Original articles

Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily

Paul H. Ratner, MD,[a] Barry R. Paull, MD,[b] Steven R. Findlay, MD,[c] Frank Hampel, Jr., MD,[d] Bruce Martin, DO,[e] Kenneth M. Kral, MS,[f] Paula R. Rogenes, PhD[f]

San Antonio,[a, e] Bryan,[b] Austin,[c] and New Braunfels,[d] Texas, and Research Triangle Park, N.C.[f]

Fluticasone propionate was compared with beclomethasone dipropionate for the treatment of allergic rhinitis in a multicenter, double-blind, randomized, placebo-controlled study during the mountain cedar (Juniperus ashei) *pollination season in central Texas. Adults (n = 313) with moderate to severe symptoms were treated with fluticasone propionate aqueous nasal spray 200 μg once a day or beclomethasone dipropionate aqueous nasal spray 168 μg twice a day or placebo for 2 weeks. Fluticasone propionate administered once daily and beclomethasone dipropionate administered twice daily were equally effective as assessed by clinician- and patient-rated scores for nasal obstruction, rhinorrhea, sneezing, and nasal itching throughout the treatment and follow-up periods. Both regimens were more effective than placebo. Adverse events were related to topical administration and were similar in frequency and nature in all three treatment groups. Fluticasone propionate and beclomethasone dipropionate displayed a similar safety profile that did not differ from placebo. We conclude that fluticasone propionate aqueous nasal spray administered as 200 μg once daily in the morning is as safe and effective as beclomethasone dipropionate aqueous nasal spray administered as 168 μg twice daily for seasonal allergic rhinitis. (J ALLERGY CLIN IMMUNOL 1992;90:285-91.)*

Key words: *Fluticasone propionate, beclomethasone dipropionate, intranasal corticosteroids, seasonal allergic rhinitis, compliance*

Allergic rhinitis, characterized by nasal obstruction, rhinorrhea, nasal itching, and sneezing, is a common disorder that contributes to absenteeism from school and work and diminished quality of life.[1] Inhaled airborne allergens (including tree, grass, and weed pollens) deposited on the nasal mucosa elicit an immunologic response, resulting in mast cell release of inflammatory mediators that produce the symptoms of rhinitis.[2]

Since complete avoidance of allergens is difficult in most circumstances, pharmacotherapeutic agents provide symptomatic relief. Intranasal corticosteroid preparations, such as beclomethasone dipropionate and flunisolide, are efficacious in the management of allergic rhinitis.[3] These preparations exert local antiinflammatory activity resulting in control of symptoms and have minimal potential for systemic effects, such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis.[3, 4]

Fluticasone propionate possesses twice the antiin-

Abbreviations used

FP ANS:	Fluticasone propionate aqueous nasal spray
BDP ANS:	Beclomethasone dipropionate aqueous nasal spray
HPA:	Hypothalamic-pituitary-adrenal
q.d.:	Once daily
b.i.d.:	Twice daily
ECG:	Electrocardiogram

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Reprint requests: Paul H. Ratner, MD, Sylvana Research, 7711 Louis Pasteur, Suite 406, San Antonio, TX 78229.
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flammatory potency of beclomethasone dipropionate, as measured by vasoconstrictor assay, but has negligible systemic bioavailability because of first-pass metabolism of the swallowed portion of the dose to an inactive 17β-carboxylic acid.[5] Fluticasone propionate aqueous nasal spray has proved effective for relieving moderate to severe symptoms of rhinitis in controlled clinical trials when administered once daily in the morning and has been well-tolerated topically with no effect on the HPA axis.[6-9]

The mountain cedar *(Juniperus ashei)* pollination season in central Texas occurs between the middle of December and early February. Mountain cedar is the only pollen present in significant amounts during this time,[10] and it induces moderate to severe symptoms of allergic rhinitis in individuals who may not have any other sensitivities.[11] Mountain cedar pollen is prolific, potent, and confined to a well-defined season in a discreet geographic location, thus providing an excellent opportunity for studying the efficacy of fluticasone propionate in allergic rhinitis caused by this specific airborne allergen.

