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

Murdoch RD¹, Bareille P¹, Ignar D², Miller S¹, Gupta A³, Boardley R¹, Zieglmayer P⁴, Zieglmayer R⁴, Lemell P⁴, Horak F⁴

¹GlaxoSmithKline, Stevenage, UK

²GlaxoSmithKline, Research Triangle Park, NC, USA

³Quantitative Sciences India, GlaxoSmithKline, Bangalore, India

⁴Vienna Challenge Chamber, Allergy Centre Vienna West, Vienna, Austria

Corresponding author: Dr R D Murdoch. GlaxoSmithKline, Stevenage, UK. Email: Robert.D.Murdoch@gsk.com

Abstract

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 socioeconomic impact. Combination pharmacotherapy is utilised by 40 to 50% of patients to treat their symptoms.

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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 randomised, double-blind, placebo-controlled, three-way, incomplete block, crossover, 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 hour 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 2 unit reduction in mean TNSS from pre-dose levels by 30 min and 1 h. Mean TOSS were also reduced following all active treatments relative to placebo (range 0.6 to 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.

Introduction

Allergic rhinitis (AR) is a common condition which typically affects 10 to 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 rhinorrhoea, 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 socioeconomic 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 minimising 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-leukotrienes. 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 of 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 hyperreactivity 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 US suggest that 40 to 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, randomised 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 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 µg or 400 µg provided 24 hour sustained efficacy

[24]. To investigate the potential for non-inferiority of once daily versus 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 to 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 randomised, double-blind, placebo-controlled, three-way, incomplete block, crossover 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 to 35 days prior to the first treatment period, eligible AR patients randomly received 3 out of 4 study treatments. Every

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patient received FDC and two out 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 randomisation 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 versus FF and LEVO alone.

Patients

Included patients were 18 to 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 were 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

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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, leukotriene 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 4 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.

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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, in order 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 to 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 (2-4h) 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 summarised.

Results

Patient population

Seventy-one patients were randomised to treatment and 68 (96%) completed the study as planned (Figure 1). Two patients withdrew their consent after completing two out 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 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 (Figure 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 (Figure 3). At the 30 min and 1 h post-dose time-points, there was an approximate 2 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 weighted 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 to 1.3 (Table 3). The impact of the treatment regimens on the individual domains of the TNSS (itch, sneeze, rhinorrhoea, and congestion) were consistent with those of the total scores (Table S1, online supplement).

Total ocular symptom score

After 8 days treatment, weighted mean TOSS (0-4 h) induced by allergen challenge was significantly reduced following all active treatments relative to placebo (range 0.6 to 0.8 unit reduction) (Figure 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 versus 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) were also consistent with those of the total scores (Table S2, online supplement)..

Safety

The proportion of patients reporting AEs was low and similar during all treatments (Placebo: 2 (6%); FF: 1 (2%); LEVO: 1 (2%); FFDC: 3 (4%)). The most frequent AE was headache (Placebo: 2 (6%); FF: 1 (2%); LEVO: 1 (2%); FFDC: 1 (1%)). There were no serious AEs. One patient experienced diarrhoea while 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/200µg 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

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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 hours (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 of 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 efficacy seen in the FDC arm relative to FF alone can possibly be attributed to the specific pharmacokinetic and pharmacodynamic properties of levocabastine. Levocabastine is a highly potent and

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selective H₁ antagonist with a K_i of 4nmol/L with a long T_{1/2} of 40hrs and good tissue penetration and permeability [28]. Clinical effects are seen within 5-15 mins and last for 24hrs (Data on file; NCT01949051) .In clinical practice and allergen challenge models it shows a marked reduction in sneeze, itch, and rhinorrhoea 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 hyper-responsiveness and a reduction in symptoms whilst the continued nasal mucosal/sub-epithelial presence of high doses, as $\mu\text{g}/\text{cm}^2$, of a highly potent H₁ antagonist acts to mop up 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 fan 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 FF [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's 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 levocabastine 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 levocabastine 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 azelastine 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 azelastine 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 (2 sprays/nostril, 200 µg) will be delivered which should provide sustained 24 hour efficacy, and it should not carry a somnolence precaution or be associated with bitter taste [37]. In a clinical comparison to azelastine, none of the subjects that received 2 sprays/nostril levocabastine twice daily reported taste disturbance compared with 5% of subjects who received 1 spray/nostril azelastine 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 2 unit difference in mean TNSS) is different to that shown in an earlier VCC study evaluating FF vs. placebo (approximate 4 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 100ug whereas the 200ug 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 NSG110341), 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

