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## Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis

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### ARTICLE INFO

#### Article history:

Received for publication March 6, 2015.

Received in revised form April 28, 2015.

Accepted for publication May 16, 2015.

### ABSTRACT

**Background:** Beclomethasone dipropionate (BDP) nasal aerosol (non-aqueous) is approved for management of seasonal and perennial allergic rhinitis (PAR) in adolescents and adults.

**Objective:** To evaluate the efficacy and safety of BDP nasal aerosol at 80  $\mu$ g/day in children with PAR.

**Methods:** This 12-week, phase 3, double-blinded, placebo-controlled, parallel-group study randomized 547 children (4–11 years old) with PAR to once-daily BDP nasal aerosol at 80  $\mu$ g/day or placebo. The primary end point was change from baseline in average morning and evening reflective total nasal symptom score (rTNSS) during the first 6 weeks of treatment in patients 6 to 11 years old. Changes from baseline in average morning and evening instantaneous TNSS (iTNSS) in children 6 to 11 years old and average rTNSS and iTNSS in children 4 to 11 years old were assessed during the first 6 weeks of treatment.

**Results:** Improvements were significantly greater with BDP nasal aerosol than with placebo during the first 6 weeks of treatment in children 6 to 11 years old in average morning and evening rTNSS and iTNSS (mean treatment difference  $-0.66$  [ $P = .002$ ] and  $-0.58$  [ $P = .004$ ], respectively). Improvements in average morning and evening rTNSS and iTNSS also were significantly greater in patients 4 to 11 years receiving BDP nasal aerosol than with placebo during the first 6 weeks of treatment ( $P = .002$  and  $P = .004$ , respectively). Similar improvements were seen during 12 weeks of treatment. The safety profile of BDP nasal aerosol was comparable to that of placebo.

**Conclusion:** The BDP nasal aerosol at 80  $\mu$ g/day in children 4 to 11 years old was well tolerated and effective in controlling nasal symptoms of PAR.

**Trial Registration:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov), identifier NCT01783548.

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### Introduction

Perennial allergic rhinitis (PAR) is common in children and is associated with persistent, year-round symptoms that include sneezing, itching, rhinorrhea, and nasal congestion.<sup>1,2</sup> PAR is differentiated from seasonal allergic rhinitis (SAR) by temporal variations in symptoms and differences in allergens (PAR is more often associated with indoor allergens, such as dust mites, animal dander, and mold; SAR is associated with seasonal allergens that include tree, grass, and weed pollens).<sup>3</sup> The effective diagnosis and treatment of PAR is particularly

important in children because, if untreated, it can result in serious impairment in social, behavioral, and academic performance.<sup>4,5</sup>

The standard treatment to control PAR symptoms is use of intranasal corticosteroids (INs), which effectively relieve the symptoms of allergic inflammation.<sup>6,7</sup> Until recently, INs have been available in only aqueous formulations.<sup>8</sup> However, substantial evidence indicates that aqueous formulations of INs are associated with side effects known to decrease patient adherence, such as discomfort and the dripping of medication down the back of the throat.<sup>9,10</sup> Beclomethasone dipropionate (BDP) is an anti-inflammatory corticosteroid for the management of allergic rhinitis (AR) that was originally developed in aqueous and dry nasal aerosol formulations.<sup>2</sup> Although the dry formulations avoided the undesirable side effects of the aqueous formulations, they used now-prohibited chlorofluorocarbons as propellants and, hence, are no longer available.<sup>8</sup>

A novel BDP nasal aerosol that uses hydrofluoroalkane as a propellant has recently been developed as a non-aqueous IN treatment

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**Disclosures:** Dr Berger has received fees for consultation, speaking, and research from Teva, Meda, Genentech, Alcon, Allergan, and Mylan and research funding from Circassia, Anacor, and Janssen. Dr Li owns stock in Teva Pharmaceuticals. Dr Tantry owns stock in Teva Pharmaceuticals. Dr Amar has received funding from Teva Pharmaceuticals.

**Funding:** Teva Branded Pharmaceutical Products R&D, Inc, Frazer, Pennsylvania.

<http://dx.doi.org/10.1016/j.anai.2015.05.012>

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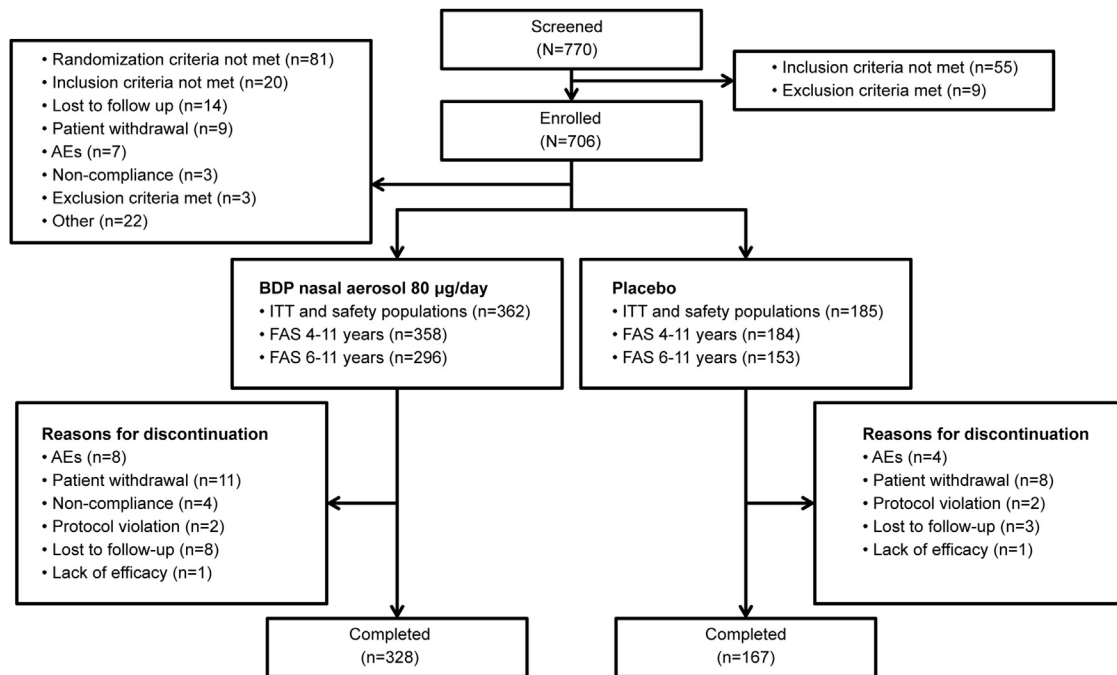


