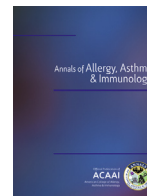




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Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis

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ABSTRACT

Background: Aerosolized intranasal corticosteroid formulations are desirable for many patients with allergic rhinitis (AR), especially children, who wish to avoid the “wet feeling” and “drip down the throat” associated with aqueous formulations. Beclomethasone dipropionate (BDP) hydrofluoroalkane nasal aerosol has been shown to be safe and effective in adolescents and adults with AR.

Objective: To evaluate the efficacy and safety of BDP nasal aerosol in pediatric patients with moderate to severe seasonal AR.

Methods: In this double-blinded, placebo-controlled study, children (6–11 years of age) with seasonal AR were randomized to once-daily treatment with BDP nasal aerosol 80 μ g (n = 239) or 160 μ g (n = 242) or placebo (n = 234). The primary end point was change from baseline in average morning and evening reflective total nasal symptom score over the 2-week treatment period.

Results: Treatment with BDP nasal aerosol showed significantly greater improvements in average morning and evening reflective total nasal symptom score vs placebo (80 μ g, -0.71 ; 160 μ g, -0.76 ; $P < .001$ for the 2 comparisons). Similarly, significantly greater improvements in average morning and evening instantaneous total nasal symptom score were seen with BDP nasal aerosol vs placebo (80 μ g, -0.63 ; 160 μ g, -0.73 ; $P < .001$ for the 2 comparisons). The incidence of adverse events from BDP nasal aerosol was comparable to that from placebo.

Conclusions: BDP nasal aerosol (80 or 160 μ g/d) provided significant and clinically meaningful nasal symptom relief and an established overall safety profile similar to that of placebo, suggesting that it is an effective and well-tolerated treatment option for pediatric patients with moderate to severe seasonal AR.

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Introduction

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa characterized by nasal congestion, nasal itching, rhinorrhea, and sneezing.^{1,2} Traditionally, AR has been classified as seasonal or perennial, depending on whether symptoms occur during seasonal exposure to allergens or throughout the year.³ AR affects patients of all ethnic groups and ages,⁴ including up to 60 million individuals in the United States and up to 40% of children.⁵

Patients with AR often have decreased quality of life because of the effect of AR on daily activities.^{4,6} The Pediatric Allergies in America survey, a national survey of children and adolescents with AR, reported that social life, sleep, and productivity at school are greatly affected by symptoms of AR.⁷ For instance, presenteeism (or decreased performance while at school) appears to be a significant burden of AR that is frequently overlooked, with 40% of parents reporting that the condition interferes with their child's performance

at school.⁷ Furthermore, when parents were asked to quantify the effect of their child's nasal allergies on productivity, parents of children with allergies reported a 30% decrease in their children's productivity at school and at home when symptoms were at their worst.⁷

Environmental control measures, pharmacologic therapies, and allergen immunotherapy have been used to avoid or alleviate the symptoms of AR.⁵ Intranasal corticosteroids (INs) are the most effective medication class for controlling the symptoms of AR.⁵ Until recently, INs were available only as aqueous nasal spray formulations. Some patients with AR have reported dissatisfaction with their nasal allergy medication, including INs,^{7,8} which may lead to poor adherence or discontinuation of medication.⁹ Bother-some side effects have been reported by adult patients and parents of children with AR as reasons for dissatisfaction with aqueous INs and other prescription nasal sprays.^{7,8} For many patients, a nonaqueous nasal aerosol IN formulation may be desirable because aqueous nasal sprays may be associated with undesirable, bothersome side effects such as “wet feeling in the nose” and “dripping of medicine down the throat.”^{7–9} The availability of nonaqueous and aqueous formulations of INs could lead to improved outcomes in all patients with chronic AR symptoms because satisfied patients are more likely to comply with their treatment regimen.⁹

Beclomethasone dipropionate (BDP), an anti-inflammatory corticosteroid, has been formulated and developed as aqueous nasal sprays (Beconase AQ, GlaxoSmithKline, Research Triangle Park, NC; Vancenase AQ, Bayer HealthCare Pharmaceuticals, Berlin, Germany) and nonaqueous nasal aerosols (chlorofluorocarbon metered-dose inhaler nasal aerosol; Beconase and Vancenase Pockethaler). However, the Montreal Protocol, adopted in 1987, limited and eventually prohibited most uses of chlorofluorocarbons because of concerns about their effects on the environment.¹⁰ As a result, all chlorofluorocarbon-propelled nasal aerosols were withdrawn from the market and are not currently available for patient use. BDP nasal aerosol is a hydrofluoroalkane-propelled aerosol that has demonstrated efficacy and safety in adolescent and adult patients (≥ 12 years of age) with seasonal AR (SAR)¹¹ or perennial AR (PAR).¹² The BDP nasal aerosol was approved and is currently available for the treatment of nasal symptoms associated with AR in adolescents and adults¹³ and under clinical development for use in pediatric patients younger than 12 years. As part of the clinical development program, this dose-range-finding study was conducted to evaluate the efficacy and safety of the BDP nasal aerosol in pediatric patients 6 to 11 years old with SAR.

