

Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis

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ABSTRACT

An aerosol formulation may be preferred by some allergic rhinitis (AR) patients, to avoid the “wet feeling” and nasal runoff associated with aqueous nasal corticosteroid sprays. Beclomethasone dipropionate (BDP) hydrofluoroalkane nasal aerosol is a recently developed, nonaqueous, nonchlorofluorocarbon formulation of BDP for the treatment of AR. This study was designed to evaluate the efficacy, safety, and quality-of-life benefits of BDP nasal aerosol in subjects with seasonal AR (SAR). Eligible subjects (≥ 12 years of age) enrolled in this 2-week study were randomized to either BDP nasal aerosol at 320 $\mu\text{g/day}$ ($n = 169$) or placebo ($n = 171$). Efficacy assessments included reflective and instantaneous total nasal symptom scores (rTNSS and iTNSS, respectively), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, reflective and instantaneous total ocular symptom scores (rTOSS and iTOSS, respectively), and physician-assessed total nasal symptom score (PNSS). Safety and tolerability were also assessed. Subjects receiving BDP nasal aerosol showed a significantly greater improvement from baseline in average A.M. and P.M. rTNSS versus placebo (treatment difference, -0.91 ; 95% confidence interval, $-1.3, -0.5$; $p < 0.001$) over 2 weeks of treatment. Greater improvements in rTNSS with BDP nasal aerosol compared with placebo were evident by day 2 and were maintained throughout the treatment period. Similarly, significant improvements were seen with BDP nasal aerosol in iTNSS ($p < 0.001$) and RQLQ score ($p = 0.005$) compared with placebo. Treatment with BDP nasal aerosol also resulted in greater improvements in rTOSS ($p = 0.002$), iTOSS ($p = 0.003$), and PNSS ($p < 0.001$) relative to placebo. BDP nasal aerosol was well tolerated and the overall safety profile was similar to placebo. Results from this clinical study indicated that BDP nasal aerosol provided significant AR symptom relief and was well tolerated in patients with SAR with an overall safety profile similar to placebo. ClinicalTrials.gov identifier: NCT01024608.

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Approximately 60 million people in the United States have allergic rhinitis (AR),¹ of which an estimated 20% of cases are seasonal AR (SAR), 40% are perennial AR (PAR), and 40% are perennial with seasonal exacerbations.² Importantly, the prevalence of AR has increased during the past 30 years and recent

reports indicate that 10–30% of adults and 40% of children have this condition.¹ Furthermore, there are significant costs associated with the management of AR; in 2005, the total costs in the United States were estimated at \$11.2 billion.³

AR is a chronic inflammatory disease characterized by nasal congestion, rhinorrhea, nasal itching, sneezing, and frequent allergic conjunctivitis.⁴ Allergen avoidance, pharmacologic therapy, and immunotherapy have been used to treat the symptoms of AR.^{1,5} Among pharmacologic treatments, intranasal corticosteroids are considered to be the most effective treatment for maintenance therapy of AR because of their established superior efficacy on the entire spectrum of AR symptoms relative to other agents including leukotriene modifiers and antihistamines.^{5,6} Intranasal corticosteroids also provide significant relief from ocular symptoms of AR.⁷

Although intranasal corticosteroids are recommended as first-line therapy for AR and provide greater symptom relief than other pharmacologic agents,^{5,6} they are currently available only as aqueous formulations. However, undesirable side effects of aqueous formulations can be troublesome for some patients.⁸ Two national surveys among patients with

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AR, Allergies in America and the Nasal Allergy Survey Assessing Limitations, highlight the bothersome side effects associated with current medications for treating AR.^{9,10} The Nasal Allergy Survey Assessing Limitations reported that one-third of patients with AR named “dripping down the throat” as a moderately or extremely bothersome side effect associated with aqueous intranasal corticosteroid formulations.⁹ Thus, there is an unmet need for a nonaqueous intranasal corticosteroid formulation. Moreover, the availability of a nonaqueous (aerosol) intranasal corticosteroid formulation would increase the available treatment options for patients with AR, which could lead to improved clinical benefits due to greater adherence to therapy.⁸

Beclomethasone dipropionate (BDP) is an anti-inflammatory corticosteroid available for the treatment of asthma and AR. BDP has previously been developed for the treatment of AR in both aqueous nasal formulations (Beconase AQ [GlaxoSmithKline, Research Triangle Park, NC]¹¹ and Vancenase AQ [Schering, Kenilworth, NJ]) and nonaqueous (dry) nasal aerosol formulations as chlorofluorocarbon (CFC) metered-dose inhaler nasal aerosols (Beconase and Vancenase Pockethaler). However, all CFC-containing nasal aerosols were withdrawn from the market and are not currently available.¹² BDP hydrofluoroalkane (HFA) inhalation aerosol (QVAR [Teva Respiratory LLC, Frazer, PA]) has been approved in the United States since 2000 for the maintenance treatment of asthma in patients ≥ 5 years of age.¹³ BDP nasal aerosol, a nonaqueous, HFA-propelled, non-CFC formulation of BDP, has recently been developed for the treatment of AR.

The study reported here was conducted as part of the clinical development program for BDP nasal aerosol. The primary objective was to evaluate the efficacy of BDP nasal aerosol (320 $\mu\text{g}/\text{day}$) in adolescents and adults (≥ 12 years of age) with SAR. The safety and tolerability of BDP nasal aerosol was also evaluated.

METHODS

Study Design and Treatment

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted during the 2009–2010 mountain cedar pollen season at four centers in Texas, in accordance with the principles of the Declaration of Helsinki and approved by Copernicus Group Institutional Review Board (Durham, NC). All subjects provided written informed consent or assent, as age appropriate.