**Figure 1.** Patient disposition. 80 µg/day = 40 µg/actuation, 1 actuation/nostril. AE, adverse event; BDP, beclomethasone dipropionate; FAS, full-analysis set; ITT, intent to treat.

for AR.<sup>11</sup> Results of several trials have shown the efficacy and safety of this treatment in adolescents and adults with PAR<sup>8,12</sup> and with SAR.<sup>11</sup> Similarly, a dose-ranging study found that a BDP nasal aerosol that used a hydrofluoroalkane propellant was safe and effective in children 6 to 11 years of age with SAR.<sup>13</sup> To extend the clinical experience with BDP non-aqueous nasal aerosol, the present study was conducted to evaluate the safety and efficacy of 80 µg/day of BDP nasal aerosol in children with PAR who were 4 to 11 years of age.

## Methods

### Study Design and Treatment

This was a randomized, double-blinded, placebo-controlled, parallel-group, phase 3 clinical trial conducted at 62 US centers to

investigate the efficacy and safety of a BDP nasal aerosol in pediatric patients with PAR. The study was reviewed and approved by a central institutional review board and conducted in accordance with the ethical standards of the Declaration of Helsinki. This study was registered with [ClinicalTrials.gov](http://ClinicalTrials.gov) (identifier NCT01783548). Patient assent and parent or legal guardian consent was obtained for all patients at the initial screening visit.

An initial run-in period of 7 to 21 days involved self-administration or assisted administration of a placebo nasal aerosol once daily. Patients (with the assistance of parents or guardians) assessed and reported the severity of symptoms, including rhinorrhea, nasal congestion, nasal itching, and sneezing. The grading scale ranged from 0 (absence of symptoms) to 3 (severe symptoms). The total nasal symptom score (TNSS) was defined as the sum of the 4

**Table 1**  
Patient demographics and baseline characteristics (intent-to-treat population)

|                                                 | BDP nasal aerosol at 80 µg/day (n = 362) | Placebo (n = 185) | Total (N = 547) |
|-------------------------------------------------|------------------------------------------|-------------------|-----------------|
| Age (y)                                         |                                          |                   |                 |
| Mean (SD)                                       | 8.0 (2.16)                               | 8.0 (2.23)        | 8.0 (2.18)      |
| Median                                          | 8.0                                      | 8.0               | 8.0             |
| Min–Max                                         | 4–11                                     | 4–11              | 4–11            |
| Age group, n (%)                                |                                          |                   |                 |
| 4–5 y                                           | 62 (17)                                  | 31 (17)           | 93 (17)         |
| 6–11 y                                          | 300 (83)                                 | 154 (83)          | 454 (83)        |
| Sex, n (%)                                      |                                          |                   |                 |
| Girls                                           | 175 (48)                                 | 71 (38)           | 246 (45)        |
| Boys                                            | 187 (52)                                 | 114 (62)          | 301 (55)        |
| Race, n (%)                                     |                                          |                   |                 |
| White                                           | 272 (75)                                 | 145 (78)          | 417 (76)        |
| Black                                           | 65 (18)                                  | 25 (14)           | 90 (16)         |
| Other <sup>a</sup>                              | 25 (7)                                   | 15 (8)            | 40 (7)          |
| Ethnicity, n (%) <sup>b</sup>                   |                                          |                   |                 |
| Hispanic or Latino                              | 144 (40)                                 | 75 (41)           | 219 (40)        |
| Not Hispanic, not Latino                        | 217 (60)                                 | 110 (59)          | 327 (60)        |
| Weight (kg), mean (SD)                          | 33.4 (13.40)                             | 33.8 (13.24)      | 33.5 (13.34)    |
| Body mass index (kg/m <sup>2</sup> ), mean (SD) | 18.6 (4.22)                              | 18.9 (4.33)       | 18.7 (4.25)     |

Abbreviations: BDP, beclomethasone dipropionate; Max, maximum; Min, minimum.

<sup>a</sup>Includes 11 Asian patients, 4 American Indian or Alaskan native patients, 2 Native Hawaiian or other Pacific Islander patients, and 23 patients of other race.

<sup>b</sup>Ethnicity was unknown for 1 patient treated with BDP nasal aerosol at 80 µg/day.

