ORIGINAL CONTRIBUTION

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Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device*

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SUMMARY

Objective: *To assess the efficacy and safety of fluticasone propionate administered using OptiNose's novel delivery device (Opt-FP) in subjects with bilateral mild-to-moderate nasal polyposis.*

Methods: *A prospective, multicentre, randomized, double-blind, placebo-controlled, parallel group study was conducted in adult subjects (n = 109) with mild-to-moderate bilateral nasal polyposis. Subjects received Opt-FP 400 g or placebo twice daily for 12 weeks. Endpoints included endoscopic assessment of polyp size using Lildholdt's Scale, peak nasal inspiratory flow (PNIF), symptom scores and use of rescue medication.*

Results: *The proportion of subjects with improvement in summed polyp score ≥ 1 (Lildholdt's Scale) was significantly higher with Opt-FP compared with placebo at 4, 8 and 12 weeks (22% vs 7%, $p = 0.011$, 43% vs 7%, $p < 0.001$, 57% vs 9%, $p < 0.001$). After 12 weeks the summed polyp score was reduced by 35% (-0.98 vs +0.23, $p < 0.001$). PNIF increased progressively during Opt-FP treatment ($p < 0.001$). Combined symptom score, nasal blockage, discomfort, rhinitis symptoms and sense of smell were all significantly improved. Rescue medication use was lower (3.1% vs 22.4%, $p < 0.001$). Opt-FP was well tolerated.*

Conclusions: *Fluticasone propionate (400 g b.i.d.) administered using OptiNose's breath-actuated bi-directional delivery device was an effective and well tolerated treatment for mild-to-moderate bilateral nasal polyposis.*

Key words: fluticasone, delivery device, nasal polyps, bi-directional, chronic rhinosinusitis

INTRODUCTION

Chronic rhinosinusitis with nasal polyps is a common inflammatory disease of the upper respiratory tract, which may impair quality of life with symptoms that include nasal blockage during the day and sleep disturbance at night [1,2]. Topical nasal corticosteroids reduce the inflammation and are frequently employed in the management of polyposis. Several studies have shown positive effects of topical nasal steroids on moderate-to-severe polyposis, but substantial polyp disease still remains at trial completion in all of these studies continuing to obstruct the middle meatus and the sinus ostia [2,3]. A significant reduction in polyp size has been observed with fluticasone propionate nasal drops (FPND) administered at a dose of 400 g twice daily, but not when delivered once daily [4,5]. However, the methods recommended for administering nasal drops to enhance delivery to the middle meatus are uncomfortable and impractical, especially for those with musculoskeletal impairments and as a result, compliance is often poor [6]. Topical delivery of mometasone and budesonide have been reported to reduce the size and subjective symptoms in bilateral moderate-to-severe polyposis, with overall better results for higher doses which in several of the studies with budesonide are higher that the currently recommended doses for nasal polyposis [2,7-12]. There is, however, evidence that drug delivery with conventional nasal sprays and nasal powder inhalers is suboptimal, with inadequate delivery to the middle meatus where polyps originate [6,13-16]. Furthermore, nasal inhalation of budesonide powder from the Turbohaler device may result in substantial lung deposition and risk of increased systemic absorption [17,18].

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Bi-directional delivery using the OptiNose device offers an alternative method with highly superior delivery to target areas in regions of the nose beyond the nasal valve, in this case the middle meatus (under the middle turbinate) where the nasal polyps originate [15,17]. Opt-FP, which contains a multi-dose spray pump, is primed and positioned in one nostril with the mouthpiece in the mouth. The user blows through the device, which causes the soft palate to close, separating the nasal and oral cavities, and triggering the spray pump (Figure 1). The airflow generated in the nose expands the narrow nasal passages and the communication located behind the nasal septum during soft palate closure before exiting through the other nostril in the opposite direction (bi-directional flow). The sealing nosepiece allows control over pressure and flow conditions and, together with optimization of particle size characteristics and the use of a breath-actuation mechanism, controlled and targeted nasal delivery of both liquid and powders can be achieved. Since delivery occurs during exhalation, lung deposition is avoided [15,17].

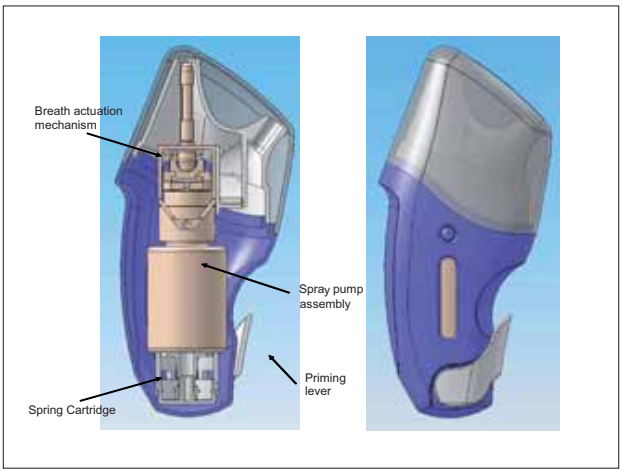


Figure 1. Breath-actuated bi-directional delivery device. The basic functional components are shown, along with the styled exterior [15].

