CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-813
Priority or Standard	S007
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Division / Office	DPARP/ODE II
Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	11/22/2014
Established Name	BDP (beclomethasone dipropionate) Nasal Aerosol
(Proposed) Trade Name	QNASL™ Nasal Aerosol
Therapeutic Class	Corticosteroid
Applicant	TEVA Branded Pharmaceutical Products
Formulation(s)	Nasal aerosol
Dosing Regimen	For Adults and adolescents 12 years of age and older: 320 mcg administered as 2 nasal sprays (80 mcg/spray) in each nostril once daily; For children 4 to 11 years of age: 80 mcg administered as 1 nasal spray (40 mcg/spray) in each nostril once daily
Indication(s)	For the treatment of nasal symptoms of seasonal and perennial allergic rhinitis
Intended Population(s)	4 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this NDA supplement is Approval of BDP (beclomethasone dipropionate) Nasal Aerosol (tradename QNASL) for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in patients 4 years of age and older.

BDP Nasal Aerosol was approved for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older on 3/24/2012. The drug product used in clinical studies in this application (b) (4) with a different product strength and delivered dose for the pediatric patient population. The pediatric studies submitted were specified as postmarketing requirements (PMRs) for the approval of BDP Nasal Aerosol. The submission of the present NDA supplement is considered fulfill the PMRs for BDP Nasal Aerosol.

BDP was approved as an oral inhalation drug as QVAR Inhalation Aerosol (NDA 20-911) on 9/15/2000 for the indication of maintenance treatment of asthma. (b) (4)

1.2 Risk Benefit Assessment

The data submitted in the NDA support the efficacy and safety of BDP Nasal Aerosol, administered 80 mcg once daily, for the treatment of nasal symptoms associated with SAR and PAR in patients 4 to 11 years of age. There were two adequate and well controlled efficacy and safety studies, one in patients with SAR (BDP-AR-305) and one in patients with PAR (BDP-AR-306). Since SAR and PAR are closely related diseases and have identical pathophysiological changes, the product demonstrated efficacy in one SAR study and one PAR study is acceptable for approval for indication of both SAR and PAR. The primary efficacy endpoint for both SAR and PAR was the change from baseline in the average AM and PM subject-reported reflective total nasal symptom score (rTNSS) over the treatment period compared with placebo. In the SAR study, a total of 238 subjects 6 to 11 years of age received BDP Nasal Aerosol 80 mcg/day for 2 weeks. In the PAR study, a total of 358 subjects 4 to 11 years of age received BDP Nasal Aerosol 80 mcg/day for 12 weeks. The BDP treatment demonstrated statistically significant improvements in rTNSS compared with placebo in two studies. The effectiveness and the once daily dosing regimen were further supported by the demonstration of statistically significant improvements in the key secondary endpoint, mean change from baseline instantaneous TNSS (iTNSS) in two studies. The primary

efficacy endpoint rTNSS and the key secondary efficacy endpoint iTNSS are commonly used and accepted as valid in drug development programs for allergic rhinitis. Evidence of benefit of BDP Nasal Aerosol 80 mcg/day for nasal symptoms associated with SAR and PAR in pediatric patients 4 to 11 years of age was demonstrated in the two studies.

In terms of risk consideration, the adverse event profile for BDP Nasal Aerosol 80 mcg/day was comparable to that for placebo in both SAR and PAR studies. There was no appreciable difference in adverse events between BDP Nasal Aerosol dose levels of 80 mcg/day, 160 mcg/day, and placebo in 2-week SAR study. There were no deaths and non-fatal serious adverse events occurred in the clinical studies. The most common adverse events with BDP Nasal Aerosol 80 mcg/day treatment were epistaxis (4%), headache (3%), pyrexia (3%), and upper respiratory infection (3%), and there were no appreciable differences with those in placebo. Because intranasal corticosteroids have been known to associated with local nasal adverse reactions, the major safety concern for BDP Nasal Aerosol is local adverse events such as nose bleeding, nasal irritation, nasal ulceration/erosion, and most seriously, nasal septum perforation. There was a single case report of nasal septum perforation in a subject treated with BDP nasal aerosol 160 mcg/day for 2 weeks. However, the event was confounded because the subject had a history of recurrent epistaxis and 2 nose surgeries that should have excluded the subject from participating in the study. There were 4 reports of nasal septum disorder, two in subjects treated with BDP Nasal Aerosol 80 mcg/day (one had a 2 mm epithelial erosion on the right septum and one had erythema on left nasal septum) and two in subjects with placebo (2 had left septum erosion). The 4 nasal septum disorders were not a special safety concern, because (1) nasal ulceration/erosion was a known adverse event associated with long term exposure to nasal corticosteroids, (2) those AEs could be results of mucosal lesions from the disease being studied (allergic rhinitis) and were also reported in subjects with placebo.

In summary, the data demonstrated the benefit of BDP Nasal Aerosol 80 mcg daily for the treatment of nasal symptoms associated with SAR and PAR in patients 4 to 11 years of age with acceptable safety profile. Based on the risk benefit assessment, approval of BDP Nasal Aerosol 80 mcg daily for the treatment of nasal symptoms associated with SAR and PAR in patients 4 to 11 years of age is recommended from a clinical perspective. No additional evaluations of post-marketing safety are deemed necessary at this time; any risks can be mitigated through professional labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical review recommends no additional postmarketing risk evaluation and mitigation strategies. The benefit-risk profile for BDP Nasal Aerosol 80 mcg daily is favorable and the risks can be mitigated through professional labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

No phase 4 study is recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in the proposed drug product is BDP (beclomethasone dipropionate), a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. BDP is rapidly activated by *in vivo* hydrolysis to the active monoester, 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor (GR). By binding GR, beclomethasone acts as an anti-inflammatory. In the proposed drug product, BDP is a nonsterile solution nasal aerosol propelled with HFA-134a propellant and includes (b) (4) ethanol (b) (4). This will be packaged into an aluminum canister and delivered via a fixed dose indicating nasal actuator. The drug product BDP (beclomethasone dipropionate) Nasal Aerosol delivers 80 mcg of beclomethasone dipropionate per actuation. The nasal actuator incorporates a counter which counts down from 120 to 0 after four priming actuations (initial counter reading 124). This MDA supplement provided CMC information supporting the new product strength (40 mcg per actuation) to be used for pediatric population. The drug product does not include any additional protective packaging. (b) (4) . Detailed product information can be found in CMC Review by Erika E Englund, Ph. D..

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 7 corticosteroid preparations formulated for intranasal administration indicated for the treatment of both seasonal and perennial rhinitis:

Table 1 Corticosteroid nasal sprays approved for allergic rhinitis

Drug	Trade name	Formulation	Indication; age (year)
Budesonide	Rhinocort Aqua	Microcrystalline aqueous suspension in manual pump	SAR and PAR; ≥6
Beclomethasone	Beconase AQ	Microcrystalline aqueous suspension in manual pump	SAR, PAR, and vasomotor rhinitis; ≥6

Triamcinolone	Nasacort AQ	Microcrystalline aqueous suspension in manual pump	SAR and PAR; ≥2
Fluticasone propionate	Flonase	Microfine aqueous suspension in metering atomizing spray pump	SAR and PAR; ≥4
Fluticasone furoate	Veramyst	Microcrystalline aqueous suspension in metering atomizing spray pump	SAR and PAR; ≥2
Ciclesonide	Omnaris Zetonna	Microcrystalline aqueous suspension in manual pump HFA nasal aerosol	SAR ≥6; PAR ≥12 SAR and PAR ≥12
Mometasone	Nasonex	Aqueous suspension in manual pump	SAR and PAR; ≥2

In addition to nasal corticosteroids, numerous anti-histamines, an iprotrapium, and a leukotriene inhibitor are available for the treatment of allergic rhinitis.

2.3 Availability of Proposed Active Ingredient in the United States

BDP Nasal Aerosol was approved for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older on 3/24/2012, and has been available in the United States as a prescription drug product since its approval. Another beclomethasone nasal spray is marketed in the United States as Beconase AQ (NDA 19-389, by GlaxoSmithKline).

2.4 Important Safety Issues With Consideration to Related Drugs

Beclomethasone given by nasal spray has low systemic bioavailability because of the limited absorption when delivered intranasally. However, it is a potent corticosteroid and therefore has the potential to produce the adverse events associated with corticosteroid administration if it is taken in high enough doses. These adverse effects include adrenal suppression, a poor response to infections and wound healing, delayed bone maturation and growth in children, osteoporosis in older individuals, cataracts and glaucoma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

BDP Nasal Aerosol was approved for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older on 3/24/2012 with PMRs for efficacy and safety studies in pediatric patients 2 to 11 years of age.

Subsequently the Applicant conducted an observational study (BDP-AR-402) to assess whether the BDP (beclomethasone dipropionate) Nasal Aerosol actuator tip fits adequately in the nostrils of younger pediatric subjects (2 to <6 years of age). The result from 205 children showed that the actuator tip had not fit adequately in 24% and 13% of

children 2 to <3 years and 3 to <4 years of age, respectively. (b) (4) The Division agreed to waive the required pediatric studies in children less than 4 years of age. In a Correspondence Letter dated 12/05/2012, the revised PMRs included 2 studies as listed below:

- 1882-1 Conduct a 2-week double-blind, placebo-controlled dose-ranging trial in children 6-11 years of age with seasonal allergic rhinitis. At least 2 doses of QNASL will be evaluated.
- 1976-1 Conduct a 12-week double-blind, placebo controlled safety and efficacy trial in children 4-11 years of age with perennial allergic rhinitis.

2.6 Other Relevant Background Information

The pivotal studies for this NDA supplement are two efficacy and safety studies in pediatric patients 4 to 11 years of age. BDP Nasal Aerosol was approved for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older on 3/24/2012, and has been available in the United States as a prescription drug product since its approval. There have not been any regulatory actions on QNASL Nasal Aerosol.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Review of the data from the pivotal studies by the Biometrics reviewer (Kiya Hamilton, Ph. D.) did not show any evidence of treatment-by-site interaction. DPARP did not request audits by the Division of Scientific Investigation. This decision is based on the facts that the molecular entity is not a new molecular entity but is a well-characterized synthetic corticosteroid, beclomethasone diproprionate, which is already approved as QVAR Inhalation Aerosol for the maintenance treatment of asthma and the efficacy data are robust and as would be expected for the product.

3.2 Compliance with Good Clinical Practices

The Applicant stated that they did not and will not use in any capacity the services of any person debarred under Section 306(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335 a(k)) as amended by the Generic Drug Enforcement Act of 1992, that it did not and will not use in any capacity the services of any person who has been debarred pursuant to Section 306 of the Federal Food, Drug, and Cosmetic Act, in

connection with this application [Module 1.3.3]. Clinical studies were conducted in compliance with recognized Good Clinical Practices.

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that no investigator received significant payments as defined in 21 CFR 54.2(f), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant as defined in 21 CFR 54.2(b) with the following 3 exceptions:

(1) (b) (6) MD (Investigator at study site # (b) (6)) has declared that he has received $47,750 for consulting and speaking from Teva Pharmaceutical Industries as of December 18, 2013. The study BDP-AR-306 initiated on 1/15/2013 (first patient screened) and completed on 10/22/2013. A total of (b) (6) subjects were randomized at the site. Dr. (b) (6) did not select or know which patients receive drug or placebo, nor did he have any influence on or knowledge of the analysis of results.

(2) (b) (6), MD (Investigator at study site # (b) (6)) has declared that he has received $53,475 for consulting and speaking from Teva Pharmaceutical Industries as of December 18, 2013. The study BDP-AR-306 initiated on 1/15/2013 (first patient screened) and completed on 10/22/2013. A total of (b) (6) subjects were randomized at the site. Dr. (b) (6) did not select or know which patients receive drug or placebo, nor did he have any influence on or knowledge of the analysis of results.

(3) (b) (6), MD (Investigator at study site # (b) (6) has declared that he has received $72,950 for consulting and speaking from Teva Pharmaceutical Industries as of December 18, 2013. The study BDP-AR-306 initiated on 1/15/2013 (first patient screened) and completed on 10/22/2013. A total of (b) (6) subjects were randomized at the site. Dr. (b) (6) did not select or know which patients receive drug or placebo, nor did Dr. (b) (6) have any influence on or knowledge of the analysis of results.

An assessment of each of the above investigators degree of participation in the clinical program demonstrated that their enrollment of subjects was not sufficient to alter the outcome of any trial or the program in general. Based on this information, as well as the multi-center nature and number of the clinical studies in the program, it is unlikely that the claimed financial interests could have influenced or biased the results of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review is approval. The active ingredient in the proposed drug product is BDP (beclomethasone dipropionate), a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. In the proposed drug product, BDP is a nonsterile solution nasal aerosol propelled with HFA-134a propellant and includes (b) (4) ethanol (b) (4). This solution is packaged into an aluminum canister and delivered via a fixed dose indicating nasal actuator. The nasal actuator incorporates a counter which counts down from 120 to 0 after four priming actuations (initial counter reading 124). This MDA supplement provided CMC information supporting the new product strength (40 mcg per actuation) to be used for pediatric population. The drug product does not include any additional protective packaging. (b) (4)

Details of the CMC information can be found in the review by Erika E Englund, Ph. D.

4.2 Clinical Microbiology

Because the proposed drug product is identical to the approved QNASL Nasal Aerosol, and the microbial limits specification acceptance criteria are identical to those in the approved application, no additional review is needed nor does the microbiology team need to be consulted.

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the Pharmacology/Toxicology review is approval. Details of the Pharmacology/Toxicology review can be found in Dr. Luqi Pei's review.

The Applicant did not submit any new preclinical data with this NDA and is relying on the preclinical data from the QVAR (NDA 20-911). Both have the same active ingredient (b) (4). At the pre-IND meeting for the proposed drug product on 04/02/2008, DPARP and the Applicant were in agreement that no new preclinical testing was required.

Beclomethasone dipropionate is a prodrug that is rapidly activated by in vivo hydrolysis to monoester, 17 monopropionate (17-BMP), which is the pharmacologically active metabolite. Complete toxicology programs have been completed with BDP to support its inhalational (QVAR) route. The systemic toxicological profile for BDP is typical for glucocorticoids. Preclinical testing also demonstrated that BDP was not a carcinogen (2 year testing), teratogen, or mutagen. It also did not impair fertility.

4.4 Clinical Pharmacology

The recommendation of the Clinical Pharmacology (CP) review is Approval. Details of the CP review can be found in the review by Sheetal Agarwal, Ph. D..

4.4.1 Mechanism of Action

Beclomethasone dipropionate (BDP) is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Corticosteroids have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and the release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines). Beclomethasone dipropionate is a prodrug that is rapidly activated by in vivo hydrolysis to the active monoester, 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor (GR). By binding GR, beclomethasone acts as an anti-inflammatory. While the exact mechanism is not known, in the setting of allergic rhinitis (AR), beclomethasone, like other nasal corticosteroids, acts at the local level to inhibit the release of inflammatory mediators which in turn decreases nasal inflammation/symptoms associated with AR. The Applicant stated that the binding affinity of 17-BMP for human GR which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of BDP. The clinical significance of these findings is unknown.

4.4.2 Pharmacodynamics

The Applicant conducted one HPA axis study (BDP-AR-307) for this NDA submission. The primary endpoint and comparison of interest was the change from baseline in 24-hour serum cortisol weighted means for BDP Nasal Aerosol 80 mcg versus placebo following 6 weeks of treatment in patients 6 to 11 years of age with PAR. Blood samples for BDP and 17-BMP (active major metabolite of BDP) were obtained at pre-dose (within 30 minutes prior to dose administration) and at 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 3, 6, 12, and 24 hours after dose administration. Plasma concentrations of BDP and 17-BMP were simultaneously determined using a validated LC-MS/MS method. The lower-limit-of-quantitation (LLOQ) of the assay was 10 pg/mL

for BDP and 20 pg/mL for 17-BMP. There was no positive control in this study because of ethical concerns with the inclusion of a positive control arm such as administration of dexamethasone, an oral corticosteroid to suppress HPA axis in children. The data showed that QNASL Nasal Aerosol 80 mcg once daily was not associated with HPA axis suppression relative to placebo in pediatric subjects (6 to 11 years of age) with PAR. The baseline geometric mean serum cortisol weighted mean values were similar in the QNASL Nasal Aerosol 80 mcg once daily and placebo treatment groups (5.97 and 6.47 mcg/dL, respectively). The new HPA axis data will be added to the approved QNASL labeling.

4.4.3 Pharmacokinetics

Following intranasal administration, most of the BDP undergoes rapid and extensive conversion to its active metabolite, 17-BMP, during absorption. In the HPA axis study (BDP-AR-307), the Applicant also evaluated steady state PK parameters for BDP and 17-BMP. When administered as BDP nasal aerosol 80 mcg/day, the mean AUC0-24 was 619.06 h*pg/mL, the mean Cmax was 142.68 pg/mL, the median Tmax was 1.00 hours, the mean λz was 0.31 hours-1 and the mean t1/2 was 3.1 hours. The results for BDP were lower for the mean AUC0-24 (200.80 h*pg/mL) and mean Cmax (44.65 pg/mL). The median tmax (0.25 hours) for BDP was shorter than for 17-BMP. The λz and t1/2 for BDP were not calculable in any of the subjects.

The *in vitro* protein binding for 17-BMP was reported to be 94 to 96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of BDP or its metabolites. The tissue distribution at steady state for BDP is moderate (20 L) but more extensive for 17-BMP (424 L). BDP undergoes extensive first-pass metabolism, forming three major metabolites via CYP3A4-catalyzed biotransformation: 17-BMP, beclomethasone-21-monopropionate, and beclomethasone. Lung slices metabolize BDP rapidly to 17-BMP and more slowly to beclomethasone. 17-BMP is the most active metabolite. The major route of elimination of inhaled BDP appears to be via hydrolysis. More than 90% of inhaled BDP is found as 17-BMP in the systemic circulation. The mean elimination half-life of 17-BMP is 2.8 hours. The terminal elimination half-lives of BDP and 17-BMP following intranasal dosing with BDP Nasal Aerosol were approximately 0.3 hours and 4.5 hours, respectively. Irrespective of the route of administration (injection, oral, or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine. It is likely that intranasal BDP follows a similar elimination pathway.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Summary of clinical studies in the NDA submission

FDA PMR No. (Teva No.)	Description of Study	Status
1882-1 (BDP-AR-305)	A 2-week dose-finding efficacy and safety study in children 6 to 11 years of age, inclusive, with SAR; doses tested: 80 mcg and 160 mcg, once daily.	-PREA commitment fulfilled. -11/6/2013 FDA grants Teva's deferral extension request. Submission of final report extended to March 2014 (initial date was December 2013).
1976-1 (BDP-AR-306)	A 12-week efficacy and safety study in children 4 to 11 years of age, inclusive, with PAR; dose tested: 80 mcg, once daily.	-PREA commitment fulfilled early, Final Report due March 2014.
1882-3 (BDP AR 307)	A 6-week pharmacodynamic study evaluating the effect of BDP nasal aerosol treatment on HPA-axis function in children 6 to 11 years of age, inclusive, with PAR; dose tested: 80 mcg, once daily.	-Initially part of PREA but later waived in FDA letter December 5, 2012. Teva decided to complete this study, which was initiated prior to the waiver letter.
BDP AR 402*	Observational study to evaluate the adequate fit of the Qnasl nasal actuator tip in pediatric patient 2-5 years of age.	-This study is the basis for the waiver of pediatric studies in patients less than 4 years of age (FDA letter 12/5/2012).

5.2 Review Strategy

There are 4 clinical study reports in this NDA supplement: one dose selection and pivotal study in SAR (2 weeks), one pivotal study in PAR (12 weeks), an HPA axis study, and an observational study to assess whether the actuator tip fits in children's nostrils. This clinical review will focus on the required 2 PMR studies in SAR and PAR.

Note that the pediatric HPA axis study is not required because the effect of BDP on HPA axis has been well characterized in QVAR program and in the QNASL program in patients 12 years of age and older. However, because the Applicant submitted the study report, the new HPA axis data will be added to the approved QNASL labeling, and the safety data will be included in the safety evaluation.

