100.0)
Perennial allergic rhinitis	183 (71.2)	85 (68.0)	92 (73.0)	177 (70.5)
Mean allergen wheal diameter mm				
Control	0.5±0.06	0.5±0.09	0.4±0.07	0.5±0.06
Ragweed	12.4±0.4	11.9±0.47	12.9±0.62	12.4±0.39
TNSS				
Period 1 (H0)#	0.5±0.05			
95% CI for the mean	0.40–0.62			
Median (interquartile range)	0 (0.0–1.0)			
Range	0–5			
Period 2 (H0)#	0.5±0.06			
95% CI for the mean	0.39–0.61			
Median (interquartile range)	0 (0.0–1.0)			
Range	0–5			
Period 3 (H2)#		6.2±0.20	5.6±0.18	
95% CI for the mean		5.77–6.55	5.27–6.00	
Median (interquartile range)		6.0 (5.0–8.0)	6.0 (4.0–7.0)	
Range		0–9	0–9	

Data are presented as n, mean±SE or n (%). Percentages are calculated from non-missing data. #: For Period 1 and Period 2, the baseline is defined as the value at H0 (start of challenge), for Period 3 baseline is defined as the last available value after challenge and before treatment administration. TNSS: total nasal symptom score.

the evaluable population (ragweed, 12.4±6.2 mm; *D. pteronyssinus*, 5.2±5.5 mm; *D. farinae*, 4.8±5.7 mm; *Alternaria*, 1.8±2.8 mm; full results from skin prick test are reported in the Supplementary Material, table S1). Similarly, no notable differences were observed between fexofenadine HCl and placebo group with regards to the skin prick results. In addition, individuals were asymptomatic before challenge test at each period. Mean±SE EEU baseline pollen exposure was comparable between all three periods: 3272.59±129.48 grains·m^{-3} (Period 1), 3296.97±144.21 grains·m^{-3} (Period 2) and 3374.64±107.61 grains·m^{-3} (Period 3). Mean±SE EEU DEP exposure (ng·m^{-3}) was also similar between periods: 640.3±22.49 ng·m^{-3} (Period 2) and 643.7±10.28 ng·m^{-3} (Period 3). In the included population, skin prick test responses to other allergens resulted in a wheal diameter smaller than 3 mm compared to control (vehicle alone); therefore, they are not presented. All subjects received study medication in Period 3 and were included in the safety population (n=253).

AUC_{0-12} of the TNSS during Period 1 and 2

Mean±SE AUC_{0-12} of the TNSS was higher in Period 2, compared with Period 1 (41.22±1.16 and 36.25±1.05, respectively; figure 3). The least square mean±SE difference (95% CI) for Log AUC_{0-12} of the TNSS was statistically significant between the two periods (0.13±0.03 (0.081–0.182); p<0.0001), demonstrating an aggravation of pollen-induced SAR symptoms in the presence of DEP *versus* pollen alone. Beginning 30 min following ragweed+DEP challenge, and continuing at all subsequent time points, TNSS scores were higher in Period 2 than in Period 1.

Effect of fexofenadine HCl versus *placebo on TNSS, TSS and individual symptom scores following pollen+DEP challenge*

The second sequential primary endpoint, mean±SE AUC_{2-12} of the TNSS in Period 3, was lower among fexofenadine HCl-treated subjects than placebo-treated subjects (18.53±1.22 *versus* 26.34±1.49, respectively;

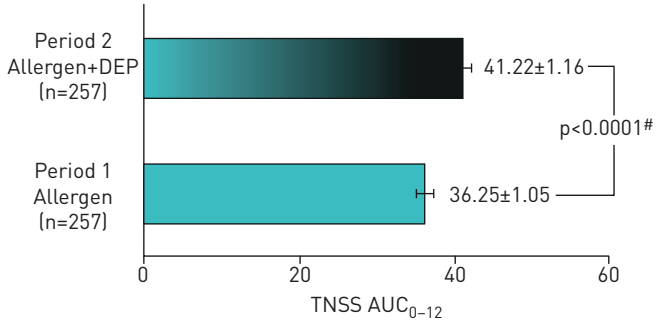

FIGURE 3 Mean±SE total nasal symptom score (TNSS) area under the curve between hour 0 and hour 12 (AUC_{0-12}) in Periods 1 and 2 (evaluable population). #: p-value was obtained using a mixed model for repeated measures (MMRM) on log transformed values of TNSS AUC_{0-12} plus 0.1, adjusted on baseline TNSS (hour 0) for each period (1 and 2) and on pollen counts at each environmental exposure unit (EEU) session, with period as a fixed categorical effect. DEP: diesel exhaust particles.

