

No hypothalamic-pituitary-adrenal function effect with beclomethasone dipropionate nasal aerosol, based on 24-hour serum cortisol in pediatric allergic rhinitis

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ARTICLE INFO

Article history:

Received for publication March 27, 2015.

Received in revised form May 20, 2015.

Accepted for publication May 23, 2015.

ABSTRACT

Background: Intranasal corticosteroids are the mainstay of allergic rhinitis (AR) treatment. Their potential to suppress the hypothalamic-pituitary-adrenal axis should be evaluated, especially after long-term daily use in children.

Objective: To evaluate the effects of treatment with non-aqueous beclomethasone dipropionate (BDP) nasal aerosol on hypothalamic-pituitary-adrenal axis function in children with perennial AR.

Methods: In this double-blinded, placebo-controlled, parallel-group study, patients (6–11 years old) with perennial AR were randomized (2:1) to BDP nasal aerosol at 80 μ g/day ($n = 67$) or placebo ($n = 32$). The primary end point was change from baseline in 24-hour serum cortisol (SC) weighted mean for BDP nasal aerosol and placebo after 6 weeks of treatment, which was analyzed in the per-protocol population.

Results: The per-protocol population included 97 patients (BDP nasal aerosol, $n = 66$; placebo, $n = 31$). Baseline geometric mean SC weighted mean values were similar in the 80- μ g/day BDP nasal aerosol and placebo groups (5.97 and 6.47 μ g/dL, respectively). After 6 weeks' treatment, geometric mean values were 6.19 and 7.13 μ g/dL, respectively, with no decrease from baseline in either group. Geometric mean SC ratio of BDP nasal aerosol at 80 μ g/day to placebo was 0.91 (95% confidence interval 0.81–1.03), indicating predefined noninferiority. SC concentration-time profiles were similar for the placebo and 80- μ g/day BDP nasal aerosol groups at baseline and week 6. BDP nasal aerosol at 80 μ g/day was generally well tolerated.

Conclusion: In pediatric patients with perennial AR, 24-hour SC profiles were comparable for BDP nasal aerosol and placebo, indicating that once-daily BDP nasal aerosol treatment did not significantly affect hypothalamic-pituitary-adrenal axis function.

Trial Registration: [ClinicalTrials.gov](http://clinicaltrials.gov); NCT01697956.

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Introduction

Allergic rhinitis (AR) is the most prevalent chronic allergic disease, affecting patients of all ethnic groups and ages, including up to 60 million individuals in the United States and up to 40% of children.^{1,2} Worldwide, AR affects 10% to 40% of children.³ Traditionally regarded as a nuisance, AR symptoms have been shown to have a profound adverse effect on children's social life, sleep, and school productivity.⁴

Intranasal corticosteroids (INs) are first-line treatment for AR.² They are considered the most effective drug class for controlling AR symptoms.² The safety and efficacy of INs are well established; however, patient and prescriber concerns about systemic effects persist, mostly driven by reports of systemic adverse effects with oral or high-dose inhaled corticosteroids.⁵ Potential systemic effects of high-dose corticosteroids include hypothalamic-pituitary-adrenal (HPA) axis suppression and changes in the growth rate of children.⁶ As a class, long-term high-dose corticosteroids might suppress the HPA axis, resulting in decreased endogenous cortisol production, leading to adverse physiologic effects.⁷ INs are widely used in pediatric patients who might receive a higher dose of corticosteroid (based on milligrams per kilogram of body weight) than adults. Therefore, it is important to

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Disclosures: Drs Li and Tantry own Teva Branded Pharmaceutical Products stock.

Funding: This study was sponsored by Teva Branded Pharmaceutical Products R&D, Inc.