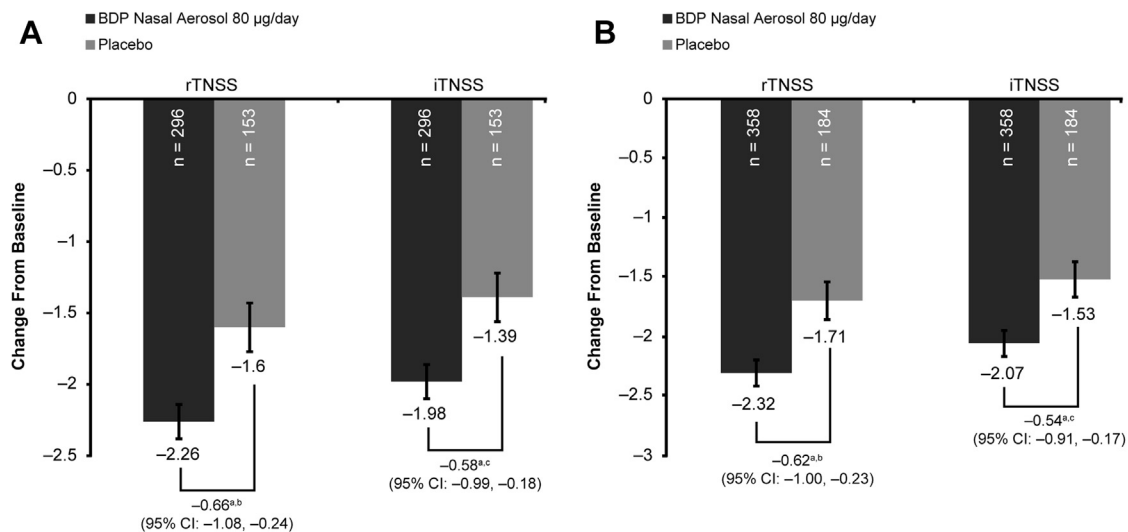


**Figure 2.** Daily average morning and evening patient-reported rTNSS and iTNSS during the first 6 weeks of treatment in patients (A) 6 to 11 years of age and (B) 4 to 11 years of age (full-analysis set). 80 µg/day = 40 µg/actuation, 1 actuation/nostril. Values represent least squares mean ± SE. <sup>a</sup>Least squares mean treatment difference from placebo. <sup>b</sup>*P* = .002. <sup>c</sup>*P* = .004. BDP, beclomethasone dipropionate; CI, confidence interval; iTNSS, instantaneous total nasal symptom score; rTNSS, reflective total nasal symptom score.

scores identified for each of these symptoms. For the treatment period, patients were randomly assigned in a 2:1 ratio to receive for 12 weeks 80 µg of BDP nasal aerosol (40 µg/actuation, 1 actuation/nostril) or a placebo nasal aerosol (non-aqueous) once daily in the morning. AR assessment diaries were completed twice daily during the treatment period. To monitor any adverse events (AEs), a follow-up phone call was made 3 to 5 days after the final treatment visit.

### Patients

The study involved boys and girls 4 to 11 years old, in general good health, and with a documented history of PAR (≥12 months for 6- to 11-year-olds, ≥6 months for 4- to 5-year-olds). At enrollment, patients were required to have a positive skin prick test result for at least 1 known PAR allergen, with a positive test result defined as a wheal diameter at least 5 mm larger than the control wheal (≥3 mm for 4- to 5-year-olds). Each patient also had to achieve a minimum patient-reported reflective TNSS (rTNSS; evaluation of symptom severity during the preceding 12 hours) of at least 6 of 12 on the day of the initial screening visit. To continue in the study, patients were required to be showing symptoms, with an average rTNSS of at least 6 for the last 4 days of the run-in period, have an average self-reported nasal

congestion score of at least 2 during the final 4 days of the run-in period, and to have taken their medication at least 80% of the time during the run-in period.

Patients were excluded from the study if there was a history of a nasal condition, including nasal polyps or other clinically significant respiratory tract malformation; recent nasal biopsy; nasal trauma or surgery; atrophic rhinitis; or rhinitis medicamentosa within the 60 days preceding the screening visit. Female patients of childbearing potential known to be sexually active; patients anticipating seasonal exacerbation of symptoms; patients with a history of respiratory infection or disorder within the 14 days preceding screening; or with known hypersensitivity to any corticosteroid or excipients of the study medication also were excluded.

Loratadine was the only rescue medication permitted for use on an as-needed basis but was restricted for the first 6 weeks of the study in patients 6 to 11 years of age. The maximum dosage allowed was 5 mL/day (for loratadine syrup, 1 mg/mL) or 5 mg/day (loratadine tablet) for 4- to 5-year-olds or 10 mL/day (for loratadine syrup, 1 mg/mL) or 10 mg/day (loratadine tablet) for 6- to 11-year-olds. Patients also were permitted the use of some medications, with restrictions, including pimecrolimus plus tacrolimus, low-dose antibiotics as prophylaxis, stable immunotherapy treatments, aspirin,

**Table 2**

Change from baseline in weekly average morning and evening patient-reported rTNSS and iTNSS over the 12 weeks of treatment (full-analysis set)

|                                       | rTNSS                                       |            | iTNSS                                       |            |
|---------------------------------------|---------------------------------------------|------------|---------------------------------------------|------------|
|                                       | BDP nasal aerosol at 80 µg/day <sup>a</sup> | Placebo    | BDP nasal aerosol at 80 µg/day <sup>a</sup> | Placebo    |
| 6- to 11-year-olds, n                 | 296                                         | 153        | 296                                         | 153        |
| Baseline, mean (SD)                   | 8.5 (1.55)                                  | 8.5 (1.62) | 7.8 (2.00)                                  | 7.7 (2.06) |
| Overall LS change from baseline, mean | -2.72                                       | -2.11      | -2.39                                       | -1.81      |
| LS difference from placebo, mean      | -0.61                                       |            | -0.58                                       |            |
| 95% CI                                | -1.04 to -0.18                              |            | -0.99 to -0.17                              |            |
| P value                               | .006                                        |            | .006                                        |            |
| 4- to 11-year-olds, n                 | 358                                         | 184        | 358                                         | 184        |
| Baseline, mean (SD)                   | 8.6 (1.53)                                  | 8.6 (1.67) | 7.9 (1.96)                                  | 7.7 (2.12) |
| Overall LS change from baseline, mean | -2.78                                       | -2.25      | -2.48                                       | -1.97      |
| LS difference from placebo, mean      | -0.53                                       |            | -0.52                                       |            |
| 95% CI                                | -0.93 to -0.13                              |            | -0.90 to -0.14                              |            |
| P value                               | .009                                        |            | .008                                        |            |

Abbreviations: BDP, beclomethasone dipropionate; CI, confidence interval; iTNSS, instantaneous total nasal symptom score; LS, least squares; rTNSS, reflective total nasal symptom score.

