CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-813
Priority or Standard	S
Submit Date(s)	05/24/2011
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Division / Office	DPARP/ODE II
Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	02/14/2012
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	320 mcg administered as 2 nasal sprays (80 mcg/spray) in each nostril once daily
Indication(s)	(b) (4)
Intended Population(s)	Adults and adolescent patients 12 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 is Approval of BDP (beclomethasone dipropionate) Nasal Aerosol for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents patients 12 years of age and older.

BDP has been approved as an oral inhalation drug as QVAR Inhalation Aerosol (NDA 20-911, approved 9/15/2000) for the indication of maintenance treatment of asthma. BDP Nasal Aerosol uses the exactly same drug product canister, components and controls as QVAR in NDA 20-911, and inserts the canisters into the newly developed plastic nasal actuator that is designed for a nasal route of delivery.

1.2 Risk Benefit Assessment

The data submitted in the NDA support the efficacy of BDP Nasal Aerosol for the treatment of nasal symptoms of SAR and PAR in adults and adolescents patients 12 years of age and older. There were two adequate and well controlled efficacy studies, one in patients with SAR (BDP-AR-301) and one in patients with PAR (BDP-AR-302). 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. The primary efficacy endpoint for both SAR and PAR 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 167 subjects received BDP Nasal Aerosol 320 mcg/day for 2 weeks. In the PAR study, a total of 232 subjects received BDP Nasal Aerosol 320 mcg/day for 6 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 320 mcg /day in SAR and PAR was demonstrated in the two studies.

The efficacy was also supported in a 2-week dose ranging study in patients with SAR (BDP-AR-201), in which 122, 123, and 118 subjects received BDP Nasal Aerosol 320 mcg, 160 mcg, and 80 mcg daily for 2 weeks, respectively. Statistically significant improvements in rTNSS and iTNSS compared with placebo were observed in patients with BDP Nasal Aerosol 320 mcg/day but not in patients with 160 or 80 mcg/day.

Other secondary efficacy endpoints evaluated in the studies included Rhinoconjuctivitis Quality of Life Questionnaire (RQLQ) scores and reflective total ocular symptom scores (rTOSS). RQLQ and rTOSS are commonly used measures of disease specific quality of life and non-nasal symptoms in drug development programs for allergic rhinitis. The data showed that BDP Nasal Aerosol 320 mcg/day treatment did not demonstrate consistently significant improvement in RQLQ and rTOSS in the SAR and PAR studies.

In terms of risk consideration, the most common adverse events (AEs) reported for BDP 320 mcg per day following short term exposure (2-6 weeks) were nasal irritation, headache, and epistaxis, and they were not significantly different from placebo. In a long term safety study, most common AEs reported for BDP Nasal Aerosol 320 mcg per day following 30 to 52 weeks' exposure were nasopharyngitis, epistaxis, upper respiratory tract infection, sinusitis, and headache. Epistaxis was the most notable AE that had a significant increase in long term BDP Nasal Aerosol 320 mcg/day exposure compared to placebo at 10.6% (44/415 subjects) versus 1.8% (2/111 subjects). Epistaxis tended to be more severe in patients treated with BDP Nasal Aerosol 320 mcg/day. With regard to rare AEs, there were no nasal septum perforations reported in the BDP Nasal Aerosol development program. In pooled data of 2- to 6-week studies, there was one nasal erosion reported in the BDP Nasal Aerosol 80 mcg/group and one nasal ulceration in the BDP Nasal Aerosol 320 mcg/group. There were 2 cases of nasal ulceration in placebo. In the long term safety study, there was one nasal ulceration and 4 cases of erosion reported in the BDP Nasal Aerosol 320 mcg/day group. There was no nasal ulceration/erosion reported in placebo group. The HPA axis study demonstrated that the treatment of BDP Nasal Aerosol 320 mcg/day for 6 weeks had no effect on HPA axis function in adult and adolescent subjects. Ocular examinations in the long term safety study showed that 52 weeks' exposure to BDP Nasal Aerosol had no effect on development of cataract or glaucoma. Several patients had increased intraocular pressure in the long term safety study with 2 patients reporting adverse events. Given the known adverse events associated with nasal corticosteroids, the imbalance in incidence of epistaxis and the rare cases of nasal ulceration/erosion and increased intraocular pressure observed in the long term exposure to BDP Nasal Aerosol do not constitute any new safety signal and were consistent with adverse reactions observed for other similar approved products.

In summary, the data demonstrated the benefit of BDP Nasal Aerosol 320 mcg daily for the treatment of nasal symptoms in SAR and PAR with acceptable safety profile. Based on the risk benefit assessment, approval of BDP Nasal Aerosol for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and adolescents patients 12 years of age and older is recommended from a clinical perspective.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-market risk evaluation and mitigation strategies are recommended for BDP Nasal Aerosol.

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 as a (b) (4) for BDP. 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). The drug product does not include any additional protective packaging. The drug product filled canisters are manufactured using the same formulation, manufacturing process, and at the same facility, with the same canister and valve as that for the currently marketed product, QVAR of NDA 20911, an inhalation aerosol for the maintenance treatment of asthma. The canister is inserted in a newly developed plastic nasal actuator that is designed for a nasal route of delivery. Detailed product information can be found in CMC Review by Craig M. Bertha, Ph. D.

On September 10, 2010, the Applicant submitted to IND 101639 a “Request for Proprietary Name Review”, requesting review of the proprietary name, QNAZE, for the proposed drug product. The Agency responded on March 10, 2011, advising the Applicant that the proposed proprietary name was unacceptable due to orthographic similarities to another product, AVAGE. The Applicant has since submitted NDA 202813 for BDP (beclomethasone dipropionate) Nasal Aerosol. Subsequently, the Applicant submitted the name, QNASL, to the NDA on May 27, 2011. Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed

name Qnasl is acceptable [Proprietary Name Review, DMEPA/OSE, Loretta Holms, BSN, Pharm.D., August 24, 2011].

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

QNASL nasal Aerosol is not marketed in the United States or any foreign country. 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

Prior to submission of this NDA, this product has been the subject of multiple regulatory proceedings (as IND 101,639). Pertinent discussions are summarized below:

04/02/2008 Pre-IND meeting

- Agreement that no additional toxicity studies needed to support the approval of the nasal aerosol product.

01/20/2009 IND submission

09/09/2009 End of Phase 2 meeting

- Statement that the proposed product is a 120-actuation trade pack with non-removable (fixed) nosepiece.
- Statement that efficacy measures in the long term safety study are primarily for compliance monitoring.
- The Division commented on the dose selected by sponsor for Phase 3 studies: "We concur that the data indicate that 320 mcg daily is the lowest effective dose. However, it may not be optimal to carry forward only this single dose in your Phase 3 studies. Your dose ranging study (BDP-AR-201) showed that the 320 mcg dose had a relatively small effect size of -0.63 (point estimate) in rTNSS difference compared to placebo. This suggests that a single dose of 320 mcg daily may not be the most effective dose for your Phase 3 studies. Consider including higher doses in your Phase 3 program. Since BDP is dosed twice daily for the asthma indication, the relatively modest efficacy seen with the 320 mcg dose may also indicate that once daily dosing may not be the most appropriate dosing interval for allergic rhinitis. Consider modifying the dose frequency to twice daily." The sponsor responded that "they are not interested in studying doses above 320 mcg for rhinitis because of the safety concerns for higher steroid doses" and noted "that the choice of the 320 mcg once daily dose is their risk."
- The sponsor asked that "approximately 1128 patients/subjects will be exposed to various doses of BDP nasal aerosol during the proposed adult and adolescent clinical development program, does Agency concur that the overall patient exposure to HFA-BDP nasal aerosol will be acceptable for approval in patients 12 years of age and above?" The Division stated that "In general, the number of patients exposed to BDP nasal aerosol in the proposed adult and adolescent clinical development program appears reasonable. However, depending on the local safety findings in the clinical program, additional safety studies with a larger

sample size may be needed. Further, if a higher dose is selected for the Phase 3 program, then the higher dose should be studied in the one year safety study."
- Statements that a long term safety study of 52 weeks' duration will include a subset of approximately 250 patients assessed for ocular safety Including LOCS III and IOP evaluation.
- Statement that HPA-axis study includes 40 patients 12 years of age and older per arm.

10/18/2010 Pre-NDA Meeting
- Agreement that information from QVAR, NDA 20-911, may be cross referenced.
- Agreement that the sponsor only provides CVs and Licenses for only the Principle Investigators, not for any Sub-Investigators, and all Sub-Investigator CVs and Licenses are available upon request.
- Agreement that at the time of NDA filing, a pediatric waiver for pediatric population 0 to under 2 years of age and a pediatric studies deferral for 2 to 11 years of age may be requested.
- Statement that the sponsor's plan to evaluate 2 doses (160 mcg and 80 mcg, once daily) in a pediatric dose-range-finding study (6-11 years of age) to determine the optimal safe and effective pediatric dose in this age group. The optimal dose for 2-5 years of age pediatric subjects will depend on the results of the dose-range-finding study in the 6-11 year old age group.
- The sponsor proposed the indication for BDP Nasal Aerosol as (b) (4) of nasal symptoms (b) (4) seasonal (b) (4) and perennial allergic rhinitis in adult/adolescent patients 12 years of age and older." The Division stated that "the general outline of your program is reasonable to support an indication for allergic rhinitis. Whether the data from your clinical program is adequate to support this indication is a review issue."

2.6 Other Relevant Background Information

QNASL nasal Aerosol has not been marketed in any other country and there have not been any foreign 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 (Dr. Kiya Hamilton) 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 two exceptions: (1) (b) (6) (Investigator # (b) (6) Study Site: (b) (6) has declared that he and his family own 9,620 shares of Teva Pharmaceutical Industries stock in various self-directed accounts that he and/or his family controls, including a retirement account. He and his family have held varying amounts of Teva stock since 1986 and current to March 2011. The study (b) (6) initiated on (b) (6) (first patient screened) and completed on (b) (6). A total of (b) (6) subjects were randomized at the site out of the (b) (6) subjects randomized overall in the study. 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; (2) (b) (6), MD (Investigator (b) (6), Study Site: (b) (6) has declared that he and his family own 9,620 shares of Teva Pharmaceutical Industries stock in various self-directed accounts that he and/or his family controls, including a retirement account. He and his family have held varying amounts of Teva stock since 1986 and current to March 2011. The study (b) (6) initiated on (b) (6) (first patient screened) and completed on (b) (6) (last patient visit). Total of (b) (6) subjects were randomized at the site out of the (b) (6) subjects randomized overall in the study. (b) (6) did not select or know which patients receive drug or placebo, nor did (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 as a (b) (4) for BDP. 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). The drug product does not include any additional protective packaging. The drug product filled canisters are manufactured using the same formulation, manufacturing process, and at the same facility, with the same canister and valve as that for the currently marketed product, QVAR of NDA 20911, an inhalation aerosol for the maintenance treatment of asthma. The canister is inserted in a newly developed plastic nasal actuator that is designed for a nasal route of delivery. Details of the CMC review can be found in Dr. Craig M. Bertha' review.

4.2 Clinical Microbiology

Because the proposed drug product is identical to the approved QVAR Inhalation Aerosol product for oral inhalation, and the microbial limits specification acceptance criteria are identical to those in that 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 and same formulation. 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 from the Clinical Pharmacology (CP) review is Approval. Details of the CP review can be found in Dr. Arun Agrawal's review.

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 PD study (BDP-AR-304) for this NDA submission. This was an HPA axis study. The primary endpoint and comparison of interest was the change from baseline in 24-hour serum cortisol weighted means for BDP Nasal Aerosol

320 mcg versus placebo following 6 weeks of treatment in adult and adolescent subjects with PAR. At baseline the 24-hour serum cortisol weighted means for BDP Nasal Aerosol 320 mcg and placebo were 9.04 and 8.45 mcg/dL, respectively. After 6 weeks of treatment, the 24-hour serum cortisol weighted means for BDP Nasal Aerosol 320 mcg and placebo were 8.18 and 8.01 mcg/dL, respectively. The ratio of week 6/baseline was o.90 (95% CI: 0.83, 0.98) for BDP Nasal Aerosol 320 mcg group and 0.95 (95% CI: 0.89, 1.00) for placebo. The mean ratio for the ratios of week 6/baseling in BDP Nasal Aerosol 320 mcg and placebo was 0.96 (95% CI: 0.87, 1.06), indicating that BDP Nasal Aerosol 320 mcg/day for 6 weeks has no effect on HPA axis in subjects 12 years of age and older. The secondary comparison was of prednisone 10 mg/day (orally administered for the last 7 days of the 6-week treatment period) compared with placebo. At Week 6, there was a significant decrease of 24-hour serum cortisol weighted means from baseline in the prednisone 10 mg/day group (from 7.33 mcg/dL to 2.31 mcg/dL). The mean ratio of week 6/baseline in prednisone 10 mg/day group was o.31, and the mean ratio for the ratios of week 6/baseling in placebo and prednisone 10 mg/day group was 3.17 (95% CI: 2.68, 3.74), indicating that prednisone 10 mg/day resulted in a substantial reduction in HPA-axis function compared with placebo. The result confirmed the sensitivity of the study to detect a potential HPA axis suppressive effect of BDP Nasal Aerosol 320 mcg daily treatment.

4.4.3 Pharmacokinetics

Pharmacokinetics of BDP Nasal Aerosol was assessed in 29 healthy volunteers after a single dose of 320 mcg or 80 mcg in study BDP-AR-101. Levels of BDP and its active metabolite, 17-BMP were measured in plasma pre-dose and at 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 24 hours after dose administration. The PK parameters assessed were summarized in Table 2 below.

Following intranasal administration, most of the BDP undergoes rapid and extensive conversion to its active metabolite, 17-BMP, during absorption. Plasma concentrations of BDP and 17-BMP have been measured in two studies with QNASL Nasal Aerosol. The single-dose pharmacokinetics of QNASL Nasal Aerosol was evaluated in a randomized, open-label, 3-period, cross-over study in 29 healthy volunteers. Systemic levels of 17-BMP and BDP after single-dose intranasal administration of BDP Nasal Aerosol at doses of 80 and 320 mcg were compared with the systemic levels of 17-BMP and BDP after administration of orally inhaled BDP Nasal Aerosol at a dose of 320 mcg (QVAR® Inhalation Aerosol). The results of this trial demonstrated that the systemic bioavailability of BDP Nasal Aerosol 320 mcg was approximately 27.5% of that of orally inhaled BDP Nasal Aerosol 320 mcg based on the plasma concentrations of 17-BMP (AUC_{last}: 1139.7 vs 4140.3 hr*pg/mL; mean ratio: 0.275; 90% CI for the mean ratio: 0.214, 0.354). The peak exposure to BDP Nasal Aerosol 320 mcg/day was approximately 19.5% of that of orally inhaled QVAR Inhalation Aerosol 320 mcg as

measured by 17-BMP (C_{max}: 262.7 vs 1343.7 pg/mL; mean ratio: 0.195; 90% CI for the mean ratio: 0.158, 0.241).

Table 2 Summary of PK parameters

	17-BMP Geometric LS Mean		BDP Geometric LS Mean	
Parameter	**BDP HFA 80 mcg Intranasal**	**BDP HFA 320 mcg Intranasal**	**BDP HFA 80 mcg Intranasal**	**BDP HFA 320 mcg Intranasal**
AUC_{last} (hr*pg/mL)	295.827	1139.742	14.584	53.561
C_{max} (pg/mL)	92.118	262.654	64.379	181.951
$AUC_{0-\infty}$ (hr*pg/mL)	747.116	1661.529	27.160	88.227
t_{max} (hr)[1]	1.000	1.000	0.083	0.083
$t_{1/2}$ (hr)[2]	3.541 (1.2076)	4.457 (1.5899)	0.306 (0.1374)	0.278 (0.1434)

1 Median t_{max}
2 Harmonic mean and the associated jackknife SD in parentheses
Source: Section 2.7.2 Summary of Clinical Pharmacology Studies, Table 3, page 18.

The repeat-dose pharmacokinetics of BDP Nasal Aerosol have also been evaluated in a randomized, double-blind trial investigating the effects of QNASL Nasal Aerosol on the HPA axis in adolescent and adult patients with PAR (BDP AR-304). The results of this repeat-dose study showed that patients treated with BDP Nasal Aerosol 320 mcg/day for 6 weeks had demonstrable plasma exposure to the active drug, 17-BMP, at steady state. The mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. Following repeated once-daily administration of BDP Nasal Aerosol, there was no accumulation or increase in plasma exposure to 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency. Plasma profiles of 17-BMP and BDP observed in this repeat-dose trial were similar to those obtained from the single-dose trial in healthy 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 (320 mcg) 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 3 Summary of clinical studies in the NDA submission

Study number	Study type	Treatment group	Treat. duration	Number of subj.	Design*	Diagnosis of subj.	Materials submitted
BDP-AR-201	Dose-finding	BDP Nasal Aerosol 80 mcg BDP Nasal Aerosol 160 mcg BDP Nasal Aerosol 320 mcg Placebo	QD* 2 weeks	118 123 122 123	RD, DB, PC, PG	SAR	Study report
BDP-AR-301	Pivotal-SAR	BDP Nasal Aerosol 320 mcg Placebo	QD 2 weeks	167 171	RD, DB, PC, PG	SAR	Study report
BDP-AR-302	Pivotal-PAR	BDP Nasal Aerosol 320 mcg Placebo	QD 6 weeks	236 238	RD, DB, PC, PG	PAR	Study report
BDP-AR-303	Safety	BDP Nasal Aerosol 320 mcg Placebo	QD 30/52 weeks	196/219 53/58	RD, DB, PC, PG	PAR	Study report
BDP-AR-304	Safety	BDP Nasal Aerosol 320 mcg Placebo Prednisone 10 mg Oral (last 7 d)	QD 6 weeks	50 46 11	RD, DB, PC, AC, PG	PAR	Study report

* RD: Randomized; CO: Cross over; DB: Double blind; PC: Placebo controlled; AC: Active controlled; PG: Parallel group; QD: Once daily

5.2 Review Strategy

There are six clinical study reports in this submission: one single-dose PK study in healthy subjects, one dose ranging finding study of two weeks, one pivotal study in SAR (2 weeks), one pivotal study in PAR (6 weeks), one long term safety study, and one HPA axis study. This clinical review will focus on dose finding study, two pivotal studies in SAR and PAR, the long term safety study, and the HPA axis study. The individual protocols, efficacy results, and safety results are discussed in detail in section 5.3 Discussion of Individual Studies/Clinical Trials. The efficacy results will be summarized in section 6 Review of Efficacy. The combined safety of the listed studies will be presented in section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 STUDY BDP-AR-201

A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multi-Center, Dose-Range-Finding Study to Assess the Efficacy and Safety of BDP HFA Nasal Aerosol in Adult and Adolescent Patients (12 Years and Older) with Seasonal Allergic Rhinitis (SAR)

PROTOCOL

Administrative
Study initiated: March 3, 2009
Study completed: May 20, 2009
Clinical Centers: 26 centers in the U.S. (including following States: TX, CO, IN, CA, OR, MO, NC, GA, UT, KS, PA, and VA)
Study report dated: September 7, 2010
Study Sponsor: TEVA Branded Pharmaceutical Products
Medical Officer: Gordon D. Raphael, M.D.

Objectives
Primary Objective: To determine the optimally safe and effective dose of BDP (beclomethasone dipropionate), applied as an HFA (hydrofluoroalkane) nasal aerosol, in subjects with SAR

Secondary Objective: To assess the safety and tolerability of intranasal BDP administered via HFA nasal aerosol at the doses tested

Study Design
This was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, 2-week, multi-center, dose-range-finding study in male or female subjects (12 years and older) with SAR. Subjects visited the clinic for three out-patient visits – Screening Visit (SV), Randomization Visit (TV0) and Final Treatment Visit (TV1). The study consisted of 2 periods: Run-in Period [7-21 days from Screening Visit (SV) to Randomization Visit (TV0)] and a Treatment Period [14 days from Randomization Visit (TV0) to Final Treatment Visit (TV1)]. During the Run-in Period, subjects self-administered a single-blind placebo nasal aerosol once daily in the morning. Subjects assessed and recorded their reflective total nasal symptom score (rTNSS, including 4 symptoms: sneezing, runny nose, itchy nose, and nasal congestion)and instantaneous total nasal symptom score (iTNSS, including 4 symptoms: sneezing, runny nose, itchy nose, and nasal congestion) twice daily and their morning (AM) reflective total non-nasal symptom score (rTNNSS, including 4 non-nasal symptoms: itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) once daily as absent (0), mild (1), moderate (2), or severe (3). During the Treatment Period (Visits TV0-TV1), subjects self-administered the double-blinded medication once daily in the morning. Subjects assessed and recorded their rTNSS and iTNSS twice daily and their AM rTNNSS once daily using the scale above.

The protocol was amended twice during the study. One amendment was for minor typographical and formatting errors throughout the protocol. The second amendment included clarification of placebo canisters, analyses of RQLQ scores in RQLQ population instead of in the original ITT population because the questionnaire was for adult subjects 18 years and older, and adolescent subjects did not complete RQLQ, and increase of one day from 14 + 2 to 15 + 2 days from the randomization to final visit to ensure a full 14-day treatment. The amendment changed the RQLQ population. No other changes in the study design and the planned analyses.

Treatment
BDP Nasal Aerosol – 40 mcg/actuation (Lot # RD08018),
BDP Nasal Aerosol – 80 mcg/actuation (Lot # RD08019), and
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # RD08020)

All subjects on active treatment received a total of 4 intranasal actuations (2 actuations per nostril) daily from 2 separate devices as detailed below:

Group 1: BDP Nasal Aerosol (80 mcg/day)
Actuator A: 40 mcg/actuation (1 actuation/nostril), once daily
Actuator B: Placebo (1 actuation/nostril), once daily.

Group 2: BDP Nasal Aerosol (160 mcg/day)
Actuator A: 40 mcg/actuation (1 actuation/nostril), once daily
Actuator B: 40 mcg/actuation (1 actuation/nostril), once daily.

Group 3: BDP Nasal Aerosol (320 mcg/day)
Actuator A: 80 mcg/actuation (1 actuation/nostril), once daily
Actuator B: 80 mcg/actuation (1 actuation/nostril), once daily.

Group 4: Placebo
Actuator A: Placebo (1 actuation/nostril), once daily
Actuator B: Placebo (1 actuation/nostril), once daily.

Study Population
A total of 487 subjects were randomized into 4 treatment groups and 470 subjects completed the trial. The ITT population included 486 subjects, in which 118 treated with BDP Nasal Aerosol 80 mcg/day, 123 treated with BDP Nasal Aerosol 160 mcg/day, 122 treated with BDP Nasal Aerosol 320 mcg/day and 123 treated with placebo.

Inclusion criteria
- Male or female subjects 12 years of age and older.
- A history of SAR to relevant seasonal allergen (tree/grass pollen) for a minimum of two years immediately preceding the study Screening Visit (SV).
- SAR of sufficient severity to require treatment (either continuous or intermittent) in the past 2 years and in the investigator's judgment was expected to be exposed to the allergen and require treatment throughout the entire study period.
- A demonstrated sensitivity to relevant tree/grass pollen known to produce SAR through a standard skin prick test. A positive test was defined as a wheal diameter at least 3 mm larger than the control wheal for the skin prick test. Documentation of a positive result within 12 months prior to screening was acceptable.
- Female of child-bearing potential (as judged by the investigator) had to be using and continue to use a medically reliable method of contraception for the entire study duration (e.g. oral, injectable, trans-cutaneous or implantable contraceptives or intrauterine devices or double-barrier protection). Females who were not sexually active agreed to use double-barrier protection should they become sexually active during the course of the study. Women of child-bearing potential, or less than 1 year postmenopausal, required a negative urine pregnancy test 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.

Exclusion criteria
- Pregnancy, nursing, or planned 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)

- History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma 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 this study
- A known hypersensitivity to any corticosteroid or any of the excipients in the formulation
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, chronic sinusitis, influenza, severe acute respiratory syndrome [SARS]) 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 2 years preceding the Screening Visit (SV)
- History of a positive test for HIV (human immunodeficiency virus), hepatitis B, or hepatitis C
- 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, etc.); intermittent use (≤3 uses per week) of inhaled short acting beta-agonists was acceptable
- Plans to travel outside the study area (the known pollen area for the investigative site) for ≥24 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 consecutive days OR ≥3 days total between the Randomization Visit (TV0) and the final TV1 visit
- Use of any prohibited concomitant medications within the prescribed (per protocol) time since the last dose period prior to the Screening Visit (SV) and/or plans to use any prohibited concomitant medication during the entire treatment duration
- Use of antibiotic therapy for any acute conditions within 14 days prior to the Screening Visit (SV). Low doses of antibiotics taken for prophylaxis were permitted if the therapy was started prior to the Screening Visit (SV) and was expected to continue at the same dose throughout the trial
- Initiation of immunotherapy during the study period or dose escalation during the study period. However, use of immunotherapy for prophylaxis was permitted if the therapy was initiated ≥90 days prior to the Screening Visit (SV) and was expected to continue at the same (maintenance dose – ≥30 days) dose throughout the trial
- Previous participation in an intranasal BDP nasal aerosol 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 topical

hydrocortisone or equivalent in any concentration covering >20% of the body surface; or presence of an underlying condition (as judged by the investigator) that could reasonably be expected to require treatment with such preparations during the course of the study

- Initiation of pimecrolimus cream ≥1% or tacrolimus ointment ≥0.03% during the study period. However, initiation of these creams or ointments 30 days or more prior to the Screening Visit (SV) and use of a stable (maintenance) dose during the study period was considered for inclusion.
- A history of epilepsy or seizures
- Treatment with any known CYP3A4 inducers/inhibitors (e.g. barbiturates, phenothiazines, cimetidine, ketoconazole, ritonavir) within 30 days prior to or during the study
- Have any of the following conditions that were judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial:
    - impaired hepatic function, including alcohol-related liver disease or cirrhosis
    - history of ocular disturbances, e.g. glaucoma or posterior subcapsular cataracts
    - any systemic infection
    - hematological, hepatic, renal, endocrine (except for controlled diabetes mellitus or postmenopausal symptoms or hypothyroidism)
    - gastrointestinal disease
    - malignancy (excluding basal cell carcinoma)
    - current neuropsychological condition with or without drug therapy.

Randomization criteria

At 2nd visit (TV0), subjects who met following criteria were randomized into 4 treatment groups:

- Subject had a minimum subject-assessed (rTNSS) of an average of 6 (out of a possible 12) on the last 7 days during the Run-in Period.
- The subject-assessed scores for rhinorrhea OR nasal congestion was on average ≥2 during the last 7 days during the Run-in Period.
  Subject had not used any of the prohibited concomitant medications during the Run-in Period. Prohibited concomitant medications include systemic/inhaled/intranasal corticosteroids, nasal decongestants, antihistamines including intranasal and ocular antihistamines, vasoconstrictors, major tranquilizers, anticholinergics, anti IgE treatment, immunosuppressive medications, leukotriene antagonists, tricyclic antidepressants, MAO inhibitors, antifungals, cromolyn, nedocromil, lodoxamide, medications metabolized via CYP3A4 (ritonavir, ketoconazole, etc.)
- Subject had not suffered from the common cold, URI (upper respiratory infection), otitis, LRI (lower respiratory infection) or acute sinusitis within 7 days prior to the Randomization Visit (TV0).

- Subject had adequately completed the allergic rhinitis (AR) Assessment Diary (failure was defined as missing ≥ 1 of the entries on >2 calendar days during the last 7 days of the Run-in Period).
- Subject had taken their single-blind medication during at least 80% of the entire Run-in Period.
- Subject had not suffered from the common cold, URI (upper respiratory infection), otitis, LRI (lower respiratory infection) or acute sinusitis within 7 days prior to the Randomization Visit (TV0).

Withdrawal criteria
A subject could withdraw or be withdrawn from the study for the following:

- Subject withdrew consent
- Sponsor requested subject to be withdrawn
- Protocol violation/non-compliance
- Pregnancy
- Lost to follow-up/failure to return
- Adverse event

Treatment Compliance
A single dose of study medication was administered at the Randomization Visit (TV0) in the study center under the supervision of the designated study personnel. Study personnel made sure that proper dose of the study medication was administered and proper study medication administration procedures were followed. Further treatment compliance was assessed by use of a subject-completed e-diary. If subjects were found to be <80% compliant at any visit with e-diary completion or study medication usage, they were counseled on the importance of taking study medications as directed by the investigator. Daily pollen counts for each study center were conducted. Subjects were asked to restrict any travel outside the investigator's known pollen area. The study was performed in the spring during tree and grass pollen seasons.

Outcomes
The efficacy and safety outcomes were measured per schedule in the Table 4 below.

Table 4 Schedule of study events

Visit:	SV	TV0	TV1/Tdv
Period Day(s):	-7 to -21	1	15+2
Weeks	-1 to -3	0	2
Written informed consent and HIPAA authorization signed	X		
Evaluation of inclusion/exclusion criteria	X		
Distribution of RQLQ booklet and review of instructions with subject		X	X
Rhinoconjunctivitis Quality of Life (RQLQ)[1]		X	X
Demographic data	X		
Medical history/ concomitant diseases/ prohibited medications history	X		
Review of Randomization criteria		X	
Randomization using Interactive Voice Response System (IVRS)		X	
Height and weight measurement	X		
Vital signs assessment- seated	X		X
Physical examination	X		X
ENT examination[2]	X	X	X
Physician assessment of nasal symptom severity	X	X	X
Skin prick test for relevant seasonal allergen (tree/grass pollen)[3]	X	X	
Urine pregnancy test in females if applicable	X		X
Review instructions on proper HFA nasal aerosol use	X	X	
Prime and dispense single-blind placebo	X		
Administer single-blind placebo	X		
Prime and dispense randomized double-blind study medication		X	
Administer randomized double-blind study medication[4]		X	
AE monitoring	X	X	X
Concomitant medication evaluation	X	X	X
Distribution of electronic diary instructions	X		
Review of electronic diary instructions with the subject	X	X	
Electronic diary review		X	X
Compliance check (study procedures and study medications)		X	X
Subject assessment and recording of 12-hour reflective and instantaneous TNSS[5]	X	→	→
Subject assessment and recording of 24-hour non-nasal symptom severity[5]	X	→	→
Call into IVRS to discontinue subject			X
Return all study medication, used and unused		X	X

1. RQLQ had to be the first procedure conducted at these visits.

2. 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, candidiasis and post-nasal drip.
3. The skin prick test was initially performed or re-performed at the Randomization Visit (TV0) if the investigator thought that the skin prick test obtained at the Screening Visit (SV) was spurious or would have been spurious if obtained at the Screening Visit (SV). Documentation of a positive result within one year before Screening Visit (SV) was acceptable to meet eligibility criteria. Intradermal and/or RAST testing was not accepted.
4. All subjects were told to refrain from taking their Run-in study medication on the morning of the Randomization Visit (TV0). Prior to the TV1 Visit, subjects took their daily dose of study medication in the morning in the customary manner following the recording of their AM reflective nasal symptom values.
5. Study medication during the Run-in and Treatment Periods was taken immediately following completion of the AM diary assessment.

(BDP-AR-201 Study Report, page 38)

Efficacy endpoints

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

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:

- 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 included the change from baseline in the following:

- iTNSS: Average AM and PM subject-reported iTNSS over the 2-week Treatment Period; AM subject-reported iTNSS over the 2-week Treatment Period.
- RQLQ: The RQLQ is a disease-specific quality of life questionnaire developed to measure the functional (physical, emotional and social) problems troublesome to adults with allergies. The RQLQ measures both atopic and non-atopic experiences as a result of a subject's nose and eye symptoms. The adult RQLQ has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms,

practical problems, nasal symptoms, eye symptoms, and emotional). Subjects were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Least severe to 6 = Extremely severe). When required at a particular visit this questionnaire was to be completed as the first activity of the visit. The adult RQLQ was used only by adult subjects (18 years and older). Adolescent subjects did not complete the RQLQ. RQLQ at Week 2 for subjects with impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater.

- Ocular: AM subject-reported 24-hour reflective total ocular symptom score (the sum of individual non-nasal symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness) over the 2-week Treatment Period in subjects with adequate symptoms during the Run-in period as defined by a mean daily 24-hour ocular score of 4 or greater over the last 7 days of the Run-in Period. The symptoms were evaluated at a scale from 0 to 3, as described in TNSS evaluation.
- Non-Nasal: Non-Nasal symptom score included evaluation for 4 symptoms, 3 ocular symptoms described above and itching of ears or palate. The symptoms were also evaluated at a scale from 0 to 3. AM subject-reported 24-hour reflective non-nasal symptom score over the 2-week Treatment Period in subjects with adequate symptoms during the Run-in period as defined by a mean daily 24-hour reflective score of 6 or greater over the last 7 days of the Run-in period.

A multiplicity adjustment was made for the primary and secondary endpoints.

Safety monitoring

- Adverse events: Adverse events were coded using the MedDRA dictionary version 11.1. The nature, incidence, severity or intensity, as well as the causality assessment were reported for each treatment-emergent AE.
- Physical examinations including 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 weeks of the 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 of 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 685 subjects were screened for enrollment in the study. Of the screened subjects, 635 were enrolled in the study and participated in the Run-in Period. Of the 635 enrolled subjects, 487 met the randomization criteria and were randomized to 4 treatment groups. As shown in Table 5**,** of the 487 randomized subjects, 118 were randomized to receive BDP Nasal Aerosol 80 mcg/day, 123 to receive BDP Nasal Aerosol 160 mcg/day, 122 to receive BDP Nasal Aerosol 320 mcg/day and 124 to receive placebo. One of the subjects randomized to placebo did not receive any of the assigned placebo treatment because this subject experienced otitis external during the Run-in Period. Hence, 486 randomized subjects constituted the ITT population and the safety population. There were 297 subjects in the RQLQ population, 380 subjects in the non-nasal population, and 398 subjects in the ocular population. The RQLQ population included only those subjects with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater. The ocular population included only those subjects with adequate ocular symptoms during the Run-in Period as defined by a mean daily 24-hour reflective score of 4 or greater for the 24-hour reflective ocular symptom score, over the last 7 days of the Run-in Period. The non-nasal population included only those subjects with adequate non-nasal symptoms during the Run-in Period as defined by a mean daily 24-hour reflective score of 6 or greater for the 24-hour reflective non-nasal symptom score, over the last 7 days of the Run-in Period.

Table 5 Subject disposition

Category	BDP HFA 80 mcg/day n (%)	BDP HFA 160 mcg/day n (%)	BDP HFA 320 mcg/day n (%)	Placebo n (%)	Overall n (%)
Randomized	118 (100)	123 (100)	122 (100)	124 (100)	487 (100)
ITT/Safety Population[1]	118 (100)	123 (100)	122 (100)	123 (99.2)	486 (99.8)
Completed	116 (98.3)	120 (97.6)	120 (98.4)	114 (91.9)	470 (96.5)
Discontinued	2 (1.7)	3 (2.4)	2 (1.6)	10 (8.1)	17 (3.5)
Adverse Event	0	1 (0.8)	2 (1.6)	6 (4.8)	9 (1.8)
Withdrew Consent	0	0	0	1 (0.8)	1 (0.2)
Pregnancy	0	1 (0.8)	0	0	1 (0.2)
Lack of Efficacy	2 (1.7)	1 (0.8)	0	0	3 (0.6)
Other	0	1 (0.8)	0	3 (2.4)	4 (0.8)

1 One subject who was randomized to placebo did not receive any treatment, and so was excluded from the ITT population.
(BDP-AR-201 Study Report, page 51)

Approximately 97% of the subjects completed the study (98.3%, 116 subjects, in the BDP Nasal Aerosol 80 mcg/day group, 97.6%, 120 subjects, in the BDP Nasal Aerosol 160 mcg/day group, 98.4%, 120 subjects, in the BDP Nasal Aerosol 320 mcg/day group, and 91.9%, 114 subjects, in the placebo group). More subjects were discontinued prematurely from the placebo group than from any of the active treatment groups.

