The improved efficacy of a fixed-dose combination of fluticasone furoate and levocabastine relative to the individual components in the treatment of allergic rhinitis

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Summary

Background Allergic rhinitis (AR) is a common chronic disease, which has significant detrimental effect on well-being and quality of life as well as substantial socio-economic impact. Combination pharmacotherapy is utilized by 40–50% of patients to treat their symptoms.

Objective To compare the effects of intranasal fluticasone furoate (FF)/levocabastine (LEVO) fixed-dose combination (FDC) with each component alone on allergen-induced nasal and ocular symptoms.

Methods A randomized, double-blind, placebo-controlled, three-way, incomplete block, cross-over, proof-of-concept study in 71 patients with AR, evaluated FF 100 µg, LEVO 200 µg and FDC (FF 100/LEVO 200 µg), once daily via intranasal spray for 8 days. On days 1 and 8, total nasal symptom score (TNSS) and total ocular symptom score (TOSS) were assessed every 15 min during a 4-h allergen exposure in the Vienna Challenge Chamber. The primary endpoint was Day 8 weighted mean TNSS.

Results After 8 days, FDC resulted in both statistically and clinically significant reductions in mean TNSS compared with FF and LEVO alone [adjusted mean differences (95% CI): FDC vs. FF: −2.26 (−2.90, −1.62); FDC vs. LEVO: −2.57 (−3.21, −1.93)]. All active treatments were significantly superior to placebo [adjusted mean difference (95% CI) from placebo: FDC: −4.1 (−4.86, −3.34); FF: −1.84 (−2.66, −1.03); LEVO: −1.53 (−2.34, −0.72)]. Onset of action was rapid following FDC and LEVO treatment with an approximate two unit reduction in mean TNSS from pre-dose levels by 30 min and 1 h. Mean TOSS was also reduced following all active treatments relative to placebo (range 0.6–0.8 unit reduction). All treatments were equally well tolerated.

Conclusions and Clinical Relevance These results suggest that once daily FF/LEVO FDC could provide a clinical therapeutic advantage to existing standard monotherapies in the treatment of moderate-to-severe AR, and support progression to evaluation in larger phase III clinical studies.

Keywords steroids, antihistamine, allergy, efficacy

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Introduction

Allergic rhinitis (AR) is a common condition, which typically affects 10–20% of the population globally, with reported prevalence rates as high as 50% in some populations [1–3]. AR describes an inflammation of the nasal mucosa associated with an IgE-mediated immune response to allergens [4, 5]. Allergen-bound IgE on the surface of mast cells induces mast cell degranulation and release of inflammatory mediators such as histamine, leukotrienes, prostaglandin D2, tryptase and kinins with histamine playing a central role in AR through its neural and vascular effects [4, 5]. The majority of patients with AR have nasal symptoms of congestion, sneezing, itching and rhinorrhea, frequently accompanied by ocular symptoms including...
redness, watery eyes, itching and burning [4]. Nasal congestion is one of the most troublesome symptoms of AR, experienced by approximately 90% of patients [6, 7]. Many AR patients suffer a major impact on their quality of life, affecting daily activities at school and work, and contributing to a significant healthcare burden and other socio-economic impacts if symptoms are not managed properly [2, 8–11].

Successful management of AR involves patient education, pharmacotherapy and consideration of immunotherapy with the aim of minimizing symptoms and improving quality of life [1, 2, 4, 12]. Pharmacotherapy for AR includes intranasal corticosteroids (INS), oral and intranasal antihistamines, non-steroidal anti-inflammatory agents, decongestants, and the less regularly used cromones and anti-leucotrienes. INS are the most effective medications available for improving all symptoms of AR, including ocular symptoms, and are particularly effective against nasal congestion [1, 2, 4, 12]. INS modulate both early- and late-stage allergic responses through reduction in mast cell degranulation and release of mediators, which are responsible for the subsequent infiltration of inflammatory cells to the site of allergen exposure causing nasal hyper-reactivity and ocular symptoms. Intranasal antihistamines are also effective against nasal and ocular symptoms, with comparable or better efficacy than oral antihistamines due to their proven effects on nasal congestion [13], and having the advantage of a more rapid onset of action due to direct delivery to the nasal mucosa. Both INS and intranasal antihistamines are thought to impact ocular symptoms through modulation of the histamine-dependent nasal–ocular reflex [14, 15].