Previous studies have shown that beclomethasone dipropionate and flunisolide nasal sprays are effective when administered two to three times daily.[12, 13] This placebo-controlled study compared the efficacy and safety of fluticasone propionate administered once daily in the morning with beclomethasone dipropionate administered twice daily in adults with allergic rhinitis during the mountain cedar season.

MATERIAL AND METHODS

Patients

Adults with moderate to severe symptoms of seasonal allergic rhinitis during the mountain cedar season in central Texas were candidates for this multicenter, double-blind, randomized, parallel-group study. For inclusion, at least a 2-year history of seasonal allergic rhinitis during the mountain cedar season and a positive (2+) skin test to mountain cedar was required. Women of nonchildbearing potential were eligible. Before entry into the study, normal adrenal function (morning plasma cortisol concentration of ≥7 μg/dl) had to be demonstrated. Patients who had received oral, inhaled, or intranasal steroids within 1 month or intranasal cromolyn within 2 weeks of initiation of the study were excluded. The study was approved by an institutional review board for each of the five centers, and written informed consent was obtained from all patients.

Methods

Screening included medical history, general physical examination, routine clinical laboratory tests, nasal examination, and nasal symptom assessment. After screening, nasal symptoms of rhinitis were recorded by patients using a visual analog scale from 0 (no symptoms) to 100 (severe symptoms) on daily diary cards during a 4- to 14-day run-in period. To qualify for enrollment, the total score of four nasal symptoms (obstruction, rhinorrhea, sneezing, and itching) had to be ≥200 (out of 400 possible points) on at least 4 of the 7 days preceding the start of treatment. Patients were not aware of this requirement.

After the run-in period, a 2-week treatment regimen was randomly assigned as follows: fluticasone propionate aqueous nasal spray 200 μg once daily (two sprays of 50 μg/spray in each nostril in the morning and two sprays of placebo vehicle in each nostril in the evening); beclomethasone dipropionate aqueous nasal spray 168 μg twice daily (two sprays of 42 μg/spray in each nostril in the morning and evening); or placebo vehicle spray twice daily (two sprays in each nostril in the morning and evening). Patients were provided with two bottles, one labeled for morning use (8 AM) and the other for evening use (8 PM). Active and placebo formulations were indistinguishable in appearance, smell, and taste. In addition, 4 mg tablets of chlorpheniramine maleate were provided as rescue medication for intolerable symptoms. Use of rescue medication was recorded on the daily diary card. No other medication that might affect the course of the rhinitis was allowed during the course of the study.

A nasal examination was conducted on days 1, 8, and 15 of the treatment period and on day 22 of the posttreatment follow-up period. Severity of individual nasal symptoms was scored by clinicians at each visit and by patients at the end of each day on visual analog scales like those described herein. Patients also rated nasal obstruction on awakening before their morning dose of study drug. At the end of the study the clinician assessed the overall effectiveness of treatment on a 7-point scale: significant improvement, moderate improvement, mild improvement, no change, mildly worse, moderately worse, or significantly worse.

At the screening visit and after 2 weeks of treatment, morning plasma cortisol concentrations were measured to evaluate HPA axis effects, and physical examinations, clinical laboratory tests, and 12-lead ECGs were performed. Nasal and oropharyngeal examinations were conducted at each visit to screen for possible candidiasis. At each study visit patients were asked whether they had experienced any problems (adverse events).

Statistical methods

Demographic variables were analyzed for overall treatment effect with use of the F-test and the Cochran-Mantel-Haenszel test.[14] The Cochran-Mantel-Haenszel test was performed on treatment pairs for clinician-rated overall assessment and use of rescue medication. The van Elteren statistic[15] was performed on treatment pairs of clinician-rated nasal symptom scores. F-tests were performed on patient-rated nasal symptom scores and plasma cortisol concentrations. The Fisher's Exact Test was used to detect statistically significant differences in numbers of patients per group reporting adverse events. All analyses except those for adverse events were adjusted for investigator effect. All testing was two-sided, with statistical significance defined as $p \leq 0.05$.