This is the first clinical study with the OptiNose breath-actuated device in patients. The aim of this study was to investigate the efficacy and safety of Opt-FP in subjects with mild-to-moderate bilateral nasal polyps where few studies exist.

MATERIALS AND METHODS

Study design

This prospective, randomized, double-blind, placebo-controlled, parallel group study enrolled adult subjects with mild-to-moderate bilateral nasal polyps at five otorhinolaryngology hospital clinics in the Czech Republic (two centres in Prague, one in Olomouc, one in Prostějov, one in České Budějovice). All subjects gave written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was reviewed and approved by the central Ethics Committee of the Faculty Hospital Motol, Czech Republic and the ethics committee's at the individual centres participating in the study.

Inclusion criteria were: age 18-65 years, a diagnosis of bilateral nasal polyposis graded as mild or moderate (see efficacy assessment for details), verified airflow through both nostrils and an ability to close the soft palate, and the ability to trigger the breath-actuation mechanism of a device in accordance with the instructions for use.

Exclusion criteria included: Large polyps (grade 3, see below), nasal polyp surgery during the 3 months before screening, cystic fibrosis, a purulent nasal infection, allergic rhinitis or other disease likely to interfere with the study parameters, depot or oral steroids during the previous 3 months, subjects with a cleft palate. Concomitant medications that would interfere with study evaluations were not permitted, including corticosteroids (except inhaled corticosteroids for asthma ≤ 1000 g beclomethasone (or equivalent) per day at a stable dose for ≥ 3 months), nasal atropine or iprotropium bromide, nasal sodium cromoglycate, leukotriene receptor antagonists, antihistamines, decongestants, beta-blockers or neuroleptics. Saline rinsing and devices that dilate the nostrils were also prohibited. As in several other similar studies, an oral antihistamine (Loratadine 10 mg tablets) was provided as rescue medication for the relief of troublesome acute allergic symptoms [4,5]. If a subject experienced a severe acute nasal blockage, the investigator could authorize the use of a short course of oxymetazoline drops or spray for a maximum of 7 consecutive days and a total maximum of 10 days during the treatment period. Oxymetazoline was not to be used within 24 hours of a scheduled study visit.

Following a 14-16 day treatment-free run-in, subjects who met the eligibility criteria were randomized in a 1:1 ratio to receive Opt-FP 400 g or placebo b.i.d. for 12 weeks. Subjects attended the clinic at the beginning and end of the run-in period and after 4, 8 and 12 weeks (time window for visits ± 2 days) of treatment. A follow-up visit was made 2 weeks after the end of treatment.

Opt-FP and placebo breath-actuated bi-directional delivery devices were identical in appearance (Figure 1). The spray pump in Opt-FP contained an aqueous suspension of fluticasone propionate (FP) 0.1% w/w in an aqueous medium containing microcrystalline cellulose and carboxymethylcellulose sodium, benzalkonium chloride, EDTA disodium salt dehydrate, dextrose anhydrous and polysorbate 80. The placebo aqueous nasal spray was formulated to match FP exactly, except for the active ingredient. The devices delivered 100 L aqueous suspension per actuation. To deliver a dose of FP 400 g b.i.d. or matching placebo, the subjects made two administrations to each nostril in the morning and the evening.

All subjects were trained in the use of the device at both screening and randomization visits. Nasal patency and the ability to close the soft palate were confirmed at screening. During treatment, compliance was assessed at each visit by examining the devices for use and by reviewing treatment administrations recorded in the diary cards.

Efficacy assessments

Nasal endoscopy was performed by the investigator without the use of decongestants and local anaesthetics using an endoscope with a diameter ≤ 2.7 mm at screening, pre-dose baseline, and after 4, 8 and 12 weeks of treatment. Polyp size was graded for each nostril using Lildholdt's scale [2,12,19,20]. Polyps were scored as 0 (no polyps), 1 (small polyps not reaching the upper edge of the inferior turbinate and causing only slight obstruction), 2 (medium polyps reaching between the upper and lower edge of the inferior turbinate and causing troublesome obstruction) or 3 (large polyps reaching below the lower edge of the inferior turbinate and causing almost/total obstruction). Some authors classify polyps causing total obstruction as grade 4 [9]. The score was presented for each nostril, the worst affected nostril and the summed score for both nostrils. Polyp size was also determined by lateral imaging [21,22], where the investigator draws the polyps visualized on nasal endoscopy examination on a standard schematic diagram of the lateral wall of each nasal cavity. Polyp size is expressed as a percentage of the lateral wall and cannot exceed 100%. A computer program is used to draw the polyps and automatically calculates the polyp area (the program is available free of charge at htpp://www.artech.se/~bende/li).

