Ann Allergy Asthma Immunol 111 (2013) 45–50

Contents lists available at SciVerse ScienceDirect

Ocular safety of fluticasone furoate nasal spray in patients with perennial allergic rhinitis: a 2-year study

Craig LaForce, MD [*]; Glen E. Journeay, MD, PhD [†]; S. David Miller, MD [‡]; Mary Jane Silvey, MBA [§]; Wei Wu, PhD [§]; Laurie A. Lee, MD [§]; and Leo T. Chylack, Jr, MD [||,¶]

[*] North Carolina Clinical Research, Raleigh, North Carolina
[†] Austin Clinical Research Inc, Austin, Texas
[‡] NorthEast Medical Research Associates, North Dartmouth, Massachusetts
[§] GlaxoSmithKline, Research Triangle Park, North Carolina
[||] Harvard Medical School, Boston, Massachusetts
[¶] Chylack Inc, Duxbury, Massachusetts

ARTICLE INFO

Article history:
Received for publication October 31, 2012.
Received in revised form April 6, 2013.
Accepted for publication April 16, 2013.

ABSTRACT

Background: This is the first study, to our knowledge, to evaluate the ocular effects of an intranasal corticosteroid during 2 years of treatment for perennial allergic rhinitis (PAR).
Objective: To assess ocular safety in adult and adolescent patients 12 years and older with PAR after 2 years of continuous treatment with fluticasone furoate nasal spray (FFNS), 110 μg once daily, and placebo.
Methods: This was a 2-year, randomized, double-blind, placebo-controlled study of once-daily FFNS, 110 ìg, and placebo in 548 patients 12 years and older with PAR. The primary ocular safety end points were time to first occurrence of an event for the Lens Opacities Classification System, Version III (LOCS III), posterior subcapsular opacity (PSO) and time to first occurrence of an event for intraocular pressure (IOP).
Results: On the basis of survival analyses, the difference between the treatment groups for time to first occurrence of a LOCS III PSO and time to first occurrence of an IOP event was not statistically significant ($P = .39$ and $P = .34$, respectively). Changes from baseline in visual acuity, LOCS III PSO, cortical opacity, LOCS III nuclear opacity and nuclear color, IOP, and horizontal cup-to-disc similar between treatment groups. There were no ophthalmic-related adverse events of LOCS III PSO or IOP that led to early withdrawal. The most common drug-related adverse event was epistaxis (FFNS, 28%; placebo, 14%).
Conclusion: These data neither support nor negate current recommendations for regular ophthalmic monitoring in patients treated with intranasal corticosteroids.
Trial Registration: clinicaltrials.gov Identifier: NCT00682643.
© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

The chronicity of perennial allergic rhinitis (PAR) often necessitates long-term pharmacologic therapy. However, there is a paucity of data describing the benefits and risks of long-term use of intranasal corticosteroids. Clinical studies lasting up to 1 year with intranasal corticosteroids demonstrated a favorable benefit-risk profile.[1,2]

Fluticasone furoate nasal spray (FFNS) (Veramyst Nasal Spray; GlaxoSmithKline, Research Triangle Park, North Carolina) is an intranasal corticosteroid approved by the Food and Drug Administration (FDA) for the symptoms of allergic rhinitis.[3] The potential for adverse effects on the eyes (eg, cataracts and glaucoma) is noted as a potential class effect in the prescribing information of all intranasal corticosteroids.

This report describes the results of a 2-year postmarketing study whose objective was to evaluate the ocular effects of continuous use of FFNS, 110 μg once daily, in adult and adolescent patients with PAR. To date, it is the first randomized, double-blind, placebo-controlled, parallel-group study, to our knowledge, to evaluate the long-term safety of the continuous use of an intranasal corticosteroid during a 2-year period in which adherence was monitored by daily diary and video-phone observations and in which regular ophthalmologic evaluations were performed by ophthalmologists trained and certified in the Lens Opacities Classification System, Version III (LOCS III). LOCS III is a widely used method of subjectively grading the type and severity of lens opacities by comparing a patient's lens opacities to a set of standard photographs that