RESULTS

No significant differences were observed in demographic characteristics among the 313 patients in

TABLE I. Demographics of patient population

Characteristic	FP ANS 200 μg q.d.	BDP ANS 168 μg b.i.d.	Placebo
No. of patients	106	103	104
Age, years			
Mean	35.0	38.5	37.8
Range	18-65	18-66	19-72
Sex, n (%)			
Male	63 (59)	54 (52)	55 (53)
Female	43 (41)	49 (48)	49 (47)
Weight, kg			
Mean	74.9	77.5	73.0
Range	47-115	46-136	42-121
Medical history, n (%)			
Asthma	27 (25)	24 (23)	20 (19)
Perennial rhinitis	72 (68)	53 (51)	58 (56)
Seasonal rhinitis*	59 (56)	61 (59)	63 (61)

*Patients with allergic rhinitis caused by seasonal allergens other than mountain cedar.

the three treatment groups (Table I). Four patients discontinued the study. Two patients in the placebo group withdrew because of adverse events (insomnia and objectionable scent of study drug). One patient receiving active drug withdrew for personal reasons, and another was withdrawn because of the use of systemic corticosteroids.

Clinician-rated nasal symptom scores

Mean total nasal symptom scores (the sum of obstruction, rhinorrhea, sneezing, and itching) were similar among the three treatment groups on day 1 and indicated that these patients had moderate to severe symptoms of rhinitis (Fig. 1, *A*). Symptom scores improved in all groups over the 2-week treatment period. Significant improvement in clinician-rated mean total nasal symptom scores occurred by the first visit after 7 days of treatment in the patients receiving fluticasone propionate once daily or beclomethasone dipropionate twice daily compared with placebo ($p < 0.001$), and scores remained significantly lower throughout the treatment period. Nasal symptom scores increased during the week after cessation of active treatment; however, the scores remained significantly lower than those of patients who had received placebo. In patients receiving fluticasone propionate or beclomethasone dipropionate, clinician-rated scores for each individual nasal symptom were significantly improved throughout the treatment period, with the exception of nasal itching on day 8 ($p = 0.058$) and nasal obstruction on day 15 ($p = 0.088$) in the fluticasone .propionate group (Table II). No statistically significant differences were observed in any clinician-rated nasal symptom score at any time between patients receiving fluticasone propionate or beclomethasone dipropionate.

Patient-rated nasal symptom scores

Comparisons of Figs. 1, *A* and *B* indicate that total nasal symptom scores were evaluated similarly by patients and clinicians. Mean total nasal symptom scores improved by day 2 of treatment in patients receiving fluticasone propionate once daily and by day 1 of treatment in patients receiving beclomethasone dipropionate twice daily compared with placebo ($p < 0.01$), and scores remained lower throughout the treatment period ($p < 0.01$). The magnitude of improvement in either the fluticasone propionate or beclomethasone dipropionate groups was almost twice as great as the placebo group. Although patient-rated total nasal symptom scores increased after discontinuation of active treatment, they remained significantly lower than those of placebo-treated patients. Scores for individual nasal symptoms of obstruction, rhinorrhea, sneezing, and itching were significantly reduced in patients receiving fluticasone propionate or beclomethasone dipropionate ($p < 0.05$, Table II). No significant differences occurred between patients receiving fluticasone propionate or beclomethasone dipropionate for any patient-rated nasal symptom score at any time during the course of this study.

Nasal obstruction on awakening, when symptoms of rhinitis are typically worst,[16] was less in the fluticasone propionate and beclomethasone dipropionate groups on day 2 of treatment ($p < 0.05$, Fig. 2). This improvement was sustained throughout the treatment and follow-up periods ($p < 0.01$, Fig. 2).

Clinician-rated overall assessment

Overall response to treatment was significantly better in patients receiving fluticasone propionate or beclomethasone dipropionate compared with patients receiving placebo ($p < 0.001$, Fig. 3). Fluticasone pro-