PNIF was measured using an In-Check portable nasal inspiratory flow meter (Clement Clarke International Ltd, Harlow, Essex, UK) at pre-dose baseline and after 4, 8 and 12 weeks of treatment. At each assessment the subject inhaled maximally three times and the highest value was recorded [23]. Subjects were trained in the use of the meter at screening and baseline.

Nasal blockage, nasal discomfort (facial and sinus pain and pressure) and rhinitis (nasal secretion, itching, irritation and sneezing) symptoms were recorded by subjects in a diary each morning and evening from screening through to the end of treatment using the following scoring system: 0 (none), 1 (mild – symptoms present but not troublesome), 2 (moderate – symptoms frequently troublesome but not interfering with daily activity or night time sleep) or 3 (symptoms troublesome and interfering with daily activity or night-time sleep). Subjects also recorded sense of smell as follows: 0 (normal), 1 (slightly impaired), 2 (moderately impaired) or 3 (absent). A global rating scale (very much improved; improved; same; worse; or very much worse) was completed by subjects after 4, 8 and 12 weeks of treatment.

Subjects recorded the use of rescue medication (loratadine tablets 10 mg and/or oxymetazoline drops or spray) in the diary each day throughout the treatment period. A tablet count was used to verify the usage of loratadine tablets.

Safety assessments

Safety assessments included adverse events, laboratory tests, vital signs and physical examination. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate or severe and a relationship to treatment assigned based on the judgment of the investigator. Blood and urine sampling for laboratory tests, measurement of vital signs and physical examination were performed at screening and follow-up. Blood samples for morning cortisol concentrations were taken between 08.00-10.00 h prior to randomization and at the end of treatment.

Statistical methods

All analyses and summaries are based on the intent-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication and had baseline and at least one post-baseline measurement. No interim analyses were performed.

For categorical variables (proportion of subjects with change in symptom score, polyp size using Lildholdt's scale, subjects global rating scale), comparison between treatment groups was made using Cochran-Mantel-Haenszel (CMH) tests. For continuous variables (polyp size measured by lateral imaging, PNIF measurements, and rescue medication usage), comparison between treatment groups was made using analysis of variance (ANOVA). The normality assumptions for the planned ANOVA tests of rescue medication usage were not met so additional non-parametric Wilcoxon Rank-Sum tests were performed. Symptom scores were collected morning and evening every day on the patient diary using a categorical scoring system. These were then summarised into one score for each symptom and each 4 week period by taking the mean of each daily score. Comparison of symptom scores between treatment groups was made using ANOVA. The level of significance, alpha (α), for this study was 0.05. All statistical testing was two-sided.

It was determined that a sample size of 50 subjects per treatment group would provide 80% power to detect a difference of 0.8 in the total polyp size score between the two treatments using a two-group test at the 5% significance level (two-sided).

RESULTS

Subjects characteristics

The study was conducted from May to October 2007. A total of 109 subjects were randomized to treatment. The study population was predominantly male and all subjects had a polyp score of 1 (mild polyps) or 2 (moderate polyps). The two treatment groups were closely similar with respect to demographics, polyp size and previous sinus surgery at baseline (Table 1). All 109 subjects received at least one dose of study medication and underwent one baseline and one post-baseline assessment, allowing inclusion in the ITT population for efficacy analyses and the safety population.

A total of 106 subjects (97%) completed the study. Three subjects withdrew, all in the placebo group (one due to worsening of polyps, two withdrew consent). Based on the recording of morning and evening administrations in the subject's diary, mean percentage compliance was high with 98.92% administrations made in the Opt-FP treatment group and 99.05% made in the placebo group. Two subjects in the placebo group were

Table 1. Demographic details and baseline characteristics for each treatment group.