Demographics

As shown in Table 6 below for the ITT population, the majority of subjects in all groups were female (65.0%), white (79.4%) and not Hispanic or Latino (88.5%). The mean age of study subjects was 38.5 years and ranged from 12 to 78 years. Demographic characteristics were comparable in each of the treatment groups.

Table 6 Subject demographics

Demographic	BDP HFA 80 mcg/day N = 118	BDP HFA 160 mcg/day N = 123	BDP HFA 320 mcg/day N = 122	Placebo N = 123	Total N = 486
Age (years)					
Mean (SD)	37.6 (13.86)	39.8 (15.26)	38.5 (14.74)	38.2 (13.95)	38.5 (14.45)
Median	40.0	40	39.5	40	
Min-Max	12-75	12-78	12-71	12-68	12-78
Gender, n (%)					
Female	76 (64.4)	86 (69.9)	81 (66.4)	73 (59.3)	316 (65.0)
Male	42 (35.6)	37 (30.1)	41 (33.6)	50 (40.7)	170 (35.0)
Race, n (%)					
White	92 (78.0)	99 (80.5)	98 (80.3)	97 (78.9)	386 (79.4)
Black	23 (19.5)	18 (14.6)	22 (18.0)	19 (15.4)	82 (16.9)
Asian	2 (1.7)	5 (4.1)	0	6 (4.9)	13 (2.7)
Other	1 (0.8)	1 (0.8)	2 (1.6)	1 (0.8)	5 (1.0)
Ethnicity, n (%)					
Hispanic or Latino	14 (11.9)	10 (8.1)	17 (13.9)	15 (12.2)	56 (11.5)
Not Hispanic, not not Latino	104 (88.1)	113 (91.9)	105 (86.1)	108 (87.8)	430 (88.5)

(BDP-AR-201 Study Report, page 55)

Medical history was generally similar among the four treatment groups and the types of conditions reported were those that might be expected in a SAR patient population such as sinus headache, drug hypersensitivity, asthma, allergic conjunctivitis, etc. All subjects had a history of seasonal rhinitis and 63.0% of subjects (overall) also reported a history of perennial rhinitis.

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 four treatment groups (9.33 for BDP Nasal Aerosol 80 mcg/day, 9.24 for BDP Nasal Aerosol 160 mcg/day, 9.17 for BDP Nasal Aerosol 320 mcg/day and 8.98 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 -1.88 (0.18) for BDP Nasal Aerosol 80 mcg/day, -1.87 (0.18) for BDP Nasal Aerosol 160 mcg/day, -2.22 (0.18) for BDP Nasal Aerosol 320 mcg/day and -1.59 (0.18) for the placebo group. The LS mean treatment difference of -0.63 between BDP Nasal Aerosol 320 mcg/day and placebo was statistically significant (p=0.013) in favor of BDP Nasal Aerosol 320 mcg/day. 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 but small and not statistically significant.

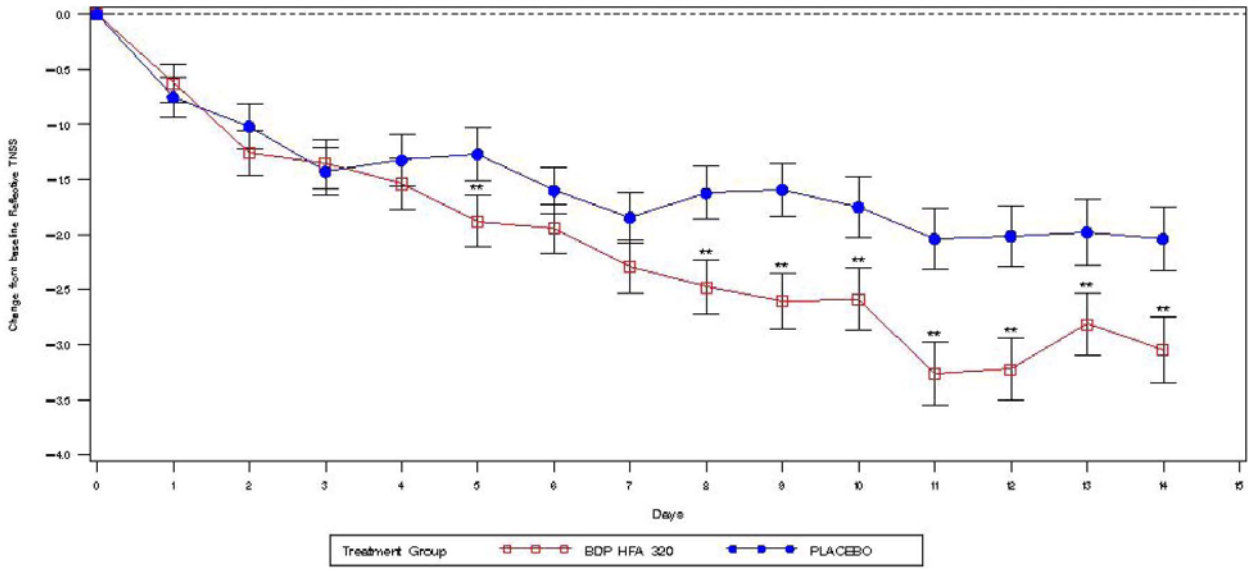
Table 7 Primary efficacy (rTNSS) analysis, Study BDP-AR-201

Statistic	BDP HFA 80 mcg/day N = 118	BDP HFA 160 mcg/day N = 123	BDP HFA 320 mcg/day N = 122	Placebo N = 123
Baseline mean (SD)	9.33 (1.72)	9.24 (1.57)	9.17 (1.66)	8.98 (1.47)
Overall LS mean (SE) change from Baseline[1]	-1.88 (0.18)	-1.87 (0.18)	-2.22 (0.18)	-1.59 (0.18)
LS Mean (SE) treatment difference from placebo	-0.29 (0.26)	-0.29 (0.25)	-0.63 (0.25)	
95% CI	(-0.80, 0.21)	(-0.78, 0.21)	(-1.13, -0.13)	
p-value	0.255	0.257	0.013*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-201 Study Report, page 59)

The daily changes in average AM and PM rTNSS from baseline over time for the BDP Nasal Aerosol 320 mcg/day and placebo groups are shown graphically in Figure 1 below. For the BDP Nasal Aerosol 320 mcg group, the significant change from baseline in the average AM and PM subject-reported rTNSS, compared with the placebo, was consistently observed on Day 8 till the end of the study.

Figure 1 Change from baseline in average AM & PM rTNSS in the BDP Nasal Aerosol 320 mcg and placebo groups



(BDP-AR-201 Study Report, page 67)

Subgroup analyses based on gender (male, female), age (12-17 years, 18-64 years,

65 years and older), and race (white, black, other) were performed. There were no significant differences found in subgroups per gender, age, and race. However, it was hard to draw conclusions from the subgroup analysis because of the small sample size of the subgroups.

The Applicant claims that this study demonstrated that 320 mcg/day was the optimally efficacious dose of BDP nasal aerosol for the treatment of adult and adolescent subjects with SAR. 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 8).

Table 8 Analysis of iTNSS

Statistic	BDP HFA 80 mcg/day N = 118	BDP HFA 160 mcg/day N = 123	BDP HFA 320 mcg/day N = 122	Placebo N = 123
Baseline mean (SD)	8.36 (2.19)	8.28 (2.15)	8.32 (1.98)	8.01 (1.93)
Overall LS mean (SE) change from Baseline[1]	-1.77 (018)	-1.71 (0.18)	-2.10 (0.18)	-1.50 (0.18)
LS Mean (SE) treatment difference from placebo 95% CI p-value	-0.27 (0.25) (-0.77, 0.22) 0.278	-0.22 (0.25) (-0.70, 0.27) 0.385	-0.60 (0.25) (-1.09, -0.11) 0.016*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-201 Study Report, page 61)

AM subject-reported 24-hour reflective ocular symptom score
The analyses of ocular symptom score were performed using ocular population (Table 9). At baseline, the means of the AM subject-reported reflective ocular symptom score were comparable in the four treatment groups. Across the 2-week treatment period, AM subject-reported reflective ocular symptom scores decreased in all treatment groups, including placebo. Although the BDP Nasal Aerosol 320 mcg group had a numerically largest decrease in the reflective ocular symptom score, no significant differences between BDP Nasal Aerosol and placebo were observed for the reflective ocular symptom scores. The analyses were also performed using the ITT Population. Similar results were seen in these analyses as for the ocular population.

Table 9 Analysis of reflective ocular symptom score

Statistic	BDP HFA 80 mcg/day N = 95	BDP HFA 160 mcg/day N = 102	BDP HFA 320 mcg/day N = 101	Placebo N = 100
Baseline mean (SD)	6.92 (1.48)	6.79 (1.48)	6.71 (1.50)	6.54 (1.30)
Overall LS mean (SE) change from Baseline[1]	-1.16 (0.16)	-1.11 (0.16)	-1.46 (0.16)	-1.17 (0.16)
LS Mean (SE) treatment difference from placebo	-0.00 (0.23)	-0.06 (0.23)	-0.29 (0.23)	
95% CI	(-0.45, 0.46)	(-0.39, 0.50)	(-0.74, 0.15)	
p-value	0.989	0.808	0.195	

1 Results from repeated measures ANCOVA over the treatment period.
(BDP-AR-201 Study Report, page 65)

AM subject-reported 24-hour reflective non-nasal symptom score

The analyses of bob-nasal symptom score were performed using non-nasal population (Table 10). At baseline, the means of the AM subject-reported reflective non-nasal symptom score were comparable in the four treatment groups. Across the 2-week treatment period, AM subject-reported non-nasal symptom scores decreased in all treatment groups, including placebo. Although the BDP Nasal Aerosol 320 mcg group had a numerically largest decrease in the reflective non-nasal symptom score, no significant differences between BDP Nasal Aerosol and placebo were observed for non-nasal symptom scores. The analyses were also performed using the ITT Population. Similar results were seen in these analyses as for the non-nasal population.

Table 10 Analysis of reflective non-nasal symptom score

Statistic	BDP HFA 80 mcg/day N = 92	BDP HFA 160 mcg/day N = 94	BDP HFA 320 mcg/day N = 97	Placebo N = 97
Baseline mean (SD)	9.19 (1.84)	9.27 (1.82)	9.01 (1.84)	8.67 (1.70)
Overall LS mean (SE) change from Baseline[1]	-1.55 (0.22)	-1.49 (0.22)	-1.91 (0.21)	-1.51 (0.22)
LS Mean (SE) treatment difference from placebo	0.04 (0.31)	0.02 (0.31)	-0.40 (0.30)	
95% CI	(-0.64, 0.57)	(-0.58, 0.62)	(-0.99, 0.19)	
p-value	0.903	0.952	0.187	

1 Results from repeated measures ANCOVA over the treatment period.
(BDP-AR-201 Study Report, page 66)

RQLQ

As summarized in Table 11 for the RQLQ population, baseline RQLQ scores were similar across the treatment groups. Improvements in RQLQ were seen in all groups. There were no significant differences from placebo for any of the BDP Nasal Aerosol treatment groups, although the difference from placebo in BDP Nasal Aerosol 320 mcg group was numerically larger than other groups. The analyses were also performed using the ITT population. Similar results were seen in these analyses as for the RQLQ population. For the ITT population the LS mean treatment difference between BDP HFA 320 mcg/day and placebo was appreciable (LS mean treatment difference -0.36; 95% CI -0.68, -0.04; p=0.026).

Table 11 Analysis of RQLQ score

Statistic	BDP HFA 80 mcg/day N = 68	BDP HFA 160 mcg/day N = 83	BDP HFA 320 mcg/day N = 69	Placebo N = 77
Baseline mean (SD)	4.29 (0.79)	4.28 (0.81)	4.31 (0.74)	4.11 (0.76)
LS Mean (SE) change from Baseline at End of Study	-1.30 (0.17)	-1.33 (0.15)	-1.62 (0.17)	-1.22 (0.16)
LS Mean (SE) treatment difference from placebo	-0.07 (0.23)	-0.11 (0.21)	-0.39 (0.23)	
95% CI	(-0.52, 0.37)	(-0.53, 0.31)	(-0.84, 0.05)	
p-value	0.747	0.605	0.083	

(BDP-AR-201 Study Report, page 64)

Safety Monitoring

Extent of exposure

Per protocol, subjects were to be dosed for 14 days. The actual mean exposure to study medication was similar for the four treatment groups: 14.8 days in the BDP Nasal Aerosol 80 mcg/day group, 14.9 days in the BDP Nasal Aerosol 160 mcg/day group, 14.9 days in the BDP Nasal Aerosol 320 mcg/day group, and 14.7 days in the placebo group.

Adverse events

Of the 486 subjects randomized to study treatment, 82 (16.9%) experienced adverse events: 22 subjects (18.6%) receiving BDP Nasal Aerosol 80 mcg/day, 18 subjects (14.6%) receiving BDP Nasal Aerosol 160 mcg/day, 22 subjects (18.0%) receiving BDP Nasal Aerosol 320 mcg/day, and 20 subjects (16.3%) receiving placebo. The majority of AEs were of mild intensity. Table 12 presents an overview of treatment-emergent AEs for subjects in each treatment group.

Table 12 Adverse events reported in BDP-AR-201

Preferred Term	BDP HFA 80 mcg (N=118) n (%)	BDP HFA 160 mcg (N=123) n (%)	BDP HFA 320 mcg (N=122) n (%)	PLACEBO (N=123) n (%)	TOTAL (N=486) n (%)
Subjects With at Least 1 AE	22(18.6)	18(14.6)	22(18.0)	20(16.3)	82(16.9)
Nasal discomfort	3(2.5)	5(4.1)	4(3.3)	4(3.3)	16(3.3)
Epistaxis	6(5.1)	3(2.4)	3(2.5)	1(0.8)	13(2.7)
Headache	0(0.0)	2(1.6)	5(4.1)	1(0.8)	8(1.6)
Upper respiratory tract infection	1(0.8)	1(0.8)	1(0.8)	2(1.6)	5(1.0)
Oropharyngeal pain	1(0.8)	0(0.0)	1(0.8)	1(0.8)	3(0.6)
Pyrexia	0(0.0)	2(1.6)	1(0.8)	0(0.0)	3(0.6)
Rhinalgia	1(0.8)	1(0.8)	1(0.8)	0(0.0)	3(0.6)
Arthralgia	1(0.8)	0(0.0)	1(0.8)	0(0.0)	2(0.4)
Dizziness	1(0.8)	0(0.0)	0(0.0)	1(0.8)	2(0.4)
Influenza	1(0.8)	1(0.8)	0(0.0)	0(0.0)	2(0.4)
Nasal septum disorder	1(0.8)	1(0.8)	0(0.0)	0(0.0)	2(0.4)
Pruritus	0(0.0)	0(0.0)	1(0.8)	1(0.8)	2(0.4)
Rash papular	0(0.0)	0(0.0)	0(0.0)	2(1.6)	2(0.4)
Sinus headache	0(0.0)	0(0.0)	1(0.8)	1(0.8)	2(0.4)
Sinusitis	1(0.8)	0(0.0)	1(0.8)	0(0.0)	2(0.4)
Abortion spontaneous incomplete	0(0.0)	1(0.8)	0(0.0)	0(0.0)	1(0.2)
Acrodermatitis	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Angioedema	0(0.0)	1(0.8)	0(0.0)	0(0.0)	1(0.2)
Blood pressure systolic increased	0(0.0)	0(0.0)	1(0.8)	0(0.0)	1(0.2)
Dermatitis acneiform	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Dermatitis contact	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Dry eye	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Dysphonia	1(0.8)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Dyspnoea	0(0.0)	0(0.0)	1(0.8)	0(0.0)	1(0.2)
Eye infection	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Eye pruritus	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Face injury	1(0.8)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Hepatic enzyme increased	1(0.8)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Herpes simplex	1(0.8)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Hypersensitivity	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)

(BDP-AR-201 Study Report, page 681)

The commonly reported AEs were local nasal adverse events. Because in the original study report the local AEs were categorized inconsistently, the Applicant submitted a Safety Information Amendment (Table 13) on Feb. 7, 2012, upon the Division's request. The most common nasal AEs were nasal irritation and epistaxis. There were no apparent differences among three BDP Nasal Aerosol treatment groups with respect to incidence of AEs. There was one case of nasal erosion reported in the BDP Nasal Aerosol 80 mcg/group as "mild erosion – septum left side – anterior 1/3 of septum – Keisselbach's area". No nasal ulceration and nasal septum perforation reported in the study.

Table 13 Summary of nasal adverse events, BDP-AR-201

Term	320 mcg N=122 n (%)	160 mcg N=123 n (%)	80 mcg N=118 n (%)	PLACEBO N=123 n (%)	Total N=486 n (%)
NASAL MUCOSAL/SEPTUM DISORDERS	7(5.7)	9(7.3)	11(9.3)	5(4.1)	32(6.6)
Erosions/Ulcerations	0(0.0)	0(0.0)	1(0.8)	0(0.0)	1(0.2)
Erosion	0(0.0)	0(0.0)	1(0.8)	0(0.0)	1(0.2)
Non-Ulcerative Lesions	5(4.1)	6(4.9)	5(4.2)	4(3.3)	20(4.1)
Abrasion/Excoriation/Scabs	0(0.0)	0(0.0)	1(0.8)	0(0.0)	1(0.2)
Irritation	5(4.1)	6(4.9)	4(3.4)	4(3.3)	19(3.9)
Other	3(2.5)	3(2.4)	6(5.1)	1(0.8)	13(2.7)
Epistaxis	3(2.5)	3(2.4)	6(5.1)	1(0.8)	13(2.7)

(NDA 202813, Safety Information Amendment, Feb. 7, 2012)

Deaths, serious adverse events, and events leading to withdrawal

No deaths occurred during the study.

There were two SAEs reported (one case of angioedema and one case of partial spontaneous abortion). Both SAEs were experienced by subjects in the BDP Nasal Aerosol 160 mcg/day group. The investigator judged that neither case was related to study treatment, and reported that both cases were recovered. The angioedema was occurred in a 27-years old female patient with SAR and PAR. Her skin prick test was positive for mixed tree pollen. This subject discontinued the study after having received BDP Nasal Aerosol 160 mcg/day for 10 days due to a moderate angioedema. The investigator judged that the angioedema was related to the concomitant use of the medication Lisinopril. The subject had 10 mg of Claritin orally but her lip swelling increased in severity. She then visited ER and treated by oral Benadryl and Pepcid, and IV Solumedrol. Her Lisinopril was changed to Amlodipine. Another SAE was occurred in a 40-years female with SAR and Par. Her allergy skin test was positive for pecan tree pollen. The subject had a positive pregnancy test result after having received 10 days of BDP Nasal Aerosol 160 mcg/day, and reported an incomplete spontaneous abortion. The subject underwent a dilation and curettage and recovered. The event was considered unrelated to study drug by the investigator.

A total of 8 subjects were withdrawn from the study due to an AE: 5 subjects from placebo, 2 subjects from BDP Nasal Aerosol 320 mcg/day, and 1 subject from BDP Nasal Aerosol 160 mcg/day. The 2 subjects from the BDP Nasal Aerosol 320 mcg group were withdrawn due to upper respiratory infection and severe sore throat, respectively. The subject from the BDP Nasal Aerosol 160 mcg group was withdrawn due to angioedema that was reported as a SAE. The 5 subjects in placebo group were withdrawn due to dizziness (1), upper respiratory infection (2), severe ocular itching (1), and excoriated acneiform rash and mild conjunctival infection (1).

Physical examinations 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:
All three doses had the similar safety profile, and revealed no new safety signals. The dose of BDP Nasal Aerosol 320 mcg once daily was a reasonable clinical dose to take into phase 3 studies.

5.3.2 Study BDP-AR-301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Study to Assess the Efficacy and Safety of BDP HFA Nasal Aerosol (320 mcg, Once Daily) in the Treatment of Seasonal Allergic Rhinitis (SAR) in Subjects 12 Years of Age and Older

PROTOCOL

Administrative
Study initiated: December 28, 2009
Study completed: February 19, 2010
Clinical Centers: 4 centers in Texas during the 2009-2010 mountain cedar pollen allergy season
Study report dated: September 27, 2010
Study Sponsor: TEVA Branded Pharmaceutical Products
Medical Officer: Julius van Bavel, M.D.

Objective
To demonstrate the efficacy of BDP (beclomethasone dipropionate) HFA, applied as a nasal aerosol, in subjects with SAR, and to assess the safety and tolerability of BDP nasal aerosol in subjects with SAR.

Study Design
This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 2-week, multi-center, outpatient study in male or female subjects (12 years and older) with SAR. Subjects visited the clinic for four out-patient visits – Screening Visit (SV), Randomization Visit (RV) on Day 1, Treatment Visit 1 (TV1) on Day 8 (±2 days), and the Final Treatment Visit (TV2) on Day 15 (+2 days). The study consisted of 2 periods: Run-in Period (7-10 days) and a Treatment Period (15 + 2 days). During the Run-in Period, subjects self-administered a single-blind placebo nasal aerosol once daily in the morning. During the Treatment Period, subjects self-administered the double blinded study medication once daily in the morning. Subjects assessed and recorded their reflective and instantaneous nasal symptoms (rhinorrhea/runny nose, nasal congestion,

nasal itching and sneezing) and their reflective and instantaneous non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) twice daily as absent (0), mild (1), moderate (2), or severe (3). The primary efficacy endpoint was the change from baseline in the average AM and PM daily subject-reported rTNSS over the 2 weeks of the Treatment Period. Safety was assessed with adverse events, vital signs, and physical examinations including ENT examinations. Subject compliance was assessed by diary entries and by inspection of the medication doses used by the subject.

This study was performed under a protocol that was virtually identical to the protocol for Study BDP-AR-201, the dose-ranging study with the differences listed below. The reader is referred to the description of the protocol BDP-AR-201 discussed in section 5.3.1 above for a detailed description of the protocol.

Differences in protocol BDP-AR-301 comparing to protocol BDP-AR-201

- **Clinical visit**

Subjects visited the clinic for four out-patient visits – Screening Visit (SV), Randomization Visit (RV) on Day 1, Treatment Visit 1 (TV1) on Day 8 (±2 days), and the Final Treatment Visit (TV2) on Day 15 (+2 days).

- **Treatment**

BDP Nasal Aerosol – 80 mcg/actuation (Lot # 090115A), and
Placebo Nasal Aerosol – 0 mcg/actuation (Lot # GK045A)

All subjects received daily BDP Nasal Aerosol 320 mcg (a total of 4 intranasal actuations, 2 actuations per nostril) or placebo HFA Nasal Aerosol.

- **Inclusion criteria**

Subjects had a positive skin prick test to mountain cedar pollen.

- **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 2.2. Using this standard deviation, 160 subjects per group provided 90% power to detect a difference between treatment groups of 0.8 in the change from baseline in rTNSS with a two-sided alpha level of 0.05.

RESULTS

Study Population

Disposition

A total of 484 subjects were screened for enrolment in the study. However, 4 additional subject numbers were recorded in error, which reflected in the database as 488 subjects were screened. Of the screened subjects, 463 were enrolled in the study and participated in the Run-in Period. Of the 463 enrolled subjects, 340 met the randomization criteria and were randomized to treatment (169 were randomized to receive BDP Nasal Aerosol 320 mcg and 171 were randomized to receive placebo) (Table 14). Two subjects who were randomized to receive BDP Nasal Aerosol 320 mcg did not receive any of the assigned study treatment. Hence, 338 randomized subjects (167 treated with BDP Nasal Aerosol 320 mcg and 171 treated with placebo) received study treatment and constituted the ITT population and the safety population. There were 250 subjects in the RQLQ population, and 304 subjects in the non-nasal population. The RQLQ population included only those subjects with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater. The non-nasal population included only those subjects with adequate non-nasal symptoms during the Run-in Period as defined by a mean daily 24-hour reflective score of 6 or greater for the 24-hour reflective non-nasal symptom score, over the last 7 days of the Run-in Period.

Approximately 98% of the subjects completed the study (97.6%, 165 subjects, in the BDP Nasal Aerosol 320 mcg/day group; 97.7%, 167 subjects, in the placebo group). Six subjects, 2 subjects treated with BDP Nasal Aerosol 320 mcg/day and 4 subjects treated with placebo, discontinued the study prematurely.

Table 14 Subject disposition, Study BDP-AR-301

Category	BDP HFA 320 mcg/day n (%)	Placebo n (%)	Overall n (%)
Randomized	169 (100)	171 (100)	340 (100)
ITT /Safety Population	167 (98.8)	171 (100)	338 (99.4)
Completed	165 (97.6)	167 (97.7)	332 (97.6)
Discontinued[1]	2 (1.2)	4 (2.3)	6 (1.8)
Adverse Event	1 (0.6)	0	1 (0.3)
Withdrew Consent	1 (0.6)	0	1 (0.3)
Lost to follow up	0	1 (0.6)	1 (0.3)
Protocol violation/ non-compliance	0	3 (1.8)	3 (0.9)

[1] A subject who discontinued for more than one reason was counted only once.
(BDP-AR-301 Study Report, page 49)

Demographics

As shown in Table 15 below for the ITT population, the majority of subjects in both groups were female (62.1%), white (84.0%) and not Hispanic or Latino (70.1%). The

mean age of study subjects was 38.6 years and ranged from 12 to 73 years. There were 27 (8.0%) adolescent subjects aged 12 – 17 years old, with 13 and 14 in BDP Nasal Aerosol 320 mcg/day group and placebo, respectively. Demographic characteristics were comparable in two treatment groups.

Table 15 Subject demographics, Study BDP-AR-301

Demographic	BDP HFA 320 mcg/day N = 167	Placebo N = 171	Total N = 338
Age (years)			
Mean (SD)	39.3 (13.4)	38.0 (13.3)	38.6 (13.3)
Median	41.0	37.0	39.0
Min-Max	12 - 68	13 - 73	12 - 73
Gender, n (%)			
Female	113 (67.7)	97 (56.7)	210 (62.1)
Male	54 (32.3)	74 (43.3)	128 (37.9)
Race, n (%)			
White	142 (85.0)	142 (83.0)	284 (84.0)
Black or African American	23 (13.8)	26 (15.2)	49 (14.5)
Asian	3 (1.8)	3 (1.8)	6 (1.8)
American Indian or Alaskan Native	1 (0.6)	1 (0.6)	2 (0.6)
Native Hawaiian, other Pacific Islander	0	1 (0.6)	1 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	52 (31.1%)	49 (28.7)	101 (29.9)
Not Hispanic, not Latino	115 (68.9%)	122 (71.3)	237 (70.1)

(BDP-AR-301 Study Report, page 53)

Medical history was generally similar in the two treatment groups and the types of conditions reported were those that might be expected in a SAR patient population such as sinus headache, drug hypersensitivity, dyspepsia, asthma, etc. All subjects had a history of seasonal rhinitis and 30.1% of subjects (overall) also reported a history of perennial rhinitis.

Prior to use of study drug, the most commonly reported medications in both treatment groups were those for the respiratory system (54 subjects, 32.3% in the BDP Nasal Aerosol 320 mcg/day group and 60 subjects, 35.1% in the placebo group), and nervous system (14 subjects, 8.4% in the BDP Nasal Aerosol 320 mcg/day group and 18 subjects, 10.5% in the placebo group). There were no appreciable differences between the two treatment groups. During the study, the most commonly used medications were those for the alimentary, musculoskeletal system and nervous system, including multivitamins, fish oil, calcium, Tylenol, Advil, aspirin, etc. There were no clinically important differences between treatment groups in concomitant medication use.

Efficacy Results

Primary efficacy endpoint

The primary efficacy analysis was summarized in Table 16 below. At baseline, the means of the average AM and PM subject-reported rTNSS were comparable in the two treatment groups (9.6 for BDP Nasal Aerosol 320 mcg/day and 9.5 for the placebo group). Across the 2-week Treatment Period, average AM and PM subject-reported rTNSS decreased in both treatment groups. The LS mean (SE) change from baseline over the Treatment Period was -2.0 (0.16) for BDP Nasal Aerosol 320 mcg/day and -1.0 (0.15) for the placebo group. The LS mean treatment difference of -0.91 between BDP Nasal Aerosol 320 mcg/day and placebo was statistically significant ($p<0.001$) in favor of BDP Nasal Aerosol 320 mcg/day.

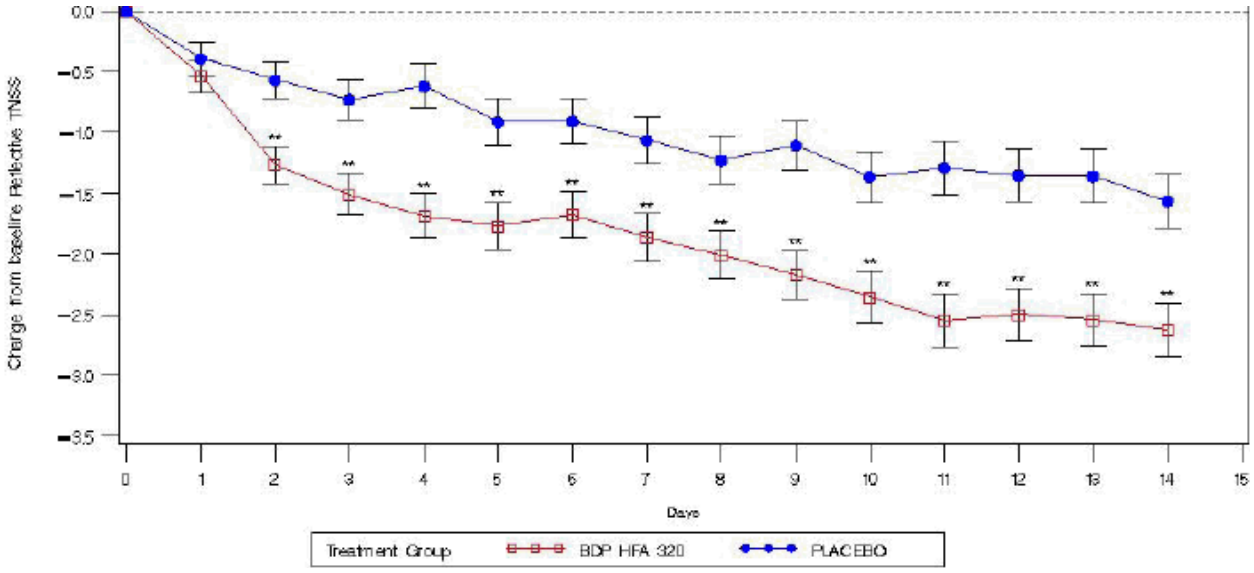
Table 16 Primary efficacy (rTNSS) analysis, Study BDP-AR-301

Statistic	BDP HFA320 mcg/day N = 167	Placebo N = 171
Baseline mean (SD)	9.6 (1.51)	9.5 (1.54)
Overall LS mean (SE) change from Baseline[1]	-2.0 (0.16)	-1.0 (0.15)
LS Mean treatment difference from placebo	-0.91	
95% CI	-1.3, -0.5	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-301 Study Report, page 56)

The daily changes in average AM and PM rTNSS from baseline over time for the BDP Nasal Aerosol 320 mcg/day and placebo groups are shown graphically in Figure 2 below. For the BDP Nasal Aerosol 320 mcg group, the significant change from baseline in the average AM and PM subject-reported rTNSS, compared with the placebo, was consistently observed on Days 2 till the end of the study.

Figure 2 Change from baseline in average AM & PM rTNSS in the treatment and placebo groups, Study BDP-AR-301



(BDP-AR-301 Study Report, page 63)

Subgroup analyses based on gender (male, female), age (12-17 years, 18-64 years, 65 years and older), and race (white, black, other) were performed for the primary efficacy analysis. There were no significant differences found in subgroups per gender, age, and race. However, it was hard to draw conclusions from the subgroup analysis because of the small sample size of the subgroups.

Secondary efficacy endpoints

The secondary efficacy endpoints were the change from baseline in the average individual reflective nasal symptom score over the 2-week Treatment Period, the change from baseline in the average AM and PM subject-reported iTNSS over the 2-week Treatment Period, average AM and PM subject-reported reflective ocular symptom score over the 2-week Treatment Period, and RQLQ at Week 2 for subjects with impaired quality of life at baseline.

Average AM and PM individual reflective nasal symptom scores

As listed in Table 17 below, significant improvements were seen in each of the average AM and PM subject-reported reflective individual nasal symptom scores over the 2-week Treatment Period.

Table 17 Analyses of individual reflective nasal symptom scores

Statistic	BDP HFA 320 mcg/day N = 167	Placebo N = 171
Sneezing		
Baseline mean (SD)	2.1 (0.66)	2.2 (0.62)
Overall LS mean (SE) change from Baseline[1]	-0.5 (0.05)	-0.3 (0.05)
LS Mean treatment difference from placebo	-0.22	
95% CI	(-0.4, -0.1)	
p-value	<0.001	
Rhinorrhea (Runny Nose)		
Baseline mean (SD)	2.5 (0.50)	2.4 (0.45)
Overall LS mean (SE) change from Baseline[1]	-0.4 (0.04)	-0.2 (0.04)
LS Mean treatment difference from placebo	-0.22	
95% CI	(-0.3, -0.1)	
p-value	<0.001	
Nasal Itching		
Baseline mean (SD)	2.4 (0.55)	2.4 (0.55)
Overall LS mean (SE) change from Baseline[1]	-0.5 (0.04)	-0.3 (0.04)
LS Mean treatment difference from placebo	-0.20	
95% CI	(-0.3, -0.1)	
p-value	0.001	
Nasal Congestion		
Baseline mean (SD)	2.6 (0.35)	2.6 (0.35)
Overall LS mean (SE) change from Baseline[1]	-0.5 (0.04)	-0.2 (0.04)
LS Mean treatment difference from placebo	-0.26	
95% CI	(-0.4, -0.2)	
p-value	<0.001	

1 Results from repeated measures ANCOVA over the treatment period.
(BDP-AR-301 Study Report, page 64)

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 18).

Table 18 Analysis of iTNSS, Study BDP-AR-301

Statistic	BDP HFA 320 mcg/day N = 167	Placebo N = 171
Baseline mean (SD)	9.0 (1.74)	8.7 (1.81)
Overall LS mean (SE) change from Baseline[1]	-1.7 (0.15)	-0.8 (0.15)
LS Mean treatment difference from placebo	-0.92	
95% CI	(-1.3, -0.5)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-301 Study Report, page 58)

AM and PM subject-reported 24-hour reflective TOSS

Reflective TOSS was calculated in ITT population (Table 19). At baseline, the means of the AM subject-reported reflective total ocular symptom score were comparable in the two treatment groups. Across the 2-week treatment period, AM and PM subject-reported reflective ocular symptom scores decreased in both treatment groups. The BDP Nasal Aerosol 320 mcg group had a significantly larger decrease in the reflective ocular symptom score. The analyses were also performed using the ocular population. Similar results were seen in these analyses as for the ITT population. The LS mean treatment difference over the 2-week treatment period between BDP HFA 320 mcg/day and placebo was -0.54 (95% CI: -0.9, -0.2; p=0.003).