figure 4). The least square mean±SE difference (95% CI) for Log AUC_{2-12} of the TNSS between treatment groups was −0.24±0.096 (−0.425–−0.047); p=0.0148). AUC_{2-12} of the TNSS at all time-points was consistently lower in fexofenadine HCl-treated *versus* placebo-treated subjects (figure 5).

Mean AUC_{2-12} of the TSS in Period 3 was lower in the fexofenadine HCl-treated group, *versus* placebo (35.16 *versus* 47.96, respectively). The least square mean±SE difference (95% CI) for log TSS AUC_{2-12} between groups was not statistically significant: −0.18±0.10 (−0.369–0.015); p=0.0711). Due to the sequential testing procedure used to maintain a 5% type I error rate throughout the multiple secondary endpoints, analyses of subsequent pre-specified secondary endpoints after TSS (Log AUC_{2-12}) in Period 3 were descriptive only. At hour 2.5, and all subsequent time points in Period 3, mean TSS in fexofenadine HCl-treated subjects was lower than among placebo-treated subjects: the least square mean differences between groups ranged from −0.6 to −1.4.

Mean AUC_{2-12} for all individual symptom scores during Period 3 was lower in fexofenadine HCl-treated subjects than in the placebo group. Mean TNSS at hour 2.5 (30 min after drug administration) and all subsequent time points during Period 3 was lower in the fexofenadine HCl group than the placebo group with least square mean differences between treatments ranging from −0.4 to −0.8. Mean AUC_{2-12} of all eight individual symptom scores in Period 3 was numerically lower in the fexofenadine HCl group *versus* placebo (figure 6). Proportional mean symptom reduction with fexofenadine *versus* placebo, was rhinorrhoea (28.8%), sneezing (39.2%), nasal itching (23.0%), nasal congestion (24.8%), itchy eyes (23.0%), watery eyes (27.5%), red or burning eyes (24.8%) and ear, palate or throat itching (18.6%); all data were cumulative, from treatment intake up to 10 h post-treatment.

Safety evaluation

One subject withdrew in Period 2 due to chest discomfort and dyspnoea. There were no discontinuations due to an adverse event in Periods 1 or 3. No subject experienced a TEAE leading to study discontinuation. The proportion of subjects reporting a TEAE was higher in the placebo group (19 (15.1%) out of 126), compared with the fexofenadine HCl group (16 (12.6%) out of 127). One (0.8%)

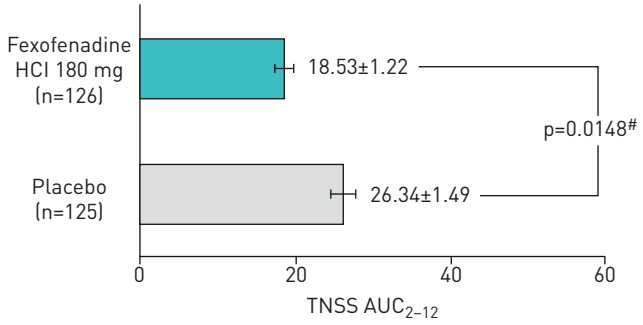

FIGURE 4 Mean±SE total nasal symptom score (TNSS) area under the curve between hour 2 and hour 12 (AUC_{2-12}) in Period 3 (modified intent-to-treat population). #: p-value was obtained using ANCOVA of log-transformed values of TNSS AUC_{2-12} plus 0.1, with treatment group as a fixed categorical effect and baseline TNSS (H2) as covariate.