Parameter	Opt-FP 400 g b.i.d. (n = 54)	Placebo b.i.d. (n = 55)
Mean age, years (range)	48.9 (18 – 65)	47.0 (23 – 63)
Male/female (%)	74/26	62/38
Mean weight, kg (range)	81.4 (62 – 115)	80.1 (49-120)
Asthma history, n (%)	17 (31.5)	18 (32.7)
Number of previous sinus surgeries, n (%)		
0	23 (43)	15 (27)
1	12 (22)	19 (35)
2	7 (13)	5 (9)
3	8 (15)	9 (16)
≥4	4 (7)	7 (13)
Polyp size in worst nostril Lildholdt's Scale n (%)		
0 (none)	0	0
1 (mild)	27 (50)	27 (49)
2 (moderate)	27 (50)	28 (51)
3 (severe)	0	0

Opt-FP = OptiNose device containing fluticasone propionate.

non-compliant with respect to oxymetazoline usage, but were included in the ITT population. A per-protocol analysis that excluded these two subjects (data not shown), showed essentially identical results to those obtained for the ITT population.

Efficacy

Polyp Size

The proportion of subjects improved (reduction in summed polyp score ≥ 1 on the Lildholdt's Scale) was significantly higher for Opt-FP compared to placebo at 4, 8 and 12 weeks (22% vs 7%, $p = 0.011$, 43% vs 7%, $p < 0.001$, 57% vs 9%, $p < 0.001$, Figure 2). The mean summed polyp size was progressively and significantly reduced compared to placebo at all time points (Figure 3). At 12 weeks the reduction was 35% ($p < 0.001$). The proportions of subjects with a reduction in polyp score ≥ 1 in both the worst nostril and in each individual nostril were also significantly higher in the Opt-FP group compared with placebo after 8 and 12 weeks of treatment.

When polyp size was measured using lateral imaging, a statistically significant reduction was observed at 4, 8 and 12 weeks of Opt-FP treatment (Figure 4). A small increase in polyp size was found during the study in subjects treated with placebo.

PNIF

There was a progressive increase in PNIF during Opt-FP treatment with significant differences at all time points compared with placebo (Figure 5). After 12 weeks of treatment, a mean increase in PNIF of 17.7 L/min was observed with Opt-FP compared to a mean reduction of 3.2 L/min with placebo ($p < 0.001$).

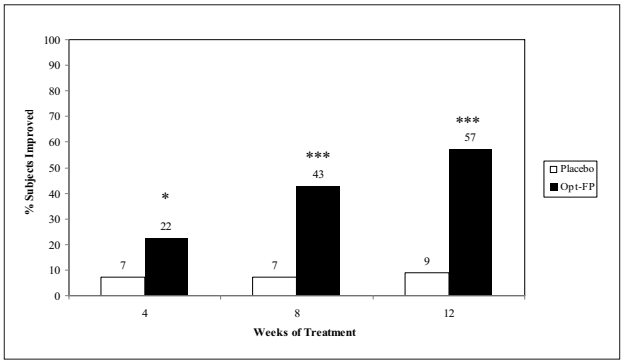


Figure 2. Proportion of subjects with improvement in summed polyp size ≥ 1 point on the Lildholdt's Scale after 4, 8 and 12 weeks of treatment. Opt-FP = OptiNose device containing fluticasone propionate. Comparison between treatment groups was made using the CMH test. Statistical significance Opt-FP vs placebo: *$p < 0.05$; ***$p \leq 0.001$.

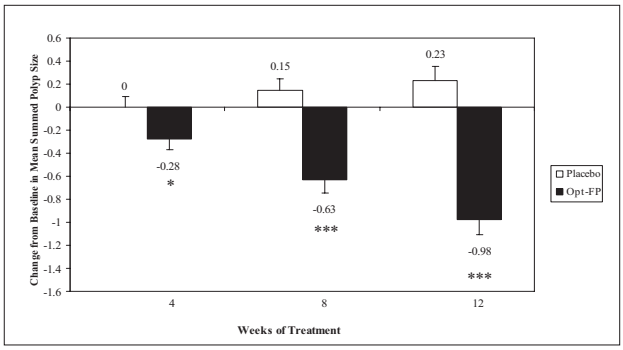


Figure 3. Change from baseline in mean summed polyp size determined using the Lildholdt's scale at 4, 8 and 12 weeks of treatment. Opt-FP = OptiNose device containing fluticasone propionate. Bars are mean ± SE. Baseline mean summed polyp scores were 2.78 and 2.80 for Opt-FP and placebo, respectively. Comparison between treatment groups was made using the CMH test. Statistical significance Opt-FP vs placebo: *$p < 0.05$; ***$p \leq 0.001$.

Nasal Symptoms

Significant improvements in morning and evening combined symptom scores at 4, 8 and 12 weeks were observed for the Opt-FP group compared with placebo (Figure 6a). This was accompanied by significant improvements in the morning and evening scores for nasal blockage, nasal discomfort and rhinitis symptoms at 4, 8 and 12 weeks and sense of smell at 8 and 12 weeks (Figures 6b-6e).