The actuator tip fit study has been reviewed previously, and will only be briefly described in this review. Based on the data obtained from the study the Division has waived the pediatric studies in patients less than 4 years of age (b) (4)

(b) (4)

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5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 STUDY BDP-AR-305

A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multi-Center, Dose-Finding Study to Assess the Efficacy and Safety of BDP HFA Nasal Aerosol in Pediatric Subjects (6 to 11 Years of Age) with Seasonal Allergic Rhinitis (SAR)

PROTOCOL

Administrative
Study initiated: March 8, 2011
Study completed: July 18, 2011
Clinical Centers: 60 centers in the U.S. (including following States: TX, CO, IN, CA, OR, MO, NC, GA, UT, KS, PA, and VA)
Study report dated: April 24, 2012
Study Sponsor: TEVA Branded Pharmaceutical Products R&D
Principal Investigator: Nathan Segall, M.D.

Objectives
Primary Objective: To evaluate the efficacy of BDP (beclomethasone dipropionate) HFA (hydrofluoroalkane), applied as a nasal aerosol at 2 dose levels (80 mcg and 160 mcg, once daily), in pediatric subjects (6 to 11 years of age) with SAR.

Secondary Objective: To assess the safety and tolerability of BDP HFA, applied as a nasal aerosol at 2 dose levels (80 mcg and 160 mcg, once daily), in pediatric subjects (6 to 11 years of age) with SAR

Study Design
This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 2-week, multi-center, dose-finding study to evaluate the efficacy and safety of BDP HFA nasal aerosol in pediatric subjects (6 to 11 years of age) with SAR. The study consisted of 2 periods: Run-in Period (7-21 days from the Screening Visit [SV] to the Randomization Visit [RV]) and a Treatment Period (15 days [+2] from the Randomization Visit [RV] to the Final Treatment Visit or termination day Visit [TV2/TdV]). During the Run-in Period, subjects (with assistance from parents/legal guardians/caregivers, as needed) administered a single-blind placebo nasal aerosol once daily in the morning. Subjects (with assistance from parents/legal guardians/ caregivers, as needed) assessed and recorded their reflective total nasal symptom

score (rTNSS, including 4 symptoms: sneezing, rhinorrhea [runny nose], itchy nose, and nasal congestion) and instantaneous total nasal symptom score (iTNSS, including 4 symptoms: sneezing, rhinorrhea [runny nose], itchy nose, and nasal congestion) twice daily as absent (0), mild (1), moderate (2), or severe (3). During the Treatment Period (Visits RV through TV2), subjects (with assistance from parents/legal guardians/ caregivers, as needed) administered the double-blinded study medication once daily in the morning. Subjects (with assistance from parents/ legal guardians/ caregivers, as needed) assessed and recorded their rTNSS and iTNSS twice daily using the scale above. Safety was monitored by physical examinations, ENT (ear, nose and throat) examinations, vital signs, and adverse events (AEs).

The protocol was amended twice during the study. One amendment, dated March 7, 2011, to the protocol was made to correct minor typographical and formatting errors throughout the protocol and added clarification of some assessments. In addition, a requirement for subjects to have a minimum subject-reported rTNSS of 6 and a minimum subject reported reflective nasal congestion score of ≥2 for the AM assessment on the day of randomization was removed as a randomization criterion in order to avoid unnecessary exclusion of eligible symptomatic subjects on the day of randomization because of unrelated occurrences (such as rain). Another amendment, dated May 2, 2011, was made to remove centrally acting sympathomimetics (e.g., Concerta, Adderall, phentermine) from the list of disallowed previous medications. During the formatting of the first amendment, these medications were inadvertently inserted into the table listing prohibited medications. There were no other changes in the study design and the planned analyses.

Treatment
BDP Nasal Aerosol – 40 mcg/actuation (Lot # 100267),
BDP Nasal Aerosol – 80 mcg/actuation (Lot # 100169A), and
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # 090528A and 100657)

Group 1: BDP Nasal Aerosol (80 mcg/day): 40 mcg/actuation (1 actuation/nostril, total 2 actuations), once daily

Group 2: BDP Nasal Aerosol (160 mcg/day): 80 mcg/actuation (1 actuation/nostril, total 2 actuations), once daily

Group 3: Placebo: 1 actuation/nostril, total 2 actuations, once daily

Study Population
A total of 1026 subjects were screened for enrollment in the study. Of the screened subjects, 906 were enrolled in the study and participated in the Run-in Period. Of the 906 enrolled subjects, 715 met the randomization criteria and were randomized to 3 treatment groups. Of the 715 randomized subjects, 239 were randomized to receive BDP Nasal Aerosol 80 mcg/day, 242 to receive BDP Nasal Aerosol 160 mcg/day, and

234 to receive placebo. One subject (1430014), randomized to BDP Nasal Aerosol 160 mcg/day, was excluded from the database because the subject was randomized in error and did not receive any assigned treatment. Hence, 714 randomized subjects constituted the safety population. One subject (Subject 1454009), who received BDP HFA 80 mcg/day but had no post-baseline efficacy assessment, was excluded from the intended to treat (ITT) population but included in the safety population. The ITT population, therefore, included 713 subjects.

The safety population (714) included all randomized subjects who received at least one dose of randomized study medication.

Inclusion criteria

- Written informed consent/assent signed and dated by the subject and parent/guardian before conducting any study-related procedure;
- Male or female subjects 6-11 years of age, as of the Screening Visit (SV);
- General good health, and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results, or put the subject at increased risk during the study;
- A documented history of SAR to a relevant seasonal allergen (tree/grass pollen) for a minimum of two years immediately preceding the study Screening Visit (SV). The SAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past, and in the investigator's judgment is expected to require treatment throughout the entire study;
- A demonstrated sensitivity to at least one seasonal allergen (tree/grass pollen) known to induce SAR through a standard skin prick test. A positive test is defined as a wheal diameter at least 5 mm larger than the diluent control wheal for the skin prick test. Documentation of a positive result within 12 months prior to Screening Visit (SV) is acceptable;
- Subject has a minimum subject-reported rTNSS of at least 6 (out of a possible 12) for the AM assessment on the day of the Screening Visit (SV);
- Subject's positive allergen test must be consistent with the medical history of SAR. Additionally the subject is expected to be adequately exposed to the SAR allergen that he/she has tested positive for via the skin prick test for the entire duration of the study;
- If a female has reached puberty and achieved menarche (as determined by the investigator), parents/guardians/caregivers will be consulted to obtain permission to counsel the subject followed by counseling the subject by the investigator regarding the possible unknown risks associated with study medication during pregnancy. Eligible female subjects of childbearing potential who are known to be sexually active will be excluded. Additionally, a urine pregnancy test must be negative at the Screening Visit (SV);
- Subject/parent/guardian/caregiver is capable of understanding the requirements, risks, and benefits of study participation, and as judged by the investigator,

capable of giving informed consent/assent and being compliant with all study requirements (visits, record-keeping, etc.).

Exclusion criteria

- Pregnancy, nursing, or plans to become pregnant or donate gametes (ova or sperm) for *in vitro* fertilization during the study period or for 30 days following the subject's last study-related visit (for eligible subjects only- if applicable). Eligible female subjects of childbearing potential who are known to be sexually active will be excluded;
- History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma (e.g., nasal piercing) or surgery, atrophic rhinitis, or rhinitis medicamentosa (all within the last 60 days prior to the Screening Visit [SV]);
- Participation in any investigational drug study within the 30 days preceding the Screening Visit (SV) or planned participation in another investigational drug study at any time during the study;
- A known hypersensitivity to any corticosteroid or any of the excipients in the study medication formulation;
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, chronic sinusitis or influenza,) not resolved within the 14 days preceding the Screening Visit (SV), or development of a respiratory infection during the Run-in Period;
- History of alcohol or drug abuse in the two (2) years preceding the Screening Visit (SV);
- History of a positive test for Human Immunodeficiency Virus (HIV), hepatitis B or hepatitis C infection;
- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of beta-agonists and any controller drug (e.g., theophylline, leukotriene antagonists). History of intermittent use (less than or equal to 3 uses per week) of inhaled short acting beta-agonists prior to the Screening Visit (SV) is acceptable;
- Plans to travel outside the study area (the known pollen area for the investigative site) for 24 or more hours during the last 7 days of the Run-In Period;
- Plans to travel outside the study area (the known pollen area for the investigative site) for 2 or more consecutive days OR 3 or more days total between the Randomization Visit (RV) and the final TV2 Visit;
- Use of any prohibited concomitant medications within the prescribed (per protocol) withdrawal periods prior to the Screening Visit (SV);
- Use of antibiotic therapy for any acute conditions within 14 days prior to the Screening Visit (SV). Low doses of antibiotics taken for prophylaxis are permitted if the therapy was started prior to the Screening Visit (SV) and is expected to continue at the same dose throughout the study;

- Initiation of immunotherapy during the study period or dose escalation during the study period. However, initiation of immunotherapy 90 days or more prior to the Screening Visit (SV) and use of a stable (30 days or more), maintenance dose during the study may be considered for inclusion;
- Treatment with any known strong CYP 3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics, ritonavir) within 30 days prior to Screening Visit (SV) or during the study;
- Non-vaccinated exposure to or active infection with chickenpox or measles within the 21 days preceding the Screening Visit (SV);
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days prior to the Screening Visit (SV); use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition (as judged by the investigator) that can reasonably be expected to require treatment with such preparations during the course of the study;
- Initiation of pimecrolmus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. However, initiation of these creams/ointments 30 days or more prior to the Screening Visit (SV) and use of a stable (maintenance) dose during the study period may be considered for inclusion;
- Study participation by clinical investigator site employees and/or their immediate relatives;
- Study participation by more than one subject from the same household at the same time. However, after the study completion/discontinuation by one subject another subject from the same household may be screened;
- Have any of the following conditions that are judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial:
    - Impaired hepatic function;
    - History of ocular disturbances (e.g., glaucoma, ocular herpes simplex, or posterior subcapsular cataracts);
    - Any systemic infection;
    - Hematological, hepatic, renal, endocrine disease;
    - Gastrointestinal disease;
    - Malignancy (excluding basal cell carcinoma);
    - Current neuropsychological condition with or without drug therapy;
    - Cardiovascular disease;
    - Respiratory disease other than mild asthma.

Randomization criteria
Only subjects meeting the following criteria will be randomized 7-21 days after the initial Screening Visit (SV):

- Subject continues to be in general good health, meeting the selection criteria

- Subject did not leave the study area (the known pollen area for the investigative site) for 24 hours or longer during the 7 days prior to the Randomization Visit (RV);
- Subject has not experienced an adverse event that would result in failure to continue to meet selection criteria;
- Subject has a minimum subject-reported reflective TNSS of an average of 6 (out of a possible 12) on the last 4 days during the Run-in Period (average of last 8 consecutive AM and PM assessments during the four consecutive 24-hour periods prior to randomization, including the AM assessment on the day of randomization);
- Subject-reported reflective nasal congestion score must be on average 2 or greater during the last 4 days during the Run-in Period (average of last 8 consecutive AM and PM assessments during the four consecutive 24-hour periods prior to randomization, including the AM assessment on the day of randomization);
- Subject (with assistance from parents/ guardians/ caregivers, as needed) must have adequately completed the Allergic Rhinitis (AR) Assessment Diary (inadequate completion is defined as missing one or more of the entries on more than 2 calendar days during the last 7 days of the Run-In Period);
- Subject has taken their single-blind medication during at least 80% of the entire Run-in Period as recorded in the AR Assessment Diary;
- Subject has not used any of the prohibited concomitant medications during the Run-In Period;
- Subject has not suffered from the common cold, upper respiratory infection, otitis media, lower respiratory infection or acute sinusitis during the 14 days prior to Randomization Visit (RV).

Subject withdrawal criteria

- Death (complete AE form and SAE report);
- Adverse Event (complete AE form);
- Subject withdrew consent;
- Request of primary care physician or investigator;
- Non-compliance;
- Protocol violation;
- Pregnancy;
- Sponsor requested subject to be withdrawn;
- Failed to return / lost to follow-up

Subjects who withdraw, are discontinued, or are lost to follow-up will not be replaced. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded in the eCRF. If there are multiple reasons for early discontinuation, the primary reason for discontinuation will be recorded. If a subject is withdrawn because of an adverse event, the event will be followed until the

medical condition returns to baseline or is considered stable or chronic. Discontinuation of subjects due to adverse events will be promptly reported to Sponsor. If a subject is lost to follow-up (fails to return for study visits), a reasonable effort should be made to determine why the subject failed to return. This information will be documented on the eCRF. All evaluations required at the scheduled end-of-study visit (TV2/TdV) will be performed when a subject is withdrawn from the study (regardless of the cause).

Treatment Compliance

A single dose of study medication will be administered at the Screening Visit (SV), Randomization Visit (RV), and Treatment Visit 1 (TV1) in the study center under the supervision of the designated site personnel. Site personnel must ensure the proper administration of the study medication. Further treatment compliance will be assessed by the subject's AR Assessment Diary. If subjects are found to be less than 80% compliant at any visit with AR Assessment Diary completion or study medication usage, they should be counseled on the importance of taking study medication and completing the AR assessment diary as directed by the investigator. Subjects are asked to restrict any travel outside the investigator's known pollen area.

Outcomes

The efficacy and safety outcomes were measured per schedule in the Table 3 below.

Table 3 Schedule of study events, Study BDP-AR-305

Visit :	SV	RV	TV1	TV2/TdV[a]
Day(s):	-7 to -21	1	8 (±2)	15 (+2)
Weeks:	-1 to -3	0	1	2
Written informed consent (assent) and HIPPA authorization signed	X			
Evaluation of inclusion/exclusion criteria	X			
Demographic data	X			
Medical history including concomitant medication history	X			
Skin prick test for appropriate allergen[b]	X	(X)		
Height and weight	X			
Vital Signs[c]	X	X	X	X
Physical examination	X			X
Ear, Nose and Throat (ENT) examination[d]	X	X	X	X
Urine pregnancy (if applicable)	X	X		X
Call/log in IVRS /IWRS for subject number	X			
Distribution of AR Assessment diary and review of diary instructions	X	X	X	
Distribution and/or review of instructions for proper use of nasal aerosol device	X	X	X	
Prime and dispense single-blind placebo	X			
Administer single-blind placebo	X			
Subject completion of twice daily AR Assessment diary	→	→	→	→
Subject administration of daily study medication in AM[e,f]	→	→	→	→
Collection and review of AR Assessment Diary		X	X	X
Compliance check (study procedures, diary and study medication)		X	X	X
Physician assessment of nasal symptoms severity		X		X
Evaluation of randomization criteria		X		
Randomization/treatment assignment via IVRS/IWRS		X		
Prime and dispense double-blind study medication		X		
Administration of double-blinded study medication		X		
Call/Log into IVRS/IWRS to discontinue subject				X
Subject return of all study medication		X		X
AE monitoring	X	X	X	X
Concomitant medication evaluation	X	X	X	X

a. The following visit windows are permitted: ±2 day for the TV1 Visit; +2 days for the Final Treatment Visit (TV2).
b. The skin prick test can be initially performed or re-performed at the Randomization Visit (RV) if the investigator feels that the skin prick test result obtained at the Screening Visit (SV) was spurious or would be spurious if obtained at the Screening Visit (SV). Documentation of a positive result within 12 months before Screening Visit (SV) is acceptable to meet eligibility criteria. Intradermal and/or RAST testing will not be permitted.
c. Sitting blood pressure and pulse rate (after at least 5 minutes of rest in the sitting position).
d. ENT exams will be performed to assess signs of AR as well as known complications of intranasal corticosteroid use (i.e., bleeding, perforation and ulceration). Throat exams will be conducted to evaluate evidence of throat irritation and candidiasis.
e. Study medication during the Run-In and Treatment Periods should be taken immediately following completion of the AM diary assessment, with the following exceptions: on the morning of

the Randomization Visit (RV) and Treatment Visit (TV1) where the study medication should be administered at the study site under the supervision of site personnel.

f. All subjects must be told to refrain from taking their study medication on the morning of the Randomization Visit (RV) and Treatment Visit (TV1). Prior to the Final Treatment Visit (TV2/TdV), subjects (with assistance from parents/guardians/caregivers, as needed) should take their daily dose of study medication in the morning in the customary manner following the recording of their AM diary assessments.

(BDP-AR-305 Study Report, page 14-15)

Efficacy endpoints

The primary efficacy endpoint was the change from baseline in the average AM and PM subject-reported rTNSS over the 2-week Treatment Period (ITT population).

The subject was asked to assess both rTNSS, i.e., an evaluation of symptom severity over the past 12 hours prior to the recording of the score), and instantaneous TNSS (iTNSS), i.e., an evaluation of the symptom severity over the last 10 minutes). The TNSS was defined as the sum of the subject-reported symptom scores for the four nasal symptoms. For each score, each subject recorded the following in the diary:

- Rhinorrhea [runny nose] severity score
- Sneezing severity score
- Nasal congestion severity score
- Nasal itching severity score

The severity scale for each symptom evaluation was defined as follows:

- 0 = absent (no sign/symptom evident)
- 1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe (sign/symptom that is hard to tolerate [i.e., causes interference with activities of daily living and/or sleeping])

The secondary efficacy endpoint was the change from baseline in the average AM and PM subject-reported iTNSS over the 2-week Treatment Period (ITT population).

Other efficacy endpoints included AM and PM subject-reported rTNSS and iTNSS over the 2-week Treatment Period and physician-assessed nasal symptom scores (PNSS).

Multiplicity adjustment was made for the primary and secondary endpoints.

Safety evaluation

Safety evaluations were made using the safety population. The evaluations included:

- Adverse events: Adverse events were coded using the MedDRA dictionary version 13.0. The nature, incidence, severity or intensity, as well as the causality assessment were reported for each treatment-emergent AE.
- Physical examinations

- Ear, nose and throat (ENT)
- Vital signs

Data Analysis

Sample size
Based on the results from previous studies, the standard deviation for the change from baseline over 2 weeks in the average of AM and PM rTNSS was assumed to be 2.4. Using this standard deviation, 120 subjects per group provided 89% power to detect a difference between treatment groups of 1.0 in the change from baseline in rTNSS with a two-sided alpha level of 0.05.

Primary and secondary efficacy analyses
The primary efficacy endpoint was the change from baseline in the average AM and PM daily subject-reported rTNSS over the 2-week Treatment Period. The primary endpoint was analyzed using a repeated-measures analysis of covariance (ANCOVA) with covariate adjustment for baseline, day, treatment, and the treatment-by- day interaction using the ITT analysis set. Baseline was defined as the average AM and PM subject-reported rTNSS over the 7 days prior to randomization. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated.

The secondary efficacy endpoints included subject-reported iTNSS, the reflective ocular symptom score (the sum of individual non-nasal symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness) and the reflective non-nasal symptom score, were analyzed in a similar fashion to the primary endpoint. The change from baseline in RQLQ was analyzed using an ANCOVA with factors for treatment, baseline, and center. The analysis of the RQLQ was conducted using the RQLQ population and ITT population.

RESULTS

Study Population

Disposition
A total of 1026 subjects were screened for enrollment in the study. Of the screened subjects, 906 were enrolled in the study and participated in the Run-in Period. Of the 906 enrolled subjects, 715 met the randomization criteria and were randomized to 3 treatment groups. As shown in Table 4**,** of the 715 randomized subjects, 239 were randomized to receive BDP Nasal Aerosol 80 mcg/day, 242 to receive BDP Nasal Aerosol 160 mcg/day, and 234 to receive placebo. One subject (1430014), randomized to BDP Nasal Aerosol 160 mcg/day, was excluded from the database because the subject was randomized in error and did not receive any assigned treatment. Hence, 714 randomized subjects constituted the safety population. One subject (Subject 1454009), who received BDP HFA 80 mcg/day but had no post-baseline efficacy

assessment, was excluded from the intended to treat (ITT) population but included in the safety population. The ITT population, therefore, included 713 subjects.