Reprints: Laurie A. Lee, MD, GlaxoSmithKline, 5 Moore Dr, Research Triangle Park, NC 27709; E-mail: laurie.a.lee@gsk.com.
Disclosures: Drs Wu and Lee are current GlaxoSmithKline employees. Ms Silvey was employed by GlaxoSmithKline during the conduct and analysis of the study. Dr Chylack was a consultant to GlaxoSmithKline and responsible for the Lens Opacities Classification System training and certification during the study. Drs LaForce, Journeay, and Miller were study investigators and consultants for GlaxoSmithKline for this study.
Funding Sources: This study was funded by GlaxoSmithKline (GSK study FFR110537).

1081-1206/13/$36.00 - see front matter © 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.anai.2013.04.013

illustrate differing degrees of nuclear (including nuclear opacity [NO] and nuclear color [NC]), cortical (C), and posterior subcapsular opacities (PSO) formation.[4–6] The design and duration of the study and the use of LOCS III were discussed and agreed on by the study sponsor and the FDA before the start of the study.

Methods

Study Design and Treatment

This study (GlaxoSmithKline protocol FFR110537; Clinical Trials.gov identifier NCT00682643 was conducted at 53 centers in the United States in compliance with Good Clinical Practice and the Declaration of Helsinki (2008) and was approved by all relevant institutional review boards. The study was initiated on June 30, 2008, and completed on February 18, 2011. Following a 7- to 14-day screening period, eligible patients were randomized in a 2:1 ratio (FFNS, 110 μg once daily:placebo) to FFNS, 110 μg once daily, and placebo nasal spray. A total of 525 randomized patients (350 to FFNS 110 μg and 175 to placebo) was planned at approximately 40 to 70 investigational sites. The randomization was stratified by age (12 to $<$18 years, 18 to $<$40 years, 40 to $<$50 years, 50 to $<$60 years, and $\geq$60 years).

Study medication was self-administered intranasally (2 actuations per nostril) once daily in the morning. Patients were seen the day of randomization, every 4 weeks, for posttreatment follow-up, and, if applicable, at early withdrawal. Administration of study treatment was monitored by daily video-phone observations by a centralized call center. Regular ophthalmologic evaluations were performed by ophthalmologists certified in LOCS III.

Patients

Male or female patients 12 years and older were eligible if they had a 2-year medical history and past treatment of PAR and a positive skin prick test result to an appropriate perennial allergen at or within 12 months of screening. Patients were excluded if they had severe physical obstruction of the nose, nasal ulcer, recent nasal or ocular injury or surgery, rhinitis medicamentosa, evidence of an intranasal candida infection, acute or chronic sinusitis, diabetes mellitus, uncontrolled hypertension, glaucoma and/or ocular herpes simplex, current cataract and/or previous history of cataract surgery, persistent asthma, ocular or upper respiratory bacterial or viral infection, severe arteriosclerotic cardiovascular disease, tachycardia, severe cerebrovascular disease, or history of current tobacco use. Patients were also excluded if they had received protocol-specified prohibited medications during the screening period. All adult patients and parents or guardians of patients younger than 18 years gave written informed consent before study participation.

Procedures

During the screening and treatment periods, patients used an electronic diary to rate symptoms of nasal congestion, rhinorrhea, nasal itching, and sneezing on a scale ranging from 0 (symptoms not present) to 3 (symptoms difficult to tolerate or interfere with activities of daily living and/or sleeping). Patients rated these symptoms each morning based on symptom severity during the preceding 24 hours.

To be eligible for randomization, patients were required to have reflective total nasal symptom scores (rTNSS) of 4 or higher during 4 of the last 7 days before the randomization visit and to have demonstrated the ability to adhere to the use of the daily electronic diary. Patients were also required to have protocol-specific baseline findings from the ophthalmic examinations that included the following measurements: the patient's pupils must have been maximally dilated ($\geq$6 mm) before LOCS III grading; LOCS III grades of 3.0 or less for NO, 3.0 or less for NC, 2.0 or less for C, and 0.5 or less for PSO; intraocular pressure (IOP) of 20 mm Hg or less; funduscopic horizontal cup-to-disc ratio (expressed as a percentage) of 66% or less; and visual acuity best-corrected distance vision of 0.18 or less on the logarithm of the minimum angle of resolution (logMAR) scale using the Early Treatment Diabetic Retinopathy Study charts. IOP was measured using Goldmann applanation tonometry and was measured at the same time each day.