Rescue Medication

Subjects treated with Opt-FP used loratadine on a significantly lower mean percentage of days than placebo, both over the whole treatment period (3.1% vs 22.4%, $p < 0.001$) and between each study visit during treatment. Subjects treated with Opt-FP did not use oxymetazoline, whereas there was some use in the placebo group reflected in use on a significantly higher mean percentage of days (0% vs 1.2%, $p = 0.025$).

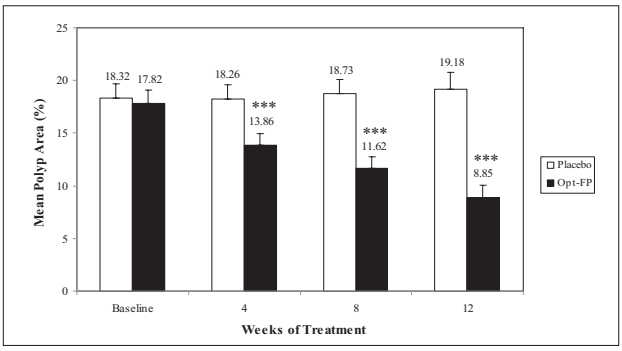


Figure 4. Mean polyp size assessed by lateral imaging at baseline and after 4, 8 and 12 weeks of treatment. Opt-FP= OptiNose device containing fluticasone propionate. Bars are mean ± SE. Comparison between treatment groups was made using ANOVA. Statistical significance Opt-FP vs placebo: ***p ≤ 0.001

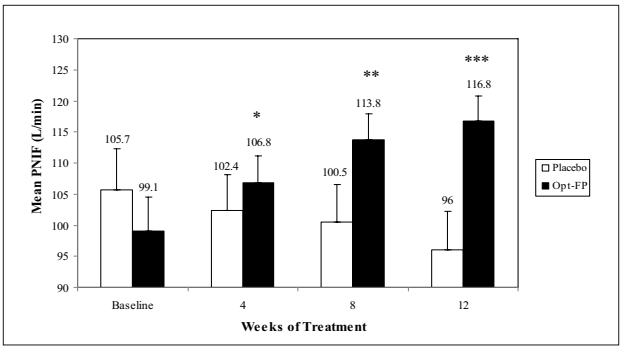


Figure 5. Mean PNIF at baseline and after 4, 8 and 12 weeks of treatment. Opt-FP = OptiNose device containing fluticasone propionate. Bars are mean ± SE. Comparison between treatment groups was made using ANOVA. Statistical significance Opt-FP vs placebo: *p < 0.05; **p ≤ 0.01; ***p ≤ 0.001.

Subjects Global Rating Scale

Significantly more subjects treated with Opt-FP considered themselves to be improved or very much improved at each time point. After 12 weeks, 76% of subjects treated with Opt-FP were improved or very much improved compared with 27% of subjects treated with placebo (p < 0.001).

Safety

Treatment with Opt-FP was well tolerated. The overall incidence of treatment-emergent adverse events (TEAEs) was low, with 13 subjects (24%) treated with Opt-FP and 11 subjects (20%) treated with placebo experiencing at least one TEAE. The majority of TEAEs were mild, with only one subject (2%) treated with Opt-FP and two subjects (4%) treated with placebo experiencing events of moderate severity. No severe TEAEs were recorded. The most common TEAE considered to be treatment-related was epistaxis occurring in 11% subjects treated with Opt-FP and none in the placebo group (Table 2). No serious adverse events were reported during the study. One subject in the placebo group withdrew due to an adverse event, worsening of polyps.

The major finding for physical examination was the presence of nasal polyps on screening for all subjects, consistent with their inclusion in the study. At follow-up, 10 (19%) subjects treated with Opt-FP and 1 (2%) subject treated with placebo had no nasal polyps evident on physical examination. The remaining physical examination results at follow-up were clinically unremarkable.

Mean results for vital signs measured at screening and follow-up showed no clinically significant changes or treatment effects overall. One subject in the Opt-FP group had hypertension diagnosed during treatment. A further three subjects (two treated with placebo, one treated with Opt-FP) had mild to moderate elevations in blood pressure at follow-up.

No clinically relevant changes in laboratory test parameters were observed. Morning plasma cortisol concentrations were unchanged after 12 weeks of treatment with Opt-FP or placebo (mean change from baseline of -0.75 g/dL for active compared with -0.38 g/dL for placebo).