Methods

Study Design and Treatment

This was a randomized, double-blinded, placebo-controlled, parallel-group, dose-range-finding study conducted at 60 US centers in accordance with the principles of the Declaration of Helsinki (clinicaltrials.gov, identifier NCT01307319). The study was approved by a central institutional review board (Quorum Review, Inc, Seattle, WA). All patients provided assent; written informed consent was provided by the patients' parent or legal guardian.

After a 7- to 21-day placebo run-in period (flexibility to accommodate the schedules of the patients, parents, or caregivers), eligible patients were randomly assigned in a 1:1:1 ratio to once-daily treatment with 80 μ g of BDP nasal aerosol (40 μ g/actuation, 1 actuation/nostril), 160 μ g of BDP nasal aerosol (80 μ g/actuation, 1 actuation/nostril), or placebo nasal aerosol (vehicle, 1 actuation/nostril) for 2 weeks of double-blinded treatment. Patients, with assistance from parents, guardians, or caregivers, self-administered the nasal aerosol (1 actuation/nostril, total 2 actuations) once daily (morning [AM]) and

assessed their nasal symptoms (congestion, itching, rhinorrhea, sneezing) twice daily (AM and evening [PM]). 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).

Patients

Boys or girls, 6 to 11 years old, with at least a 2-year history of SAR, who were in general good health and free of any concomitant conditions or treatment that could interfere with study conduct were eligible. Patients must have demonstrated sensitivity to at least 1 seasonal allergen (tree/grass pollen) using a standard skin prick test. Sensitivity was defined as a wheal diameter at least 5 mm larger than the control.

Patients with a history of nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma (eg, nasal piercing) or surgery, atrophic rhinitis, or rhinitis medicamentosa—all within 60 days of screening—were excluded. In addition, patients with a known hypersensitivity to any corticosteroid or any of the excipients in the study medication, those with a history of respiratory tract infection or disorder within 14 days of screening, or development of a respiratory tract infection during the placebo run-in period were excluded.

Rescue medications were not allowed, to avoid any external interference with the efficacy outcome. Short-acting antihistamines, long-acting antihistamines, and corticosteroid treatment (intranasal, topical, and ocular) were discontinued 7, 10, and 28 days before screening, respectively. Patients were not permitted to use medications that could affect AR, such as decongestants, anticholinergics, antileukotrienes, and intranasal cromolyn, for specified times before and during the study. Patients were permitted to use some medications with restrictions (eg, pimecrolimus/tacrolimus, low-dose antibiotics, stable dose of immunotherapy, aspirin, and topical hydrocortisone) to treat concurrent diseases or conditions. No other medications were permitted except for the study medication and medications to treat adverse events (AEs).

The total nasal symptom score (TNSS) was defined as the sum of the score for the 4 individual patient-reported nasal symptoms of congestion, itching, rhinorrhea, and sneezing. To be eligible for randomization, patients must have achieved an average minimum patient-reported reflective TNSS (rTNSS) of 6 (of possible 12) and an average minimum patient-reported reflective nasal congestion score of 2 in the last 4 days of the placebo run-in period, indicating moderate to severe symptoms. In addition, patients must have continued to be in general good health, adequately completed their AR assessment diary, and taken their single-blinded study medication at least 80% of the time during the placebo run-in period.

Study End Points and Assessments

The primary end point was the change from baseline in average AM and PM patient-reported rTNSS over the 2-week treatment period. The secondary end point was the change from baseline in average AM and PM patient-reported instantaneous TNSS (iTNSS) over the 2-week treatment period. Baseline for TNSS was defined as the average AM and PM patient-reported TNSS over the 4 days before randomization. Additional efficacy end points included patient-reported individual nasal symptoms (congestion, itching, rhinorrhea, and sneezing), physician-assessed total nasal symptom score (PNSS) at week 2, and physician-assessed individual nasal symptoms at week 2. PNSS was calculated by summing the individual nasal symptom scores for congestion, itching, rhinorrhea, and sneezing as determined by the investigator at defined clinical visits by questioning of the patient and based on ear, nose, and throat examination. Baseline for PNSS was based on the physician

assessment during the randomization visit. Safety was monitored by physical examinations; ear, nose, and throat examinations; vital sign assessments; and AEs.

Statistical Methods

Assuming a standard deviation of 2.0, 235 patients per treatment group (total 705 patients) would provide 90% power to detect a treatment difference of 0.60 in the change from baseline in rTNSS among the BDP nasal aerosol and placebo groups, with a 2-sided α level of 0.05.

