

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202813Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	202-813 (Related IND 101,639)
Submissions Date:	05/24/2011 (SDN 1)
Submission Type:	505(b)(2)
Brand Name:	QNASL
Generic Name:	Beclomethasone Dipropionate (BDP) HFA nasal aerosol
Sponsor:	Teva Respiratory, LLC
Route of Administration:	Intranasal
Dosage Form:	Nasal aerosol spray solution
Dosage Strength:	Each actuation of the aerosol delivers 80 mcg of BDP
OND Division:	Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Arun Agrawal, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
Indication:	(b) (4)
Dosage Administration:	Adults and children 12 years of age and over: 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day)

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1.0 EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 202-813 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Sponsor markets an approved beclomethasone dipropionate (BDP) HFA oral inhalation aerosol for the treatment of asthma (QVAR[®], NDA 20-911), and is seeking approval of a BDP HFA nasal aerosol, utilizing the same chemical formulation and concentration as the QVAR, with a nasal actuator for use by the intranasal route for the treatment of allergic rhinitis (AR). In support of this NDA, data from two clinical pharmacology studies and four clinical studies were submitted. The goals of the clinical pharmacology program were: (i) to compare the systemic exposure of the proposed product following intranasal administration to that from QVAR following oral inhalation (relative bioavailability, study BDP-AR-101), and (ii) to characterize the effects of intranasal administration of the proposed product on hypothalamic-pituitary-adrenal (HPA)-axis function (study BDP-AR-304).

Relative Bioavailability (Study BDP-AR-101): This single dose, randomized, open-label, 3-period, crossover trial in healthy volunteers determined pharmacokinetics of BDP and its active major metabolite beclomethasone 17-monopropionate (17-BMP, it is reported to be mainly responsible for the pharmacological activity following BDP administration) following (a) intranasal administration of BDP HFA at 80 mcg and 320 mcg, and (b) oral inhalation of BDP HFA 320 mcg (QVAR). The AUC_{last} for 320 mcg intranasal aerosol was 27.5% and 12.7% of that of oral inhalation for 17-BMP and BDP, respectively. The C_{max} for intranasal aerosol was 19.5% and 6.1% of that of oral inhalation for 17-BMP and BDP, respectively. Overall, systemic exposures of BDP and 17-BMP were much lower following intranasal dosing as compared to oral inhalation at the same dose of 320 mcg.

PK parameters for 17-BMP and BDP

Parameter	Geometric LS Mean			320 mcg Intranasal / 320 mcg Orally Inhaled
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg Orally Inhaled	Ratio (90% CI)
17-BMP				
AUC _{last} (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)
C _{max} (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)
BDP				
AUC _{last} (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)
C _{max} (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)

Effect on HPA Axis Function (Study BDP-AR-304): This repeat-dose, randomized, double-blind, parallel-group trial investigated the effects of BDP HFA nasal aerosol (320 mcg) on the HPA-axis function, as assessed by 24-hour serum cortisol measurements, in adolescent and adult patients with perennial allergic rhinitis (PAR). This trial compared the effects of 6 weeks of daily treatment with BDP HFA nasal aerosol with the effects of 6 weeks of daily treatment with placebo, or with the effects of 7 days of daily treatment with active control prednisone (10 mg once daily) on HPA-axis function. Overall, BDP HFA intranasal treatment did not result in serum cortisol suppression relative to its pretreatment baseline and to the placebo treatment, while the active control prednisone treatment resulted in a substantial reduction in serum cortisol levels.

Summary of serum cortisol (mcg/dL) weighted mean

Statistic	BDP HFA320 mcg/day N = 48	Placebo N = 41
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	Placebo N = 41
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol for 6 weeks, 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 6 weeks of daily treatment, 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.

Overall, adequate clinical pharmacology information was provided in support of this NDA.

2.0 QUESTION BASED REVIEW

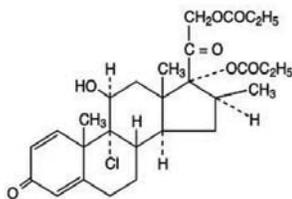
2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

BDP was previously formulated and developed as an aqueous nasal spray (Vancenase AQ, Beconase AQ) for the treatment of AR. Both of these products were also marketed as CFC metered dose inhaler (MDI) nasal aerosols prior to being withdrawn from market with the phase out of CFC-containing nasal products. Sponsor has developed this BDP HFA nasal aerosol, utilizing the same chemical formulation and concentration as their approved orally inhaled BDP HFA formulation (QVAR) for asthma, with a nasal actuator to be used by the intranasal route for the treatment of AR.

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

BDP is an anti-inflammatory steroid di-ester of beclomethasone and is chemically related to dexamethasone. BDP nasal aerosol is a pressurized, non-aqueous solution in a metered-dose aerosol device intended only for intranasal use. It contains a solution of BDP in HFA propellant and dehydrated ethanol. Chemical structure of BDP is as follows:



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

BDP is a synthetic corticosteroid. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells and the release of inflammatory mediators. In vitro binding affinity of 17-BMP for human glucocorticoid receptor is reportedly 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide, and 25 times that of BDP. BDP HFA is being indicated for the treatment of AR, however, the precise mechanism of its action is not known.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Adults and children 12 years of age and over: 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).

2.1.5 What is the to-be-marketed formulation?

The to-be-marketed formulation contains a solution of BDP in HFA propellant and dehydrated ethanol.

Formulation Configuration

Ingredient	80 mcg/Actuation (ex-actuator) (% w/w)
Beclomethasone Dipropionate (anhydrous), USP	(b) (4)
Dehydrated Alcohol, USP	
HFA-134a	

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Following two clinical pharmacology studies were submitted in support of this product:

Relative Bioavailability (Study BDP-AR-101): This was a Phase 1, single-center, single-dose, randomized, open-label, 3-period crossover, PK study in male or female healthy volunteers (18-45 years old). This study was designed to evaluate the hypothesis that systemic exposure of intranasally administered BDP would be less as compared to that of approved orally inhaled BDP (QVAR) thus bridging the systemic safety of QVAR to the proposed intranasal BDP HFA nasal aerosol.