The study consisted of a 7- to 10-day placebo run-in period (from screening to randomization) followed by a 2-week treatment period. During the placebo run-in period, subjects self-administered a single-blind placebo nasal aerosol (2 actuations/nostril) once daily

(morning [A.M.]) and assessed their nasal symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing) and ocular symptoms (itching/burning eyes, tearing/watering eyes, and eye redness) twice daily (A.M. and evening [P.M.]). Each symptom was evaluated on a severity scale ranging from 0 (no signs/symptoms) to 3 (severe signs/symptoms) and reported as reflective (symptoms over the previous 12 hours) and instantaneous (symptoms at the time of evaluation) using a paper AR assessment diary. Daily treatment compliance was monitored *via* subject-completed assessment diaries. Additional treatment compliance data were obtained at various study visits *via* the integrated dose counter on the nasal actuator.

Eligible subjects were randomized 1:1 to once-daily treatment with either BDP nasal aerosol (320 $\mu\text{g}/\text{day}$, 80 $\mu\text{g}/\text{actuation}$, 2 actuations/nostril) or placebo nasal aerosol (vehicle, 2 actuations/nostril). During the 2-week treatment period, randomized subjects self-administered the assigned double-blind nasal aerosol once daily (A.M.) and assessed their nasal and ocular symptoms twice daily (A.M. and P.M.).

Subjects

Eligible subjects were ≥ 12 years of age, were in good health, and had a history of SAR for at least 2 years. Subjects had to have established skin-prick test sensitivity to mountain cedar pollen, defined as a wheal diameter at least 5 mm larger than the control, and their SAR symptoms must have been of sufficient severity to have required continuous or intermittent treatment in the past. In addition, SAR symptoms must have been expected to require treatment throughout the duration of the study.

Subjects were excluded if they had nasal polyps, clinically significant nasal tract malformations, recent nasal biopsy, nasal trauma or surgery, atrophic rhinitis, or rhinitis medicamentosa within 60 days of screening. Subjects were also excluded if they had a respiratory infection or disorder within 14 days of screening or if they developed a respiratory infection during the placebo run-in period. Subjects with active asthma requiring daily treatment with inhaled or systemic corticosteroids and/or β -agonists were also excluded, although a history of intermittent inhaled short-acting β -agonist use (≤ 3 uses/week) before screening was acceptable. Subjects were excluded if they had a known sensitivity to any corticosteroid or study medication excipient. Female subjects of childbearing potential were required to use a medically reliable method of contraception throughout the study. Rescue medications were not permitted during the study. Treatment with short-acting antihistamines was discontinued 7 days before screening and throughout the study. Likewise, treatment with long-acting antihistamines was dis-

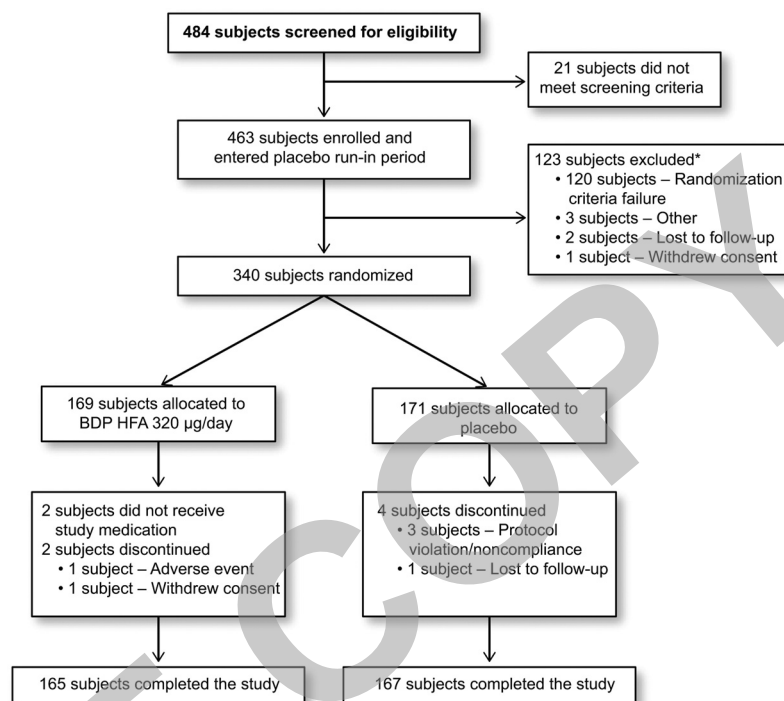


Figure 1. Subject disposition. *Subjects could be counted in more than one category. BDP HFA, beclomethasone dipropionate hydrofluoroalkane.

continued 10 days before screening and throughout the study. Intranasal corticosteroid treatment was discontinued at least 28 days before screening.

To be eligible for randomization, subjects must have achieved an average minimum reflective total nasal symptom score (rTNSS) of 6, an average minimum reflective nasal congestion score of 2, and an average minimum reflective total ocular symptom score (rTOSS) of 4 at baseline. Subjects must have also adequately completed their AR assessment diary and taken their single-blind study medication $\geq 80\%$ during the placebo run-in period.

Efficacy and Quality-of-Life Assessments

The primary efficacy end point was the change from baseline in average A.M. and P.M. subject-reported rTNSS over the 2-week treatment period. Secondary efficacy end points included average A.M. and P.M. subject-reported instantaneous TNSS (iTNSS) over the 2-week treatment period, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ¹⁴) score at week 2 for subjects with impaired quality of life at baseline (defined as RQLQ score ≥ 3.0 at randomization), and average A.M. and P.M. subject-reported rTOSS and instantaneous TOSS (iTOSS) over the 2-week treatment period. Additional end points included physician-assessed total nasal symptom score (PNSS) at week 2¹⁵ and individual symptom components of TNSS, TOSS, and PNSS.