<sup>a</sup>80 µg/day = 40 µg/actuation, 1 actuation/nostril.

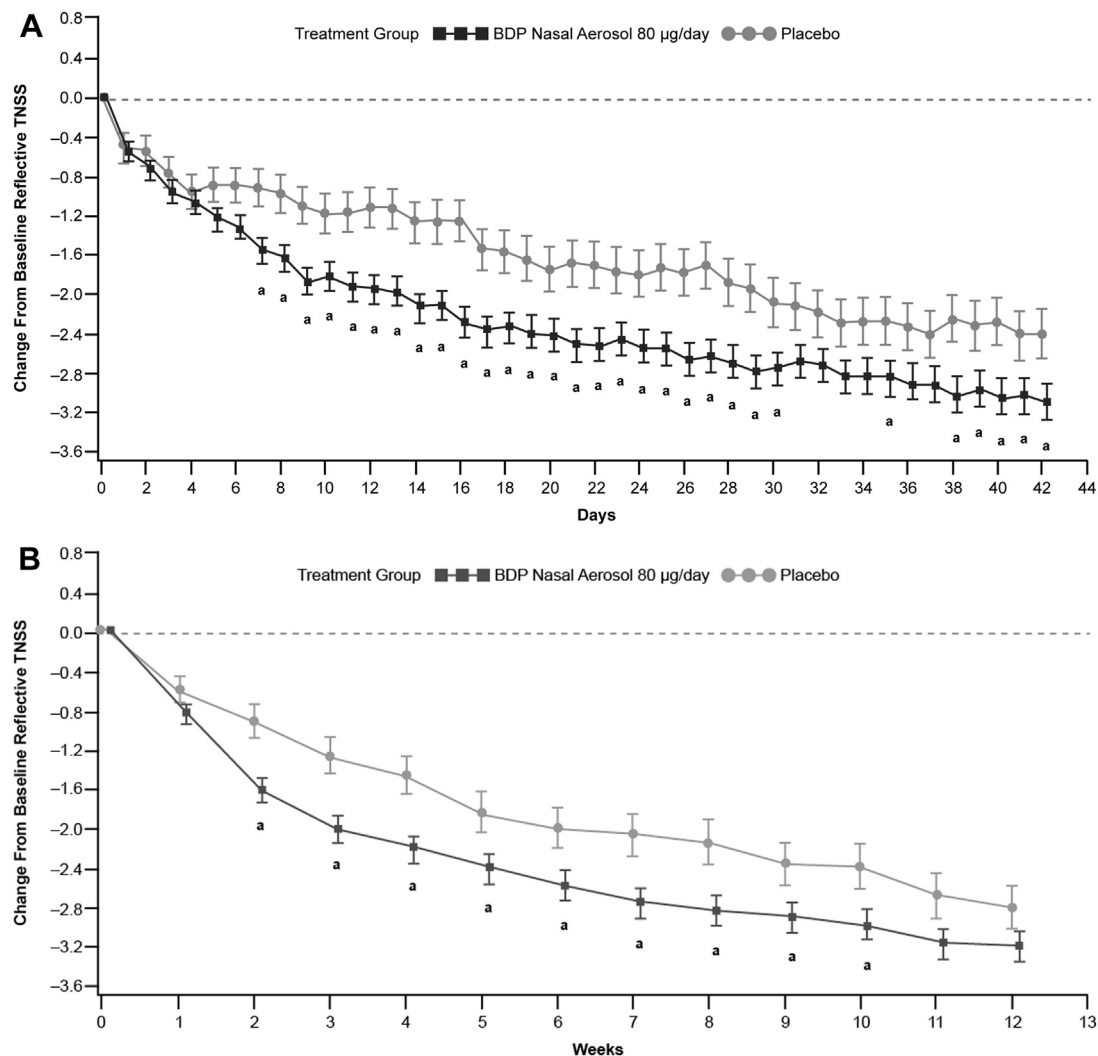


**Figure 3.** Average morning and evening patient-reported reflective TNSS in patients 6 to 11 years of age (A) daily during the first 6 weeks of treatment and (B) weekly during 12 weeks of treatment (full-analysis set). 80 µg/day = 40 µg/actuation, 1 actuation/nostril. <sup>a</sup>P < .05, compared with placebo. BDP, beclomethasone dipropionate; TNSS, total nasal symptom score.

topical hydrocortisone, and central nervous system stimulants for attention deficit disorder. No other medications were permitted during the study, with the exception of those necessary to treat AEs.