Study Treatments

Treatment	Dose/actuation	Dose	Route of administration	Duration of Treatment
A	40 mcg/actuation 1 actuation/nostril	80 mcg/day	Intranasal	Single dose
B	80 mcg/actuation 2 actuations/nostril	320 mcg/day	Intranasal	Single dose
C	80 mcg/actuation 4 inhalations	320 mcg/day	Oral inhalation	Single dose

Treatment C: QVAR 80 mcg oral inhalation aerosol

Pharmacokinetics of 17-BMP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 27.5% and 19.5% of that of orally inhaled BDP HFA 320 mcg for 17-BMP, respectively. The Tmax was higher (1.0 vs. 0.25 hr), and the t1/2 slightly lower (4.5 vs. 5.0 hr), for nasal aerosol as compared to oral inhalation. Overall, the systemic exposure of 17-BMP following intranasal administration of 320 mcg BDP HFA was approximately 1/4th as compared to orally inhaled BDP HFA at 320 mcg dose. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were approximately 26% and 35% of that of 320 mcg BDP HFA nasal aerosol for 17-BMP, respectively. The Tmax for both treatment groups was 1.0 hr, and the t1/2 was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose.

PK parameters for 17-BMP

Parameter	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg orally Inhaled	Ratio (90%CI)	Ratio (90% CI)
AUC _{last} (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)	0.071 (0.055, 0.092)
C _{max} (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)	0.069 (0.055, 0.085)
AUC _{0-∞} (hr*pg/mL)	747.116	1661.529	4419.331	0.376 (0.322, 0.439)	0.169 (0.137, 0.209)
t _{max} (hr) ¹	1.000	1.000	0.250	0.750 ² (0.459, 0.834) ²	0.750 ² (0.417, 0.834) ²
t _{1/2} (hr) ³	3.541 (1.2076)	4.457 (1.5899)	5.017 (1.3825)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.1, Table 5 and Table 6

¹ The values represent the median t_{max} for each treatment.

² The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

³ The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Pharmacokinetics of BDP: The AUC_{last} and C_{max} for BDP HFA nasal aerosol 320 mcg were 12.7% and 6.1% of that of orally inhaled BDP 320 mcg for BDP, respectively. The T_{max} and t_{1/2} were similar for both the treatments. The AUC_{last} and C_{max} for 80 mcg BDP HFA nasal aerosol were 27.2% and 35.4% of that of 320 mcg BDP HFA nasal aerosol for BDP, respectively. The T_{max} and t_{1/2} were similar for both the treatments.

PK parameters for BDP

Parameter	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg Orally Inhaled	Ratio (90%CI)	Ratio (90% CI)
AUC _{last} (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)	0.034 (0.026, 0.046)
C _{max} (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)	0.022 (0.017, 0.028)
AUC _{0-∞} (hr*pg/mL)	27.160	88.227	434.510	0.203 (0.165, 0.250)	0.063 (0.036, 0.108)
t _{max} (hr) ¹	0.083	0.083	0.083	0.000 ² (0.000, 0.000) ²	0.000 ² (0.000, 0.000) ²
t _{1/2} (hr) ³	0.306 (0.1374)	0.278 (0.1434)	0.313 (0.2455)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.2, Table 8 and Table 9

¹ The values represent the median t_{max} for each treatment.

² The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

³ The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Overall, BDP HFA nasal aerosol (320 mcg) exhibited considerably lower systemic exposure of BDP and 17-BMP as compared to that of orally inhaled BDP 320 mcg dose.

Effect on HPA-Axis Function (Study BDP-AR-304): This was a randomized, double-blind, placebo- and active-controlled (prednisone 10 mg/day), parallel-group, 6-week study to investigate the effect of BDP HFA nasal aerosol on the HPA-axis when administered to subjects 12-45 years of age with PAR.

Subjects were randomly assigned in a 4:4:1 ratio to receive BDP HFA nasal aerosol 320 mcg/day, placebo nasal aerosol, or placebo nasal aerosol plus prednisone 10 mg/day. Subjects self administered the double-blinded nasal aerosol (BDP HFA nasal aerosol or placebo) once daily in the morning as 2 actuations per nostril for 6 weeks and also took a double-blind capsule (prednisone 10 mg or placebo) once daily during the last 7 days of treatment. At the end of treatment, subjects were domiciled for PD measurements of HPA-axis function and PK measurements for BDP and 17-BMP.

The serum cortisol weighted mean (0-24 hr) at baseline and at week 6, and the ratio of week 6 over baseline were calculated. Geometric mean serum cortisol weighted mean values were similar in the BDP HFA 320 mcg/day and placebo treatment groups at baseline and after 6 weeks of treatment. The ratio of week 6/baseline was 0.90 for BDP HFA 320 mcg/day and 0.95 for placebo. The geometric mean ratio for BDP HFA 320 mcg/day to placebo was 0.96. The ratio of week 6/baseline was 0.31 for the prednisone active treatment. The geometric mean ratio for placebo to prednisone group was 3.17, indicating that prednisone resulted in approximately three-fold reduction in serum cortisol levels compared with placebo alone.

Summary of analyses of logarithmically-transformed serum cortisol (mcg/dL) weighted mean

Statistic	BDP HFA320 mcg/day N = 48	Placebo N = 41
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	Placebo N = 41
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Source: [Section 5.3.4.2, Study BDP-AR-304, Section 11.4.1, Table 12 and Table 13](#)
 Serum cortisol values below the limit of quantitation were imputed as the lower limit of quantitation/2 (0.5 mcg/dL).
 Results from ANCOVA model including effects for treatment, center, and logarithmically transformed Baseline serum cortisol weighted mean as covariate.

Following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol for 6 weeks, 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 daily treatment 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.

Overall, this study demonstrated that intranasal BDP HFA 320 mcg/day was not associated with suppression of serum cortisol levels in subjects ≥ 12 years of age with PAR.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

BDP and 17-BMP were measured in plasma (details provided in Appendices). This is a locally (nasal) acting product and therefore, no exposure response relationship was evaluated.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

Sponsor conducted following four clinical efficacy and safety studies:

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

Study BDP-AR-201 was a double-blind, randomized, placebo-controlled, parallel-group, multi-center, dose ranging study. The primary objective of this study was to determine the optimally safe and effective dose of BDP HFA nasal aerosol in subjects with SAR. Patients received 3 doses of BDP HFA nasal aerosol (80, 160, and 320 mcg) and placebo daily for 2 weeks. The primary efficacy endpoint was the average AM and PM subject-reported reflective TNSS (rTNSS) over the 2-week treatment period. The LS mean difference between BDP HFA nasal aerosol treatment was -0.63, -0.29, and -0.29 for 320 mcg/day, 160 mcg/day, and 80 mcg/day, respectively. Thus, the largest effect size was obtained with 320 mcg/day treatment. Based on the results of this study, a daily dose of 320 mcg was identified as the optimally safe and effective dose for Phase 3 studies. Study BDP-AR-301 was a two week pivotal efficacy and safety study in SAR patients, study BDP-AR-302 was a six week pivotal efficacy and safety study in PAR patients, while study BDP-AR-301 was a 52 week long term safety study in PAR patients. Please refer to clinical review by Dr. Xu Wang for final assessment of efficacy and safety findings in these four clinical studies.