<http://dx.doi.org/10.1016/j.anai.2015.05.019>

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evaluate through an optimally designed study the effect of long-term treatment with corticosteroids on HPA axis function, especially in children.⁸

Beclomethasone dipropionate (BDP) nasal aerosol, an anti-inflammatory corticosteroid in a non-aqueous formulation, has a well-established efficacy and safety profile^{9–12} and is approved for management of AR in adolescents and adults.¹³ BDP nasal aerosol also has been shown to be generally well tolerated and effective in children with seasonal AR.¹⁴ Results of a previous study showed that BDP nasal aerosol was not associated with HPA axis suppression in adolescent and adult patients with perennial AR (PAR).¹⁰ A subgroup analysis in adolescent patients (12–17 years old) showed similar 24-hour cortisol profiles for BDP nasal aerosol and placebo after 6 weeks of treatment, suggesting that there was no apparent HPA axis suppression.^{10,15} However, the influence of BDP nasal aerosol treatment on HPA axis function in children is unknown. Therefore, the effect of 6 weeks of once-daily treatment with 80 µg/day of BDP nasal aerosol compared with placebo on HPA axis function in children (6–11 years old) with PAR was evaluated in this study.

Methods

Study Design and Treatment

This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study conducted in the United States (Fig 1). After a 7- to 21-day placebo run-in period, patients were randomly assigned (2:1) to receive 80 µg/day of BDP nasal aerosol (QNASL, Teva Respiratory, Frazer, Pennsylvania; 1 40-µg actuation per nostril, total of 2 actuations) or placebo nasal aerosol. Patients (on their own or with assistance from parents, guardians, or caregivers, as needed) administered the double-blinded nasal aerosol once daily in the morning for a total duration of 6 weeks. HPA axis function was assessed before randomization and after 6 weeks of treatment. Daily adherence to study medication administration was verified using video adherence monitoring (PAREXEL International, Durham, North Carolina).

This study was approved by the Quorum Review Institutional Review Board (Seattle, Washington) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent or assent was obtained by the patient or the patient's parents or legal guardians, as age appropriate. The study was registered at ClinicalTrials.gov (identifier NCT01697956).

Patients

Boys and girls 6 to 11 years of age with a documented history of PAR were included. A positive skin prick test result was required, which demonstrated sensitivity to at least 1 relevant perennial allergen (defined as a wheal diameter ≥ 3 mm larger than the control). The following patients were excluded: history of nasal polyps or clinically significant respiratory tract malformations; recent nasal biopsy or surgery; nasal trauma, atrophic rhinitis, or rhinitis medicamentosa within 60 days before screening; respiratory infection or disorder within 14 days before screening or respiratory infection during the placebo run-in period; INS treatment within 28 days of screening; history or current evidence of clinically relevant allergies or idiosyncrasies to drugs or food; active asthma necessitating treatment with inhaled corticosteroids or systemic corticosteroids or routine use of β -agonists or any controller drug; use of inhaled corticosteroids or systemic corticosteroids for 30 or 60 days, respectively; known hypersensitivity to corticosteroids or any of the excipients in the study medication formulation; antibiotic therapy for an acute condition within 14 days before screening; or participation in an investigational drug study within 30 days before screening.

Patients were not permitted to use any prohibited concomitant medications within the prescribed withdrawal periods before screening, including treatment with strong CYP3A4 inhibitors; topical corticosteroids in concentrations greater than 1% hydrocortisone (or equivalent) or covering more than 20% of the body surface within the previous 30 days; or initiation of pimecrolimus cream of at least 1%, tacrolimus ointment of at least 0.03%, or immunotherapy during the study period. Stable (maintenance) use of pimecrolimus cream, tacrolimus ointment, or immunotherapy if initiated before screening; history of intermittent use (≤ 3 per week) of inhaled short-acting β -agonists; or use of low-dose antibiotics for prophylactic purposes if initiated before screening were permitted. Rescue medication (1 mg/mL of loratadine) was allowed on an as-needed basis (maximum 10 mL/day) during the study.

End Points and Assessments

The primary end point of the study was the change from baseline in 24-hour serum cortisol (SC) weighted mean for BDP nasal aerosol compared with placebo after 6 weeks of treatment in the per-protocol (PP) population. Pharmacokinetics (PK) end points, evaluated