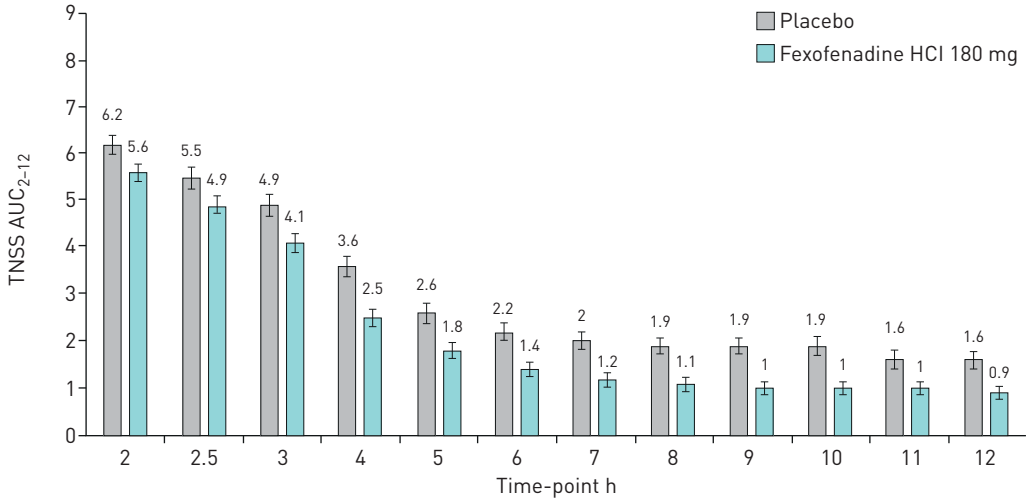

FIGURE 5 Mean±SE total nasal symptom score (TNSS) area under the curve for hour 2 to hour 12 (AUC_{2-12}) by time point in Period 3 (modified intent-to-treat (mITT) population).

fexofenadine HCl-treated subject experienced a TEAE (dry mouth). The most frequently reported TEAEs were seasonal allergies (fexofenadine HCl, n=6 (4.7%); placebo, n=7 (5.6%)) and upper respiratory tract infection (fexofenadine HCl, n=2 (1.6%); placebo, n=2 (1.6%); table 2; additional details are available in the Supplementary Material).

Discussion

This study demonstrated that a 3 h exposure to DEP and ragweed pollen significantly increased SAR symptom severity over a 12 h observation period. Furthermore, a single dose of fexofenadine HCl 180 mg significantly decreased all analysed symptoms compared with placebo. A limit to the comprehensive assessment of fexofenadine HCl efficacy could be the lack of comparison with placebo in the presence of pollen alone. However, the objective of the study was not to demonstrate the efficacy of fexofenadine HCl, which has been well documented in previous clinical trials [16, 17] showing significant decreases in ragweed-induced allergic symptoms in an EEU model [18].

The symptomatic effects of DEP were seen at the first post-exposure measurement (hour 0.5). Symptom aggravation occurred during the initial 3 h exposure to ragweed+DEP and persisted during the 9 h