2.2.4 Exposure Response

No formal PK/PD studies were conducted to establish the relationship between exposure and response as this is a locally (nasal) acting product and systemic exposures will not be an indicator of local efficacy and safety.

2.2.5 Does this drug prolong the QT or QTc interval?

No formal QTc study was conducted.

2.2.6 What are the general PK characteristics of the drug and its major metabolite?

No distribution, metabolism, or elimination studies were performed for BDP HFA nasal aerosol. Following information is provided from the current NDA and previously approved BDP products such as QVAR and Beconase AQ.

2.2.6.1 What are the single dose PK parameters?

The systemic exposure and C_{max} of 17-BMP for 80 mcg BDP HFA nasal aerosol dose was 26% and 35.1% of that of 320 mcg dose, respectively. The T_{max} for both treatment groups was 1.0 hr; while the t_{1/2} was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose as compared to 320 mcg dose. The systemic exposure and C_{max} of BDP for 80 mcg BDP dose was 27.2% and 35.4% of that of 320 mcg BDP dose, respectively. The T_{max} and t_{1/2} were similar for both the doses.

PK parameters for 17-BMP and BDP

Parameter	Geometric LS Mean		80 mcg Intranasal / 320 mcg Intranasal
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	Ratio (90% CI)
	17-BMP		
AUClast (hr*pg/mL)	295.827	1139.742	0.260 (0.201, 0.335)
C _{max} (pg/mL)	92.118	262.654	0.351 (0.284, 0.434)
T _{max} (hr)	1	1	0.000 (0.000, 0.250)
T _{1/2} (hr)	3.541	4.457	
	BDP		
AUClast (hr*pg/mL)	14.584	53.561	0.272 (0.205, 0.361)
C _{max} (pg/mL)	64.379	181.951	0.354 (0.272, 0.460)
T _{max} (hr)	0.083	0.083	0.000 (0.000, 0.000)
T _{1/2} (hr)	0.306	0.278	

2.2.6.2 What are the multiple dose PK parameters following daily 6 weeks of dosing?

The multiple dose PK of 320 mcg BDP HFA nasal aerosol was evaluated in a randomized, double-blind trial investigating the effects of BDP HFA nasal aerosol on the HPA axis function in adolescent and adult patients with perennial allergic rhinitis. The mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC₀₋₂₄ was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. 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.

2.2.6.3 What are the characteristics of drug absorption?

Most of the BDP undergoes extensive conversion to its active metabolite, 17-BMP, during absorption. T_{max} for BDP was approximately 5 minutes after intranasal administration of 320 mcg dose indicating rapid absorption while the T_{max} for 17-BMP was 1.0 hr. AUCs for BDP and 17-BMP increased in a dose dependent manner between 80 and 320 mcg doses. Further, this study also showed that the systemic bioavailability of BDP HFA nasal aerosol 320 mcg, as measured by levels of 17-BMP, was approximately four-fold lower than that of orally inhaled BDP HFA 320 mcg (QVAR).

2.2.6.4 What are the characteristics of drug distribution?

Protein binding for 17-BMP was reported to be 94-96% over the concentration range of 1000 to 5000 pg/mL. V_{dss} for BDP was moderate (20 L) but more extensive for 17-BMP (424 L).

2.2.6.5 What are the characteristics of drug metabolism?

BDP undergoes extensive metabolism via CYP3A4 to form 3 metabolites: 17-BMP, 21-BMP and beclomethasone (BOH). 17-BMP is the major and most active metabolite.

2.2.6.6 What are the characteristics of drug elimination?

The $t_{1/2}$ of BDP and 17-BMP following intranasal dosing of 320 mcg BDP HFA nasal aerosol were approximately 0.3 hr and 4.5 hr, 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 parent drug and its metabolites are excreted in urine. Intranasal BDP is expected to follow a similar elimination pathway once systemically available.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Plasma levels of BDP and 17-BMP increased in a dose dependent manner following a single dose of BDP HFA nasal aerosol at 80 mcg and 320 mcg in healthy volunteers.

2.2.6.8 How do the PK parameters change with time following chronic dosing?

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.

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal PK studies were performed with the BDP HFA nasal aerosol in any special population.

2.3.1.1 Pediatrics

Sponsor is currently seeking approval for ≥ 12 year old AR patients and has requested a deferral for patients 2-11 years of age. Further, sponsor is seeking waiver of AR studies in children < 2 years of age [REDACTED] ^{(b) (4)}

[REDACTED] These issues were discussed and agreed on at the pre-NDA meeting between the sponsor and the Division (meeting date 10/18/2010, meeting minutes 11/05/2010). Following is a list of sponsor proposed studies:

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 6-11 yrs, 6 wks	Safety
(b) (4)	Pediatric safety study in PAR pts 2-5 yrs, 12 wks	Safety
	Pediatric HPA Axis study in children 2-5 yrs, 6 wks	Safety

This application was discussed at the PeRC meeting on 01/25/2012. A waiver for studies in pediatric patients less than 2 years of age is justified because of local (nasal) safety concerns with the use of corticosteroids via nasal inhalation in children less than 2 years of age. In addition, appropriate alternatives to corticosteroid nasal sprays exist for use in children less than 2 years of age. A deferral of studies in patients 2 years to less than 12 years of age is appropriate because the product is ready for approval in the older age group. Sponsor is not planning on conducting long-term growth studies with the new product and plans to rely on existing data with QVAR.

PeRC agreed with the waiver for studies in patients birth to less than 2 years of age, and with the plan and assessment for 2-11 year olds.

2.3.1.2 Geriatrics

Clinical studies of BDP HFA nasal aerosol did not include sufficient number of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, administration to elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

2.3.1.3 Renal Impairment

No formal studies were conducted to assess the impact of renal impairment on PK.