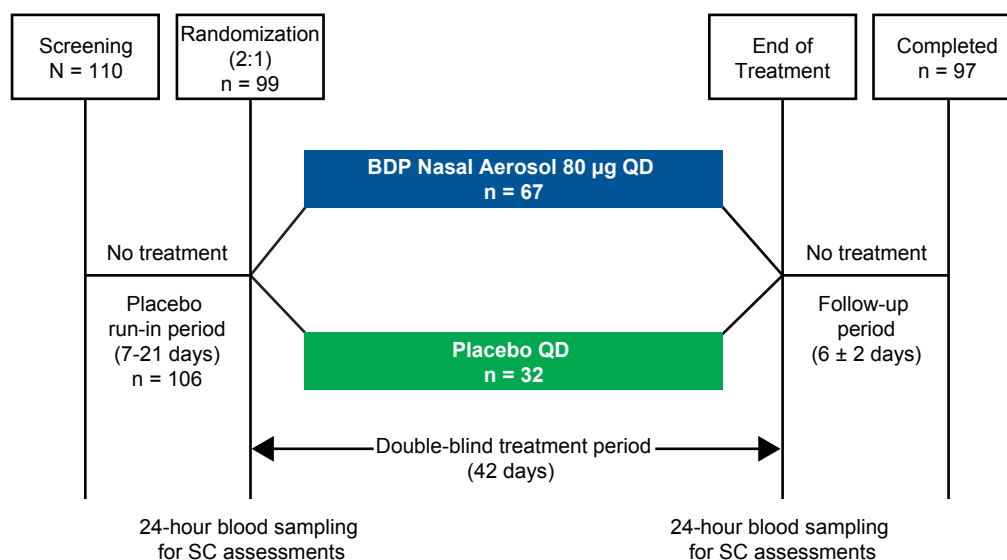


Figure 1. Study design. BDP, beclomethasone dipropionate; QD, once daily; SC, serum cortisol.

to measure plasma levels of BDP and its active metabolite beclomethasone-17-monopropionate (17-BMP), included the area under the plasma concentration-time curve (AUC) from time 0 (time of dosing) to the time of the last measurable analyte concentration and from dosing to 24 hours after dosing, the observed maximum plasma concentration, the time to observed maximum plasma concentration, and the apparent terminal elimination half-life.

Blood samples were taken at various time points over a 24-hour period during a 2-day and 2-night domiciled inpatient visit at baseline (before randomization) and after 6 weeks of treatment for SC analysis (primary end point; Fig 1). Serum concentrations of BDP and 17-BMP for PK evaluations were performed on the 24-hour blood samples collected on day 42 immediately before and then after the last dose of study medication. Validated liquid chromatography-tandem mass spectrometry methods were used to determine SC levels (Quest Diagnostics, Inc, San Juan Capistrano, California) and serum BDP and 17-BMP concentrations (XenoBiotic Laboratories, Inc, Plainsboro, New Jersey; lower limits of quantitation were 1 µg/mL, 10 pg/mL, and 20 pg/mL, respectively).

Safety Assessments

Safety was monitored by physical examination; ear, nose, and throat examination; vital sign evaluation; clinical laboratory assessments (blood chemistry and hematology; Quest Diagnostics); and recording of spontaneous and elicited adverse events (AEs).

Statistical Analyses

Based on results of a previous study¹⁰ and other similar studies, the SD of the logarithmically transformed data on the change from baseline (expressed as a ratio) in 24-hour SC weighted mean was assumed to be

0.30. Using this SD, 90 patients (~60 and 30 patients in the BDP nasal aerosol and placebo groups, respectively) would yield approximately 90% power to demonstrate noninferiority between treatments. With this sample size, noninferiority would be demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) for the geometric mean ratio of BDP nasal aerosol to placebo was greater than 0.80.

For the primary comparison, the SC weighted mean (time of dosing to the time of the last measurable analyte concentration) was determined for each patient at baseline and at week 6 by dividing the AUC from time 0 (time of dosing) to the time of the last measurable analyte concentration by the sample collection time interval and then deriving the ratio of week 6 over baseline. After natural logarithmic transformation, the ratio was analyzed using an analysis of covariance model, with covariate adjustment for treatment, center, and logarithmically transformed baseline-weighted AUC using the PP analysis set. Point estimates for the treatment difference (BDP nasal aerosol minus placebo) and the associated 95% CIs were calculated on a logarithmic scale and then exponentiated to provide an estimate of the geometric mean ratio (BDP nasal aerosol/placebo) and associated CI.

The PK parameter estimates and plasma concentrations of BDP and 17-BMP were summarized descriptively. PK analysis was performed on plasma concentration-time data using noncompartmental PK methods. Noncompartmental PK analysis is highly dependent on the estimation of total drug exposure, which is most often estimated by AUC. Safety data were summarized.