Table 4 Subject disposition, Study BDP-AR-305

Category	*BDP HFA 80 mcg/day n (%)*	*BDP HFA 160 mcg/day n (%)*	*Placebo n (%)*	*Overall n (%)*
Randomized	*239*	*242*	*234*	*715*
Safety Population	*239 (100)*	*241 (99.6)*	*234 (100)*	*714 (99.9)*
ITT Population	*238 (99.6)*	*241 (99.6)*	*234 (100)*	*713 (99.7)*
Completed	*235 (98.3)*	*234 (96.7)*	*227 (97.0)*	*696 (97.3)*
Discontinued[1]	*4 (1.7)*	*7 (2.9)*	*7 (3.0)*	*18 (2.5)*
Adverse Event	*2 (0.8)*	*2 (0.8)*	*1 (0.4)*	*5 (0.7)*
Lost to follow-up	*1 (0.4)*	*0*	*1 (0.4)*	*2 (0.3)*
Protocol violation	*1 (0.4)*	*1 (0.4)*	*0*	*2 (0.3)*
Consent withdrawn	*0*	*1 (0.4)*	*2 (0.9)*	*3 (0.4)*
Other[2]	*0*	*3 (1.2)*	*3 (1.3)*	*6 (0.8)*

[1] Excludes Subject 1430014 who was randomized in error and did not receive any study medication
[2] Other included subjects who discontinued from study due to parents' schedule conflict, family vacation, traveling, or emergency.
(BDP-AR-305 Study Report, page 57)

Approximately 97% of the subjects completed the study (98.3%, 235 subjects, in the BDP Nasal Aerosol 80 mcg/day group, 96.7%, 234 subjects, in the BDP Nasal Aerosol 160 mcg/day group, and 97.0%, 227 subjects, in the placebo group

Demographics
As shown in Table 5 below for the safety population, the majority of subjects in all groups were white (70.7%) and not Hispanic or Latino (80.7%). The males (53.5%) were slightly more than females (46.5%). The mean age of study subjects was 9.0 years and ranged from 6 to 11 years. Demographic characteristics were comparable in each of the treatment groups.

Table 5 Subject demographics, Study BDP-AR-305

Category	BDP nasal aerosol 80 mcg/day (N=238)	BDP nasal aerosol 160 mcg/day (N=241)	Placebo (N=234)
Age (years)			
Mean (SD)	8.9 (1.73)	9.1 (1.62)	9.1 (1.65)
Median	9.0	9.0	9.0
Min, max	6, 11	6, 11	6, 11
Gender, 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)
Not Hispanic, not Latino	198 (83.2)	188 (78.0)	189 (80.8)
BMI (kg/m^2)			
Mean (SD)	19.0 (4.16)	19.4 (4.52)	19.1 (4.72)
Median	18.0	18.0	18.0
Min, max	13, 38	11, 43	12, 47

(BDP-AR-305 Study Report, Table 14.1.2.2)

Medical history was generally similar among the 3 treatment groups and the types of conditions reported were those that might be expected in a SAR patient population such as asthma, eczema, sinus headache, drug hypersensitivity, allergic conjunctivitis, sinusitis, food allergy, and epistaxis. All subjects had a history of seasonal rhinitis and 41.3% of subjects (overall) also reported a history of perennial rhinitis.

During the study, the commonly used concomitant medications were summarized in Table 6 below. The most commonly used concomitant medications were salbutamol (albuterol), ibuprofen, acetaminophen, multivitamins, and allergy medicines. There were no clinically important differences in concomitant medication use among the 3 treatment groups.

Table 6 Summary of concomitant medications, Study BDP-AR-305

Concomitant Medication	*BDP HFA 80 mcg/day N = 239 n (%)*	*BDP HFA 160 mcg/day N = 241 n (%)*	*Placebo N = 234 n (%)*	*Total N = 714 n (%)*
Salbutamol (albuterol)	*23 (9.6)*	*24 (10.0)*	*19 (8.1)*	*66 (9.2)*
Ibuprofen	*14 (5.9)*	*18 (7.5)*	*15 (6.4)*	*47 (6.6)*
Multivitamins, plain	*13 (5.4)*	*14 (5.8)*	*18 (7.7)*	*45 (6.3)*
Allergens NOS[1]	*16 (6.7)*	*15 (6.2)*	*12 (5.1)*	*43 (6.0)*
Paracetamol (acetaminophen)	*16 (6.7)*	*12 (5.0)*	*14 (6.0)*	*42 (5.9)*
Multivitamins other combinations	*7 (2.9)*	*4 (1.7)*	*7 (3.0)*	*18 (2.5)*
Methylphenidate hydrochloride	*5 (2.1)*	*3 (1.2)*	*3 (1.3)*	*11 (1.5)*
Obetrol	*2 (0.8)*	*5 (2.1)*	*2 (0.9)*	*9 (1.3)*

[1] NOS – Not other specified
(BDP-AR-305 Study Report, page 63)

Efficacy Results

Primary efficacy endpoint

The primary efficacy analysis was summarized in Table 7 below. At baseline, the means of the average AM and PM subject-reported rTNSS were comparable in the 3 treatment groups (8.1 for BDP Nasal Aerosol 80 mcg/day, 8.1 for BDP Nasal Aerosol 160 mcg/day, and 8.2 for the placebo group). Across the 2-week Treatment Period, average AM and PM subject-reported rTNSS decreased in all treatment groups, including placebo. The LS mean (SE) change from baseline over the Treatment Period was -1.6 (0.13) for BDP Nasal Aerosol 80 mcg/day, -1.7 (0.13) for BDP Nasal Aerosol 160 mcg/day, and -1.0 (0.13) for the placebo group. The LS mean treatment differences of -0.63 and -0.73 were observed between BDP Nasal Aerosol 80 mcg/day, 160 mcg/day and placebo, respectively. Those differences were statistically significant ($p<0.001$) in favor of BDP Nasal Aerosol 80 and 160 mcg/day treatment. The change from baseline in the average AM and PM subject-reported rTNSS for BDP Nasal Aerosol 80 mcg/day and BDP Nasal Aerosol 160 mcg/day relative to placebo were similar.

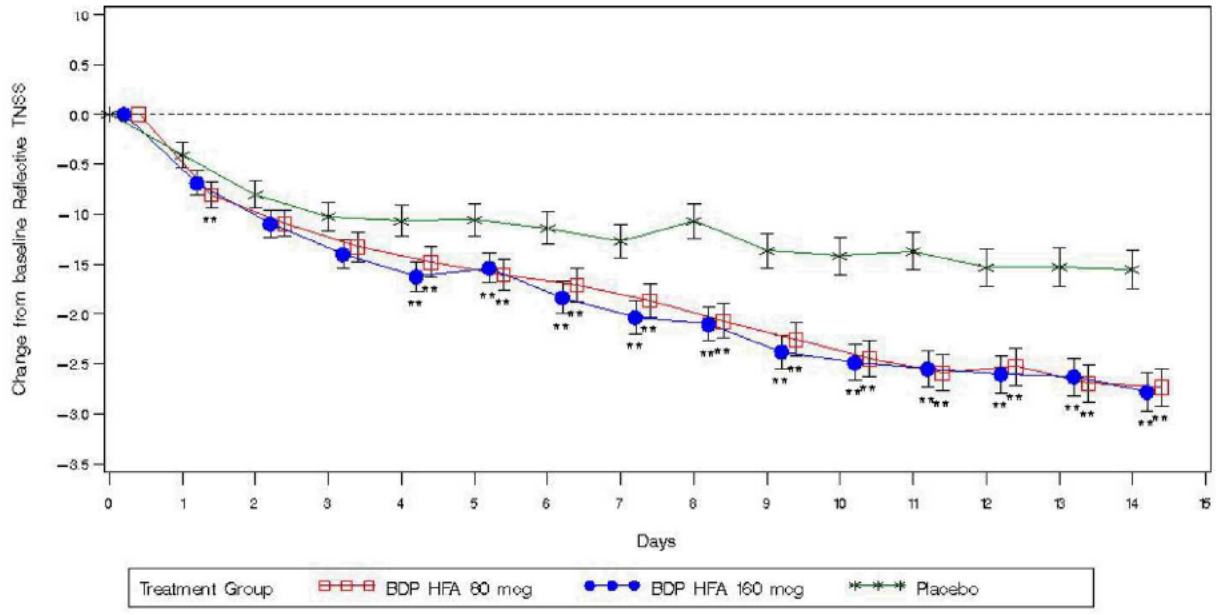
Table 7 Primary efficacy (rTNSS) analysis, Study BDP-AR-305

Statistic	*BDP HFA 80 mcg/day N = 238*	*BDP HFA 160 mcg/day N = 241*	*Placebo N = 234*
Baseline mean (SD)	*8.9 (1.62)*	*9.0 (1.71)*	*9.0 (1.70)*
Overall LS mean (SE) change from Baseline[1]	*-1.9 (0.14)*	*-2.0 (0.14)*	*-1.2 (0.14)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.71* *-1.1, -0.3* *<0.001**	*-0.76* *-1.1, -0.4* *<0.001**	

[1] Results from repeated measures ANCOVA over the treatment period
* Statistically significant
(BDP-AR-305 Study Report, page 64)

The changes in average AM and PM rTNSS from baseline over time for the BDP Nasal Aerosol 80, 160 mcg/day, and placebo are shown graphically in Figure 1 below. For the both BDP Nasal Aerosol treatment groups, the significant change from baseline in the average AM and PM subject-reported rTNSS, compared with the placebo, was consistently observed on Day 4 till the end of the 2-week study.

Figure 1 Change from baseline in average AM & PM rTNSS, Study BDP-AR-305



* Statistically significant
(BDP-AR-305 Study Report, page 65)

Subgroup analyses based on gender (male, female) and race (white, black, others) were performed (Table 8, and 9). There were no significant differences found in

subgroups per gender, and race. However, it was hard to draw conclusions from the subgroup analysis because of the small sample size of the subgroups.

Table 8 Primary efficacy (rTNSS) analysis by gender, Study BDP-AR-305

	Study BDP-AR-305					
	Females (N=332)			Males (N=381)		
Category	BDP nasal aerosol 80 mcg/day (N=105)	BDP nasal aerosol 160 mcg/day (N=116)	Placebo (N=111)	BDP nasal aerosol 80 mcg/day (N=133)	BDP nasal aerosol 160 mcg/day (N=125)	Placebo (N=123)
Baseline mean (SD)	8.8 (1.57)	9.0 (1.70)	8.9 (1.67)	8.9 (1.66)	9.1 (1.72)	9.1 (1.72)
Overall change from baseline[a] over 2 weeks						
LS mean (SE)	-2.0 (0.22)	-1.9 (0.21)	-1.4 (0.21)	-1.9 (0.17)	-2.0 (0.18)	-1.1 (0.18)
LS mean treatment difference from placebo	-0.60	-0.54	-	-0.82,	-0.95	-
95% CI	-1.2, -0.0	-1.1, 0.0	-	-1.3, -0.3	-1.4, -0.5	-

(BDP-AR-305 Study Report, Table 14.2.4.1)

Table 9 Primary efficacy (rTNSS) analysis by race, Study BDP-AR-305

	Study BDP-AR-305								
	White (N=505)			Black (N=162)			Other (N=46)		
Category	BDP nasal aerosol 80 mcg/ day (N=169)	BDP nasal aerosol 160 mcg/ day (N=172)	Placebo (N=164)	BDP nasal aerosol 80 mcg/ day (N=55)	BDP nasal aerosol 160 mcg/ day (N=55)	Placebo (N=52)	BDP nasal aerosol 80 mcg/ day (N=14)	BDP nasal aerosol 160 mcg/ day (N=14)	Placebo (N=18)
Baseline mean (SD)	8.7 (1.64)	8.9 (1.66)	8.9 (1.70)	9.3 (1.43)	9.4 (1.85)	9.3 (1.63)	8.9 (1.81)	9.1 (1.62)	9.1 (1.75)
Change from baseline[a] over the first 2 weeks									
LS mean (SE)	-1.8 (0.16)	-2.1 (0.16)	-1.1 (0.16)	-2.1 (0.31)	-1.7 (0.31)	-1.6 (0.32)	-2.7 (0.43)	-1.6 (0.43)	-0.7 (0.38)
LS mean treatment difference from placebo	-0.67	-0.93	-	-0.49	-0.14	-	-2.00	-0.88	-
95% CI	-1.1, -0.2	-1.4, -0.5	-	-1.4, 0.4	-1.0, 0.7	-	-3.1, -0.9	-2.0, 0.2	-

(BDP-AR-305 Study Report, Table 14.2.4.2)

The Applicant claims that this study demonstrated that 80 mcg/day was the optimally efficacious dose of BDP Nasal Aerosol for the treatment of nasal symptoms in pediatric patients. The analyses of secondary efficacy endpoints also provide support for this conclusion.

Secondary efficacy endpoints

Average AM and PM subject-reported iTNSS

Results for change from baseline in the average AM and PM subject-reported iTNSS over the 2-week Treatment Period were consistent with those observed for the primary efficacy endpoint (Table 10).

Table 10 Analysis of iTNSS, Study BDP-AR-305

Statistic	*BDP HFA 80 mcg/day N = 238*	*BDP HFA 160 mcg/day N = 241*	*Placebo N = 234*
Baseline mean (SD)	*8.1 (1.99)*	*8.1 (2.13)*	*8.2 (2.10)*
Overall LS mean (SE) change from Baseline[1]	*-1.6 (0.13)*	*-1.7 (0.13)*	*-1.0 (0.13)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.63* *-1.0, -0.3* *<0.001**	*-0.73* *-1.1, -0.4* *<0.001**	

1 Results from repeated measures ANCOVA over the treatment period
* Statistically significant
(BDP-AR-305 Study Report, page 66)

AM subject-reported rTNSS and PM subject-reported rTNSS

As observed for the average AM and PM subject-reported rTNSS, the greater improvements for both AM rTNSS and PM rTNSS were seen in BDP Nasal Aerosol 80 mcg/day and 160 mcg/day than in placebo over the 2-week treatment period, as summarized in Table 11 below.

Table 11 Summary of AM rTNSS and PM rTNSS, Study BDP-AR-305

Statistic	*BDP HFA 80 mcg/day N = 238*	*BDP HFA 160 mcg/day N = 241*	*Placebo N = 234*
AM rTNSS			
Baseline mean (SD)	*8.8 (1.68)*	*9.0 (1.76)*	*8.9 (1.78)*
Overall LS mean (SE) change from Baseline[1]	*-1.9 (0.14)*	*-2.0 (0.14)*	*-1.2 (0.14)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.76* *-1.1, -0.4* *<0.001*	*-0.81* *-1.2, -0.4* *<0.001*	
PM rTNSS			
Baseline mean (SD)	*9.0 (1.71)*	*9.1 (1.77)*	*9.1 (1.76)*
Overall LS mean (SE) change from Baseline[1]	*-1.9 (0.14)*	*-2.0 (0.14)*	*-1.2 (0.14)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.68* *-1.1, -0.3* *<0.001*	*-0.74* *-1.1, -0.3* *<0.001*	

[1] Results from repeated measures ANCOVA over the treatment period
(BDP-AR-305 Study Report, page 70)

AM and PM subject-reported individual reflective nasal symptom scores

With regard to individual nasal symptom (sneezing, rhinorrhea [running nose], nasal itching, and nasal congestion) changes in response to BDP Nasal Aerosol treatment, the data summarized in Table below showed that BDP Nasal Aerosol 80 and 160 mcg/day treatment resulted in significantly improvement on all 4 nasal symptoms of SAR patients.

Table 12 Summary of AM & PM individual reflective nasal symptom scores, Study BDP-AR-305

Statistic	*BDP HFA 80 mcg/day N = 238*	*BDP HFA 160 mcg/day N = 241*	*Placebo N = 234*
Sneezing			
Baseline mean (SD)	*2.0 (0.72)*	*1.9 (0.78)*	*1.9 (0.77)*
Overall LS mean (SE) change from Baseline[1]	*-0.5 (0.04)*	*-0.5 (0.04)*	*-0.3 (0.04)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.17* *-0.3, -0.1* *0.002*	*-0.19* *-0.3, -0.1* *<0.001*	
Rhinorrhea (Runny Nose)			
Baseline mean (SD)	*2.2 (0.58)*	*2.3 (0.57)*	*2.2 (0.60)*
Overall LS mean (SE) change from Baseline[1]	*-0.5 (0.04)*	*-0.5 (0.04)*	*-0.3 (0.04)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.20* *-0.3, -0.1* *<0.001*	*-0.21* *-0.3, -0.1* *<0.001*	
Nasal Itching			
Baseline mean (SD)	*2.2 (0.62)*	*2.2 (0.65)*	*2.2 (0.62)*
Overall LS mean (SE) change from Baseline[1]	*-0.5 (0.04)*	*-0.5 (0.04)*	*-0.3 (0.04)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.15* *-0.3, -0.0* *0.007*	*-0.15* *-0.3, -0.0* *0.005*	
Nasal Congestion			
Baseline mean (SD)	*2.6 (0.36)*	*2.6 (0.37)*	*2.6 (0.38)*
Overall LS mean (SE) change from Baseline[1]	*-0.5 (0.04)*	*-0.5 (0.04)*	*-0.3 (0.04)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.19* *-0.3, -0.1* *<0.001*	*-0.21* *-0.3, -0.1* *<0.001*	

[1] Results from repeated measures ANCOVA over the treatment period
(BDP-AR-305 Study Report, page 72)

AM subject-reported iTNSS and PM subject-reported iTNSS

As observed for the average AM and PM subject-reported iTNSS, the greater improvements for both AM iTNSS and PM iTNSS were seen in BDP Nasal Aerosol 80 and 160 mcg/day than in placebo over the 2-week treatment period, as summarized in Table 13 below.

Table 13 Summary of AM iTNSS and PM iTNSS, Study BDP-AR-305

Statistic	*BDP HFA 80 mcg/day N = 238*	*BDP HFA 160 mcg/day N = 241*	*Placebo N = 234*
AM iTNSS			
Baseline mean (SD)	*8.1 (2.05)*	*8.1 (2.19)*	*8.2 (2.17)*
Overall LS mean (SE) change from Baseline[1]	*-1.6 (0.13)*	*-1.7 (0.13)*	*-0.9 (0.13)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.69* *-1.1, -0.3* *<0.001*	*-0.78* *-1.1, -0.4* *<0.001*	
PM iTNSS			
Baseline mean (SD)	*8.0 (2.09)*	*8.1 (2.20)*	*8.1 (2.20)*
Overall LS mean (SE) change from Baseline[1]	*-1.6 (0.13)*	*-1.7 (0.13)*	*-1.1 (0.13)*
LS Mean treatment difference from placebo *95% CI* *p-value*	*-0.56* *-0.9, -0.2* *0.003*	*-0.68* *-1.0, -0.3* *<0.001*	

[1] Results from repeated measures ANCOVA over the treatment period
(BDP-AR-305 Study Report, page 76)

Safety Evaluation

Safety evaluations were made using the safety population. The safety population included all randomized subjects who received at least one dose of randomized study medication.

Extent of exposure

Per protocol, subjects were to be dosed for 2 weeks. The actual mean exposure to study medication was similar for the 3 treatment groups: 15.3 days in the BDP Nasal Aerosol 80 mcg/day group, 15.4 days in the BDP Nasal Aerosol 160 mcg/day group, and 15.2 days in the placebo group.

Adverse events

Of the 714 subjects randomized to study treatment, 95 (13.3%) experienced adverse events: 33 subjects (13.8%) receiving BDP Nasal Aerosol 80 mcg/day, 30 subjects (12.4%) receiving BDP Nasal Aerosol 160 mcg/day and 32 subjects (13.7%) receiving placebo. A total of 9 subjects experienced AEs that were of severe intensity (4 subjects

treated with BDP Nasal Aerosol 80 mcg/day and 5 subjects treated with BDP Nasal Aerosol 160 mcg/day). No subjects experienced an SAE and no death occurred in the study. Four subjects (2 subjects treated with BDP Nasal Aerosol 80 mcg/day and 2 subjects treated with BDP Nasal Aerosol 160 mcg/day) were withdrawn from the study due to AEs. Table 14 presented an overview of treatment-emergent AEs for subjects in each treatment group.