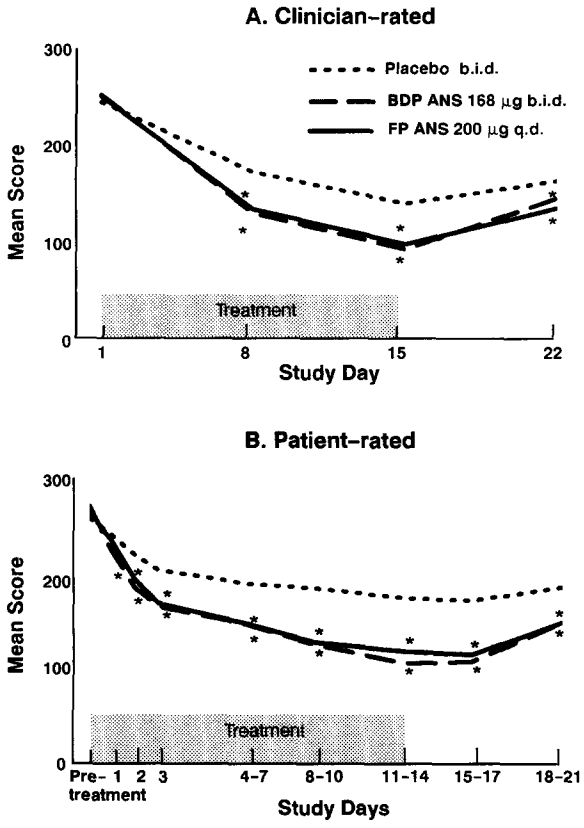

FIG. 1. A, Clinician-rated mean total symptom scores at pretreatment and at each visit. Standard errors ranged from 6.0 to 8.8. **B,** Patient-rated mean total symptom scores of 3 to 4 days summarized from daily diaries. Standard errors ranged from 5.1 to 9.4. *P* values based on mean scores for pretreatment and on differences from pretreatment for subsequent days. $*p < 0.05$ versus placebo.

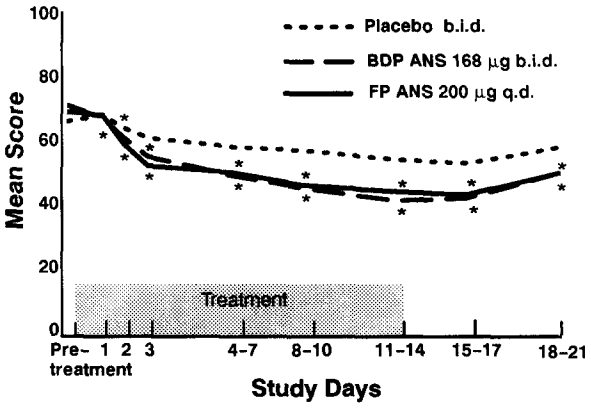

FIG. 2. Patient-rated nasal obstruction on awakening before morning dose of study drug. Standard errors ranged from 1.7 to 2.7. *P* values based on mean scores for pretreatment and on differences from pretreatment for subsequent days. $*p < 0.05$ versus placebo.

pionate or beclomethasone dipropionate therapy achieved significant or moderate improvement more frequently than placebo. Two patients in the placebo group only were judged to have a moderate or significant worsening of their rhinitis. Differences in overall assessment between fluticasone propionate and beclomethasone dipropionate were not statistically significant.

Use of rescue medication

Most patients used chlorpheniramine maleate during the pretreatment run-in period (Fig. 4). Rescue medication use by patients receiving fluticasone propionate once daily or beclomethasone dipropionate twice daily was significantly reduced and remained about the same in those patients receiving placebo. During the final week of treatment, 32% to 36% of the patients receiving active treatment used rescue medication compared with approximately 50% of the patients receiving placebo ($p < 0.05$). Differences between patients receiving fluticasone propionate or beclomethasone dipropionate were not statistically significant.

Safety evaluations

No significant differences were observed in the frequency of adverse events related to topical administration of drug across treatment groups (Table III). Most events were considered mild and resolved over the course of the study. More patients receiving treatment with fluticasone propionate reported episodes of epistaxis and/or blood in nasal mucus. There were no reports of candidiasis. Mean morning plasma cortisol concentrations were within the normal range and were similar in all three treatment groups before and after treatment. No clinically significant differences occurred between treatment groups for any safety variable evaluated.

DISCUSSION

This study provides good evidence that fluticasone propionate aqueous nasal spray administered once daily in the morning for 2 weeks is as effective as beclomethasone dipropionate aqueous nasal spray administered twice daily in relieving moderate to severe symptoms of seasonal allergic rhinitis. Fluticasone propionate and beclomethasone dipropionate were equally effective as judged by no statistically significant differences for any clinician- or patient-rated efficacy variable at any time during the study.