Results

Patient Disposition

A total of 106 patients were enrolled from 6 centers (Fig 2). Of these, 67 patients were randomly assigned to receive BDP nasal

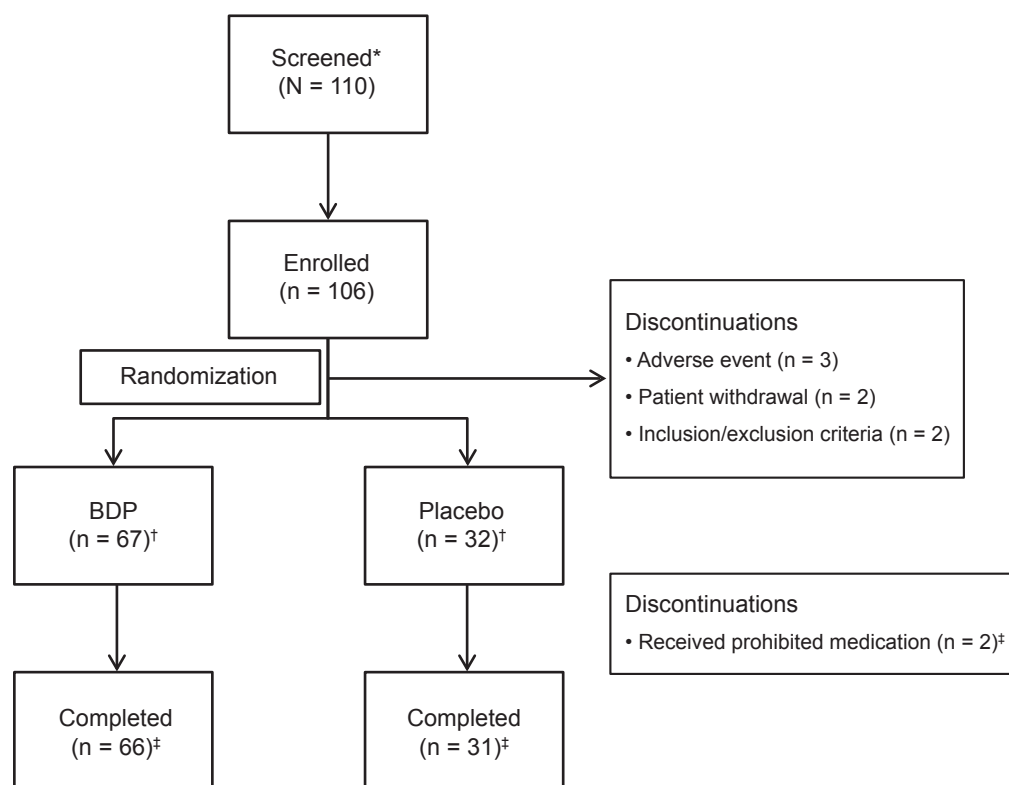


Figure 2. Patient disposition. The intent-to-treat patient population included all randomized patients. The safety population included all randomized patients who received at least 1 dose of randomized study medication based on the treatment actually received. BDP, beclomethasone dipropionate. [†]Patients were enrolled at Clinical Research Institute/Prism Research, St Paul, Minnesota; Central Texas Health Research, New Braunfels, Texas; Sneeze, Wheeze, and Itch Associates, Normal, Illinois; Sylvana Research Associates, San Antonio, Texas; Clinical Research, Atlanta, Georgia; and WCCT Global, Cypress, California. [‡]Safety and intent-to-treat populations. [§]One patient in each treatment group had major protocol deviations and was excluded from per-protocol analyses.

Table 1
Patient demographics and baseline characteristics (per-protocol population^a)

Characteristic	BDP nasal aerosol 80 µg/day (n = 66)	Placebo (n = 31)	Total (n = 97)
Age (y)			
Mean (SD)	9.2 (1.5)	8.5 (1.7)	9.0 (1.6)
Median	9.0	8.0	9.0
Range	6–11	6–11	6–11
Sex, n (%)			
Boys	35 (53)	11 (35)	46 (47)
Girls	31 (47)	20 (65)	51 (53)
Race, n (%)			
White	48 (73)	24 (77)	72 (74)
Black	17 (26)	6 (19)	23 (24)
Other	1 (2)	1 (3)	2 (2)
Ethnicity, n (%)			
Hispanic or Latino	16 (24)	10 (32)	26 (27)
Not Hispanic, not Latino	50 (76)	21 (68)	71 (73)
Weight (kg), mean (SD)	37.5 (12.8)	34.9 (12.9)	36.7 (12.9)
BMI (kg/m ²), mean (SD)	18.8 (4.0)	18.2 (3.7)	18.6 (3.9)

Abbreviations: BDP, beclomethasone dipropionate; BMI, body mass index.