Table 14 Adverse events reported in Study BDP-AR-305

Preferred Term	BDP HFA 80 mcg (N=239) n (%)	BDP HFA 160 mcg (N=241) n (%)	Placebo (N=234) n (%)	Total (N=714) n (%)
Subjects With at Least 1 AE	33(13.8)	30(12.4)	32(13.7)	95(13.3)
Epistaxis	4(1.7)	9(3.7)	10(4.3)	23(3.2)
Headache	7(2.9)	3(1.2)	1(0.4)	11(1.5)
Nasal discomfort	1(0.4)	3(1.2)	2(0.9)	6(0.8)
Nausea	1(0.4)	2(0.8)	2(0.9)	5(0.7)
Vomiting	1(0.4)	2(0.8)	2(0.9)	5(0.7)
Cough	2(0.8)	0(0.0)	2(0.9)	4(0.6)
Arthropod bite	2(0.8)	1(0.4)	0(0.0)	3(0.4)
Dermatitis contact	1(0.4)	1(0.4)	1(0.4)	3(0.4)
Gastroenteritis viral	1(0.4)	1(0.4)	1(0.4)	3(0.4)
Nasopharyngitis	1(0.4)	0(0.0)	2(0.9)	3(0.4)
Otitis media	2(0.8)	1(0.4)	0(0.0)	3(0.4)
Asthma	2(0.8)	0(0.0)	0(0.0)	2(0.3)
Excoriation	2(0.8)	0(0.0)	0(0.0)	2(0.3)
Nasal septum disorder	1(0.4)	0(0.0)	1(0.4)	2(0.3)
Pharyngitis	2(0.8)	0(0.0)	0(0.0)	2(0.3)
Pharyngitis streptococcal	0(0.0)	0(0.0)	2(0.9)	2(0.3)
Sneezing	1(0.4)	0(0.0)	1(0.4)	2(0.3)
Upper respiratory tract infection	1(0.4)	0(0.0)	1(0.4)	2(0.3)
Viral upper respiratory tract infection	0(0.0)	1(0.4)	1(0.4)	2(0.3)
Abdominal pain	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Burns second degree	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Cerumen impaction	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Conjunctivitis	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Dyspepsia	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Dyspnoea	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Ear infection	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Ear pain	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Eczema	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Eye pain	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Gastritis	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Gingival bleeding	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Hordeolum	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Joint sprain	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Lacrimation increased	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Laryngitis	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Ligament sprain	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Lymphadenopathy	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Nasal septum perforation	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Otitis externa	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Otitis media acute	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Pain in extremity	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Pityriasis rosea	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Product taste abnormal	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Pyrexia	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Rash	0(0.0)	0(0.0)	1(0.4)	1(0.1)
Rash erythematous	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Rash papular	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Rhinitis seasonal	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Sinusitis	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Skin laceration	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Somnolence	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Staphylococcal infection	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Thermal burn	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Tympanic membrane disorder	0(0.0)	1(0.4)	0(0.0)	1(0.1)
Upper limb fracture	1(0.4)	0(0.0)	0(0.0)	1(0.1)
Visual impairment	1(0.4)	0(0.0)	0(0.0)	1(0.1)

(BDP-AR-305 Study Report, pages 200-201)

The incidence of AEs was similar across the three treatment groups. There were no apparent differences among 2 doses of BDP Nasal Aerosol treatment groups with respect to incidence of AEs. The most commonly reported AE by MedDRA preferred term was epistaxis which was reported by fewer subjects in the BDP Nasal Aerosol 80 mcg/day group (4 subjects, 1.7%), than in the BDP Nasal Aerosol 160 mcg/day group (9 subjects, 3.7%) and the placebo group (10 subjects, 4.3%). Headache was reported in more subjects in the BDP Nasal Aerosol 80 mcg/day group (7 subjects, 2.9%) than in the BDP Nasal Aerosol 160 mcg/day group (3 subjects, 1.2%) or the placebo group (1 subject, 0.4%). These were the only AEs reported by more than 2% of subjects in any treatment group.

There was one report of nasal septum perforation in a subject treated with BDP HFA 160 mcg/day (Subject 1429006). The subject was an 8 years old female with a history of epistaxis and 2 nasal surgeries prior to participating in the study. This AE was reported to be of moderate severity, and the study treatment was not discontinued prematurely due to this AE. No action was taken for this AE and the outcome was reported as “recovering/resolving”. There were two reports of nasal septum disorder, one in a subject treated with BDP Nasal Aerosol 80 mcg/day (2 mm epithelial erosion on the right septum) and one in a subject treated with placebo (left septum erosion). No actions were taken for the 2 AEs and the outcomes were reported as “recovered/resolved”.

There were 4 subjects were withdrawn from the study due to AEs. Two subjects were treated with BDP Nasal Aerosol 80 mcg/day and experienced asthma during the study; two subjects were treated with BDP Nasal Aerosol 160 mcg/day, and one experienced a popular rash and another had a severe rhinitis during the study. The investigator judged that these AEs were not related to study treatment. None of these AEs were reported as SAEs.

The incidence of AEs that are commonly associated with intra-nasal corticosteroids was low and similar in both BDP Nasal Aerosol treatment groups and placebo group.

Physical examinations, ENT and vital signs
In all treatment groups, no significant changes in physical examinations including ENT and vital signs were observed during the study.

Reviewer’s comment:
The 2 BDP Nasal Aerosol doses, 80 mag/day and 160 mcg/day, had the similar efficacy measures and safety profiles, and revealed no new safety signals in the study. The dose of BDP Nasal Aerosol 80 mcg/day demonstrated efficacy in pediatric patients 6-11 years of age and was acknowledged as the optimal dose for the pediatric patients 4-11 years of age..

5.3.2 Study BDP-AR-306

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 12-week Clinical Study Designed to Assess the Efficacy and Safety of BDP Nasal Aerosol (80 mcg, Once Daily) in Pediatric Subjects (4 to 11 Years of Age) with Perennial Allergic Rhinitis (PAR)

PROTOCOL

Administrative
Study initiated: January 26, 2013
Study completed: October 22, 2013
Clinical Centers: 51 centers in the U.S.
Study report dated: February 11, 2014
Study Sponsor: TEVA Branded Pharmaceutical Products R&D
Principal investigator: Robert L Jacobs, M.D.

Objective
Primary Objective: To evaluate the efficacy of beclomethasone dipropionate (BDP) Nasal Aerosol (80 mcg, once daily) in subjects 4 to 11 years of age inclusive with PAR

Secondary Objective: To assess the safety and tolerability of BDP nasal aerosol (80 mcg, once daily) in subjects 4 to 11 years of age inclusive with PAR

Study Design
This was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group study in male and female pediatric subjects 4 to 11 years of age with PAR. Each subject participated in the study for approximately 15 weeks. The study consisted of 3 periods: single-blind placebo Run-in Period (7-21 days from the Screening Visit [SV] to the Randomization Visit [RV]), 12-week (85 [+3] days) double-blind Treatment Period (Randomization Visit [RV] to Treatment Visit 7 [TV7]), and a follow-up phone call (Final Visit [FV]), 3-5 days following Treatment Visit 7 [TV7]. Each subject completed a screening visit (SV), eight treatment visits (RV, TV1, TV2, TV3, TV4, TV5, TV6 and TV7), and a follow-up phone call (FV).

During the Run-in Period, subjects (either on their own or with assistance from parents/guardians/caregivers, as needed) administered a single-blind placebo nasal aerosol once daily in the morning after completing the morning (AM) Allergic Rhinitis (AR) Assessment Diary. Subjects (with assistance from parents/guardians/caregivers, as needed) assessed and recorded their reflective and instantaneous nasal symptoms (rhinorrhea [runny nose], nasal congestion, nasal itching, and sneezing) twice daily as absent (0), mild (1), moderate (2), or severe (3).

During the Treatment Period (RV through TV7), subjects were randomly assigned to either BDP nasal aerosol (80 mcg/day) or placebo nasal aerosol in a 2:1 ratio. Subjects (either on their own or with assistance from parents/guardians/caregivers, as needed) administered the double- blinded nasal aerosol (BDP nasal aerosol or placebo) once daily in the morning for 12 weeks after completing the AM AR Assessment Diary. Subjects (with assistance from parents/guardians/caregivers, as needed) assessed and recorded their reflective and instantaneous nasal symptoms twice daily using the scale above. A follow-up phone call (FV) occurred 3-5 days following Treatment Visit 7 (TV7) to monitor adverse events (AEs).

Safety was monitored by physical examinations, ear, nose and throat (ENT) examinations, vital signs, and AEs.

Rescue medication, loratadine 1 mg/mL syrup, 5 mg tablets, or 10 mg tablets, was provided for all subjects but no rescue medication was allowed prior to the Randomization Visit (RV) for subjects 4 to 5 years of age and no rescue medication was allowed prior to Treatment Visit 4 (TV4) for subjects 6 to 11 years of age. The dosage form was determined by the investigator and according to the age appropriate prescribing information. Only 1 dosage form was permitted for each subject. Usage of rescue medication was recorded on the Rescue Medication Diary. Subjects were instructed that use of the rescue medication should be minimal and used only “as needed” when the subject’s symptoms were intolerable up to a maximum of 5 mL/day (loratadine syrup) or 5 mg/day (loratadine tablets) for subjects 4 to 5 years of age and 10 mL/day (loratadine syrup) or 10 mg/day (loratadine tablets) for subjects 6 to 11 years of age.

One protocol amendment, dated February 15, 2013, was made. The amendment incorporated procedures for testing the suitability of the BDP nasal aerosol actuator tip to adequately fit in the nostrils of subjects who were 4 to 5 years of age, clarified the definitions of screen failure and randomization failure, permitted the tablet form of loratadine as a rescue medication, added an optional prescreening visit and permitted afternoon study visits during the treatment portion of the study (Treatment Visit 1 [TV1] through Treatment Visit 6 [TV6], inclusive). One change was made to the analyses defined in the protocol. For 12-week rTNSS and iTNSS data, analyses were based on the weekly average (not daily average) and the time unit was week. There were no other changes in the study design and the planned analyses.

Treatment
BDP Nasal Aerosol – 40 mcg/actuation (Lot # 120292),
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # 120293)

> **Group 1: BDP Nasal Aerosol (80 mcg/day):** 40 mcg/actuation (1 actuation/nostril, total 2 actuations), once daily

Group 3: Placebo: 1 actuation/nostril, total 2 actuations, once daily

Study Population
A total of 770 subjects were screened for enrollment in the study. Of the screened subjects, 706 were enrolled in the study and participated in the Run-in Period. Of the 706 enrolled subjects, 547 met the randomization criteria and were randomized to BDP Nasal Aerosol 80 mcg/day and placebo at the 2:1 ratio. Of the 547 randomized subjects, 362 were randomized to receive BDP Nasal Aerosol 80 mcg/day, and 185 to receive placebo. The intent-to-treat (ITT) and safety population included all 547 randomized subjects.

Of the 547 subjects randomized, 454 were aged 6 to 11 years (300 treated with BDP Nasal Aerosol 80 mcg/day and 154 treated with placebo) and 93 were aged 4 to 5 years (62 treated with BDP Nasal Aerosol 80 mcg/day and 31 treated with placebo).

Inclusion criteria
- Written informed consent/(assent- if applicable) signed and dated by the parent/caregiver (legal guardian) and subject (if applicable) before conducting any study-related procedure;
- Male or female subjects 4 to 11 years of age, inclusive, as of the Screening Visit (SV);
- If a female has reached puberty and achieved menarche (as determined by the investigator), parents/guardians/caregivers will be consulted to obtain permission to counsel the subject followed by counseling the subject by the investigator regarding the possible unknown risks associated with study medication during pregnancy. Eligible female subjects of childbearing potential who are known to be sexually active will be excluded; Additionally, a urine pregnancy test must be negative at the Screening Visit (SV);
- General good health, and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results, or put the subject at increased risk during the study;
- A documented history of PAR to a relevant perennial allergen for a minimum of 12 months (6 months for subjects 4 to 5 years of age) immediately preceding the study Screening Visit (SV). The PAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past, and in the investigator's judgment is expected to require treatment throughout the entire study;
- A demonstrated sensitivity to at least one allergen known to induce PAR through a standard skin prick test. A positive test is defined as a wheal diameter at least 5 mm (3 mm for subjects aged 4-5 years) larger than the control wheal for the skin prick test. Documentation of a positive result within 12 months prior to Screening Visit (SV) is acceptable;
- Subject's positive allergen test must be consistent with the medical history of PAR. Additionally the subject is expected to be exposed to the PAR allergen that

he/she has tested positive, via the skin prick test, for the entire duration of the study;
- Subject has a minimum subject-reported reflective Total Nasal Symptom Score (rTNSS) of at least 6 (out of a possible 12) for the AM assessment on the day of the Screening Visit (SV);
- Subject/parent/guardian is capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, is capable of giving informed consent/(assent- if applicable) and being compliant with all study requirements (visits, record-keeping, etc).

Exclusion criteria

- History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma (e.g., nasal piercing) or surgery, atrophic rhinitis, or rhinitis medicamentosa (all within the last 60 days prior to the Screening Visit [SV]);
- Parent/guardian/caregiver of a 4-5 year old subject (under the supervision of site personnel) determines that the study nasal aerosol actuator tip does not fit adequately in both the nostrils of the subject;
- Subjects allergic to a seasonal aeroallergen (e.g., trees, grasses or weeds) with seasonal exacerbation occurring or anticipated to occur during this study period;
- Participation in any investigational drug study within the 30 days preceding the Screening Visit (SV) or planned participation in another investigational drug study at any time during this study period;
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, chronic sinusitis or influenza) within the 14 days preceding the Screening Visit (SV), or development of a respiratory infection during the Run-In Period;
- Use of any prohibited concomitant medications within the prescribed (per protocol) withdrawal periods prior to the Screening Visit (SV);
- A known hypersensitivity to any corticosteroid or any of the excipients in the study medication formulation;
- History of alcohol or drug abuse in the two (2) years preceding the Screening Visit (SV), if applicable;
- History of a positive test for HIV, hepatitis B or hepatitis C infection;
- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of beta-agonists and any controller drug (e.g., theophylline, leukotriene antagonists). History of intermittent use (less than or equal to 3 uses per week) of inhaled short acting beta-agonists prior to the Screening Visit (SV) is acceptable;
- Use of antibiotic therapy for acute conditions within 14 days prior to the Screening Visit (SV). Low doses of antibiotics taken for prophylaxis are permitted if the therapy was started prior to the Screening Visit (SV) and is expected to continue unchanged throughout the study;

- Initiation of immunotherapy during the study period or dose escalation during the study period. However, initiation of immunotherapy 90 days or more prior to the Screening Visit (SV) and use of a stable (maintenance) dose (30 days or more) may be considered for inclusion;
- Previous participation in a BDP nasal aerosol study as a randomized subject;
- Treatment with any known strong CYP3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics, ritonavir) within 30 days prior to Screening Visit (SV) or during the study;
- Non-vaccinated exposure to or active infection with chickenpox or measles within the 21 days preceding the Screening Visit (SV);
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days prior to the Screening Visit (SV); use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition (as judged by the investigator) that can reasonably be expected to require treatment with such preparations during the course of the study;
- Initiation of pimecrolimus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. However, initiation of these creams/ointments 30 days or more prior to the Screening Visit (SV) and use of a stable (maintenance) dose during the study period may be considered for inclusion;
- Study participation by clinical investigator site employees and/or their immediate relatives;
- Study participation by more than one subject from the same household at the same time. However, after the study completion by one subject another subject from the same household may be screened;
- Have any of the following conditions (if applicable) that are judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial:
    - Impaired hepatic function
    - History of ocular disturbances (e.g., glaucoma, ocular herpes simplex, or posterior subcapsular cataracts)
    - Any systemic infection
    - Hematological, hepatic, renal, and/or endocrine disease
    - Gastrointestinal disease
    - Malignancy (excluding basal cell carcinoma)
    - Current neuropsychological condition with or without drug therapy
    - Cardiovascular disease (e.g., uncontrolled hypertension)
    - Respiratory disease other than mild asthma

Randomization criteria

- Subject continues to be in general good health, meeting the selection criteria;

- Subject has not experienced an adverse event that would result in failure to continue to meet selection criteria;
- Subject has not used any of the prohibited concomitant medications during the Run-In period;
- Subject has not suffered from the common cold, upper respiratory infection (URI), otitis media, lower respiratory infection (LRI) or acute sinusitis during the 14 days prior to Randomization Visit (RV);
- Subject has a minimum subject-reported rTNSS of 6 and a minimum subject-reported reflective nasal congestion score of 2 or greater for the AM assessment on the day of randomization;
- Subject has a minimum subject-reported rTNSS of an average of 6 (out of a possible 12) on the last 4 days during the Run-In Period (average of last 8 consecutive AM and PM assessments during the four consecutive 24-hour periods prior to randomization, including the AM assessment on the day of randomization);
- Subject-reported reflective nasal congestion score must be on average 2 or greater on the last 4 days during the Run-In Period (average of last 8 consecutive AM and PM assessments during the four consecutive 24-hour periods prior to randomization, including the AM assessment on the day of randomization);
- Subject has taken their single-blind medication during at least 80% of the entire Run-In Period as documented by the subject diary;
- Subject must have adequately completed the Allergic Rhinitis (AR) Assessment Diary (inadequate completion is defined as missing one or more of the entries on more than 2 calendar days during the last 7 days of the Run-In Period)**.**

Subject withdrawal criteria

- Death (complete AE form and SAE report);
- Adverse Event (complete AE form);
- Subject withdrew consent;
- Request of primary care physician or investigator;
- Non-compliance;
- Protocol violation;
- Sponsor requested subject to be withdrawn;
- Failed to return / lost to follow-up

Subjects who withdraw, are discontinued, or are lost to follow-up will not be replaced. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded in the eCRF. If there are multiple reasons for early discontinuation, the primary reason for discontinuation will be recorded. If a subject is withdrawn because of an adverse event, the event will be followed until the medical condition returns to baseline or is considered stable or chronic. Discontinuation of subjects due to adverse events will be promptly reported to Sponsor. If a subject is lost to follow-up (fails to

return for study visits), a reasonable effort should be made to determine why the subject failed to return. This information will be documented on the eCRF. All evaluations required at the scheduled end-of-study visit (TV7/TdV) will be performed when a subject is withdrawn from the study (regardless of the cause).

Treatment Compliance
A single dose of single-blind placebo medication was administered at the Screening Visit (SV) and a single dose of double-blind study medication was administered at the Randomization Visit (RV) and Treatment Visits 1 through 7 (TV1, TV2, TV3, TV4, TV5, TV6 and TV7) in the study center under the supervision of the designated study personnel. Study personnel made sure that proper study medication administration procedures were followed. Subjects (with assistance from parents/guardians/caregivers, as needed) administered single-blind study medication once daily in the morning during the 7- to 21-day Run-in Period and administered (with assistance from parents/ guardians/ caregivers, as needed) the double-blind study medication once daily in the morning for the 12-week (85-day) Treatment Period. Treatment compliance was assessed by use of the subject-completed AR Assessment Diary. Subjects (or parents/ guardians/ caregivers) recorded the time the study medication had been taken. A single dose of study medication will be administered at the Screening Visit (SV), Randomization Visit (RV), and Treatment Visit 1 (TV1) in the study center under the supervision of the designated site personnel. Site personnel must ensure the proper administration of the study medication. Further treatment compliance will be assessed by the subject's AR Assessment Diary. If subjects are found to be less than 80% compliant at any visit with AR Assessment Diary completion or study medication usage, they should be counseled on the importance of taking study medication and completing the AR assessment diary as directed by the investigator. Subjects are asked to restrict any travel during the study.

Outcomes
The efficacy and safety outcomes were measured per schedule in the Table 15 below.