Patients were instructed to avoid any antiallergy medications during the study, with the exception of 10-mg loratadine tablets (not to exceed one tablet each day), which were allowed during the treatment period only as rescue medication. Oral decongestants (phenylephrine or pseudoephedrine) were permitted for use for no more than 3 consecutive days at any one time during the treatment period; use of these decongestants was not permitted in the 2 days before an ophthalmic examination.

Ophthalmic Examination Discontinuation Criteria

Patients were withdrawn from the study if they met any of the following criteria for either eye: increase of greater than 10 mm Hg from baseline on IOP, increase of 2.0 or more from baseline in any of the LOCS III grades (PSO, C, NC, NO), increase of 0.3 or more on logMAR scale, or cataract surgery performed during the study.

Study Assessments

Safety was assessed by ophthalmic examinations (at weeks 12, 24, 36, 52, 64, 76, 88, and 104), vital signs, nasal examinations, monitoring of adverse events, and clinical laboratory assessments. The primary ocular safety measures were time to first occurrence of an event for LOCS III PSO and time to first occurrence of an event for IOP. Multiple measures of treatment adherence were used in the study, including patients responding to a study medication question on the e-diary, video-phone observations, bottle weights, and efficacy based on daily rTNSS.

Statistical Analyses

The sample size for this phase 4 study was based on the study design (eg, study duration and study population); the feasibility of conducting a postmarketing, 2-year, long-term safety study; and consultations with the FDA. All analyses and summaries were based on the intent-to-treat population (randomized and received at least one dose of study medication). The primary analysis for PSO was the survival analysis of time to first occurrence of an event for PSO, using proportional hazards model adjusting for age and baseline value (SAS statistical software, version 9.1; SAS Institute Inc, Cary, North Carolina). The date of an event for PSO was defined as the date of ophthalmic examination for which an increase of 0.3 or more from baseline in PSO was observed for the first time after randomization during the study. Time to first occurrence of an event for PSO was measured from the date of randomization (ie, treatment initiation) to the date of first occurrence of an event or the date of treatment termination. The primary analysis for IOP was performed using the survival analysis, in the same manner as for PSO. An event for IOP was defined as an increase of 7 mm Hg or more from baseline in IOP.

Results

Patient Demographics and Baseline Characteristics

The intent-to-treat population included 548 patients (FFNS, 367; placebo, 181). A total of 303 patients (55%) completed the 104-week study treatment. The incidence of early withdrawal was 46% in the FFNS group and 43% in the placebo group. The most common reasons for premature withdrawal were protocol deviation and withdrawal of consent. The disposition of patients throughout the study is shown in Figure 1. Most patients were female, not