The primary end point was analyzed using repeated-measures analysis of covariance with covariate adjustment for baseline, day, treatment, and treatment-by-day interaction using the intent-to-treat (ITT) population (all randomized patients who received ≥ 1 dose of study medication and had ≥ 1 postbaseline assessment). As part of the mixed-model analysis of covariance, a first-order autoregressive structure was used to model intrasubject correlation in conjunction with treating patient as a random effect. The use of the first-order autoregressive structure yielded a correlation structure in which observations from the same patient were considered correlated, with observations closer in time being more correlated. Estimated treatment differences and 95% confidence intervals (CIs) for treatment differences were calculated. The secondary end point (change from baseline in average AM and PM patient-reported iTNSS) and patient-reported individual nasal symptoms were analyzed in a similar fashion to the primary end point. Analysis of covariance with factors for treatment, baseline, and center was used to analyze the change from baseline in PNSS and physician-assessed individual nasal symptoms at week 2. To adjust for multiple comparisons in the primary and secondary analyses, a sequential approach was applied to control type 1 error rate within a particular treatment comparison and within a particular end point. Safety data were summarized by incidence, means, changes, and shifts depending on the measurement.

Results

Patient Disposition and Demographics

Overall, 1,026 patients were screened for eligibility, and 906 patients enrolled and participated in the placebo run-in period (eFig 1). Of those enrolled, 715 were randomly assigned (BDP nasal aerosol 80 $\mu\text{g}/\text{d}$, $n = 239$; BDP nasal aerosol 160 $\mu\text{g}/\text{d}$, $n = 242$; placebo, $n = 234$). In total, 696 patients (97.3%) completed the study. The ITT population consisted of 713 patients. The safety population (all randomized patients who received ≥ 1 dose of study medication) consisted of 714 patients. Demographic and baseline characteristics were comparable among the treatment groups at baseline (Table 1). Mean compliance rates with the study medication were at least 98% in each treatment group.

Efficacy

Patient-reported nasal symptom scores

Beclomethasone dipropionate nasal aerosol at a dose of 80 or 160 $\mu\text{g}/\text{d}$ resulted in significant improvements vs placebo in average AM and PM rTNSS over the 2-week treatment period (least-squares mean treatment difference -0.71 [$P < .001$] and -0.76 [$P < .001$], respectively; Fig 1). Greater improvements in average AM and PM rTNSS were reported by day 4 with 80 and 160 $\mu\text{g}/\text{d}$ of BDP nasal aerosol compared with placebo ($P < .05$) and were maintained throughout the 2 weeks of treatment (Fig 2A). In addition, BDP nasal aerosol at a dose of 80 or 160 $\mu\text{g}/\text{d}$ resulted in significant improvements vs placebo in average AM and PM patient-reported iTNSS over the 2-week treatment period (least-squares mean treatment difference -0.63 [$P < .001$] and -0.73 [$P < .001$], respectively; Fig 1). Similar to the effect observed for

Table 1

Patient demographic and baseline characteristics (intent-to-treat population^a)

	BDP nasal aerosol 80 $\mu\text{g}/\text{d}$ ($n = 238$)	BDP nasal aerosol 160 $\mu\text{g}/\text{d}$ ($n = 241$)	Placebo ($n = 234$)
Age (y)			
Mean (SD)	8.9 (1.7)	9.1 (1.6)	9.1 (1.7)
Median	9.0	9.0	9.0
Minimum–maximum	6–11	6–11	6–11
Sex, n (%)			
Female	105 (44.1)	116 (48.1)	111 (47.4)
Male	133 (55.9)	125 (51.9)	123 (52.6)
Race, n (%)			
White	169 (71.0)	172 (71.4)	164 (70.1)
Black or African American	55 (23.1)	55 (22.8)	52 (22.2)
Asian	2 (0.8)	4 (1.7)	6 (2.6)
Other	12 (5.0)	10 (4.1)	12 (5.1)
Ethnicity, n (%)			
Hispanic or Latino	40 (16.8)	53 (22.0)	45 (19.2)
Neither Hispanic nor Latino	198 (83.2)	188 (78.0)	189 (80.8)
Height (cm), mean (SD)	137.4 (12.8)	138.8 (12.3)	137.5 (12.5)
Weight (kg), mean (SD)	36.7 (12.9)	38.1 (13.0)	36.7 (12.4)
BMI (kg/m^2), mean (SD)	19.0 (4.2)	19.4 (4.5)	19.1 (4.7)
Baseline rTNSS ^b			
Mean (SD)	8.9 (1.62)	9.0 (1.71)	9.0 (1.70)
Minimum ^c –maximum	6.0–12.0	5.6–12.0	6.0–12.0
Baseline iTNSS, mean (SD) ^b	8.1 (1.99)	8.1 (2.13)	8.2 (2.10)
Baseline PNSS, mean (SD) ^d	8.2 (2.30)	8.0 (2.36)	8.3 (2.17)

Abbreviations: BDP, beclomethasone dipropionate; BMI, body mass index; iTNSS, instantaneous total nasal symptom score; PNSS, physician-assessed total nasal symptom score; rTNSS, reflective total nasal symptom score; SD, standard deviation.

^aThe intent-to-treat population included all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline assessment.

^bBaseline for TNSS was defined as the average morning and evening patient-reported TNSS over the 4 days before randomization.