Baseline for TNSS and TOSS was defined as the average of responses obtained during the last 4 days of the placebo run-in period. Baseline for PNSS was based

on physician assessment at the randomization visit. TNSSs and PNSSs were defined as the sum of the scores for the four individual nasal symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing), whereas TOSS was defined as the sum of the scores for the three individual ocular symptoms (itching/burning eyes, tearing/watering eyes, and eye redness). At the randomization visit and treatment visit 2 (week 2), physicians assessed the severity of each subject's nasal symptoms using the same scale as described for subject-reported nasal symptoms. The PNSS was obtained by summing the individual PNSSs based on questioning of each subject (overall feeling since their last visit) and ear, nose, and throat (ENT) examination by the investigator. The RQLQ, a disease-specific quality-of-life questionnaire designed to evaluate the functional problems (physical, emotional, and social) troublesome to subjects with AR, was completed by all English-speaking adult subjects (≥ 18 years of age) at the randomization visit (baseline) and treatment visit 2 (week 2). The RQLQ consists of 28 questions in seven domains (activities, sleep, nonnose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional).¹⁴

Safety Assessments

Physical examinations and vital signs measurements were performed at screening and the final study visit. ENT assessments were performed at each study visit. Treatment-emergent adverse events (AEs) were monitored throughout the study.

Table 1 Subject demographic and baseline characteristics (ITT population)

	BDP HFA 320 µg/day (n = 167)	Placebo (n = 171)	Total (n = 338)
Gender, n (%)			
Female	113 (67.7)	97 (56.7)	210 (62.1)
Male	54 (32.3)	74 (43.3)	128 (37.9)
Age, yr			
Mean (SD)	39.3 (13.4)	38.0 (13.3)	38.6 (13.3)
Range	12–68	13–73	12–73
Race, n (%)			
White	142 (85.0)	142 (83.0)	284 (84.0)
Black or African American	23 (13.8)	26 (15.2)	49 (14.5)
Asian	3 (1.8)	3 (1.8)	6 (1.8)
Other	1 (0.6)	2 (1.2)	3 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	52 (31.1)	49 (28.7)	101 (29.9)
Neither Hispanic nor Latino	115 (68.9)	122 (71.3)	237 (70.1)
Baseline values, mean (SD)			
Average A.M. and P.M. rTNSS	9.6 (1.51)	9.5 (1.54)	
Average A.M. rTNSS	9.6 (1.59)	9.5 (1.60)	
Average P.M. rTNSS	9.6 (1.60)	9.5 (1.65)	
Average A.M. and P.M. iTNSS	9.0 (1.74)	8.7 (1.81)	
Average A.M. iTNSS	9.0 (1.75)	8.8 (1.84)	
Average P.M. iTNSS	8.9 (1.93)	8.5 (2.01)	
Average A.M. and P.M. rTOSS	6.7 (1.50)	6.6 (1.46)	
Average A.M. and P.M. iTOSS	6.5 (1.63)	6.2 (1.64)	
PNSS	9.2 (1.85)	9.4 (1.71)	
RQLQ score*	4.3 (0.78)	4.4 (0.80)	

*RQLQ population (n = 129 [BDP HFA 320 µg/day]; n = 121 [placebo]).

A.M. = morning; BDP HFA = beclomethasone dipropionate hydrofluoroalkane; iTNSS = instantaneous total nasal symptom score; iTOSS = instantaneous total ocular symptom score; ITT = intent-to-treat; P.M. = evening; PNSS = physician-assessed total nasal symptom score; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score.

Statistical Methods

Using a standard deviation of 2.2, it was estimated that 160 subjects/treatment group would provide 90% power to detect a difference between the treatment groups of 0.8 in the change from baseline in average A.M. and P.M. subject-reported rTNSS with a two-sided α -level of 0.5. The primary end point was analyzed using a repeated-measures ANCOVA with covariate adjustment for baseline, day, treatment, and the treatment-by-day interaction using the intent-to-treat (ITT) population. A first-order autoregressive structure was used to model intrasubject correlation and in conjunction with treating subject as a random effect. Estimated treatment differences and 95% confidence intervals (CIs) for the treatment difference were calculated. Secondary nasal symptom and ocular symptom end points were analyzed in a similar fashion to the primary end point. The change from baseline in RQLQ score at week 2 was analyzed using an ANCOVA with

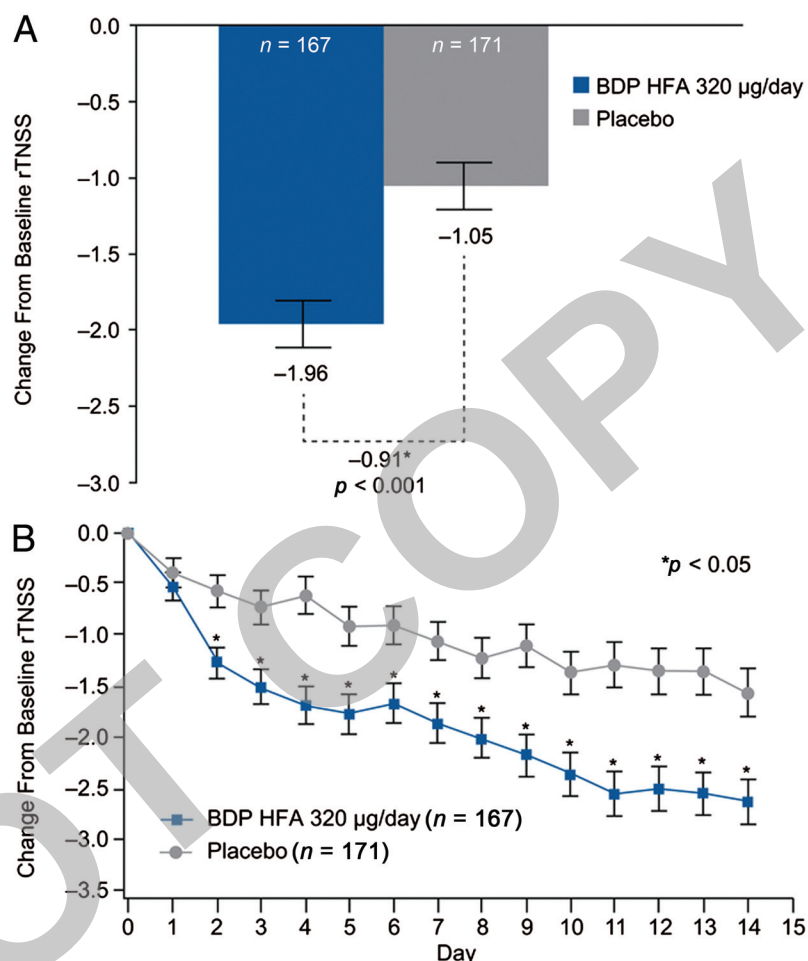
factors for treatment, baseline, and center. A fixed-sequence step-down multiplicity procedure was used to test the primary and secondary end points (in the following order: average A.M. and P.M. rTNSS, average A.M. and P.M. iTNSS, RQLQ score, and average A.M. and P.M. rTOSS) while controlling the family-wise error rate at 5%. Safety data were summarized by incidence, means, changes, and shifts depending on the measure using the safety population, which included all randomized subjects who received at least 1 dose of study medication.