Polypharmacy is common in AR; patient surveys in Europe and the United States suggest that 40–50% of patients are using two or more medications to treat their symptoms [16, 17]. ARIA (allergic rhinitis and its impact in asthma) guidelines recommend a combination of an INS and an antihistamine for patients with moderate-to-severe symptoms of AR uncontrolled on monotherapy [2]; however, randomized clinical trials evaluating the effect of combined administration of oral antihistamines and INS in patients with seasonal allergic rhinitis (SAR) have failed to show enhanced benefit compared with INS alone [18]. Conversely, a fixed-dose combination (FDC) nasal spray containing an INS (fluticasone propionate) and an intranasal antihistamine (azelastine) dosed twice daily provided superior benefit on nasal symptoms in SAR patients compared with either component alone [19].

Fluticasone furoate (FF) is a potent and effective INS approved globally for once daily treatment of AR [20–22]. Of the antihistamines approved for AR therapy, levocabastine (LEVO) may serve as an optimal partner for combination with FF. Levocabastine is a potent and selective second generation intranasal H1-receptor antagonist, which is considered to be well tolerated based on extensive intranasal use [23]. Although the approved dosing regimen of LEVO nasal spray is 200 µg twice daily; evidence from a clinical nasal allergen challenge study demonstrated that single doses of LEVO 200 or 400 µg provided 24 h sustained efficacy [24]. To investigate the potential for non-inferiority of once daily vs. twice daily dosing, an allergen chamber study in which SAR patients were dosed to steady state with 200 µg LEVO once or twice daily for seven days prior to nasal allergen challenge, demonstrated that the efficacy of once daily and twice daily dosing of LEVO at trough was comparable (Data on file; NCT01949051). This suggests that once daily dosing of LEVO may be sufficient. It is therefore proposed that a once daily fixed-dose combination (FDC) of FF and LEVO may provide superior relief of AR nasal symptoms compared with either single agent. As such, a FDC of FF and LEVO has been progressed into early clinical development for once daily therapy of AR. The strengths and delivered dose per spray of FF and LEVO in the proposed FF/LEVO FDC are the same as that of the marketed fluticasone furoate and levocabastine products, respectively.

The aim of the current study was to compare the effects of 8 days of once daily intranasal administration of FF/LEVO FDC with the single agents on seasonal allergen-induced nasal and ocular symptoms in AR patients.

Materials and methods

Study design

This was a randomized, double-blind, placebo-controlled, three-way, incomplete block, cross-over study to evaluate the effect of single and repeat doses of placebo, FF 100 µg, LEVO 200 µg, and FDC (FF 100/LEVO 200 µg), taken once a day via a proprietary intranasal spray device. The study was conducted in the Vienna Challenge Chamber (VCC) at a single centre in Austria between October 2013 and February 2014. Following a screening visit, 2–35 days prior to the first treatment period, eligible AR patients randomly received three of four study treatments. Every patient received FDC and two of three of the other treatments according to a treatment ratio of 4 : 3 : 3 : 2 for FDC:FF:LEVO:placebo. Each treatment was taken for 8 days with a 14 to 28 day washout in-between. All treatments looked and smelled identical, and there were no patient reported taste differences. The treatments were given as two actuations per nostril in the morning, in a fasted state. The randomization of subjects within each chamber session to differing treatment regimens removed any patient by patient influence in symptom reporting.
The primary endpoint was weighted mean total nasal symptom score (TNSS) during a 4-h allergen exposure on Day 8 of treatment (measured from 1 h post-dosing) following FDC treatment vs. FF and LEVO alone.

Patients

Included patients were 18–65 years of age with a diagnosis of AR, defined as rhinitis symptoms for several months per year and present for more than one year, and who had a positive response to screening grass pollen challenge (TNSS ≥ 6). The grass mix contained *Phleum pratense*, *Dactylis glomerata*, *Lolium perenne*, *Anthoxanthum odoratum* and *Holcus lanatus*. Demonstration of both a positive skin prick test (wheal ≥ 4 mm) and a positive RAST class determination (RAST class ≥ 2) to grass pollen was also required at screening or within the last 12 months. Patients weighed ≥ 50 kg and had a body mass index within the range 19–30 kg/m², were non-smokers (smoked < 10 packs years in their lifetime and had not smoked in the last 6 months) and, other than AR, were judged to be healthy by the investigator based on medical history, physical examination and laboratory tests.