^cTwo patients in the BDP 160- $\mu\text{g}/\text{d}$ group with baseline rTNSS < 6 were inadvertently randomized and included in the intent-to-treat population.

^dBaseline for PNSS was based on the physician assessment during the randomization visit.

rTNSS, greater improvements in average AM and PM iTNSS were noted with BDP nasal aerosol compared with placebo ($P < .05$) by day 2 (160 $\mu\text{g}/\text{d}$) and day 7 (80 $\mu\text{g}/\text{d}$); these effects were maintained over the 2-week treatment period (Fig 2B). There were greater improvements in each of the reflective and instantaneous individual nasal symptom scores (congestion, itching, rhinorrhea, sneezing) after 2 weeks of treatment with BDP nasal aerosol at a dose of 80 or 160 $\mu\text{g}/\text{d}$ compared with placebo ($P < .05$; Table 2). Furthermore, there were greater improvements with BDP nasal aerosol (80 and 160 $\mu\text{g}/\text{d}$) compared with placebo for the assessments of AM rTNSS, PM rTNSS, AM iTNSS, and PM iTNSS ($P < .01$ for all comparisons), showing the efficacy of BDP nasal aerosol over 24 hours. Least-squares mean treatment differences from placebo for the BDP nasal aerosol 80- and 160- $\mu\text{g}/\text{d}$ treatment groups, respectively, were as follows: AM rTNSS, -0.76 (95% CI -1.1 to -0.4) and -0.81 (95% CI -1.2 to -0.4); PM rTNSS, -0.68 (95% CI -1.1 to -0.3) and -0.74 (95% CI -1.1 to -0.3); AM iTNSS, -0.69 (95% CI -1.1 to -0.3) and -0.78 (95% CI -1.1 to -0.4); and PM iTNSS, -0.56 (95% CI -0.9 to -0.2) and -0.68 (95% CI -1.0 to -0.3).

Physician-assessed nasal symptom scores

Improvements in PNSS from baseline were seen in all treatment groups; the change from baseline in PNSS was greater for BDP nasal aerosol compared with placebo at week 2 ($P < .001$ for 80 $\mu\text{g}/\text{d}$, $P = .004$ for 160 $\mu\text{g}/\text{d}$; eFig 2). Greater improvements from baseline were seen for all 4 physician-assessed individual nasal symptoms with BDP nasal aerosol 80 $\mu\text{g}/\text{d}$ compared with placebo ($P < .05$ for all comparisons; Table 2). Similarly, greater improvements from baseline were seen for physician-assessed individual nasal symptoms, including congestion, itching, and rhinorrhea, with BDP nasal aerosol 160 $\mu\text{g}/\text{d}$ compared with placebo ($P < .05$), with the exception of sneezing (Table 2).

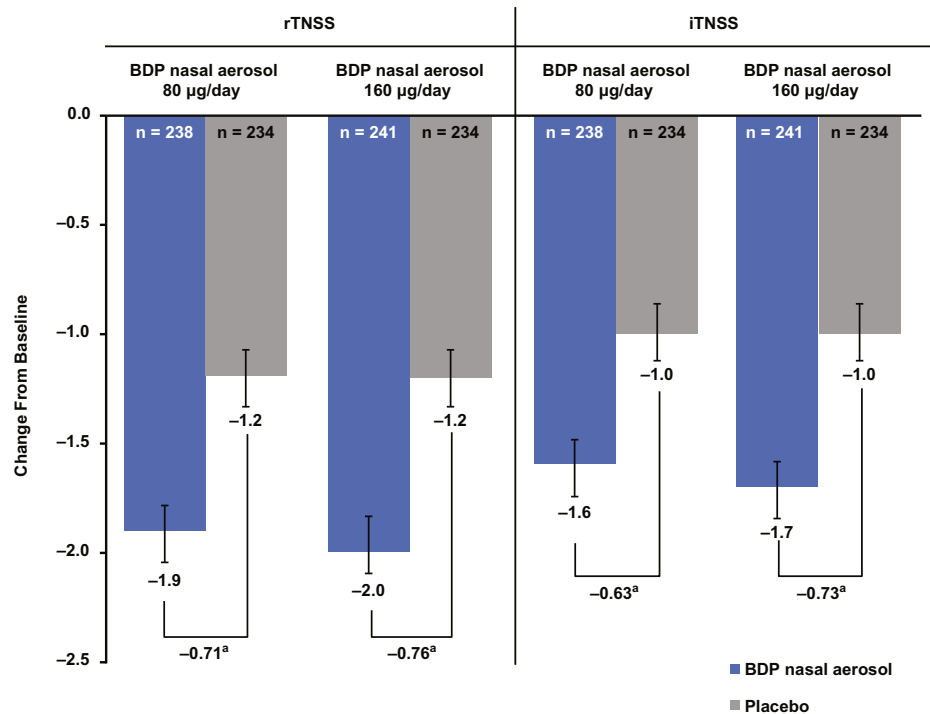


Figure 1. Treatment with beclomethasone dipropionate (BDP) nasal aerosol resulted in significantly greater improvements in average morning and evening patient-reported reflective total nasal symptom score (rTNSS) and instantaneous total nasal symptom score (iTNSS) over the 2-week treatment period compared with placebo (intent-to-treat population). Values represent least-squares mean $\pm$ standard error. ^aTreatment difference. $P < .001$ for all comparisons.