^aThe per-protocol population included all data from randomized patients obtained before experiencing major protocol deviations.

aerosol at 80 µg/day and 32 to receive placebo. During the study, 2 patients made major protocol violations: 1 patient on BDP nasal aerosol used a prohibited medication (Obetrol) and was less than 60% adherent to the study drug protocol and 1 patient on placebo used a prohibited medication (Obetrol). These patients were excluded from all PP analyses. Therefore, the PP population included 97 patients (66 in the BDP nasal aerosol group and 31 in the placebo group), and the safety population was composed of 99 patients (67 in the BDP nasal aerosol and 32 in the placebo group). Baseline demographics and patient characteristics were comparable between treatment groups (Table 1). Mean adherence rates, as measured by video monitoring, were at least 97% in each group.

24-Hour Serum Cortisol Concentration (PP Population)

Baseline geometric mean SC weighted mean values were similar in the BDP nasal aerosol and placebo groups (5.97 and 6.47 µg/dL, respectively). After 6 weeks of treatment, the geometric mean values were 6.19 and 7.13 µg/dL, respectively, with no decrease from baseline in either group (Table 2). The geometric mean SC ratio of BDP nasal aerosol to placebo was 0.91 (95% CI 0.81–1.03), with the lower limit of the 2-sided 95% CI being higher than 0.80, indicating predefined noninferiority.

Serum Cortisol Concentration-Time Profiles

At baseline and at week 6, 24-hour SC concentration-time profiles were similar between treatment groups and showed the expected diurnal variation in SC measurements (Fig 3).

Pharmacokinetics

Sixty-six patients receiving treatment with BDP nasal aerosol contributed plasma samples for the BDP and 17-BMP PK assessments. As expected, mean values for AUC from time 0 (time of dosing) to the time of the last measurable analyte concentration, AUC from dosing to 24 hours after dosing, and maximum plasma concentration were lower for BDP (45.6 pg · h/mL, 200.8 pg · h/mL, and 44.7 pg/mL, respectively) than for 17-BMP (573.8 pg · h/mL, 619.1 pg · h/mL, and 142.7 pg/mL, respectively). Mean time to observed maximum plasma concentration and terminal elimination half-life were 1.3 hours and not calculable, respectively, for BDP, and 1.2 and 3.1 hours, respectively, for 17-BMP. There was no apparent accumulation of BDP or 17-BMP after 6 weeks of repeated

Table 2
Logarithmically transformed serum cortisol weighted means (per-protocol population^a)

	BDP nasal aerosol 80 µg/day (n = 66)		Placebo (n = 31)	
	Geometric mean (SE)	95% CI	Geometric mean (SE)	95% CI
Baseline (µg/dL)	5.97 (1.04)	5.53–6.45	6.47 (1.04)	5.99–6.99
Week 6 (µg/dL)	6.19 (1.04)	5.69–6.74	7.13 (1.05)	6.48–7.85
Ratio of week 6 to baseline (µg/dL)	1.04 (1.04)	0.96–1.12	1.10 (1.05)	0.99–1.22
Ratio of BDP nasal aerosol to placebo	0.91	0.81–1.03		

Abbreviations: BDP, beclomethasone dipropionate; CI, confidence interval; SE, standard error.

^aThe per-protocol population included all data from randomized patients obtained before experiencing major protocol deviations. Serum cortisol values recorded as lower than 1.0 µg/dL were imputed as 0.5 µg/dL (conversion to SI units: 27.59 × µg/dL = nmol/L).

administration of BDP nasal aerosol, primarily because of the short plasma elimination half-lives relative to the dosing frequency.