#### Study End Points and Assessments

The primary end point was the change from baseline in the average morning and evening rTNSS during the first 6 weeks of treatment for patients 6 to 11 years old. Secondary end points included the change from baseline in the average morning and evening instantaneous TNSS (iTNSS; evaluation of symptom severity during the past 10 minutes) in 6- to 11-year-olds and the change from baseline in average rTNSS and iTNSS in 4- to 11-year-olds during the first 6 weeks of treatment. The baseline score was defined as the average morning and evening patient-reported TNSS during the 4 days preceding randomization. Additional end points included the average rTNSS for each day for the 6- to 11- and 4- to 11-year-old groups and the average patient-reported individual nasal symptoms during the first 6 weeks of treatment for 6- to 11-year-olds. Efficacy end points also were assessed during 12 weeks of treatment. As mentioned earlier, although the primary end point was the change from baseline in the average morning and evening rTNSS during the first 6 weeks of treatment for patients, the study was conducted for evaluation of safety during 12 weeks.

Safety was monitored at weeks 1, 2, 4, 6, 8, 10, and 12 by physical examination; ear, nose and throat examination; vital sign monitoring; and the occurrence of AEs during the 12-week study.

#### Statistical Methods

The intent-to-treat patient population included all randomized patients, with treatment according to randomization group regardless of actual treatment received. The full-analysis set, used in efficacy analyses, was composed of all patients in the intent-to-treat population who received at least 1 dose of study medication and had at least 1 subject-reported rTNSS assessment after the baseline. Safety analyses were performed on the safety population, which was composed of all randomized patients who received at least 1 dose of study medication, with treatment assigned according to the treatment received rather than by randomized treatment group. In this study, the safety population was identical to the intent-to-treat population because all patients received the treatment to which they were randomly assigned.

The primary end point was analyzed with a mixed model for repeated measures, with covariate adjustment for baseline, day, treatment, and treatment-by-day interaction using the full-analysis set for children 6 to 11 years of age. Day was treated as an unordered categorical variable. A first-order autoregressive structure was

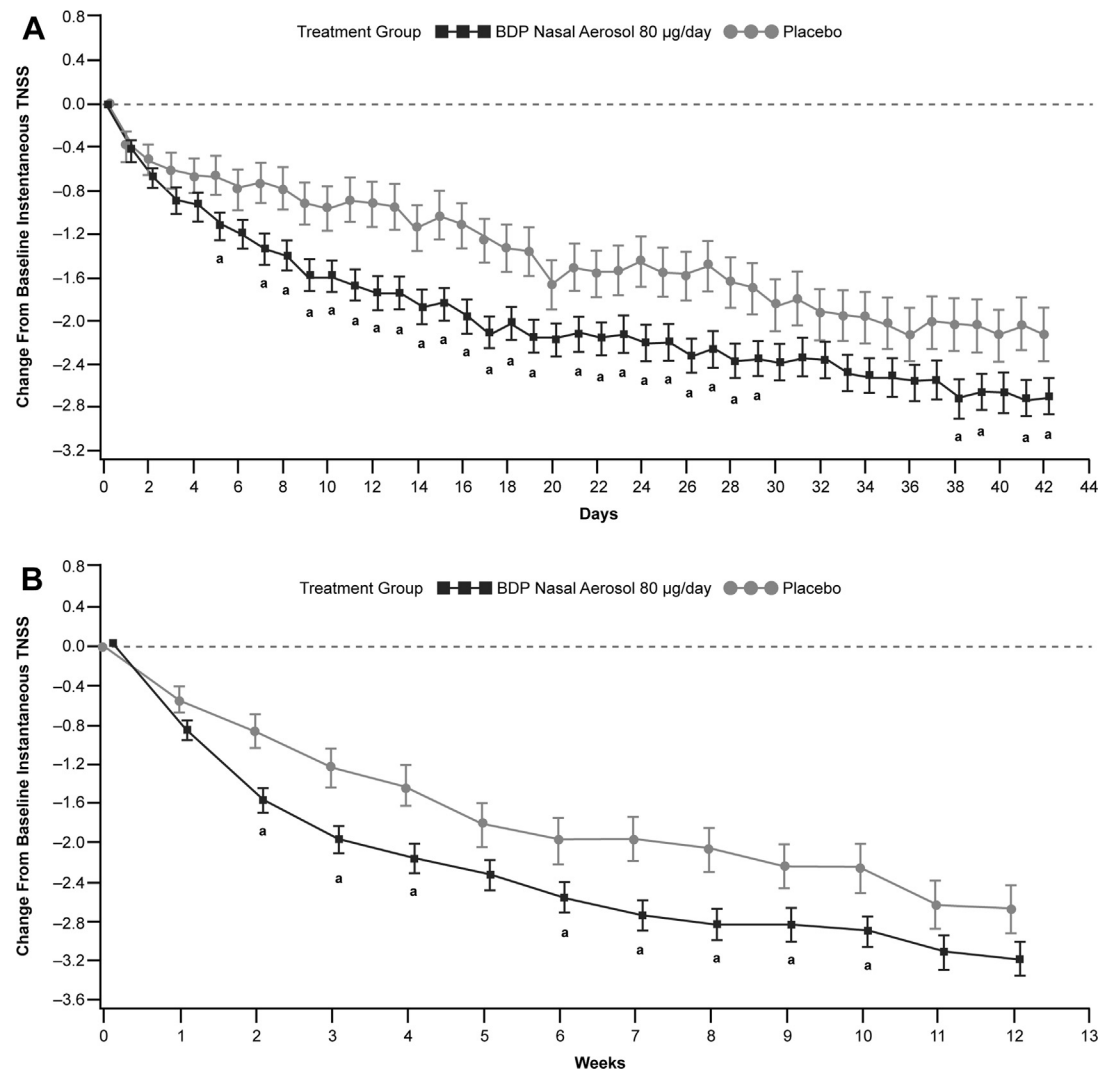


**Figure 4.** Average morning and evening patient-reported instantaneous TNSS in patients 6 to 11 years of age (A) daily during the first 6 weeks of treatment and (B) weekly during 12 weeks of treatment (full-analysis set). 80 µg/day = 40 µg/actuation, 1 actuation/nostril. <sup>a</sup>*P* < .05, compared with placebo. BDP, beclomethasone dipropionate; TNSS, total nasal symptom score.

used to model inpatient correlation, and, in conjunction with treating patient as a random effect, this yielded a correlation structure in which observations from the same patient were considered to be correlated, with observations closer in time being more correlated. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated. Imputation for missing data was not performed because the extent of missing data was predicted to be low. Type 1 error was controlled for treatment comparisons by use of a sequential approach. In addition, an exploratory analysis was performed to evaluate possible geographic differences in treatment effects. To investigate center effects, the primary end point was analyzed using a mixed model for repeated measures; however, center and treatment-by-center interaction were added as additional covariates. Secondary and additional end points were analyzed in a similar fashion to the primary end point.