Table 19 Analysis of reflective ocular symptom score, Study BDP-AR-301

Statistic	BDP HFA 320 mcg/day N = 167	Placebo N = 171
Baseline mean (SD)	6.7 (1.50)	6.6 (1.46)
Overall LS mean (SE) change from Baseline[1]	-1.3 (0.13)	-0.7 (0.12)
LS Mean treatment difference from placebo	-0.56	
95% CI	(-0.9, -0.2)	
p-value	0.002*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-301 Study Report, page 61)

RQLQ

As summarized in Table 20 for the RQLQ population, baseline RQLQ scores were similar across the two treatment groups. Improvements in RQLQ were seen in both groups. The BDP Nasal Aerosol 320 mcg group had a significantly larger decrease in the average RQLQ score.

Table 20 Analysis of RQLQ score, Study BDP-AR-301

Statistic	BDP HFA 320 mcg/day N = 129	Placebo N = 121
Baseline mean (SD)	4.3 (0.78)	4.4 (0.80)
LS Mean (SE) change from Baseline at End of Study	-1.2 (0.12)	-0.8 (0.12)
LS Mean treatment difference from placebo	-0.48	
95% CI	(-0.8, -0.1)	
p-value	0.005*	

* Statistically significant.
(BDP-AR-301 Study Report, page 60)

The analysis was also performed using the ITT population. Similar results were seen in these analyses as were seen for the RQLQ population. For the ITT population the LS mean treatment difference between BDP HFA 320 mcg/day and placebo was -0.40 (95% CI: -0.7, -0.1; p=0.008), and for the PP population the LS mean treatment difference was -0.40 (95% CI: -0.7, -0.1; p=0.009).

Safety Monitoring

Extent of exposure

The actual mean exposure to study medication was similar for the two treatment groups, being 15.1 days in the BDP Nasal Aerosol 320 mcg/day group and 15.0 days in the placebo group.

Adverse events

Of the 338 subjects randomized to study treatment, 47 (13.9%) experienced adverse events: 23 subjects (13.8%) receiving BDP Nasal Aerosol 320 mcg/day, and 24 subjects (14.0%) receiving placebo. Table 21 presents an overview of treatment-emergent AEs for subjects in Study BDP-AR-301.

Table 21 Adverse events reported in Study BDP-AR-301

Preferred Term	BDP HFA 320 mcg (N=167) n (%)	PLACEBO (N=171) n (%)	TOTAL (N=338) n (%)
Subjects With at Least 1 AE	23(13.8)	24(14.0)	47(13.9)
NASAL DISCOMFORT	11(6.6)	10(5.8)	21(6.2)
HEADACHE	3(1.8)	2(1.2)	5(1.5)
EPISTAXIS	2(1.2)	1(0.6)	3(0.9)
NAUSEA	2(1.2)	0(0.0)	2(0.6)
URTICARIA	2(1.2)	0(0.0)	2(0.6)
ANGINA PECTORIS	1(0.6)	0(0.0)	1(0.3)
BASAL CELL CARCINOMA	1(0.6)	0(0.0)	1(0.3)
CHOLECYSTITIS	1(0.6)	0(0.0)	1(0.3)
CONSTIPATION	1(0.6)	0(0.0)	1(0.3)
COUGH	1(0.6)	0(0.0)	1(0.3)
DRY MOUTH	1(0.6)	1(0.6)	2(0.6)
DYSGEUSIA	1(0.6)	0(0.0)	1(0.3)
EYE PRURITUS	1(0.6)	0(0.0)	1(0.3)
HYPERSENSITIVITY	1(0.6)	0(0.0)	1(0.3)
HYPERTENSIVE CRISIS	1(0.6)	0(0.0)	1(0.3)
INSOMNIA	1(0.6)	0(0.0)	1(0.3)
JOINT SPRAIN	1(0.6)	0(0.0)	1(0.3)
MITRAL VALVE PROLAPSE	1(0.6)	0(0.0)	1(0.3)
NASOPHARYNGITIS	1(0.6)	2(1.2)	3(0.9)
ORAL HERPES	1(0.6)	0(0.0)	1(0.3)
RASH PAPULAR	1(0.6)	0(0.0)	1(0.3)
ARTHRALGIA	0(0.0)	1(0.6)	1(0.3)
CHAPPED LIPS	0(0.0)	1(0.6)	1(0.3)
EYE IRRITATION	0(0.0)	1(0.6)	1(0.3)
FATIGUE	0(0.0)	1(0.6)	1(0.3)
GASTROENTERITIS	0(0.0)	1(0.6)	1(0.3)
HERNIA	0(0.0)	1(0.6)	1(0.3)
HERPES SIMPLEX	0(0.0)	1(0.6)	1(0.3)
HYPERTENSION	0(0.0)	1(0.6)	1(0.3)
MYDRIASIS	0(0.0)	1(0.6)	1(0.3)
NASAL MUCOSAL DISORDER	0(0.0)	1(0.6)	1(0.3)

(BDP-AR-301 Study Report, page 503)

The commonly reported AEs were local nasal adverse events. Because in the original study report the local AEs were categorized inconsistently, the Applicant submitted a Safety Information Amendment (Table 22) on Feb. 7, 2012, upon the Division's request. The most common nasal AE was nasal irritation, which counted 6.6% and 6.4% in the BDP Nasal Aerosol 320 mcg/day and placebo group, respectively. There were no apparent differences among three BDP Nasal Aerosol treatment groups with respect to incidence of AEs. No nasal ulceration and nasal septum perforation reported in the study.

Table 22 Summary of nasal adverse events, BDP-AR-301

Term	320 mcg N=167 n (%)	PLACEBO N=171 n (%)	Total N=338 n (%)
NASAL MUCOSAL/SEPTUM DISORDERS	12(7.2)	12(7.0)	24(7.1)
Non-Ulcerative Lesions	11(6.6)	11(6.4)	22(6.5)
Irritation	11(6.6)	11(6.4)	22(6.5)
Other	2(1.2)	1(0.6)	3(0.9)
Epistaxis	2(1.2)	1(0.6)	3(0.9)

(NDA 202813, Safety Information Amendment, Feb. 7, 2012)

Deaths, serious adverse events, and events leading to withdrawal

No deaths occurred during the study.

There was one subject (0.6%) in the BDP Nasal Aerosol 320 mcg/day group and there were four subjects (2.3%) in the placebo group who experienced SAEs. The SAEs were cholecystitis in the BDP Nasal Aerosol 320 mcg/day group and chapped lips and dry mouth, fatigue, gastroenteritis, and nasal discomfort in the placebo group. The case of cholecystitis in the BDP Nasal Aerosol 320 mcg/day group was considered unrelated to study drug by the investigator. The subject who reported cholecystitis was withdrawn from the study. This was the only withdrawal due to an AE in the study.

Physical examinations and vital signs

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

Reviewer's comment:
The BDP Nasal Aerosol 320 mcg/day and placebo groups had the similar safety profile, and revealed no new safety signals.

5.3.3 Study BDP-AR-302

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Study to Assess the Efficacy and Safety of BDP HFA Nasal Aerosol (320 mcg, Once Daily) in the Treatment of Perennial Allergic Rhinitis (PAR) in Adult and Adolescent Subjects (12 Years of Age and Older)

PROTOCOL

Administrative
Study initiated: June 9, 2010
Study completed: October 8, 2010
Clinical Centers: 35 centers in the U.S. (including following States: TX, PA, VA, CA, NJ, NC, SC, NE, OH, OR, IN, MO, GA, FL, and RI)
Study report dated: March 8, 2011
Study Sponsor: TEVA Branded Pharmaceutical Products
Medical Officer: Paul Dorinsky, M.D.

Objective
To evaluate the efficacy of BDP (beclomethasone dipropionate) HFA (hydrofluoroalkane), applied as a nasal aerosol, in subjects with PAR, and to assess the safety and tolerability of BDP Nasal Aerosol in subjects with PAR.

Study Design
This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 6-week, multi-center, outpatient study in male or female subjects (12 years and older) with PAR. The study consisted of 2 periods: Run-in Period (7-21 days) and a Treatment Period (43 days). Subjects visited the clinic for four out-patient visits – Screening Visit (SV), Randomization Visit (RV) on Day 1, Treatment Visit 1 (TV1) on Day 14 (+5 days), and the Final Treatment Visit (TV2) on Day 43 (+1/-3 days). During the Run-in Period, subjects self-administered a single-blind placebo nasal aerosol once daily in the morning. During the Treatment Period, subjects self-administered the double blinded study medication once daily in the morning. Subjects assessed and recorded their reflective and instantaneous nasal symptoms (rhinorrhea/runny nose, nasal congestion, nasal itching and sneezing) and their reflective and instantaneous non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) twice daily as absent (0), mild (1), moderate (2), or severe (3). The primary efficacy endpoint was the change from baseline in the average AM and PM daily subject-reported rTNSS over the 6 weeks of the Treatment Period. Safety was monitored by physical examinations, electrocardiograms (ECGs), safety laboratory assessments, ear, nose and throat (ENT) examinations, vital sign assessments (blood pressure and pulse rate) and adverse events (AEs). Subjects recorded the dose counter display number prior to actuation, the number of actuations used, the dose counter display number after the actuations had been used and comments about any discrepancy between the counter and actuations taken. Subject compliance was assessed by diary entries and by inspection of the medication doses used by the subject.

This study was performed under a protocol that was virtually identical to the protocol for Study BDP-AR-201, the dose-ranging study with the differences listed below. The

reader is referred to the description of the protocol BDP-AR-201 discussed in section 5.3.1 above for a detailed description of the protocol.

Differences in protocol BDP-AR-302 comparing to protocol BDP-AR-201

- **Study duration and clinical visit**

This was a 6-week study. Subjects visited the clinic for four out-patient visits – Screening Visit (SV), Randomization Visit (RV) on Day 1, Treatment Visit 1 (TV1) on Day 14 (+5 days), and the Final Treatment Visit (TV2) on Day 43 (+1/-3 days).

- **Treatment**

BDP Nasal Aerosol – 80 mcg/actuation (Lot # 0900403), and
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # 090528)

All subjects received daily BDP Nasal Aerosol 320 mcg (a total of 4 intranasal actuations, 2 actuations per nostril) or placebo HFA Nasal Aerosol.

- **Inclusion criteria**

A documented history of PAR to a relevant perennial allergen for a minimum of two years; In the investigator's judgment, the PAR must have been of sufficient severity to have required treatment (either continuous or intermittent) during this period and was expected to require treatment for the study duration; A demonstrated sensitivity to at least one allergen known to induce PAR through a standard skin prick test.

- **Exclusion criteria**

Allergic to a seasonal aeroallergen (e.g., trees, grasses or weeds) with seasonal exacerbation occurring or anticipated to occur during the study.

- **Randomization criteria**

Subject had a minimum subject-assessed rTNSS of an average of 6 (out of a possible 12) on the last 4 days during the Run-in Period; Subject-assessed reflective scores for nasal congestion were on average ≥2 during the last 4 days during the Run-in Period.

- **Sample size**

Based on the results from previous studies, the standard deviation for the change from baseline over 6 weeks in the average of AM and PM rTNSS was assumed to be 2.0. Using this standard deviation, 235 subjects per group provided 90% power to detect a difference between treatment groups of 0.6 in the change from baseline in rTNSS with a two-sided alpha level of 0.05.

RESULTS

Study Population

Disposition

A total of 675 subjects were screened for enrolment in the study. However, 4 additional subject numbers were recorded in error, which reflected in the database as 679 subjects were screened. Of the screened subjects, 574 were enrolled in the study and participated in the Run-in Period. Of the 574 enrolled subjects, 474 met the randomization criteria and were randomized to treatment (236 were randomized to receive BDP Nasal Aerosol 320 mcg and 238 were randomized to receive placebo) (Table 23). Eight subjects who were randomized were not included in the ITT population as they had no post-baseline average AM and PM daily subject-reported rTNSS values (4 in the BDP Nasal Aerosol 320 mcg group and 4 in placebo group). These 8 subjects were excluded from efficacy analyses. Hence, 466 randomized subjects (232 treated with BDP Nasal Aerosol 320 mcg and 234 treated with placebo) constituted the ITT population. There were 257 subjects in the RQLQ population, and 374 subjects in the device completer population. The RQLQ population included only those subjects with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater. The device completer population included only those subjects who had administered at least 80% of actuations during the last 4-week treatment period of this 6-week study.

Approximately 92.2% of the subjects completed the study (93.6%, 221 subjects, in the BDP Nasal Aerosol 320 mcg/day group; 90.8%, 216 subjects, in the placebo group). A total of 37 subjects, 15 subjects (6.4%) treated with BDP Nasal Aerosol 320 mcg/day and 22 subjects (9.2%) treated with placebo, discontinued the study prematurely.

Table 23 Subject disposition, Study BDP-AR-302

Category	BDP HFA 320 mcg/day n (%)	Placebo n (%)	Overall n (%)
Randomized	236 (100)	238 (100)	474 (100)
Safety population	236 (100)	238 (100)	474 (100)
ITT population	232 (98.3)	234 (98.3)	466 (98.3)
Completed	221 (93.6)	216 (90.8)	437 (92.2)
Discontinued prematurely[1]	15 (6.4)	22 (9.2)	37 (7.8)
Adverse Event[2]	1 (0.4)	7 (2.9)	8 (1.7)
Withdrew Consent	6 (2.5)	6 (2.5)	12 (2.5)
Pregnancy	1 (0.4)	0	1 (0.2)
Lost to follow up/failure to return	5 (2.1)	2 (0.8)	7 (1.5)
Protocol violation/ non-compliance	1 (0.4)	1 (0.4)	2 (0.4)
Other	1 (0.4)	6 (2.5)	7 (1.5)

1 A subject who discontinued for more than one reason was counted only once.
2 Included 2 AEs that started during the run-in period which led to withdrawal during the treatment period.
(BDP-AR-302 Study Report, page 56)

As shown in Table 24 below for the ITT population, the majority of subjects in both groups were female (68.5%), white (79.6%) and not Hispanic or Latino (88.0%). The mean age of study subjects was 37.0 years and ranged from 12 to 82 years. There were 44 (9.4%) adolescent subjects aged 12 – 17 years old, with 23 and 21 in BDP Nasal Aerosol 320 mcg/day group and placebo, respectively. Demographic characteristics were comparable in two treatment groups.

Table 24 Subject demographics, Study BDP-AR-302

Demographic	BDP HFA 320 mcg/day N = 232	Placebo N = 234	Total N = 466
Age (years)			
Mean (SD)	36.8 (14.5)	37.2 (13.7)	37.0 (14.1)
Median	37.0	38.0	37.5
Min-Max	12 - 82	12 - 71	12 - 82
Gender, n (%)			
Female	158 (68.1)	161 (68.8)	319 (68.5)
Male	74 (31.9)	73 (31.2)	147 (31.5)
Race, n (%)			
White	186 (80.2)	185 (79.1)	371 (79.6)
Black or African American	40 (17.2)	40 (17.1)	80 (17.2)
Asian	6 (2.6)	5 (2.1)	11 (2.4)
American Indian or Alaskan Native	1 (0.4)	2 (0.9)	3 (0.6)
Other	1 (0.4)	6 (2.6)	7 (1.5)
Ethnicity, n (%)			
Hispanic or Latino	26 (11.2)	30 (12.8)	56 (12.0)
Not Hispanic, not Latino	206 (88.8)	204 (87.2)	410 (88.0)
BMI, kg/m^2			
Mean (SD)	28.1 (5.7)	28.3 (6.9)	28.2 (6.3)

(BDP-AR-302 Study Report, page 60)

Medical history was generally similar in the two treatment groups and the types of conditions reported were those that might be expected in a PAR patient population such as sinus headache, asthma, drug hypersensitivity, sinusitis, dyspepsia, etc. All subjects had a history of seasonal rhinitis and 60.8% of subjects (overall) also reported a history of SAR.

Prior to use of study drug, the most commonly reported medications in both treatment groups were those for the respiratory system (144 subjects, 61.0% in the BDP Nasal Aerosol 320 mcg/day group and 136 subjects, 57.1% in the placebo group). There

were no appreciable differences between the two treatment groups. During the study, the most commonly used medications were those for the alimentary, musculoskeletal system and nervous system, including multivitamins, fish oil, calcium, Tylenol, ibuprofen, aspirin, salbutamol, paracetamol, etc. There were no clinically important differences between treatment groups in concomitant medication use.

Treatment compliance

Treatment compliance was assessed by use of a subject-completed e-diary. Mean compliance rates based on the subject diary were > 96% in both groups. There were only two subjects in the BDP Nasal Aerosol 320 mcg group and 1 subject in the placebo group had compliance rates <60% and 3 subjects in the BDP Nasal Aerosol 320 mcg/day group and 6 subjects in the placebo group had compliance rates of 60-80%.

Efficacy Results

Primary efficacy endpoint

The primary efficacy analysis was summarized in Table 25 below. At baseline, the means of the average AM and PM subject-reported rTNSS were comparable in the two treatment groups (8.9 for BDP Nasal Aerosol 320 mcg/day and 9.0 for the placebo). Across the 6-week Treatment Period, average AM and PM subject-reported rTNSS decreased in both treatment groups. The LS mean (SE) change from baseline over the Treatment Period was -2.5 (0.14) for BDP Nasal Aerosol 320 mcg/day group and -1.6 (0.14) for the placebo group. The LS mean treatment difference of -0.84 between BDP Nasal Aerosol 320 mcg/day and placebo was statistically significant (p<0.001) in favor of BDP Nasal Aerosol 320 mcg/day.

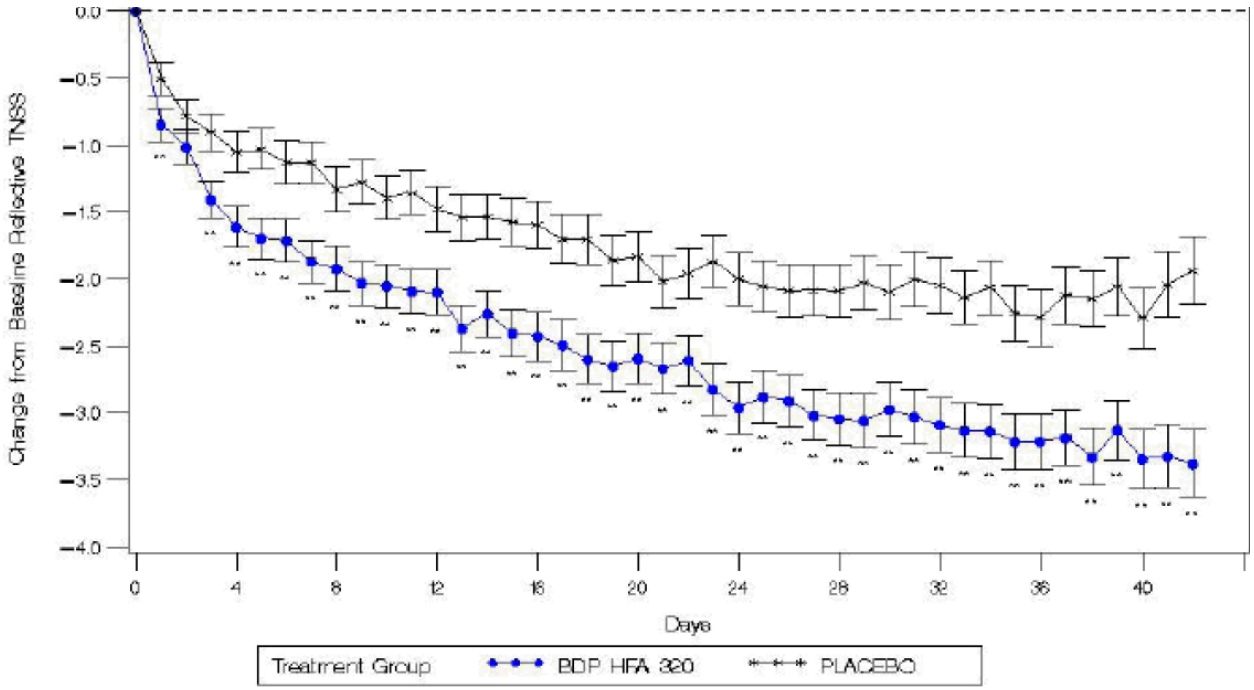
Table 25 Primary efficacy (rTNSS) analysis, Study BDP-AR-302

Statistic	BDP HFA320 mcg/day N = 232	Placebo N = 234
Baseline mean (SD)	8.9 (1.70)	9.0 (1.73)
Overall LS mean (SE) change from Baseline[1]	-2.5 (0.14)	-1.6 (0.14)
LS mean treatment difference from placebo	-0.84	
95% CI	(-1.2, -0.5)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-302 Study Report, page 64)

The daily changes in average AM and PM rTNSS from baseline over time for the BDP Nasal Aerosol 320 mcg/day and placebo groups are shown graphically in Figure 3 below. For the BDP Nasal Aerosol 320 mcg group, the significant change from baseline in the average AM and PM subject-reported rTNSS, compared with the placebo, was consistently observed on Day 3 till the end of the study.

Figure 3 Chang from baseline in AM & PM rTNSS, Study BDP-AR-302



(BDP-AR-302 Study Report, page 70)

Subgroup analyses based on gender (male, female), age (12-17 years, 18-64 years, 65 years and older), and race (white, black, other) were performed for the primary efficacy analysis. There were no significant differences found in subgroups per gender, age, and race. However, it was hard to draw conclusions from the subgroup analysis because of the small sample size of the subgroups.

Secondary efficacy endpoints

The secondary efficacy endpoints were the change from baseline in the average individual reflective nasal symptom score over the 6-week Treatment Period, the change from baseline in the average AM and PM subject-reported iTNSS over the 6-week Treatment Period, and RQLQ at Week 2 for subjects with impaired quality of life at baseline.

Average AM and PM individual reflective nasal symptom scores

As listed in Table 26 below, significant improvements were seen in each of the average AM and PM subject-reported reflective individual nasal symptom scores over the 6-week Treatment Period.

Table 26 Individual reflective nasal symptom score analysis, Study BDP-AR-302

Statistic	BDP HFA 320 mcg/day N = 232	Placebo N = 234
Sneezing		
Baseline mean (SD)	1.8 (0.74)	1.9 (0.69)
Overall LS mean (SE) change from Baseline[1]	-0.7 (0.04)	-0.4 (0.04)
LS mean treatment difference from placebo 95% CI p-value	-0.27 (-0.4, -0.2) <0.001	
Rhinorrhea (Runny Nose)		
Baseline mean (SD)	2.3 (0.57)	2.3 (0.60)
Overall LS mean (SE) change from Baseline[1]	-0.6 (0.04)	-0.4 (0.04)
LS mean treatment difference from placebo 95% CI p-value	-0.20 (-0.3, -0.1) <0.001	
Nasal Itching		
Baseline mean (SD)	2.2 (0.61)	2.2 (0.66)
Overall LS mean (SE) change from Baseline[1]	-0.6 (0.04)	-0.4 (0.04)
LS mean treatment difference from placebo 95% CI p-value	-0.21 (-0.3, -0.1) <0.001	
Nasal Congestion		
Baseline mean (SD)	2.6 (0.39)	2.6 (0.38)
Overall LS mean (SE) change from Baseline[1]	-0.6 (0.04)	-0.4 (0.04)
LS mean treatment difference from placebo 95% CI p-value	-0.18 (-0.3, -0.1) <0.001	

1 Results from repeated measures ANCOVA over the treatment period.
(BDP-AR-302 Study Report, page 73)

Average AM and PM subject-reported iTNSS

Results for change from baseline in the average AM and PM subject-reported iTNSS over the 6-week Treatment Period were consistent with those observed for the primary efficacy endpoint (Table 27).

Table 27 Analysis of iTNSS, Study BDP-AR-302

Statistic	BDP HFA 320 mcg/day N = 232	Placebo N = 234
Baseline mean (SD)	8.1 (1.98)	8.3 (1.96)
Overall LS mean (SE) change from Baseline[1]	-2.1 (0.13)	-1.4 (0.13)
LS mean treatment difference from placebo	-0.78	
95% CI	(-1.1, -0.4)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-302 Study Report, page 64)

RQLQ

As summarized in Table 28 for the RQLQ population, baseline RQLQ scores were similar across the two treatment groups. Improvements in RQLQ were seen in both groups. The BDP Nasal Aerosol 320 mcg group had a significantly larger decrease in the average RQLQ score.

Table 28 Analysis of RQLQ score, Study BDP-AR-302

Statistic	BDP HFA 320 mcg/day N = 132	Placebo N = 125
Baseline mean (SD)	4.2 (0.74)	4.2 (0.81)
LS Mean (SE) change from Baseline at End of Study	-1.5 (0.14)	-0.9 (0.14)
LS mean treatment difference from placebo	-0.58	
95% CI	(-0.9, -0.2)	
p-value	0.001*	

* Statistically significant.
(BDP-AR-302 Study Report, page 67)

The analysis was also performed using the ITT population. Similar results were seen in these analyses as were seen for the RQLQ population. For the ITT population the LS mean treatment difference between BDP HFA 320 mcg/day and placebo was -0.56 (95% CI: -0.8, -0.3; p<0.001), and for the PP population the LS mean treatment difference was -0.50 (95% CI: -0.7, -0.2; p<0.001).

Device dose counter performance

Assessment of the nasal device dose counter was based on data recorded by the subject in the Diary. Subjects recorded the dose counter display number prior to actuation, the number of actuations used, the dose counter display number after the

actuations had been used and comments about any discrepancy between the counter and actuations taken. The data were from the device completer population, a subset of subjects who had administered at least 80% of actuations during the last 4-week treatment period. The majority of subjects (79.1%) in the device completer population reported no discrepancies in dose counter usage (151 subjects, 79.9% in the BDP Nasal Aerosol 320 mcg/day group and 145 subjects, 78.4% in the placebo group). One discrepancy was noted for 16 subjects (8.5%) in the BDP Nasal Aerosol 320 mcg/day group and 19 subjects (10.3%) in the placebo group and two discrepancies were noted for 12 subjects (6.4%) in the BDP Nasal Aerosol 320 mcg/day group and 12 subjects (6.5%) in the placebo group. Only 10 subjects (5.3%) in the BDP Nasal Aerosol 320 mcg/day group and 9 subjects (4.9%) in the placebo group reported more than two discrepancies. As shown in Table 29, the discrepancy rate was low. The most commonly occurring discrepancy was count not fire (nasal device counter advances but the nasal device does not actuate) which had an occurrence rate of 0.17 per 100 actuations. The important potential discrepancy was fire not count; the rate for this was 0.09 per 100 actuations. The rate of total actuation discrepancies was 0.38 per 100 actuations (0.41 per 100 actuations in the BDP Nasal Aerosol 320 mcg/day group and 0.34 per 100 actuations in the placebo group).

Table 29 Recorded discrepancy rate per 100 actuations, Study BDP-AR-302

	BDP HFA 320 mcg/day N = 189	Placebo N = 185	Total N=374
Count not fire	0.22	0.12	0.17
Count unknown fire	0.04	0.08	0.06
Count up unknown fire	0.05	0.06	0.06
Fire not count	0.10	0.08	0.09
Total number of actuation discrepancies	0.41	0.34	0.38

(BDP-AR-302 Study Report, page 86)

Assessment of device weights was also conducted for the device completer population. For the 2 treatment groups, the overall mean difference in canister weight between pre-dose and post-dose was 6.4 g, with an estimated total of 39,001 actuations used (compared with 41,884 actuations based on dose counter data). In the BDP Nasal Aerosol 320 mcg/day group, the mean difference in canister weight between pre-dose and post-dose was 6.3 g, with an estimated total of 19,277 actuations used (compared with 21,203 actuations based on dose counter data). The estimated actuations based on canister weight were matched well with the dose counter data.

Table 30 Assessment of canister weight, Study BDP-AR-302

	BDP HFA 320 mcg/day N = 189	Placebo N = 185	Total N=374
Pre-dose mean (SD) canister weight, g	44.7 (0.17)	49.0 (0.17)	46.8 (2.16)
Post-dose mean (SD) canister weight, g	38.3 (0.84)	42.4 (0.99)	40.3 (2.23)
Mean (SD) change from pre-dose to post-dose, g	6.3 (0.84)	6.6 (0.96)	6.4 (0.91)

(BDP-AR-302 Study Report, page 87)

Device performance/acceptance

Results from the Nasal Device Ease of Use/Satisfaction Questionnaire are summarized in Table 31. The majority of subjects assessed that the device was very easy or somewhat easy to use (89.7%), the device was very easy or somewhat easy to tell when the device was empty (87.6%), and it was very easy or somewhat easy to take medication as directed (89.7%). There was no significant difference in the assessment of device performance/acceptance between 2 treatment groups.

Table 31 Assessment of device performance/acceptance, Study BDP-AR-302

	BDP HFA 320 mcg/day N = 232	Placebo N = 234	Total N=466
Device very easy or somewhat easy to use	210 (90.5)	208 (88.9)	418 (89.7)
Very easy or somewhat easy to tell remaining medication	214 (92.2)	211 (90.2)	425 (91.2)
Very easy or somewhat easy to monitor how many doses used	207 (89.2)	209 (89.3)	416 (89.3)
Very easy or somewhat easy to tell when nasal device is empty	206 (88.8)	202 (86.3)	408 (87.6)
Very easy or somewhat easy to tell when device needs to be replaced	205 (88.4)	204 (87.2)	409 (87.8)
Very easy or somewhat easy to take medication as directed	210 (90.9)	208 (88.9)	418 (89.7)

(BDP-AR-302 Study Report, page 89)

Safety Monitoring

Extent of exposure

The actual mean exposure to study medication was similar for the two treatment groups, being 41.2 days in the BDP Nasal Aerosol 320 mcg/day group and 39.9 days in the placebo group.

Adverse events

Of the 474 subjects who were randomized to study treatment (safety population), 112 (23.6%) experienced adverse events: 48 subjects (20.3%) receiving BDP Nasal Aerosol 320 mcg/day, and 64 subjects (26.9%) receiving placebo. Table 32 presents an overview of treatment-emergent AEs for subjects in Study BDP-AR-302.

Table 32 Adverse events reported in Study BDP-AR-302

Preferred Term	BDP HFA 320 mcg/day (N=236) n (%)	Placebo (N=238) n (%)	TOTAL (N=474) n (%)
Subjects With at Least 1 AE	48(20.3)	64(26.9)	112(23.6)
Nasal discomfort	14(5.9)	12(5.0)	26(5.5)
Epistaxis	4(1.7)	4(1.7)	8(1.7)
Headache	3(1.3)	5(2.1)	8(1.7)
Upper respiratory tract infection	3(1.3)	4(1.7)	7(1.5)
Oropharyngeal pain	2(0.8)	4(1.7)	6(1.3)
Rhinitis allergic	0(0.0)	5(2.1)	5(1.1)
Nasopharyngitis	2(0.8)	2(0.8)	4(0.8)
Cough	2(0.8)	1(0.4)	3(0.6)
Lacrimation increased	2(0.8)	1(0.4)	3(0.6)
Migraine	2(0.8)	1(0.4)	3(0.6)
Nasal mucosal disorder	2(0.8)	1(0.4)	3(0.6)
Otitis media	2(0.8)	1(0.4)	3(0.6)
Sinus headache	3(1.3)	0(0.0)	3(0.6)
Acute sinusitis	1(0.4)	1(0.4)	2(0.4)
Arthropod sting	1(0.4)	1(0.4)	2(0.4)
Asthma	1(0.4)	1(0.4)	2(0.4)
Back pain	1(0.4)	1(0.4)	2(0.4)
Eye irritation	1(0.4)	1(0.4)	2(0.4)
Musculoskeletal pain	1(0.4)	1(0.4)	2(0.4)
Nasal inflammation	1(0.4)	1(0.4)	2(0.4)
Nasal septum disorder	0(0.0)	2(0.8)	2(0.4)
Nasal ulcer	0(0.0)	2(0.8)	2(0.4)
Nausea	2(0.8)	0(0.0)	2(0.4)
Neck pain	1(0.4)	1(0.4)	2(0.4)
Pharyngitis streptococcal	1(0.4)	1(0.4)	2(0.4)
Postnasal drip	1(0.4)	1(0.4)	2(0.4)
Pyrexia	2(0.8)	0(0.0)	2(0.4)
Rhinalgia	0(0.0)	2(0.8)	2(0.4)
Sinusitis	0(0.0)	2(0.8)	2(0.4)
Abdominal pain	1(0.4)	0(0.0)	1(0.2)
Abdominal pain upper	0(0.0)	1(0.4)	1(0.2)

(BDP-AR-302 Study Report, page 607)

The commonly reported AEs were local nasal adverse events. Because in the original study report the local AEs were categorized inconsistently, the Applicant submitted a Safety Information Amendment (Table 33) on Feb. 7, 2012, upon the Division's request. Note there were three nasal ulcerations reported in the study. One nasal ulceration cases reported in the BDP Nasal Aerosol 320 mcg/day was described as "possible ulceration of the mucosa, right naris." There were two nasal ulceration cases reported in placebo group. The most common nasal AE were irritation and epistaxis. Nasal irritation was reported by the subjects of 5.9% and 5.5% in the BDP Nasal Aerosol 320 mcg/day and placebo, respectively. Epistaxis was reported by the subjects of 1.7% in both the BDP Nasal Aerosol 320 mcg/day and placebo group. There were no apparent

differences among three BDP Nasal Aerosol treatment groups with respect to incidence of AEs. No nasal septum perforation was reported in the study.

Table 33 Summary of nasal adverse events, BDP-AR-302

Term	320 mcg N=236 n (%)	PLACEBO N=238 n (%)	Total N=474 n (%)
NASAL MUCOSAL/SEPTUM DISORDERS	21(8.9)	29(12.2)	50(10.5)
Erosions/Ulcerations	1(0.4)	2(0.8)	3(0.6)
Ulceration	1(0.4)	2(0.8)	3(0.6)
Non-Ulcerative Lesions	15(6.4)	13(5.5)	28(5.9)
Abrasion/Excoriation/Scabs	1(0.4)	1(0.4)	2(0.4)
Irritation	14(5.9)	13(5.5)	27(5.7)
Other	9(3.8)	16(6.7)	25(5.3)
Dermatitis	1(0.4)	0(0.0)	1(0.2)
Epistaxis	4(1.7)	4(1.7)	8(1.7)
Nasal Deptal Disorder	0(0.0)	1(0.4)	1(0.2)
Nasal Discharge	1(0.4)	1(0.4)	2(0.4)
Nasal Discomfort	2(0.8)	2(0.8)	4(0.8)
Nasal Dryness	0(0.0)	1(0.4)	1(0.2)
Nasal Mucosal Discolouration	0(0.0)	1(0.4)	1(0.2)
Nasal Polyps	1(0.4)	0(0.0)	1(0.2)
Nasal Septal Disorder	0(0.0)	1(0.4)	1(0.2)
Rhinitis Allergic	0(0.0)	5(2.1)	5(1.1)
Rhinitis Perennial	1(0.4)	0(0.0)	1(0.2)
Rhinorrhoea	1(0.4)	0(0.0)	1(0.2)
Sneezing	0(0.0)	1(0.4)	1(0.2)

(NDA 202813, Safety Information Amendment, Feb. 7, 2012)

Deaths, serious adverse events, and events leading to withdrawal

No deaths occurred during the study.