Safety

Overall, 35 of 99 patients (35%) experienced an AE (22 [33%] in the BDP nasal aerosol group; 13 [41%] in the placebo group; Table 3). The most commonly reported treatment-emergent AEs were epistaxis and pyrexia, which is consistent with the expectations for this population. Treatment-emergent AEs were mostly mild to moderate; however, 1 patient reported severe upper abdominal pain and vomiting and 1 patient reported severe allergic dermatitis (they received BDP nasal aerosol) and severe nasal congestion (1 patient who received placebo); all severe treatment-emergent AEs resolved and none were considered related to treatment. The AEs judged by the investigator as possibly related to the study drug included epistaxis in 2 patients in the BDP nasal aerosol group (1 of whom also had otitis media) and upper abdominal pain in 1 patient in the placebo group; none were severe. There were no serious AEs and no deaths, and no patients withdrew because of AEs during the double-blinded treatment period. The safety profile for physical examination; ear, nose, and throat examination; vital sign assessments; and clinical laboratory assessments was similar between the treatment groups (data not shown).

Discussion

In this study, after 6 weeks of treatment, BDP nasal aerosol (80 µg/day) showed noninferiority to placebo with respect to 24-hour SC concentrations, indicating that BDP nasal aerosol was not associated with a significant effect on HPA axis function in children with PAR. The present data further support the safety of BDP nasal aerosol treatment in children with AR. As previously reported by Storms et al,¹⁴ treatment with BDP nasal aerosol is generally well tolerated and effective for treatment of children with seasonal AR.

The results obtained in this study in children are consistent with those reported in adolescent and adult patients.¹⁰ BDP nasal aerosol treatment at a higher dose (320 µg/day) also did not result in HPA axis suppression relative to placebo in adolescents and adults with PAR after 6 weeks of long-term daily administration. A subgroup analysis in adolescents also did not show any HPA axis suppression. Taken together, these results provide evidence that once-daily treatment with BDP nasal aerosol is not associated with changes in HPA axis function compared with placebo. The present study results also are comparable with those seen in studies of other INSS (eg, fluticasone furoate, ciclesonide, mometasone furoate) in