Safety

Overall, 95 patients (13.3%) developed a treatment-emergent AE (TEAE; defined as any AE occurring after randomization): 33 (13.8%) in the BDP nasal aerosol 80- μ g/d group, 30 (12.4%) in the BDP nasal aerosol 160- μ g/d group, and 32 (13.7%) in the placebo group. Thirty-eight patients (5.3%) developed treatment-related AEs (as judged by the investigator): 9 patients (3.8%) in the BDP nasal aerosol 80- μ g/d group, 15 patients (6.2%) in the BDP nasal aerosol 160- μ g/d group, and 14 patients (6.0%) in the placebo group. The only TEAEs that were reported in at least 2% of patients in any treatment group were epistaxis (defined as any observation of blood, including a single drop on a tissue) and headache. Epistaxis was reported by 4 patients (1.7%) in the BDP nasal aerosol 80- μ g/d group, 9 (3.7%) in the BDP nasal aerosol 160- μ g/d group, and 10 (4.3%) in the placebo group; headache was reported in 7 patients (2.9%) in the BDP nasal aerosol 80- μ g/d group, 3 (1.2%) in the BDP nasal aerosol 160- μ g/d group, and 1 (0.4%) in the placebo group. Overall, most AEs were mild or moderate in intensity. However, 9 patients developed severe AEs (4 patients [1.7%] in the BDP nasal aerosol 80- μ g/d group [pharyngitis and upper respiratory tract infection, upper limb fracture, cough, and pityriasis rosea] and 5 patients [2.1%] in the BDP nasal aerosol 160- μ g/d group [conjunctivitis, nausea and vomiting, otitis media, headache, nasal discomfort, seasonal rhinitis, and papular rash]). Four of the severe AEs were judged by the investigator to be related to the study treatment (pharyngitis and cough [BDP nasal aerosol 80- μ g/d group]; headache and nasal discomfort [BDP nasal aerosol 160- μ g/d group]).

One patient (who had a history of epistaxis and 2 nasal surgeries before study entry) in the BDP nasal aerosol 160- μ g/d group reported nasal septum perforation. There were 2 reports of nasal septum disorder (1 patient from the BDP nasal aerosol 80- μ g/d group [right septum epithelial erosion] and 1 from the placebo group [left septum erosion]). No serious AEs were reported, and no deaths occurred during this study. Five patients withdrew from the

study because of AEs: 2 (0.8%) in the BDP nasal aerosol 80- μ g/d group (severe pityriasis rosea; asthma), 2 (0.8%) in the BDP nasal aerosol 160- μ g/d group (papular rash; severe seasonal rhinitis), and 1 (0.4%) in the placebo group (rhinorrhea). For the patient in the placebo group who withdrew from the study, the AE commenced during the placebo run-in period and the patient discontinued during the double-blinded treatment period. None of the discontinuations were caused by serious AEs or AEs considered by the investigator to be related to the study treatment. Overall, the BDP nasal aerosol was well tolerated and showed a safety profile comparable to that of placebo.

Discussion

The efficacy and safety of once-daily treatment with 320 μ g of BDP nasal aerosol in adolescent and adult patients with AR has been established.^{11,12} However, the efficacy and safety of BDP nasal aerosol in pediatric patients with SAR has not been previously reported. In the present study, once-daily treatment with 80 or 160 μ g of BDP nasal aerosol resulted in significant improvements in nasal symptoms compared with placebo in pediatric patients with SAR after 2 weeks of treatment. These improvements were seen as soon as day 2 (average AM and PM iTNSS) and day 4 (AM and PM rTNSS). Furthermore, improvements in patient-reported individual nasal symptom scores and physician-assessed nasal symptom scores were observed after treatment with 80 or 160 μ g/d of BDP nasal aerosol. Overall, the results reported in this study after 2 weeks of once-daily treatment with 80 or 160 μ g of BDP nasal aerosol in pediatric patients with SAR are consistent with results reported after 2 or 6 weeks of once-daily treatment with 320 μ g of BDP nasal aerosol in adolescents and adults with SAR¹¹ or PAR,¹² respectively.