2.3.1.4 Hepatic Impairment

No formal studies were conducted to assess the impact of hepatic impairment on PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of other drugs, herbal products, diet, smoking, and alcohol use were not evaluated in this submission.

2.4.2 Drug-drug interactions

No formal drug interaction studies were conducted for BDP HFA nasal aerosol.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?

Not applicable as this is a nasal aerosol spray product.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

The to-be marketed formulation was used in the pharmacokinetic and clinical trials.

2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is a nasal aerosol spray product.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

LC-MS/MS methods used to determine BDP and 17-BMP in human plasma met the validation acceptance criteria for selectivity/specificity, linearity, precision and accuracy, sensitivity, recovery, dilution integrity, and stabilities. The validated calibration curve ranges were 10-2500 pg/mL for BDP and 20-5000 pg/mL for 17-BMP. Cortisol was quantified by LC-MS/MS (b) (4). Additional analytical details are provided in Appendices.

3.0 DETAILED LABELING RECOMMENDATIONS

Below are some sections from the proposed label. Reviewer suggested changes: ~~double strikethrough~~ text should be deleted from labeling and double underlined text should be added to labeling.



(b) (4)

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual Study Synopses:

4.2.1 Relative Bioavailability (Study BDP-AR-101): This was a Phase 1, single-center, single-dose, randomized, open-label, 3-period crossover, PK study in male or female healthy volunteers (18-45 years old). This study was designed to evaluate the hypothesis that systemic exposure of intranasally administered BDP would be less as compared to that of approved orally inhaled BDP (QVAR) thus bridging the systemic safety of QVAR to the proposed intranasal BDP HFA nasal aerosol.

Study Treatments

Treatment	Dose/actuation	Dose	Route of administration	Duration of Treatment
A	40 mcg/actuation 1 actuation/nostril	80 mcg/day	Intranasal	Single dose
B	80 mcg/actuation 2 actuations/nostril	320 mcg/day	Intranasal	Single dose
C	80 mcg/actuation 4 inhalations	320 mcg/day	Oral inhalation	Single dose

Treatment C: QVAR

Pharmacokinetics of 17-BMP: The AUC_{last} and C_{max} for BDP HFA nasal aerosol 320 mcg were 27.5% and 19.5% of that of orally inhaled BDP HFA 320 mcg for 17-BMP, respectively. The T_{max} was higher (1.0 vs. 0.25 hr), and the t_{1/2} slightly lower (4.5 vs. 5.0 hr), for nasal aerosol as compared to oral inhalation. Overall, the systemic exposure of 17-BMP following intranasal administration of 320 mcg BDP HFA was approximately 1/4th as compared to orally inhaled BDP HFA at 320 mcg dose. The AUC_{last} and C_{max} for 80 mcg BDP HFA nasal aerosol were approximately 26% and 35% of that of 320 mcg BDP HFA nasal aerosol for 17-BMP, respectively. The T_{max} for both treatment groups was 1.0 hr, and the t_{1/2} was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose.

Parameter	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg orally Inhaled	Ratio (90%CI)	Ratio (90% CI)
AUC _{last} (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)	0.071 (0.055, 0.092)
C _{max} (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)	0.069 (0.055, 0.085)
AUC _{0-∞} (hr*pg/mL)	747.116	1661.529	4419.331	0.376 (0.322, 0.439)	0.169 (0.137, 0.209)
t _{max} (hr) ¹	1.000	1.000	0.250	0.750 ² (0.459, 0.834) ²	0.750 ² (0.417, 0.834) ²
t _{1/2} (hr) ³	3.541 (1.2076)	4.457 (1.5899)	5.017 (1.3825)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.1, Table 5 and Table 6

¹ The values represent the median t_{max} for each treatment.

² The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

³ The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Pharmacokinetics of BDP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 12.7% and 6.1% of that of orally inhaled BDP 320 mcg, respectively. The Tmax and t1/2 were similar for both the treatments. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were 27.2% and 35.4% of that of 320 mcg BDP HFA nasal aerosol, respectively. The Tmax and t1/2 were similar for both the treatments.

Parameter	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg Orally Inhaled	Ratio (90%CI)	Ratio (90% CI)
AUC _{last} (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)	0.034 (0.026, 0.046)
C _{max} (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)	0.022 (0.017, 0.028)
AUC _{0-∞} (hr*pg/mL)	27.160	88.227	434.510	0.203 (0.165, 0.250)	0.063 (0.036, 0.108)
t _{max} (hr) ¹	0.083	0.083	0.083	0.000 ² (0.000, 0.000) ²	0.000 ² (0.000, 0.000) ²
t _{1/2} (hr) ³	0.306 (0.1374)	0.278 (0.1434)	0.313 (0.2455)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.2, Table 8 and Table 9

¹ The values represent the median t_{max} for each treatment.

² The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

³ The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Overall, BDP HFA 320 mcg nasal aerosol exhibited considerably lower systemic exposure of BDP and 17-BMP as compared to that of orally inhaled BDP HFA 320 mcg (QVAR) dose.

Bionalytical Details:

Sample Analysis Summary for Beclomethasone Dipropionate and Beclomethasone 17-Propionate