There was only one subject, who received the BDP Nasal Aerosol 320 mcg/day experienced SAE in the study. The subject was a 29 years old female with multiple medical conditions including PAR, SAR, migraine, eczema, Crohn's disease, dysmenorrheal, and insomnia who reported a SAE of cardiac arrhythmia.

Clinical laboratory evaluation

There were no significant changes in clinical laboratory tests during the study. There were no notable differences between the 2 treatment groups.

ECG assessment

ECG assessments were performed at screening and final visits. There were no significant changes observed during the study. No subject had changes from normal to abnormal.

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

Reviewer's comment:
The BDP 320 mcg/day and placebo groups had the similar safety profile, and revealed no new safety signals.

5.3.4 Study BDP-AR-303

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Study to Assess the Long-term Efficacy and Safety of BDP HFA Nasal Aerosol (320 mcg, Once Daily) in Adult and Adolescent Subjects (12 Years of Age and Older) with Perennial Allergic Rhinitis (PAR)

PROTOCOL

Administrative
Study initiated: October 26, 2009
Study completed: February 25, 2011
Clinical Centers: 36 centers in the U.S. (including following States: TX, PA, CO, NY, MN, KS, WI, LA, MD, AL, MT, IL, CA, NC, OH, OR and GA)
Study report dated: April 27, 2011
Study Sponsor: TEVA Branded Pharmaceutical Products
Medical Officer: Charles P. Andrews, M.D.

Objective
To demonstrate long-term (30/52 weeks) efficacy and safety of BDP (beclomethasone dipropionate) HFA (hydrofluoroalkane), applied as a nasal aerosol, in adult and adolescent subjects with PAR.

Study Design
This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center, outpatient study in male or female subjects (12 years of age and older) with PAR. 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 of 30 weeks (from the Randomization Visit, RV, to Treatment Visit TV6/TdV) or 52 weeks (from the Randomization Visit, RV, to Treatment Visit TV10/TdV). During the Run-in Period, subjects self-administered a single-blind placebo nasal aerosol once daily in the

morning. Subjects assessed and recorded their reflective and instantaneous nasal symptoms (rhinorrhea/runny nose, nasal congestion, nasal itching and sneezing) once daily in the morning as absent (0), mild (1), moderate (2), or severe (3). During the Treatment Period, subject self-administered the double-blinded study medication once daily in the morning, assessed and recorded their reflective and instantaneous nasal symptoms once daily in the morning using the scale above. A total of 526 patients, with a documented history of PAR for at least 2 years, were randomized at a 4:1 ratio to receive BDP Nasal Aerosol 320 mcg/day (415) and placebo (111). There were 249 patients finished at 30 weeks (196 in treatment and 53 in placebo), and rest of the patients (277) finished at 52 weeks (219 in treatment and 58 in placebo). The PAR had to be of sufficient severity (rTNSS ≥5 out of 12) and to be expected to require treatment throughout the entire study. Subjects had a positive skin prick test to at least one allergen known to induce PAR. Safety monitoring included AEs, physical examinations including ENT examinations, vital signs. Intraocular pressure (IOP) measurements, best-corrected visual acuity (BCVA) assessments and Lens Opacities Classification System III (LOCS III) assessments were performed by certified ophthalmologists only in subjects who participated in the 52-week Treatment Period. The primary outcome of this study was the long term safety measures. The efficacy measures were taken in this long term study primarily for the purpose of compliance monitoring.

This study was performed under a protocol that was similar to the protocol for Study BDP-AR-302, a 6-week efficacy and safety study of the BDP Nasal Aerosol 320 mcg/day in PAR, with the differences listed below.

Differences in protocol BDP-AR-303 comparing to protocol BDP-AR-302

- **Study duration and clinical visit**

This was a long term safety study with the Treatment Period of 30 weeks (249 subjects) or 52 weeks (277 subjects). Efficacy endpoints were measured primarily for the purpose of monitoring treatment compliance. Nasal symptom scores were recorded AM only, rather than the average of AM and PM scores. Subjects who received the 30-week treatment visited the clinic for 8 out-patient visits: Screening Visit (SV), Randomization Visit (RV) on Day 1, Treatment Visit 1 (TV1) on Day 22 (week 3), TV2 on day 43 (week 6), TV3 on day 85 (week 12), TV4 on day 127 (week 18), TV5 on day 169 (week 24), and TV6/TdV on day 211 (week 30). Subjects who received the 52-week treatment visited the clinic for 12 out-patient visits: above 8 clinic visit, plus TV7 on day 253 (week 36), TV8 on day 295 (week 42), TV9 on day 337 (week 28), and TV10/TdV on day 365 (week 52).

- **Treatment**

BDP Nasal Aerosol – 80 mcg/actuation (Lot # 090115A), and
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # GJK045A)

All subjects received daily BDP Nasal Aerosol Nasal Aerosol 320 mcg (a total of 4 intranasal actuations, 2 actuations per nostril) or placebo HFA Nasal Aerosol.

- **Exclusion criteria**

Removed an exclusion criterion whereby subjects allergic to seasonal aeroallergens were to be excluded from the study.

Removed an exclusion criterion relating to a history of ocular disturbances for all subjects and replaced this with a more detailed exclusion criterion describing excluded ocular disturbances which was only applicable for subjects included in the 52-week Treatment Period.

Added details of prohibited medications (intraocular corticosteroids, pilocarpine, phospholine idodide and thiazide diuretics) for subjects participating in the 52-week Treatment Period.

Added following exclusion criteria of ocular disturbances or conditions for subjects participating in the 52-week Treatment Period:

History of increased intraocular pressure, glaucoma, posterior subcapsular cataracts, retinal detachment surgery, incisional eye surgery (other than unilateral cataract extraction or LAZIK), penetrating ocular trauma or severe blunt ocular trauma; Evidence of uveitis, iritis, or other inflammatory eye disease; Inability to dilate the pupil to at least 6.0 mm at the screening eye examination; Presence of miotic pupils due to chronic miotic use or posterior synechiae; Best-corrected visual acuity less than 20/30 (or LogMAR equivalent: fewer than 74 letters identified correctly); Evidence of congenital cataract.

Inability to grade with LOCS III the following: NO (nuclear opalescence), C (cortical), or P (posterior subcapsular opacification) in either eye at the screening eye examination, or LOCS III grades at baseline:

NO (nuclear opalescence) ≥4.0
NC (nuclear color) ≥4.0
C (cortical) ≥3.0
P (posterior subcapsular opacification) ≥2.0

- **Eye evaluations**

Overall eye evaluations were performed in a subset of approximately 250 subjects at 19 pre-selected sites (subjects participating in the 52-week Treatment Period only). An ophthalmologist who had been trained and certified in the study eye procedures (Lens Opacities Classification System Version III [LOCS III]) performed all eye examinations. Whenever possible, the same certified ophthalmologist completed these assessments for the same subject throughout that subject's participation in the trial. The certified ophthalmologist evaluated each subject without reviewing any prior study appointment eye test results. The following procedures were performed at each eye examination:

Visual acuity (unrefracted and, as appropriate, refracted) by the standard technique (Logarithmic Visual Acuity Chart) used by the certified ophthalmologist using the same equipment for all examinations in individual subjects. The measurement of visual acuity was made first with current spectacle correction (if distance glasses were worn). If the LogMAR (logarithm of the minimum angle of resolution) visual acuity for each eye without any spectacle correction, or with the current spectacle correction was better than 20/30 (or less than or equal to the LogMAR equivalent of +0.18), then a refraction was not need to be determined for that eye. If the LogMAR visual acuity for each eye with current spectacle correction was worse than 20/30 (or more than the LogMAR equivalent of +0.18), then a refraction was needed to determine the current refractive error and the best-corrected visual acuity (BCVA, also measured with the LogMAR chart). The BCVA was used in determining if the drug or cataract was having an adverse effect on vision. A different LogMAR chart was used for each eye and the conditions for measuring acuity were specified in the instructions that accompanied the LogMAR charts. A negative change in LogMar represents an improvement in BCVA.

Intraocular pressure (IOP) measured using an adequately calibrated tonometer affixed to a slit lamp biomicroscope. Both eyes were tested, with the test of the right eye preceding that of the left eye. The measurement was made on an eye that had not received medications to dilate the pupil. Subjects were not to hold their breath during the measurement and opened any tight-fitting collars on shirts or dresses. Three sequential measurements were made and the second measurement was usually recorded as the IOP. A value ≥21 mmHg was considered as abnormal eye pressure.

Slit lamp eye examination were performed to evaluate the structures of the eye. Pupillary dilatation was performed to obtain maximal pupillary dilatation prior to examining the lens and LOCS III grading, which is a grading system for slit lamp examination to evaluate eye changes of cataract[1]. The ophthalmologist ascertained if the depth of the anterior chamber was deep enough to allow safe pupillary dilatation. If the anterior chamber depth was too shallow (less than 6.0 mm for either eye), the subject was excluded from the protocol.

LOCS III grading of nuclear opalescence (NO), nuclear color (NC), cortical (C) and posterior subcapsular (P) lens opacities was performed at the end of each eye examination after maximal pupillary dilatation had been achieved. If the size of the maximally dilated pupil was at least 6.0 mm, LOCS III grading was done. If not, the subject was excluded from the protocol. The LOCS III scales are decimalized numbers ranging from 0.1 (representing a clear or colorless lens) to

1 Chylack LT, Wolfe JK, Signer DM, et al. The Lens Opacities Classification System III. Arch Ophthalmol. 1993;111:831-6.

5.9 (on the C and P scales) or 6.9 on the NO and NC scales. The higher numbers represent advanced stages of opacification or coloration.

The following definitions for changes in LOCS III grading of opacities was used:

- Class I: an increase in LOCS III grade of at least 0.5 for NO or posterior subcapsular opacity or 0.8 for cortical opacity or cataract surgery in either eye;
- Class II: an increase in LOCS III grade of at least 0.9 for NO or posterior subcapsular opacity or 1.5 for cortical opacity or cataract surgery in either eye;
- Class III: an increase in LOCS III grade of at least 0.9 for NO or posterior subcapsular opacity or 1.5 for cortical opacity or cataract surgery in either eye and a LOCS III score of at least 2.0 for at least one type of opacity.

- **Randomization criteria**

Subject had a minimum subject-assessed rTNSS of an average of 5 (out of a possible 12) on the last 7 days during the Run-in Period; Subject-assessed reflective scores for nasal congestion were on average ≥2 during the last 7 days during the Run-in Period.

- **Sample size**

The sample size of 500 for this study (400 subjects on BDP Nasal Aerosol 320 mcg/day and 100 subjects on placebo) was chosen in order to obtain 6-month safety data in at least 300 subjects and 1-year safety data in at least 100 subjects treated with BDP Nasal Aerosol 320 mcg/day in accordance with the FDA guidance.

Based on the results from previous studies, the standard deviation for the change from baseline in weekly average of 24-hour rTNSS over 30 weeks was assumed to be 2.0. Using this standard deviation, this sample size provided approximately 90% power to detect a difference between treatment groups of 0.70 in the change from baseline in TNSS with a two-sided alpha level of 0.05.

RESULTS

Study Population

Disposition

A total of 857 subjects were screened for enrolment in the study. However, 2 subject numbers were assigned in error. In addition, 8 subjects were assigned numbers but underwent no study procedures. Therefore, 10 additional subject numbers were reflected in the total of 867 subjects in the table as these subject numbers. Of the 857 screened subjects, 775 were enrolled in the study and participated in the Run-in Period. Of the 775 enrolled subjects, 529 were randomized to study treatment (Table 34). Of the total 529 randomized subjects, 3 subjects randomized to the BDP Nasal Aerosol

320 mcg/day group were randomized in error and did not receive any study treatment. Thus, the safety population constituted 526 subjects, 415 randomized and treated with BDP Nasal Aerosol 320 mcg/day and 111 randomized and treated with placebo. There were 249 subjects finished the 30-week Treatment Period and 277 subjects finished the 52-week Treatment Period. Two of the randomized and treated subjects (one in BDP treatment group and one in placebo group) were excluded from the ITT population because no diary data were provided for efficacy assessment. Hence, 524 randomized subjects (414 treated with BDP Nasal Aerosol 320 mcg/day and 110 treated with placebo) received study treatment and constituted the ITT population. There were 281 subjects in the RQLQ population, and 245 subjects in the ocular safety population. The RQLQ population included only those subjects aged 18 years and older with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater. In the RQLQ population, 132 patients finished the 52-week Treatment Period (109 treated with BDP Nasal Aerosol 320 mcg/day and 23 treated with placebo). The ocular safety population was a subset of the safety population that only included those subjects randomized to the 52-week Treatment Period who underwent at least one post-baseline assessment related to ocular safety (BCVA, IOP, LOCS III).

Most of the study subjects (92.2%) completed the study (80.1%, 335 subjects, in the BDP Nasal Aerosol 320 mcg/day group; 76.6%, 85 subjects, in the placebo group). A total of 109 subjects, 83 subjects (19.9%) treated with BDP Nasal Aerosol 320 mcg/day and 26 subjects (23.4%) treated with placebo, discontinued the study prematurely. The major of the early discontinuation was consent withdrawal.

Table 34 Subject disposition, Study BDP-AR-303

Category	BDP HFA 320 mcg/day n (%)	Placebo n (%)	Overall n (%)
Randomized	418 (100)	111 (100)	529 (100)
Safety population	415 (99.3)	111 (100)	526 (99.4)
ITT population	414 (99.0)	110 (99.1)	524 (99.1)
Completed	335 (80.1)	85 (76.6)	420 (79.4)
Discontinued prematurely	83 (19.9)	26 (23.4)	109 (20.6)
Adverse Event	17 (4.1)	3 (2.7)	20 (3.8)
Withdrew Consent	44 (10.5)	13 (11.7)	57 (10.8)
Sponsor requested withdrawal	3 (0.7)	1 (0.9)	4 (0.8)
Pregnancy	1 (0.2)	2 (1.8)	3 (0.6)
Lost to follow up/failure to return	11 (2.6)	2 (1.8)	13 (2.5)
Protocol violation/ non-compliance	4 (1.0)	5 (4.5)	9 (1.7)
Other	3 (0.7)	0	3 (0.6)

(BDP-AR-303 Study Report, page 67)

As shown in Table 35 below for the ITT population, the subjects were aged 12 to 74 years old with an average of 38 years. The majority of subjects in both groups were female (67.2%), white (83.6%) and not Hispanic or Latino (89.1%). The mean age of study subjects was 37.0 years and ranged from 12 to 82 years. Demographic characteristics were comparable in two treatment groups.

Table 35 Subject demographics, Study BDP-AR-303

Demographic	BDP HFA 320 mcg/day N = 414	Placebo N = 110	Total N = 524
Age (years)			
Mean (SD)	37.4 (13.6)	35.7 (12.9)	37.1 (13.4)
Median	38.5	36.0	38.0
Min-Max	12 – 74	12 - 67	12 - 74
Gender, n (%)			
Female	286 (69.1)	66 (60.0)	352 (67.2)
Male	128 (30.9)	44 (40.0)	172 (32.8)
Race[1], n (%)			
White	341 (82.4)	97 (88.2)	438 (83.6)
Black or African American	63 (15.2)	14 (12.7)	77 (14.7)
Asian	13 (3.1)	1 (0.9)	14 (2.7)
American Indian or Alaskan Native	7 (1.7)	2 (1.8)	9 (1.7)
Native Hawaiian, other Pacific Islander	3 (0.7)	0	3 (0.6)
Other	1 (0.2)	0	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	45 (10.9)	12 (10.9)	57(10.9)
Not Hispanic, not Latino	369 (89.1)	98 (89.1)	467 (89.1)
BMI, kg/m^2			
Mean (SD)	28.8 (6.7)	28.4 (6.7)	28.7 (6.7)

1 A subject was allowed to choose more than one race type.
(BDP-AR-303 Study Report, page 72)

Medical history was generally similar in the two treatment groups and the types of conditions reported were those that might be expected in a PAR patient population such as sinus headache, asthma, drug hypersensitivity, sinusitis, etc. All subjects had a history of PAR and 57.4% of subjects (overall) also reported a history of SAR.

Prior to use of study drug, the most commonly reported medications in both treatment groups were those for the allergy and respiratory system (144 subjects, 61.0% in the BDP Nasal Aerosol 320 mcg/day group and 136 subjects, 57.1% in the placebo group). There were no appreciable differences between the two treatment groups. During the study, the most commonly used medications were those for the allergy, alimentary, musculoskeletal system and nervous system, including loratadine, tropicamine, ibuprofen, phenylephrine, albuterol, Advil, fish oil, vitamin C, aspirin, etc. There were no clinically important differences between treatment groups in concomitant medication use.

Treatment compliance

Treatment compliance was assessed by use of a subject-completed e-diary. Mean compliance rates based on the subject diary were approximately 85% in each treatment

group for all subjects. Twenty-seven subjects (6.5%) in the BDP Nasal Aerosol 320 mcg group and 6 subjects (5.4%) in the placebo group had compliance rates <60%. Mean compliance rates were good in both the 30-week and 52-week Treatment Period, although rates for subjects randomized to the 30-week Treatment Period (87.9% for BDP Nasal Aerosol 320 mcg/day and 86.0% for placebo) were slightly higher than those for subjects randomized to the 52-week Treatment Period (83.2% for BDP Nasal Aerosol 320 mcg/day and 85.1% for placebo).

Efficacy Results

The primary outcome of this study was the long term safety measures. The efficacy measures were taken in this long term study primarily for the purpose of compliance monitoring.

Primary efficacy endpoint

The primary efficacy measure was the change from baseline in the subject-reported 24-hour rTNSS over the first 30 weeks of the Treatment Period. The primary efficacy analysis was summarized in Table 36 below. At baseline, the means of the average 24-hour subject-reported rTNSS were comparable in the two treatment groups (9.2 for BDP Nasal Aerosol 320 mcg/day and 9.4 for the placebo). Over the 30-week Treatment Period, the LS mean (SE) change from baseline was -3.4 (0.11) for BDP Nasal Aerosol 320 mcg/day group and -2.4 (0.22) for the placebo group. The LS mean treatment difference of -0.97 between BDP Nasal Aerosol 320 mcg/day and placebo was statistically significant (p<0.001) in favor of BDP Nasal Aerosol 320 mcg/day.

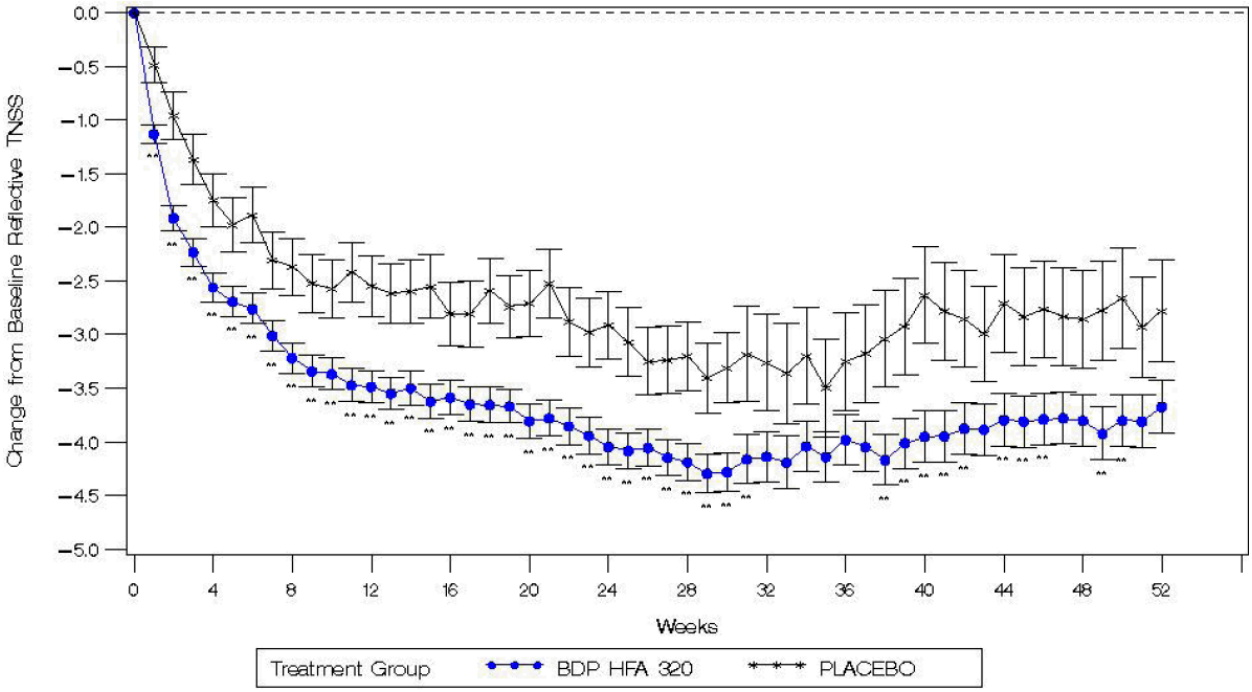
Table 36 Primary efficacy (rTNSS over 30 weeks) analysis, Study BDP-AR-303

Statistic	BDP HFA320 mcg/day N = 414	Placebo N = 110
Baseline mean (SD)	9.2 (1.77)	9.4 (1.83)
First 30 weeks overall LS mean (SE) change from Baseline[1]	-3.4 (0.11)	-2.4 (0.22)
LS mean treatment difference from placebo	-0.97	
95% CI	(-1.5, -0.5)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-303 Study Report, page 77)

The weekly changes in average 24-hour rTNSS from baseline over time for the BDP Nasal Aerosol 320 mcg/day and placebo groups are shown graphically in Figure 4 below. Improvements in subject-reported 24-hour rTNSS were seen from Week 1 in both treatment groups. The changes from baseline in the subject-reported rTNSS with BDP Nasal Aerosol 320 mcg/day were greater than for placebo from Week 1 onwards.

Figure 4 Change from baseline in 24-hour rTNSS, Study BDP-AR-303



(BDP-AR-303 Study Report, page 86)

Subgroup analyses based on gender (male, female), age (12-17 years, 18-64 years, 65 years and older), and race (white, black, other) were performed for the primary efficacy analysis. There were no significant differences found in subgroups per gender, age, and race. However, it was hard to draw conclusions from the subgroup analysis because of the small sample size of the subgroups.

Secondary efficacy endpoints

The secondary efficacy endpoints were the change from baseline in the average 24-hour subject-reported rTNSS over the 52-week Treatment Period, the change from baseline in the average 24-hour subject-reported iTNSS over the 30-week and 52-week Treatment Period, and RQLQ change at over the 30-week and 52-week Treatment Period.

Subject-Reported 24-Hour rTNSS over the 52 weeks

Results for the change from baseline in the subject-reported 24-hour rTNSS over 52 weeks of treatment were consistent with those observed for the primary efficacy endpoint (Table 37).

Table 37 Analysis of rTNSS over 52 weeks, Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 414	Placebo N = 110
Baseline mean (SD)	9.2 (1.77)	9.4 (1.83)
52 weeks overall LS mean (SE) change from Baseline[1]	-3.7 (0.12)	-2.6 (0.23)
LS mean treatment difference from placebo	-1.09	
95% CI	(-1.6, -0.6)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-303 Study Report, page 81)

Average 24-hour subject-reported iTNSS over the 30 and 52 weeks

Results for change from baseline in the average AM and PM subject-reported iTNSS over the 30-week and 52-week Treatment Period were consistent with those observed for the primary efficacy endpoint (Table 38, Table 39).

Table 38 Analysis of iTNSS over 30 weeks, Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 414	Placebo N = 110
Baseline mean (SD)	7.7 (2.16)	8.0 (2.27)
Overall LS mean (SE) change from Baseline[1]	-2.9 (0.11)	-2.0 (0.21)
LS mean treatment difference from placebo	-0.96	
95% CI	(-1.4, -0.5)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-303 Study Report, page 79)

Table 39 Analysis of iTNSS over 52 weeks, Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 414	Placebo N = 110
Baseline mean (SD)	7.7 (2.16)	8.0 (2.27)
52 weeks overall LS mean (SE) change from Baseline[1]	-3.1 (0.11)	-2.0 (0.22)
LS mean treatment difference from placebo	-1.10	
95% CI	(-1.6, -0.6)	
p-value	<0.001*	

1 Results from repeated measures ANCOVA over the treatment period.
* Statistically significant.
(BDP-AR-303 Study Report, page 83)

RQLQ

As summarized in Table 40 for the RQLQ population, baseline RQLQ scores were similar across the two treatment groups. Over the treatment of 30 weeks and 52 weeks, improvements in RQLQ score were seen in both treatment groups. Although the differences in RQLQ decrease in 2 treatment groups were not statistically significant, the BDP Nasal Aerosol 320 mcg group had a numerically larger decrease in the average RQLQ score.

Table 40 Analysis of RQLQ, Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 222	Placebo N = 59
Week 30		
Baseline mean (SD)	4.2 (0.75)	3.9 (0.79)
LS Mean (SE) change from Baseline at Week 30	-2.2 (0.09)	-1.9 (0.19)
LS Mean treatment difference from placebo	-0.30	
95% CI	(-0.7, 0.1)	
p-value	0.143	
Week 52		
Baseline mean (SD)	4.1 (0.70)	4.1 (0.82)
LS Mean (SE) change from Baseline at Week 52	-2.0 (0.14)	-1.5 (0.30)
LS Mean treatment difference from placebo	-0.49	
95% CI	(-1.1, 0.1)	
p-value	0.130	

(BDP-AR-303 Study Report, page 85)

The RQLQ analyses were also performed using the ITT population. Similar results were seen as for the RQLQ population. For the ITT population, the LS mean treatment difference between BDP HFA 320 mcg/day and placebo at Week 30 was -0.24 (95% CI: -0.5, 0.0; p=0.100), and at Week 52 was -0.27 (95% CI: -0.7, 0.1; p=0.198). For the PP population the LS mean treatment difference was -0.14 (95% CI: -0.4, 0.2; p=0.361) at Week 30 and was -0.20 (95% CI: -0.6, 0.2; p=0.359) at Week 52.

Safety Monitoring

Extent of exposure

The actual mean exposure to study medication was similar for the two treatment groups. For subjects randomized to the 30-week Treatment Period, mean (SD) exposures were 190 (51) days in the BDP Nasal Aerosol 320 mcg/day group and 194

(46) days in the placebo group. For subjects randomized to the 52-week Treatment Period, mean (SD) exposure was some what longer for subjects randomized to BDP Nasal Aerosol 320 mcg/day (311 days, SD=110) than for subjects randomized to placebo (286 days, SD=128). The median exposure for subjects randomized to the 52-week Treatment Period was 365 days for both treatment groups. Overall, 352 subjects were treated with BDP Nasal Aerosol 320 mcg/day for more than 180 days (6 months) and 169 subjects were treated with BDP Nasal Aerosol 320 mcg/day for more than 360 days (approximately 1 year).

Adverse events

Of the 526 subjects who were randomized to study treatment (safety population), 349 (66.3%) experienced adverse events: 283 subjects (68.2%) receiving BDP Nasal Aerosol 320 mcg/day, and 66 subjects (59.5%) receiving placebo. Along with the longer treatment duration, a higher proportion (71.1%) of the 277 subjects participating in the 52-week Treatment Period experienced an AE than that of the 249 subjects participating in the 30-week Treatment Period (61.0%). The intensity of AEs was assessed by the investigator as being either mild (an AE was easily tolerated), moderate (an AE discomforting to interfere with daily activity), or severe (an AE preventing normal daily activity). The majority of AEs were of mild or moderate intensity. Table 41 presents an overview of treatment-emergent AEs with an incidence of 2% or more in either group in Study BDP-AR-303.

Table 41 Adverse events with incidence of 2% or more in Study BDP-AR-303

Adverse Event	BDP HFA 320 mcg N = 415	Placebo N = 111
	Subject n (%)	Subject n (%)
Any AE	283 (68.2)	66 (59.5)
Nasopharyngitis	67 (16.1)	14 (12.6)
Epistaxis	44 (10.6)	2 (1.8)
Upper respiratory tract infection	43 (10.4)	7 (6.3)
Sinusitis	34 (8.2)	8 (7.2)
Headache	28 (6.7)	6 (5.4)
Sinus headache	15 (3.6)	2 (1.8)
Oropharyngeal pain	14 (3.4)	2 (1.8)
Bronchitis	13 (3.1)	4 (3.6)
Nasal discomfort	12 (2.9)	2 (1.8)
Urinary tract infection	11 (2.7)	4 (3.6)
Gastroenteritis viral	10 (2.4)	4 (3.6)
Acute sinusitis	9 (2.2)	6 (5.4)
Cough	9 (2.2)	5 (4.5)
Viral upper respiratory tract infection	9 (2.2)	2 (1.8)
Back pain	8 (1.9)	3 (2.7)
Rhinorrhoea	7 (1.7)	3 (2.7)
Sneezing	4 (1.0)	3 (2.7)
Arthralgia	3 (0.7)	5 (4.5)
Influenza	3 (0.7)	4 (3.6)

(BDP-AR-303 Study Report, page 108)

The commonly reported AEs were local nasal adverse events. Because in the original study report the local AEs were categorized inconsistently, the Applicant submitted a Safety Information Amendment (Table 42) on Feb. 7, 2012, upon the Division's request. Note there was one nasal ulceration reported in the BDP Nasal Aerosol 320 mcg/day group, which was described as "right anterior nasal septal mucosal ulceration with espoded cartilage" 125 days after starting the treatment, and withdrawn from the study. The ulceration was treated with Bactroban ointment and resolved 37 days after treatment was discontinued. There were also 4 nasal erosions, which might progress to early mild ulcerations, reported in the BDP Nasal Aerosol 320 mcg/day group. There were no reports of nasal septum perforation. The most commonly reported AEs in the

BDP Nasal Aerosol 320 mcg/day group were epistaxis (10.8%) and irritation (4.3%). It is noted that the BDP Nasal Aerosol 320 mcg/day group had a significantly higher incidence of epistaxis (10.6%) than that of the placebo group (1.8%). Epistaxis tended to be more severe in patients treated with BDP Nasal Aerosol 320 mcg/day. Of epistaxis that occurred in patients treated with BDP Nasal Aerosol 320 mcg/day, 27, 12, and 6 cases were of mild, moderate, and severe intensity, respectively. In contrast, 2 epistaxis cases in patients treated with placebo were of mild (1) and moderate (1) intensity. The BDP Nasal Aerosol 320 mcg/day group also had a higher incidence of overall nasal adverse events (19.8%) than that of the placebo group (13.5%).

Table 42 Summary of nasal adverse events, BDP-AR-303

Term	320 mcg N=415 n (%)	PLACEBO N=111 n (%)	Total N=526 n (%)
NASAL MUCOSAL/SEPTUM DISORDERS	82(19.8)	15(13.5)	97(18.4)
Erosions/Ulcerations	5(1.2)	0(0.0)	5(1.0)
Erosion	4(1.0)	0(0.0)	4(0.8)
Ulceration	1(0.2)	0(0.0)	1(0.2)
Non-Ulcerative Lesions	22(5.3)	4(3.6)	26(4.9)
Abrasion/Excoriation/Scabs	5(1.2)	1(0.9)	6(1.1)
Irritation	18(4.3)	3(2.7)	21(4.0)
Other	67(16.1)	11(9.9)	78(14.8)
Epistaxis	45(10.8)	2(1.8)	47(8.9)
Facial Bones Fracture	0(0.0)	1(0.9)	1(0.2)
Infection	1(0.2)	0(0.0)	1(0.2)
Nasal Congestion	2(0.5)	0(0.0)	2(0.4)
Nasal Discharge	3(0.7)	1(0.9)	4(0.8)
Nasal Discomfort	2(0.5)	1(0.9)	3(0.6)
Nasal Dryness	1(0.2)	0(0.0)	1(0.2)
Nasal Edema	5(1.2)	1(0.9)	6(1.1)
Nasal Mucosal Colouration	3(0.7)	0(0.0)	3(0.6)
Rhinitis Allergic	2(0.5)	1(0.9)	3(0.6)
Rhinitis Medicamentosa	1(0.2)	0(0.0)	1(0.2)
Rhinitis Perennial	1(0.2)	2(1.8)	3(0.6)
Rhinitis Seasonal	1(0.2)	0(0.0)	1(0.2)
Rhinorrhea	3(0.7)	1(0.9)	4(0.8)
Rhinorrhoea	4(1.0)	2(1.8)	6(1.1)
Sinus Congestion	1(0.2)	0(0.0)	1(0.2)
Sneezing	4(1.0)	3(2.7)	7(1.3)
Squamous Cell Carcinoma	1(0.2)	0(0.0)	1(0.2)

(NDA 202813, Safety Information Amendment, Feb. 7, 2012)

Adverse events were reviewed for events that might be indicative of a systemic corticosteroid effect. One subject in the BDP Nasal Aerosol 320 mcg/day group was reported as experiencing adrenal insufficiency of moderate intensity as a preliminary diagnosis. After further medical evaluation, the diagnosis was revised to idiopathic

hypothyroidism, and the subject's condition improved with the Cytomel treatment. The subject was discontinued from the study due to non-compliance (not due to the AE).

Deaths, serious adverse events, and events leading to withdrawal

No deaths occurred during the study.

A total of 11 subjects experienced SAEs (8 subjects, 1.9%, treated with BDP Nasal Aerosol 320 mcg/day and 3 subjects, 2.7%, treated with placebo). There were 3 SAEs leading to early discontinuation of the study, and all the 3 cases were in the BDP Nasal Aerosol 320 mcg/day group. Only one SAE, increased intraocular pressure experienced by a subject treated with BDP Nasal Aerosol 320 mcg/day, was considered by the investigator to be possibly related to study treatment. This subject was discontinued from the study due to the SAE. Intraocular pressure measurements returned to baseline values following iridotomy treatment. The other two SAEs that led to premature discontinuation were two cases of colon cancer in the BDP Nasal Aerosol 320 mcg/day group. Also, 2 subjects in the BDP Nasal Aerosol 320 mcg/day group had SAEs that were unresolved at the end of the study (squamous cell carcinoma, and humerus fracture/rotator cuff syndrome). Table 43 summarizes SAEs reported in the long term safety study.

Table 43 SAEs reported in Study BDP-AR-303

Subject	Age and Gender	SAE (Preferred Term)	Intensity	Study Drug Related?[1] (Yes/No)	Onset (days)	Outcome
BDP HFA 320 mcg/day						
32803006	37, F	Nephrolithiasis	Severe	No	164	Recovered
33383012	45, F	Intraocular pressure increased	Severe	Yes	211	Recovered
34533001	40, F	Colon cancer	Severe	No	10	Recovered
34533021	40, F	Bladder injury	Moderate	No	198	Recovered
		Menorrhagia	Severe	No	198	Recovered
		Pelvic adhesions	Severe	No	198	Recovered
37033001	29, M	Pneumothorax	Severe	No	70	Recovered
37153006	50, F	Colon cancer	Severe	No	57	Recovered
37283005	55, F	Squamous cell carcinoma	Moderate	No	301	Unresolved[2]
37283006	62, F	Fall	Moderate	No	363	Recovered
		Humerus fracture	Moderate	No	363	Unresolved[2]
		Rotator cuff syndrome	Moderate	No	363	Unresolved[2]
Placebo						
33043009	33, F	Ovarian cyst	Mild	No	69	Recovered
33383005	48, M	Arthralgia	Severe	No	101	Recovered
37113007	19, F	Viral infection	Moderate	No	67	Recovered

1 Relationship to study drug determined by the investigator
2 Unresolved at the time of this report
(BDP-AR-303 Study Report, page 115)

There were 20 subjects with treatment-emergent AEs that led to discontinuation from the study, 17 subjects (4.1%) in the BDP Nasal Aerosol 320 mcg/day group and 3 subjects (2.7%) in the placebo group. The AE that most commonly led to study discontinuation was epistaxis, reported in 5 subjects in the BDP Nasal Aerosol 320 mcg/day group and no subject in the placebo group. In addition to 3 SAEs leading to study discontinuation, the other AEs leading to study discontinuation in the BDP Nasal Aerosol 320 mcg/day group were nasal septum ulceration (1), nasal discomfort (2), sinusitis (2), nasal congestion (1), headache (1), and nasal mucosal disorder (1). The 3 AEs leading to study discontinuation in the placebo group were sinusitis (2) and nasal discomfort (1).