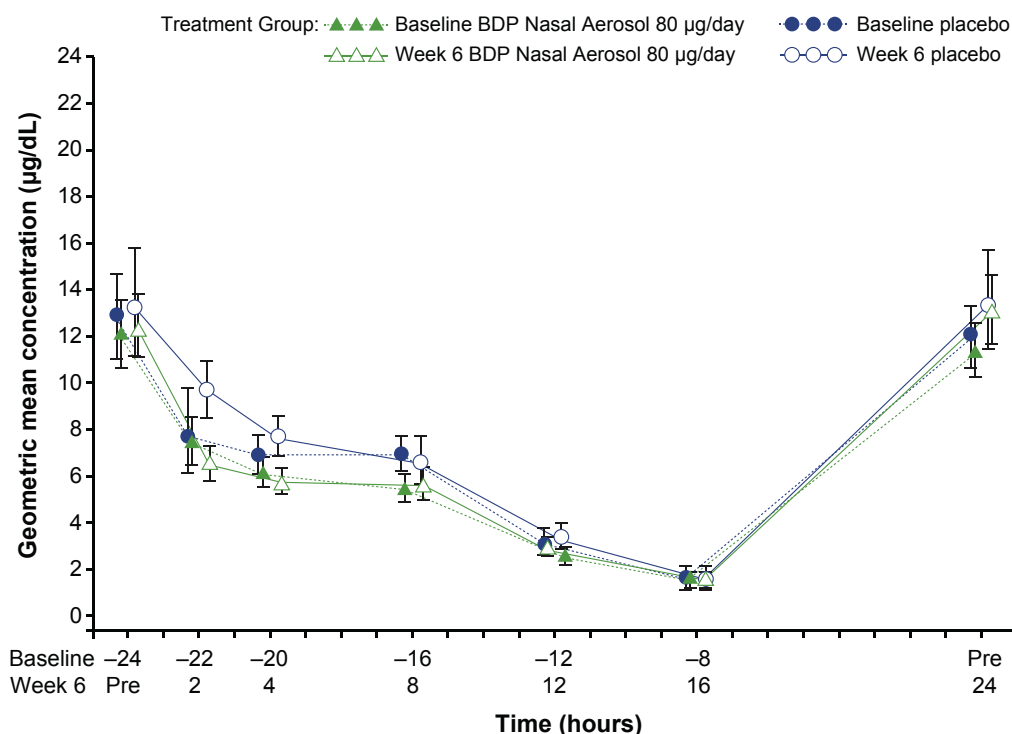


Figure 3. Geometric mean serum cortisol concentration-time profiles at baseline and after 6 weeks of treatment by treatment group (per-protocol population). Error bars represent 95% confidence intervals. The per-protocol population included all data from randomized patients in the intent-to-treat population obtained before experiencing major protocol deviations. Serum cortisol values lower than 1.0 µg/dL were imputed as 0.5 µg/dL (conversion to SI units: $27.59 \times \mu\text{g/dL} = \text{nmol/L}$). BDP, beclomethasone dipropionate; Pre, pre-dose.

children with PAR, which showed no HPA axis suppression at recommended doses.^{16–18} The lack of systemic effects on the HPA axis with BDP nasal aerosol is likely a result of the low systemic bioavailability of this non-aqueous formulation. As reported by Ratner et al,¹⁹ the systemic exposure after a single dose of intranasally administered BDP nasal aerosol at 320 µg was approximately 4-fold lower than with orally inhaled BDP at 320 µg in healthy individuals. However, determining whether these results would be predictive of long-term effects of BDP nasal aerosol is difficult. A 52-week study in adolescents and adults showed no systemically relevant safety concerns with 320 µg/day of once-daily BDP nasal aerosol treatment compared with placebo.¹¹ A high dose of an aqueous formulation of BDP (168 µg twice daily, 336 µg total

daily dose) also did not show an effect on HPA axis function after 52 weeks of treatment in children with PAR, but did show a decrease in growth velocity.²⁰ In a study in children with asthma, a logistic-regression model identified the log-daily INS dose per millimeter squared as a significant predictor of HPA axis suppression.²¹ However, in that study, the INS dose (400 µg/day of BDP) was substantially higher than the 80-µg/day dose in the present study. All patients also were treated with inhaled corticosteroids (daily budesonide equivalent dose per millimeter squared 439 µg, median duration 41 months), and 42% received a topical corticosteroid (median duration 30 months). In this study, use of inhaled corticosteroids or systemic corticosteroids was not permitted. Although evidence suggests that systemic adverse effects are minimal with available INSs at prescribed doses,²² additional optimally designed long-term studies are needed to confirm systemic safety in children.

Therefore, this HPA axis study was optimally designed to be consistent with other similar studies and recent recommendations, and with available US Food and Drug Administration draft guidelines.^{8,16,23,24} In particular, the guidelines state that for HPA axis evaluation, measurement of timed (12- or 24-hour) urinary free cortisol levels or obtaining SC concentration-time profiles before and after 6 weeks of treatment is the preferred method of assessment.²³ Therefore, 24-hour SC concentrations were measured in this study. It is important to emphasize that HPA axis response to stress was not evaluated in this study. The lack of a positive control (eg, prednisone) to validate the sensitivity of the assay is a potential limitation of this study. A positive control arm was not included in this study because of ethical and safety concerns of deliberately suppressing HPA axis function in children. This issue is unlikely to affect the study results because a previous adolescent and adult HPA axis study showed an approximate 3-fold decrease in HPA axis function after prednisone (positive control) treatment compared with placebo, thereby validating the assay sensitivity.¹⁰

Table 3
Summary of TEAEs (safety population^a)

	BDP nasal aerosol 80 µg/day (n = 67)	Placebo (n = 32)
Patients with AEs, n (%)	22 (33)	13 (41)
Patients with treatment-related AEs, n (%)	2 (3)	1 (3)
TEAEs in >1 patient in either treatment group, n (%)		
Epistaxis	5 (7)	1 (3)
Pyrexia	5 (7)	1 (3)
Upper abdominal pain	2 (3)	1 (3)
Nasopharyngitis	2 (3)	1 (3)
Oropharyngeal pain	2 (3)	0
Otitis media	2 (3)	1 (3)
Vomiting	2 (3)	1 (3)
Upper respiratory tract infection	1 (1)	2 (6)
Arthralgia	0	2 (6)

Abbreviations: AE, adverse events; BDP, beclomethasone dipropionate; TEAEs, treatment-emergent adverse events.

^aThe safety population included all randomized patients who received at least 1 dose of randomized study medication.