Compared with placebo, total nasal symptom scores improved after two doses of either active treatment. Significant improvement in total nasal symptom

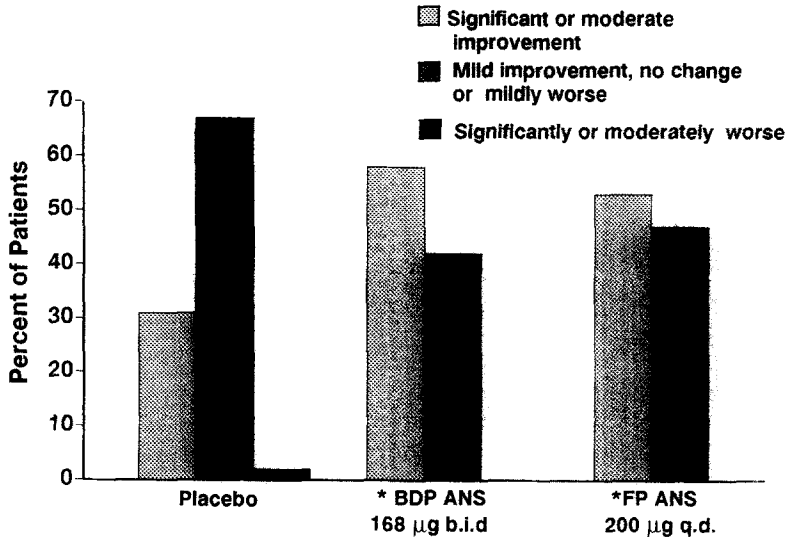

FIG. 3. Clinician-rated overall assessment of response to 2 weeks of treatment. *$p < 0.001$ versus placebo.

TABLE II. Clinician- and patient-rated mean rhinitis symptom scores after treatment with FP ANS or BDP ANS or placebo

	FP ANS 200 μg q.d.			BDP ANS 168 μg b.i.d.			Placebo		
Assessment	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Nasal obstruction									
Clinician-rated	68	45*	39	71	45*	38*	69	53	46
Patient-rated	71	43*	37*	73	42*	36*	68	54	49
Rhinorrhea									
Clinician-rated	72	38*	26*	72	37*	28*	67	49	41
Patient-rated	71	40*	33*	72	41*	31*	69	53	49
Sneezing									
Clinician-rated	49	20*	13*	50	21*	11*	46	32	21
Patient-rated	60	31*	25*	61	32*	20*	57	40	38
Nasal itching									
Clinician-rated	65	34	23*	63	30*	20*	65	43	35
Patient-rated	65	38*	30*	67	37*	26*	67	48	43

Patient-rated scores represent mean of diary card scores recorded by patients over the 4-day period preceding days 1, 8, and 15. Standard errors for clinician- and patient-rated mean rhinitis symptoms scores ranged from 1.8 to 3.0 and 1.6 to 2.8, respectively.
*$p < 0.05$ change from day 1, versus placebo.

scores was noted by patients receiving fluticasone propionate once daily at the end of day 2. Similarly, significant improvement was noted by patients receiving beclomethasone dipropionate at the end of day 1; however, these patients received an evening dose in addition to the morning dose on day 1. When onset of activity with twice-daily dosing of both drugs was recently compared, fluticasone propionate reduced every symptom of rhinitis more rapidly than beclomethasone dipropionate ($p < 0.01$).[17]

Although placebo-treated patients in the current study demonstrated improvement in symptoms of rhinitis consistent with previous observations,[18] efficacy evaluations consistently supported the superiority of fluticasone propionate over placebo. Improvement in clinician- and patient-rated nasal symptom scores and

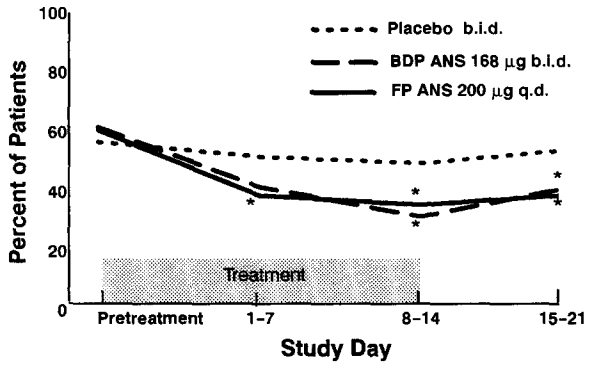

FIG. 4. Percent of patients using rescue medication before, during, and after treatment. *$p < 0.05$ versus placebo.