RESULTS

Subject Disposition and Demographics

In total, 484 subjects were screened, 463 subjects were enrolled, and 340 subjects were randomized (169 to BDP nasal aerosol and 171 to placebo [Fig. 1]). Overall, 332 subjects completed the study (97.6% in the

Figure 2. (A) Treatment comparison of average A.M. and P.M. subject-reported rTNSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). (B) Daily average of A.M. and P.M. subject-reported rTNSS (ITT population). A.M., morning; BDP HFA, beclomethasone dipropionate hydrofluoroalkane; ITT, intent-to-treat; LS, least squares; P.M., evening; rTNSS, reflective total nasal symptom score; SE, standard error.



BDP nasal aerosol group and 97.7% in the placebo group). Six subjects discontinued prematurely (two subjects in the BDP nasal aerosol group and four subjects in the placebo group). The ITT population consisted of 338 subjects who received at least 1 dose of study medication and had at least one postbaseline assessment; 2/340 subjects were not included in the ITT population because they did not receive study medication. The RQLQ population consisted of 250 subjects from the ITT population who had an RQLQ score of ≥ 3.0 at randomization, were ≥ 18 years of age, and understood English. The safety population included 338 subjects. Demographic and baseline characteristics (for all efficacy and quality-of-life measures evaluated) were similar between the treatment groups (Table 1).

Efficacy

Average A.M. and P.M. Subject-Reported TNSS. At baseline, the average A.M. and P.M. rTNSSs were similar between the treatment groups (9.6 [BDP nasal aerosol group] versus 9.5 [placebo group]). These scores indicate that subjects enrolled in this study had moderate-to-moderately severe SAR at baseline (Table 1).

Treatment with BDP nasal aerosol resulted in a significantly greater improvement in rTNSS over the 2-week treatment period compared with placebo (least squares [LS] mean treatment difference, -0.91 ; 95% CI, -1.3 , -0.5 ; $p < 0.001$; Fig. 2 A). Greater improvements in rTNSS with BDP nasal aerosol compared with placebo were reported as early as day 2 and were maintained throughout the 2-week treatment period (Fig. 2 B). As seen for rTNSS, treatment with BDP nasal aerosol also resulted in a significantly greater improvement in iTNSS over the 2-week treatment period compared with placebo (LS mean treatment difference, -0.92 ; 95% CI, -1.3 , -0.5 ; $p < 0.001$; Fig. 3 A). Greater improvements in iTNSS were reported by day 1 with BDP nasal aerosol compared with placebo and were maintained throughout the 2-week treatment period (Fig. 3 B).

A.M. Subject-Reported TNSS and P.M. Subject-Reported TNSS. As seen for average A.M. and P.M. subject-reported rTNSS, greater improvements with BDP nasal aerosol than with placebo were seen in both A.M. rTNSS and P.M. rTNSS over the 2-week treatment period (Fig. 4 A). Similar results were observed with A.M. and P.M. iTNSS (Fig. 4 B).

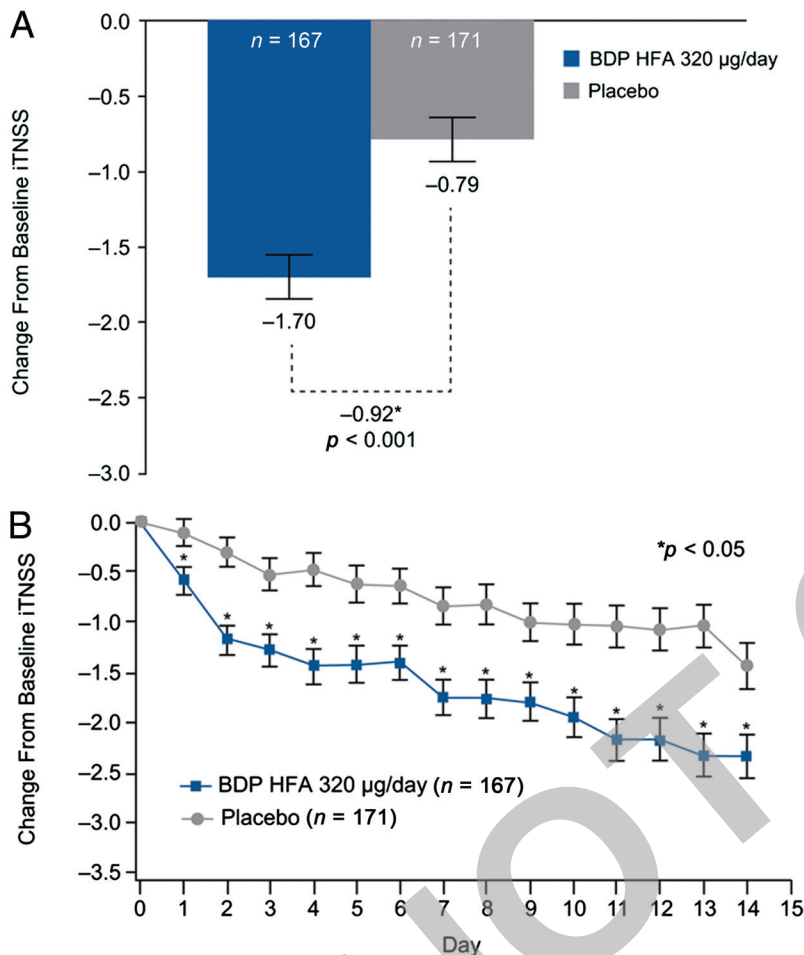


Figure 3. (A) Treatment comparison of average A.M. and P.M. subject-reported iTNSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). (B) Daily average of A.M. and P.M. subject-reported iTNSS (ITT population). A.M., morning; BDP HFA, beclomethasone dipropionate hydrofluoroalkane; iTNSS, instantaneous total nasal symptom score; ITT, intent-to-treat; LS, least squares; P.M., evening; SE, standard error.