Report Title	Sample Analysis Report in Support of the Study Entitled, "A Randomized, Open-Label, 3-Period Crossover Study to Investigate the Pharmacokinetics, Safety and Tolerability of BDP HFA Nasal Aerosol in Healthy Volunteers"
Report Number	RPT02256
Analytes	Beclomethasone Dipropionate and Beclomethasone 17-Propionate
Internal Standards (IS)	Beclomethasone Dipropionate-d ₁₀ for BDP and Beclomethasone 17-Propionate-d ₅ for 17-BMP
Sample Receipt Dates (Quantity Received)	3/31/2009 (510 samples, collected on 3/18-29/2009) 4/14/2009 (459 samples, collected on 3/28-4/12/2009) 4/28/2009 (493 samples, collected on 4/8-26/2009) 6/30/2009 (1462 samples, back-up)
Storage Conditions Upon Receipt	Approximately -70 °C
LC-MS/MS Method	RPT02138
Stability History of Samples	61 Days at ~ -70 °C
Matrix/Anticoagulant	Plasma/ K ₂ EDTA
Sample Size	0.5 mL of human plasma
Sample Extraction Date Range	April 7, 2009 – May 11, 2009
Extraction Method	Solid phase extraction
Precursor→Product Ion Pairs	521.3→319.3 for Beclomethasone Dipropionate 465.4→279.3 for Beclomethasone 17-Propionate 531.3→319.3 for Beclomethasone Dipropionate-d ₁₀ 470.4→279.3 for Beclomethasone 17-Propionate-d ₅
Standard Curve Range	10-2500 pg/mL for Beclomethasone Dipropionate 20-5000 pg/mL for Beclomethasone 17-Propionate
R-Squared (Mean)	0.9924 for Beclomethasone Dipropionate 0.9931 for Beclomethasone 17-Propionate
Standards Rejected from Linear Regression	36 for Beclomethasone Dipropionate 25 for Beclomethasone 17-Propionate
QC Sample Range	30-2000 pg/mL for Beclomethasone Dipropionate 60-4000 pg/mL for Beclomethasone 17-Propionate
QC Inter-Day Precision (%CV) QCL, QCM, QCH (Mean)	11.78, 6.70, 10.35 for Beclomethasone Dipropionate 9.29, 8.16, 7.22 for Beclomethasone 17-Propionate
QC Inter-Day Accuracy (%RE) QCL, QCM, QCH (Mean)	1.33, -2.70, -1.00 for Beclomethasone Dipropionate 0.50, 0.50, -2.00 for Beclomethasone 17-Propionate

4.2.2 Effect on HPA-Axis Function (Study BDP-AR-304):

This was a randomized, double-blind, placebo- and active-controlled (prednisone 10 mg/day), parallel-group, 6-week study to investigate the effect of BDP HFA nasal aerosol on the HPA-axis function when administered in subjects 12-45 years of age with PAR

Subjects were randomly assigned in a 4:4:1 ratio to receive BDP HFA nasal aerosol 320 mcg/day, placebo nasal aerosol, or placebo nasal aerosol plus prednisone 10 mg/day. Subjects self administered the double-blinded nasal aerosol (BDP HFA nasal aerosol or placebo) once daily in the morning as 2 actuations per nostril for 6 weeks and also took a double-blind capsule (prednisone 10 mg or placebo) once daily during the last 7 days of treatment. At the end of treatment subjects were domiciled for PD measurements of HPA-axis function and PK measurements of BDP and 17-BMP. The serum cortisol weighted mean (0-24 hours) at baseline and at week 6 and the ratio of week 6 over baseline was calculated. Further, pharmacokinetics of 17-BMP and BDP were determined after 6 weeks of treatment with BDP HFA 320 mcg/day.

Effect on HPA-Axis Function: Geometric mean serum cortisol weighted mean values were similar in the BDP HFA 320 mcg/day and placebo treatment groups at baseline and after 6 weeks of treatment. The ratio of week 6/baseline was 0.90 for BDP HFA 320 mcg/day and 0.95 for placebo. The geometric mean ratio for BDP HFA 320 mcg/day to placebo was 0.96. The ratio of week 6/baseline was 0.31 for the prednisone group. The geometric mean ratio for placebo to prednisone group was 3.17, indicating that prednisone resulted in approximately three-fold reduction in serum cortisol levels compared with placebo treatment.

Summary of analyses of logarithmically-transformed serum cortisol (mcg/dL) weighted mean

Statistic	BDP HFA320 mcg/day N = 48	Placebo N = 41
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	Placebo N = 41
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Source: [Section 5.3.4.2, Study BDP-AR-304, Section 11.4.1, Table 12](#) and [Table 13](#)

Serum cortisol values below the limit of quantitation were imputed as the lower limit of quantitation/2 (0.5 mcg/dL)

Results from ANCOVA model including effects for treatment, center, and logarithmically transformed Baseline serum cortisol weighted mean as covariate.

Pharmacokinetics: 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 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.

Overall, this study demonstrated that BDP HFA 320 mcg/day was not associated with HPA-axis effect in subjects ≥ 12 years of age with PAR. Cross study comparison with data from study BDP-AR-101 indicates that following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol 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.

Bioanalytical details

Table 1 Sample analysis summary for beclomethasone dipropionate and beclomethasone 17-propionate

Report Title	Sample Analysis Report in Support of the Study Entitled, "A Randomized, Double-Blind, Placebo- and Active- Controlled, Parallel-Group, 6-Week Study Designed 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)"
Report Number	RPT02532
Reference Standards	Beclomethasone Dipropionate and Beclomethasone 17-Propionate
Internal Standard (IS)	Beclomethasone Dipropionate-d10 and Beclomethasone 17-Propionate-d5
Sample Receipt Dates	3337 samples (1667 primary and 1670 back-up) were received between 8/4/10 and 9/9/10
Storage Conditions Upon Receipt	-70°C
LC-MS/MS Method	XBL08054-M02
Validated Storage Stability	up to 61 days at -70°C
Species/Matrix/Anticoagulant	human/plasma/K2-EDTA
Sample Size	0.5 mL
Sample Extraction Date Range	8/16/10 to 9/29/10
Extraction Method	Solid phase extraction
Precursor→Product Ion Pairs	521.3→337.3 for Beclomethasone Dipropionate 465.4→279.3 for Beclomethasone 17-Propionate 531.3→319.3 for Beclomethasone Dipropionate-d10 470.4→279.3 for Beclomethasone 17-Propionate-d5
Calibration Curve Range	10 pg/mL to 2500 pg/mL for Beclomethasone Dipropionate 20 pg/mL to 5000 pg/mL for Beclomethasone 17-Propionate
R-Squared (Mean)	0.9942 for Beclomethasone Dipropionate 0.9941 for Beclomethasone 17-Propionate
Standards Rejected from Linear Regression	32 for Beclomethasone Dipropionate 15 for Beclomethasone 17-Propionate
QC Sample Range	30 pg/mL to 2000 pg/mL for Beclomethasone Dipropionate 60 pg/mL to 4000 pg/mL for Beclomethasone 17-Propionate
QC Inter-Day Precision (%CV) QCL, QCM, QCH	13.22, 7.71, 6.82 for Beclomethasone Dipropionate 10.60, 5.83, 4.20 for Beclomethasone 17-Propionate
QC Inter-Day Accuracy (%RE) QCL, QCM, QCH	5.67, -3.30, -2.50 for Beclomethasone Dipropionate 2.17, -4.00, -3.00 for Beclomethasone 17-Propionate