Patients with nasal abnormalities likely to affect study outcomes, a history of frequent nosebleeds or a diagnosis of rhinitis medicamentosa were excluded. Patients with recent upper respiratory tract infection were required to be free of associated nasal symptoms for > 3 weeks prior to screening. In addition, the following medications were not permitted in the time frame specified prior to each visit: nasal and oral decongestants: 24 h; nasal or oral antihistamines: 72 h; nasal or inhaled corticosteroids, leucotriene receptor antagonists, 5-lipoxygenase inhibitors, methylxanthines, non-prescription drugs: 7 days; short course oral corticosteroids: 12 weeks; chronic oral corticosteroids: 6 months.

Written informed consent was obtained from all patients, and the study was approved by the 'Ethikkommission der Österreichischen ARGE für klinische Pharmakologie und Therapie und Institut für Hypertoniker' (Ethics committee of the Austrian Working Group for Clinical Pharmacology and Therapeutics and Institute for Hypertension; project number EK02-13; protocol study number 200286; NCT01957202).

Allergen challenge

Allergen challenge was conducted at screening and on days 1 and 8 of each treatment period in the VCC, using a validated method [25–27]. The VCC could accommodate up to 20 subjects in one sitting, all of whom were under constant supervision by, and could communicate with, medical staff outside the chamber. Communication was possible through clear glass windows and via an intercom system. During the challenge, the chamber was charged with fresh air, which was conditioned (filtered, heated, dried, cooled and humidified) accordingly and then loaded with a qualitatively and quantitatively determined allergen load. The challenge agent used in the chamber was a mixture of four grass types (Timothy, Orchard, Perennial rye and Sweet vernal grasses) (Allergon, Sweden). Air temperature (24°C), humidity (40%) and allergen load (approximately 1500 grains per cubic metre) were constantly monitored and maintained.

At screening, patients underwent a 2-h VCC allergen challenge to establish eligibility. On Day 1, treatment dosing was at the 2 h time-point after starting the allergen challenge at 0 h, to assess the onset and magnitude of symptom relief. TNSS and TOSS measurements were made every 15 min during the 4 h allergen challenge. On Day 8 of each treatment period, patients scored their TNSS and total ocular symptom score (TOSS) at 1 h post-dose, immediately on entering the chamber and prior to starting the challenge, and then at 15-min intervals during the 4 h allergen challenge. The frequency of the multiple assessments during the period in the chamber precluded any patient/patient interaction and resulting bias.

**Total nasal symptom score**

Nasal congestion, rhinorrhoea, nasal itch and sneeze were each scored on a four-point scale from 0 to 3 (where 0 = absent symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms) giving a TNSS from 0 to 12.

**Total ocular symptom score**

Patients scored their eye symptoms for redness, itchiness and tearing, each on a scale of 0–3 (absent to most severe symptoms), giving a total ocular symptom score (TOSS) from 0 to 9. The score represented an average for both eyes.

Safety

Adverse events (AEs) were collected throughout the study starting from Day 1 of the first treatment period. Vital signs (heart rate and blood pressure) were measured at the screening visit, and on each allergen challenge day at pre-dose and immediately after leaving the challenge chamber. Routine haematology, blood chemistry and urinalysis assessments, and single 12-lead ECGs were assessed at screening and at follow-up, approximately one week after the last challenge. FEV₁ was measured on allergen challenge study days at
pre-challenge, after 2 h and at the end of the challenge procedure.

Statistical analysis

The study was designed to test for superiority of FDC over FF or LEVO alone in effect on TNSS score. It was estimated that a sample size of 72 patients would provide at least 90% power to detect a minimum difference of 1 unit in TNSS between FDC relative to FF, and FDC relative to LEVO using a 1-sided 95% confidence interval. The within subject and between subject standard deviation (SD) was assumed as 1.7.