Clinical laboratory evaluation
No clinical laboratory evaluations were made in this study.

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

ENT examinations
Results of ENT examinations for the BDP Nasal Aerosol 320 mcg/day group and for the placebo group were similar at each clinic visit for all subjects, including subjects randomized to the 30-week Treatment Period and subjects randomized to the 52-week Treatment Period.

Ocular assessments
All evaluations of ocular safety were made using the ocular safety population. This was a subset of the safety population that only included subjects randomized to the 52-week Treatment Period who underwent at least one post-baseline assessment related to ocular safety.

Best Corrected Visual Acuity (BCVA)
BCVA (unrefracted and, as appropriate, refracted) was measured using a LogMAR (logarithm of the minimum angle of resolution) Visual Acuity Chart or its equivalent by a certified ophthalmologist. A negative change in LogMAR represents an improvement in BCVA.

BCVA at Baseline, Week 30 and Week 52 are summarized in Table 44. At Baseline, for the average of both eyes, the mean BCVA was logMAR -0.030 in the BDP Nasal Aerosol 320 mcg/day group and logMAR -0.041 in the placebo group. Only small changes from Baseline were seen at Week 30 or Week 52 in each treatment group. At Week 30 in the BDP Nasal Aerosol 320 mcg/day group, the LS mean change was logMAR 0.004 and in the placebo group the LS mean change was logMAR -0.005. At Week 52, the LS mean change from Baseline was logMAR -0.002 for BDP Nasal Aerosol 320 mcg/day and logMAR -0.014 for placebo. The estimated treatment difference was logMAR 0.008 (p=0.414) at Week 30 and logMAR 0.012 (p=0.222) at Week 52. The 95% CIs for the observed differences between treatments at Week 30 and Week 52 included zero, and no BCVA changes were clinically meaningful.

There was one AE of visual impairment of mild intensity reported in a subject treated with BDP Nasal Aerosol 320 mcg/day. The subject was referred to an ophthalmologist for prescription of new corrective lenses. This AE was not considered to be related to study treatment by the investigator.

Table 44 Summary of Best Corrected Visual Acuity (average of both eyes), Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 197	Placebo N = 48
Baseline[1] mean (SD)	-0.030 (0.0937)	-0.041 (0.0944)
Week 30 LS mean (SE) change from Baseline[1]	0.004 (0.0051)	-0.005 (0.0091)
LS mean treatment difference from placebo	0.008	
95% CI	(-0.012, 0.028)	
p-value	0.414	
Week 52 LS mean (SE) change from Baseline[1]	-0.002 (0.0049)	-0.014 (0.0087)
LS mean treatment difference from placebo	0.012	
95% CI	(-0.007, 0.031)	
p-value	0.222	

1 Baseline was taken at the screening visit.
(BDP-AR-303 Study Report, page 136)

Intraocular Pressure (IOP)

Intraocular pressure measurements are summarized in Table 45. Generally, a value of ≥21 mmHg is considered as an abnormal eye pressure. At Baseline, for the average of both eyes, mean IOP measurements were similar in the two treatment groups (15.036 mmHg for BDP Nasal Aerosol 320 mcg/day and 14.990 mmHg for placebo). Small decreases in mean IOP were observed at Week 30 (LS mean change of -0.429 mmHg for BDP Nasal Aerosol 320 mcg/day and -0.711 mmHg for placebo) and at Week 52 (LS mean change of -0.251 mmHg for BDP Nasal Aerosol 320 mcg/day and -0.497 mmHg for placebo). The estimated mean treatment difference was 0.282 mmHg (p=0.433) at Week 30 and 0.246 mmHg (p=0.451) at Week 52. The 95% CIs for the observed differences between treatments at Week 30 and Week 52 included zero, and IOP changes were not statistically significant and clinically meaningful.

Adverse events of increased intraocular pressure were reported for 2 subjects, both treated with BDP Nasal Aerosol 320 mcg/day. The increased intraocular pressure was of moderate intensity for one subject (Subject 33383021) and of severe intensity and reported as an SAE for the other (Subject 33383012). Both cases occurred in the same investigator site. Subject 33383012 was a 45-year-old female who had baseline IOP values of 20 and 20 mmHg in left and right eye. This subject was found to have elevated IOP of 32 and 33 mmHg at TV6 (week 30). A recheck of her pressures confirmed the elevated values (30 mmHg in each eye) and the persistently raised IOP was reported as an SAE. The subject was withdrawn from the study. The subject underwent peripheral iridotomy of both eyes, and a subsequent rechecks showed that pressures were normal at 17 and 20 mmHg. Subject 33383021 was a 17-year- male

who had baseline IOP values of 20 mmHg in the right eye and 19 mmHg in the left eye. This subject was found to have elevated intraocular pressures at TV6 (week 30). He was not discontinued from treatment with BDP Nasal Aerosol 320 mcg/day because of the mild increase of IOP values (22 and 26 mmHg). Follow-up measurements made 3 weeks later were similar to Baseline values (20 and 19 mmHg). Subsequent IOP measurements confirmed that similar or lower IOP throughout the rest of the 52-week treatment period.

Table 45 Summary of Intraocular Pressure (mmHg, average of both eyes), Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 197	Placebo N = 48
Baseline[1] mean (SD)	15.036 (2.8019)	14.990 (3.6122)
Week 30		
LS mean (SE) change from Baseline[1]	-0.429 (0.1806)	-0.711 (0.3230)
LS mean treatment difference from placebo	0.282	
95% CI	(-0.425, 0.988)	
p-value	0.433	
Week 52		
LS mean (SE) change from Baseline[1]	-0.251 (0.1634)	-0.497 (0.2934)
LS mean treatment difference from placebo	0.246	
95% CI	(-0.396, 0.888)	
p-value	0.451	

1 Baseline was taken at the screening visit. (BDP-AR-303 Study Report, page 137)

Although only 2 cases of increased IOP were reported as AEs, there were 26 subjects (15 subjects, 7.6%, in BDP HFA 320 mcg/day group and 11 subjects, 22.9%, in placebo group) who had IOP values ≥21 mmHg on either left or right eye at screening (SV), week-30 (TV6), or week-52 (TV10) measurement (Table 46). Of these, 14 subjects (12 subjects, 6.1%, with BDP HFA 320 mcg and 2 subjects, 4.2%, treated with placebo) had IOP values ≥21 mmHg in the treatment period of the study. Most subjects had IOP of 21 or 22 mmHg. Except for the 2 cases reported as AEs, only two subjects (Subject 33383024 with BDP Nasal Aerosol 320 mcg and Subject 33383025 with placebo) had IOP values above 22 mmHg in the treatment period of the study.

Table 46 Subjects with IOP measurement ≥21 mmHg during the study

Subject	SV		TV6		TV10	
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye
BDP HFA 320 mcg/day						
33103015	22	21	20	22	20	19
33103016	15	21	20	19	17	20
33383012[1,5]	20	20	32	33	-	-
33383019[5]	21	20	17	19	20	21
33383021[1,5]	20	19	22	26	16	16
33383024[2,5]	21	16	24	23	22	22
33383026[5]	20	18	18	18	21	22
37113001	20	21	17	19	22	22
37123048	24	24	13	15	17	15
37283011	20	21	18	18	20	21
37713010[5]	17	17	-	-	14	21
37713017[3,5]	20	19	21	22	18	19
37713022[4,5]	18	20	22	22	19	19
37713041[5]	18	20	21	21	18	19
37713049[5]	21	18	17	16	16	16
Placebo						
33103011	21	21	21	21	16	18
33833005[5]	19	21	15	14	16	17
33383025[5]	17	19	17	19	22	23
37123011	22	21	17	17	17	17
37123042	21	21	15	16	16	18
37283009	20	21	19	18	18	18
37713004[5]	22	22	19	19	16	15
37713015[5]	21	20	20	20	-	-
37713024[5]	20	22	-	-	-	-
37713037[5]	21	21	-	-	-	-
37713055[5]	21	18	12	13	13	12

[1] Reported as AE
[2] 23 and 23 mmHg recorded approximately 3 months after the study
[3] 17 and 16 mmHg recorded approximately 3 months after the study
[4] 14 and 16 mmHg recorded approximately 1 month after the study
[5] 17 subjects who showed elevated IOP values were randomized at two investigative sites (3338 or 3771)
(BDP-AR-303 Study Report, page 139)

Lens Opacities Classification System III (LOCS III)
LOCS III provides a grading of nuclear opalescence (NO), nuclear color (NC), cortical (C) and posterior subcapsular (P) lens opacities after maximal pupillary dilatation has been achieved. The LOCS III scales are decimalized numbers ranging from 0.1 (representing a clear or colorless lens) to 5.9 (on the C and P scales) or 6.9 on the NO and NC scales. The higher numbers represent advanced stages of opacification or coloration. The increases in LOCS III scores used to define LOCS III Class I, II and III were described in
below. The Class I includes all Class II and III changes and Class II changes include all Class III changes. A positive shift (increase) in LOCS III grading score indicated a deterioration or worsening in lenticular opacities.

Table 47 Definitions of LOCS III grading classes

Type	Increase in LOCS III Scores (in at Least One Category in Either Eye)			Additional Criteria
	NO	C	P	
Class I*	≥0.5	≥0.8	≥0.5	-
Class II*	≥0.9	≥1.5	≥0.9	-
Class III*	≥0.9	≥1.5	≥0.9	LOCS III grade of ≥2.0 for any type of opacity (NO, P and C)

* Cataract surgery was recorded as a shift for every class.

LOCS III assessments for NO, NC, C and P are presented in Table 48. At Baseline, for the average of both eyes, mean results were similar in the two treatment groups for NO, C and P (NO: 1.372 for BDP Nasal Aerosol 320 mcg/day and 1.289 for placebo; C: 0.189 for BDP Nasal Aerosol 320 mcg/day and 0.195 for placebo; P: 0.114 for BDP Nasal Aerosol 320 mcg/day and 0.125 for placebo). Values for NC were slightly higher in the BDP Nasal Aerosol 320 mcg/day group (1.005) than in the placebo group (0.730). Only small and non-significant changes from Baseline were observed in both treatment groups over 30 and 52 weeks of treatment for all four components of LOCS III.

Table 48 LOCS III assessment (average of both eyes), Study BDP-AR-303

Statistic	BDP HFA 320 mcg/day N = 197	Placebo N = 48
Nuclear Opalescence		
Baseline[1] mean (SD)	1.372 (0.7365)	1.289 (0.6499)
Week 30		
LS mean (SE) change from Baseline[1]	-0.040 (0.0254)	-0.046 (0.0456)
LS mean treatment difference from placebo	0.006	
95% CI	(-0.094, 0.106)	
p-value	0.904	
Week 52		
LS mean (SE) change from Baseline[1]	0.020 (0.0264)	0.041 (0.0471)
LS mean treatment difference from placebo	-0.021	
95% CI	(-0.124, 0.082)	
p-value	0.684	
Nuclear Color		
Baseline[1] mean (SD)	1.005 (0.7038)	0.730 (0.5900)
Week 30		
LS mean (SE) change from Baseline[1]	-0.031 (0.0239)	-0.067 (0.0439)
LS mean treatment difference from placebo	0.036	
95% CI	(-0.059, 0.131)	
p-value	0.459	
Week 52		
LS mean (SE) change from Baseline[1]	0.049 (0.0265)	-0.008 (0.0479)
LS mean treatment difference from placebo	0.057	
95% CI	(-0.047, 0.162)	
p-value	0.282	
Cortical Opacity		
Baseline[1] mean (SD)	0.189 (0.2069)	0.195 (0.1635)
Week 30		
LS mean (SE) change from Baseline[1]	-0.006 (0.0119)	0.026 (0.0214)
LS mean treatment difference from placebo	-0.031	
95% CI	(-0.078, 0.015)	
p-value	0.187	
Week 52		
LS mean (SE) change from Baseline[1]	0.013 (0.0159)	0.024 (0.0284)
LS mean treatment difference from placebo	-0.010	
95% CI	(-0.073, 0.052)	
p-value	0.743	
Posterior Subcapsular Opacity		
Baseline[1] mean (SD)	0.114 (0.0555)	0.125 (0.1189)
Week 30		
LS mean (SE) change from Baseline[1]	-0.000 (0.0035)	0.011 (0.0063)
LS mean treatment difference from placebo	-0.011	
95% CI	(-0.025, 0.003)	
p-value	0.124	
Week 52		
LS mean (SE) change from Baseline[1]	0.003 (0.0030)	0.000 (0.0054)
LS mean treatment difference from placebo	0.003	
95% CI	(-0.009, 0.015)	
p-value	0.655	

1 Baseline was taken at the screening visit. (BDP-AR-303 Study Report, pages 142-143)

The majority of subjects in both treatment groups had no change in LOCS III grading of opacities at both Week 30 (92.7% for BDP HFA 320 mcg/day and 95.3% for placebo) and Week 52 (87.8% for BDP HFA 320 mcg/day and 91.1% for placebo. At Week 30, 7.3% of subjects in the BDP HFA 320 mcg/day group and 4.7% of subjects in the placebo group had a Class I shift and 1.7% and 2.3%, respectively had a Class II shift. At Week 52, 12.2% of subjects in the BDP HFA 320 mcg/day group and 8.9% of subjects in the placebo group had a Class I shift and 4.3% and 2.2%, respectively, had a Class II shift. A few subjects (2 subjects at Week 30 and 6 subjects at Week 52) had a Class III increase and the proportion of subjects with such an increase was similar in the two treatment groups (at Week 30, 0.6% versus 2.3% and at Week 52, 2.7% versus 2.2% for BDP HFA 320 mcg/day and placebo, respectively). Figure 5 and Figure 6 demonstrated the percentage of subjects with LOCS III class shift at week 30 and 52.

There were no reports of development of cataracts during the study.

Figure 5 Percentage of subjects with LOCS III class shift in either eye at week 30

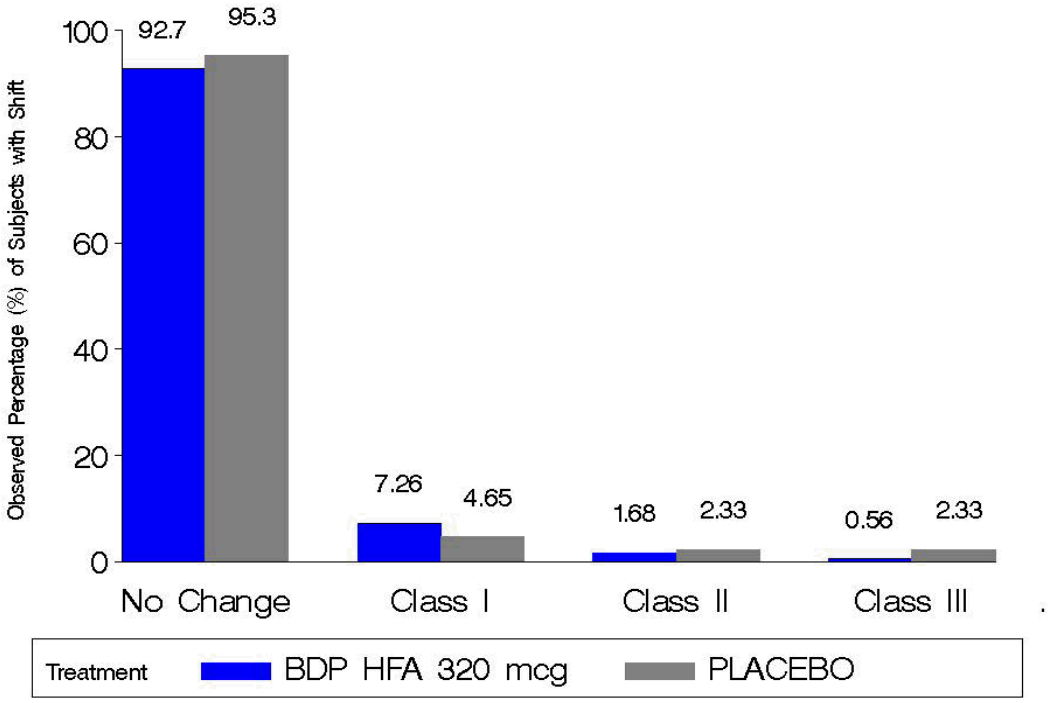
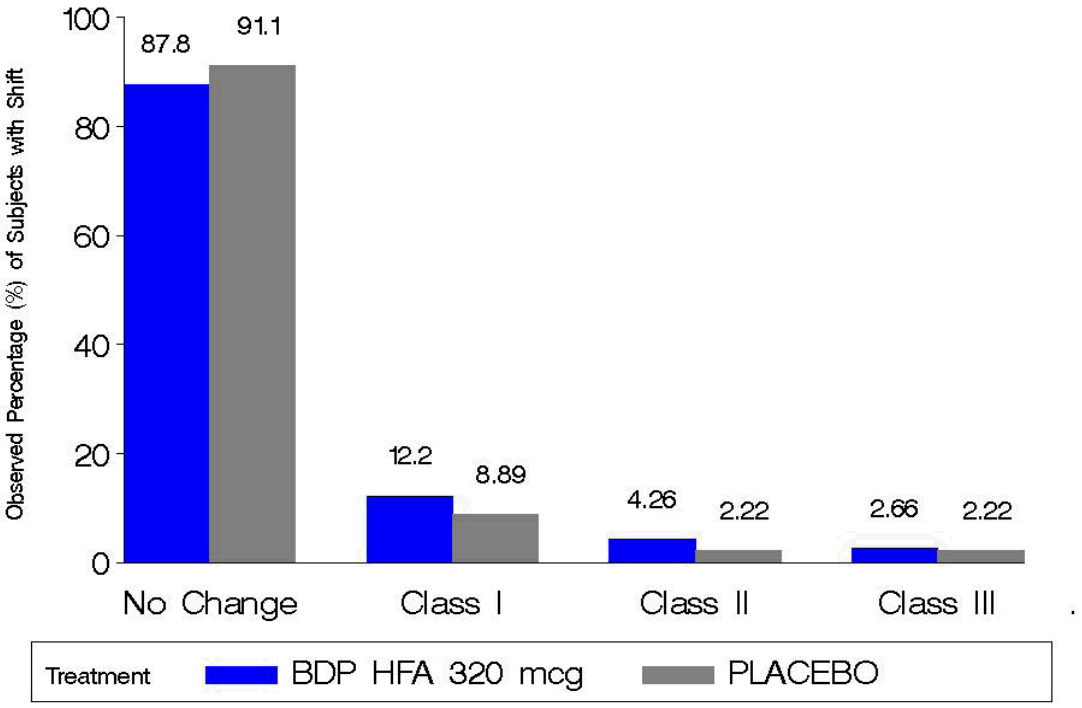


Figure 6 Percentage of subjects with LOCS III class shift in either eye at week 52



Reviewer's comments:
There were no clinically important differences between the BDP Nasal Aerosol 320 mcg/day treatment and placebo in mean best-corrected visual acuity and LOCS III assessments for lens opacities (including nuclear opalescence, nuclear color, cortical opacity, and posterior subcapsular opacity).

Although there were 26 subjects (15 subjects, 7.6%, treated with BDP HFA 320 mcg/day and 11 subjects, 22.9%, treated with placebo) who had IOP values ≥21 mmHg on either left or right eye at screening, week-30, or week-52 measurement, there were 4 cases of IOP above 22 mmHg after receiving the treatment (3 with BDP Nasal Aerosol 320 mcg/day and one with placebo). The isolated cases of IOP change did not reveal a new safety signal. .

5.3.5 Study BDP-AR-304

A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, 6-Week Study to Investigate the Effects of BDP HFA Nasal Aerosol on the Hypothalamic-Pituitary- Adrenal (HPA) Axis when Administered in Adolescent and Adult Subjects (12 to 45 Years of Age) with Perennial Allergic Rhinitis (PAR)

PROTOCOL

Administrative
Study initiated: June 07, 2010
Study completed: September 04, 2010
Clinical Centers: 3 clinical centers in TX and MA participated in the study
Study report dated: January 25, 2011
Study Sponsor: TEVA Branded Pharmaceutical Products R&D, Inc.
Medical Officer: Paul H. Ratner, M.D.

Objective
To compare the effect of 6 weeks of treatment with BDP Nasal Aerosol versus placebo on HPA-axis function, as assessed by 24-hour serum cortisol weighted mean, in subjects 12 to 45 years of age with PAR and to compare the effect of 7 days of treatment with the active-control, prednisone, versus placebo on HPA-axis function, as assessed by 24-hour serum cortisol weighted mean, in subjects 12 to 45 years of age with PAR

Study Design
This was a Phase 3, randomized, double-blind, placebo- and active (prednisone)-controlled, parallel-group study in male or female subjects (12 to 45 years of age) with PAR. Each subject participated in the study for approximately 9 weeks. The study consisted of 3 periods: Run-in Period (7-14 days from Screening Visit, SV, to Randomization Visit, RV), Treatment Period (42 days from Randomization Visit, RV, to Treatment Visit TV4) and a follow-up period (7 days from Treatment Visit 4 to Final Visit, FV). Each subject completed screening visit, five treatment visits (RV, TV1, TV2, TV3 and TV4), a Post-Treatment Visit (PTV), and a Final Visit (FV). There were two domiciled, inpatient clinic visits during the study; a 2-day/2-night inpatient clinic visit at the end of the Run-In Period and a 2-day/2-night inpatient clinic visit at the end of the Treatment Period. During the Run-in Period, subjects self-administered a single-blind placebo nasal aerosol once daily in the morning. Subjects were domiciled before randomization on Day 2 through Day 1 for pharmacodynamic measurements of HPA-axis function. During the Treatment Period (Visits RV through TV4), subjects were randomly assigned to one of the three double-blind treatment arms (BDP Nasal Aerosol 320 mcg/day, placebo, or placebo/prednisone 10 mg/day). The randomization was in a 4:4:1 ratio for BDP Nasal Aerosol, placebo, and placebo plus prednisone. During the Treatment Period, subjects self-administered the double-blinded nasal aerosol (BDP Nasal Aerosol or placebo) once daily in the morning for 6 weeks (42 days) and also took a double-blind capsule (prednisone or placebo) once daily during the last 7 days of the Treatment Period. Subjects were domiciled at the end of the Treatment Period (Day 41 through Day 43) for pharmacodynamic measurements of HPA-axis function and pharmacokinetic measurements of BDP and beclomethasone-17-monopropionate (17-BMP). The primary pharmacodynamic variable was the 24-hour serum cortisol weighted mean for BDP Nasal Aerosol and placebo after 42 days of treatment. Safety

was monitored by physical examinations, ear, nose and throat (ENT) examinations, vital signs, electrocardiograms (ECGs), clinical laboratory assessments and adverse events (AEs).

This study was performed under a protocol that was similar to the protocol for Study BDP-AR-302, a 6-week efficacy and safety study of the BDP Nasal Aerosol 320 mcg/day in PAR, with the differences listed below.

Differences in protocol BDP-AR-304 comparing to protocol BDP-AR-302

- **Clinical visits and domiciles at clinical center**

Study subject completed screening visit, five treatment visits (RV, TV1, TV2, TV3 and TV4), a Post-Treatment Visit (PTV), and a Final Visit (FV). There were two domiciled, inpatient clinic visits during the study; a 2-day/2-night inpatient clinic visit at the end of the Run-In Period and a 2-day/2-night inpatient clinic visit at the end of the Treatment Period for pharmacodynamic measurements of HPA-axis function.

- **Treatment**

BDP Nasal Aerosol Nasal Aerosol – 80 mcg/actuation (Lot # 090403), and
Placebo HFA Nasal Aerosol – 0 mcg/actuation (Lot # 090528)

Prednisone 10 mg capsule (Lot# C1530109B), and
Placebo capsule (Lot# 70458461)

Treatment A: BDP Nasal Aerosol 320 mcg (a total of 4 intranasal actuations, 2 actuations per nostril) once daily for 6 weeks (42 days), plus a placebo capsule once daily during the last 7 days of the 6-week Treatment Period. This treatment group is referred to as BDP Nasal Aerosol 320 mcg/day.

Treatment B: Placebo nasal aerosol (2 actuations per nostril – total 4 actuations, once daily) for 6 weeks (42 days), plus a placebo capsule once daily during the last 7 days of the 6-week Treatment Period. This treatment group is referred to as placebo.

Treatment C: Placebo nasal aerosol (2 actuations per nostril – total 4 actuations, once daily) for 6 weeks (42 days) plus a capsule of 10 mg prednisone once daily during the last 7 days of the 6-week (42-day) Treatment Period. This treatment group is referred to as placebo/prednisone 10 mg/day.

- **Inclusion criteria**

Male or female subjects 12 to 45 years of age.

- **Sample size**

Based on the results from previous studies, the standard deviation for the change from baseline over 2 weeks in 24-hour serum cortisol weighted mean (0-24 hours) was

assumed to be 0.25. A sample size of 108 subjects was selected to ensure study completion of 90 subjects. The randomization was in a 4:4:1 ratio for BDP Nasal Aerosol, placebo, and placebo plus prednisone. Forty subjects per arm would provide at least 90% power to demonstrate the non-inferiority of BDP Nasal Aerosol 320 mcg/day to placebo. Non-inferiority would be demonstrated if the lower limit of a two-sided 95% CI for the geometric mean ratio of BDP Nasal Aerosol 320 mcg/day to placebo was greater than 0.80. This sample size also provided at least 90% power to detect a difference of 30% between placebo/prednisone 10 mg/day and placebo (expressed as a ratio) in 24-hour serum cortisol weighted mean.

- **Study outcomes**

There were no efficacy measures included in this study.

Blood samples of 6 mL for serum cortisol measurements were obtained at baseline (-24, -23, -22, -20, -18, -16, -14, -12, -8, -2, and 0 hours prior to study medication administration at RV (Study Day 1), and at Treatment Visit TV4 (Study Day 42) at pre-dose (hour 0) and 1, 2, 3, 4, 6, 8, 10, 12, 16, 22, and 24 hours after dose administration.

Blood samples of 6 mL for pharmacokinetic analysis of BDP and 17-BMP were obtained at Treatment Visit TV4 (Study Day 42) at pre-dose and at 0.08 (5 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 24 hours after dose administration.

RESULTS

Study Population

Disposition

A total of 139 subjects were screened for enrolment in the study. However, one additional subject number was entered in error, which reflected in the database as 140 subjects were screened. Of the screened subjects, 128 were enrolled in the study and participated in the Run-in Period. Of the 128 enrolled subjects, 107 met the randomization criteria and were randomized to treatment (50 were randomized to receive BDP Nasal Aerosol 320 mcg/day, and 46 were randomized to receive placebo, and 11 were randomized to receive placebo/prednisone 10 mg/day) (Table 49). All randomized subjects were included in the safety population. Eight subjects were discontinued prematurely and did not have a post-baseline pharmacodynamic assessment and so were excluded from the ITT population. Hence, 99 randomized subjects (49 treated with BDP Nasal Aerosol 320 mcg/day, 41 treated with placebo, and 9 treated with receive placebo/prednisone 10 mg/day) constituted the ITT population. There was one subject in the BDP Nasal Aerosol 320 mcg/day group excluded from the primary analysis as he started working night shifts during the study and so the per protocol (PP) population consisted of 98 subjects. The RQLQ population included only

those subjects with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit (TV0) of 3.0 or greater. The device completer population included only those subjects who had administered at least 80% of actuations during the last 4-week treatment period of this 6-week study.

Of 107 randomized subjects, 99 (92.5%) completed the study. There were 8 subjects (1 subject treated with BDP Nasal Aerosol 320 mcg/day, 5 subjects treated with placebo, and 2 subjects treated with placebo/prednisone 10 mg/day) who discontinued the study prematurely.

Table 49 Subject disposition, Study BDP-AR-304

Category	BDP HFA 320 mcg/day n (%)	Placebo n (%)	Placebo/ prednisone 10 mg/day n (%)	Overall n (%)
Randomized	50 (100)	46 (100)	11 (100)	107 (100)
Safety Population	50 (100)	46 (100)	11 (100)	107 (100)
ITT Population	49 (98.0)	41 (89.1)	9 (81.9)	99 (92.5)
PP Population	48 (96.0)	41 (89.1)	9 (81.9)	98 (91.6)
Completed	49 (98.0)	41 (89.1)	9 (81.9)	99 (92.5)
Prematurely Discontinued[1]	1 (2.0)	5 (10.9)	2 (18.2)	8 (7.5)
Adverse Event[2]	0	1 (2.2)	0	1 (0.9)
Withdrew Consent	1 (2.0)	2 (4.3)	2 (18.2)	5 (4.7)
Other[3]	0	2 (4.3)	0	2 (1.9)

(BDP-AR-304 Study Report, page 52)

As shown in Table 50 for the PP population, the majority of subjects in all groups were female (55.1%), white (88.8%) and not Hispanic or Latino (62.2%). The mean age of study subjects was 27.4 years and ranged from 12 to 45 years. Twenty-five subjects (25.5%) were 12 to 17 years of age in the PP population. Demographic characteristics were generally comparable in the treatment groups.

Table 50 Subject demographics, Study BDP-AR-304

Demographic	BDP HFA 320 mcg/day N = 48	Placebo N = 41	Placebo/ prednisone 10 mg/day N = 9	Total N = 98
Age (years)				
Mean (SD)	28.3 (10.0)	26.6 (10.6)	26.2 (11.9)	27.4 (10.4)
Median	31.0	25.0	26.0	26.5
Min-Max	12 - 45	12 - 45	12 - 45	12 - 45
Gender, n (%)				
Female	25 (52.1)	22 (53.7)	7 (77.8)	54 (55.1)
Male	23 (47.9)	19 (46.3)	2 (22.2)	44 (44.9)
Race, n (%)[1]				
White	42 (87.5)	38 (92.7)	7 (77.8)	87 (88.8)
Black or African American	7 (14.6)	2 (4.9)	1 (11.1)	10 (10.2)
Asian	1 (2.1)	0	0	1 (1.0)
American Indian or Alaskan Native	0	0	1 (11.1)	1 (1.0)
Other	0	1 (2.4)	0	1 (1.0)
Ethnicity, n (%)				
Hispanic or Latino	18 (37.5)	17 (41.5)	2 (22.2)	37 (37.8)
Not Hispanic, not Latino	30 (62.5)	24 (58.5)	7 (77.8)	61 (62.2)
BMI (kg/m^2)				
Mean (SD)	27.9 (7.9)	27.0 (6.2)	28.4 (7.9)	27.6 (7.2)

(BDP-AR-304 Study Report, page 54)

Medical history was generally similar in the three treatment groups and the types of conditions reported were those that might be expected in a PAR patient population such as sinus headache, asthma, drug hypersensitivity, sinusitis, etc. All subjects had a history of seasonal rhinitis and 78.5% of subjects also reported a history of SAR.

Prior to use of study drug, the most commonly reported medications in both treatment groups were those for the respiratory system (11 subjects, 22.0%, in the BDP Nasal Aerosol 320 mcg/day group; 9 subjects, 19.6%, in the placebo group; and 3 subjects, 27.3%, in the placebo/prednisone 10 mg/day group). There were no appreciable differences among the three treatment groups. During the study, the most commonly used medications were those for the alimentary, musculoskeletal system and nervous system, including multivitamins, ibuprofen, neproxen, salbutamol, paracetamol, etc. There were no clinically important differences among the treatment groups in concomitant medication use.

Treatment Compliance

Video monitoring was used as a daily treatment compliance assessment to record real-time dose administration. The video monitoring contractor contacted the subjects by appointment to conduct the dose observational sessions either using a video phone or webcam device. Mean compliance rates with the nasal aerosol based on video monitoring was at least 98% in each treatment group, and with the study capsules was at least 96% in each treatment group. No subjects had compliance rates lower than 80%.

Study Outcomes

Pharmacodynamic (HPA axis) Results

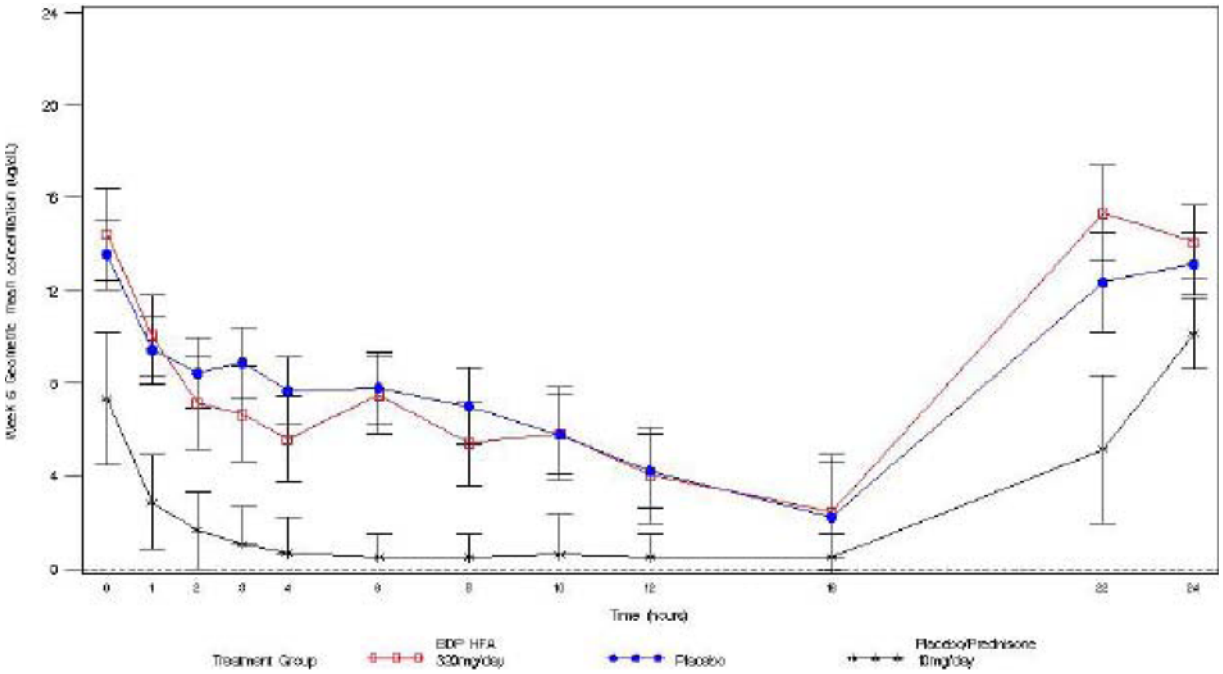
The primary analysis was the 24-hour serum cortisol weighted geometric mean for BDP Nasal Aerosol and placebo after 42 days of treatment in the PP population. Baseline serum cortisol weighted geometric mean values were similar in the BDP Nasal Aerosol 320 mcg/day and placebo treatment groups (9.04 and 8.45 mcg/dL, respectively). After 6 weeks of treatment the geometric geometric mean values were also similar (8.18 and 8.01 mcg/dL, respectively) and there was little change from baseline values in either treatment group. The ratio of Week 6/Baseline was 0.90 (95% CI: 0.83, 0.98) for BDP Nasal Aerosol 320 mcg/day group and 0.95 (95% CI: 0.89, 1.00) for placebo group. The geometric mean ratio for BDP Nasal Aerosol 320 mcg/day to placebo was 0.96 (95% CI: 0.87, 1.06). Thus, BDP Nasal Aerosol 320 mcg/day for 6 weeks did not cause a statistically significant lower 24-hour serum cortisol level. The secondary analysis compared the effect of placebo/prednisone 10 mg/day (active control) versus placebo on HPA-axis function as measured by 24-hour serum cortisol weighted mean. Mean baseline values were similar in the two treatment groups (8.45 mcg/dL for placebo and 7.33 mcg/dL for placebo/prednisone 10 mg/day). At Week 6, the geometric mean was, as expected, markedly lower in the placebo/prednisone 10 mg/day group (2.31 mcg/dL) than in the placebo group (8.01 mcg/dL). A marked decrease from Baseline was seen in the placebo/prednisone 10 mg/day group compared with the change from Baseline in the placebo group: the ratio of Week 6/Baseline was 0.31 (95% CI: 0.23, 0.43) for placebo/prednisone 10 mg/day and 0.95 (95% CI: 0.89, 1.00) for placebo. The geometric mean ratio for placebo to placebo/prednisone 10 mg/day was 3.17 (95% CI: 2.68, 3.74), indicating that placebo/prednisone 10 mg/day for 7 days resulted in an expected greater reduction in HPA-axis function compared with placebo (an approximate threefold reduction). Table 51 summarizes the serum cortisol level changes in 6 weeks by treatment groups. Figure 7 demonstrates that at Week 6, the 24-hour serum cortisol profile for BDP Nasal Aerosol 320 mcg/day was similar to that for the placebo. For the placebo/prednisone 10 mg/day group, mean serum cortisol concentrations at each time point were substantially lower than those observed in the other 2 groups following 7-days of prednisone 10 mg/day.