Adherence to daily medication must be carefully monitored, and the possibility of decreased adherence over time must be considered in an optimal HPA axis study design and in interpretation of the results.⁸ Therefore, adherence to daily study medication was monitored through video monitoring in this study, as were PK assessments after treatment. Mean adherence rates to study medication, as measured by video monitoring, were at least 97% in each treatment group. These strong adherence data support the study results and indicate that the lack of HPA axis suppression with BDP nasal aerosol is not attributable to the lack of daily adherence to study medication. Reasonable plasma exposure to 17-BMP seen after 6 weeks of treatment further supports these adherence findings and overall validity of the results.

Results of this study showed that treatment with once-daily BDP nasal aerosol (80 µg/day) is not associated with HPA axis suppression compared with placebo in children with PAR assessed by 24-hour SC concentration-time profiles. BDP nasal aerosol was generally well tolerated.

Acknowledgments

Medical writing and editorial assistance during the preparation of this article was provided by ApotheCom, Yardley, Pennsylvania, with funding provided by Teva. The authors thank the study investigators and the study team for their valuable contributions during the conduct of this study.

References

- [1] Bousquet J, Khaltaev N, Cruz AA, et al; World Health Organization, GA(2)LEN, and AllerGen. Allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Allergy*. 2008;63:8–160.
- [2] Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008;122:S1–S84.
- [3] Turner PJ, Kemp AS. Allergic rhinitis in children. *J Paediatr Child Health*. 2012;48:302–310.
- [4] Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol*. 2009;124:S43–S70.
- [5] Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Investig Allergy Clin Immunol*. 2012;22:1–12.
- [6] Blaiss MS. Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc*. 2011;32:413–418.
- [7] Marques AH, Silverman MN, Sternberg EM. Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. *Ann N Y Acad Sci*. 2009;1179:1–18.
- [8] Fan Y, Ma L, Pippins J, Limb S, Xu Y, Sahajwalla C. Impact of study design on the evaluation of inhaled and intranasal corticosteroids' effect on hypothalamic-pituitary-adrenal axis function, part I: general overview of HPA axis study design. *J Pharm Sci*. 2013;102:3513–3527.
- [9] Meltzer EO, Jacobs RL, LaForce CF, Kelley CL, 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.
- [10] 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.
- [11] 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. Presented at the Annual Meeting of the American Academy of Allergy, Asthma & Immunology; Orlando, Florida; March 2–6, 2012.
- [12] 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.
- [13] QNASL (beclomethasone dipropionate) nasal aerosol [package insert]. Frazer, PA: Teva Respiratory, LLC; 2012.
- [14] 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.
- [15] 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. Presented at the Annual Meeting of the American Academy of Allergy, Asthma & Immunology; Orlando, Florida; March 2–6, 2012.
- [16] Tripathy I, Levy A, Ratner P, Clements D, Wu W, Philpot E. HPA axis safety of fluticasone furoate nasal spray once daily in children with perennial allergic rhinitis. *Pediatr Allergy Immunol*. 2009;20:287–294.
- [17] Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics*. 2000;105:E22.
- [18] Berman G, Hampel F, Wang B, et al. An evaluation of the effect of ciclesonide hydrofluoroalkane nasal aerosol on hypothalamic pituitary adrenal axis in pediatric patients with perennial allergic rhinitis. Presented at the American College of Allergy, Asthma & Immunology 2012 Annual Scientific Meeting; Anaheim, California; November 8–13, 2012.
- [19] Ratner PH, Melchior A, Dunbar SA, Tantry SK, Dorinsky PM. 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.
- [20] Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics*. 2000;105:E23.
- [21] Zöllner EW, Lombard CJ, Galal U, Hough FS, Irusen EM, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children. *Pediatrics*. 2012;130:e1512–e1519.
- [22] Carr WW. New therapeutic options for allergic rhinitis: back to the future with intranasal corticosteroid aerosols. *Am J Rhinol Allergy*. 2013;27:309–313.
- [23] US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry. Allergic rhinitis: clinical development programs for drug products. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071293.pdf>. Published 2000. Accessed March 12, 2015.
- [24] US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry. Orally inhaled and intranasal corticosteroids: evaluation of the effects on growth in children. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071968.pdf>. Published 2007. Accessed March 12, 2015.