The study 200286 (NCT01957202) was funded by GSK. RDM, PB, DI, SM, RB and AG are GSK employees. PZ, RZ, PL and FH are employees of the Vienna Challenge

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Table 1: Patient demographics

Randomised, N	71
Age in years, mean (range)	29 (19–54)
Male, n (%)	35 (49)
Body mass index in kg/m ² , 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)

Table 2: Statistical analysis of weighted mean TNSS (0-4hrs) for primary and secondary treatment comparisons on Day 8

Parameter	Treatment Comparison	Adjusted Mean	Adjusted Mean	Adjusted Mean Difference	95% CI of Difference	% Improvement (TEST vs.REF)
	TEST vs. REF	TEST	REF			
	Primary Treatment Comparison					
Weighted Mean TNSS (0-4hrs)	FDC vs. FF	1.933	4.189	-2.255	(-2.895, -1.616)	53.9%
	FDC vs. Levo	1.933	4.500	-2.566	(-3.208, -1.925)	57.1%
	Secondary Treatment Comparison					
	Levo vs. Placebo	4.500	6.030	-1.531	(-2.342, -0.719)	25.4%
	FF vs. Placebo	4.189	6.030	-1.842	(-2.654, -1.029)	30.5%
	FDC vs. Placebo	1.933	6.030	-4.097	(-4.857, -3.337)	67.9%
	FF vs. Levo	4.189	4.500	-0.311	(-0.994, 0.372)	6.9%

Within Subject SD: Square root (Mean square error)=1.73

%Improvement = 100 x (1-TEST/REF)

FDC: fixed dose combination; Levo: levocabastine

Table 3: Statistical Analysis for Magnitude of Symptom Relief on Day 1 – Weighted Mean TNSS (2-4hrs)

Parameter	Treatment Comparison TEST vs. REF	Adjusted Mean TEST	Adjusted Mean REF	Adjusted Mean Difference	95% CI of Difference	% Improvement (TEST vs. REF)
Magnitude of symptom relief weighted mean TNSS (2-4hrs)	FDC vs. FF	-2.267	-0.904	-1.364	(-1.853, -0.874)	150.8%
	FDC vs. Levo	-2.267	-2.588	0.320	(-0.169, 0.809)	-12.5%
	LEVO vs. Placebo	-2.588	-1.335	-1.252	(-1.870, -0.635)	93.8 %
	FF vs. Placebo	-0.904	-1.335	0.432	(-0.179, 1.042)	-32.3%
	FDC vs. Placebo	-2.267	-1.335	-0.932	(-1.506, -0.358)	69.8%
	FF vs. Levo	-0.904	-2.588	1.684	(1.160, 2.208)	-65.1%

Within Subject SD: Square root (Mean square error)=1.32

%Improvement = 100 x (TEST/REF-1); negative values apply when test is worse than reference

FDC: fixed dose combination; Levo: levocabastine

Table 4: Statistical Analysis of Weighted Mean of TOSS (0-4hrs) for Primary and Secondary Treatment Comparisons on Day 8

Parameter	Treatment Comparison TEST vs. REF	Adjusted Mean TEST	Adjusted Mean REF	Adjusted Mean Difference	95% CI of Difference	% Improvement (TEST vs. REF)
Weighted Mean TOSS (0-4hrs)	Primary Treatment Comparison					
	FDC vs. FF	0.546	0.761	-0.215	(-0.509, 0.079)	28.3%
	FDC vs. Levo	0.546	0.621	-0.075	(-0.370, 0.221)	12.1%
	Secondary Treatment Comparison					
	Levo vs. Placebo	0.621	1.321	-0.701	(-1.080, -0.322)	53.0%
	FF vs. Placebo	0.761	1.321	-0.560	(-0.934, -0.187)	42.4%
	FDC vs. Placebo	0.546	1.321	-0.775	(-1.123, -0.428)	58.7%
	FF vs. Levo	0.761	0.621	0.140	(-0.175, 0.456)	-22.5%

Within Subject SD: Square root (Mean square error)=0.79

%Improvement = 100 x (1-TEST/REF); negative values apply when test is worse than reference