Table 51 Serum cortisol level (mcg/dL, log transformed) by treatment groups

Statistics	BDP HFA 320 mcg/day N=48	Placebo N=41	Placebo/prednisone 10 mg/day N=9
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)	7.33 (1.11)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)	2.31 (1.20)
Week 6/Baseline ratio (SE)	0.90 (1.04)	0.95 (1.03)	0.31 (1.14)
Ratio of BDP to Placebo (95% CI)	0.96 (0.87, 1.06)	--	--
Ratio of Placebo to Placebo/prednisone (95% CI)	--	--	3.17 (2.68, 3.74)

(BDP-AR-304 Study Report, pages 60-61)

Figure 7 Geographic mean (SD) serum cortisol level time profile by treatment group at week 6



(BDP-AR-304 Study Report, page 63)

Subgroup analyzes based on age (12 to 17 years and 18 to 45 years) were conducted. There were 73 subjects (74.5%) 18 to 45 years of age and 25 subjects (25.5%) 12 to 17 years of age in the PP population. For subjects 12 to 17 years of age, the geometric mean serum cortisol values after 42 days of treatment were similar for BDP Nasal Aerosol 320 mcg/day and placebo (6.56 mcg/dL and 7.18 mcg/dL, respectively) whereas the mean value was significantly lower after treatment with placebo/prednisone 10 mg/day (3.00 mcg/dL). The geometric mean ratio for BDP Nasal Aerosol 320 mcg/day to placebo was 0.92 (95% CI: 0.72, 1.16). For the secondary analysis which compared the effect of placebo/prednisone 10 mg/day (active control) versus placebo,

the geometric mean ratio for placebo to placebo/prednisone 10 mg/day was 2.56 (95% CI: 1.76, 3.71). For subjects 18 to 45 years of age, the geometric mean ratio for BDP Nasal Aerosol 320 mcg/day to placebo was 0.98 (95% CI: 0.88, 1.09), and the geometric mean ratio for placebo to placebo/prednisone 10 mg/day was 3.51 (95% CI: 2.89, 4.27). The effects of BDP Nasal Aerosol 320 mcg/day and prednisone treatment were similar in two age subgroups (Table 52).

Table 52 Serum cortisol levels (mcg/dL, log transformed) by treatment and age subgroups

Statistic	BDP HFA320 mcg/ day	Placebo	Placebo/ prednisone 10 mg/day
Subjects 12 to 17 years,	**N=11**	**N=11**	**N=3**
Baseline geometric mean (SE)	7.28 (1.33)	7.29 (1.41)	8.02 (1.10)
Week 6 geometric mean (SE)	6.56 (1.46)	7.18 (1.32)	3.00 (1.53)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.41)	0.98 (1.16)	0.37 (1.47)
Ratio of BDP to Placebo 95% CI	0.92 (0.72, 1.16)	-	-
Ratio of Placebo to Placebo/prednisone 10 mg/day 95% CI	-	-	2.56 (1.76, 3.71)
Subjects 18 to 45 years,	**N=37**	**N=30**	**N=6**
Baseline geometric mean (SE)	9.65 (1.64)	8.92 (1.31)	7.01 (1.46)
Week 6 geometric mean (SE)	8.73 (1.49)	8.33 (1.27)	2.02 (1.80)
Week 6/Baseline geometric mean ratio (SE)	0.91 (1.29)	0.93 (1.21)	0.29 (1.49)
Ratio of BDP to Placebo 95% CI	0.98 (0.88, 1.09)	-	-
Ratio of Placebo to Placebo/prednisone 10 mg/day 95% CI	-	-	3.51 (2.89, 4.27)

(BDP-AR-304 Study Report, page 68)

Reviewer's comment:
The study results show that the BDP Nasal Aerosol 320 mcg/day treatment for 6 weeks was not associated with HPA-axis suppression relative to placebo in adult and adolescent subjects (12 to 45 years old) with PAR.

Pharmacokinetics

Steady-state PK parameters were calculated for 17-BMP and BDP from the plasma profiles using non-compartmental PK methods. For 17-BMP the mean AUC_{0-t} was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL.

The results for BDP were lower than for 17-BMP for the mean AUC0-t (50.61 h*pg/mL) for the mean AUC0-24 (86.05 h*pg/mL) and for Cmax (89.12 pg/mL). The median tmax (0.25 hours) and mean t1/2 (0.48 hours) were shorter for BDP than for 17-BMP. The PK results showed that following repeated once-daily dosing for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

Reviewer's comment:
For detailed PK information, readers are referred to Clinical Pharmacology Review by Arun Agrawal, Ph.D.

Adverse events

Of the 107 subjects who received study treatment, a total of 30 (28.0%) experienced AEs: 9 subjects (18.0%) receiving BDP Nasal Aerosol 320 mcg/day, 18 subjects (39.1%) receiving placebo, and 3 subjects (27.3%) receiving placebo/prednisone 10 mg/day. No deaths occurred in the study. No subjects experienced an SAE and no subjects were withdrawn due to an AE that commenced during the treatment period. Table 53 presents an overview of treatment-emergent AEs for subjects in each treatment group. The adverse events did not reveal a safety signal.

Table 53 Adverse events reported in Study BDP-AR-304

Preferred Term	BDP HFA 320 mcg/day (N=50) n (%)	Placebo (N=46) n (%)	Placebo /Prednisone 10 mg/day (N=11) n (%)	TOTAL (N=107) n (%)
Subjects With at Least 1 AE	9(18.0)	18(39.1)	3(27.3)	30(28.0)
Epistaxis	2(4.0)	1(2.2)	1(9.1)	4(3.7)
Nasal discomfort	1(2.0)	2(4.3)	1(9.1)	4(3.7)
Headache	2(4.0)	1(2.2)	0(0.0)	3(2.8)
Neck pain	1(2.0)	1(2.2)	0(0.0)	2(1.9)
Abdominal pain upper	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Blood oestrogen increased	0(0.0)	0(0.0)	1(9.1)	1(0.9)
Contusion	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Dermatitis contact	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Drug withdrawal headache	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Dry mouth	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Dysmenorrhoea	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Dyspepsia	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Dysphonia	0(0.0)	0(0.0)	1(9.1)	1(0.9)
Excoriation	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Gastroenteritis	0(0.0)	0(0.0)	1(9.1)	1(0.9)
Menstruation delayed	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Migraine	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Muscle strain	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Nasal inflammation	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Nasopharyngitis	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Nausea	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Oropharyngeal pain	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Pain in extremity	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Presyncope	1(2.0)	0(0.0)	0(0.0)	1(0.9)
Rash	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Sleep disorder	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Sneezing	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Tension headache	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Toothache	0(0.0)	1(2.2)	0(0.0)	1(0.9)
Urinary tract infection	0(0.0)	1(2.2)	0(0.0)	1(0.9)

(BDP-AR-304 Study Report, page 187)

Clinical laboratory evaluation

There were no significant changes in clinical laboratory tests during the study. There were no notable differences between the 3 treatment groups.

ECG assessment

ECG assessments were performed at screening and post study visit. There were no significant changes observed during the study. No subject had changes from normal to abnormal.

Physical examinations and vital signs

In the 3 treatment groups, no significant changes in physical examinations and vital signs were observed during the study. Results of ENT examinations for the 3 treatment groups were similar. There were 4 cases of epistaxis (2 in the BDP Nasal Aerosol 320 mcg/day group, 1 in placebo, and 1 in placebo/prednisone 10 mg/day group) reported as adverse events in the category of respiratory, thoracic and mediastinal disorders.

6 Review of Efficacy

Efficacy Summary

The data submitted in the NDA support the efficacy of BDP Nasal Aerosol for the treatment of nasal symptoms of SAR and PAR in adults and adolescents patients 12 years of age and older. There were two adequate and well controlled pivotal studies, one in patients with SAR (BDP-AR-301) and one in patients with PAR (BDP-AR-302). Since SAR and PAR are closely related diseases and have identical pathophysiological changes, the product demonstrating efficacy in one SAR study and one PAR study are acceptable for approval for both SAR and PAR in adults and adolescents patients 12 years of age and older. The primary efficacy endpoint for both SAR and PAR 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 167 subjects received BDP Nasal Aerosol 320 mcg/day for 2 weeks. In the PAR study, a total of 232 subjects received BDP Nasal Aerosol 320 mcg/day for 6 weeks. The BDP 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 320 mcg /day in SAR and PAR was demonstrated in the two studies.

The dose selection of BDP Nasal Aerosol 320 mcg/day was supported in a 2-week dose ranging study in patients with SAR (BDP-AR-201), in which 122, 123, and 118 subjects received BDP Nasal Aerosol 320 mcg, 160 mcg, and 80 mcg daily for 2 weeks, respectively. Statistically significant improvements in rTNSS and iTNSS compared with placebo were observed in patients with BDP Nasal Aerosol 320 mcg/day but not in patients with 160 or 80 mcg/day.

The effects of BDP Nasal Aerosol 320 mcg/day treatment on improvement of the disease-specific quality of life as measured by the mean change in Rhinoconjuctivitis Quality of Life Questionnaire (RQLQ), and on ocular symptoms as measured by reflective total ocular symptom score (rTOSS) were inconsistent. The difference of changes from baseline of the RQLQ scores between BDP Nasal Aerosol 320 mcg/day and placebo in the Phase 3 SAR study (BDP-AR-301) and PAR study (BDP-AR-302) for the ITT population was -0.40 and -0.56, respectively. Since the minimally clinical significance of the difference in the RQLQ score is considered to be 0.50, it seems that the treatment of BDP Nasal Aerosol 320 mcg/day improves disease-specific quality of life in PAR, but not in SAR. However, the clinically significant change in RQLQ score in patients with PAR was not replicated, because in the long term safety study BDP-AR-303 the difference of RQLQ changes between BDP Nasal Aerosol 320 mcg/day and placebo for the ITT population was only -0.24. The non-nasal symptoms were assessed by rTOSS only in the SAR studies. In the Phase 3 SAR study BDP-AR-301 the difference of rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo was -0.56, with a p value of 0.002. However, this statistically significant difference in rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo was not replicated. In the dose ranging study in SAR (BDP-AR-201), the difference of rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo was only -0.29, with a p value of 0.195.

Subgroup analyses showed that gender, age and race had no apparent effect on efficacy of BDP Nasal Aerosol 320 mcg/day in the treatment of SAR and PAR.

There were no studies designed to assess the onset of action of BDP Nasal Aerosol in this NDA submission.

In summary, based on the data provided in this application, BDP Nasal Aerosol 320 mcg once daily is efficacious for the treatment of nasal symptoms of SAR and PAR in adults and adolescents age 12 years and above. However, the effects of BDP Nasal Aerosol 320 mcg once daily treatment on improvement of the disease-specific quality of life and on non-nasal symptoms were equivocal. Thus, the indication should be limited to the treatment of nasal symptoms of SAR and PAR, rather than the Applicant proposed broad indication as (b) (4)

6.1 Indication

The proposed indication of BDP Nasal Aerosol is for the treatment of the symptoms of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

Reviewer's comment:
The proposed indication implies (b) (4) *of the proposed drug product. Because the data submitted did not support the effects of BDP Nasal Aerosol 320 mcg once daily treatment on improvement of the* (b) (4) *the indication should be limited to the treatment of nasal symptoms of SAR and PAR, rather than the Applicant proposed broad indication as* (b) (4) *"*

6.1.1 Methods

Efficacy was assessed from the results of randomized, double-blind, placebo-controlled clinical trials in subjects 12 years of age and older.

6.1.2 Demographics

In each study, BDP Nasal Aerosol 320 mcg /day treatment groups were comparable to placebo for demographic characteristics as shown in Table 54 for 2-week SAR studies (BDP-AR-201 and BDP-Ar-301) and in Table 55 for a 6-week PAR study (BDP-AR-302) and a long term safety study (BDP-AR-303). The demographic characteristics of subjects with SAR and PAR were also similar. Across the studies and treatment groups, the age range was similar and the mean age ranged from 35.7 years to 39.3 years. More females than males participated in each study. The majority of subjects (≥78% in each treatment group) were white, and the proportion of black subjects ranged from 12.7% to 18.0%. The proportion of Hispanic subjects was highest in Study BDP-AR-301, being 31.1% and 28.7% for BDP 320 mcg/day group and placebo, respectively; in other studies the proportion ranged from 10.9% to 13.9% across the treatment groups.

With regard to the baseline characteristics, all subjects had a history of seasonal allergic rhinitis in SAR studies. A concomitant history of PAR was reported in 63.0% of subjects in Study BDP-AR-201 and in 31.7% of subjects in Study BDP-AR-301. In the PAR studies, all subjects had a history of PAR. A concomitant history of SAR was reported in 60.8% of subjects in Study BDP-AR-302 and 57.4% in Study BDP-AR-303. There were no clinically important differences between treatment groups for medical history and concomitant medication use in any of the studies.

Table 54 Subject demographics of SAR studies (BDP-AR-201 and BDP-AR-301)

Category	BDP-AR-201		BDP-AR-301	
	BDP HFA 320 mcg/day N=122	Placebo N=123	BDP HFA 320 mcg/day N=167	Placebo N=171
Age (years)				
Mean (SD)	38.5 (14.74)	38.2 (13.95)	39.3 (13.4)	38.0 (13.3)
Median	39.5	40	41.0	37.0
Min-Max	12-71	12-68	12-68	13-73
Gender, n (%)				
Female	81 (66.4)	73 (59.3)	113 (67.7)	97 (56.7)
Male	41 (33.6)	50 (40.7)	54 (32.3)	74 (43.3)
Race, n (%)				
White	98 (80.3)	97 (78.9)	142 (85.0)	142 (83.0)
Black	22 (18.0)	19 (15.4)	23 (13.8)	26 (15.2)
Asian	0	6 (4.9)	3 (1.8)	3 (1.8)
Other	2 (1.6)	1 (0.8)	1 (0.6)	2 (1.2)
Ethnicity, n (%)				
Hispanic or Latino	17 (13.9)	15 (12.2)	52 (31.1%)	49 (28.7)
Not Hispanic, not Latino	105 (86.1)	108 (87.8)	115 (68.9%)	122 (71.3)

Table 55 Subject demographics in PAR studies (BDP AR-302 and BDP-AR-303)

Category	BDP-AR-302		BDP-AR-303	
	BDP HFA 320 mcg/day N=232	Placebo N=234	BDP HFA 320 mcg/day N=414	Placebo N=110
Age (years)				
Mean (SD)	36.8 (14.5)	37.2 (13.7)	37.4 (13.6)	35.7 (12.9)
Median	37.0	38.0	38.5	36.0
Min-Max	12-82	12-71	12-74	12-67
Gender, n (%)				
Female	158 (68.1)	161 (68.8)	286 (69.1)	66 (60.0)
Male	74 (31.9)	73 (31.2)	128 (30.9)	44 (40.0)
Race[1], n (%)				
White	186 (80.2)	185 (79.1)	341 (82.4)	97 (88.2)
Black	40 (17.2)	40 (17.1)	63 (15.2)	14 (12.7)
Asian	6 (2.6)	5 (2.1)	13 (3.1)	1 (0.9)
Other	2 (0.9)	8 (3.4)	11 (2.7)	2 (1.8)
Ethnicity, n (%)				
Hispanic or Latino	26 (11.2)	30 (12.8)	45 (10.9)	12 (10.9)
Not Hispanic, not Latino	206 (88.8)	204 (87.2)	369 (89.1)	98 (89.1)

1 A subject was allowed to choose more than one race type.

6.1.3 Subject Disposition

A total of 1824 subjects were randomized and treated in the four clinical studies using BDP Nasal Aerosol and 1814 subjects were included in the ITT populations, including subjects who received the 80 mcg/day and 160 mcg/day doses in study BDP-AR-201. A summary of the number of subjects in study populations by protocol is summarized in Table 56. The ITT population was the primary population used for analysis of the primary efficacy endpoint in each study. Per protocol (PP) population was to show that the majority of subjects (>85%) in each study were included in the PP populations had no protocol violations and contributed efficacy data prior to experiencing a protocol violation. The RQLQ population was for adult subjects (18 years of age and older) who understood English and with impaired quality of life at Baseline (defined as an RQLQ score of ≥3.0). Thus, the proportion of subjects included in the RQLQ population ranged from 53.1% to 73.5% across the studies.

Table 56 Summary of study populations

	BDP-AR-201	BDP-AR-301	BDP-AR-302	BDP-AR-303
Randomized	487	340	474	529
Safety Population[1]	486 (99.8)	338 (99.4)	474 (100)	526 (99.4)
ITT Population[2]	486 (99.8)	338 (99.4)	466 (98.3)	524 (99.1)
PP Population[3]	432 (88.7)	320 (94.1)	435 (91.8)	453 (85.6)
RQLQ Population[4]	297 (61.0)	250 (73.5)	257 (54.2)	281 (53.1)

1 Safety population was all randomized subjects who received at least one dose of study medication.
2 ITT population included all randomized subjects who received at least one dose of study medication and who had at least one post-baseline efficacy assessment.
3 Per protocol (PP) population was a subset of the ITT population and included all data obtained prior to a major protocol deviation
4 The RQLQ population was a subset of the ITT population that included only those subjects with an impaired quality of life at Baseline as defined by a RQLQ score at the Randomization Visit of ≥3.0.

Reviewer's comment:
Although the RQLQ population was defined as a subpopulation of ITT population, the study reports included data obtained from analyses using both RQLQ and ITT population. The conclusions were the same from analyses using two populations. Readers are referred to Section 5.3 Discussion of Individual Studies/Clinical Trials for data presentation.

As shown in Table 57 (2-week SAR studies) and Table 58 (6-week PAR study BDP-AR-302 and the long term safety study BDP-AR-303), the proportion of subjects discontinuing the study prematurely was low. As expected, the highest premature discontinuation rates were seen in the long term study (BDP-AR-303) in which the subjects were treated for 30 and 52 weeks. In each study, the proportion of subjects discontinued from BDP Nasal Aerosol 320 mcg/day treatment was lower than the proportion of subjects discontinued from placebo treatment.

Table 57 Subject disposition in SAR studies (BDP-AR-201 and BDP-AR-301)

Category	BDP-AR-201		BDP-AR-301	
	BDP HFA 320 mcg/day N=122 n (%)	Placebo N=123 n (%)	BDP HFA 320 mcg/day N=167 n (%)	Placebo N=171 n (%)
Discontinued[1]	2 (1.6)	10 (8.1)	2 (1.2)	4 (2.3)
Adverse Event	2 (1.6)	6 (4.9)	1 (0.6)	0
Withdrew Consent	0	1 (0.8)	1 (0.6)	0
Lost to follow up	0	0	0	1 (0.6)
Protocol violation/ non-compliance	0	0	0	3 (1.8)
Other	0	3 (2.4)	0	0

1 A subject who discontinued for more than one reasons was counted only once.

Table 58 Subject disposition in PAR studies (BDP-AR-302 and BDP-AR-303)

Category	BDP-AR-302		BDP-AR-303	
	BDP HFA 320 mcg/day N=236 n (%)	Placebo N=238 n (%)	BDP HFA 320 mcg/day N=418 n (%)	Placebo N=111 n (%)
Discontinued[1]	15 (6.4)	22 (9.2)	83 (19.9)	26 (23.4)
Adverse Event	1 (0.4)	7 (2.9)	17 (4.1)	3 (2.7)
Withdrew Consent	6 (2.5)	6 (2.5)	44 (10.5)	13 (11.7)
Pregnancy	1 (0.4)	0	1 (0.2)	2 (1.8)
Lost to follow up/failure to return	5 (2.1)	2 (0.8)	11 (2.6)	2 (1.8)
Protocol violation/ non-compliance	1 (0.4)	1 (0.4)	4 (1.0)	5 (4.5)
Sponsor requested withdrawal	0	0	3 (0.7)	1 (0.9)
Other	1 (0.4)	6 (2.5)	3 (0.7)	0

1 A subject who discontinued for more than one reasons was counted only once.

Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the change from baseline in the average AM and PM subject-reported reflective TNSS (rTNSS) over the Treatment Period. The subject was asked to assess 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 in two pivotal SAR and PAR studies (BDP-AR-301 and 302) and the dose ranging study (BDP-AR-201). In the long term safety study, BDP-AR-303, nasal symptoms were recorded by the subject once daily in the morning primarily for the purpose of monitoring the treatment compliance. The averaged baseline measurements were compared to the averaged rTNSS measurements made over the course of the study using a repeated measures ANCOVA statistical analysis.

Reviewer's comment:
Efficacy endpoints in BDP-AR-303 were of supportive value, because they were measured primarily for the purpose of monitoring treatment compliance in the long term safety study.

Table 59 below summarized the primary efficacy analyses of the 4 studies. In the two pivotal studies (BDP-AR-301 and 302), greater improvements in subject-reported rTNSS over the Treatment Period were seen with BDP Nasal Aerosol 320 mcg/day than with placebo and the difference was clinically meaningful and statistically significant ($p<0.001$). The effectiveness of the BDP Nasal Aerosol 320 mcg/day treatment was also supported in the dose ranging study and the long term safety study. The overall data demonstrated that BDP Nasal Aerosol 320 mcg/day was efficacious in the treatment of nasal symptoms of patients with SAR and PAR.

Table 59 Summary of primary efficacy analysis (ITT population)

Study	BDP-AR-201 (SAR)		BDP-AR-301 (SAR)		BDP-AR-302 (PAR)		BDP-AR-303 (PAR)*	
Treatment	320 mcg N=122	Placebo N=123	320 mcg N=167	Placebo N=171	320 mcg N=232	Placebo N=234	320 mcg N=414	Placebo N=110
rTNSS								
Baseline	9.2	9.0	9.6	9.5	8.9	9.0	9.2	9.4
Change from baseline	-2.2	-1.6	-2.0	-1.0	-2.5	-1.6	-3.4	-2.4
Dif. from placebo (p value)	-0.63 (0.013)		-0.91 (<0.001)		-0.84 (<0.001)		-0.97 (<0.001)	

*The primary efficacy analysis was from data of the first 30 weeks of the 52-week treatment period and was the AM measurement only. The changes from baseline in the 24-hour rTNSS over 52 weeks of treatment were consistent with those observed for the first 30 weeks, the difference of rTNSS between BDP Nasal Aerosol 320 mcg/day and placebo was -1.09 ($p <0.001$).

Analysis of Secondary Endpoints(s)

Key secondary efficacy endpoints included the change from baseline in the following:

- iTNSS: Average AM and PM subject-reported iTNSS over the Treatment Period.
- RQLQ: The RQLQ is a disease-specific quality of life questionnaire developed to measure the functional (physical, emotional and social) problems troublesome to adults with allergies. The RQLQ measures both atopic and non-atopic experiences as a result of a subject's nose and eye symptoms, assessing the

impact of rhinitis on activities of daily living and overall well-being. The adult RQLQ has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Least severe to 6 = Extremely severe). When required at a particular visit this questionnaire was to be completed as the first activity of the visit. The adult RQLQ was used only by adult subjects (18 years and older). Adolescent subjects did not complete the RQLQ. The questionnaire has been shown to be reliable, responsive, and to have construct validity. The minimally clinical significance of the difference in the RQLQ score is considered to be 0.5[1].

- Reflective total ocular symptom score (rTOSS): AM subject-reported 24-hour reflective ocular symptom score (the sum of individual non-nasal symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness) over the Treatment Period in subjects with adequate symptoms during the Run-in period as defined by a mean daily 24-hour ocular score of 4 or greater over the last 7 days of the Run-in Period. The symptoms were evaluated at a scale from 0 to 3, as described in TNSS evaluation. The maximum rTOSS is 9.

Table 60 below summarized the secondary efficacy analyses of the 4 studies. In all studies, greater improvements in subject-reported iTNSS over the Treatment Period were seen with BDP Nasal Aerosol 320 mcg/day than with placebo and the difference was statistically significant ($p<0.001$ to $p=0.016$). The improvements of iTNSS were consistent with that of the primary efficacy endpoint rTNSS, and supported that BDP Nasal Aerosol 320 mcg/day was efficacious in the treatment of nasal symptoms of in SAR and PAR.

With regard to the improvement of the disease-specific quality of life as measured by the change in RQLQ and the non-nasal symptoms as measured by rTOSS, the results of BDP Nasal Aerosol 320 mcg/day treatment were inconsistent. The difference of changes from baseline of the RQLQ scores between BDP Nasal Aerosol 320 mcg/day and placebo in pivotal SAR study (BDP-AR-301) and PAR study (BDP-AR-302) for the ITT population was -0.40 and -0.56, respectively. Since the minimally clinical significance of the difference in the RQLQ score is considered to be 0.5, it seems that the treatment of BDP Nasal Aerosol 320 mcg/day improves disease-specific quality of life in PAR study, but not in SAR study. However, the clinically significant change in RQLQ score in patients with PAR was not replicable, because in the long term safety study BDP-AR-303 the difference of RQLQ changes between BDP Nasal Aerosol 320 mcg/day and placebo for the ITT population was only -0.24. The non-nasal symptoms were assessed by rTOSS only in one pivotal SAR study BDP-AR-301, in which the difference of rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo

1 Juniper EF, Guyatt GH, Griffith LE, et al. Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 1996; 98(4):843

was -0.56, with a p value of 0.002. However, this statistically significant difference in rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo was not replicated in the dose ranging study in SAR (BDP-AR-201), in which the difference of rTOSS changes between BDP Nasal Aerosol 320 mcg/day and placebo was only -0.29, with a p value of 0.195.

Table 60 Summary of secondary efficacy analyses (ITT population)

Study	BDP-AR-201 (SAR)		BDP-AR-301 (SAR)		BDP-AR-302 (PAR)		BDP-AR-303 (PAR)*	
Treatment	320 mcg N=122	Placebo N=123	320 mcg N=167	Placebo N=171	320 mcg N=232	Placebo N=234	320 mcg N=414	Placebo N=110
iTNSS								
Baseline	8.3	8.0	9.0	8.7	8.1	8.3	7.7	8.0
Change from baseline	-2.1	-1.5	-1.7	-0.8	-2.1	-1.4	-2.9	-2.0
Dif. from placebo (p)	-0.60 (0.016)		-0.92 (<0.001)		-0.78 (<0.001)		-0.96 (<0.001)	
RQLQ								
Baseline	4.3	4.1	4.3	4.4	4.2	4.2	4.2	3.9
Change from baseline	-1.6	-1.2	-1.2	-0.8	-1.5	-0.9	-2.2	-1.9
Dif. from placebo (p)	-0.36 (0.026)		-0.40 (0.008)		-0.56 (0.001)		-0.24 (0.100)	
rTOSS$								
Baseline	6.7	6.5	6.7	6.6				
Change from baseline	-1.5	-1.2	-1.3	-0.7				
Dif. from placebo (p)	-0.29 (0.195)		-0.56 (0.002)					

* The secondary efficacy analyses were from data of the first 30 weeks of the 52-week treatment period. The changes from baseline in the 24-hour iTNSS and RQLQ over 52 weeks of treatment were consistent with those observed for the first 30 weeks.
$ rTOSS was evaluated in SAR studies only.

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 two pivotal studies (BDP-AR-301 and BDP-AR-302), significant decrease in rTNSS was observed on day 2 till the end of the 2-week study in SAR (Figure 2) and on day 3 till the end of the 6-week study in PAR (Figure 3).

6.1.7 Subpopulations

Subgroup analyses for the primary efficacy endpoint, rTNSS were conducted based on gender, age, and race. Subjects were divided 3 subgroups by age: 12 to≤18, 19 to 64, and ≥65 years of age; and 3 subgroups by race: White, Black, Other races. A summary of subpopulation analyses for rTNSS in efficacy studies in SAR and PAR can be found in Table 61 below. The data showed that gender, age and race had no apparent effect on efficacy of BDP Nasal Aerosol in the treatment of SAR and PAR. The subgroup analyses for secondary endpoints generally demonstrated similar trends.

There was no evidence observed for an effect of gender on efficacy across the studies. The improvements in rTNSS with BDP Nasal Aerosol 320 mcg/day were greater

compared with placebo in both gender subgroups in subjects with SAR and in subjects with PAR. In each study the majority of subjects (≥87%) were 18 to 64 years of age. The differences in rTNSS change for BDP Nasal Aerosol 320 mcg/day compared with placebo were greater in all age subgroups in both SAR studies and in PAR study BDP-AR-302. In long term safety study BDP-AR-303, in the subgroup of subjects 12 to 17 years of age, the placebo group had a greater change in rTNSS that that in BDP Nasal Aerosol 320 mcg/day group. By further examining the data, it was found that the number of subjects 12 to 17 years of age who received placebo was small in the study (9 subjects only) and 2 of the 9 subjects on placebo had unusually large, sustained improvements from baseline in rTNSS (i.e., >5.0) which persisted throughout almost the entire 52 weeks of treatment. It is likely that the unusually large rTNSS responses in the two subjects skewed the rTNSS scores for the placebo group in this study and thus masked treatment differences between BDP Nasal Aerosol 320 mcg/day and placebo in 12 to 17 age group.

The majority of subjects (≥78%) were white in each study. The number of black subjects ranged from 13.4% to 16.7% and the number of subjects of other races were small. There was no evidence observed for a consistent effect of race on efficacy across the studies. The improvements in rTNSS with BDP Nasal Aerosol 320 mcg/day were greater compared with placebo in all race subgroups in subjects with SAR with the exception of black subjects in study BDP-AR-301 and in all race subgroups in subjects with PAR. In study BDP-AR-301, the mean change in rTNSS was smaller in BDP Nasal Aerosol 320 mcg/day group than that in placebo in blacks. Because of the small number of black subjects enrolled in the study, this observation was most likely due to chance, and was not an evidence that BDP Nasal Aerosol 320 mcg/day had different effect in blacks.

Table 61 Summary of subgroup analyses for rTNSS (by gender, age, and race)

Subgroup	BDP-AR-201 (SAR)		BDP-AR-301(SAR)		BDP-AR-302(PAR)		BDP-AR-303 (PAR)*	
	320 mcg N=122	Placebo N=123	320 mcg N=167	Placebo N=171	320 mcg N=232	Placebo N=234	320 mcg N=414	Placebo N=110
Gender: Female								
Baseline	9.2	9.0	9.5	9.9	8.8	9.1	9.3	9.6
Change from baseline	-2.4	-1.5	-1.6	-1.3	-2.7	-1.8	-3.5	-2.5
Dif. from Placebo (95% CI)	-0.93 (-1.6, -0.3)		-0.32 (-0.9, 0.2)		-0.92 (-1.4, -0.5)		-0.99 (-1.6, -0.4)	
Gender: Male								
Baseline	9.2	9.0	9.8	9.1	9.0	8.9	9.1	9.2
Change from baseline	-1.8	-1.7	-2.7	-0.7	-2.0	-1.3	-3.1	-2.2
Dif. from Placebo (95% CI)	-0.09 (-0.9, 0.7)		-2.03 (-2.8, -1.3)		-0.66 (-1.3, 0)		-0.88 (-1.7, -0.1)	
Age: 12-17 years								
Baseline	9.4	9.1	10.0	9.4	8.7	8.5	9.5	10.2
Change from baseline	-2.7	-1.5	-1.3	-0.6	-1.7	-0.6	-2.2	-2.3
Dif. from Placebo (95% CI)	-1.19 (-3.0, 0.6)		-0.68 (-1.9, 0.5)		-1.07 (-2.2, 0.1)		0.10 (-1.5, 1.7)	

Age: 18-64 years								
Baseline	9.2	9.0	9.6	9.5	8.9	9.1	9.2	9.4
Change from baseline	-2.2	-1.6	-2.0	-1.1	-2.52	-1.7	-3.5	-2.4
Dif. from Placebo (95% CI)	-0.55 (-1.1, 0)		-0.92 (-1.4, -0.5)		-0.77 (-1.2, -0.4)		-1.09 (-1.6, -0.6)	
Age: ≥65 years								
Baseline	8.7	8.8	9.4	9.8	8.0	8.1	9.2	7.7
Change from baseline	-2.4	-0.9	-3.2	-0.7	-3.8	-1.4	-2.8	-1.7
Dif. from Placebo (95% CI)	-1.52 (-4.3, 1.3)		-2.49 (-6.0, 1.0)		-2.41 (-4.5, -0.3)		-1.06 (-4.7, 2.6)	
Race: White								
Baseline	9.1	9.0	9.6	9.5	8.8	9.0	9.1	9.4
Change from baseline	-2.0	-1.4	-2.0	-0.9	-2.5	-1.7	-3.4	-2.4
Dif. from Placebo (95% CI)	-0.60 (-1.1, -0.1)		-1.12 (-1.6, -0.7)		-0.80 (-1.2, -0.4)		-0.94 (-1.5, -0.4)	
Race: Black								
Baseline	9.5	8.9	9.7	9.6	9.3	9.0	9.7	9.6
Change from baseline	-3.0	-2.1	-1.5	-1.7	-2.4	-1.4	-3.3	-2.3
Dif. from Placebo (95% CI)	-0.89 (-2.2, 0.4)		0.14 (-1.2, 1.4)		-0.91 (-1.9, 0)		-1.07 (-2.8, 0.7)	
Race: Other races								
Baseline	10.2	8.4	10.2	10.3	9.3	8.9	9.8	9.9
Change from baseline	-3.4	-2.3	-2.1	-2.0	-1.6	-0.7	-3.9	-2.7
Dif. from Placebo (95% CI)	-1.05 (-5.1, -0.7)		-0.09 (-3.6, 3.5)		-0.85 (-2.6, 0.9)		-1.18 (-3.4, 1.0)	

*The primary efficacy analysis was from data of the first 30 weeks of the 52-week treatment period.