Treatment comparisons of weighted mean TNSS and TOSS (0–4 h) on Day 8 of treatment were analysed using a mixed effects analysis of variance model adjusting for terms due to period and treatment, fitted as fixed effects, and with subject fitted as a random effect. Period level and subject level baselines were fitted as continuous covariates. The magnitude of symptom relief was defined as the weighted Mean (2–4 h) change from pre-dose TNSS and TOSS at Day 1, and treatment comparisons were analysed using the same mixed effects analysis of variance model. Mean profile plots were used to assess the time to onset of symptom relief following a single dose on Day 1. All safety endpoints were summarized.

Results

Patient population

Seventy-one patients were randomized to treatment and 68 (96%) completed the study as planned (Fig. 1). Two patients withdrew their consent after completing two of three treatment periods, and one patient withdrew due to an adverse event on Day 1 of treatment period 3.

The mean age of the total population was 29 years (range, 19–54 years), the majority were Caucasian (97%), with a balanced representation of males and females (Table 1).

Total nasal symptom score

For the primary outcome, 8 days of treatment with FDC resulted in both a statistically and clinically significant reduction in allergen-induced weighted mean TNSS (0–4 h) relative to FF and LEVO alone (Fig. 2). Mean TNSS was reduced by at least 2 units more with FDC treatment than with either component alone (Table 2). All active treatments were also significantly more effective than placebo in reducing mean TNSS (adjusted mean difference from placebo: FDC: −4.1; FF: −1.84; LEVO: −1.53) (Table 2).

On treatment Day 1, when allergen challenge started at 0 h and dosing was at 2 h, a rapid onset of action was observed following the first dose of FDC and LEVO alone with a reduction in weighted mean TNSS occurring within 15 min of dosing (Fig. 3). At the 30 min and 1 h post-dose time-points, there was an approximate two unit reduction in TNSS from pre-dose levels following both of these treatments, and this level of suppression of symptoms was maintained or exceeded for the remainder of the Day 1 challenge. There was no significant difference between FF and placebo in reducing mean TNSS following first dose of treatment.

The magnitude of the symptom reduction with FDC or LEVO alone relative to placebo was in the range 0.9–1.3 (Table 3). The impact of the treatment regimens on the individual domains of the TNSS (itch, sneeze, rhinorrhea and congestion) were consistent with those of the total scores (Table S1).

Total ocular symptom score

After 8 days treatment, weighted mean TOSS (0–4 h) induced by allergen challenge was significantly reduced

Table 1. Patient demographics

| Randomized, n | 71 |
| Age in years, mean (range) | 29 (19–54) |
| Male, n (%) | 35 (49) |
| Body mass index in kg/m², mean (range) | 23.0 (19.1–29.8) |
| Height (cm), mean (SD) | 173.5 (10.4) |
| Weight (kg), mean (range) | 69.8 (50–104) |
| Race, n (%) |
| White, Caucasian | 69 (97) |
| Asian – East Asian heritage | 2 (3) |

Fig. 1. Study flow. FF: fluticasone furoate; Levo: levocabastine; FDC: fixed-dose combination.
following all active treatments relative to placebo (range 0.6–0.8 unit reduction) (Fig. 4, Table 4). There were no significant differences in weighted mean TOSS between active treatments, and there were no significant differences between treatments in onset and magnitude of symptom relief on TOSS at Day 1, with the exception of LEVO vs. placebo [adjusted mean difference: −0.5 (95% CI −0.95, −0.12)]. The impact of the treatment regimens on the individual domains of the TOSS (itch, redness and tearing) was also consistent with those of the total scores (Table S2).

**Safety**

The proportion of patients reporting AEs was low and similar during all treatments [Placebo: 2 (6%); FF: 1 (2%); LEVO: 1 (2%); FDC: 3 (4%)]. The most frequent AE was headache [Placebo: 2 (6%); FF: 1 (2%); LEVO: 1 (2%); FDC: 1 (1%)]. There were no serious AEs. One patient experienced diarrhoea whilst on FDC treatment and was withdrawn from the study; however, the investigator did not consider the event to be related to treatment.

During all treatments, there were no clinically relevant changes in any vital signs, ECG values or laboratory parameters.