## Results

### Patient Disposition and Demographics

A total of 770 individuals were screened and 706 patients were enrolled in the initial placebo run-in period (Fig 1). Of the enrolled patients, 547 were randomly assigned to receive 80 µg of BDP nasal

aerosol (*n* = 362) or placebo nasal aerosol once daily (*n* = 185) and composed the safety population. The full-analysis set consisted of 449 patients 6 to 11 years of age (BDP nasal aerosol at 80 µg/day, *n* = 296; placebo, *n* = 153) and 542 patients 4 to 11 years of age (BDP nasal aerosol at 80 µg/day, *n* = 358; placebo, *n* = 184). Demographic characteristics were similar between treatment groups; however, there were more boys than girls in the placebo arm than in the 80-µg/day BDP nasal aerosol treatment arm (Table 1). Overall, 90% of randomized patients completed the study; reasons for discontinuation are shown in Figure 1.

### Efficacy

Improvements in the average morning and evening rTNSS were significantly greater with once-daily treatment of BDP nasal aerosol at 80 µg/day than with placebo during the first 6 weeks of treatment in children 6 to 11 years of age (mean treatment difference −0.66 [*P* = .002]; Fig 2A). Similarly, improvement in the average morning and evening iTNSS was significantly greater for patients treated with BDP nasal aerosol than those treated with placebo during the first 6 weeks in children 6 to 11 years of age (mean treatment difference −0.58 [*P* = .004]; Fig 2A). For children 4 to 11 years of age, improvements in the average rTNSS and average

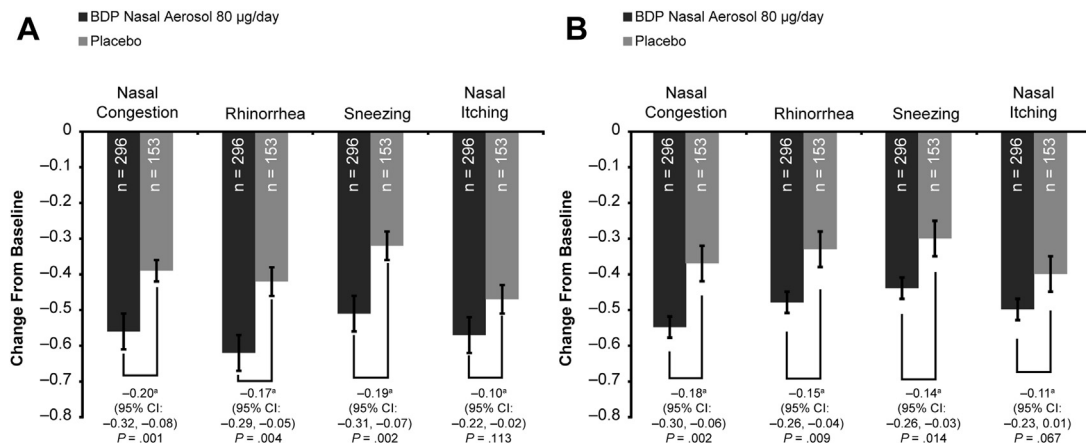


**Figure 5.** Change from baseline in daily average patient-reported reflective (A) and instantaneous (B) individual nasal symptoms during the first 6 weeks of treatment in patients 6 to 11 years of age (full-analysis set). Values represent least squares mean  $\pm$  SE. 80  $\mu$ g/day = 40  $\mu$ g/actuation, 1 actuation/nostril. <sup>a</sup>Least squares mean treatment difference from placebo. BDP, beclomethasone dipropionate; CI, confidence interval.

iTNSS were significantly greater for patients treated with BDP nasal aerosol at 80  $\mu$ g/day than those treated with placebo during the first 6 weeks of the study (mean treatment difference  $-0.62$  [ $P = .002$ ] and  $-0.54$  [ $P = .004$ ] respectively; Fig 2B). Similar results were observed for rTNSS and iTNSS during 12 weeks of treatment (mean treatment difference  $-0.61$  [ $P = .006$ ] and  $-0.58$  [ $P = .006$ ], respectively, in children 6–11 years of age, and  $-0.53$  [ $P = .009$ ] and  $-0.52$  [ $P = .008$ ], respectively, in children 4–11 years of age; Table 2).

The improvement in the daily average morning and evening rTNSS for patients 6 to 11 years of age also was significantly greater in patients treated with the BDP nasal aerosol than in those in the placebo group from day 7 onward, with the exception of days 31 to 34, 36, and 37 (Fig 3A). On a week-by-week basis, the improvement in rTNSS for patients 6 to 11 years of age was significantly greater from week 2 through week 10 (Fig 3B). Improvements in iTNSS during 6 and 12 weeks were similar to rTNSS results (Fig 4A, B). Results for patients 4 to 11 years old were similar (data not shown).