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 mcg, 160 mcg, and 320 mcg in subjects with SAR in the dose ranging study BDP-AR-201. A total of 486 adult and adolescent subjects with SAR were randomized and treated in the study, of whom 118 were received BDP Nasal Aerosol 80 mcg/day, 123 received BDP Nasal Aerosol 160 mcg/day, 122 received BDP Nasal Aerosol 320 mcg/day, and 123 received placebo. The analysis of the primary efficacy endpoint rTNSS for study BDP-AR-201 can be found in Table 7 in section 5.3. At baseline, the means of the average AM and PM rTNSS (the primary efficacy variable) were comparable in the four 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 -2.22 in BDP Nasal Aerosol 320 mcg/day group. The mean difference of -0.63 between BDP Nasal Aerosol 320 mcg/day and placebo was statistically significant (p=0.013) in favor of BDP Nasal Aerosol 320 mcg/day. The changes from baseline in the average AM and PM rTNSS for BDP Nasal Aerosol 80 mcg/day, BDP Nasal Aerosol 160 mcg/day, and placebo group were -1.88, -1.87, and -1.56, respectively. The observed treatment differences between the 80 and 160 mcg/day treatment groups and the placebo group were small

and not statistically significant. All three doses of BDP Nasal Aerosol were well tolerated and showed no meaningful differences compared with placebo in the incidence of AEs in adult and adolescent subjects with SAR in this 2-week study. The data support the recommended dose of BDP Nasal Aerosol 320 mcg per day in the treatment of SAR.

Reviewer's comments:
Readers are referred to Section 5.3.1 for detailed review of the dose ranging study BDP-AR-201.

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 320 mcg per day remained effective for the 52 weeks of exposure in PAR patients.

6.1.10 Additional Efficacy Issues/Analyses

Device dose counter evaluation was conducted by comparing the actuations counted and the canister weights pre- and post-dosing. The estimated actuations based on canister weight were matched well with the dose counter data. The device performance/acceptance was also evaluated by using the Nasal Device Ease of Use/Satisfaction Questionnaire in the pivotal PAR study BDP-AR-302. The majority of subjects assessed that the device was very easy or somewhat easy to use (89.7%), the device was very easy or somewhat easy to tell when the device was empty (87.6%), and it was very easy or somewhat easy to take medication as directed (89.7%). There was no significant difference in the assessment of device performance/acceptance between 2 treatment groups.

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of BDP Nasal Aerosol 320 mcg per day for the treatment of nasal symptoms in SAR and PAR in patients 12 years of age and older. The evidence for safety is based primarily on the assessments of safety data from clinical studies submitted, including one 2-week dose finding study, one 2-week pivotal study in SAR, one 6-week pivotal study in PAR, a long term safety study, and a HPA axis study.

No deaths were reported and nonfatal SAEs were rare. The overall incidences of SAEs in the clinical studies reviewed were similar between subjects treated with BDP Nasal Aerosol 320 mcg/day and placebo. 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 were no nasal septum perforations reported in BDP Nasal Aerosol clinical program. There were no apparent differences in local AEs between three BDP Nasal Aerosol doses (80, 160, and 320 mcg/day) and placebo in the short term (2 to 6 weeks) studies. In the long term safety study, one nasal septum ulceration and 4 nasal erosions occurred in subjects received BDP Nasal Aerosol 320 mcg/day in contrast to that no nasal ulceration or erosion reported in placebo group.

In the short term studies (2 to 6 weeks), the most common adverse events in BDP Nasal Aerosol 320 mcg treatment group were nasal irritation (5.2%), headache (2.3%), and epistaxis (1.9%), and they were not significantly different from those in placebo group. The long term (30 or 52 weeks) administration of BDP Nasal Aerosol 320 mcg/day or placebo was associated with higher incidence of adverse events. The most common adverse events in BDP Nasal Aerosol 320 mcg treatment were nasopharyngitis (16.1%), epistaxis (10.6%), upper respiratory tract infection (10.4%), sinusitis (8.2%), headache (6.7%), and nasal irritation (4.3%). While in placebo group the incidence of these common AEs were nasopharyngitis (12.6%), epistaxis (1.8%), upper respiratory tract infection (6.3%), sinusitis (7.2%), headache (5.4%), and nasal irritation (2.7%). Epistaxis was the most notable AE that had a significant increase in BDP Nasal Aerosol 320 mcg treatment group compared to placebo at 10.8% (45/415 subjects) versus 1.8% (2/111 subjects). Epistaxis also tended to be more severe in patients treated with BDP Nasal Aerosol 320 mcg/day. Of epistaxis that occurred in patients treated with BDP Nasal Aerosol 320 mcg/day, 27, 12, and 6 cases were of mild, moderate, and severe intensity, respectively. While 2 epistaxis cases in patients treated with placebo were of mild (1) and moderate (1) intensity.

Ocular examinations were conducted in the long term safety study (BDP-AR-303) to assess possible ocular effects of BDP Nasal Aerosol. A subset of 245 subjects (197 in the BDP Nasal Aerosol 320 mcg group and 48 in placebo group) had eye examinations conducted at screening, week 30 and week 52 for visual acuity, intraocular pressure (IOP), and cataract. The visual acuity and lens opacities (evaluated by LOCS III) were not affected by the BDP Nasal Aerosol treatment in the study. There were 2 cases of increased IOP reported as AEs in the study and both subjects were treated with BDP Nasal Aerosol 320 mcg/day. One increased IOP case was an SAE with IOP of 32 and 33 mmHg and treated by peripheral iridotomy. The mean IOP change from baseline was a small decrease in both the BDP Nasal Aerosol and placebo groups. The effect of BDP Nasal Aerosol on HPA axis was also assessed in adolescent and adult subjects of 12 to 45 years old. The HPA axis study demonstrated that the treatment of BDP Nasal

Aerosol 320 mcg/day for 6 weeks had no effect on HPA axis function in adult and adolescent subjects (12 years of age and older).

Epistaxis is known to associate with long term nasal exposure to corticosteroids, higher incidences of epistaxis associated with long term nasal exposures have been recorded in other nasal corticosteroid programs. The higher incidences of epistaxis in BDP Nasal Aerosol 320 mcg treatment group did not reveal a new safety signal. In summary, the safety evaluation supports the approval of BDP Nasal Aerosol 320 mcg/day in patients 12 years and older for the treatment of nasal symptoms of SAR and PAR.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based on data from all phase 2b/3 PAR/SAR studies (Table 3), including 2-week dose finding study in SAR patients (BDP-AR-201), 2-week PAR pivotal study (BDP-AR-301), 6-week PAR pivotal study (BDP-AR-302), long term safety study (BDP-AR-303), and HPA axis study (BDFP-AR-304).

7.1.2 Categorization of Adverse Events

The Applicant's categorization of AE data by system, organ, class and preferred term according to the MedDRA dictionary version 12.0 were appropriately coded. 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 appropriately pooled based on the length of the treatment periods (2-6 weeks), as study designs and patient population were identical. Except for the dose finding study in which three dose levels were administered, the dose of the test drug was same in all clinical studies reviewed (BDP Nasal Aerosol 320 mcg/day). The data from the long-term safety study (30-52 weeks) were not pooled and gave an assessment of AEs separately, because cumulatively more adverse events would be

reported in studies of the longer duration. Pooled data were simply combined across studies without the use of any weighing data method.

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 short-term (2-6 weeks) and long term studies are summarized in Table 63 and Table 63, respectively. A total of 816 patients received BDP Nasal Aerosol in the 4 short term studies (BDP-AR-201, 301, 302, and 304). The exposures to BDP Nasal Aerosol 160 mcg and 80 mcg were only in a 2-week dose finding study BDP-AR-201. The majority of the patients were exposed to BDP Nasal Aerosol 320 mcg. For the subjects who received BDP Nasal Aerosol 320 mcg, the mean duration of the treatment was 28.2 days, with 96.3% and 47.9% of the subjects had treatment duration of >15 days and >29 days, respectively. In the long term study, a total of 415 patients received the treatment of BDP Nasal Aerosol 320 mcg (352 patients (84.6%) received for >180 days and 169 patients (40.7%) received for >360 days).

Table 62 Exposure (days) in 2/6 week studies

Statistics	**BDP HFA 320 mcg/day N=575**	**BDP HFA 160 mcg/day N=123**	**BDP HFA 80 mcg/day N=118**	**Placebo N=578**
Mean (SD)	28.2 (13.7)	15.4 (1.6)	15.3 (1.2)	27.3 (13.9)
Median	17	15	15	16
Min, Max	1, 49	4, 25	6, 19	1, 49
Days of exposure, n (%)				
1-14	19 (3.3)	4 (3.3)	4 (3.4)	44 (7.6)
15-28	281 (48.9)	119 (96.7)	114 (96.6)	272 (47.1)
29-42	128 (22.3)	0	0	128 (22.1)
>42	147 (25.6)	0	0	134 (23.3)

Source: Section 2.7.4. ISS Table 4, page 25

Table 63 Exposure (days) in long term safety study

	BDP HFA 320 mcg/day	Placebo
30-Week Treatment Period Subjects	**N=196**	**N=53**
Mean (SD)	190 (51.3)	194 (46.1)
Median	210	210
Min, Max	1, 227	29, 220
Days of Exposure n (%)		
1-90	18 (9.2)	3 (5.7)
91-180	12 (6.1)	4 (7.5)
>180	166 (84.7)	46 (86.8)
52-Week Treatment Period Subjects	**N=219**	**N=58**
Mean (SD)	311 (110)	286 (128)
Median	365	365
Min, Max	4, 372	1, 374
Days of Exposure n (%)		
1-90	23 (10.5)	10 (17.2)
91-180	10 (4.6)	4 (6.9)
181-210	5 (2.3)	1 (1.7)
211-360	12 (5.5)	4 (6.9)
>360	169 (77.2)	39 (67.2)
All Subjects		
Days of Exposure n (%)	**N=415**	**N=111**
>180[1]	352 (84.8)	90 (81.1)
>360	169 (40.7)	39 (35.1)

Source: Section 2.7.4. ISS Table 5, page 26

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.

7.2.2 Explorations for Dose Response

There was no dose dependency for AEs observed in BDP Nasal Aerosol clinical studies. In pooled data from short term studies, patients received three doses of BDP Nasal Aerosol, 80, 160, and 320 mcg per day. Table 65 in Section 7.4.1 showed that

incidences of overall AEs and individual AEs were all similar among different dose groups and between the treatment and placebo groups.

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 the final visit in the 6-week PAR pivotal study (BDP-AR-302) and the HPA axis study (BDP-AR-304). The following clinical laboratory tests were performed:

- Serum Chemistry: Albumin, sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate, glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total protein, total bilirubin, and lactate dehydrogenase (LDH).
- Hematology: Hemoglobin, hematocrit, erythrocytes (red blood cell count), white blood cell count and differential, platelet count, mean cell hemoglobin (MCH), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC).

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 during the two studies. 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 in the same formulation 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-304). Also nasal administered corticosteroids may directly contact eyes through the passage of nasolacrimal duct and have local eye effects. Ocular examinations were conducted to evaluate the ocular effect of BDP Nasal Aerosol in the long term safety study BDP-AR-303. The HPA axis study and ocular study are 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 any of the studies reviewed in this NDA.

7.3.2 Nonfatal Serious Adverse Events

In the 2-week dose ranging study in SAR patients (BDP-AR-201), there were two SAEs reported (one case of angioedema and one case of partial spontaneous abortion). Both SAEs were experienced by subjects in the BDP Nasal Aerosol 160 mcg/day group. In the 2-week pivotal study in SAR patients (BDP-AR-301), there were one subject (0.6%) in the BDP Nasal Aerosol 320 mcg/day group and four subjects (2.3%) in the placebo group who experienced SAEs. The SAEs were cholecystitis in the BDP Nasal Aerosol 320 mcg/day group and chapped lips and dry mouth, fatigue, gastroenteritis, and nasal discomfort in the placebo group. In the 6-week pivotal study in PAR patients (BDP-AR-302), only one subject (0.4%), who received the BDP Nasal Aerosol 320 mcg/day experienced SAE. The subject with multiple medical conditions reported a SAE of cardiac arrhythmia. In the long term safety study (BDP-AR-303), a total of 11 subjects experienced AEs that were of severe intensity (8 subjects, 1.9%, treated with BDP Nasal Aerosol 320 mcg/day and 3 subjects, 2.7%, treated with placebo). No study subjects experienced SAEs in the 6-week HPA Axis study (BDP-AR-304).

The case review of SAEs did not reveal new safety concerns that related to BDP Nasal Aerosol 320 mcg/day treatment. For detailed information of the SAEs reported in each study, readers are referred to Section 5.3 Discussion of Individual Studies/Clinical Trials.

7.3.3 Dropouts and/or Discontinuations

The dropouts due to adverse events in the clinical studies reviewed were summarized in Table 64. The overall incidences of dropout in the clinical studies were low. In dose finding study (BDP-AR-201) and the PAR pivotal study (BDP-AR-302), the incidences of dropout due to adverse events were higher in placebo than that in BDP Nasal Aerosol 320 mcg/day treatment. In the SAR pivotal study (BDP-AR-301), there was one dropout due to adverse events in 338 subjects. The case was of cholecystitis in the BDP Nasal Aerosol 320 mcg/day group, and was unlikely related to the study treatment. In HPA Axis study (BDP-AR-304), there was no dropout due to adverse events. In general, adverse events associated with dropouts were those seen with SAR/PAR such as sinusitis, nasopharyngitis, nasal congestion, headache, and respiratory infections, or

other conditions unlikely related with study disease and treatment such as cholecystitis and angioedema.

The early dropout rate was higher in a long term safety study (BDP-AR-303) that that in short term studies. There were 20 subjects with treatment-emergent AEs that led to discontinuation from the study, 17 subjects (4.1%) in the BDP Nasal Aerosol 320 mcg/day group and 3 subjects (2.7%) in the placebo group. The AE that most commonly led to study discontinuation was epistaxis, reported in 5 subjects in the BDP Nasal Aerosol 320 mcg/day group and no subject in the placebo group. In addition to 3 SAEs (one case of increased intraocular pressure and two cases of colon cancer) leading to study discontinuation, the other AEs leading to study discontinuation in the BDP Nasal Aerosol 320 mcg/day group were nasal septum ulceration (2 subjects), nasal discomfort (2 subjects), sinusitis (2), nasal congestion (1), headache (1), and nasal mucosal disorder (1). The SAE of increased IOP was from a female subject of 45-year-old who had baseline IOP values of 20 and 20 mmHg in left and right eye. This subject was found to have elevated IOP of 32 and 33 mmHg at TV6 (week 30). A recheck of her pressures confirmed the elevated values (30 mmHg in each eye) and the persistently raised IOP was reported as an SAE. The subject was withdrawn from the study and underwent peripheral iridotomy of both eyes. A subsequent rechecks after the treatment showed that pressures were normal at 17 and 20 mmHg. Three AEs leading to study discontinuation in the placebo group were sinusitis (2) and nasal discomfort (1).

Table 64 Summary of dropouts due to adverse events

Study number	Study type	Treatment group	Treat. duration	Number of subj.	Dropout due to adverse events
BDP-AR-201	Dose-finding, in SAR	BDP Nasal Aerosol 80 mcg	QD, 2 weeks	118	0
		BDP Nasal Aerosol 160 mcg		123	1
		BDP Nasal Aerosol 320 mcg		122	2
		Placebo		123	5
BDP-AR-301	Pivotal-SAR	BDP Nasal Aerosol 320 mcg	QD, 2 weeks	167	1
		Placebo		171	0
BDP-AR-302	Pivotal-PAR	BDP Nasal Aerosol 320 mcg	QD, 6 weeks	236	0
		Placebo		238	6
BDP-AR-303	Safety study, in PAR	BDP Nasal Aerosol 320 mcg	QD, 30/52 weeks	196/219	17
		Placebo		53/58	3
BDP-AR-304	Safety study, In PAR	BDP Nasal Aerosol 320 mcg	QD, 6 weeks	50	0
		Placebo		46	0
		Prednisone 10 mg Oral (last 7d)		11	0

7.3.4 Significant Adverse Events

Serious adverse events are discussed in section 7.3.2 above. In addition, 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 were no nasal septum perforations reported in BDP Nasal Aerosol clinical program.

In the pooled data of 2 to 6 week studies, there were one nasal erosion reported in the BDP Nasal Aerosol 80 mcg/group and one nasal ulceration in the BDP Nasal Aerosol 320 mcg/group. There were 2 cases of nasal ulceration in placebo.

In the long term safety study, there were one nasal ulceration and 4 cases of erosion, which were actually early ulceration, reported in the BDP Nasal Aerosol 320 mcg/day group. There was no nasal ulceration/erosion reported in placebo group in the long term safety study.

Reviewer's comment:
There were no nasal septum perforations reported in the BDP Nasal Aerosol *clinical program. The isolated nasal ulceration/erosion cases 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 could also 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% of any treatment group in the pooled 2- and 6-week studies are summarized in Table 65. The incidences of all adverse events were 17.7%, 14.6%, and 18.6% in BDP Nasal Aerosol 320 mcg, 160 mcg and 80 mcg, respectively. There was no apparent dose relationship with regard to the incidence of adverse events in the pooled 2- and 6-week studies. Placebo group had the highest incidence of overall adverse events (21.8%). The most common adverse events in BDP Nasal Aerosol 320 mcg treatment were nasal irritation (5.2%), headache (2.3%), and epistaxis (1.9%), and they were no apparent differences with those in placebo group. Because these common adverse events were known conditions associated with allergic rhinitis and there were no apparent differences in incidence rate comparing the BDP Nasal Aerosol treatment to placebo, the common adverse events reveal no safety signals for the BDP Nasal Aerosol treatment in the 2- and 6-week studies.

Table 65 Adverse events occurred in ≥1% of any study group in pooled 2/6-week studies

Preferred term	BDP HFA 320 mcg/day N=575	BDP HFA 160 mcg/day N=123	BDP HFA 80 mcg/day N=118	Placebo N=578
Any AE (%)	102 (17.7)	18 (14.6)	22 (18.6)	126 (21.8)
Nasal irritation	30 (5.2)	6 (4.9)	4 (3.4)	28 (4.8)
Headache	13 (2.3)	2 (1.6)	0	9 (1.6)
Epistaxis	11 (1.9)	3 (2.4)	6 (5.1)	7 (1.2)
Oropharyngeal pain	4 (0.7)	0	1 (0.8)	6 (1.0)
Upper Respiratory tract infection	4 (0.7)	1 (0.8)	1 (0.8)	6 (1.0)
Pyrexia	3 (0.5)	2 (1.6)	0	0

The adverse events in preferred terms experienced in >1% of BDP Nasal Aerosol 320 mcg treatment group in the long term safety study are summarized in Table 66. The long term (30 or 52 weeks) administration of BDP Nasal Aerosol or placebo was associated with higher incidence of adverse events. The incidence of overall adverse events in subjects who received long term treatment of BDP Nasal Aerosol 320 mcg/day was 68.2%, which was higher than that of placebo (59.5%). The most common adverse events in BDP Nasal Aerosol 320 mcg treatment were nasopharyngitis (16.1%), epistaxis (10.6%), upper respiratory tract infection (10.4%), sinusitis (8.2%), and headache (6.7%). Epistaxis was the most notable AE that had a significant increase in BDP Nasal Aerosol 320 mcg treatment group compared to

placebo at 10.6% (44/415 subjects) versus 1.8% (2/111 subjects). Also it appeared that BDP Nasal Aerosol 320 mcg treatment was associated with more severe epistaxis cases. Of epistaxis that occurred in patients treated with BDP Nasal Aerosol 320 mcg/day, 27, 12, and 6 cases were of mild, moderate, and severe intensity, respectively. While the 2 epistaxis cases in patients treated with placebo were of mild (1) and moderate (1) intensity.

Table 66 Adverse events occurred in ≥1% of BDP Nasal Aerosol 320 mcg treatment group in long term safety study

Adverse Event	BDP HFA 320 mcg N = 415	Placebo N = 111
	Subject n (%)	Subject n (%)
Any AE	283 (68.2)	66 (59.5)
Nasopharyngitis	67 (16.1)	14 (12.6)
Epistaxis	44 (10.6)	2 (1.8)
Upper respiratory tract infection	43 (10.4)	7 (6.3)
Sinusitis	34 (8.2)	8 (7.2)
Headache	28 (6.7)	6 (5.4)
Sinus headache	15 (3.6)	2 (1.8)
Oropharyngeal pain	14 (3.4)	2 (1.8)
Bronchitis	13 (3.1)	4 (3.6)
Nasal discomfort	12 (2.9)	2 (1.8)
Urinary tract infection	11 (2.7)	4 (3.6)
Gastroenteritis viral	10 (2.4)	4 (3.6)
Acute sinusitis	9 (2.2)	6 (5.4)
Cough	9 (2.2)	5 (4.5)
Viral upper respiratory tract infection	9 (2.2)	2 (1.8)
Back pain	8 (1.9)	3 (2.7)
Rhinorrhoea	7 (1.7)	3 (2.7)
Sneezing	4 (1.0)	3 (2.7)

Further exam of data showed that the incidences of overall AEs and common AEs adverse events and epistaxis were dependent on the duration of BDP Nasal Aerosol 320 mcg treatment. In the subgroup of subjects who received 30 weeks of BDP Nasal Aerosol 320 mcg treatment, the incidence of overall AEs was 61.7% (121/196 subjects), versus the 74% (162/269 subjects) in the group received 52 weeks of the treatment.

For most common AEs, the incidences were also associated with the duration of the treatment. In the subgroup who received 30 weeks of BDP Nasal Aerosol 320 mcg treatment, the incidences of nasopharyngitis, epistaxis, upper respiratory tract infection, and sinusitis were 15.8%, 8.2%, 9.2%, and 6.6%, as compared to the incidences of 16.4%, 12.8%, 11.4%, and 9.6%, respectively, in the subgroup who received 52 weeks of BDP Nasal Aerosol 320 mcg treatment.

Reviewer's comment:
Epistaxis is known to associate with long term nasal exposure to corticosteroids. As references, Veramyst (fluticasone furoate) Nasal Spray had an epistaxis incidence of 20% in a 52-week study, and Zetonna (ciclesonide) Nasal Aerosol had an epistaxis incidence of 11.4% in a 26-week study [Product Labels of Veramyst and Zetonna]. The reported incidence of epistaxis in BDP Nasal Aerosol 320 mcg treatment group did not reveal a new safety signal in the 52 weeks long term safety study.

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-302) and the HPA axis study (BDP-AR-304). All laboratory values obtained at the final visit were compared to baseline values at screening. The changes or shifts were categorized as "to low", "within normal/no change", and "to high", based on the reference range, regardless of the extent that was above or below the reference range. Any clinically significant laboratory abnormalities were to be reported as AEs.

There were no significant changes in clinical laboratory tests during the two studies. In pooled data, 90% or more of subjects were in the "within normal/no change" group for most test items. There were no notable differences between the treatment of BDP Nasal Aerosol 320 mcg and placebo groups. Only two AEs were reported that were due to abnormalities in hematology or blood chemistry tests as anemia and increased blood glucose. The two reports came from one subject in study BDP-AR-302. The subject was a 53-year-old female with a medical history of PAR and SAR, asthma, back pain, musculoskeletal pain, sinusitis, and increased blood pressure, who was randomized to receive BDP Nasal Aerosol 320 mcg/day. At screening, the subject's hemoglobin value was 11.9 g/L and the glucose value was 111 mmol/L. At the end of study the hemoglobin value was 11.5 g/L and the glucose value was 132 mmol/L. The two AEs were reported as of mild intensity.

Reviewer's comment:
The clinical laboratory finding does not reveal any safety signals.

7.4.3 Vital Signs

In all five studies reviewed, vital signs ((systolic and diastolic blood pressure and pulse rate) were measured at screening and the final visit. In all the studies only small mean 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 seven AEs reported due to increased blood pressure in five studies. In the 6-week PAR pivotal study (BDP-AR-302) one subject who received placebo reported increased blood pressure. In the long term safety study (BDP-AR-304), five subjects in the treatment of BDP Nasal Aerosol 320 mcg and one subject in placebo reported hypertension. None of these cases of hypertension were of severe intensity, and were considered by the investigators to be not related to the study treatment.

Reviewer's comment:
The isolated cases of hypertension in the 52 weeks long term safety study are not a safety signal in this allergic rhinitis program.

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-302) and the HPA axis study (BDP-AR-304). The changes of ECG that were observed in the two 6-week studies were similar across the treatment and placebo groups. No clinically significant changes 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, perforation and ulceration). Clinically significant findings were reported as AEs. Local adverse events indentified by nasal examination have been discussed in section 7.3.3 (for nasal ulceration/erosion) and in section 7.4.1 (for epistaxis).

Ocular Examinations

To assess ocular effects of BDP Nasal Aerosol, ocular examinations were conducted in the long term safety study BDP-AR-303. A certified ophthalmologist performed all eye evaluations. A subset of 245 subjects (197 in BDP Nasal Aerosol 320 mcg group and

48 in placebo group) were conducted eye examinations at screening, week 30 and week 52 for best corrected visual acuity (BCVA), intraocular pressure (IOP), and cataract. BCVA was evaluated by Logarithmic Visual Acuity Chart, and the measurement was logarithm of the minimum angle of resolution (LogMAR). A negative change in LogMar represents an improvement in BCVA. IOP was measured using an adequately calibrated tonometer affixed to a slit lamp biomicroscope. A value ≥21 mmHg was considered as abnormal eye pressure. The evaluation of cataract was through a procedure Lens Opacities Classification System Version III (LOCS III). LOCS III graded nuclear opalescence (NO), nuclear color (NC), cortical (C) and posterior subcapsular (P) lens opacities after maximal pupillary dilatation had been achieved at least 6.0 mm. The LOCS III scales were decimalized numbers ranging from 0.1 (representing a clear or colorless lens) to 5.9 (on the C and P scales) and 6.9 on the NO and NC scales. The higher numbers represented advanced stages of opacification or coloration.

At Baseline, for the average of both eyes, the mean BCVA was logMAR -0.030 in the BDP Nasal Aerosol 320 mcg/day group and logMAR -0.041 in the placebo. Only small changes from Baseline were seen at week 30 or week 52 in each group. At week 30 in BDP Nasal Aerosol 320 mcg/day group, the mean change was logMAR 0.004 and in placebo group the mean change was logMAR -0.005. At week 52, the mean change from baseline was logMAR -0.002 for BDP Nasal Aerosol 320 mcg/day and logMAR -0.014 for placebo. The estimated treatment difference was logMAR 0.008 (p=0.414) at week 30 and logMAR 0.012 (p=0.222) at week 52. No BCVA changes were considered clinically meaningful.

There was one AE of visual impairment of mild intensity reported in a subject treated with BDP Nasal Aerosol 320 mcg/day. The subject was referred to an ophthalmologist for prescription of new corrective lenses. This AE was not considered to be related to study treatment by the investigator.

IOP measurements were similar in the two groups (15.036 mmHg for BDP Nasal Aerosol 320 mcg/day and 14.990 mmHg for placebo) at baseline. Small decreases in IOP were observed in both treatment groups at week 30 (mean change of -0.429 mmHg for BDP Nasal Aerosol 320 mcg/day and -0.711 mmHg for placebo) and at Week 52 (mean change of -0.251 mmHg for BDP Nasal Aerosol 320 mcg/day and -0.497 mmHg for placebo). The mean difference between BDP Nasal Aerosol 320 mcg group and placebo was 0.282 mmHg (p=0.433) at week 30 and 0.246 mmHg (p=0.451) at week 52, respectively. Similar results were seen for the right eye and the left eye.

There were 26 subjects (15 subjects, 7.6%, in BDP HFA 320 mcg/day group and 11 subjects, 22.9%, in placebo group) who had IOP values ≥21 mmHg on either left or right eye at screening , week-30, or week-52 measurement. Most subjects had IOP of 21 or 22 mmHg. Adverse events of increased intraocular pressure were reported for 2 subjects. Both cases were in the group treated with BDP Nasal Aerosol 320 mcg/day at

the same investigator site. One case was reported as a SAE. The subject was a 45 years old female who had baseline IOP values of 20 mmHg, and elevated IOP values of 32 and 33 mmHg at week 30. The subject was withdrawn from the study, and underwent peripheral iridotomy of both eyes. A subsequent rechecks showed that pressures were normal at 17 and 20 mmHg. Another case was reported as an AE. The subject was a 17 years old male who had baseline IOP values of 20 and 19 mmHg in the right and left eye, respectively, and mildly elevated IOP values of 22 and 26 mmHg at week 30. The subject continued the treatment of BDP Nasal Aerosol 320 mcg. Follow-up measurements made 3 weeks later were similar to Baseline values (20 and 19 mmHg). Subsequent IOP measurements confirmed that similar or lower IOP throughout the rest of the 52-week treatment period.

At Baseline, mean values of LOCS III scales were similar in BDP Nasal Aerosol 320 mcg group and placebo for NO, C and P (NO: 1.372 for BDP Nasal Aerosol 320 mcg/day and 1.289 for placebo; C: 0.189 for BDP Nasal Aerosol 320 mcg/day and 0.195 for placebo; P: 0.114 for BDP Nasal Aerosol 320 mcg/day and 0.125 for placebo). Values for NC were slightly higher in the BDP Nasal Aerosol 320 mcg/day group (1.005) than in the placebo group (0.730). The majority of subjects in both treatment groups had no change in LOCS III grading of opacities at both Week 30 (92.7% for BDP HFA 320 mcg/day and 95.3% for placebo) and Week 52 (87.8% for BDP HFA 320 mcg/day and 91.1% for placebo. At Week 30, 7.3% of subjects in the BDP HFA 320 mcg/day group and 4.7% of subjects in the placebo group had a Class I shift and 1.7% and 2.3%, respectively had a Class II shift. At Week 52, 12.2% of subjects in the BDP HFA 320 mcg/day group and 8.9% of subjects in the placebo group had a Class I shift and 4.3% and 2.2%, respectively, had a Class II shift. A few subjects (2 subjects at Week 30 and 6 subjects at Week 52) had a Class III increase and the proportion of subjects with such an increase was similar in the two treatment groups (at Week 30, 0.6% versus 2.3% and at Week 52, 2.7% versus 2.2% for BDP HFA 320 mcg/day and placebo, respectively). There were no reports of development of cataracts during the study.

Reviewer's comment:
There were no clinically important differences between the BDP Nasal Aerosol 320 mcg/day treatment and placebo in mean best-corrected visual acuity. There were 26 subjects (15 subjects, 7.6%, treated with BDP HFA 320 mcg/day and 11 subjects, 22.9%, treated with placebo) who had IOP values ≥21 mmHg on either left or right eye at screening, week-30, or week-52 measurement. However, there were only 4 cases of IOP above 22 mmHg after receiving the treatment (3 with BDP Nasal Aerosol 320 mcg/day and one with placebo) and 2 of the increased IOP were reported as AEs. The majority of subjects in both treatment groups had no change in LOCS III grading of opacities in the study. Only 2 subjects at Week 30 and 6 subjects at Week 52) had a Class III increase and the proportion of subjects with such an increase was similar in the two treatment groups (at Week 30, 0.6% versus 2.3% and at Week 52, 2.7% versus 2.2% for BDP HFA 320 mcg/day and placebo, respectively). There were no reports of

development of cataracts during the study. The ocular examinations did not reveal new safety signals.

HPA Axis Study

The effect of BDP Nasal Aerosol on hypothalamic - pituitary- adrenal **(**HPA) axis was assessed in adolescent and adult subjects of 12 to 45 years old with PAR (study BDP-AR-304). Subjects were randomized in a 4:4:1 ratio to receive 6 weeks BDP Nasal Aerosol 320 mcg/day, placebo nasal aerosol, or placebo nasal aerosol plus prednisone 10 mg/day during the last 7 days. The primary analysis was the 24-hour serum cortisol weighted geometric mean for BDP Nasal Aerosol and placebo after 42 days of treatment.

The primary endpoint 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. Baseline serum cortisol weighted geometric means were similar in the BDP Nasal Aerosol 320 mcg/day and placebo groups (9.04 and 8.45 mcg/dL, respectively). After 6 weeks of treatment the geometric means were also similar (8.18 and 8.01 mcg/dL, respectively) and there was little change from baseline values in either treatment group. The ratio of Week 6 value/Baseline value was 0.90 for BDP Nasal Aerosol 320 mcg/day group and 0.95 for placebo group. The geometric mean ratio for BDP Nasal Aerosol 320 mcg/day to placebo was 0.96 (95% CI: 0.87, 1.06). Thus, BDP Nasal Aerosol 320 mcg/day for 6 weeks did not cause a statistically significant lower 24-hour serum cortisol level.

The secondary analysis compared the effect of placebo aerosol plus prednisone 10 mg/day for 7 days (active control) versus placebo aerosol on HPA-axis function as measured by 24-hour serum cortisol weighted mean. Mean baseline values were similar in the two groups (8.45 mcg/dL for placebo and 7.33 mcg/dL for placebo plus prednisone 10 mg/day). At Week 6, the geometric mean was, as expected, markedly lower in the placebo aerosol plus prednisone 10 mg/day for 7 days (2.31 mcg/dL) than in the placebo aerosol group (8.01 mcg/dL). A marked decrease from baseline was seen in the placebo plus prednisone 10 mg/day for 7 days compared with the change from baseline in the placebo aerosol group: the ratio of Week 6/Baseline was 0.31 for placebo plus prednisone 10 mg/day group and 0.95 for placebo. The geometric mean ratio for placebo to placebo plus prednisone 10 mg/day for 7 days was 3.17 (95% CI: 2.68, 3.74), indicating that placebo plus prednisone 10 mg/day for 7 days resulted in an approximate threefold reduction in HPA axis function compared with placebo.

The study demonstrated that BDP Nasal Aerosol 320 mcg/day for 6 weeks was not associated with HPA-axis suppression relative to placebo in adult and adolescent subjects (12 years of age and older) with PAR.

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 occurred in BDP Nasal Aerosol clinical studies. In pooled data from short term studies, patients received three doses of BDP Nasal Aerosol 80, 160, and 320 mcg per day. Table 64 in Section 7.4.1 showed that incidences of overall AEs and individual AEs were all similar among different dose groups and between treatment and placebo groups.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was demonstrated in the 52-week long term safety study. The incidence of overall adverse events in subjects who received long term treatment of BDP Nasal Aerosol 320 mcg/day was 68.2%, which was higher than that in the short term studies of 2 to 6 weeks (17.7%). Also the incidence of epistaxis in patients received long term treatment of BDP Nasal Aerosol 320 mcg was 10.6%, higher than that in the short term studies (1.9%).

Further exam of the long term safety study data showed that the incidences of overall AEs and common AEs adverse events and epistaxis were dependent on the duration of BDP Nasal Aerosol 320 mcg treatment. In the subgroup of subjects who received 30 weeks of BDP Nasal Aerosol 320 mcg treatment, the incidence of overall AEs was 61.7%, versus 74% in the group received 52 weeks of the treatment. The incidence of epistaxis was 8.2% in subjects received 30 weeks of BDP Nasal Aerosol 320 mcg treatment versus 12.8% in the group received 52 weeks of the treatment.