DISCUSSION

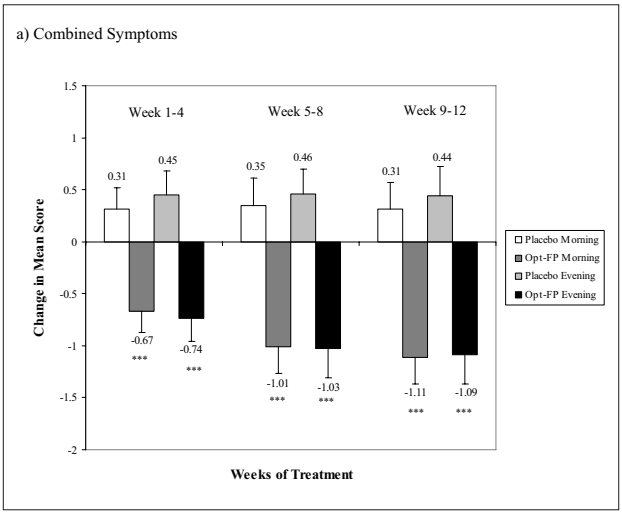
The objective of topical steroid treatment in polyposis is to reduce the polyp size, the inflammation and associated symptoms, and to reduce, delay or eliminate the need for surgical treatment [2,13]. Recent studies and guidelines suggest that topical steroid treatment alone may reduce polyp size and prevent recurrences after surgery [2]. Surgery is often recommended and required in severe polyposis with large grade 2 and grade 3-4 polyps and accompanying symptoms when medical treatment, including short term oral steroids, has failed [2]. A reduction in polyp size of ≥ 1 point in the Lildholdt's Scale is generally recognized as a clinically meaningful improvement [4,5,7,8].

In this study including only grade 1 and grade 2 polyps, a significant difference in the proportion of subjects with such a reduction was observed at 4 weeks compared with placebo and continued to decrease over time, with 57% subjects (placebo

Table 2. Number (%) subjects with adverse events considered to be related to treatment.

Parameter	Opt-FP 400 g b.i.d. (n = 54)	Placebo b.i.d. (n = 55)
Epistaxis	6 (11.1)	0 (0.0)
Sneezing	2 (3.7)	1 (1.8)
Nasal discomfort	0 (0.0)	1 (1.8)
Nasal polyps	0 (0.0)	1 (1.8)
Rhinalgia	0 (0.0)	1 (1.8)
Rhinorrhoea	0 (0.0)	1 (1.8)
Rhinitis	1 (1.9)	0 (0.0)
Headache	0 (0.0)	1 (1.8)

Opt-FP = OptiNose device containing fluticasone propionate.



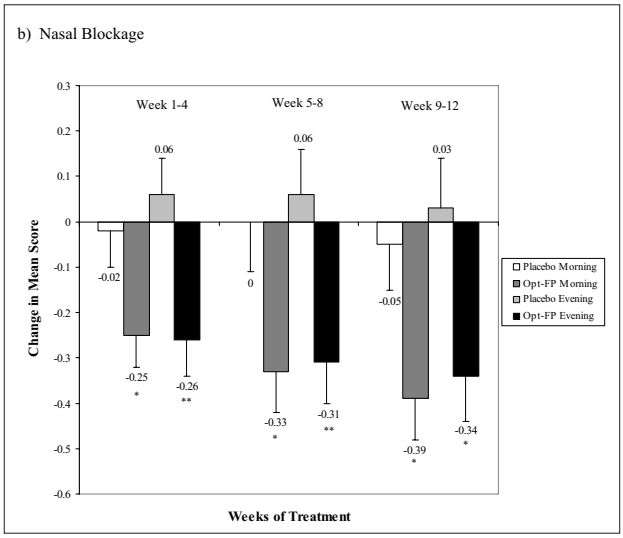
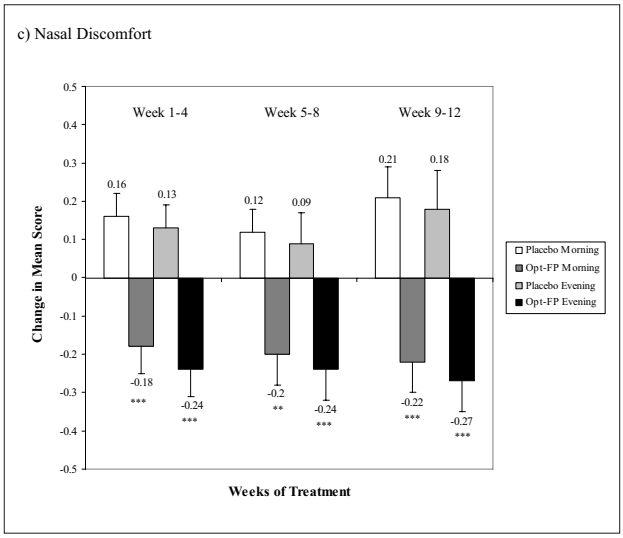
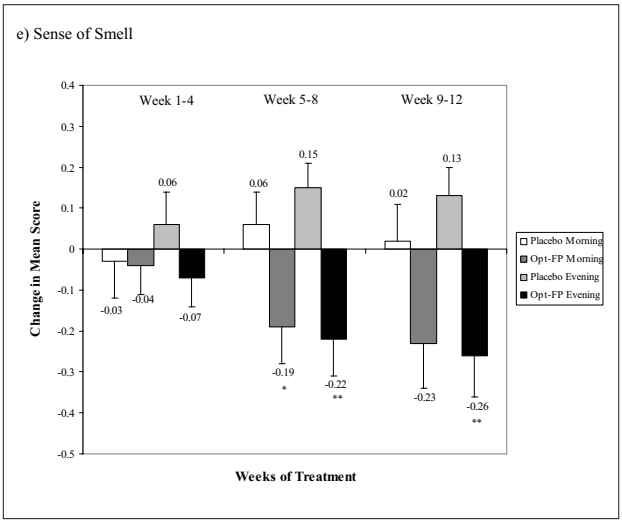
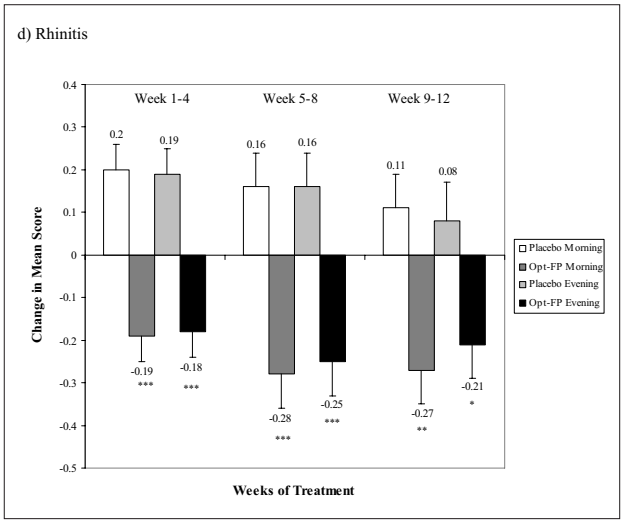