Average A.M. and P.M. Subject-Reported TOSS. At baseline, the average A.M. and P.M. rTOSS was similar for both treatment groups (Table 1). Although improvements in rTOSS from baseline were seen in both treatment groups, the change observed with BDP nasal aerosol was significantly greater versus placebo (LS mean treatment difference, -0.56 ; 95% CI, $-0.9, -0.2$; $p = 0.002$; Fig. 5 A). Greater improvements in rTOSS were reported by day 2 with BDP nasal aerosol compared with placebo and were maintained from day 4 onward ($p < 0.05$; data not shown). Similarly, greater improvements in average A.M. and P.M. iTOSS were observed with BDP nasal aerosol compared with placebo over the 2-week treatment period (LS mean treatment difference, -0.49 ; 95% CI, $-0.8, -0.2$; $p = 0.003$; Fig. 5 B). Greater improvements in iTOSS were reported on day 4 and from day 6 onward with BDP nasal aerosol compared with placebo ($p < 0.05$; data not shown).

Subject-Reported Individual Nasal and Ocular Symptom Scores. As seen with overall symptom improvement, treatment with BDP nasal aerosol resulted in greater improvements from baseline in average A.M. and P.M.

reflective and instantaneous individual nasal symptom scores for all four of the component symptoms of the TNSS ($p \leq 0.001$) as well as in average A.M. and P.M. reflective and instantaneous individual ocular symptom scores for all three of the component symptoms of the TOSS ($p < 0.05$) compared with placebo (Table 2).

Physician-Assessed Symptom Scores. At baseline, the mean PNSS was comparable for both the treatment groups (Table 1). Improvements from baseline in PNSS were observed in both treatment groups; however, the improvement was greater with BDP nasal aerosol compared with placebo at week 2 (LS mean treatment difference, -0.97 ; 95% CI, $-1.5, -0.4$; $p < 0.001$). There were also greater improvements in each of the four individual physician-assessed nasal symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing) for subjects treated with BDP nasal aerosol compared with placebo (data not shown).

Subject-Reported Quality of Life. Treatment with BDP nasal aerosol resulted in significant improvements in quality of life compared with placebo (LS mean treatment difference, -0.48 ; 95% CI, $-0.8, -0.1$; $p = 0.005$;

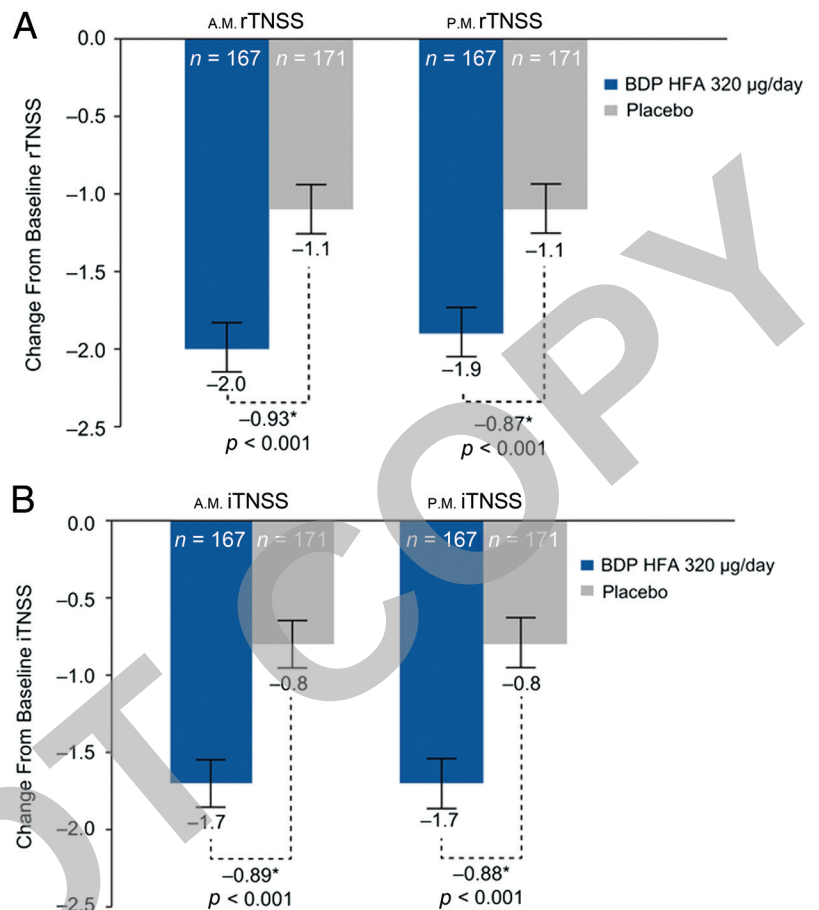


Figure 4. (A) Treatment comparison of A.M. subject-reported rTNSS and P.M. subject-reported rTNSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). (B) Treatment comparison of A.M. subject-reported iTNSS and P.M. subject-reported iTNSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). A.M., morning; BDP HFA, beclomethasone dipropionate hydrofluoroalkane; iTNSS, instantaneous total nasal symptom score; ITT, intent-to-treat; LS, least squares; P.M., evening; rTNSS, reflective total nasal symptom score; SE, standard error.