A treatment difference (active treatment minus placebo) of at least 0.55 units in TNSS has been viewed as a clinically meaningful or important improvement.¹⁴ Because the significant treatment difference in rTNSS and iTNSS observed in the present study was greater

Table 2
Treatment with BDP nasal aerosol resulted in greater improvements in average morning and evening patient-reported reflective and instantaneous individual nasal symptom scores over the 2-week treatment period and physician-assessed individual nasal symptoms at week 2 compared with placebo (intent-to-treat population)

	BDP nasal aerosol 80 µg/d (n = 238)			BDP nasal aerosol 160 µg/d (n = 241)		
	Patient-reported reflective assessment	Patient-reported instantaneous assessment	Physician-assessed individual symptoms	Patient-reported reflective assessment	Patient-reported instantaneous assessment	Physician-assessed individual symptoms
Nasal congestion						
LS mean treatment difference from placebo	–0.19	–0.20	–0.19	–0.21	–0.23	–0.16
95% CI	–0.3 to –0.1	–0.3 to –0.1	–0.4 to 0.0	–0.3 to –0.1	–0.3 to –0.1	–0.3 to 0.0
P value	<.001	<.001	.015	<.001	<.001	.041
Nasal itching						
LS mean treatment difference from placebo	–0.15	–0.13	–0.27	–0.15	–0.13	–0.19
95% CI	–0.3 to 0.0	–0.2 to 0.0	–0.4 to –0.1	–0.3 to 0.0	–0.2 to 0.0	–0.4 to 0.0
P value	.007	.019	.001	.005	.012	.024
Rhinorrhea						
LS mean treatment difference from placebo	–0.20	–0.16	–0.28	–0.21	–0.18	–0.25
95% CI	–0.3 to –0.1	–0.3 to –0.1	–0.4 to –0.1	–0.3 to –0.1	–0.3 to –0.1	–0.4 to –0.1
P value	<.001	.003	<.001	<.001	<.001	.001
Sneezing						
LS mean treatment difference from placebo	–0.17	–0.14	–0.22	–0.19	–0.18	–0.14
95% CI	–0.3 to –0.1	–0.2 to 0.0	–0.4 to –0.1	–0.3 to –0.1	–0.3 to –0.1	–0.3 to 0.0
P value	.002	.006	.005	<.001	<.001	.074

Abbreviations: BDP, beclomethasone dipropionate; CI, confidence interval; LS, least-squares.

than the 0.55-unit threshold, treatment with 80 or 160 µg/d of BDP nasal aerosol is considered a clinically meaningful improvement in nasal symptoms in pediatric patients with SAR.¹⁴ Also, for the 2 doses

tested, numerically greater nasal symptom improvements seen in the AM iTNSS (predose) indicate that the efficacy was maintained over the entire 24-hour dosing interval, thus confirming BDP nasal

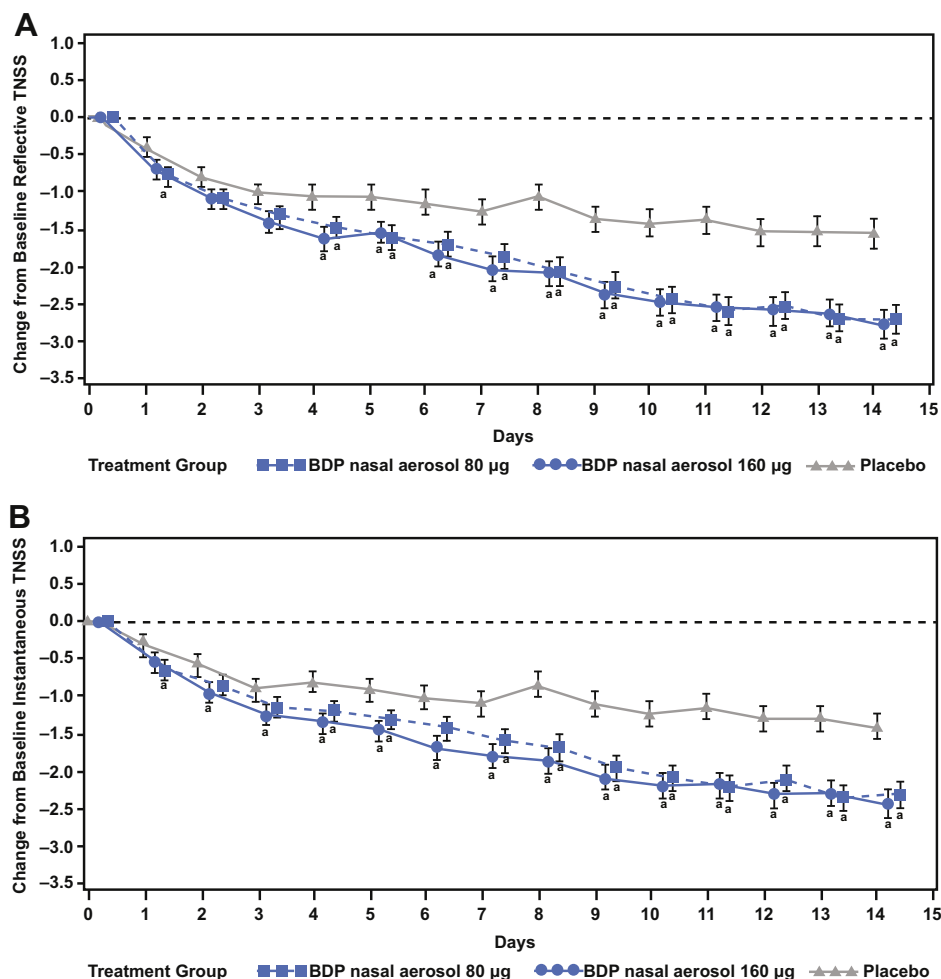


Figure 2. Change from baseline in average morning and evening patient-reported (A) reflective and (B) instantaneous total nasal symptom score (TNSS) over time (intent-to-treat population). ^aDenotes time points with $P < .05$ for treatment difference compared with placebo. BDP, beclomethasone dipropionate.