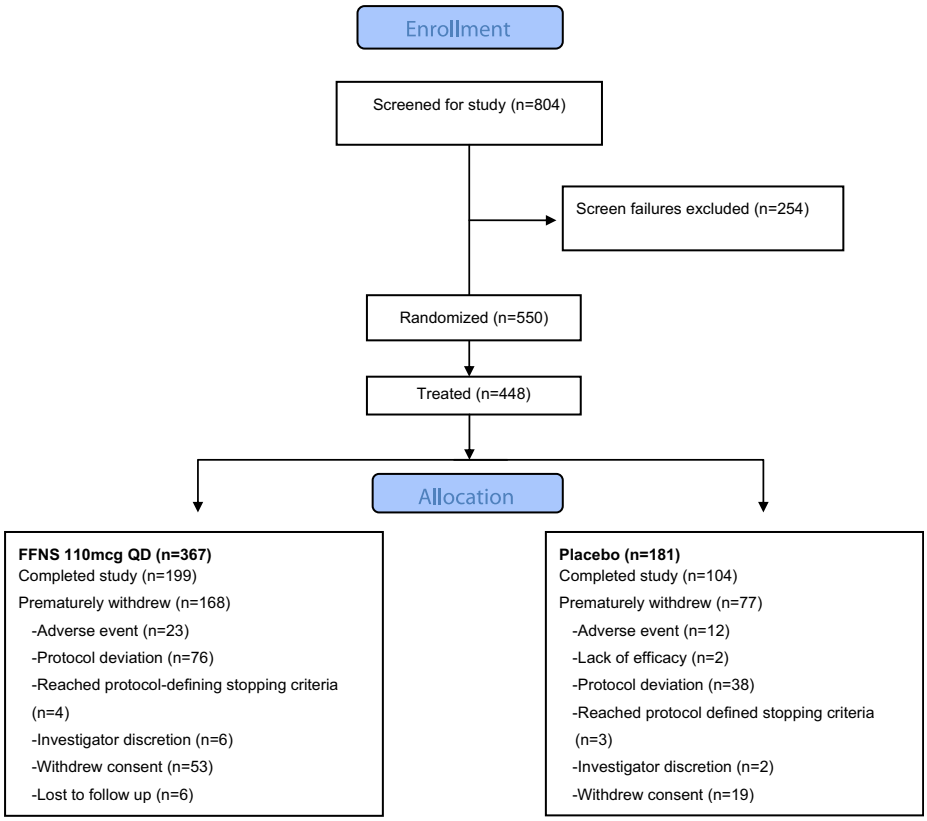

Figure 1. Flow and disposition of patients throughout study. Abbreviation: FFNS, fluticasone furoate nasal spray.

Hispanic/Latino, or white. Baseline mean rTNSSs were 8.23 and 8.27 (evaluated using a 12-point scale) in the FFNS and placebo groups, respectively, indicating that patients in both treatment groups had PAR of moderate severity (Table 1). Mean exposure to treatment was 523.9 days in the FFNS group and 542.0 days in the placebo group. Median exposure was 725.0 days in both groups.

Primary Ophthalmic End Points

Time to First Occurrence of an Event for LOCS III PSO

The difference between the treatment groups for time to first occurrence of an event for LOCS III PSO based on the survival analysis was not statistically significant ($P = .40$) (Table 2). Fourteen patients (4%) in the FFNS group and 4 patients (2%) in the placebo group had an event for LOCS III PSO. Of the 14 patients in the FFNS group who had a LOCS III PSO event, 10 patients completed the study. One FFNS patient had an event for PSO at weeks 36 and 64; these increases were observed during the remainder of the treatment period. Another FFNS patient had an event for PSO at weeks 36, 64, 76, and 88; at weeks 52 and 104 the *P* values were equal to baseline. Two additional FFNS patients had an event for PSO on 2 occasions during the treatment period; for both patients, values were equal to baseline or +0.2 of the baseline value on subsequent visit(s), including end of treatment or early withdrawal. In addition, 2 FFNS patients experienced an event for PSO at the end of their study treatment with no subsequent measurements. The remaining 8 patients in the FFNS group who had an event for PSO experienced the event on one occasion only after which their values were within ±0.2 of baseline value for the remaining on-treatment assessments.

One patient in the placebo group had an event for PSO at weeks 36, 52, 76, and 88. Another patient had an event for PSO on 2 occasions, weeks 52 and 64, in both eyes; the values were equal to baseline on subsequent visits. The 2 remaining patients in the placebo group who had an event for PSO experienced this event on one occasion only.

Table 1
Patient demographics and baseline data[a]