7.5.3 Drug-Demographic Interactions

Subgroup analysis of the AE data did not reveal any apparent drug-demographic interactions.

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

The Applicant plans to study BDP Nasal Aerosol in pediatric population to support efficacy and safety and to assess the effect of BDP Nasal Aerosol on HPA axis in pediatric subjects 2 to 11 years of age. 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 BDP Nasal Aerosol clinical program. 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

The Applicant submitted a 120-day safety update for BDP Nasal Aerosol on September 21, 2011.

7.7.1 Update Safety Data of Completed Studies

There were two female subjects became pregnant while receiving the study treatment. The reports of the pregnant were received after the completion of the study report. Both cases were negative in pregnant test at screening. One case of pregnant was a 26-year old female and randomized to receive BDP Nasal Aerosol 320 mcg/day treatment in the PAR pivotal study BDP-AR-302. According to the event report, the subject received 4 weeks treatment before she was found to be pregnant. There were no complications with the pregnancy had been reported and she did not experience any adverse events during the study. Per the pregnancy outcome report, a healthy baby was delivered spontaneously and vaginally, and there were no reported complications during pregnancy, labor or delivery. Another case of pregnant was a 27-year old female and randomized to receive placebo in the long term safety study BDP-AR-304. The subject was found to be pregnant at week 50 of this 52-week study. Per the pregnancy outcome report, a healthy baby was delivered by elective Cesarian section. There were no reported complications during pregnancy, labor or delivery.

7.7.2 Safety Data from Clinical Studies Not Included in the Submission

The Applicant had initiated a pediatric program and conducted a pediatric study for BDP Nasal Aerosol. (b) (4)

8 Postmarket Experience

BDP Nasal Aerosol has not been marketed in any country and there are no post marketing data available.

9 Appendices

9.1 Literature Review/References

The Applicant references 27 articles from the scientific literature in support of the safety and efficacy of BDP Nasal Aerosol. This reviewer searched PubMed with the search terms "beclomethasone dipropionate" and "safety," limited to clinical trials written in English and published in the past 10 years. A total of 37 articles were retrieved. No new safety signals were identified from this literature search.

9.2 Labeling Recommendations

Labeling negotiations are ongoing at the time of this review. Based on the efficacy data, BDP Nasal Aerosol 320 mcg daily treatment improves nasal symptoms associated with SAR and PAR. The effects of BDP Nasal Aerosol 320 mcg/day treatment on improvement of the disease-specific quality of life as measured by the mean change in RQLQ, and on non-nasal symptoms as measured by rTOSS were equivocal. However, the Applicant proposed indication (b) (4) (b) (4) (b) (4). Since of BDP Nasal Aerosol were not supported by data, the indication will be changed to "for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis".

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held for this NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
02/17/2012

ANTHONY G DURMOWICZ
02/17/2012

MEDICAL OFFICER REVIEW
Division of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 202-813	**TRADE NAME:**	BDP Nasal Aerosol
APPLICANT/SPONSOR:	TEVA Global	**USAN NAME:**	beclomethasone dipropionate
MEDICAL OFFICER:	Xu Wang, M.D., Ph.D.		
TEAM LEADER:	Anthony G. Durmowicz, M.D.	**CATEGORY:**	Corticosteroid
DATE:	7/22/2011	**ROUTE:**	Nasal Aerosol

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
05/24/2011	05/24/2011	NDA 202,813	NDA submission

RELATED APPLICATIONS

Document Date	Application Type	Comments
09/27/2010	IND 101,639	Pre-NDA meeting package

REVIEW SUMMARY:

This is a 505(b)(2) application for BDP (beclomethasone dipropionate) Nasal Aerosol. BDP has been approved as an oral inhalation drug as QVAR Inhalation Aerosol (NDA 20-911, approved 9/15/00). The Applicant owns the QVAR (NDA 20-911). BDP Nasal Aerosol uses the exact same drug product canister, components and controls as QVAR in NDA 20-911, and inserts the canisters into the newly developed plastic nasal actuator that is designed for a nasal route of delivery. The proposed indication for the BDP Nasal Aerosol in this submission is the treatment (b) (4) of seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents patients 12 years of age and older.

The clinical program for BDP Nasal Aerosol consists of 11 clinical studies. The six adult and adolescent studies were conducted first and the data are submitted in the present NDA. The pediatric program will be conducted later for patients 2 to 11 years of age, and the data will be provided in a supplemental NDA submission at a later date. The safety data from the orally inhaled route of administration of this formulation will provide further supportive evidence for the development of this product via the nasal route.

The development program has been conducted in accordance with the FDA guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000). The submission is adequately indexed to allow for clinical review. The recommendation for the submission is "fileable" from a clinical perspective

There is one comment to be communicated to the Applicant in the 74-day letter.

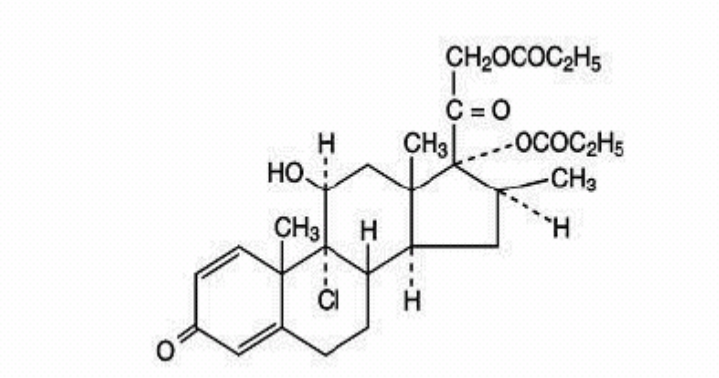
OUTSTANDING ISSUES: The proposed indication implies (b) (4) of the proposed drug. This will be a review issue whether or not the data support this claim.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILABLE** ___X____	**NOT FILABLE**_____	
	APPROVAL_____	**APPROVABLE**_____	**NOT APPROVABLE**_____
OTHER ACTION:	**COMMENTS FOR SPONSOR**_____X_		

1. GENERAL INFORMATION

Generic name: BDP HFA Nasal Aerosol
Chemical name and structure: Beclomethasone Dipropionate



Pharmacologic category: Corticosteroid
Molecular weight: (b) (4)

This is a 505(b)(2) application for BDP (beclomethasone dipropionate) Nasal Aerosol. BDP has been approved as an oral inhalation drug as QVAR 40 mcg and 80 mcg Inhalation Aerosol (NDA 20-911, approved 9/15/00). The Applicant owns the QVAR (NDA 20-911). BDP HFA Nasal Aerosol uses the exact same drug product canister, components and controls as QVAR in NDA 20-911, and inserts the canisters into the newly developed plastic nasal actuator that is designed for a nasal route of delivery. BDP Nasal Aerosol is a pressurized, non-aqueous solution in a metered-dose aerosol device intended for intranasal use only. It contains a solution of BDP in propellant HFA-134a (1,1,1,2-tetrafluoroethane) and dehydrated ethanol. The proposed indication for the BDP Nasal Aerosol in this submission is the treatment (b) (4) of seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents patients 12 years of age and older.

The clinical program for BDP Nasal Aerosol consists of 11 clinical studies. The six adult and adolescent studies were conducted first and the data are submitted in the present NDA. The six clinical studies include a phase 1 PK study, a phase 2 dose ranging study, a pivotal study for SAR, a pivotal study for PAR, a long term safety study, and a HPA Axis study. The pediatric program will be conducted later for patients 2 to 11 years of age, and the data will be provided in a supplemental NDA submission at a later date. The safety data from the orally inhaled route of administration of this formulation will provide further supportive evidence for the development of this product via the nasal route.

The application is submitted electronically.

1. CLINICAL DEVELOPMENT PROGRAM

The Applicant planned 11 clinical studies to demonstrate the efficacy and safety of the BDP Nasal Spray in allergic rhinitis (SAR and PAR). The proposed studies are listed in Table 1

below. The adult and adolescent studies were conducted first and the data are included in the present NDA submission. The pediatric program will be conducted later, and the data will be provided in a supplemental NDA submission at a later date. The safety data from the orally inhaled route of administration of this formulation will provide further supportive evidence for the development of this product via the nasal route.

Table 1. Clinical development program for BDP Nasal Aerosol

Study	Description	Endpoint
BDP-AR-101	Phase 1 PK study, single dose	PK, safety
BDP-AR-201	Phase 2 dose range study in SAR, 2 wks	Efficacy, safety
BDP-AR-301	Pivotal study in SAR patients, 2 wks	Efficacy, safety
BDP-AR-302	Pivotal study in PAR patients, 6 wks	Efficacy, safety
BDP-AR-303	Long term safety study in PAR, 52 wks	Efficacy, safety
BDP-AR-304	HPA Axis study in subjects ≥12 yrs, 6 wks	Safety
BDP-AR-305	Pediatric study in SAR pts 6-11 yrs, 2 wks	Efficacy, safety
BDP-AR-306	Pediatric study in PAR pts 6-11 yrs, 12 wks	Efficacy, safety
BDP-AR-307	Pediatric HPA Axis study in children 6-11yrs, 6 wks	Safety
(b) (4)	Pediatric safety study in PAR pts 2-5 yrs, 12 wks	Safety
(b) (4)	Pediatric HPA Axis study in children 2-5 yrs, 6 wks	Safety

2. FOREIGN MARKETING AND REGULATORY HISTORY

The proposed product, BDP HFA 320 mcg Nasal Aerosol, has not been marketed in any country. The same chemical formulation and concentration of BDP has been available as the orally inhaled BDP HFA formulation (QVAR Inhalation Aerosol) since September 2000 for the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. Post-marketing data are available for this formulation in the respective Annual Periodic Adverse Drug Experience Reports.

The sponsor had a pre-IND meeting with the Division on April 2, 2008 to discuss the development plan for the proposed product (named (b) (4) Nasal Aerosol at the time), and subsequently submitted the IND (#101,639) to assess the assess the efficacy and safety of BDP Nasal Spray in SAR patients 12 years and older on January 20, 2009. The sponsor also discussed the format and organization of data in the NDA submission [IND 101,639, BDP Nasal Aerosol, Pre-NDA Meeting Minutes, 11/05/2010].

3. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [m1\11-forms\112-fda-form-356h]

- Index [index.xml]
- Summary [m2\22-intro and 25-clin-over]
- Clinical technical section
  - Clinical summary
    - Clinical efficacy [m2\273-Summary of clinical efficacy]
    - Clinical safety [m2\274-Summary of clinical safety]
    - Integrated summary of Safety [m5\5353-ISS]
    - Integrated summary of efficacy [m5\5353-ISE]
  - Clinical study reports
    - Study reports of controlled clinical studies [m5\5351]
    - Risk/benefit analysis: not provided
    - Good Clinical Practice certification [m5\53513-clin-stud-rep-Section 5 – Ethics]
  - Debarment certification [m1\13-administrative-information\133-debarment-certification]
  - Pediatric use [m1\19-pediatric-administrative-information\191-request-waiver-pediatric-studies; 192- request-deferral-pediatric studies]
- Labeling [m1\us\114-labeling\1141-draft-labeling]
- Case report forms [m5\535124-clin-stud-rep-Case report forms]
- Financial disclosure [m1\13-administrative-information\134-financial-certification-disclosure]

4. CLINICAL STUDIES

There are six clinical study reports in this submission (Table 2). The efficacy evaluation in the adult and adolescent population consists of one pivotal study in SAR (BDP-AR-3-1) for 2 weeks and one pivotal study in PAR (BDP-AR-302) for 6 weeks. The dose ranging study BDP-AR-201 also provided efficacy data in SAR patients. In addition to safety data in pivotal studies, the Applicant conducted a long term safety study of 52 weeks and a HPA Axis study.

Table 2. Summary of clinical studies in the NDA submission

Study number	Study type	Treatment group	Treat. duration	Number of subj.	Design*	Diagnosis of subj.	Materials submitted
BDP-AR-101	Bioavailability	BDP Nasal Aerosol 320 mcg BDP Nasal Aerosol 80 mcg BDP HFA 320 mcg oral inhal.	Single dose	30	RD, Open label, CO	Healthy subjects	Study report
BDP-AR-201	Dose-finding	BDP Nasal Aerosol 80 mcg	QD 2 weeks	118	RD, DB, PC, PG	SAR	Study report

		BDP Nasal Aerosol 160 mcg BDP Nasal Aerosol 320 mcg Placebo		123 122 123			
BDP-AR-301	Pivotal-SAR	BDP Nasal Aerosol 320 mcg Placebo	QD 2 weeks	167 171	RD, DB, PC, PG	SAR	Study report
BDP-AR-302	Pivotal-PAR	BDP Nasal Aerosol 320 mcg Placebo	QD 6 weeks	236 238	RD, DB, PC, PG	PAR	Study report
BDP-AR-303	Safety	BDP Nasal Aerosol 320 mcg Placebo	QD 30/52 weeks	196/219 53/58	RD, DB, PC, PG	PAR	Study report
BDP-AR-304	Safety	BDP Nasal Aerosol 320 mcg Placebo Prednisone 10 mg Oral (last 7 d)	QD 6 weeks	50 46 11	RD, DB, PC, AC, PG	PAR	Study report

* RD: Randomized; CO: Cross over; DB: Double blind; PC: Placebo controlled; AC: Active controlled; PG: Parallel group

Reviewer's comment:
The clinical development program for the SAR/PAR indications has been conducted in accordance with the FDA guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000).

Study BDP-AR-201

This was a double-blind, randomized, placebo-controlled, parallel-group, multi-center, dose-ranging study. The objective of the study is to determine the optimally safe and effective dose of BDP (beclomethasone dipropionate) Nasal Aerosol in subjects with SAR. A total of 486 patients, aged 12 years and older, with a history of SAR for at least 2 years were randomized to receive 3 doses of BDP Nasal Aerosol (80, 160, and 320 mcg daily) and placebo for 2 weeks. The primary efficacy endpoint was the average AM and PM subject-reported reflective TNSS (rTNSS) over the 2-week treatment period. Secondary endpoints included average AM and PM subject-reported instantaneous TNSS (iTNSS) over the 2-week treatment period, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Ocular Symptom score, and non-nasal symptom score. Safety monitoring included AEs, physical examinations including ENT examinations, and vital signs.

The mean changes from baseline in the primary endpoint rTNSS and in iTNSS were summarized in Table 3 below. At baseline, the mean of the average AM and PM subject-reported rTNSS (out

of 12) was 9.33, 9.24, 9.17, and 8.98 for the BDP Nasal Aerosol 80 mcg/day, 160 mcg/day, 320 mcg/day and placebo groups, respectively. Across the 2-week treatment period, average AM and PM subject-reported rTNSS decreased in all treatment groups, including placebo. The LS mean change from baseline was -1.88 for BDP Nasal Aerosol 80 mcg/day, -1.87 for 160 mcg/day, -2.22 (0.18) for 320 mcg/day and -1.59 for the placebo. The LS mean difference between BDP Nasal Aerosol treatment was -0.63, -0.29, and -0.29 for 320 mcg/day, 160 mcg/day, and 80 mcg/day, respectively. Although these differences with placebo were not statistically significant (with the 95% CI that included zero), the treatment with BDP Nasal Aerosol did show a decreased rTNSS. The largest effect size was obtained in the group of 320 mcg/day treatment. The LS mean changes from baseline in iTNSS were similar to those in rTNSS, numerically greater in treatment groups that in placebo. No significant differences between BDP Nasal Aerosol and placebo were observed for ocular symptom scores or non-nasal symptom scores.

Of the 486 subjects randomized to study treatment, 82 (16.9%) experienced treatment-emergent AEs: 22 subjects (18.6%) receiving BDP HFA 80 mcg/day, 18 subjects (14.6%) receiving BDP HFA 160 mcg/day, 22 subjects (18.0%) receiving BDP 320 mcg/day, and 20 subjects (16.3%) receiving placebo. There was no death in the study. A total of 17 subjects experienced SAEs. The most commonly reported AEs were nasal discomfort, epistaxis, and headache. There were no significant differences between treatment groups with respect to incidence of AEs and no evidence for dose-related differences.

Table 3 Mean change from baseline in rTNSS and iTNSS, BDP-AR-201

Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	p Value
Reflective Total Nasal Symptom Scores (rTNSS)						
BDP HFA 320 mcg/day	122	9.17 (1.66)	-2.22 (0.18)	-0.63	-1.13, 0.13	0.013
BDP HFA 160 mcg/day	123	9.24 (1.57)	-1.87 (0.18)	-0.29	-0.78, 0.21	0.257
BDP HFA 80 mcg/day	118	9.33 (1.72)	-1.88 (0.18)	-0.29	-0.80, 0.21	0.255
Placebo	123	8.98 (1.47)	-1.59 (0.18)			
Instantaneous Total Nasal Symptom Scores (iTNSS)						
BDP HFA 320 mcg/day	122	8.32 (1.98)	-2.10 (0.18)	-0.60	-1.09, -0.11	≤0.016
BDP HFA 160 mcg/day	123	8.28 (2.15)	-1.71 (0.18)	-0.22	-0.70, 0.27	0.385
BDP HFA 80 mcg/day	118	8.36 (2.19)	-1.77 (0.18)	-0.27	-0.77, 0.22	0.278
Placebo	123	8.01 (1.93)	-1.50 (0.18)			

Study BDP-AR-301

This was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical study to assess the efficacy and safety of BDP Nasal Aerosol (320 mcg, once daily) in the treatment of SAR in subjects 12 years of age and older. A total of 340 patients, 12 years of age and older, with a documented history of SAR to the relevant seasonal allergen (mountain cedar pollen) for a minimum of two years immediately preceding the study participated in the study. The SAR had to be of sufficient severity (rTNSS ≥6 out of 12) to be randomized. There were 169 and 171 patients received BDP Nasal Aerosol 320 mcg once daily and placebo for 2 weeks, respectively. The primary efficacy endpoint was the average AM and PM subject-reported reflective TNSS (rTNSS) over the 2-week treatment period. Secondary endpoints included average AM and PM subject-reported instantaneous TNSS (iTNSS) over the 2-week treatment period, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and Total Ocular Symptom Score (TOSS). Safety monitoring included AEs, physical examinations including ENT examinations, and vital signs.

The mean changes from baseline in the primary endpoint rTNSS and in iTNSS, RQLQ, and Ocular Symptom score were summarized in Table 4 below. At baseline, the mean of the average AM and PM subject-reported rTNSS was 9.6, for BDP Nasal Aerosol 320 mcg/day and 9.5 for placebo group. Across the 2-week treatment period the LS mean change from baseline in average AM and PM subject-reported rTNSS was -2.0 for BDP Nasal Aerosol 320 mcg/day and -1.0 for the placebo group. The treatment difference between BDP Nasal Aerosol 320 mcg/day and placebo in rTNSS was -0.91 ($p<0.001$). The treatment difference between BDP Nasal Aerosol 320 mcg/day and placebo in iTNSS, RQLQ, and Ocular Symptom Score were -0.92 ($p<0.001$), -0.48 ($p=0.005$), and -0.56 ($p=0.002$), respectively.

In this study, a total of 47 patients (13.9%) experienced at least one treatment emergent AE: 23 (13.8%) in the BDP Nasal Aerosol 320 mcg/day group and 24 (14.0%) in the placebo group. The most commonly reported AE was nasal discomfort reported in 11 subjects (6.6%) in the BDP Nasal Aerosol 320 mcg/day group and 10 subjects (5.8%) in the placebo group. No other AE was reported in more than 2% of subjects in either treatment group. Only 1 subject in the BDP Nasal Aerosol 320 mcg/day group and 4 subjects in the placebo group experienced AEs of severe intensity. No patients died during the study.

Table 4 Mean change from baseline in rTNSS, iTNSS and RQLQ, BDP-AR-301

Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	p Value
Reflective Total Nasal Symptom Scores (rTNSS)						
BDP HFA 320 mcg/day	167	9.6 (1.51)	-2.0 (0.16)	-0.91	-1.3, -0.5	<0.001
Placebo	171	9.5 (1.54)	-1.0 (0.15)			
Instantaneous Total Nasal Symptom Scores (iTNSS)						
BDP HFA 320 mcg/day	167	9.0 (1.74)	-1.7 (0.15)	-0.92	-1.3, -0.5	<0.001
Placebo	171	8.7 (1.8)1	-0.8 (0.15)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)						
BDP HFA 320 mcg/day	129	4.3 (0.78)	-1.2 (0.12)	-0.48	-0.8, -0.1	0.005
Placebo	121	4.4 (0.80)	-0.8 (0.12)			
Reflective Ocular Symptom Scores						
BDP HFA 320 mcg/day	167	6.7 (1.50)	-1.3 (0.13)	-0.56	-0.9, -0.2	0.002
Placebo	171	6.6 (1.46)	-0.7 (0.12)			

Study BDP-AR-302

This was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical study to assess the efficacy and safety of BDP Nasal Aerosol (320 mcg, once daily) in the treatment of perennial allergic rhinitis (PAR) in subjects 12 years of age and older. A total of 474 patients, with a documented history of PAR for at least 2 years, were randomized to receive the treatment (236) and placebo (238) for 6 weeks. The PAR had to be of sufficient severity (rTNSS ≥6 out of 12). The primary efficacy endpoint was the average AM and PM subject-reported reflective TNSS (rTNSS) over the 6-week treatment period. Secondary endpoints included average AM and PM subject-reported instantaneous TNSS (iTNSS) over the 6-week treatment period, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety monitoring included AEs, physical examinations including ENT examinations, vital signs, ECG, and laboratory tests.

The mean changes from baseline in the primary endpoint rTNSS, and in iTNSS and RQLQ were summarized in Table 5 below. At baseline, the mean of the average AM and PM subject-reported rTNSS was 8.9 for BDP Nasal Aerosol 320 mcg/day and 9.0 for placebo group. Across the 6-week treatment period the LS mean change from baseline in average AM and PM subject-reported rTNSS was -2.5 for BDP Nasal Aerosol 320 mcg/day and -1.6 for the placebo group. The treatment difference between BDP Nasal Aerosol 320 mcg/day and placebo in rTNSS was -0.84 ($p<0.001$). The treatment difference between BDP Nasal Aerosol 320 mcg/day and placebo in iTNSS and RQLQ -0.78 ($p<0.001$) and -0.58 ($p=0.005$) ($p=0.001$), respectively.

In this study, a total of 112 patients (23.6%) experienced at least one treatment emergent AE: 48 (20.3%) in the BDP Nasal Aerosol 320 mcg/day group and 64 (26.9%) in the placebo group. The most commonly reported AE was nasal discomfort, reported in 14 subjects (5.9%) in the BDP Nasal Aerosol 320 mcg/day group and 12 subjects (5.0%) in the placebo group, headache, reported in 3 subjects (1.3%) in the BDP Nasal Aerosol 320 mcg/day group and 5 subjects (2.1%) in the placebo group. No other AE was reported in more than 2% of subjects in either treatment group. Only 1 subject in the BDP Nasal Aerosol 320 mcg/day group experienced AEs of severe intensity. No patients died during the study.

Table 5 Mean change from baseline in rTNSS, iTNSS and RQLQ, BDP-AR-302

Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	p Value
Reflective Total Nasal Symptom Scores (rTNSS)						
BDP HFA 320 mcg/day	232	8.9 (1.70)	-2.5 (0.14)	-0.84	-1.2, -0.5	<0.001
Placebo	234	9.0 (1.73)	-1.6 (0.14)			
Instantaneous Total Nasal Symptom Scores (iTNSS)						
BDP HFA 320 mcg/day	232	8.1 (1.98)	-2.1 (0.13)	-0.78	-1.1, -0.4	<0.001
Placebo	234	8.3 (1.96)	-1.4 (0.13)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)						
BDP HFA 320 mcg/day	132	4.2 (0.74)	-1.5 (0.14)	-0.58	-0.9, -0.2	0.001
Placebo	125	4.2 (0.81)	-0.9 (0.14)			

Study BDP-AR-303

This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group clinical study to assess the long term safety of BDP Nasal Aerosol (320 mcg, once daily) in the treatment of PAR in subjects 12 years of age and older. A total of 526 patients, with a documented history of PAR for at least 2 years, were randomized at a 4:1 ratio to receive the treatment (415) and placebo (111). There were 249 patients finished at 30 weeks (196 in treatment and 53 in placebo), and 277 patients finished at 52 weeks (219 in treatment and 58 in placebo). The PAR had to be of sufficient severity (rTNSS ≥5 out of 12) and to be expected to require treatment throughout the entire study. Subjects had a positive skin prick test to at least one allergen known to induce PAR. Safety monitoring included AEs, physical examinations including ENT examinations, vital signs, and ocular examinations including best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurements and Lens Opacities Classification System III (LOCS III). The efficacy was also measured in this long term study. The primary efficacy endpoint was the average 24-hour reflective TNSS (rTNSS) over the 30-week treatment period. Secondary endpoints included average 24-hour instantaneous TNSS (iTNSS) over the 30- and

52-week treatment period, rTNSS over the 30-week treatment period, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

The mean changes from baseline in the primary endpoint rTNSS, and in iTNSS and RQLQ were summarized in Table 6 below. Across the 30- and 52-week treatment periods, the LS mean changes from baseline in average 24hour subject-reported rTNSS and iTNSS in BDP Nasal Aerosol (320 mcg, once daily) group were significantly greater than those in placebo group. The changes of RQLQ in BDP Nasal Aerosol (320 mcg, once daily) group were numerically greater than those in placebo group.

Table 6 Mean change from baseline in rTNSS, iTNSS and RQLQ, BDP-AR-303

Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	p Value
Reflective Total Nasal Symptom Scores (rTNSS 30 Week Treatment)						
BDP HFA 320 mcg/day	414	9.2 (1.77)	-3.4 (0.11)	-0.97	-1.5, -0.5	<0.001
Placebo	110	9.4 (1.83)	-2.4 (0.22)			
Reflective Total Nasal Symptom Scores (rTNSS 52 Week Treatment)						
BDP HFA 320 mcg/day	414	9.2 (1.77)	-3.7 (0.12)	-1.09	-1.6, -0.6	<0.001
Placebo	110	9.4 (1.83)	-2.6 (0.23)			
Instantaneous Total Nasal Symptom Scores (iTNSS 30 Week Treatment)						
BDP HFA 320 mcg/day	414	7.7 (2.16)	-2.9 (0.11)	-0.96	-1.4, -0.5	<0.001
Placebo	110	8.0 (2.27)	-2.0 (0.21)			
Instantaneous Total Nasal Symptom Scores (iTNSS 52 Week Treatment)						
BDP HFA 320 mcg/day	414	8.1 (1.98)	-3.1 (0.11)	-1.10	-1.6, -0.6	<0.001
Placebo	110	8.0 (1.96)	-2.0 (0.22)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ 30 Week Treatment)						
BDP HFA 320 mcg/day	222	4.2 (0.75)	-2.2 (0.09)	-0.30	-0.7, -0.1	0.143
Placebo	59	3.9 (0.79)	-1.9 (0.19)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ 52 Week Treatment)						
BDP HFA 320 mcg/day	222	4.1 (0.70)	-2.0 (0.14)	-0.49	-1.1, 0.1	0.130
Placebo	59	4.1 (0.82)	-1.5 (0.30)			

The treatment emergent AEs in this study are summarized in Table 7 below. Of the 526 subjects, 349 (66.3%) experienced at least one treatment emergent AE: 283 (68.2%) in the BDP Nasal Aerosol 320 mcg/day group and 66 (59.5%) in the placebo group. The most commonly reported AEs (5% or more subjects) were nasopharyngitis, epistaxis, upper respiratory tract

infection, sinusitis, and headache. The majority of AEs in both treatment and placebo groups were of mild or moderate intensity and with the exception of epistaxis. Epistaxis was reported as mild in 27 subjects (6.5%), moderate in 12 subjects (2.9%) and severe in 5 subjects (1.2%) in the BDP Nasal Aerosol 320 mcg/day group, and was reported as mild in 1 subject (0.9%) and moderate in 1 subject (0.9%) in the placebo group. Epistaxis was the AE that was most commonly considered by the investigator to be treatment-related (10.6% of subjects in the BDP Nasal Aerosol 320 mcg/day group and 1.8% in the placebo group). There were no reports of nasal septum perforation. There were two reports of nasal septum ulceration, both of which occurred in the BDP Nasal Aerosol 320 mcg/day group. No subjects died during the study.

Table 7 Treatment emergent adverse events (≥ 2%) in long term study BDP-AR-303

Adverse Event	BDP HFA 320 mcg N = 415	Placebo N = 111
	Subject n (%)	Subject n (%)
Any AE	283 (68.2)	66 (59.5)
Nasopharyngitis	67 (16.1)	14 (12.6)
Epistaxis	44 (10.6)	2 (1.8)
Upper respiratory tract infection	43 (10.4)	7 (6.3)
Sinusitis	34 (8.2)	8 (7.2)
Headache	28 (6.7)	6 (5.4)
Sinus headache	15 (3.6)	2 (1.8)
Oropharyngeal pain	14 (3.4)	2 (1.8)
Bronchitis	13 (3.1)	4 (3.6)
Nasal discomfort	12 (2.9)	2 (1.8)
Urinary tract infection	11 (2.7)	4 (3.6)
Gastroenteritis viral	10 (2.4)	4 (3.6)
Acute sinusitis	9 (2.2)	6 (5.4)
Cough	9 (2.2)	5 (4.5)
Viral upper respiratory tract infection	9 (2.2)	2 (1.8)
Back pain	8 (1.9)	3 (2.7)
Rhinorrhoea	7 (1.7)	3 (2.7)
Sneezing	4 (1.0)	3 (2.7)
Arthralgia	3 (0.7)	5 (4.5)
Influenza	3 (0.7)	4 (3.6)

The Applicant also conducted safety study (BDP-AR-6631034) to assess the effect of the proposed drug product on HPA Axis. The data indicated that a 6-week treatment period with BDP Nasal Aerosol 320 mcg daily in adult and adolescent PAR patients did not suppress the serum 24-hour cortisol level.

5. REQUESTS FOR PEDIATRIC STUDIES WAIVER AND DEFERRAL

The Sponsor requests a waiver of studies in children 0<2 years of age for the following reasons:

(b) (4)

(b) (4)

(b) (4)

The sponsor also requests deferring studies in pediatric population between the ages of 2 to 11 years old. The adult and adolescent data are included in the present NDA submission, which will be followed by a supplemental NDA submission for the pediatric program, at a later date.

Reviewer's comments:
The requests for waiver of pediatric studies in children 0<2 years of age, and for deferring studies in pediatric population between the ages of 2 to 11 years old are acceptable. This reviewer recommends that the waiver and the deferral of pediatric studies as requested be granted.

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed product labeling in the new structured label format is included in this submission with annotation noting comparator products from which specific paragraphs were derived. A brief review of the proposed labeling has been performed. The Clinical Studies section of the proposed label presents data on reduction of reflective total nasal symptom scores (rTNSS) and instantaneous total nasal symptom scores (iTNSS), (b) (4)

Reviewer's comment:
The proposed indication for BDP Nasal Aerosol is [redacted] *It will be a review issue if the proposed indication* [redacted] *is supported by clinical data or the indication should be for nasal symptoms, as indicated by the reduction of TNSS.*

7. DSI REVIEW AND AUDIT

The clinical team is not requesting DSI audit as part of this application.

SUMMARY

This is a 505(b)(2) application for BDP (beclomethasone dipropionate) Nasal Aerosol. BDP has been approved as an oral inhalation drug as QVAR 40 mcg and 80 mcg Inhalation Aerosol (NDA 20-911, approved 9/15/00). The Applicant owns the QVAR (NDA 20-911). BDP Nasal Aerosol uses the exact same drug product canister, components and controls as QVAR in NDA 20-911, and inserts the canisters into the newly developed plastic nasal actuator that is designed for a nasal route of delivery. The proposed indication for the BDP Nasal Aerosol in this submission is the treatment [redacted] of seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents patients 12 years of age and older.

The clinical program for BDP Nasal Aerosol consists of 11 clinical studies. The six adult and adolescent studies were conducted first and the data are submitted in the present NDA. The pediatric program will be conducted later for patients 2 to 11 years of age, and the data will be provided in a supplemental NDA submission at a later date. The safety data from the orally inhaled route of administration of this formulation will provide further supportive evidence for the development of this product via the nasal route.

The development program has been conducted in accordance with the FDA guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000). The submission is adequately indexed to allow for further review. The recommendation for the submission is "fileable" from a clinical perspective

There is one comment to be communicated to the Applicant in the 74-day letter.

8. REVIEW TIMELINE

The schedule for review is provided in the table below. Write-up will be concomitant with the review process. Clinical review will focus initially on the dose ranging study and the pivotal studies, followed by the integrated summary of efficacy (ISE), integrated summary of safety

(ISS), and any data provided in the long term safety study, clinical pharmacology studies, and 4-month safety update. The review will culminate with the proposed label. The draft primary review will be finished January 24, 2012, two months in advance of the action date.

Milestone	Target date for completion
Filing and planning meeting	July 23, 2011
74-day letter	August 6, 2011
Pivotal studies	October 30, 2011
ISE and ISS	December 30, 2011
Label	January 10, 2012
Draft review complete	January 24, 2012
Wrap-up meeting	February 13, 2012
Sponsor teleconference	February 27, 2012
PDUFA Action date (10 months)	March 24, 2012

9. COMMENTS FOR THE SPONSOR

The following comment is to be communicated to the sponsor.

We note that the proposed indication for BDP Nasal Aerosol is (b) (4) *It is a review issue whether or not the data support this claim.*

Reviewed by:

_____
Xu Wang, M.D., Ph.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

_____
Anthony G. Durmowicz, M.D.
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: NDA 202-813
HFD-570/Division File
HFD-570/ Durmowicz /Medical Team Leader
HFD-570/Gilbert McClain/Deputy Director
HFD-570/Wang/Medical Reviewer
HFD-715/Hamilton/Biometrics Reviewer
HFD-570/Pei/Pharmacology-Toxicology Reviewer
ONDQA/Bertha/CMC Reviewer
OCP/Agrawal/Clinical Pharmacology Reviewer
HFD-570/Hill/CSO

Clinical Filing Checklist

NDA/BLA Number: 202-813 **Applicant: TEVA** **Stamp Date: May 24, 2011**

Drug Name: BDP Nasal Aerosol **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Beconase AQ (NDA 19-389)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: BDP-AR-201 Study Title: A double-blind, randomized, placebo-controlled, parallel-group, multi-center, dose-range-finding study to assess the efficacy and safety of BDP HFA Nasal Aerosol in adults and adolescent patients (12 years and older) with seasonal allergic rhinitis (SAR) Sample Size: 486 Arms: 4 arms (80 160, 320 mcg, and placebo) Location in submission: Module 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1: BDP-AR-301 Indication: For the treatment (b) (4) of seasonal and perennial allergic rhinitis in adult and adolescent patients 12 years of age and older Pivotal Study #2; BDP-AR-302 Indication: Same as that in the study #1				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Ver 11
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No foreign study data
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following comment is to be communicated to the sponsor.

We note that the proposed indication for BDP Nasal Aerosol is (b) (4) *It is a review issue whether or not the data support this claim.*

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
07/22/2011

ANTHONY G DURMOWICZ
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