aerosol as an effective once-daily treatment for SAR. Improvements seen for the AM rTNSS and iTNSS were similar in magnitude to those observed for PM rTNSS and iTNSS, respectively, over the 2-week treatment period, further supporting the maintenance of efficacy throughout the 24-hour period.

The most frequent TEAE was epistaxis, which occurred in similar proportions in each treatment group. Although nasal septum perforation was reported in 1 patient randomly assigned to 160 $\mu\text{g}/\text{d}$ of BDP nasal aerosol, the patient did, in fact, complete the study. It should be noted that this patient had a history of epistaxis and 2 nasal surgeries before screening. No deaths or serious TEAEs were reported in this study. Five patients withdrew because of TEAEs (2 patients in the BDP nasal aerosol 80- $\mu\text{g}/\text{d}$ group, 2 in the BDP nasal aerosol 160- $\mu\text{g}/\text{d}$ group, and 1 in the placebo group), although none of these AEs were considered by the investigator to be related to the study medication. Consistent with results reported in adolescent and adult patients with AR,^{11,12} results from the present study indicate that the incidence of AEs in patients treated with BDP nasal aerosol was similar to that of placebo in pediatric patients with SAR. Because corticosteroids should be used at the lowest effective dose, especially in children, 80 $\mu\text{g}/\text{d}$ is considered the optimally safe and efficacious dose of BDP nasal aerosol for use in pediatric patients. Future clinical studies will focus on further evaluation of the efficacy and safety of 80 $\mu\text{g}/\text{d}$ of BDP nasal aerosol in pediatric patients with AR.

Although the safety and efficacy of INs are well established, concerns remain among health care providers and patients regarding the potential for systemic AEs.^{15,16} As a class, corticosteroids have the potential to suppress hypothalamic–pituitary–adrenal (HPA) axis function. In pediatric and adolescent patients, HPA-axis suppression can lead to decreased growth velocity.¹⁷ For example, a high dose of an aqueous nasal spray formulation of BDP (168 μg twice daily; total, 336 $\mu\text{g}/\text{d}$) has been associated with a decrease in growth velocity, but not HPA-axis function, in pediatric patients with PAR.¹⁸ However, the design of that study called for twice-daily administration of study medication (ie, morning and evening) and evening administration of exogenous corticosteroids is known to increase the potential for suppression of endogenous cortisol secretion (because of the diurnal rhythms of cortisol secretion). In the present study, BDP nasal aerosol was administered once daily in the morning, thus decreasing the risk for endogenous cortisol suppression. In addition, the present study with BDP nasal aerosol demonstrated the efficacy for improving nasal symptoms of AR in pediatric patients with a greater than 4-fold lower dose of BDP (80 $\mu\text{g}/\text{d}$) compared with the previous aqueous formulation (336 $\mu\text{g}/\text{d}$). Based on the morning administration and low dose of BDP nasal aerosol needed, the potential risk of HPA-axis suppression and growth velocity decrease is likely to be less with BDP nasal aerosol compared with previous aqueous formulations. In addition, results from several recently reported studies that evaluated the safety and efficacy of treatment with BDP nasal aerosol in adolescent and adult patients with PAR did not show systemically relevant safety profile differences between 320 $\mu\text{g}/\text{d}$ of BDP nasal aerosol and placebo with respect to HPA-axis function or long-term safety.^{19,20} The lack of HPA-axis suppression also was seen in the subgroup analysis of adolescent patients (12–17 years of age, $n = 25$) similar to that seen for the overall study population ($n = 98$).¹⁹

With all INs, it is suggested that the lowest effective dose be used to manage the nasal symptoms associated with AR. It is important to note that the results of a pharmacokinetic study evaluating the systemic levels of beclomethasone 17-monopropionate (active metabolite of BDP) after a single dose of intranasally administered or orally inhaled BDP hydrofluoroalkane in healthy patients indicated that 320 μg of BDP nasal aerosol has less systemic bioavailability (approximately 4-fold lower) compared with 320 μg of orally inhaled BDP hydrofluoroalkane in healthy patients.²¹ Furthermore, the systemic bioavailability of 80 μg of BDP nasal aerosol was

approximately 4-fold lower compared with 320 μg of BDP nasal aerosol, indicating dose proportionality.²¹ Taken together, the established safety profile of orally inhaled BDP aerosol, the systemic bioavailability data, and the present data supporting the efficacy and safety of BDP nasal aerosol in children suggest an overall safe and acceptable tolerability profile of 80 $\mu\text{g}/\text{d}$ of BDP nasal aerosol for pediatric patients. However, additional studies are needed to further evaluate the safety of once-daily treatment with 80 μg of BDP nasal aerosol in pediatric patients.