The improvement in the average patient-reported individual nasal symptoms during the first 6 weeks of treatment for 6- to 11-year-olds was significantly greater for rhinorrhea, nasal congestion, and sneezing in the group treated with the BDP nasal aerosol than in those who received placebo (Fig 5). At week 6, physician-assessed nasal symptoms showed that, in children 4 to 11 years of age, improvement in nasal congestion (mean treatment difference  $-0.19$ , 95% confidence interval  $-0.34$  to  $-0.03$ ,  $P = .017$ ) and nasal itching (mean treatment difference  $-0.17$ , 95% confidence interval  $-0.33$  to  $-0.02$ ,  $P = .031$ ) was significant compared with placebo. Average patient-reported individual nasal symptoms during the first 12 weeks of treatment were not analyzed.

### Safety

The incidence of AEs was similarly low in the 2 treatment groups; 37% of recipients of BDP nasal aerosol at 80  $\mu$ g/day and 34% of placebo recipients reported treatment-emergent AEs. No individual treatment-emergent AE was reported in more than 5% of patients in the 80- $\mu$ g/day BDP nasal aerosol group. Similarly, treatment-related AEs (TRAES) were similar between treatment groups (Table 3). The most commonly reported TRAES were epistaxis, nasal discomfort, headache, and nasal inflammation. Only 3 patients (3%) 4 to 5 years old reported AEs considered related to treatment (nausea in 1 patient treated with BDP nasal aerosol at 80  $\mu$ g/day and epistaxis and nasal discomfort in 1 patient each and treated with placebo).

Twelve patients who were randomly assigned to treatment groups discontinued because of AEs (8 [2%] in the 80- $\mu$ g/day BDP nasal aerosol group and 4 [2%] in the placebo treatment group). In the 80- $\mu$ g/day BDP nasal aerosol treatment group, discontinuations were because of exacerbation of asthma and nasal discomfort (2 patients each) and epistaxis, streptococcal pharyngitis, auricular swelling, worsening allergic conjunctivitis, body rash, worsening sinusitis, and motor tics (1 patient each). Severe TRAES were reported in 3 patients (<1%) receiving the BDP nasal aerosol at 80  $\mu$ g/day (headache, epistaxis, and oropharyngeal pain) and in 2 (1%) receiving placebo (epistaxis and nasal discomfort). There were no reports of nasal septal perforation and only 2 cases of nasal septum disorder (1 in each treatment group). There were no reports of serious AEs occurring during the treatment period, and no deaths occurred during this study.

### Discussion

The efficacy and safety of hydrofluoroalkane-propelled, non-aqueous BDP nasal aerosol have been established in adolescents and adults with PAR and with SAR.<sup>8,11,12</sup> Non-aqueous BDP nasal aerosol also has been shown to be effective and safe for the treatment of children with SAR.<sup>13</sup> However, until the present study, there had been no investigation into the efficacy and safety of non-aqueous BDP nasal aerosol in children with PAR. The primary objective of

**Table 3**

Treatment-related adverse events (safety population)

|                               | BDP nasal aerosol at 80 $\mu$ g/day <sup>a</sup> (n = 362) | Placebo (n = 185) |
|-------------------------------|------------------------------------------------------------|-------------------|
| Any TRAE, n (%)               | 16 (4)                                                     | 7 (4)             |
| Epistaxis, n (%)              | 9 (2)                                                      | 3 (2)             |
| Nasal discomfort, n (%)       | 5 (1)                                                      | 1 (<1)            |
| Headache, n (%)               | 2 (<1)                                                     | 1 (<1)            |
| Nasal inflammation, n (%)     | 2 (<1)                                                     | 1 (<1)            |
| Nasal mucosal disorder, n (%) | 1 (<1)                                                     | 1 (<1)            |
| Nasal septum disorder, n (%)  | 1 (<1)                                                     | 1 (<1)            |
| Oropharyngeal pain, n (%)     | 1 (<1)                                                     | 1 (<1)            |
| Nausea, n (%)                 | 1 (<1)                                                     | 0                 |
| Mucosal inflammation, n (%)   | 1 (<1)                                                     | 0                 |
| Excoriation, n (%)            | 1 (<1)                                                     | 0                 |
| Nasal edema, n (%)            | 1 (<1)                                                     | 0                 |
| Urticaria, n (%)              | 1 (<1)                                                     | 0                 |

Abbreviations: BDP, beclomethasone dipropionate; TRAE, treatment-related adverse event.

<sup>a</sup>80  $\mu$ g/day = 40  $\mu$ g/actuation, 1 actuation/nostril.

the present study was to evaluate the effectiveness of once-daily treatment with 80  $\mu\text{g/day}$  of BDP nasal aerosol compared with placebo. Administration of non-aqueous BDP nasal aerosol at 80  $\mu\text{g/day}$  compared with placebo showed a statistically significant and clinically meaningful ( $>0.55 \text{ U}^{14}$ ) improvement in nasal symptoms that was sustained for 12 weeks of treatment. These results are in accordance with findings from a previous study that showed a clinically meaningful improvement in nasal symptoms in children with SAR who were receiving BDP nasal aerosol at 80 and 160  $\mu\text{g/day}$ .<sup>13</sup> In the present study, the benefits of treatment with the BDP nasal aerosol were seen within the first week, with patients also reporting significant improvement in the immediate presentation of overall symptoms (iTSS) and for individual nasal symptoms. Furthermore, symptom improvements were maintained for 12 weeks of treatment, suggesting sustained effectiveness with BDP nasal aerosol treatment in this pediatric PAR patient population. These results are in accordance with those from previous investigations of BDP nasal aerosol for the management of AR in varying age groups.<sup>11–13</sup>