(b) (4)

Filing/Survey Form

	Information		Information
NDA Number	202-813	Brand Name	QNASL
OCP Division (I, II, III, IV, V)	II	Generic Name	Beclomethasone Dipropionate (BDP) HFA Nasal Aerosol
Medical Division	DPARP	Drug Class	Corticosteroid (allergy medicine)
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	BDP HFA nasal aerosol is a corticosteroid indicated for the treatment of the (b) (4)
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	BDP HFA nasal aerosol is a non-aqueous nasal spray solution.
Pharmacometrics Reviewer		Dosing Regimen	The recommended dose of BDP HFA nasal aerosol is 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).
Date of Submission	May 24, 2011	Route of Administration	Intranasal
Estimated Due Date of OCP Review	Feb 17, 2012	Sponsor	Teva Respiratory, LLC
Medical Division Due Date	Feb 17, 2012	Priority Classification	Standard
PDUFA Due Date	March 24, 2012		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	3	3	Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports
Tabular Listing of All Human Studies	X	2	2	
HPK Summary	X	2	2	
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	RPT02138 (validation), XLB RPT02256 (Study BDP-AR-101), XLB RPT02532, (Study BDP-AR 304)
I. Clinical Pharmacology	X	2	2	
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	2	2	
Healthy Volunteers-				
single dose:	X	1	1	Study # BDP-AR-101
multiple dose:				
Patients-				
single dose:				

multiple dose:	X	1	1	Study # BDP-AR-304
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	Study # BDP-AR-101
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	1	1	HPA Axis effect, Study # BDP-AR-304
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	1	1	
solution as reference:				
alternate formulation as reference:	X	1	1	Study # BDP-AR-101: alternate route of dosing (inhalation vs. intranasal)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Waiver requested for 0-<2 year old, Deferral requested for 2-11 year old
Literature References	X			
Total Number of Studies	X	3	3	Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports

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/s/

ARUN AGRAWAL
02/14/2012

SURESH DODDAPANENI
02/14/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-813 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DPARP		
Applicant:	Teva Pharmaceutical Products	Biopharmaceutics Lead: Angelica Dorantes, Ph.D	
Trade Name:	--		
Generic Name:	Beclomethasone Dipropionate Nasal Aerosol	Date Assigned:	June 09, 2011
Indication:	Seasonal (SAR) and Perennial (PAR) Allergic rhinitis	Date of Review:	Dec 20, 2011
Formulation/strengths	Nasal Aerosol		
Route of Administration	Nasal		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
May 24, 2011 Sep 27, 2011	May 24, 2011	June 9, 2011	March 24, 2012
Type of Submission:	Original NDA		
Type of Consult:	In vitro Bioequivalence (BE) study		
REVIEW SUMMARY:			
<p>Teva has developed a new product for Beclomethasone Dipropionate (BDP) Nasal Aerosol to be indicated for the treatment (b) (4) of SAR and PAR in adults and adolescents (12 years of age and older). The canister (chemical formulation and concentrations) is the same as that in Teva's approved QVAR® Inhalation Aerosol (NDA 20-911), a product approved for the treatment of asthma. However, the proposed product has a new actuator specifically designed for a nasal route of delivery.</p> <p>This application is being filed under paragraph 505(b)(2) and is relying on Beconase AQ (NDA 19-389) as a reference listed drug. The 80 mcg/actuation dosage strength is the dosage strength proposed for the final trade product (80 mcg per actuation, 2 actuations per nostril – a total of 4 actuations per day resulting in a 320 mcg/day dose). Each canister of the proposed trade product provides approximately 120 actuations.</p> <p>In the clinical development program for BDP HFA Nasal Aerosol, two different canisters containing either 100 or 120 actuations were utilized. According to the Applicant, the manufacturing process used to produce the 120-actuation canister is identical to that of the approved 100-actuation canisters of QVAR Inhalation Aerosol with the exception of having a different fill weight. As part of the Phase 2 meeting package the Applicant proposed to conduct a full BA/BE program to establish a link between the product formulations used throughout the development program. The Agency recommended that in vitro performance evaluation would be sufficient to establish a link between these products. The Applicant conducted an in vitro bioequivalence study comparing the BDP HFA nasal Aerosol 100 actuation and 120 actuation products using three different lots of BDP Nasal</p>			

Aerosol 80 mcg, 100 actuation and BDP Nasal Aerosol 80 mcg/Spray 120 Actuation. The Biopharmaceutics review is focused on the acceptability of this in vitro BE study.

Based on the results of the in vitro BE analysis there are no differences in the *in vitro* performance (single actuation content through actuation life, droplet size distribution by laser diffraction, particle/droplet size distribution by cascade impactor, spray patten, plume geometry, priming and repriming in various orientations) of canisters containing 100 or 120 actuations.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-813 (000) for Beclomethasone Dipropionate Nasal Aerosol submitted on May 24, 2011, and this NDA is found acceptable from the Biopharmaceutics perspective.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorates, Ph. D.
Biopharmaceutics Lead
Office of New Drug Quality Assessment

c.c. ASchroeder, CBertha

Background

BDP has been previously formulated and developed as an aqueous nasal spray (*Vancenase AQ*®, *Beconase AQ*®) for the treatment of allergic rhinitis (AR). Both of these products were also marketed as chlorofluorocarbon (CFC) metered-dose inhaler (MDI) nasal aerosols prior to their being withdrawn from the market with the phase out of CFC-containing nasal products.

The Applicant has developed a new BDP hydrofluoroalkane (HFA) product (BDP HFA Nasal Aerosol) utilizing the same chemical formulation and concentrations as the orally inhaled BDP HFA formulation (*QVAR* [beclomethasone dipropionate] Inhalation Aerosol) with a new nasal actuator for use by the intranasal route in the treatment of AR.

Drug Product

The formulation presented in Table 1 has been developed as a pressurized solution formulation to provide a target label claim of 80 mcg/actuation (ex-actuator). The BDP is dissolved in a mixture of dehydrated alcohol and HFA-134a to form a stable solution. The development of the BDP Nasal Aerosol formulation is based on previous knowledge and experience gained during the development and commercial manufacture of *QVAR* Inhalation Aerosol. Relevant knowledge from the development of *QVAR* has been applied to the development of the BDP Nasal Aerosol drug product.