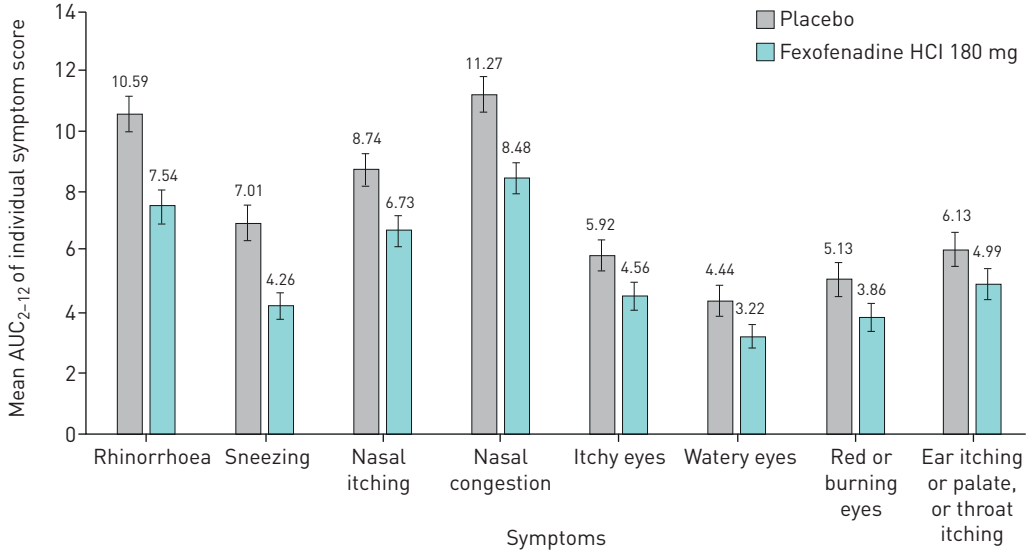

FIGURE 6 Mean±SE area under the curve between hour 2 and hour 12 (AUC_{2-12}) of individual symptom scores after pollen+diesel exhaust particles exposure (modified intent-to-treat population).

TABLE 2 Incidence of treatment-emergent adverse events by primary system organ class and preferred term at an incidence of ⩾2% (safety population)[#]

Primary system organ class (preferred term)	Placebo	Fexofenadine HCl
Subjects	126	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 allergic rhinitis	7 (5.6)	6 (4.7)
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)

Data are presented as n or n (%). HCl: hydrochloride. [#]: Subjects may have experienced more than one type of adverse event within any primary system organ class.

following the subject's departure from the EEU. The extended effect of DEP observed several hours after the exposure period suggests that even relatively short exposures to an air pollutant could have a significant impact on SAR symptoms during the late phase of the allergic reaction [19], consistent with prior studies [20]. A study of 18 atopic individuals found increased allergen-induced inflammation of the lower respiratory tract following diesel exhaust exposure [21]. A co-exposure to allergens and diesel exhaust augments inflammatory cells and TH2-related cytokines, while lowering host defence peptides and altering DNA methylation and protein responses in the lungs [22–24]. Diaz-Sanchez *et al.* [25] documented a significant increase in IgG4 in nasal lavage samples from ragweed-sensitised individuals after ragweed+DEP exposure *versus* ragweed alone, which was believed to be mediated *via* an increase in ragweed-specific IgE. These investigators also found that exposing dust mite-allergic subjects to DEP increased mean symptom scores and decreased, by approximately 80%, the inducing dose of dust mite allergen, *versus* no DEP exposure.

Recently, the exposure to pollutants and climate change has been linked to allergic rhinitis symptom exacerbation [26]. In an 11-country survey, the majority of participants attributed climate changes (81.1%) and pollutants (51.2%) as contributors to their allergic rhinitis symptoms [27]. In another survey conducted in four regions including Europe, 71.15% of participants attributed the increasing prevalence of allergic rhinitis to "increased exposure to allergens, irritants and pollutants" [28]. Another recent study showed a harmful effect of air pollution (particularly ozone) on allergic rhinitis control, especially during grass pollen season. Positive associations were found between air pollutants (ozone and $PM_{2.5}$) and allergic rhinitis symptoms. Differences between pollen seasons were also found, suggesting an interaction between air pollution and pollen exposure (*e.g.* the dose-dependent deleterious effects of pollen exposure were magnified by air pollutant exposure) [29]. While a growing body of evidence supports a link between allergic diseases and air pollution [3, 30], other studies show mixed results [31, 32]. Mölter *et al.* [32] found no significant association between asthma prevalence and exposure to selected air pollutants in a meta-analysis of five European birth cohorts. Similarly, Burte *et al.* [31] found no association between long-term air pollution exposure and the incidence of self-reported rhinitis among the same European cohorts analysed by Mölter *et al.* [32]. Reasons for these heterogeneous observations may include differences in study design, exposure assessment, air pollutants included and air pollution monitoring site locations. Ultimately, air pollution has an important role in the development and prevalence of allergic symptoms, but its precise influences have not been fully established [2, 26, 33, 34].

The EEU is designed to replicate effectively an outdoor environment while removing those variables that may affect allergy research. The EEU allows for allergen specificity; control over antigen exposure level;

temperature; and air quality [35]. Although a high degree of concordance has been reported for allergic symptoms induced in the EEU and those experienced through natural exposure [35], the results of this study are limited to the controlled environment of analysis and additional real-world evidence is needed.