Figure 6. Change in mean morning and evening scores for a) combined symptoms, b) nasal blockage, c) nasal discomfort, d) rhinitis symptoms and e) sense of smell. Opt-FP = OptiNose device containing fluticasone propionate. Negative values indicate a reduction or improvement in symptoms, positive values an increase or worsening of symptoms. Bars are mean ± SE. Baseline morning individual symptom scores were 4.26 and 4.06 for combined symptoms, 0.96 and 1.03 for nasal blockage, 0.67 and 0.55 for nasal discomfort, 0.83 and 0.92 for rhinitis symptoms, and 1.80 and 1.55 for sense of smell in the Opt-FP and placebo groups, respectively. Baseline evening individual symptom scores were 3.99 and 3.57 for combined symptoms, 0.86 and 0.85 for nasal blockage, 0.65 and 0.49 for nasal discomfort, 0.71 and 0.81 for rhinitis symptoms, and 1.77 and 1.43 for sense of smell in the Opt-FP and placebo groups, respectively. Comparison between treatment groups was made using ANOVA. Statistical significance Opt-FP vs placebo: *$p < 0.05$; **$p \le 0.01$; ***$p \le 0.001$.







9%, (= 48%), $p < 0.001$) improved after 12 weeks of treatment with Opt-FP. The most relevant comparison with the present study was in patients with bilateral mild-to-moderate polyposis receiving the same drug at the same dose (FPND 400 g twice daily) [4] where 41% of subjects experienced a reduction in summed polyp score ≥ 1 (placebo 15%, (= 26%), $p < 0.01$) after 12 weeks. The fraction of patients reporting overall improvement was 65% at 4 weeks ($p < 0.001$) to 76% ($p <$

0.001) at 12 weeks for Opt-FP, whereas a decrease from 57% ($p < 0.01$) at 4 weeks to 50% (NS) at 12 weeks was reported for FPND [4].

With Opt-FP, the change from baseline in summed polyp score after 12 weeks of treatment was -0.98 with a differential score of 1.21 due to a moderate increase in polyp size in the placebo group. Interestingly, an increase in the placebo polyps score was also seen in one of the few other studies restricted to small and medium-sized polyps [24]. This study was limited to the eosinophilic polyps subgroup known to respond better to topical steroids than the neutrophilic subgroup [2]. In all the 6 studies including large polyps (mean baseline polyp size 3.9-5) included in a recent meta-analysis, a reduction in polyps size was seen also in the placebo group resulting in smaller score differentials [3]. This suggests that larger polyps may be more sensitive to placebo treatment than smaller polyps. The non-linear nature of the Lildholdt's score should also be considered when comparing studies with different baseline polyp size [4,5].