Variable	FFNS, 110 μg daily (n = 367)	Placebo (n = 181)
Age, mean (range), y	37.0 (12-70)	38.0 (12-65)
Age group, y		
12 to <18	45 (12)	21 (12)
18 to <40	149 (41)	75 (41)
40 to <50	105 (29)	50 (28)
50 to <60	53 (14)	27 (15)
≥60	15 (4)	8 (4)
Female patients	255 (69)	116 (64)
Ethnicity		
Not Hispanic/Latino	328 (89)	166 (92)
Hispanic/Latino	39 (11)	15 (8)
Race		
White	303 (83)	146 (81)
Black	50 (14)	29 (16)
Other	14 (4)	6 (3)
Duration of PAR, y		
≥2 to <5	20 (5)	9 (5)
≥5 to <10	57 (16)	31 (17)
≥10	290 (79)	141 (78)
Nasal symptom score,[b] mean (SE)		
rTNSS	8.23 (2.389)	8.37 (2.347)
Rhinorrhea	2.08 (0.686)	2.14 (0.648)
Nasal congestion	2.35 (0.603)	2.35 (0.641)
Nasal itching	1.95 (0.787)	2.04 (0.718)
Sneezing	1.86 (0.768)	1.85 (0.781)

Abbreviations: FFNS, fluticasone furoate nasal spray; PAR, perennial allergic rhinitis; rTNSS, reflective total nasal symptom score.
[a]Data are presented as number (percentage) of patients unless otherwise indicated.
[b]Maximum score is 12.

Table 2
Analysis of time to first occurrence of LOCS III PSO (intent-to-treat population)

Time to First PSO	FFNS, 110 μg daily (n = 367)	Placebo (n = 181)
Postbaseline ophthalmic data, No.	344	168
Censored patients, No. (%)	353 (96)	177 (98)
Uncensored patients (events), No. (%)	14 (4)	4 (2)
Cumulative percentage with event[a]		
Week 12	0.88	0.60
Week 24	1.84	1.24
Week 36	2.56	1.93
Week 52	3.72	2.68
Week 64	3.72	2.68
Week 76	3.72	2.68
Week 88	4.59	2.68
Week 104	5.09	2.68
P value vs placebo[b]	.40	

Abbreviations: FFNS, fluticasone furoate nasal spray; LOCS III, Lens Opacities Classification System, Version III; PSO, posterior subcapsular opacity.
[a]Kaplan-Meier estimates based on the LIFETEST table.
[b]From the Wald χ^2 test based on a proportional hazards model adjusting for age and baseline value.

Time to First Occurrence of an Event for IOP

On the basis of survival analysis, the difference between the treatment groups for time to first occurrence of an IOP event was not statistically significant ($P = .34$) (Table 3). Seven patients (2%) in the FFNS group and 1 patient (<1%) in the placebo group had an event for IOP. Of the 7 patients in the FFNS group who had an IOP event, all but 1 patient completed the study. One FFNS patient had a maximum increase in IOP from baseline of 7 mm Hg (from 10 to 17 mm Hg) on 2 occasions (weeks 76 and 88). This patient's IOP at week 104 was 16 mm Hg. The remaining 6 FFNS patients who had an IOP event during the treatment period experienced the IOP event on one occasion only, including 2 patients with an IOP event at week 104. The placebo patient who experienced an IOP event had an increase in IOP from baseline of 8 mm Hg on one occasion (week 76) in both eyes.

Secondary Ophthalmic End Points

Change From Baseline in LOCS III PSO

There were no changes or very small changes in LOCS III PSO from baseline throughout the study duration. The findings were similar in both treatment groups by visit during the study (mean change from baseline for both eyes ranged from −0.01 to 0.01 for FFNS and 0.00 to 0.01 for placebo). The maximum increase in LOCS III PSO during the 2-year treatment period was 1.0 in the FFNS group and 0.9 in the placebo group; none met the early withdrawal criteria of increase in LOCS III PSO of 2.0 or higher in either eye. At weeks 52 and 104, most patients (>95%) in both treatment groups had LOCS III PSO values that were within ±0.1 of baseline for each eye.

Table 3
Analysis of time to first occurrence of IOP event (intent-to-treat population)

Time to First IOP Event	FFNS, 110 μg daily (n = 367)	Placebo (n = 181)
Postbaseline ophthalmic data, No.	344	168
Censored patients, No. (%)	360 (98)	180 (>99)
Uncensored patients (events), No. (%)	7 (2)	1 (<1)
Cumulative percentage with event[a]		
Week 12	0.00	0.00
Week 24	0.32	0.00
Week 36	0.32	0.00
Week 52	0.71	0.00
Week 64	1.12	0.00
Week 76	1.98	0.00
Week 88	1.98	0.84
Week 104	2.96	0.84
P value vs placebo[b]	.34	

Abbreviations: FFNS, fluticasone furoate nasal spray; IOP, intraocular pressure.
[a]Kaplan-Meier estimates based on the LIFETEST table.
[b]From the Wald χ^2 test based on a proportional hazards model adjusting for age and baseline value.