Table 3). Moreover, for six of the seven individual domains of the RQLQ, improvements from baseline were greater with BDP nasal aerosol than with placebo ($p < 0.05$; Table 3).

Safety

There were no clinically meaningful differences between BDP nasal aerosol and placebo in terms of incidence, type, or severity of AEs. Of the 338 subjects included in the safety population, 47 (13.9%) experienced at least 1 treatment-emergent AE, 23 (13.8%) in the BDP nasal aerosol group and 24 (14.0%) in the placebo group. In the BDP nasal aerosol and placebo groups, respectively, nasal discomfort (6.6% versus 5.8%) was the most commonly reported treatment-emergent AE followed by headache (1.8% versus 1.2%) and epistaxis (1.2% versus 0.6%; Table 4). The majority of AEs were of mild or moderate intensity. However, one subject in the BDP nasal aerosol group and four subjects in the placebo group experienced AEs of severe intensity (cholecystitis [BDP nasal aerosol group]; chapped lips and dry mouth, fatigue, gastroenteritis, and nasal discomfort [placebo group]). AEs were considered by the investigator to be treatment related in 14 subjects (8.4%) in the BDP nasal aerosol group and 15

subjects (8.8%) in the placebo group. In both treatment groups, the most common treatment-related AE was nasal discomfort (6.6% [BDP nasal aerosol group] versus 5.8% [placebo group]). No other AE (regardless of relationship to treatment) was reported in $>2\%$ of subjects in either treatment group. One treatment-emergent serious AE was reported in the BDP nasal aerosol group (hypertensive crisis), which was not considered to be treatment related by the investigator and was the only AE that led to study discontinuation. There were no deaths reported in the study. Also, no relevant treatment-related findings were observed for vital signs, ENT examinations, or physical examinations.

DISCUSSION

The results of this study indicated that treatment with BDP nasal aerosol at a dose of 320 µg/day provides statistically significant and clinically meaningful¹⁶ improvements compared with placebo in the primary and all key secondary efficacy measures. A treatment difference of 0.55 U in TNSS has been viewed as a clinically important/meaningful effect,¹⁶ and the treatment difference observed for nasal symptoms in this study was considerably larger than the 0.55-U threshold (*i.e.*, 0.91 for rTNSS and 0.92 for

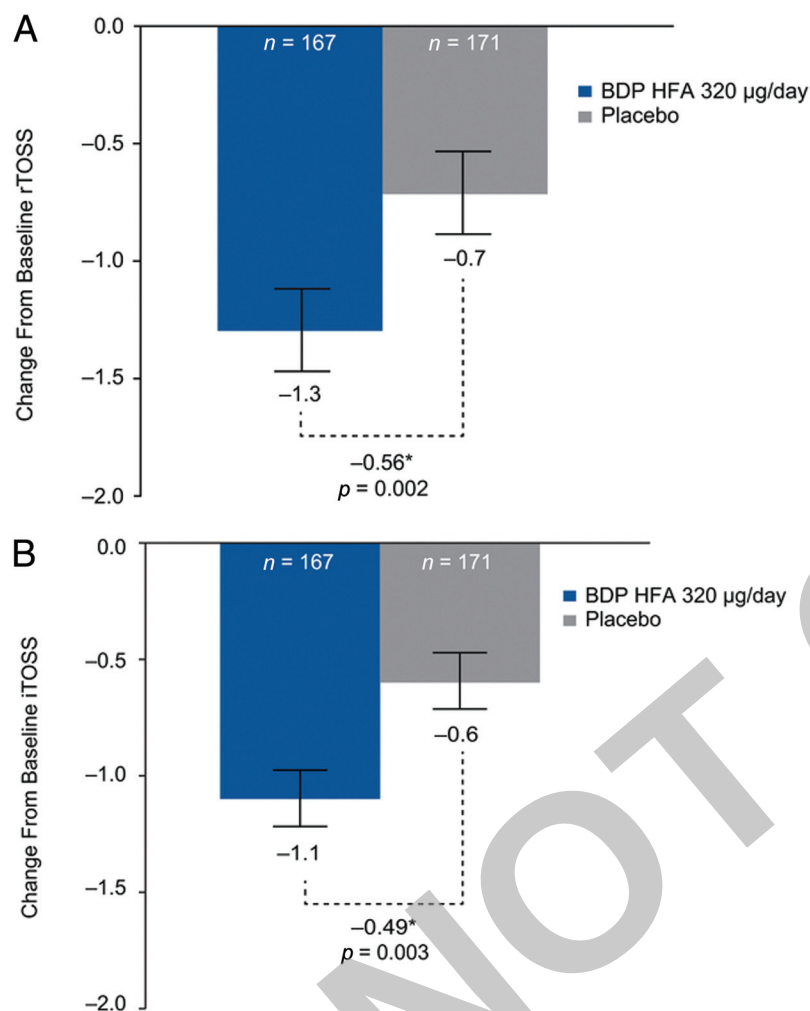


Figure 5. (A) Treatment comparison of average A.M. and P.M. subject-reported rTOSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). (B) Treatment comparison of average A.M. and P.M. subject-reported iTOSS over the 2-week treatment period (ITT population). *LS mean treatment difference from placebo. Values represent LS mean ($\pm$ SE). A.M., morning; BDP HFA, beclomethasone dipropionate hydrofluoroalkane; iTOSS, instantaneous total ocular symptom score; ITT, intent-to-treat; LS, least squares; P.M., evening; rTOSS, reflective total ocular symptom score; SE, standard error.

iTNSS). Furthermore, the treatment effect of BDP nasal aerosol was reported as early as day 1 and was maintained over the 2-week treatment period. The improvement in nasal symptoms reported in this study after treatment with BDP nasal aerosol in subjects with SAR are similar to those reported from a recent study in subjects with PAR after treatment with BDP nasal aerosol.¹⁷