In conclusion, treatment with BDP nasal aerosol at a dose 80 or 160 $\mu\text{g}/\text{d}$ resulted in significant and clinically meaningful improvements in nasal symptoms associated with moderate to severe SAR. The 2 doses of BDP nasal aerosol were well tolerated, and the incidence of AEs was similar to that of placebo. Overall, these data suggest that 80 $\mu\text{g}/\text{d}$ of BDP nasal aerosol will be an effective and well-tolerated treatment option for pediatric patients with SAR.

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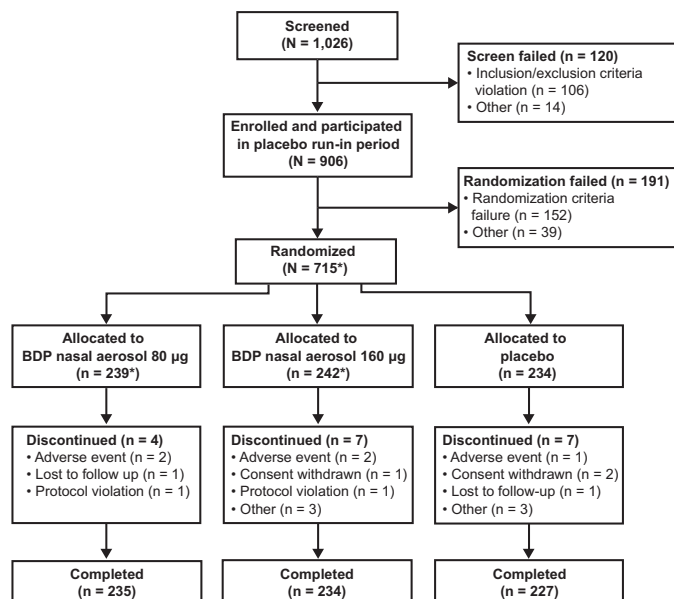
Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.07.033>

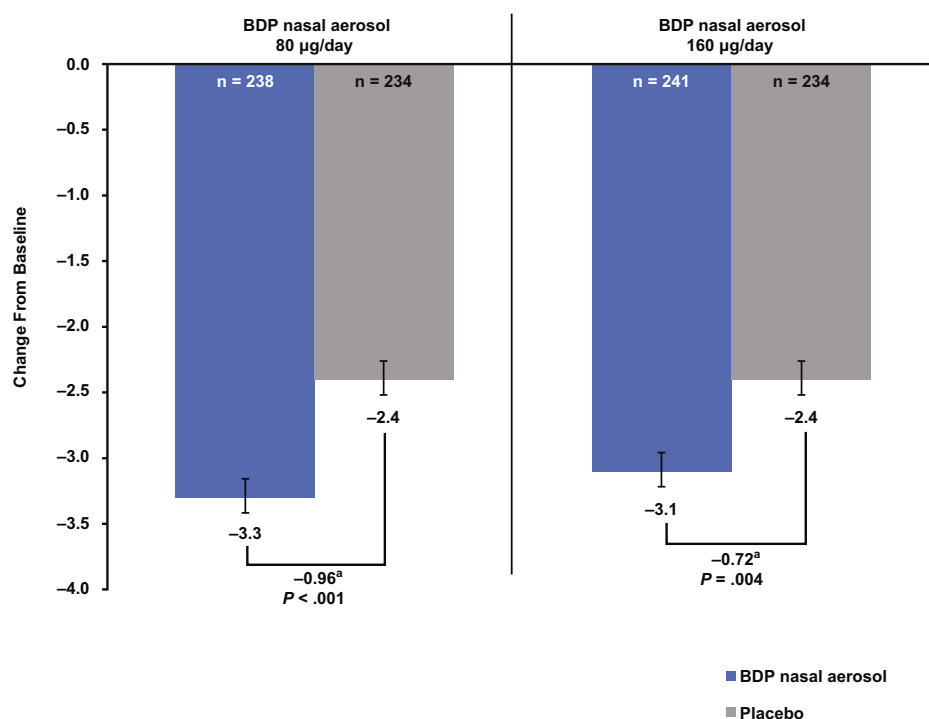
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eFigure 1. Patient disposition. *One patient was randomly assigned to BDP nasal aerosol 160 µg/day in error and never received any study medication. One patient who was randomly assigned to BDP nasal aerosol 80 µg/day had no post-baseline efficacy assessments and was excluded from the intent-to-treat population. BDP, beclomethasone dipropionate.



eFigure 2. Treatment with beclomethasone dipropionate (BDP) nasal aerosol resulted in greater improvements in physician-assessed nasal symptom score at week 2 compared with placebo (intent-to-treat population). Values represent least-squares mean ± standard error. ^aTreatment difference.