Change From Baseline in LOCS III C, NO, and NC

Changes from baseline in LOCS III C, NO, and NC were small and similar in both treatment groups during the entire treatment period (mean change from baseline for both eyes ranged from −0.01 to 0.13 for FFNS and 0.00 to 0.24 for placebo).

Change From Baseline in IOP

The change from baseline in IOP during the visits was small and similar in both treatment groups. Mean change from baseline for both eyes ranged from −0.9 to −0.3 for FFNS and −1.0 to −0.3 for placebo. The maximum increase in IOP during the 2-year treatment period was 8 mm Hg (one patient in each treatment group). The IOP returned to within 2 mm Hg from baseline measurements for both of these 2 patients at week 104. At weeks 52 and 104, most patients (>95%) had IOP values of within ±5 mm Hg of the baseline value. In more than 99% of the data, the difference between 2 eyes for each patient was within normal variability. There were 2 patients who had deviations of 6 mm Hg between eyes at one study visit, yet the IOP remained within 1 mm Hg of the baseline value and neither patient had an event during the study.

Change From Baseline in logMAR Visual Acuity

At weeks 52 and 104, more than 70% of patients had logMAR visual acuity values within ±0.1 of baseline for each eye in both treatment groups. At week 52, no patient had changes in baseline of 0.3 or higher in logMAR visual acuity values in either eye. At week 104, 3 patients (2 in the FFNS group and 1 in the placebo group) had changes from baseline of 0.3 or higher in logMAR visual acuity. None of these patients had an event in LOCS III PSO or IOP.

Change From Baseline in Horizontal Cup-to-Disc Ratio

Very small mean changes or no change from baseline were observed in horizontal cup-to-disc ratio in either treatment group (mean change from baseline range for both eyes was 0.0 to 0.7 for FFNS and 0.0 for placebo).

Other Safety Measures

Patients Who Met Ophthalmic Examination Early Withdrawal Criteria

Fifteen patients met ophthalmic examination early withdrawal criteria (10 patients [3%] in the FFNS group and 5 [3%] in the placebo group). Of these, 7 patients (4 in the FFNS group and 3 in the placebo group) were identified and withdrawn for an ophthalmic-related adverse event. There were no events of LOCS III PSO or IOP that led to early withdrawal.

Adverse Events

Adverse events were reported for 82% of the patients in each treatment group. The most common adverse event was epistaxis (FFNS, 34%; placebo, 19%). Nasal ulcer and nasal septum ulceration adverse events were reported in a higher proportion of patients in the FFNS group (8% and 7%, respectively) compared with the placebo group (2% and 3%, respectively).

The overall incidence of adverse events considered to be related to study medication by the investigator was 34% in the FFNS group and 23% in the placebo group. The most common drug-related adverse event reported was epistaxis (FFNS, 28%; placebo, 14%). The other commonly reported drug-related adverse events were nasal ulcer (FFNS, 7%; placebo, 1%) and nasal septum ulceration (FFNS, 5%; placebo, 3%) followed by nasal discomfort (FFNS, 3%;

placebo, 2%). The remaining drug-related adverse events occurred in less than 1% of patients across the treatment groups. One patient in the placebo group had a nasal septal perforation that was considered to be drug related by the investigator.

Adverse events that led to early withdrawal were reported in 23 patients (6%) in the FFNS group and 12 patients (7%) in the placebo group. Nonfatal serious adverse events (none thought to be drug related) were reported in 12 patients (3%) in the FFNS group and 7 (4%) in the placebo group. There were no cataract- or glaucoma-related adverse events observed during the study.