In addition to investigating the efficacy and safety of BDP nasal aerosol in children 6 to 11 years of age, the present study included a subpopulation of 4- and 5-year-old children. This allowed the analysis of safety and provided supportive efficacy data for a subset of the pediatric population not previously evaluated in trials of non-aqueous BDP nasal aerosol. Inclusion of children 4 and 5 years of age in this analysis did not substantially alter the average change in rTSS between BDP nasal aerosol and placebo, indicating that a clinically meaningful improvement in nasal symptoms also was found for children 4 to 11 years of age. The relatively small number of patients 4 to 5 years of age precluded conclusions regarding efficacy end points in this age group. The inclusion of younger patients in clinical trials of AR treatments is of particular importance because 40% of children with AR will have symptoms by 6 years of age.<sup>1</sup>

The safety and tolerability profile of BDP nasal aerosol was comparable to that of placebo in the pediatric PAR patient population of the present study. Overall, BDP nasal aerosol at a dosage of 80  $\mu\text{g/day}$  was well tolerated in pediatric patients. The incidence of AEs was low, and the safety profile was similar to that of placebo. The most commonly occurring TRAEs were epistaxis, nasal discomfort, headache, and nasal inflammation, which are consistent with TRAEs identified in other studies of BDP nasal aerosol.<sup>8,11,12</sup> Therefore, the most commonly reported clinically relevant AEs were those expected for an INS in aqueous and non-aqueous formulations. The safety profile in patients 4 to 5 years of age was similar to that observed for children 6 to 11 years of age.

Although safety profiles of INSs are well established, there is some concern regarding the potential for systemic complications associated with long-term treatment. These concerns are based primarily on the systemic AEs that have been reported with oral and high-dose inhalation corticosteroids, including growth inhibition, hypothalamic–pituitary–adrenal (HPA) axis suppression, decreased bone mineral density, myopathy, cataracts, glaucoma, hypertension, hyperglycemia, and thin skin.<sup>3,15</sup> In comparison, the intranasal route is thought to decrease the likelihood of systemic effects because of lower bioavailability.<sup>16</sup> However, for a pediatric population receiving INSs for extended periods, any potential for growth inhibition and HPA axis suppression is relevant. Corticosteroids are known to have an effect on almost every aspect of a child's growth axis,<sup>17</sup> and results of several studies have indicated that long-term intranasal delivery of BDP is associated with a slower growth rate in pediatric populations.<sup>16,18</sup> However, with long-term studies of inhaled corticosteroids suggesting that there is

no effect on final adult height,<sup>19</sup> the clinical relevance of this growth inhibition is unclear.<sup>16</sup> Evidence also suggests that INSs do not have a significant effect on the HPA axis.<sup>8,15</sup> Six weeks of treatment with once-daily BDP nasal aerosol at 320  $\mu\text{g/day}$  did not affect HPA axis function in adolescent (12–17 years of age) and adult patients with PAR.<sup>8</sup> Control of nasal symptoms in the present study was achieved with a 4-fold lower dose.

In conclusion, this study clearly showed that once-daily treatment with BDP nasal aerosol at a dose of 80  $\mu\text{g}$  was well tolerated and provided significant and clinically meaningful improvement in the nasal symptoms of PAR in a pediatric population 4 to 11 years of age. Therefore, these findings support the safety and efficacy of BDP nasal aerosol for the continuous and sustained management of AR in a pediatric patient population 4 to 11 years of age.

## Acknowledgments

The authors thank the study participants, the study team, and the investigators for their valuable contributions in conducting this study. The authors also acknowledge writing and editorial support by ApotheCom (Yardley, Pennsylvania), with funding by Teva.

## References

- [1] Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001;108(suppl 1):S2–S8.
- [2] Ratner PH, Melchior A, Dunbar SA, Tantry SK, Dorinsky P. 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*. 2012;34:1422–1431.
- [3] Turner PJ, Kemp AS. Allergic rhinitis in children. *J Paediatr Child Health*. 2012;48:302–310.
- [4] Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. *J Allergy Clin Immunol*. 2000;105:S616–S621.
- [5] Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol*. 2001;108(suppl 1):S45–S53.
- [6] Berger WE. Overview of allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;90:7–12.
- [7] Kim K, Weiswasser M, 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*. 2007;20:229–249.
- [8] Ratner PH, Miller SD, Hampel FC Jr, Melchior A, Dunbar SA, Tantry SK. Once-daily treatment with beclomethasone dipropionate nasal aerosol does not affect hypothalamic–pituitary–adrenal axis function. *Ann Allergy Asthma Immunol*. 2012;109:336–341.
- [9] Fromer LM, Ortiz G, Ryan SF, Stolfow SW. Insights on allergic rhinitis from the patient perspective. *J Fam Pract*. 2012;61(suppl 2):S16–S22.
- [10] Naclerio RM, Hadley JA, Stolfow S, Nelson HS. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc*. 2007;28:S11–S17.
- [11] van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2012;33:386–396.
- [12] Meltzer EO, Jacobs RL, LaForce CF, Kelley L, Dunbar SA, Tantry SK. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. *Allergy Asthma Proc*. 2012;33:249–257.
- [13] Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2013;111:408–414.
- [14] Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy*. 2010;40:242–250.
- [15] Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Invest Allergy Clin Immunol*. 2012;22:1–12.
- [16] Allen DB. Do intranasal corticosteroids affect childhood growth? *Allergy*. 2000;55(suppl 62):15–18.
- [17] Allen DB. Systemic effects of intranasal steroids: an endocrinologist's perspective. *J Allergy Clin Immunol*. 2000;106(suppl 4):S179–S190.
- [18] Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics*. 2000;105:E23.
- [19] Blaiss MS. Safety considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc*. 2007;28:145–152.