Table 15 Schedule of study events, Study BDP-AR-306

Visit :	SV[a]	RV	TV1[b]	TV2[b]	TV3[b]	TV4[b]	TV5[b]	TV6[b]	TV7/ TdV[b]	FV[c]
Day(s):	-7 to -21	1	8 (±2)	15 (±2)	29 (±2)	43 (±2)	57 (±2)	71 (±2)	85 (+3)	3-5 days following TV7/TdV
Weeks:	-1 to -3	0	1	2	4	6	8	10	12	13
Written informed consent/(assent – if applicable)	X									
Evaluation of inclusion/exclusion criteria	X									
Demographic data	X									
BDP nasal aerosol actuator tip suitability testing procedure (for only subjects 4 to 5 years of age)	X									
Medical history including concomitant medication history	X									
Skin prick test for appropriate perennial allergen[d]	X	(X)								
Height and weight	X									
Vital sign assessments[e]	X	X	X	X	X	X	X	X	X	
Physical examination	X								X	
Ear, nose and throat (ENT) examination[f]	X	X	X	X	X	X	X	X	X	
Urine pregnancy (if applicable)	X	X		X	X	X	X	X	X	
Physician assessment of nasal symptom severity (PNSS)		X	X	X	X	X	X	X	X	
Call/Log into IWRS for subject number	X									
Distribution of AR Assessment diary and/or review of diary instructions	X	X	X	X	X	X	X	X		
Distribution and/or review of instructions for proper use of nasal aerosol device	X	X	X	X	X	X	X	X		
Prime and dispense single-blind placebo	X									
Supervised administration of single-blind placebo at the study center[g]	X									
Subject completion of twice daily AR Assessment diary[h]	→	→	→	→	→	→	→	→	→	
Subject self-administration of study medication in AM[i,j]	→	→	→	→	→	→	→	→	→	
Evaluation of randomization criteria		X								
Randomization/treatment assignment via IWRS		X								
Collection of completed AR assessment diary		X	X	X	X	X	X	X	X	
Compliance check (study procedures, diary and study medication)		X	X	X	X	X	X	X	X	
Prime and dispense randomized double-blind study medication		X				X				
Supervised administration of double-blinded study medication at the study center		X	X	X	X	X	X	X		
Dispense rescue medication		X[k]				X[l]				
Call/Log into IWRS to discontinue subject									X	
Subject return of all study medication		X				X			X	
Follow-up phone call										X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X
Concomitant medication evaluation	X	X	X	X	X	X	X	X	X	

a. A prescreening visit occurred up to 30 days before the Screening Visit (SV) to discuss the study procedures and requirements for eligibility (e.g., medication washout); informed consent and assent, if applicable, had to be obtained at the prescreening visit.
b. The following visit windows were permitted: ±2 days for Treatment Visit 1 (TV1), Treatment Visit 2 (TV2), Treatment Visit 3 (TV3), Treatment Visit 4 (TV4), Treatment Visit 5 (TV5), and Treatment Visit 6 (TV6) and +3 days for Treatment Visit 7 (TV7). However, the subject was to be provided with additional medication, as needed, to make sure the subject had enough medication to comply with the study requirement.
c. A follow-up phone call occurred 3-5 days following Treatment Visit 7/Treatment Discontinuation Visit (TV7/TdV) to monitor adverse events.
d. The skin prick test could have been initially performed or re-performed at the Randomization Visit (RV) if the investigator felt that the skin prick test result obtained at the Screening Visit (SV) was spurious or would be spurious if obtained at the Screening Visit (SV). Documentation of a positive result within 12 months before Screening Visit (SV) was acceptable to meet eligibility criteria.
e. Sitting blood pressure and pulse rate (after at least 5 minutes of rest in the sitting position).

f. ENT exams were performed to assess signs of AR as well as known complications of intranasal corticosteroid use (i.e., bleeding, perforation and ulceration). Throat exams were conducted to evaluate evidence of throat irritation and candidiasis.
g. Parent/guardian/caregiver of a 4 or 5-year-old subject (under the supervision of site personnel) assessed whether the study nasal aerosol actuator tip fit adequately in both the nostrils of the subject. If it was determined that the fit was not adequate, then the subject was not eligible to participate in the study.
h. Daily compliance with administration of study medication was recorded in the AR Assessment diary.
i. Study medication during the Run-In and Treatment Periods was to be administered by the subject (with assistance from parent/guardians/caregivers, as needed), immediately following completion of the AM diary assessment, except on the morning of the Randomization Visit (RV), Treatment Visit 1 (TV1), Treatment Visit 2 (TV2), Treatment Visit 3 (TV3), Treatment Visit 4 (TV4), Treatment Visit 5 (TV5), and Treatment Visit 6 (TV6) where the study medication was to be administered at the study site by the subject (with assistance of parent/guardian/caregiver, as needed) under the supervision of site personnel.
j. Prior to Treatment Visit 7 (TV7/TdV), subjects were to take their daily dose of study medication at home in the morning in the customary manner following the recording of their AM diary assessments.
k. For subjects 4 to 5 years of age only: No rescue medication was provided or allowed to be taken prior to the Randomization Visit (RV). Loratadine, 1 mg/mL syrup, up to a maximum of 5 mL/day or 5 mg/day as a tablet (as per the age appropriate prescribing information) was permitted on an "as needed basis" after the Randomization Visit (RV). The dosage form was determined by the investigator and according to the age appropriate prescribing information. Only 1 dosage form was permitted for each subject.
l. For subjects 6 to 11 years of age: No rescue medication was provided or allowed to be taken prior to Treatment Visit 4 (TV4). Loratadine, 1 mg/mL syrup, up to a maximum of 10 mL/day, or up to a maximum of 10 mg/day as a tablet(s) (as per the age-appropriate prescribing information) was permitted on an "as needed basis" after Treatment Visit 4 (TV4). The dosage form was determined by the investigator and according to the age appropriate prescribing information. Only 1 dosage form was permitted for each subject.

(BDP-AR-306 Study Report, pages 60-62)

Efficacy endpoints

The primary efficacy endpoint was the change from baseline in the average AM and PM subject-reported rTNSS over the first 6 weeks' Treatment Period for subjects 6 to 11 years of age.

The subject was asked to assess both rTNSS, i.e., an evaluation of symptom severity over the past 12 hours prior to the recording of the score), and instantaneous TNSS (iTNSS), i.e., an evaluation of the symptom severity over the last 10 minutes). The TNSS was defined as the sum of the subject-reported symptom scores for the four nasal symptoms. For each score, each subject recorded the following in the diary:

- Rhinorrhea [runny nose] severity score
- Sneezing severity score
- Nasal congestion severity score
- Nasal itching severity score

The severity scale for each symptom evaluation was defined as follows:

- 0 = absent (no sign/symptom evident)
- 1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe (sign/symptom that is hard to tolerate [i.e., causes interference with activities of daily living and/or sleeping])

The secondary efficacy endpoints were the change from baseline in the average AM and PM subject-reported iTNSS over the first 6 weeks' Treatment Period for subjects 6 to 11 years of age, the change from baseline in the average AM and PM subject-reported rTNSS over the first 6 weeks' Treatment Period for subjects 4 to 11 years of age, and the change from baseline in the average AM and PM subject-reported iTNSS over the first 6 weeks' Treatment Period for subjects 4 to 11 years of age.

The efficacy endpoints were analyzed using a repeated-measures analysis of covariance (ANCOVA) with covariate adjustment for baseline, day, treatment, and the treatment-by-day interaction. Baseline was defined as the average AM and PM subject-reported TNSS over the 7 days prior to randomization. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated.

Safety evaluation
Safety evaluations were made using the safety population. The evaluations included:

- Adverse events: Adverse events were coded using the MedDRA dictionary version 15.1. The nature, incidence, severity or intensity, as well as the causality assessment were reported for each treatment-emergent AE.
- Physical examinations
- Ear, nose and throat (ENT)
- Vital signs

Data Analysis

Sample size
Based on the results from a completed Phase 3 study of BDP Nasal Aerosol in pediatric subjects 6 to 11 years of age with SAR (BDP-AR-305) and other similar studies, the standard deviation for the change from baseline over the first six weeks of treatment in the average of AM and PM rTNSS was assumed to be 2.0. Using this standard deviation, 450 subjects aged 6 to 11 years (300 on active treatment of BDP nasal aerosol and 150 on placebo) would provide approximately 90% power to detect a difference of 0.65 in rTNSS change from baseline between treatment groups with a two-sided alpha level of 0.05. In addition, the study was to enroll 90 subjects aged 4 to 5 years (60 on active treatment of BDP nasal aerosol and 30 on placebo), approximately one sixth of the total number randomized, to provide sufficient safety and supportive efficacy data for this younger age group.

RESULTS

Study Population

Disposition

Subject disposition is shown in Table 16 below, 547 subjects were randomized to treatment: 362 randomized to receive BDP Nasal Aerosol 80 mcg/day and 185 were randomized to receive placebo. All randomized subjects received study treatment and were included in the safety and ITT populations. The sponsor defined a full analysis set (FAS) population who received at least one dose of randomized study medication and had at least one post-baseline subject-reported rTNSS assessment. The FAS population consisted of 542 subjects (358 treated with BDP nasal aerosol 80 mcg/day and 184 treated with placebo). The analyses for the efficacy endpoints were performed using FAS population. Approximately 90% of the subjects completed the study (91%, 328 subjects, in the BDP Nasal Aerosol 80 mcg/day group and 90%, 167 subjects, in the placebo group). A total of 52 subjects, 34 subjects (9%) treated with BDP Nasal Aerosol 80 mcg/day and 18 subjects (10%) treated with placebo, discontinued the study prematurely. There were only 2% subjects prematurely discontinued due to adverse events in both BDP Nasal Aerosol 80 mcg/day and placebo groups.

Table 16 Subject disposition, Study BDP-AR-306

Category	Number (%) of Subjects		
	BDP nasal aerosol 80 mcg/day	Placebo	Overall
Randomized (ITT Population)	362 (100)	185 (100)	547 (100)
Safety Population	362 (100)	185 (100)	547 (100)
FAS	358 (99)	184 (>99)	542 (>99)
Per Protocol Population	356 (98)	178 (96)	534 (98)
Completed	328 (91)	167 (90)	495 (90)
Discontinued study	34 (9)	18 (10)	52 (10)
Adverse Event	8 (2)	4 (2)	12 (2)
Withdrawal by subject	11 (3)	8 (4)	19 (3)
Non-compliance	4 (1)	0	4 (<1)
Protocol violation	2 (<1)	2 (1)	4 (<1)
Lost to follow-up	8 (2)	3 (2)	11 (2)
Lack of efficacy	1 (<1)	1 (<1)	2 (<1)

[1] A subject who discontinued for more than one reason was counted only once.
(BDP-AR-306 Study Report, page 75)

Demographics
As shown in Table 17 below, the mean age of subjects was 8.0 years (range 4 to 11 years) and 55% were male and the majority of subjects (76%) were white, 40% were of Hispanic or Latino ethnicity. Demographic characteristics were generally comparable in the two treatment groups, but there was a slightly higher proportion of male subjects in the placebo group than in the BDP Nasal Aerosol 80 mcg/day group (62% and 52%, respectively).

Table 17 Subject demographics, Study BDP-AR-306

Category	BDP nasal aerosol 80 mcg/day (N=358)	Placebo (N=184)
Age (years)		
Mean (SD)	8.0 (2.17)	8.0 (2.23)
Median	8.0	8.0
Min, max	4, 11	4, 11
Gender, n (%)		
Female	173 (48)	70 (38)
Male	185 (52)	114 (62)
Race, n (%)		
White	271 (76)	145 (78)
Black	63 (18)	25 (14)
Other[a]	24 (7)	15 (8)
Ethnicity, n (%)[b]		
Hispanic or Latino	142 (40)	74 (40)
Not Hispanic, not Latino	215 (60)	110 (60)
BMI (kg/m^2)		
Mean (SD)	18.5 (4.10)	18.9 (4.34)
Median	17.3	17.2
Min, max	11.9, 39.8	12.8, 35.2

[a] Includes 11 Asian subjects, 4 American Indians or Alaskan natives, 2 Native Hawaiians or other Pacific Islanders and 23 subjects of other race
[b] Ethnicity unknown for 1 subject treated with BDP Nasal Aerosol 80 mcg/day
(BDP-AR-306 Study Report, Table 15.2.2)

There were 93 subjects aged 4 to 5 years in the study. The demographics of the subjects aged 4 to 5 years were shown in Table 18 below. The demographic characteristics were generally comparable in the subjects 4 to 5 years of age with that in the overall study subjects.

Table 18 Demographics of subjects 4 to 5 years of age, Study BDP-AR-306

Category	BDP nasal aerosol 80 mcg/day N=62	Placebo N=31	Total N=93
Age (years)			
Mean (SD)	4.5 (0.5)	4.4 (0.5)	4.5 (0.5)
Median	5.0	4.0	5.0
Min-Max	4-5	4-5	4-5
Gender, n (%)			
Female	31 (50)	14 (45)	45 (48)
Male	31 (50)	17 (55)	48 (52)
Race, n (%)			
White	44 (71)	21 (68)	65 (70)
Black	10 (16)	7 (23)	17 (18)
Other[1]	8 (13)	3 (10)	11 (12)
Ethnicity, n (%)[2]			
Hispanic or Latino	28 (45)	14 (45)	42 (45)
Not Hispanic, not Latino	33 (53)	17 (55)	50 (54)
Weight (kg)			
Mean (SD)	20.3 (3.17)	19.6 (2.64)	20.1 (3.01)
Body mass index (kg/m^2)			
Mean (SD)	16.5 (2.18)	16.2 (1.61)	16.4 (2.00)

[1] Includes 2 Asian subjects, 1 American Indians or Alaskan natives, and 8 subjects of other race
[2] Ethnicity unknown for 1 subject treated with BDP Nasal Aerosol 80 mcg/day
(BDP-AR-306 Study Report, page 80)

Medical history was generally similar in the two treatment groups and the types of conditions reported were those that might be expected in a pediatric PAR patient population such as asthma, eczema, headache, food allergy, otitis media, etc. All subjects had a history of PAR. There were 32% of the subjects had a history of SAR.

During the study, the commonly used concomitant medications were summarized in Table 19 below. The most commonly used concomitant medications were salbutamol (albuterol), paracetamol (acetaminophen), ibuprofen, and vitamins. There were no clinically important differences in concomitant medication use among the 2 treatment groups. Rescue medication (loratadine) was used by a lower proportion of subjects in the BDP Nasal Aerosol 80 mcg/day group (35% of subjects) than in the placebo group (45% of subjects).

Table 19 Summary of concomitant medications, Study BDP-AR-306

WHO Preferred Term	Number (%) of Subjects		
	BDP nasal aerosol 80 mcg/day N=362	Placebo N=185	Total N=547
Salbutamol	39 (11)	19 (10)	58 (11)
Paracetamol	35 (10)	19 (10)	54 (10)
Ibuprofen	39 (11)	13 (7)	52 (10)
Vitamins NOS	15 (4)	14 (8)	29 (5)
Amoxicillin	8 (2)	6 (3)	14 (3)
Salbutamol sulfate	4 (1)	7 (4)	11 (2)
Allergen extracts	7 (2)	3 (2)	10 (2)
Cefdinir	6 (2)	3 (2)	9 (2)
Diphenhydramine hydrochloride	6 (2)	3 (2)	9 (2)
Epinephrine	7 (2)	2 (1)	9 (2)
Azithromycin	7 (2)	0	7 (1)
Loratadine[1]	6 (2)	1 (<1)	7 (1)
Levosalbutamol hydrochloride	6 (2)	1 (<1)	7 (1)
Methylphenidate hydrochloride	3 (<1)	4 (2)	7 (1)
Hydrocortisone	2 (<1)	3 (2)	5 (<1)

[1] This does not include loratadine used as a rescue medication which was recorded separately.
(BDP-AR-306 Study Report, page 85)

Efficacy Results

Primary efficacy endpoint

The primary efficacy analysis was summarized in Table 20 below. The primary efficacy measure was the change from baseline in the average of the AM and PM daily subject-reported rTNSS over the first 6 weeks of treatment in subjects 6 to 11 years of age. At baseline, the means of the average AM and PM subject-reported rTNSS were the same in the two treatment groups (8.6 for both groups). Across the first 6-week Treatment Period, average AM and PM subject-reported rTNSS decreased in both treatment groups. The LS mean (SE) changes from baseline were -2.26 (0.12) for BDP Nasal Aerosol 80 mcg/day and -1.60 (0.17) for the placebo group. The LS mean treatment difference of -0.66 between BDP Nasal Aerosol 80 mcg/day and placebo was statistically significant (p=0.002) in favor of BDP Nasal Aerosol 80 mcg/day.

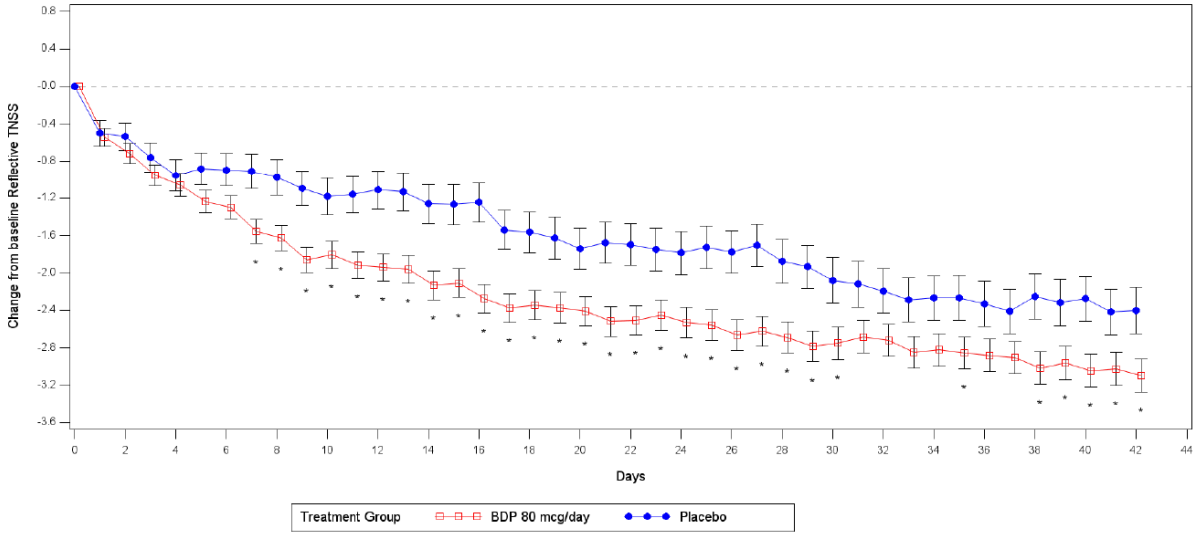
Table 20 Primary efficacy (rTNSS) analysis, Study BDP-AR-306

Statistic	BDP nasal aerosol 80 mcg/day N=296	Placebo N=153
Baseline mean (SD)	8.6 (1.56)	8.6 (1.60)
Overall change from baseline[1]		
LS mean (SE)	–2.26 (0.12)	–1.60 (0.17)
LS Mean treatment difference from placebo	–0.66	
95% CI	–1.08, –0.24	
p-value	0.002*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-305 Study Report, page 87)

The daily changes in average AM and PM rTNSS from baseline over the first 6 weeks of treatment period in subjects 6 to 11 years of age for the BDP Nasal Aerosol 80 mcg/day and placebo groups are shown graphically in Figure 2 below. The BDP Nasal Aerosol 80 mcg/day group had a consistently improvement in the average AM and PM subject-reported rTNSS since Day 7 through the first 6 weeks of the treatment period compared with the placebo.