Lateral imaging

Lateral imaging was developed as a means of reproducibly assessing polyp size [21,22]. In the present study, there was good agreement between the results obtained with lateral imaging and the Lildholdt's Scale. The effect was highly significant after 4 weeks of treatment with Opt-FP, confirming that lateral imaging is a very sensitive means of evaluating treatments on polyp size.

PNIF, symptom scores and other parameters

The improvement of PNIF and a range of nasal symptoms, the reduced use of rescue medication and improvements in the global rating scale observed with Opt-FP treatment were all consistent with the reduction in polyp size observed, along with the other clinical benefits of topical corticosteroids.

All the subjective parameters assessed were significantly improved in the present study, including the sense of smell which is a clinical parameter with important implications for patient well being and quality of life. Only a few studies with topical steroids including large polyps have shown significant effects on the sense of smell [2]. The FPND studies and the budesonide spray study that included only grade 1 and 2 polyps showed no significant effects on the sense of smell [4,5,24], in contrast to the significant improvement in the sense of smell observed in the present study.

Progression of clinical effects with time

In the FPND study in mild-to-moderate polyposis showing good effects initially at 4 weeks but, in contrast to the present study, there is minimal improvement at 8 and 12 weeks for the reduction in polyp size and the overall symptom score at 12 week is actually decreased from 4 and 8 week to non-significant levels when compared to placebo [4]. When used as instructed, drops may improve deposition to the middle meatus [25], explaining the good initial effects [4]. Treatment with FPND in patients indicated for FESS reduced the need for surgery [13]. However, the difficulty and discomfort of the delivery procedure and body position may reduce compliance with time. As the polyps retract they are no longer easily reached by nasal powder inhalation, conventional spray pumps and drops [6,16].

In a recent study in 20 patients including grade 3 polyps there was a significantly positive correlation between pre-treatment endoscopic and tomographic scores and patients with a higher tomographic score presented a significantly worse clinical response [20]. However, despite poorer overall clinical outcome in the 8 subjects with high CT score and polyp scores of 5 or 6 (mean 5.25), the mean reduction in polyp score was 1.9 as compared to 1.0 in the 12 patients with summed polyp score of 3 or 4 (mean 3.6). Thus, this confirms the limited value of comparing reduction in polyp scores in studies with different baseline polyp score, but also suggest that it is easier to achieve a greater absolute reduction in polyp score in patients with large polyps. We suggest that a reduction in polyp size will positively influence nasal airflow and the steroid will reduce secretion and mucosal swelling, but as long as substantial polyp masses continue to obstruct the middle meatus, positive effects on sinus pathology are unlikely. In this study, as in the studies in the recent meta-analysis, the summed polyp size at study completion is larger or similar to the summed baseline polyp size of 2.8 in our study [3,7-9,20,26]. The true challenge is to remove or minimize the polyps in the middle meatus and to prevent re-formation of polyps after effective medical or surgical intervention.

Improved deposition beyond the nasal valve and to the middle meatus with Opt-FP has been documented in healthy volunteers [15] and also observed in polyp patients (unpublished observations). On this background we speculate that the OptiNose device may continue to reach the polyps as they retract into the middle meatus and normalize sinus ventilation and clearance [15] In the present study the polyps disappeared in 10 (18.5%) subjects treated with Opt-FP, which is key to restore normal sinus ventilation and nasal function including sense of smell.

Safety and Tolerability

Opt-FP was well tolerated with no decrease in morning cortisol. The most frequently reported adverse event was epistaxis, a known effect associated with the administration of nasal steroids. The incidence of 11.1% in this study was comparable to that reported during treatment with 200 g MFNS of 13.7% [8] and FPND 400 g b.i.d. of 9% [4]. As epistaxis was not observed with placebo, it clearly was not caused by insertion of the nosepiece of the breath-actuated bi-directional delivery device into the nostril. This is an important observation for this new device, which in this study delivered more than 70,000 doses over 12 weeks. The user feedback, following 12

weeks use in an at-home setting and assessment of the returned devices coupled with the clinical results, clearly indicates that the device is robust, functions well and is well tolerated by the patients in an at-home setting.

CONCLUSIONS

In conclusion, the results demonstrate that Opt-FP (400 g b.i.d.) is an effective and well tolerated treatment for mild-to-moderate bilateral nasal polyposis. The progressive, highly significant and consistent effects in both subjective and objective parameters obtained with Opt-FP in this patient group suggests that enhanced deposition to the middle meatus is desirable for efficient treatment of small and medium sized polyps.

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