**Discussion**

This study clearly demonstrates that treatment with FDC FF/LEVO 100 µg/200 µg once daily was both statistically and clinically superior to either single
component in treating the allergen-induced nasal symptoms of AR. The FF/LEVO FDC demonstrated a rapid onset of action, similar to that with LEVO alone, which demonstrates that the addition of an INS and thixotropic vehicle to the combination product had no impact on the already-proven rapid action of LEVO. All active treatment regimens resulted in significant improvements in symptom scores relative to placebo. The non-inferiority of once daily dosing compared with twice daily dosing of LEVO has been confirmed in a parallel study, which evaluated allergen-induced TNSS values after 7 days treatment, measured 24 h (for once daily regimen) and 12 h (twice daily regimen) after last dosing (Data on file; NCT01949051). Although chamber studies do not mimic the real-life conditions of a wild-type setting, they do provide a completely controlled environment in which to assess the effects of AR medications without the confounding factors encountered in conventional studies, such as variable daily pollen exposures and patient day-to-day routines [27]. In addition, patients have reported that they experience similar symptoms when challenged in a chamber environment to those during natural pollen exposure [27].

Intranasal corticosteroids are considered to be the most effective pharmacological intervention for allergic rhinitis [1, 2, 4, 12]. This is brought about by a combination of local vasoconstrictor effects and modulation of both the early and late allergic responses through reductions in mast cell degranulation and release of mediators, which are responsible for the subsequent infiltration of inflammatory cells to the nasal mucosa and underlying tissue resulting in the classic symptomatology and nasal hyper-reactivity. Despite this impressive array of effects, most patients and, indeed those in this challenge study, do not see complete abrogation of itch, sneeze, rhinorrhoea or congestion. The added

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**Fig. 3.** Adjusted mean total nasal symptom score (95% CI) over time by treatment on day 1. FF: fluticasone furoate; Levo: levocabastine; FDC: fixed-dose combination.

**Table 3.** Statistical analysis for magnitude of symptom relief on day 1 – weighted mean total ocular symptom score (2–4 h)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment comparison</th>
<th>Adjusted mean TEST</th>
<th>Adjusted mean REF</th>
<th>Adjusted mean difference</th>
<th>95% CI of difference</th>
<th>% improvement (TEST vs. REF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnitude of symptom relief weighted mean TNSS (2–4 h)</td>
<td>FDC vs. FF</td>
<td>−2.267</td>
<td>−0.904</td>
<td>−1.364</td>
<td>(−1.853, −0.874)</td>
<td>150.8%</td>
</tr>
<tr>
<td></td>
<td>FDC vs. Levo</td>
<td>−2.267</td>
<td>−2.588</td>
<td>0.320</td>
<td>(−0.169, 0.809)</td>
<td>−12.5%</td>
</tr>
<tr>
<td></td>
<td>LEVO vs. Placebo</td>
<td>−2.588</td>
<td>−1.135</td>
<td>−1.252</td>
<td>(−1.870, −0.635)</td>
<td>93.8 %</td>
</tr>
<tr>
<td></td>
<td>FF vs. Placebo</td>
<td>−0.904</td>
<td>−1.135</td>
<td>0.232</td>
<td>(−0.179, 1.042)</td>
<td>−32.3%</td>
</tr>
<tr>
<td></td>
<td>FDC vs. Placebo</td>
<td>−2.267</td>
<td>−1.135</td>
<td>−1.132</td>
<td>(−1.506, −0.758)</td>
<td>69.8%</td>
</tr>
<tr>
<td></td>
<td>FF vs. Levo</td>
<td>−0.904</td>
<td>−2.588</td>
<td>1.684</td>
<td>(1.160, 2.208)</td>
<td>−65.1%</td>
</tr>
</tbody>
</table>