TABLE III. No. (%) of patients reporting drug-related adverse events

Adverse event*	FP ANS 200 μg q.d.	BDP ANS 168 μg b.i.d.	Placebo
No. of evaluable patients	106	103	104
Sore throat	2 (2%)	2 (2%)	1 (1%)
Blood in nasal mucus	6 (6%)	1 (1%)	2 (2%)
Nasal burning	5 (5%)	2 (2%)	4 (4%)
Epistaxis	3 (3%)	2 (2%)	0
Headache	0	1 (1%)	3 (3%)
Any event	19 (18%)	10 (10%)	19 (18%)

*Event listed only if reported by three or more patients across treatment groups.

better clinician-rated overall assessment confirmed that fluticasone propionate was significantly more effective than placebo in relieving moderate to severe symptoms of allergic rhinitis. In addition, fewer patients treated with fluticasone propionate used antihistamine rescue medication, which supports the therapeutic effectiveness of fluticasone propionate.

Beclomethasone dipropionate was chosen as the active comparator in this study because it has an excellent safety profile, documented clinical efficacy,[19] and has become the standard comparative agent in studies involving intranasal corticosteroid preparations.[3] Beclomethasone dipropionate is available in an aqueous nasal spray formulation which facilitated the double-blind design of the study. Fluticasone propionate aqueous nasal spray is comparable to beclomethasone dipropionate aqueous nasal spray and shares the aforementioned advantages of beclomethasone dipropionate. Beclomethasone dipropionate is approved for use two to four times daily. Since simplifying the dosage regimen promotes compliance with the prescribed regimen,[18] and given that this study has demonstrated that a once-daily regimen with fluticasone propionate is as effective as a twice-daily regimen with beclomethasone dipropionate, one would anticipate enhanced patient compliance with fluticasone propionate. Although beclomethasone dipropionate may be effective when administered once daily, this regimen was not evaluated in the present study.

The immunologic response in atopic individuals after allergen exposure consists of an early, late, and rechallenge phase characterized by inflammation and a hypersensitive nasal mucosa. This study was not designed to assess the mechanism by which fluticasone propionate acts to relieve symptoms of rhinitis. However, topical administration of intranasal corticosteroid preparations significantly reduces the release of histamine and inflammatory mediators, in addition to improving the symptoms of rhinitis.[20] The effectiveness of fluticasone propionate on established symptoms has been demonstrated in this study; previous trials have also determined that fluticasone propionate can be used as a prophylactic agent before the beginning of an allergy season.[7, 21, 22]

Fluticasone propionate aqueous nasal spray in doses of 200 μg once daily was well tolerated in this study. Local drug-related adverse events are commonly associated with the administration of nasal sprays in the presence of rhinitis,[4] and in this regard fluticasone propionate was no different from beclomethasone dipropionate or placebo. These results confirm those of other placebo-controlled studies in which the tolerability of fluticasone propionate was evaluated.[6, 8, 9] In all three studies the frequency of adverse events was similar across treatment groups, including placebo, which is in agreement with the findings of our study. There was no evidence of effects on the HPA axis after 2 weeks of treatment with either fluticasone propionate or beclomethasone dipropionate in the present study. Previous studies have shown that fluticasone propionate in doses up to 800 μg daily for 2 weeks or in doses up to 1600 μg daily for 4 weeks has no effect on the HPA axis as assessed by morning plasma cortisol concentrations, response to cosyntropin stimulation, or 24-hour urinary-free cortisol excretion.[8, 9]

We conclude that fluticasone propionate aqueous nasal spray administered once daily in the morning is as safe and effective as beclomethasone dipropionate administered twice daily for the treatment of moderate to severe symptoms of seasonal allergic rhinitis. The aqueous nasal spray formulation was well tolerated by patients and the single daily dosage regimen represents a significant advance, in terms of potential for

patient compliance, for the management of seasonal allergic rhinitis.

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