Figure 2 Change from baseline in average AM & PM rTNSS (6 weeks), Study BDP-AR-306

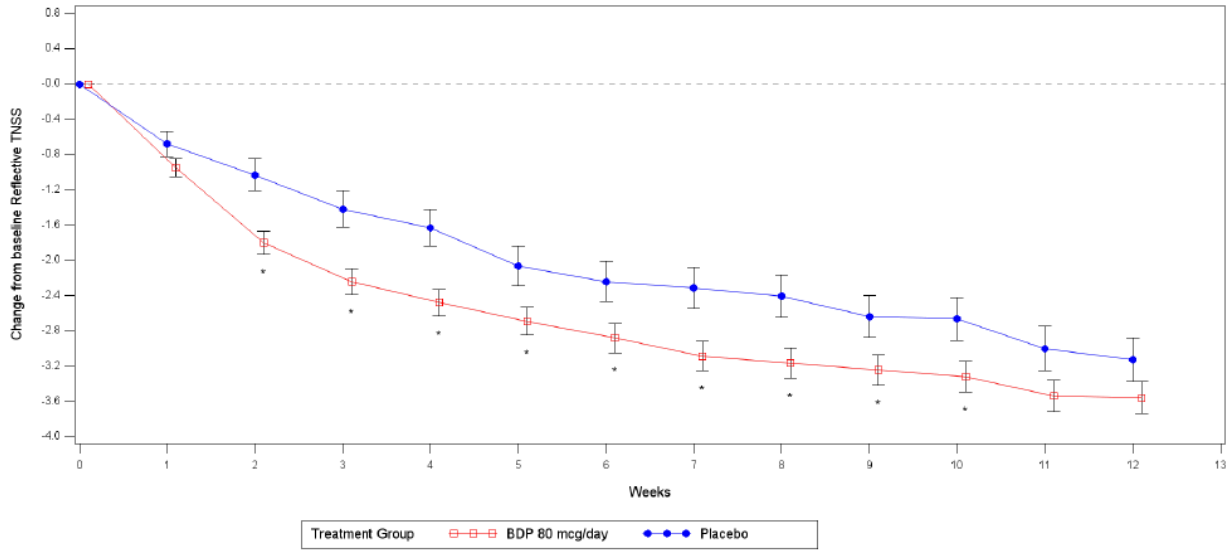


(BDP-AR-306 Study Report, page 94)

The change in weekly average AM and PM rTNSS from baseline over the 12 weeks of treatment period in subjects 6 to 11 years of age for the BDP Nasal Aerosol 80 mcg/day

and placebo groups are shown graphically in Figure 3 below. The BDP Nasal Aerosol 80 mcg/day group had a consistently improvement in the average AM and PM subject-reported rTNSS since week 2 through the 12 weeks of the treatment period in subjects 6 to 11 years of age compared with the placebo.

Figure 3 Change from baseline in average AM & PM rTNSS (12 weeks), Study BDP-AR-306



(BDP-AR-306 Study Report, page 95)

Subgroup analyses for the primary efficacy endpoint rTNSS and the key secondary efficacy endpoint iTNSS were performed for subjects 4 to 5 years of age over the first 6 weeks' treatment period. There were 93 subjects in the 4 to 5 years of age subgroup, 62 treated with BDP Nasal Aerosol 80 mcg/day and 31 treated with placebo. As observed for the population overall, the improvement in the average AM and PM subject-reported rTNSS over the first 6 weeks of treatment were numerically greater with BDP Nasal Aerosol 80 mcg/day than with placebo. The LS mean treatment difference was −0.39 (95% CI: −1.33, 0.56). The analysis for the average AM and PM subject-reported iTNSS over the first 6 weeks of treatment were similar to those seen for the rTNSS. The improvements in the average AM and PM subject-reported iTNSS over the first 6 weeks of treatment were numerically greater with BDP nasal aerosol 80 mcg/day than with placebo. The LS mean treatment difference was −0.33 (95% CI: −1.26, 0.61).

Subgroup analyses based on gender (male, female) and race (white, black, others) were also performed for the primary and secondary efficacy endpoints (Table 21 and 22). There were no significant differences found in subgroups per gender and race in terms of the improvements in primary and secondary efficacy endpoints. However, it was hard to draw conclusions from the subgroup analyses because of the small sample size of the subgroups.

Table 21 Primary efficacy (rTNSS) analysis by gender, Study BDP-AR-306

	Study BDP-AR-306			
	Females (N=198)		Males (N=251)	
Category	BDP nasal aerosol 80 mcg/day (N=142)	Placebo (N=56)	BDP nasal aerosol 80 mcg/day (N=154)	Placebo (N=97)
Baseline mean (SD)	8.8 (1.60)	8.8 (1.53)	8.5 (1.51)	8.5 (1.64)
Change from baseline[a] over the first 6 weeks				
LS mean (SE)	-2.08 (0.17)	-1.85 (0.28)	-2.44 (0.18)	-1.45 (0.22)
LS mean treatment difference from placebo	-0.23	-	-0.98	-
95% CI	-0.88, 0.41	-	-1.55, -0.42	-

(BDP-AR-306 Study Report, Summary 15.8.1.7.1)

Table 22 Primary efficacy (rTNSS) analysis by race, Study BDP-AR-306

	Study BDP-AR-306					
	White (N=350)		Black (N=71)		Other (N=28)	
Category	BDP nasal aerosol 80 mcg/day (N=227)	Placebo (N=123)	BDP nasal aerosol 80 mcg/day (N=53)	Placebo (N=18)	BDP nasal aerosol 80 mcg/day (N=16)	Placebo (N=12)
Baseline mean (SD)	8.6 (1.57)	8.5 (1.60)	8.8 (1.57)	9.2 (1.61)	8.6 (1.36)	8.7 (1.54)
Change from baseline[a] of the first 6 weeks						
LS mean (SE)	-2.35 (0.14)	-1.76 (0.20)	-1.80 (0.28)	-1.20 (0.49)	-2.57 (0.47)	-0.58 (0.55)
LS mean treatment difference from placebo	-0.59	-	-0.60	-	-1.99	-
95% CI	-1.07, -0.11	-	-1.73, 0.53	-	-3.48, -0.50	-

(BDP-AR-306 Study Report, Summary 15.8.1.7.2)

Subgroup analyses for the primary efficacy rTNSS and key secondary efficacy (iTNSS) were performed in subjects 4 to5 years of age (Table 23). There were 93 subjects in the 4 to 5 years of age subgroup, 62 treated with BDP nasal aerosol 80 mcg/day and 31 treated with placebo. Assessment of nasal symptoms in the younger patient population has been challenging due to the subjective nature and the need for increased parental involvement in the process. The BDP Nasal Aerosol 80 mcg/day demonstrated the numerical improvement in the changes of both rTNSS and iTNSS assessments compared to placebo in subjects 4 to 5 years of age. The LS mean treatment difference from placebo was -0.39 (95% CI -1.33, 0.56) for the rTNSS and -0.33 (95% CI -1.26, 0.61) for the iTNSS, respectively. The subgroup analyses of efficacy endpoints in 4 to 5 years of age support the efficacy of BDP Nasal Aerosol 80 mcg/day treatment in pediatric patients 4 to 11 years of age.

Table 23 Efficacy (rTNSS and iTNSS) analyses in subjects 4 to 5 years of age, Study BDP-AR-306

	Study BDP-AR-306			
	Subjects 4 to 5 years of age			
	rTNSS (N=93)		iTNSS (N=93)	
Category	BDP nasal aerosol 80 mcg/day (N=62)	Placebo (N=31)	BDP nasal aerosol 80 mcg/day (N=62)	Placebo (N=31)
Baseline mean (SD)	8.8 (1.38)	8.9 (1.91)	8.4 (1.75)	8.0 (2.37)
Change from baseline[a] over the first 6 weeks				
LS mean (SE)	-2.61 (0.27)	-2.22 (0.39)	-2.51 (0.27)	-2.18 (0.39)
LS mean treatment difference from placebo	-0.39	-	-0.33	-
95% CI	-1.33, 0.56	-	-1.26, 0.61	-

(BDP-AR-306 Study Report, Summary 15.8.1.11)

Secondary efficacy endpoints

The secondary efficacy endpoints included the change from baseline in the average AP and PM iTNSS over the first 6 weeks' Treatment Period for subjects 6 to 11 years of age, the change from baseline in the average AM and PM rTNSS and iTNSS over the first 6 weeks Treatment Period in subjects 4 to 11 years of age. Table 24 below summarized the analyses of secondary efficacy endpoints. The BDP Nasal Aerosol 80 mcg/day treatment had statistically significant improvement in all secondary efficacy endpoints compared with placebo, which was consistent with that in the primary efficacy endpoint.

Table 24 Summary of secondary efficacy endpoints, Study BDP-AR-306

Statistic	BDP nasal aerosol 80 mcg/day	Placebo
Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 6-11 years of age		
Number of subjects	296	153
Baseline mean (SD)	7.9 (2.05)	7.8 (2.12)
Overall change from baseline[1]		
LS mean (SE)	–1.98 (0.12)	–1.39 (0.17)
LS Mean treatment difference from placebo	–0.58	
95% CI	–0.99, –0.18	
p-value	0.004*	
Average AM and PM subject-reported rTNSS over the first 6 weeks of treatment for subjects 4-11 years of age		
Number of subjects	358	184
Baseline mean (SD)	8.7 (1.53)	8.7 (1.66)
Overall change from baseline[1]		
LS mean (SE)	–2.32 (0.11)	–1.71 (0.16)
LS Mean treatment difference from placebo	–0.62	
95% CI	–1.00, –0.23	
p-value	0.002*	
Average AM and PM subject-reported iTNSS over the first 6 weeks of treatment for subjects 4-11 years of age		
Number of subjects	358	184
Baseline mean (SD)	8.0 (2.00)	7.8 (2.16)
Overall change from baseline[1]		
LS mean (SE)	–2.07 (0.11)	–1.53 (0.15)
LS Mean treatment difference from placebo	–0.54	
95% CI	–0.91, –0.17	
p-value	0.004*	

*statistically significant ($p<0.05$)
(BDP-AR-306 Study Report, page 89)

The efficacy measures were also collected for AM rTNSS and PM rTNSS for the first 6 weeks and for the entire treatment period of 12 weeks in subjects 4 to 11 years of age. Table 25 showed that the statistically significant improvements were seen in AM rTNSS and PM rTNSS for the first 6 weeks and for the entire treatment period of 12 weeks with BDP nasal aerosol 80 mcg/day in subjects 4 to 11 years of age compared with placebo.

Table 25 Summary of AM rTNSS and PM rTNSS over the first 6 weeks and 12 weeks in subjects 4 to 11 years of age, Study BDP-AR-306

Statistic	BDP nasal aerosol 80 mcg/day N=358	Placebo N=184
AM rTNSS over first 6 weeks of treatment		
Baseline mean (SD)	8.7 (1.59)	8.7 (1.68)
Overall change from baseline[1]		
LS mean (SE)	–2.35 (0.12)	–1.73 (0.16)
LS Mean treatment difference from placebo	–0.62	
95% CI	–1.00, –0.23	
p-value	0.002*	
AM rTNSS over 12-week treatment period		
Baseline mean (SD)	8.5 (1.61)	8.6 (1.69)
Overall change from baseline[2]		
LS mean (SE)	–2.79 (0.12)	–2.27 (0.17)
LS Mean treatment difference from placebo	–0.52	
95% CI	–0.92, –0.11	
p-value	0.012*	
PM rTNSS over first 6 weeks of treatment		
Baseline mean (SD)	8.7 (1.60)	8.7 (1.80)
Overall change from baseline[1]		
LS mean (SE)	–2.30 (0.12)	–1.68 (0.16)
LS Mean treatment difference from placebo	–0.62	
95% CI	–1.02, –0.22	
p-value	0.002*	
PM rTNSS over 12-week treatment period		
Baseline mean (SD)	8.6 (1.55)	8.6 (1.81)
Overall change from baseline[2]		
LS mean (SE)	–2.79 (0.12)	–2.23 (0.17)
LS Mean treatment difference from placebo	–0.56	
95% CI	–0.97, –0.15	
p-value	0.008*	

*statistically significant ($p<0.05$)
(BDP-AR-306 Study Report, page 103)

Table 26 below summarized the subject-reported reflective individual nasal symptom scores for subjects 6 to 11 years of age over the first 6 weeks of treatment. The statistically significant improvements for rhinorrhea, nasal congestion and sneezing were seen with BDP Nasal Aerosol 80 mcg/day compared with placebo over the 6-week assessment period. For nasal itching, the difference was numerically in favor of BDP Nasal Aerosol treatment.

Table 26 Summary of AM and PM reflective individual nasal symptom scores over the first 6 weeks of treatment in subjects 6 to 11 years of age, Study BDP-AR-306

Statistic	BDP nasal aerosol 80 mcg/day N= 296	Placebo N=153
Rhinorrhea (Runny Nose)		
Baseline mean (SD)	2.1 (0.63)	2.1 (0.58)
Overall change from baseline[1]		
LS mean (SE)	–0.56 (0.03)	–0.39 (0.05)
LS Mean treatment difference from placebo	–0.17	
95% CI	–0.29, –0.05	
p-value	0.004*	
Nasal congestion		
Baseline mean (SD)	2.5 (0.37)	2.5 (0.38)
Overall change from baseline[1]		
LS mean (SE)	–0.62 (0.04)	–0.42 (0.05)
LS Mean treatment difference from placebo	–0.20	
95% CI	–0.32, –0.08	
p-value	0.001*	
Nasal Itching		
Baseline mean (SD)	2.1 (0.59)	2.2 (0.59)
Overall change from baseline[1]		
LS mean (SE)	–0.57 (0.04)	–0.47 (0.05)
LS Mean treatment difference from placebo	–0.10	
95% CI	–0.22, 0.02	
p-value	0.113	
Sneezing		
Baseline mean (SD)	1.9 (0.73)	1.8 (0.71)
Overall change from baseline[1]		
LS mean (SE)	–0.51 (0.04)	–0.32 (0.05)
LS Mean treatment difference from placebo	–0.19	
95% CI	–0.31, –0.07	
p-value	0.002*	

(BDP-AR-306 Study Report, page 105)

Safety Monitoring
Safety evaluations were made using the safety population. The safety population included all randomized subjects who received at least one dose of randomized study medication.

Extent of exposure
The actual mean exposure to study medication was similar for the two treatment groups, being 81.2 days in the BDP Nasal Aerosol 80 mcg/day group and 80.9 days in the placebo group.

Adverse events
Of the 547 subjects randomized to study treatment and placebo groups, a total of 198 subjects (36%) experienced adverse events: 135 subjects (37%) received BDP Nasal

Aerosol 80 mcg/day, and 63 subjects (34%) received placebo. Table 27 presented an overview of treatment-emergent AEs reported at ≥1% for any group in Study BDP-AR-306.

Table 27 Adverse events reported in Study BDP-AR-306

MedDRA 15.1 preferred term, n (%)	BDP 80 mcg/day (N=362)	Placebo (N=185)	Total (N=547)
Subjects with at least 1 AE	135 (37)	63 (34)	198 (36)
Headache	16 (4)	14 (8)	30 (5)
Epistaxis	18 (5)	8 (4)	26 (5)
Pyrexia	14 (4)	6 (3)	20 (4)
Upper respiratory tract infection	15 (4)	5 (3)	20 (4)
Vomiting	12 (3)	4 (2)	16 (3)
Nasopharyngitis	12 (3)	3 (2)	15 (3)
Pharyngitis streptococcal	12 (3)	1 (<1)	13 (2)
Cough	10 (3)	2 (1)	12 (2)
Oropharyngeal pain	8 (2)	2 (1)	10 (2)
Asthma	5 (1)	3 (2)	8 (1)
Nasal discomfort	6 (2)	1 (<1)	7 (1)
Urticaria	7 (2)	0	7 (1)
Otitis media	4 (1)	2 (1)	6 (1)
Sinusitis	4 (1)	2 (1)	6 (1)
Nausea	4 (1)	1 (<1)	5 (<1)
Abdominal pain upper	1 (<1)	3 (2)	4 (<1)
Diarrhoea	3 (<1)	1 (<1)	4 (<1)
Gastroenteritis	1 (<1)	3 (2)	4 (<1)
Gastroenteritis viral	3 (<1)	1 (<1)	4 (<1)
Nasal inflammation	2 (<1)	2 (1)	4 (<1)
Pharyngitis	1 (<1)	3 (2)	4 (<1)
Viral infection	3 (<1)	1 (<1)	4 (<1)
Acute sinusitis	1 (<1)	2 (1)	3 (<1)

(BDP-AR-306 Study Report, page 671)

The incidence of AEs was similar in the 2 treatment groups. There were no significant differences AEs reported for the BDP Nasal Aerosol treatment and placebo groups. The most commonly reported (≥2%) AEs in BDP Nasal Aerosol 80 mcg/day group by MedDRA preferred term were headache, epistaxis, pyrexia, upper respiratory tract infection, vomiting, nasopharyngitis, cough, pharyngitis streptococcal, oropharyngeal pain, urticarial, and nasal discomfort.

There was no report of nasal septum perforation in this study. There were two reports of nasal septum disorder, one in a subject treated with BDP Nasal Aerosol 80 mcg/day (erythema on the left nasal septum) and one in a subject treated with placebo (left side nasal septum erosion). No actions were taken for the 2 AEs and the outcomes were reported as “recovered/resolved”.

In subjects 4 to 5 years of age, the most commonly reported AEs were pyrexia (5 subjects, 8%, in the BDP Nasal Aerosol 80 mcg/day group and 1 subject, 3%, in the placebo group), nasopharyngitis (4 subjects, 6%, in the BDP Nasal Aerosol 80 mcg/day group and 1 subject, 3%, in the placebo group), upper respiratory tract infection (3 subjects, 5%, in the BDP Nasal Aerosol 80 mcg/day group and none subjects in the placebo group), cough (2 subjects, 3%, in the BDP Nasal Aerosol 80 mcg/day group and 2 subjects, 6%, in the placebo group), headache (no subjects in the BDP Nasal Aerosol 80 mcg/day group and 2 subjects, 6%, in the placebo group), and epistaxis (no

subjects in the BDP nasal aerosol 80 mcg/day group and 2 subjects, 6%, in the placebo group). The profile and incidence of the AEs reported in subjects 4 to 5 years were not significantly different from those in overall subjects 4 to 11 years of age.

There were 12 subjects were withdrawn from the study due to AEs. Eight (8) subjects were treated with BDP Nasal Aerosol 80 mcg/day and 4 subjects were treated with placebo. The causes of withdrawal from the study included asthma/bronchial hyper-reactivity (3), upper respiratory infection (2), skin rash/swelling (2), epistaxis (2), nose discomfort (2), and conjunctivitis (1). None of these AEs were reported as SAEs. The investigator judged that 3 of these AEs (one epistaxis in placebo group and 2 nasal discomfort in BDP Nasal Aerosol 80 mcg/day group) were related to study treatment.

The incidence of AEs that are commonly associated with intranasal corticosteroids was low and similar in both BDP Nasal Aerosol 80 mcg/day and placebo. The AEs reported in the study did not reveal a new safety signal for BDP Nasal Aerosol.

No deaths occurred during the study. No subjects experienced a non-fatal SAE during the 12-weeks treatment period.

Physical examinations, ENT and vital signs
In both BDP Nasal Aerosol 80 mcg/day and placebo groups, no significant changes in physical examinations including ENT and vital signs were observed during the study.

Reviewer's comment:
The BDP Nasal Aerosol 80 mcg/day and placebo h*ad the similar efficacy measures and safety profiles, and revealed no new safety signals in the study.*

5.3.3 Study BDP-AR-307

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 6-Week Study Designed to Investigate the Effect of BDP Nasal Aerosol on the Hypothalamic-Pituitary-Adrenal (PHA) Axis in Pediatric Subjects (6 to 11 years of Age) with PAR

PROTOCOL

Administrative
Study initiated: Oct. 20, 2012
Study completed: Feb. 21, 2013
Clinical Centers: 6 centers in the U.S.
Study report dated: July 25, 2013
Study Sponsor: TEVA Branded Pharmaceutical Products
Principal Investigator: Frank C Hampel, Jr, MD

Objective
To compare the effect of 6 weeks of treatment with beclomethasone dipropionate (BDP) Nasal Aerosol versus placebo on HPA-axis function, as assessed by 24-hour serum cortisol weighted mean, in subjects 6 to 11 years of age with PAR.