In the current study, subjects administered their once-daily study medication in the A.M. after recording their symptom scores. The significant nasal symptom improvements seen with BDP nasal aerosol versus placebo in the A.M. (predose) iTNSS indicate that efficacy was maintained over the entire 24-hour dosing interval. In addition, improvements in A.M. rTNSS and iTNSS were similar to those observed for P.M. rTNSS and iTNSS, respectively, over the 2-week treatment period, suggesting that BDP nasal aerosol is effective as a once-daily treatment for SAR. Furthermore, improvements with BDP nasal aerosol were shown for each of the four individual symptoms comprising the TNSS, thus supporting the efficacy of BDP nasal aerosol for treating all nasal symptom components associated

with AR. Similarly, significant benefits of BDP nasal aerosol over placebo were shown for ocular symptoms (rTOSS, iTOSS, and each of the three individual ocular symptoms composing the TOSS). Thus, results of this study clearly show that treatment with BDP nasal aerosol provides relief of both nasal and ocular symptoms of AR. This is consistent with recent reports that intra-nasal corticosteroids are effective in treating both nasal and ocular symptoms of AR.^{7,18,19}

Similar to the observed improvements in subject-reported nasal and ocular symptoms, BDP nasal aerosol-treated subjects also reported greater improvements in quality of life as assessed by the RQLQ score (RQLQ population; RQLQ score ≥ 3.0 at baseline) compared with placebo-treated subjects. Although the improvement in RQLQ score with BDP nasal aerosol versus placebo was statistically significant (treatment difference, -0.48 ; $p = 0.005$), the treatment difference was just below the minimal clinically important threshold (-0.50).¹⁴ A similar statistically significant improvement in RQLQ score was also seen when the analysis was performed using the ITT population.

Table 2 Treatment comparison of average A.M. and P.M. subject-reported reflective and instantaneous individual nasal and individual ocular symptom scores (ITT population)

	Reflective Assessment	Instantaneous Assessment
Nasal symptoms		
Nasal congestion		
LS mean treatment difference from placebo	−0.26	−0.23
95% CI	−0.4, −0.2	−0.3, −0.1
<i>p</i> Value	<0.001	<0.001
Rhinorrhea		
LS mean treatment difference from placebo	−0.22	−0.22
95% CI	−0.3, 0.1	−0.3, 0.1
<i>p</i> Value	<0.001	<0.001
Nasal itching		
LS mean treatment difference from placebo	−0.20	−0.23
95% CI	−0.3, −0.1	−0.4, −0.1
<i>p</i> Value	0.001	<0.001
Sneezing		
LS mean treatment difference from placebo	−0.22	−0.22
95% CI	−0.4, −0.1	−0.3, −0.1
<i>p</i> Value	<0.001	<0.001
Ocular symptoms		
Itching/burning eyes		
LS mean treatment difference from placebo	−0.17	−0.13
95% CI	−0.3, −0.0	−0.2, −0.0
<i>p</i> Value	0.006	0.022
Tearing/watering eyes		
LS mean treatment difference from placebo	−0.19	−0.18
95% CI	−0.3, −0.1	−0.3, −0.1
<i>p</i> Value	0.002	0.004
Eye redness		
LS mean treatment difference from placebo	−0.19	−0.17
95% CI	−0.3, −0.1	−0.3, −0.1
<i>p</i> Value	0.002	0.005

A.M. = morning; CI = confidence interval; ITT = intent-to-treat; LS = least squares; P.M. = evening.

BDP nasal aerosol was well tolerated in the current study. The incidence of AEs was low in both treatment groups and the overall safety profile of BDP nasal aerosol was similar to placebo. In addition, the incidence of epistaxis was low and there was no epistaxis-related subject discontinuation. There was no evidence of treatment-related findings in ENT examinations in either group. One treatment-emergent serious AE (hypertensive crisis) was reported in the BDP nasal aerosol group in a subject with a history of labile hypertension at screening. The investigator did not consider this AE to be treatment related. In this context, it is important to note that results of a pharmacokinetic study evaluating the systemic levels of beclomethasone 17-monopropionate and BDP after a single dose of intranasally administered or orally inhaled BDP HFA in healthy subjects indicated 320 µg of BDP nasal aerosol has systemic bioavailability, which is approximately four-

fold lower compared with 320 µg of orally inhaled BDP HFA in healthy subjects.²⁰ These systemic bioavailability data, coupled with the fact that the subject had an active medical history of labile hypertension, further support the investigator's conclusion that the hypertensive crisis was not likely to be related to BDP nasal aerosol treatment.

Evaluation of the safety of intranasal corticosteroids is of particular importance during chronic daily use, especially in pediatric and adolescent patients. This short-term, 2-week study included adolescent subjects (12–17 years of age) but was not designed to assess systemic safety outcomes such as growth or hypothalamic–pituitary–adrenal (HPA) axis function. Results from recently reported studies evaluating the safety and efficacy of chronic daily treatment with BDP nasal aerosol in adolescent and adult subjects with PAR did not show systemically relevant safety profile differ-

Table 3 Treatment comparison of overall RQLQ score and individual domains of the RQLQ score (RQLQ population)

	BDP HFA 320 μ g/day vs Placebo LS Mean Treatment Difference* (95% CI; n = 250)	p Value
Overall RQLQ score	-0.48 (-0.8, -0.1)	0.005
Domain		
Activities	-0.5 (-0.8, -0.1)	0.009
Emotional	-0.4 (-0.8, -0.0)	0.039
Eye symptoms	-0.5 (-0.9, -0.1)	0.009
Nasal symptoms	-0.6 (-1.0, -0.3)	<0.001
Nonnose/eye symptoms	-0.4 (-0.8, -0.1)	0.015
Practical problems	-0.7 (-1.1, -0.3)	<0.001
Sleep	-0.4 (-0.8, 0.0)	0.055

*Negative change from baseline denotes improvement.