Within subject SD, square root (mean square error) = 1.32. % improvement = 100 × (TEST/REF−1); negative values apply when test is worse than reference. FDC, fixed-dose combination; Levo, levocabastine.
efficacy seen in the FDC arm relative to FF alone can possibly be attributed to the specific pharmacokinetic and pharmacodynamic properties of LEVO. LEVO is a highly potent and selective H1 antagonist with a Ki of 4 nmol/L with a long T1/2 of 40 h and good tissue penetration and permeability [28]. Clinical effects are seen within 5–15 min and last for 24 h (Data on file; NCT01949051). In clinical practice and allergen challenge models, it shows a marked reduction in sneeze, itch and rhinorrhea but little effect on congestion. Intranasal steroids on the other hand are especially effective on congestion. It is interesting to speculate that, at steady state dosing, INS reduce the inflammatory cell infiltrate, leading to lowered nasal hyperresponsiveness and a reduction in symptoms whilst the continued nasal mucosal/sub-epithelial presence of high doses, as µg/cm², of a highly potent H1 antagonist acts to block residual histamine from the ongoing seasonal allergen-induced mediator release and breaks the inflammatory cycle leading to enhanced clinical benefit.

All three active regimens had a positive effect on ocular symptoms within the allergen challenge chamber setting. Environmental chambers, whilst well validated, do have limitations when assessing ocular symptoms. In this study, the VCC introduced pollen which was gently recirculated, maintaining a constant concentration, and as such, patients inhaled by tidal breathing through the nose and nasal symptoms predominated. In contrast, chambers have been developed with horizontal

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Table 4. Statistical analysis of weighted mean of total ocular symptom score (0–4 h) for primary and secondary treatment comparisons on day 8

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment comparison</th>
<th>Adjusted mean TEST</th>
<th>Adjusted mean REF</th>
<th>Adjusted mean difference</th>
<th>95% CI of difference</th>
<th>% improvement (TEST vs. REF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted ean TOSS (0–4 h)</td>
<td>Primary treatment comparison</td>
<td>0.546</td>
<td>0.761</td>
<td>-0.215</td>
<td>(-0.509, 0.079)</td>
<td>28.3%</td>
</tr>
<tr>
<td>FDC vs. FF</td>
<td>0.546</td>
<td>0.761</td>
<td>-0.215</td>
<td>(-0.509, 0.079)</td>
<td>28.3%</td>
<td></td>
</tr>
<tr>
<td>FDC vs. Levo</td>
<td>0.546</td>
<td>0.621</td>
<td>-0.075</td>
<td>(-0.370, 0.221)</td>
<td>12.1%</td>
<td></td>
</tr>
<tr>
<td>Secondary treatment comparison</td>
<td>Levo vs. Placebo</td>
<td>0.621</td>
<td>1.321</td>
<td>-0.701</td>
<td>(-1.080, -0.322)</td>
<td>53.0%</td>
</tr>
<tr>
<td>FF vs. Placebo</td>
<td>0.761</td>
<td>1.321</td>
<td>-0.560</td>
<td>(-0.934, -0.187)</td>
<td>42.4%</td>
<td></td>
</tr>
<tr>
<td>FDC vs. Placebo</td>
<td>0.546</td>
<td>1.321</td>
<td>-0.775</td>
<td>(-1.123, -0.428)</td>
<td>58.7%</td>
<td></td>
</tr>
<tr>
<td>FF vs. Levo</td>
<td>0.761</td>
<td>0.621</td>
<td>0.140</td>
<td>(-0.175, 0.456)</td>
<td>-22.5%</td>
<td></td>
</tr>
</tbody>
</table>

Within subject SD, square root (mean square error) = 0.79. % improvement = 100 × (1-TEST/REF); negative values apply when test is worse than reference. FDC, fixed-dose combination; Levo, levocabastine.