The primary endpoint was the change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean for BDP Nasal Aerosol versus placebo following 6 weeks of treatment. Analyses were based on data collected over 0-24 hours. The serum cortisol weighted mean over time zero to the time of the last measurable value (0-t), calculated by dividing the area under the concentration-time curve (AUC) from time zero to the time of the last measurable value over the 24-hour period by the sample collection time interval, was determined for each subject at baseline (Randomization Visit [RV]) and at Week 6 (Post Treatment Visit [PTV]) and the ratio of Week 6 over baseline was derived. Following natural log transformation, the ratio was analyzed using an analysis of covariance (ANCOVA) model with covariate adjustment for baseline serum cortisol weighted mean 0-t (log transformed), center, and treatment. Point estimates for the treatment difference (BDP Nasal Aerosol minus placebo) and the associated 95% CI were calculated on the log scale and then exponentiated to provide an estimate of, and confidence interval (CI) for, the geometric mean ratio (BDP Nasal Aerosol/placebo).

Study Results

Subjects
A total of 99 subjects were randomized and received study treatment (67 to BDP Nasal Aerosol 80 mcg/day and 32 to placebo). Two subjects, one in each treatment group, were discontinued prematurely due to protocol violations. Hence, 99 randomized subjects (67 treated with BDP nasal aerosol 80 mcg/day and 32 treated with placebo) completed the study. The mean age of study subjects was 9.0 years and ranged from 6 to 11 years. The majority of subjects in both groups were white (74%) and not Hispanic or Latino (73%). There were more males in the BDP Nasal Aerosol 80 mcg/day group than in the placebo group (53% compared with 35%). Other demographic characteristics were generally comparable in the two treatment groups.

Pharmacodynamics (HPA axis)
The primary endpoint was the change from baseline in the 24-hour serum cortisol mean for BDP Nasal Aerosol 80 mcg/day and placebo after 42 days of treatment. Baseline geometric mean serum cortisol values were similar in the BDP Nasal Aerosol 80 mcg/day and placebo treatment groups (5.97 and 6.47 mcg/dL, respectively). After 6 weeks of treatment the geometric mean values were 6.19 and 7.13 mcg/dL, respectively and there was a small increase from baseline values in both treatment groups. The ratio of Week 6/Baseline was 1.04 (95% CI: 0.96, 1.12) for BDP Nasal Aerosol 80 mcg/day

and 1.10 (95% CI: 0.99, 1.22) for placebo. The geometric mean ratio for BDP Nasal Aerosol 80 mcg/day to placebo was 0.91 (95% CI: 0.81, 1.03). The study demonstrated that BDP Nasal Aerosol 80 mcg/day was not associated with HPA-axis suppression relative to placebo in pediatric subjects (6 to 11 years of age) with PAR.

In the HPA axis study (BDP-AR-307), the Applicant also evaluated steady state PK parameters for BDP and 17-BMP. When administered as BDP nasal aerosol 80 mcg/day, the mean AUC0-24 was 619.06 h*pg/mL, the mean Cmax was 142.68 pg/mL, the median tmax was 1.00 hours, the mean λz was 0.31 hours-1 and the mean t1/2 was 3.1 hours. The results for BDP were lower for the mean AUC0-24 (200.80 h*pg/mL) and mean Cmax (44.65 pg/mL). The median tmax (0.25 hours) for BDP was shorter than for 17-BMP. The λz and t1/2 for BDP were not calculable in any of the subjects.

Safety
Safety was monitored by AEs, physical examinations, ENT examinations, vital signs, and clinical laboratory evaluations (serum chemistry and hematology).

No subject died during the study and no nonfatal SAEs were reported. There were no withdrawals due to AEs. There were no notable differences between BDP Nasal Aerosol 80 mcg/day and placebo in hematology and blood chemistry results. No relevant treatment-related findings were observed for vital signs or ENT or physical examinations. Table 28 showed all AEs reported in the study. The overall incidence of AEs was lower in the BDP nasal aerosol 80 mcg/day group (33%) than in the placebo group (41%). The most commonly reported AEs by MedDRA preferred term were epistaxis and pyrexia. Epistaxis was reported in 7% (5 subjects) in the BDP nasal aerosol 80 mcg/day group and 3% (1 subject) in the placebo group. Pyrexia was reported in 7% (5 subjects) in the BDP nasal aerosol 80 mcg/day group and 3% (1 subject) in the placebo group.

Table 28 Adverse events reported in Study BDP-AR-307

MedDRA 15.1 preferred term, n (%)	BDP 80 mcg/day (N=67)	Placebo (N=32)	Total (N=99)
Subjects with at least 1 AE	22 (33)	13 (41)	35 (35)
Epistaxis	5 (7)	1 (3)	6 (6)
Pyrexia	5 (7)	1 (3)	6 (6)
Abdominal pain upper	2 (3)	1 (3)	3 (3)
Nasopharyngitis	2 (3)	1 (3)	3 (3)
Otitis media	2 (3)	1 (3)	3 (3)
Upper respiratory tract infection	1 (1)	2 (6)	3 (3)
Vomiting	2 (3)	1 (3)	3 (3)
Arthralgia	0	2 (6)	2 (2)
Gastroenteritis	1 (1)	1 (3)	2 (2)
Oropharyngeal pain	2 (3)	0	2 (2)
Abdominal discomfort	1 (1)	0	1 (1)
Abdominal pain	1 (1)	0	1 (1)
Acute sinusitis	0	1 (3)	1 (1)
Conjunctivitis	1 (1)	0	1 (1)
Conjunctivitis infective	1 (1)	0	1 (1)
Cystitis	0	1 (3)	1 (1)
Dermatitis allergic	1 (1)	0	1 (1)
Ear pain	1 (1)	0	1 (1)
Gastroenteritis viral	1 (1)	0	1 (1)
Gastrointestinal viral infection	1 (1)	0	1 (1)
Influenza	1 (1)	0	1 (1)
Influenza like illness	0	1 (3)	1 (1)
Joint injury	0	1 (3)	1 (1)
Laceration	0	1 (3)	1 (1)
Ligament sprain	0	1 (3)	1 (1)
Nasal congestion	0	1 (3)	1 (1)
Oedema peripheral	0	1 (3)	1 (1)
Periorbital haematoma	0	1 (3)	1 (1)
Rash	1 (1)	0	1 (1)
Thermal burn	0	1 (3)	1 (1)
Tonsillitis	1 (1)	0	1 (1)
Toothache	1 (1)	0	1 (1)
Vessel puncture site pain	0	1 (3)	1 (1)
Viral upper respiratory tract infection	1 (1)	0	1 (1)

(BDP-AR-306 Study Report, page 83)

5.3.4 Study BDP-AR-402

An Observational Study to Assess Whether the BDP Nasal Aerosol (b) (4) Actuator Tip Fits Adequately in the Nostrils of Younger Children (2 to <6 Years of Age)

PROTOCOL

Administrative
Study initiated: June 20, 2012
Study completed: July 17, 2012
Clinical Centers: 2 centers in the U.S.
Study report dated: March 21, 2013
Study Sponsor: TEVA Branded Pharmaceutical Products
Responsible Medical Officer: Tushar Shah, MD

Objective
To assess whether the BDP (beclomethasone dipropionate) Nasal Aerosol actuator tip fits adequately in the nostrils of younger pediatric subjects (2 to <6 years of age)

This was a single-visit, observational, non-treatment study designed to assess whether the BDP Nasal Aerosol actuator tip fits adequately in the nostrils of younger pediatric subjects (2 to <6 years of age). No efficacy evaluations were performed in this study. The study consisted of 1 outpatient visit, during which the investigator or medically qualified designee inserted the nasal actuator tip into each nostril (right and left) of the subject to assess whether the nasal actuator tip fit adequately, based on medical and professional judgment. A fresh actuator tip was used for each subject. Demographic data and the BDP Nasal Aerosol actuator tip suitability testing procedure, which included a short questionnaire assessing the suitability of the nasal actuator tip to fit the nostrils, were completed by the investigator or medically qualified designee. There was no administration of study medication in this observational study. Safety of the procedure of inserting the nasal actuator tip in the nostrils was monitored and local adverse events (if any) were documented.

Study Results
A total of 205 subjects were screened for enrollment into the study. All of the 205 screened subjects were enrolled (51 subjects in the 2 to <3 years of age group; 52 subjects in the 3 to <4 years of age group; 51 subjects in the 4 to <5 years of age group; and 51 subjects in the 5 to <6 years of age group) and completed the study. The majority of the enrolled subjects were male (54%), white (61%), and not Hispanic or Latino (57%). For each age group, the demographic and baseline characteristics were generally comparable.

The actuator tip fit study has been reviewed previously. Based on the data obtained from the study the Division has waived the pediatric studies in patients less than 4 years of age.

6 Review of Efficacy

Efficacy Summary

The data submitted in the NDA supplement support the efficacy of BDP Nasal Aerosol for the treatment of nasal symptoms of SAR and PAR in pediatric patients 4 to 11 years of age. There were two adequate and well controlled clinical studies, one in patients with SAR (BDP-AR-305) and one in patients with PAR (BDP-AR-306). Since SAR and PAR are closely related diseases and have identical pathophysiological changes, the drug product demonstrating efficacy in one SAR study and one PAR study are acceptable for approval for nasal symptoms associated with SAR and PAR in pediatric patients 4 to 11 years of age. The primary efficacy endpoint in both SAR and PAR studies was the change from baseline in the mean AM and PM subject-reported reflective total nasal symptom scores (rTNSS) over the treatment period compared with placebo. In the SAR study, a total of 238 subjects received BDP Nasal Aerosol 80 mcg/day for 2 weeks. In the PAR study, a total of 358 subjects received BDP Nasal Aerosol 80 mcg/day for 12 weeks, although the primary efficacy endpoint was the change from baseline in the mean AM and PM subject-reported rTNSS during the first 6 weeks of the treatment period. The BDP Nasal Aerosol treatment demonstrated a statistically significant improvement in rTNSS compared with placebo in two studies. The effectiveness and the once daily dosing regimen were further supported by the demonstration of statistically significant improvements in the key secondary endpoint, mean change from baseline instantaneous TNSS (iTNSS) in two studies. The primary efficacy endpoint rTNSS and the key secondary efficacy endpoint iTNSS are commonly used and accepted as valid in drug development programs for allergic rhinitis. Evidence of benefit of BDP Nasal Aerosol 80 mcg /day in SAR and PAR in pediatric patients 4 to 11 years of age was demonstrated in the two studies.

The dose selection of BDP Nasal Aerosol 80 mcg/day was supported in the 2-week SAR study (BDP-AR-305), in which 238 and 241 subjects received BDP Nasal Aerosol 80 mcg or 160 mcg for 2 weeks, respectively. Statistically significant improvements in rTNSS and iTNSS were observed in patients with BDP Nasal Aerosol doses of 80 and 160 mcg/day compared with placebo. There were no significant differences in efficacy measures for the 2 dose groups. The 80 mcg/day dose of BDP Nasal Aerosol was determined to be the optimal safe and effective dose for the treatment of nasal symptoms associated with SAR and PAR in the pediatric patient population.

Subgroup analyses showed that gender, age and race had no apparent effect on efficacy of BDP Nasal Aerosol 80 mcg/day in the treatment of nasal symptoms associated with SAR and PAR in pediatric patients 4 to 11 years of age.

In summary, based on the data provided in this application, BDP Nasal Aerosol 80 mcg once daily is efficacious for the treatment of nasal symptoms associated with SAR and PAR in pediatric patients 4 to 11 years of age.

6.1 Indication

The proposed indication of BDP Nasal Aerosol for this pediatric supplement is for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in pediatric patients 4 to 11 years of age.

The currently approved indication of BDP Nasal Aerosol is for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in patients 12 years of age and older.

6.1.1 Methods

Efficacy was assessed from the results of 2 randomized, double-blind, placebo-controlled clinical trials in pediatric subjects. The trials are described in detail under section 5.3 Discussion of Individual Studies/Clinical Trials.

6.1.2 Demographics

Detailed demographic data from the pivotal trials are shown in Section 5.3. Patient inclusion/exclusion criteria were appropriate for defining the patient population, and the patients enrolled in the clinical development program appear to be representative of the general population of SAR and PAR. In each trial, BDP Nasal Aerosol 80 mcg /day treatment group was comparable to placebo for demographic characteristics as shown in Table 5 for the 2-week SAR study (BDP-AR-305) and in Table 17 for the 12-week PAR study (BDP-AR-306). Across the studies and treatment groups, there were more males than females, and the majority of the study subjects were white and non-Hispanic ethnicity. The mean age of subjects was 9.0 years and ranged from 6 to 11 years in the 2-week SAR study (BDP-AR-305). The 12-week PAR study (BDP-AR-306) included a subgroup of subjects 4 to 5 years of age and had a mean age of 8.0 years with the range from 4 to 11 years.

With regard to the baseline characteristics, in SAR study (BDP-AR-305) all subjects had a history of SAR with 41% subjects reported concomitant PAR; in PAR study (BDP-AR-306) all subjects had a history of PAR with 32% subjects reported concomitant SAR. There were no clinically important differences between treatment groups for medical history and concomitant medication use in the 2 trials. Overall, recruitment appeared to

have been performed appropriately, and the patients enrolled in the clinical development program appeared to be representative of a general SAR and PAR population.

6.1.3 Subject Disposition

Subject disposition for the Phase 3 trials is described in Section 5.3 in the individual study summaries. Overall, a total of 1096 subjects were randomized and treated in the 2 clinical studies with BDP Nasal Aerosol. In the 2-week SAR study, over 97% of the subjects completed the study. The percentage of subjects with early discontinuation was higher in placebo (3%) than that in BDP Nasal Aerosol 160 mcg/day (2.9%) and 80 mcg/day (1.7%) groups. In the 12-week PAR study, 90% of the subjects completed the study. The percentage of subjects with early discontinuation was slightly higher in placebo group (10%) than that in the treatment group (9%). The most common reason cited for early discontinuation was withdrawal by subjects.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the change from baseline in the mean AM and PM subject-reported reflective TNSS (rTNSS) over the treatment period. The subject was asked to assess and record both rTNSS, i.e., an evaluation of symptom severity over the past 12 hours prior to the recording of the score, and instantaneous TNSS (iTNSS), i.e., an evaluation of the symptom severity over the last 10 minutes). The TNSS was defined as the sum of the subject-reported symptom scores for the four nasal symptoms. For each score, each subject recorded the following in the diary:

- Runny nose severity score
- Sneezing severity score
- Nasal congestion severity score
- Nasal itching severity score

The severity scale for each symptom evaluation was defined as follows:

- 0 = absent (no sign/symptom evident)
- 1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe (sign/symptom that is hard to tolerate [i.e., causes interference with activities of daily living and/or sleeping])

The primary efficacy endpoint was measured for 2 weeks in the 2-week SAR study (BDP-AR 305), and for the first 6 weeks in the 12-week PAR study (BDP-AR-306). The average baseline measurements were comparable between BDP and placebo groups. The changes from baseline for the averaged rTNSS measurements over the treatment period were analyzed using a repeated measures ANCOVA model.

In study BDP-AR-305, analysis of the primary endpoint (change from baseline in the average AM and PM daily rTNSS over the 2 weeks of the treatment period) showed the least squares (LS) mean and standard error (SE) for change from baseline subject-reported rTNSS was -1.9 (0.14) for BDP Nasal Aerosol 80 mcg/day, -2.0 (0.14) for BDP Nasal Aerosol 160 mcg/day and -1.2 (0.14) for the placebo group. The LS mean treatment difference between BDP Nasal Aerosol 160 mcg/day and placebo was -0.76 (95% CI: -1.1, -0.4) and was statistically significant ($p<0.001$) in favor of BDP Nasal Aerosol 160 mcg/day. The LS mean treatment difference between BDP Nasal Aerosol 80 mcg/day and placebo was -0.71 (95% CI: -1.1, -0.3) and was also statistically significant ($p<0.001$) in favor of BDP nasal aerosol 80 mcg/day.

In study BDP-AR-306, analysis of the primary endpoint (change from baseline in the average AM and PM daily rTNSS over the first 6 weeks of the treatment period for subjects 6 to 11 years of age) showed the LS mean (SE) change from baseline subject-reported rTNSS was -2.26 (0.12) for BDP nasal aerosol 80 mcg/day and -1.60 (0.17) for the placebo group. The LS mean treatment difference between BDP nasal aerosol 80 mcg/day and placebo was -0.66 (95% CI: -1.08, -0.24) and was statistically significant ($p=0.002$) in favor of BDP nasal aerosol 80 mcg/day.

Reviewer's comment:
The treatment difference in rTNSS between BDP Nasal Aerosol 80 mcg/day and placebo in both SAR and PAR studies were greater than 0.55, which is considered a clinically meaningful change[1].

6.1.5 Analysis of Secondary Endpoints(s)

This section provides analyses of secondary efficacy endpoints supporting to the analysis of the primary efficacy endpoint. The individual results for these endpoints for each trial have been described in Section 5.3. The improvements of secondary efficacy endpoints were consistent with that of the primary efficacy endpoint, and supported that BDP Nasal Aerosol 80 mcg/day was efficacious in the treatment of nasal symptoms associated with SAR and PAR.

iTNSS
The change from baseline in the average AM and PM subject-reported iTNSS was consistent with those observed for the primary efficacy endpoint. The BDP Nasal Aerosol 80 mcg/day treatment had statistically significant improvement in iTNSS compared with placebo. The treatment differences in iTNSS between BDP Nasal Aerosol 80 mcg/day and placebo were -0.63 and -0.58 in the 2-weeks SAR study in subjects 6 to 11 years of age and in the first 6 weeks of the 12-week PAR study in

[1] Barnes ML, Vaidyanathan S, Williamson PA, et al. The minimal clinically important difference in allergic rhinitis. Clin & Exp Allergy 2010; 40(2):242-250.

subjects 6 to 11 years of age, respectively. These differences were statistically significant (P<0.05). The change from baseline in the average AM and PM subject-reported iTNSS was also evaluated in subjects 4 to 11 years of age for the first 6 weeks in the 12-week PAR study with a treatment difference between BDP Nasal Aerosol 80 mcg/day and placebo of -0.54 (P<0.05).

rTNSS
In study BDP-AR-306, a key secondary efficacy endpoint was the change from baseline in the average AM and PM rTNSS over the first 6 weeks treatment period for subjects 4 to 11 years of age. The treatment difference between BDP Nasal Aerosol 80 mcg/day and placebo in the change from baseline of the average AM and PM rTNSS over the first 6 weeks treatment period for subjects 4 to 11 years of age was -0.62 (p=0.002). The efficacy as measured with rTNSS in subjects 4 to 11 years of age was consistent with that measured in subjects 6 to 11 years of age.

Individual Nasal Symptom Scores
IN both SRA and PAR studies, individual nasal symptoms, i.e. sneezing, rhinorrhea [running nose], nasal itching, and nasal congestion, were evaluated. The data showed that the AM and PM subject-reported individual reflective nasal symptom scores were all improved in response to BDP Nasal Aerosol treatment. In comparison with the placebo, the improvements were statistically significant (p<0.05) for 4 nasal symptoms in the SAR study, and for 3 nasal symptoms (sneezing, rhinorrhea [running nose], and nasal congestion) in PAR study.

6.1.6 Other Endpoints

There were no studies designed to assess the onset of action of BDP Nasal Aerosol in this NDA submission. However, in the 2-week SAR study (BDP-AR-305), the significant decrease in rTNSS was observed on day 4 till the end of the 2-week study in SAR (Figure 1). In the 12-week PAR study (BDP-AR-306), the significant decrease in rTNSS was observed on day 7 till the end of 6 weeks (Figure 2) and over the entire treatment period of 12 weeks (Table 21).

6.1.7 Subpopulations

Subgroup analyses for the primary efficacy endpoint, rTNSS, were conducted based on gender and race in both SAR and PAR studies. Although the sample sizes were not equally distributed across the subgroups and statistical analyses showed variable significant levels, the results do not suggest differential efficacy on the basis of gender or race.