FDC: fixed dose combination; Levo: levocabastine

Figures legend

Figure 1: Study flow

FF: fluticasone furoate; Levo: levocabastine; FDC: fixed dose combination

Figure 2: Adjusted mean TNSS (95% CI) over time by treatment on Day 8

FF: fluticasone furoate; Levo: levocabastine; FDC: fixed dose combination

Figure 3: Adjusted mean TNSS (95% CI) over time by treatment on Day 1

FF: fluticasone furoate; Levo: levocabastine; FDC: fixed dose combination

Figure 4: Adjusted mean TOSS (95% CI) over time by treatment on Day 8

FF: fluticasone furoate; Levo: levocabastine; FDC: fixed dose combination

Figure 1: Study flow

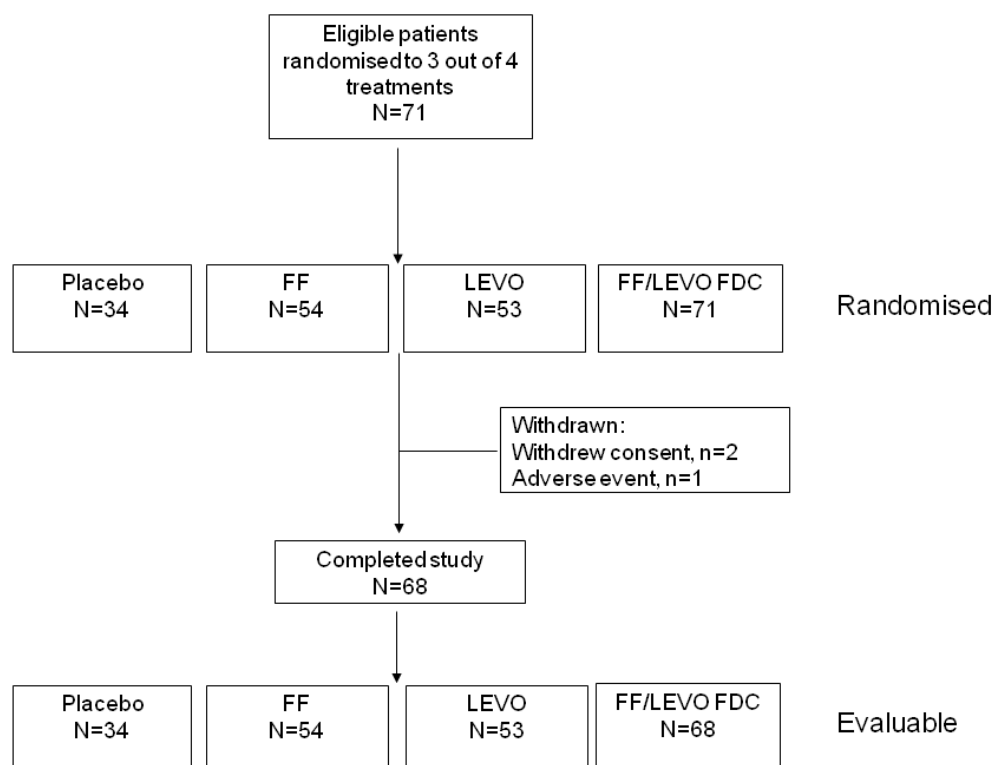


Figure 2: Adjusted mean TNSS (95% CI) over time by treatment on Day 8

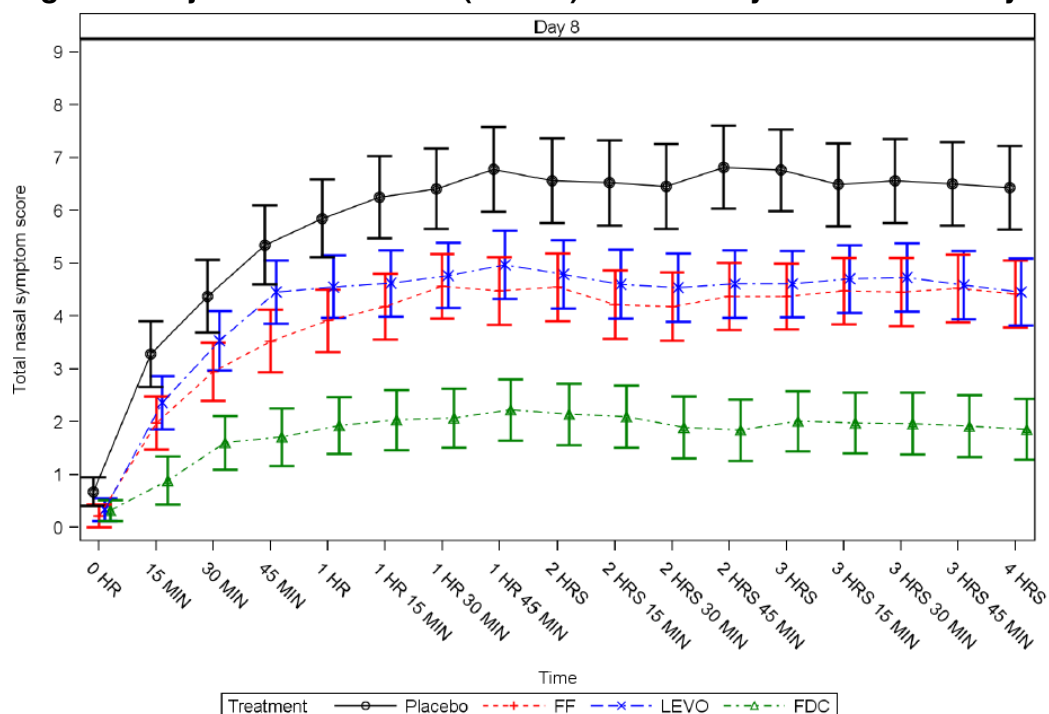


Figure 3: Adjusted mean TNSS (95% CI) over time by treatment on Day 1

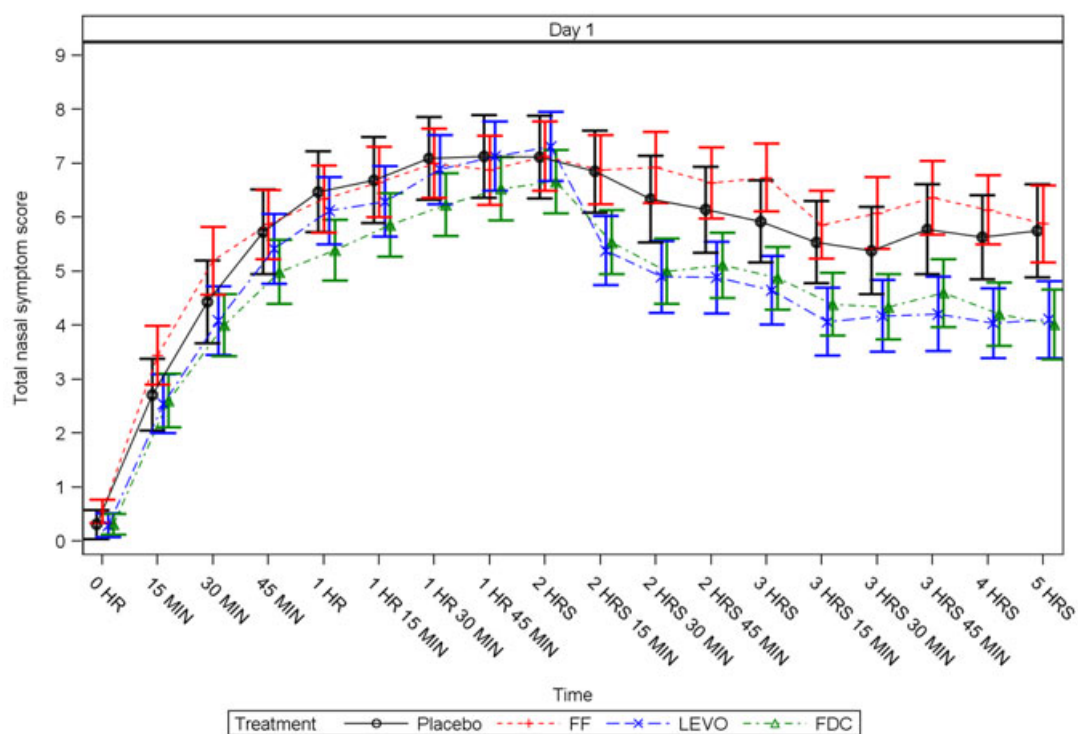


Figure 4: Adjusted mean TOSS (95% CI) over time by treatment on Day 8