Table 1. Formulation Configuration

Ingredient	80 mcg/Actuation (ex-actuator) (% w/w)
Beclomethasone Dipropionate (anhydrous), USP	(b) (4)
Dehydrated Alcohol, USP	
HFA-134a	

Development Program

Teva's clinical program consisted of one Phase I PK study, one Phase II dose-finding SAR study and 4 Phase III efficacy and safety studies (pivotal SAR efficacy study, pivotal PAR efficacy study, long term safety PAR study, and HPA-axis PAR study).

In the clinical development program for BDP HFA Nasal Aerosol, two different canisters containing either 100 or 120 actuations were utilized (Table 2).

Table 2. Details of the Actuators Used in the BDP HFA Nasal Aerosol Clinical Program

Study Number	Actuations/ Canister	Clinical Development Phase	Nosepiece	Counter
BDP-AR-101	100	Phase I	Removable	Non-functional
BDP-AR-201	100	Phase II	Removable	Non-functional
BDP-AR-301 BDP-AR-303	100	Phase III	Removable	Functional
BDP-AR-302 BDP-AR-304	120	Phase III	Fixed	Functional

According to the Applicant, the manufacturing process used to produce the 120-actuation canister is identical to that of the approved 100-actuation canisters of *QVAR* Inhalation Aerosol with the exception of having a different fill weight.

Bridging Study Conducted Between Phase III Actuators

The Applicant conducted an in vitro bioequivalence study comparing the BDP HFA nasal Aerosol 100 actuation and 120 actuation products using three different lots of BDP Nasal Aerosol 80 mcg, 100 Actuation and BDP Nasal Aerosol 80 mcg/Spray 120 Actuation. Table 3 below summarizes the bridging study outline and criteria used in the comparison.

Table 3. Bridging Study Outline and Criteria

Test	Study Measure(s)	Measure(s) for Statistical Evaluation	Lifestage	Statistical Evaluation
Single Actuation Content Through Container Life	Drug mass per single actuation	Same as previous column	B, M, E	PBE
Droplet Size Distribution by Laser Diffraction	D ₁₀ , D ₅₀ , D ₉₀ , Span, and Q(t) diagrams at 2 distances	D ₁₀ , D ₅₀ , D ₉₀ , Span	B, E	PBE
Particle/Droplet Size Distribution by Cascade Impactor	Drug mass on individual components and groupings	Groupings	B, M, E	PBE
Spray Pattern	D _{min} , D _{max} , and ovality ratio at 2 distances	Qualitative – shape comparison	B	PBE
		Quantitative – same as previous column		
Plume Geometry	Plume width, and cone angle of one side view at one delay time	Width and angle of one side view at one delay time	B	PBE
Priming and Repriming	Drug mass per single actuation at first primed or reprimed actuation	Same as previous column	B	Point Estimate Relative to Label Claim, PBE

Single Actuation Content (SAC) Through Container Life Analysis

Delivered dose testing was performed to examine the SAC of the active drug substance, BDP, through life. SAC through container life is based on single actuation data per determination. For this study, ten units were selected from each canister batch for analysis. The devices were primed and actuations were collected to determine delivered (ex-actuator) drug mass from units at the beginning, middle and end of canister life. The delivered mass of drug substance is expressed both as the actual amount and as a percentage of label claim. A comparison of geometric means for the 100 and 120 Actuation products was performed on SAC Delivered Dose data for three life stages. Table 4 summarizes the results of the statistical analysis.

Table 4. SAC Geometric Mean Through Life

	SAC Delivered Dose Results (mcg)					
	BEG		MID		END	
	100 Actuation	120 Actuation	100 Actuation	120 Actuation	100 Actuation	120 Actuation
Geometric Mean						
STDEV						

(b) (4)

Droplet Size Distribution (DSD) by Laser Diffraction

This determination was conducted using a laser diffraction method on ten units from each lot of BDP Nasal Aerosol. The study was performed on primed units at beginning and end of canister life. DSD measurements were made at 3cm and 6cm from the delivery orifice to the beam. Single spray droplet size distribution and span measurements based on volume (mass) were analyzed. Triplicate measurements were conducted at each life-stage and distance to assess precision. Droplet size distribution, D₁₀, D₅₀, D₉₀, and span [(D₉₀ - D₁₀)/D₅₀] were reported for each actuation. Profiles of the droplet size and obscuration, or percent Transmission over the complete life of the spray [Q(t) diagram], was collected for a 20% representative sampling of the units at the beginning and end of life at 3cm and 6cm. A comparison of geometric means for 100 actuation and 120 actuation products was performed on DSD D₁₀, D₅₀, D₉₀ and Span data for two life stages at a distance of 3cm and 6cm. Table 5 show a summary of the analysis at 6 cm.

Table 5. DSD Geometric Mean through Life at 6 cm

		DSD Results at 6 cm (microns)			
		BEG		END	
		100 Actuation	120 Actuation	100 Actuation	120 Actuation
D ₁₀	Geometric Mean	(b) (4)			
	STDEV				
D ₅₀	Geometric Mean				
	STDEV				
D ₉₀	Geometric Mean				
	STDEV				
Span	Geometric Mean				
	STDEV				

Spray Pattern

Spray Pattern analysis was performed using the Proveris SprayView® NMDI system. For this study, ten units were selected from each canister batch for analysis. Single measurements were performed at the beginning of canister life at 3cm and 6cm distance from the nosepiece opening. The quantitation of the shortest axis (D_{min}), longest axis (D_{max}) and the Ovality Ratio (D_{max}/D_{min}) were determined by automated analysis. A comparison of geometric means for 100 actuation and 120 actuation products was performed for D_{min}, D_{max} and Ovality data at 3 cm and 6 cm. Table 6 show the spray pattern results for 3 cm only.