In the 12-week PAR study (BDP-AR-306), subgroup analyses for rTNSS and iTNSS were conducted on subjects 4 to 5 years of age. The treatment difference between BDP Nasal Aerosol 80 mcg/day and placebo in the change from baseline of the average

rTNSS and iTNSS over the first 6 weeks treatment period for subjects 4 to 5 years of age was -0.39 and -0.33, respectively. The efficacy as measured with rTNSS and iTNSS in subjects 4 to 5 years of age was consistent with that measured in subjects 4 to 11 years of age. The results do not suggest differential efficacy on subjects in this age group.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The safety and efficacy of BDP Nasal Aerosol was investigated at daily doses of 80 and 160 mcg in subjects with SAR in study BDP-AR-305. A total of 714 subjects with SAR were randomized and 714 were treated in the study, of whom 239 were received BDP Nasal Aerosol 80 mcg/day (one subject had no efficacy measures and was excluded from data set), 241 received BDP Nasal Aerosol 160 mcg/day, and 234 received placebo. At baseline, the means of the average AM and PM rTNSS (the primary efficacy variable) were comparable in the 3 treatment groups. Across the 2-week treatment period, average AM and PM rTNSS decreased in all treatment groups, including the placebo group. The changes from baseline in the average AM and PM rTNSS was -1.9, -2.0, and -1.2 in BDP Nasal Aerosol 80 mcg/day, 160 mcg/day, and placebo, respectively. The differences between BDP Nasal Aerosol 80 mcg/day and placebo, and 160 mcg/day and placebo were both statistically significant ($p<0.001$) in favor of BDP Nasal Aerosol treatment. The difference between BDP Nasal Aerosol 80 mcg/day and 160 mcg/day group was small and not clinically significant. The 2 doses of BDP Nasal Aerosol were well tolerated and showed no meaningful differences compared with placebo in the incidence of AEs in this 2-week study. The data support the recommended dose of BDP Nasal Aerosol 80 mcg/day.

Reviewer's comments:
Readers are referred to Section 5.3.1 for detailed review of the dose selection study BDP-AR-305.

Due to the similar pathophysiologic process of different types of allergic rhinitis, it is reasonable to extend this selected dose of BDP Nasal Aerosol from SAR study to PAR.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were observed in the clinical studies. BDP Nasal Aerosol 80 mcg per day remained effective for the 2 weeks of exposure in SAR patients and for the 12 weeks of exposure in PAR patients.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of BDP Nasal Aerosol 80 mcg/day for the treatment of nasal symptoms associated with SAR and PAR in pediatric patients 4 to 11 years of age. The evidence for safety is based primarily on the assessments of safety data from clinical studies submitted, including one 2-week study in subjects with SAR, one 12-week study in subjects with PAR, and one 6-week HPA axis study.

No deaths or non-fatal SAEs were reported. The overall incidences of AEs in the clinical studies reviewed were similar between subjects treated with BDP Nasal Aerosol 80 mcg/day and placebo. The most common adverse events with BDP Nasal Aerosol 80 mcg/day treatment were epistaxis (4%), headache (3%), pyrexia (3%), and upper respiratory infection (3%), and they were no appreciable differences with those in placebo. Because intranasal corticosteroid has been known to associated with local complications, the major safety concern for BDP Nasal Aerosol is local adverse events because intranasal corticosteroid use is known to be associated with local complications such as epistaxis, nasal discomfort, nasal ulcerations, and most seriously, nasal septum perforation. There was one report of nasal septum perforation in a subject treated with BDP nasal aerosol 160 mcg/day for 2 weeks. The single case of nasal septum perforation reported in the study was not a safety signal, because the subject had a history of epistaxis and 2 nose surgeries that should have pre-excluded the subject from participating in the study. There were 4 reports of nasal septum disorder, two in subjects treated with BDP Nasal Aerosol 80 mcg/day (one had a 2 mm epithelial erosion on the right septum and one had erythema on left nasal septum) and two in subjects with placebo (2 had left septum erosion). The 4 nasal septum disorders were not a special safety concern, because (1) nasal ulceration/erosion was a known adverse event associated with long term exposure to nasal corticosteroids, (2) those AEs were also reported in subjects with placebo, and could be results of mucosal lesions from the disease being studied (allergic rhinitis).

In summary, the safety evaluation supports the approval of BDP Nasal Aerosol 80 mcg/day in subjects 4 to 11 years of age for the treatment of nasal symptoms associated with SAR and PAR. No additional post-marketing safety trials are necessary for this ICS product.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based on data from 3 clinical studies, including 2-week dose ranging study in SAR patients (BDP-AR-305), 12-week PAR study (BDP-AR-306), and 6-week HPA axis study (BDFP-AR-307).

7.1.2 Categorization of Adverse Events

The Applicant's categorization of AE data by system, organ, class and preferred term was coded according to the MedDRA dictionary version 13.0 for study BDP-AR-305 and version 15.1 for studies BDP-AR-306 and BDP-AR-307. The Applicant also categorized adverse events into treatment-emergent and treatment-related. Treatment-emergent AEs were all adverse events reported during the treatment period, while treatment-related AEs were those adverse events deemed being treatment drug-related by the investigators. This categorization was subjective to each investigator's clinical judgment, and there were no clear criteria on which to assess the causality of AEs. Therefore, safety assessment of this review is based on treatment-emergent AEs, regardless the deemed relations to the treatment drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were pooled based on the BDP Nasal Aerosol dose levels (80 mcg/day, 160 mcg/day and placebo).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall the size of the safety database was adequate for this application. The extent of exposure in the pooled data is summarized in Table 30 below. A total of 909 subjects received BDP Nasal Aerosol in the 3 studies (BDP-AR-305, 306, and 307). The exposure to BDP Nasal Aerosol 160 mcg was only in the 2-week SAR study BDP-AR-305. The majority of the patients were exposed to BDP Nasal Aerosol 80 mcg in the pooled data. For the subjects who received BDP Nasal Aerosol 80 mcg, the mean exposure to the treatment was 53.7 days. For subjects who received BDP Nasal Aerosol 160 mcg or placebo, the mean exposure was 15.4 and 44.0 days, respectively.

Table 30 Exposure (days) in pooled studies*

Parameter	BDP nasal aerosol 80 mcg/day N=668	BDP nasal aerosol 160 mcg/day N=241	Placebo N=451
Mean (SD)	53.7 (32.88)	15.4 (1.81)	44.0 (33.06)
Median	69.5	15.0	17.0
Min, max	1, 97	5, 25	1, 91
Days of Exposure n (%)			
1–14	27 (4)	19 (8)	27 (6)
15–28	225 (34)	222 (92)	214 (47)
29–42	68 (10)	NA	34 (8)
43–56	7 (1)	NA	5 (1)
57–70	9 (1)	NA	1 (<1)
>70	332 (50)	NA	170 (38)

*Pooled data from studies BDP-AR-305/306/307.

Demographic characteristics were comparable between BDP treatment and placebo groups in all studies. The demographic data for each study reviewed can be found in section 5.3 Discussion of Individual Studies/Clinical Trials.

7.2.2 Explorations for Dose Response

There was no dose dependency for AEs observed in BDP Nasal Aerosol clinical studies. In the 2-week SAR study, subjects who received BDP Nasal Aerosol 80 mcg/day and 160 mcg/day had no significant difference in adverse events profile.

7.2.3 Special Animal and/or In Vitro Testing

No special animal study and in vitro study were submitted with this application.

7.2.4 Routine Clinical Testing

Routine clinical laboratory examinations were only collected at screening and at the final visit in the 6-week HPA axis study (BDP-AR-307). The central laboratory provided each investigative site with instructions for collection and transport of laboratory specimens. All laboratory values obtained at the final visit were compared to baseline values at screening. There were no significant changes in clinical laboratory tests. There were no notable differences between the treatment and placebo group. No adverse events were

reported that were due to abnormalities in hematology or serum chemistry tests. The laboratory findings are discussed in section 7.4.2 below.

7.2.5 Metabolic, Clearance, and Interaction Workup

Specific metabolic, clearance and interaction safety studies were not conducted for this development program. However reference was made to the QVAR program (NDA 20-911). This is appropriate because QVAR contains the same active ingredient (b) (4) as BDP Nasal Aerosol.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Given the known potential for inhaled corticosteroids to suppress HPA axis, the Applicant conducted a HPA axis study to evaluate the effect of BDP Nasal Aerosol on 24-hour serum cortisol level (BDP-AR-307). The HPA axis study is described in detail in Section 7.4.5 Special Safety studies/Clinical Trials.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the studies reviewed in this NDA supplement.

7.3.2 Nonfatal Serious Adverse Events

There were no non-fatal serious adverse events in the studies reviewed in this NDA supplement.

7.3.3 Dropouts and/or Discontinuations

The dropouts due to adverse events were low in the clinical studies reviewed. In the 2-week SAR study 4 subjects (2 subjects treated with BDP Nasal Aerosol 80 mcg/day and 2 subjects treated with BDP Nasal Aerosol 160 mcg/day) were withdrawn from the study due to AEs. In 12-week PAR study, there were 12 subjects withdrawn from the study due to AEs. Eight (8) subjects were treated with BDP Nasal Aerosol 80 mcg/day and 4 subjects were treated with placebo. The causes of withdrawal from the study included asthma/bronchial hyper-reactivity (3), upper respiratory infection (2), skin rash/swelling (2), epistaxis (2), nose discomfort (2), and conjunctivitis (1). None of these AEs were coded as SAEs. The review of subjects who discontinued from the studies did not reveal a safety signal.

7.3.4 Significant Adverse Events

Although there were no serious adverse events occurred in the studies, the local adverse events were of particular concern because the nasal administration route and the action of BDP Nasal Aerosol. The major local AEs of concern included nasal septum perforations, ulcerations, and epistaxis. These were detected based on medical history and ENT exam by the site investigator. The inclusion/exclusion criteria also excluded those with a history of physical findings of nasal pathology, including nasal polyps or other significant respiratory tract malformations; recent nasal biopsy; nasal trauma; nasal ulcers or perforations; or surgery (all within the last 60 days prior to screening visit).

The local AEs are discussed in Section 7.3.5 below.

7.3.5 Submission Specific Primary Safety Concerns

It is known that intranasal corticosteroid use may have local complications such as nose bleeding, nasal irritation, nasal ulceration/erosion, and most seriously, nasal septum perforation. Therefore the major safety concern for BDP Nasal Aerosol is local adverse events.

There was one report of nasal septum perforation in a subject treated with BDP nasal aerosol 160 mcg/day for 2 weeks. The subject was an 8 years old female with a history of epistaxis and 2 nasal surgeries prior to participating in the study. This AE was reported to be of moderate severity, and the study treatment was not discontinued prematurely due to this AE. No action was taken for this AE and the outcome was reported as “recovering/resolving”.

There were 4 reports of nasal septum disorder in the pooled safety data, two in subjects treated with BDP Nasal Aerosol 80 mcg/day (one had a 2 mm epithelial erosion on the right septum and one had erythema to left nasal septum) and two in subjects treated with placebo (2 had left septum erosion). No actions were taken for these AEs and the outcomes were reported as “recovered/resolved”.

Reviewer’s comment:
The single case of nasal septum perforation reported in the clinical study did not reveal a safety signal, because the subject had a history of epistaxis and 2 nose surgeries that should have pre-excluded the subject from participating in the study. The 4 nasal septum disorders were not a special safety concern, because (1) nasal ulceration/erosion was a known adverse event associated with long term exposure to nasal corticosteroids, and (2) those AEs were reported in subjects with placebo, and could be results of mucosal lesions from the disease being studied (allergic rhinitis).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The adverse events in preferred terms experienced in 1% or more in any treatment group in the pooled data are summarized in Table 31. The percentage of subjects with at least one AE was 28%, 12%, and 24% in BDP Nasal Aerosol 80 mcg, 160 mcg and placebo, respectively. Note that the difference in percentage of subjects with AE in the pooled data was associated with the difference in exposure time in the 3 groups. Because the data of BDP Nasal Aerosol 80 mcg and placebo group included subjects of 12-week study while the data of BDP Nasal Aerosol 160 mcg was only for 2-week study, the average exposure time was 53.7, 15.4, and 44.0 days in BDP Nasal Aerosol 80 mcd, 160 mcg, and placebo, respectively. The most common adverse events in BDP Nasal Aerosol 80 mcg treatment were epistaxis (4%), headache (3%), pyrexia (3%), and upper respiratory infection (3%), and they were no appreciable differences with those in placebo group. Because these common adverse events were known conditions associated with allergic rhinitis and there were no appreciable differences in incidence rate compared with placebo, the common adverse events reveal no safety signals for the BDP Nasal Aerosol 80 mcg/day treatment in the 6- and 12-week studies in subjects 4 to 11 years of age.

Table 31 Adverse events occurred in ≥1% of any study group in pooled data

Preferred Term	Number (%) of subjects		
	BDP nasal aerosol 80 mcg/day N=668	BDP nasal aerosol 160 mcg/day N=241	Placebo N=451
Subjects with at least 1 adverse event	190 (28)	30 (12)	108 (24)
Epistaxis	27 (4)	9 (4)	19 (4)
Headache	23 (3)	3 (1)	15 (3)
Pyrexia	19 (3)	1 (<1)	7 (2)
Upper respiratory tract infection	17 (3)	0	8 (2)
Vomiting	15 (2)	2 (<1)	7 (2)
Nasopharyngitis	15 (2)	0	6 (1)
Cough	12 (2)	0	4 (<1)
Pharyngitis streptococcal	12 (2)	0	3 (<1)
Oropharyngeal pain	10 (1)	0	2 (<1)
Otitis media	8 (1)	1 (<1)	3 (<1)
Nasal discomfort	7 (1)	3 (1)	3 (<1)
Asthma	7 (1)	0	3 (<1)
Urticaria	7 (1)	0	0

Reviewer's comment:
Epistaxis is known to associate with nasal exposure to corticosteroids. Also, the nasal exposure to the propellant HFA as the pressurized aerosol may result in mucosal lesions and epistaxis. The reported incidence of epistaxis was the same in BDP Nasal Aerosol treatment groups and in placebo and it did not reveal a new safety signal for BDP Nasal Aerosol treatment in subjects 4 to 11 years of age.

7.4.2 Laboratory Findings

Clinical laboratory examinations (blood chemistry and hematology) were only collected at screening and the final visit in the 6-week PAR pivotal study (BDP-AR-307). There were no significant changes in clinical laboratory tests during the study. No adverse events were reported that were due to abnormalities in hematology or serum chemistry tests.

7.4.3 Vital Signs

In all clinical studies reviewed, vital signs (systolic and diastolic blood pressure and pulse rate) were measured at screening and at the final visit. There were only small changes in vital signs were observed. The changes that were observed were similar across the treatment and placebo groups. Any clinically meaningful changes were to be reported as AEs. There were no AEs reported due to changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

Standard 12-lead ECG examinations were only performed at screening and the final visit in the 6-week PAR pivotal study (BDP-AR-307). No clinically significant findings were reported.

7.4.5 Special Safety Studies/Clinical Trials

Nasal examinations
The major safety concern for BDP Nasal Aerosol is the local toxicity. ENT exams were performed by the investigator with all study visits to identify and assess signs of allergic rhinitis and known complications of intranasal corticosteroid use (i.e., epistaxis, nasal septum perforation and ulceration). Clinically significant findings were reported as AEs. Local adverse events identified by nasal examination have been discussed in section 7.3.5 (for nasal septum perforation and nasal ulceration/erosion) and in section 7.4.1 (for epistaxis).

7.4.6 Immunogenicity

Immunogenicity was not assessed as BDP is not an immunogenic molecule.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no dose dependency for AEs observed in BDP Nasal Aerosol clinical studies. In the 2-week SAR study, patients received 2 doses of BDP Nasal Aerosol (80 mcg/day and 160 mcg/day). Table 31 in Section 7.4.1 shows that incidences of overall AEs and individual AEs were all similar between different dose groups and placebo.

7.5.2 Time Dependency for Adverse Events

Although there was no apparent time dependency for the most commonly observed adverse events in the 2-week SAR study and 12-week PAR study, the percentage of

subjects with at least one AE was higher in patients with longer exposure to BDP Nasal Aerosol. In the pooled data, 28% of subjects with the average exposure time of 53.7 days reported at least one AE, while 12% of subjects with the average exposure time of 53.7 days reported at least one AE. Adverse events associated with chronic corticosteroid use may be expected to be increased with prolonged use.

7.5.3 Drug-Demographic Interactions

Subgroup analysis of the AE data by gender, race and age did not indicate any apparent drug-demographic interactions. The overall rate of AEs was similar across gender, race, and age subgroups, without any clear patterns in relation to these subgroups.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not assessed in this development program.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed in this development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Specific evaluations for carcinogenicity were not conducted for this application. Beclomethasone dipropionate is a well-known chemical entity and is not known to be carcinogenic.

7.6.2 Human Reproduction and Pregnancy Data

No adequate and well-controlled human reproductive studies were conducted in this development program. Pregnancy or lactation was an exclusion criterion for all clinical studies and any female subject who became pregnant during the clinical program was discontinued from study treatment.

BDP HFA has been approved as the formulation of QVAR Inhalation Aerosol for the maintenance treatment of asthma in patients 5 years of age and older (NDA 20-911). As with the approved *QVAR* labeling, administration of BDP Nasal Aerosol during pregnancy or lactation should only be considered if the expected benefit to the mother justifies any potential risk to the fetus or baby (i.e. classified as FDA Pregnancy Category C).

7.6.3 Pediatrics and Assessment of Effects on Growth

This is a pediatric supplement for the approved QNASL Nasal Aerosol. There are no pediatric growth studies in this development program, and the growth effect of BDP Nasal Aerosol will reference the QVAR program.

Reviewer's comment:
It is appropriate to reference QVAR program for the growth effect of BDP Nasal Aerosol, because the systemic exposure would be higher in QVAR inhalation aerosol program than the nasal administration in the QNASL program.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported in this application. Based on the low systemic bioavailability, and the nature of BDP Nasal Aerosol, drug abuse potential, withdrawal, and rebound are not anticipated.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

This application is a pediatric supplement for QNASL Nasal Aerosol, which was approved for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older on March 23, 2012. Since its approval the Applicant has submitted periodic postmarketing safety report for QNASL Nasal Aerosol every 3 months. The data are summarized in Table 32 below. There are no new safety signals in these submissions.

Table 32 Postmarketing experience

Postmarketing report period	SAEs	AEs	Note
Approval to May 31, 2012	1 (swelling/urticarial)	13	No new safety signals
June 1 to August 31, 2012	1 (epistaxis/headache)	20	No new safety signals
Sept. 1 to Nov. 30, 2012	0	43	No new safety signals
Dec. 1, 2012 to Feb. 28, 2013	0	37	No new safety signals
March 1 to May 31, 2013	1 (swelling face/erythema)	51	No new safety signals
June 1 to August 31, 2013	0	47	No new safety signals
Sept. 1 to Nov. 30, 2013	1 (sinus infection)	31	No new safety signals
Dec. 1, 2013 to Feb. 28, 2014	0	32	No new safety signals
March 1 to May 31, 2014	0	29	No new safety signals
June 1 to August 31, 2014	0	27	No new safety signals

9 Appendices

9.1 Literature Review/References

The Applicant included a list of 28 articles from the scientific literature in support of the safety and efficacy of BDP Nasal Aerosol. To supplement this list, the clinical review conducted a PubMed literature search [search terms: “beclomethasone dipropionate” and “safety” with limit to: “English”, “10 years”] which yielded 46 articles. These articles were briefly scanned in terms of their relevance to the current application. No new safety signals were identified from the literature.

9.2 Labeling Recommendations

The final labeling negotiation is ongoing at the time of this review. Based on the results from the pediatric studies, the labeling is revised by adding pediatric efficacy and safety data, and changing the patient population from “adults and adolescents 12 years of age and older” to “patients 4 years of age and older”.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held for this NDA.

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/s/

XU WANG
11/25/2014

ANTHONY G DURMOWICZ
11/25/2014