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Fig. 4. Adjusted mean total ocular symptom score (95% CI) over time by treatment on day 8. FF: fluticasone furoate; Levo: levocabastine; FDC: fixed-dose combination.
dispersion for the detailed assessment of ocular symptoms and dry eye syndrome [29]. Despite these limitations, the changes seen were clinically relevant and comparable with ocular symptom reduction seen in large-scale clinical trials with intranasal AZF [30]. In these studies, TOSS scores of 0.55, 0.74 and 0.6 were achieved. The reduction in TOSS in the steroid-containing treatments (FF and FF/LEVO FDC) is consistent with findings in other studies, which have shown similar effects of INS in reducing eye symptoms [21, 31, 32]. The mechanisms by which ocular symptoms are related to allergic reactions in the nose are not fully understood but probably involve several factors. It has been postulated that ocular effect improvements may, in part, be mediated by reduction in nasal drainage [33]. Recent evidence suggests that some of the ocular symptoms associated with AR may be mediated by a nasal–ocular neural reflex, which involves the stimulation of nasal afferent nerves by histamine released in response to allergen inhaled through the nose. This hypothesis is supported by evidence that pre-treatment with a single intranasal dose of azelastine can suppress ocular symptoms [14]. This nasal–ocular reflex has been shown to be sensitive to priming, as worsening ocular symptoms were demonstrated with successive nasal allergen challenges, and modulation of the reflex accompanied by a reduction in ocular symptoms was demonstrated following 1 week of treatment with intranasal FF [15]. These effects were also associated with a reduction in eosinophil count in nasal scrapings, supporting the mechanism that INS reduce local inflammation with subsequent reduction in neural stimulation.

Interestingly, LEVO produced ocular symptom benefit comparable to FF and it appeared, in this model, that the combination of agents did not augment the response of the constituent components. It is possible that a higher initial symptom score, as demonstrated in the FF pivotal clinical trials, may have led to a greater effect with FDC over the constituent components. Conversely, the results may indicate that the maximal effect achievable through the nasal–ocular reflex was achieved. Ocular symptoms will be assessed in larger phase III trials, which will compare the FDC, FF and LEVO in SAR patients.

A marketed fixed-dose combination of FP, an INS, and azelastine (Az), an intranasal antihistamine, which has been shown to provide superior symptomatic benefit over either single component in patients with both seasonal and perennial AR [19, 34]. The FP/Az nasal spray is provided in a top down device and is prescribed as 1 spray per nostril twice daily providing a dose of Az of 274 μg twice daily, which is half the standard nominal dose, and a dosing regimen shown to be sub-optimal in the treatment of seasonal AR [35]. Due to the Az component, it carries a somnolence precaution and is associated with bitter taste [36]. The FF/LEVO FDC differs from the FP/Az combination in that it is intended for once daily dosing, the standard efficacious dose of levocabastine (two sprays/nostril, 200 μg) will be delivered which should provide sustained 24 h efficacy, and it should not carry a somnolence precaution or be associated with bitter taste [37]. In a clinical comparison with Az, none of the subjects that received two sprays/nostril LEVO twice daily reported taste disturbance compared with 5% of subjects who received 1 spray/nostril Az twice daily which is the dosing regimen for the proprietary FP/Az combination [38]. Finally, the FF/LEVO FDC will be presented in the MistPro™ side-actuated device which patients prefer due to the delivery of a gentle mist that results in less drippage down the throat and from the nose [39].

The reduction in mean TNSS with FF alone relative to placebo shown in the current study (approximately two unit difference in mean TNSS) is different to that shown in an earlier VCC study evaluating FF vs. placebo (approximately four unit difference from placebo) [40]. It is likely that the differences seen between studies in chambers are as large as those seen within ‘wild-type’ studies, which often vary by a magnitude of 100% [30]. The other confounding factor was that the current study explored 100 μg, whereas the 200 μg was used in the previously quoted study [40]. Whilst it is known that the dose–response within the chamber to FP is very flat (GSK data on file Study Number SG110341), these data are lacking for FF; however, the decrease in dose, within the current study, may explain the variance. The fact that both studies were robust in design ensures that the question being posed within an individual study was adequately addressed. Both studies were conducted in the VCC, which is a proven and robust methodology that has shown reproducible results on TNSS scores in previous AR studies [25, 26].

In summary, the results of this study suggest that once daily FDC FF/LEVO would provide a clinical therapeutic advantage to existing standard monotherapies in the treatment of moderate-to-severe AR, with the potential to reduce the requirement for polypharmacy and the total daily dose of topical antihistamine. Progression of the FF/LEVO FDC to evaluation in larger phase III clinical studies is warranted.

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Conflict of interest
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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Statistical analysis of weighted mean individual components of total ocular symptom score (0–4 h) for primary and secondary treatment comparisons on day 8.

Table S2. Statistical analysis of weighted mean individual components of total ocular symptom score (0–4 h) for primary and secondary treatment comparisons on day 8.