Pharmacological options for the treatment of allergic rhinitis are well established, but additional research is needed on the efficacy of conventional pharmacotherapy in patients exposed to air pollution [26]. A review of the studies investigating allergic rhinitis symptoms aggravated by air pollutants showed that fexofenadine HCl is the only allergic rhinitis medication with demonstrated efficacy and tolerability for the management of DEP-aggravated symptoms [26, 30]. DEP exposure has been shown to trigger numerous pro-inflammatory signalling pathways other than histamine-mediated ones [30]. DEP increases circulating neutrophils, eosinophils, and cytokines, and induces the expression of adhesion molecules as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) which are critical for T cell activation [9, 21]. Additionally, an exacerbation of the inflammatory response may result from the generation of reactive oxygen species and oxidant overload [26]. Noteworthy, it has been demonstrated that fexofenadine HCl has additional anti-inflammatory properties besides the anti-histaminergic activity [36]. Fexofenadine HCl decreases cytokine levels, including ICAM-1 and VCAM-1 among others, inhibits eosinophil adherence and chemotaxis, inhibits cyclo-oxygenase 2, and reduces the production of leukotrienes and prostaglandins [36]. These additional effects of fexofenadine could further contribute to the improvement of allergic rhinitis symptoms aggravated by the inflammatory response induced by DEP; however, more research is needed to demonstrate this hypothesis.

In summary, DEP exposure can significantly exacerbate ragweed-induced SAR symptoms and fexofenadine HCl 180 mg is an effective and well-tolerated treatment to alleviate these pollution-aggravated symptoms.

Acknowledgments: The authors thank the subjects who took part in this study. The authors would also like to acknowledge Lisa Steacy and Daniel Adams for their roles as study manager/coordinators, Terry Walker (all of the Allergy Research Unit, Kingston Health Sciences Centre, Kingston, ON, Canada), who was responsible for EEU operations, and Mikhail Melikov, MPH in Biostatistics and Epidemiology of IT&M STATS, who reviewed the statistical analysis. The authors would also like to acknowledge Claire Lydon of iMed Comms, an Ashfield Company, part of UDG Healthcare plc, and Martina Klinger Sikora and Mark Davies of inScience Communications, for medical writing support that was funded by Sanofi.

Author contributions: P. Picard was instrumental in analysing the data and performing the statistical analysis. M. Murrieta-Aguttes and S. Furey designed the study. M. Murrieta-Aguttes and A.K. Ellis contributed to the protocol preparation, review of SAP and result interpretation. C. Carlsten contributed to study design and interpretation of results. All authors have participated in the development of this publication and have provided their approval for its submission.

Conflict of interest: A.K. Ellis reports study investigator fees from Sanofi during the conduct of the study; and grants, advisory board and speaker fees from ALK, Abello and AstraZeneca; her institution has received fees for advisory boards and speaking from Aralez; her institution has received fees for an advisory board and speaking from Baush Health; grants and her institution has received fees for advisory boards from Circassia Ltd and GlaxoSmithKline; her institution has received fees for an advisory board from Johnson & Johnson; grants, and her institution has received fees for an advisory board and speaking from Merck; her institution has received fees for an advisory board and speaking from Mylan; grants, and her institution has received fees for an advisory board and speaking from Novartis; her institution has received fees for an advisory board and speaking from Pediapharma; grants, and her institution has received fees for an advisory board and speaking from Pfizer; her institution has received fees for speaking from Boehringer Ingelheim, MEDA, Medesus and Takeda; grants from Green Cross Pharmaceuticals, Bayer LCC and Regeneron; her institution has received fees for an advisory board and speaking from Sanofi, all outside the submitted work. M. Murrieta-Aguttes is an employee of Sanofi. S. Furey is an employee of Sanofi. P. Picard has nothing to disclose. C. Carlsten has nothing to disclose.

Support statement: The study was supported by Sanofi, which provided financial support for the conduct of the research and preparation of the article. Funding information for this article has been deposited with the Crossref Funder Registry.

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