BDP HFA = beclomethasone dipropionate hydrofluoroalkane; CI = confidence interval; LS = least squares; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

Table 4 Treatment-emergent AEs with an incidence of $\geq 1\%$ in either treatment group (safety population)

AE, n (%)	BDP HFA 320 μ g/day (n = 167)	Placebo (n = 171)
Nasal discomfort	11 (6.6)	10 (5.8)
Headache	3 (1.8)	2 (1.2)
Epistaxis	2 (1.2)	1 (0.6)
Nausea	2 (1.2)	0
Urticaria	2 (1.2)	0
Nasopharyngitis	1 (0.6)	2 (1.2)

AE = adverse event; BDP HFA = beclomethasone dipropionate hydrofluoroalkane.

ences between BDP nasal aerosol and placebo with respect to HPA axis function or long-term safety.^{21–23} However, future studies will need to focus on such systemic safety outcomes, especially in pediatric patients. In this regard, corticosteroids as a class are known to affect systemic safety outcomes such as growth, and a high dose (168 μ g twice daily; total daily dose, 336 μ g) of an aqueous formulation of BDP was previously shown to be associated with an effect on growth, but not on HPA axis function, in children with PAR.²⁴ It is important to note that results from a recent dose-ranging study suggested that BDP nasal aerosol at a considerably lower dose of 80 μ g/day was effective and well tolerated in children (6–11 years of age).²⁵ Additional studies are needed to evaluate the safety of this dose in pediatric patients.

In conclusion, treatment with BDP nasal aerosol at 320 μ g/day resulted in significant and clinically meaningful improvements in both nasal and ocular symp-

toms associated with SAR in adolescent and adult subjects. Beneficial effects of treatment with BDP nasal aerosol were reported as soon as day 1 of treatment and were maintained over the 2-week treatment period. Additionally, BDP nasal aerosol was well tolerated and the overall safety profile of BDP nasal aerosol was similar to placebo. Together, these data indicate that BDP nasal aerosol provides an effective and well-tolerated once-daily treatment option for the treatment of SAR.

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REFERENCES

- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122:S1–S84, 2008.
- Skoner DP. Allergic rhinitis: Definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 108(suppl 1):S2–S8, 2001.
- Blaiss MS. Allergic rhinitis: Direct and indirect costs. *Allergy Asthma Proc* 31:375–380, 2010.
- Greiner AN, Hellings PW, Rotiroti G, et al. Allergic rhinitis. *Lancet* 378:2112–2122, 2011.
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
- Weiner JM, Abramson MJ, and Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: Systematic review of randomised controlled trials. *BMJ* 317: 1624–1629, 1998.
- Bielory L. Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal corticosteroid mo-

- metasone furoate. *Ann Allergy Asthma Immunol* 100:272–279, 2008.
8. Luskin AT, Blaiss MS, Farrar JR, et al. Is there a role for aerosol nasal sprays in the treatment of allergic rhinitis. *Allergy Asthma Proc* 32:168–177, 2011.
 9. Fromer LM, Ortiz G, Ryan SF, et al. Insights on allergic rhinitis from the patient perspective. *J Fam Pract* 61(suppl):S16–S22, 2012.
 10. Naclerio RM, Hadley JA, Stoloff S, et al. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc* 28:S11–S17, 2007.
 11. GlaxoSmithKline. Beconase AQ (beclomethasone dipropionate, monohydrate) nasal spray package insert. Research Triangle Park, NC; April 2005.
 12. Montreal Protocol. Available online at www.epa.gov/ozone/intpol/; accessed March 13, 2012.
 13. Teva Respiratory, LLC. QVAR 40 μ g (beclomethasone dipropionate HFA, 40 μ g) inhalation aerosol for oral inhalation only; QVAR 80 μ g (beclomethasone dipropionate HFA, 80 μ g) inhalation aerosol for oral inhalation only package insert. Frazer, PA; September 2010.
 14. Juniper EF, Guyatt GH, Griffith LE, et al. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 98:843–845, 1996.
 15. Kim K, Weiswasser M, and Nave R. Safety of once-daily ciclesonide nasal spray in children 2 to 5 years of age with perennial allergic rhinitis. *Pediatr Asthma Allergy Immunol* 20:229–249, 2007.
 16. Barnes ML, Vaidyanathan S, Williamson PA, et al. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy* 40:242–250, 2010.
 17. Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. *Allergy Asthma Proc* 33:249–257, 2012.
 18. Blaiss MS. Evolving paradigm in the management of allergic rhinitis-associated ocular symptoms: Role of intranasal corticosteroids. *Curr Med Res Opin* 24:821–836, 2008.
 19. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: A single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 119:1430–1437, 2007.
 20. Ratner PH, Melchior A, Dunbar SA, et al. Pharmacokinetic profile of beclomethasone dipropionate hydrofluoroalkane after intranasal administration versus oral inhalation in healthy subjects: results of a single-dose, randomized, open-label, 3-period crossover study. *Clin Ther* 34:1422–1431, 2012.
 21. Ratner PH, Miller SD, Hampel FC, et al. BDP HFA nasal aerosol 320 μ g once daily is not associated with HPA axis suppression in subjects with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 107(suppl B1–B2):A118, Abstract P358, 2011.
 22. Hampel FC, Ratner PH, Miller SD, et al. Once-daily treatment with beclomethasone dipropionate hydrofluoroalkane nasal aerosol (320 mcg/d) is not associated with hypothalamic-pituitary-adrenal axis suppression in adolescent subjects with perennial allergic rhinitis. *J Allergy Clin Immunol* 129(suppl):AB188, 2012.
 23. Nayak AS, Andrews CP, Bernstein DI, et al. Long-term (52-week) treatment with beclomethasone dipropionate hydrofluoroalkane nasal aerosol (320 mcg once daily) is safe and effective in adult and adolescent subjects with perennial allergic rhinitis. *J Allergy Clin Immunol* 129(suppl):AB189, 2012.
 24. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics* 105:E23, 2000.
 25. Segall N, Mansfield L, Amar N, et al. Once-daily treatment with beclomethasone dipropionate hydrofluoroalkane nasal aerosol is safe and effective in children (6–11 years of age) with seasonal allergic rhinitis. *J Allergy Clin Immunol* 129(suppl):AB188, 2012. □