Clinical Laboratory Tests, Vital Signs, and Nasal Examinations

No notable changes were found from baseline in clinical laboratory variables and vital signs in either treatment group. Most patients (≥87%) had no changes from baseline in mucosal bleeding, ulcers turbinates or septum, and polyposis turbinates or septum throughout the study. The proportion of patients who had worsening in mucosal bleeding and ulcerated turbinates was higher in the FFNS group than in the placebo group.

Adherence to Treatment

Mean treatment adherence from weeks 1 to 104 based on the patient diary and video-phone observations was high (93% and 88%, respectively). Adherence based on nasal device weight also supported patient adherence because mean daily use of nasal spray was similar between the treatment groups. The efficacy data were used as a measure for treatment adherence. At baseline, the mean daily rTNSS was similar for both treatment groups (FFNS, 8.2; placebo, 8.4). The mean difference from baseline (FFNS minus placebo) was greater for the FFNS group compared with the placebo group throughout the study (Fig 2). The least squares mean difference between the 2 treatments was −0.774 for weeks 1 to 4, greater than 1.0 from weeks 5 to 8 onward, and 1.153 for the entire treatment period (95% confidence interval, −1.59 to −0.72).

Discussion

The results from this study demonstrated that continuous treatment with FFNS for 2 years in patients with PAR did not adversely affect ocular safety as measured by monitoring of lens opacification (with LOCS III), IOP, visual acuity, and funduscopic horizontal cup-to-disc ratio. The events of PSO and IOP were not accompanied by evidence of clinical disease, and there were no cataract- or glaucoma-related adverse events during the study.

No significant difference was found in the time to first event for PSO and IOP between the FFNS and placebo groups. However, the events for PSO and IOP were more frequent in the FFNS group compared with the placebo group. There were no changes, or very small changes, in LOCS III PSO from baseline throughout the study. The maximum increases in LOCS III PSO during the 2-year treatment period were 1.0 in the FFNS group and 0.9 in the placebo group, confirming that there were no events (≥2.0 increase in PSO) that required early withdrawal of patients. Of significance is the finding that more than 95% of patients in both treatment groups had 1 and 2 year LOCS III PSO values that were within ±0.1 of baseline. These data indicate the lack of any adverse effect of FFNS on the status of the posterior subcapsular region of the lens. Many patients had increases in LOCS III PSO of 0.3 or greater that were not sustained (absent or ≤0.3 at later visits). Such increases were possibly due to methodologic noise and not a true biologic development because cataract progression (age related and drug related) is almost always unidirectional (it only gets worse); retrogression of the cataract severity is biologically implausible.[7] The choice of the LOCS III method of classifying lens opacification was reasonable for a study in which there was a need to document newly appearing opacification and acceleration of the naturally slow progression of age-related cataract formation. LOCS II and III have been used in many similar studies in the past 2 decades.[7–9]

Changes from baseline in IOP throughout the study were small. The maximum increase in IOP was 8 mm Hg in either group. An IOP between 10 and 21 mm Hg is generally considered within normal limits; however, during a 24-hour period it can vary by 5 mm Hg because of normal diurnal variation.[10] IOP events of an increase of 7 mm Hg or greater in both treatment groups were transient and, therefore, of uncertain clinical significance. As with events for PSO, a relationship to study treatment for IOP events seems unlikely because the patients' exposure increased, yet the ocular findings often did not persist.

The clinical implications of these data regarding patient care are unknown. Current recommendations for patients using intranasal corticosteroids warn that patients with a change in vision or with a history of increased IOP, glaucoma, or cataracts should be monitored closely.

The strengths of this study included the following: (1) a well-defined and well-balanced population of treated and placebo patients; (2) a relatively long period of observation with patients manifesting excellent adherence to drug use schedules; (3) balanced dropout rates; (4) a validated and appropriate system for

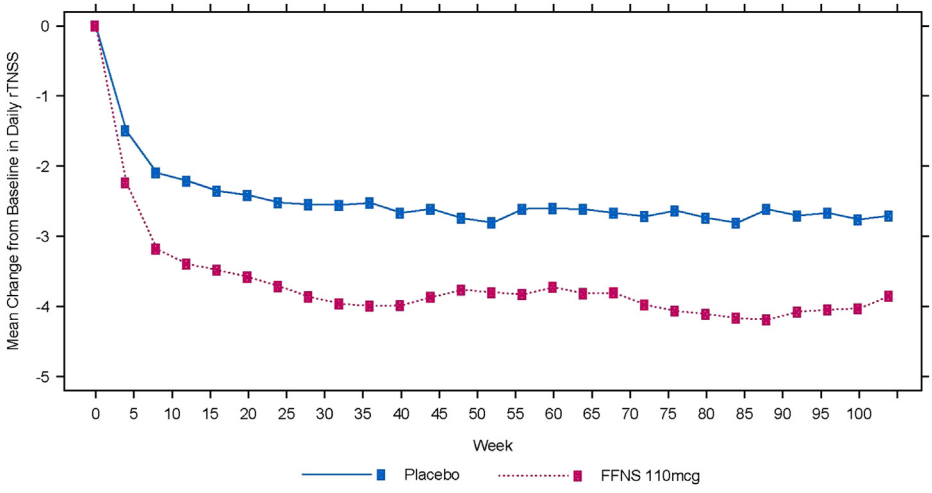

Figure 2. Mean change from baseline in daily reflective total nasal symptom scores (rTNSSs) (intent-to-treat population). Abbreviation: FFNS, fluticasone furoate nasal spray.

classifying changes in the lens (LOCS III) used by physicians who were uniformly trained, certified, and periodically recertified in the use of the LOCS III system; (5) rigorous standardization of the examination and lens classification procedures; and (6) confirmation of the validity of the LOCS III system in detecting the expected age-related increases in NO, NC, C, and PSO.

In conclusion, survival analyses conducted after 2 years of treatment in patients with PAR did not reveal significant differences between FFNS and placebo in time to occurrence of ocular events for PSOs and increased IOP. The data neither support nor negate current recommendations for regular ophthalmic monitoring in patients treated with intranasal corticosteroids.

Acknowledgments

The authors wish to acknowledge the following individuals for their contributions and critical review during the development of the manuscript on behalf of GlaxoSmithKline: Kim Poinsett-Holmes, PharmD, of Poinsett Publications Inc for medical writing and editorial assistance; Laura Sutton, PharmD (GlaxoSmithKline), for editorial assistance; and the study investigators and participants.

References

[1] Blaiss MS. Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc*. 2011;32:413–418.
[2] Rosenblut A, Bardin PG, Muller B, et al. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy*. 2007;62:1071–1077.
[3] Veramyst® (fluticasone furoate) Nasal Spray [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; August 2011.
[4] Davison JA, Chylack LT. Clinical application of the lens opacities classification system III in the performance of phacoemulsification. *J Cataract Refract Surg*. 2003;29:138–145.
[5] Benčić G, Zorić-Geber M, Šarić D, Čorak M, Mandić Z. Clinical importance of the lens opacities classification system III (LOCS III) in phacoemulsification. *Coll Antropol*. 2005;29(suppl 1):91–94.
[6] Chylack LT Jr, Wolfe JK, Singer DM, et al. The Longitudinal Study of Cataract Study Group. The Lens Opacities Classification System III. *Arch Ophthalmol*. 1993;111:831–836.
[7] Leske MC, Wu SY, Nemesure B, Li X, Hennis A, Connell AM. Incidence and progression of lens opacities in the Barbados Eye Studies. *Ophthalmology*. 2000;107:1267–1273.
[8] Lim LS, Husain R, Gazzard G, Seah SK, Aung T. Cataract progression after prophylactic laser peripheral iridotomy: potential implications for the prevention of glaucoma blindness. *Ophthalmology*. 2005;112:1355–1359.
[9] Husain R, Tong L, Fong A, et al. Prevalence of cataract in rural Indonesia. *Ophthalmology*. 2005;112:1255–1262.
[10] Bross-Soriano D, Hanenberg-Milver C, Schimelmitz-Idi J, Arrieta-Gomez JR, Astorga del Toro R, Bravo-Escobar G. Effects of three nasal topical steroids in the intraocular pressure compartment. *Otolaryngol Head Neck Surg*. 2004;130:187–191.