Table 6. Spray Pattern Geometric Mean at 3 cm

		Spray Pattern Results for 3 cm	
		100 Actuation	120 Actuation
Dmin (mm)	Geometric Mean	(b) (4)	
	STDEV		
Dmax (mm)	Geometric Mean		
	STDEV		
Ovality Ratio	Geometric Mean		
	STDEV		

Plume Geometry

Plume geometry was collected using laser imaging/high speed photography with an automated actuation system. For this study, ten units were selected from each canister batch for analysis. Measurements were performed at the beginning of canister life at a 6cm distance from the nosepiece opening. Plumes were characterized individually for each of the triplicate actuations per run for each unit. The image was measured at a single delay time using snapshot analysis mode. The measurements were gathered while the fully developed phase of the plume was still in contact with the actuator nosepiece tip. The plume angle and plume width were determined. The plume angle was based on the conical region of the plume extending from a vertex that occurred at or near the actuator tip. Plume width was the determined as the distance from the edges of the plume at 6cm from the orifice, once the plume angle is determined. Table 7 shows a comparison of geometric means for 100 actuation and 120 actuation products performed for Plume Angle and Plume Width data at 6 cm

Table 7. Plume Geometry Geometric Mean at 6 cm

		Plume Geometry Results for 6 cm	
		100 Actuation	120 Actuation
Plume Angle (deg)	Geometric Mean	(b) (4)	
	STDEV		
Plume Width (mm)	Geometric Mean		
	STDEV		

Statistical Analysis

Criteria for the Population BE Approach to In vitro Data

Under the PBE method, for each comparative in vitro test described in the 2003 draft BA/BE guidance, FDA recommends the calculation of a 95 percent confidence interval as a measure of equivalence between the test and reference products that includes the ratio of the geometric means of the two products and the difference in variability between

test and reference products. The confidence interval is compared to an acceptance limit that is based on fixed statistical parameters (i.e., the regulatory constants, σ_{T0} and Epsilon and takes into consideration the observed within-study variability of the test and reference products. Inherent in the PBE method is the principle that the acceptance limits for the confidence interval depend on the relative variability of the test and reference products observed in the study. In the case of low variability data for the reference product, the acceptance limits narrow, toward the 90-111 percent criteria used in the geometric mean method, enabling only test products with comparable variability to meet the criteria. Conversely, in the case of high variability data for the reference product, the acceptance limits might be slightly wider. This permits approval of generic products that are comparably or less variable than the reference product (even if the ratio of the geometric means falls slightly outside of the 90-111 criteria) and, guards against approval of generic products that are more variable than the reference product (even if the ratio of the geometric means falls within the 90-111 percent criteria).

In summary, to test for population bioequivalence, 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion (refer to Statistical Information from the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data) are computed. For linearized θ_p , if this upper bound is negative, conclude population bioequivalence. If the upper bound is positive, do not conclude population bioequivalence.

Linearized tests are based on regulatory limit (θ_p) of 2.0891, scaling variance (σ_{T0}^2) of 0.1 and variance terms offset (ϵ_p) equal to 0.01.

The means and variances of the LN-transformed values for each parameter were calculated for each product and the between sample variance of the pooled batches within each product provided an estimate of the between batch variance. The overall mean of each product and the 95 % upper confidence bound of either the reference scaled or constant-scaled linearized criterion was calculated.

Results of BE Testing

Table 8 provides a summary of the statistical analysis using the population bioequivalence approach ran by the Applicant.

Table 8. Summary results of statistical analysis of in vitro PBE for test (120 actuator) and reference (100 actuator)

Test	Measured	PBE Results (0.9-1.11)
Single Actuation Content at beginning	beginning, middle and end of life for delivered dose	<i>Passed</i>
Droplet size distribution by laser diffraction	DSD at 4 cm and 7 cm (D10, D50, D90, span)	<i>Passed</i>
Particle Size Distribution	beginning, middle and end of life for Group 1 (adapter- Stage 1), Group 2 (Stage 2-6), and Group 3 (Stage 7-MOC)	<i>Passed</i>
Spray pattern	At 3 cm: <ul style="list-style-type: none"> ➤ Ovality (and Dmin) ➤ Area (and Dmax) At 6 cm <ul style="list-style-type: none"> ➤ Ovality and Area (Dmin, Dmax) 	At 3 cm: <ul style="list-style-type: none"> ➤ Ovality (and Dmin): <i>passed</i> ➤ Area (and Dmax): <i>passed</i> At 6 cm <ul style="list-style-type: none"> ➤ Ovality and Area (Dmin, Dmax): <i>passed</i>
Priming	beginning of life for delivered dose	Passed
Plume Geometry	Plume angle Plume width	Plume angle: <i>Passed</i> Plume width: <i>Passed</i>
Repriming	of life for delivered dose in valve-up and valve-down orientations	Passed

This Reviewer’s Analysis of the Data

This reviewer ran the statistical analysis using SAS codes developed by the OGD to test for PBE to the raw data provide by the Applicant on Sep 27, 2011. The same outcome of results as summarized in Table 8 was obtained by this reviewer’s analysis. An example of the SAS output is shown below.

In Vitro PBE Analysis - Approximate Confidence Interval Using Moment-
Based Simplified Parameter Estimates
for
NDA 202813 Beclomethasone Nasal Aerosol - Spray pattern: Dist6

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0018
	CI:	-0.0012
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0208

CI: -0.0205
 Pass/Fail: PASS

Overall Test Outcome: Pass/Fail: PASS

Notes: Constant-scaled tests are based on $\sigma_{T0} = 0.10$ and $\epsilon = 0.01$. Linearized tests are based on regulatory limit (θ_P) of 2.0891. For linearized θ_P , if the upper bound of the confidence interval is < 0 , PASS. For linearized θ_P , if the upper bound of the confidence interval is > 0 , FAIL. If the estimate of $\sigma_R > \sigma_{T0}$, use reference scaling. If $\sigma_R < \sigma_{T0}$, use constant scaling. If $\sigma_R = 0.10$, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

Ratio	TEST	REFERENCE	T/R
(orig scale) Mean:	1.13	Mean: 1.13	Ratio: 100.43
(99.7,101.2)		90% CI for ratio:	
(log scale) Mean:	0.13	Mean: 0.12	Diff: 0.00
(log scale) CV:	24.29	CV: 24.53	
(log scale) SigmaBT:	-	SigmaBR: -	Ratio: -
(log scale) SigmaWT:	-	SigmaWR: -	Ratio: -
(log scale) SigmaT:	0.031	SigmaR: 0.030	Ratio: 1.025

Class Levels (total number bottles/product = 60; number of sectors = 1):

Class Level Information for
 Input Dataset NDA 202813 Beclomethasone Nasal Aerosol - Spray
 Pattern: Dist6

By Product			
Product	Class	Levels	Values
REF	PRODUCT container	1	REF
		30	31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	LOT	3	090114A 090115A 090116A
TEST	PRODUCT container	1	TEST
		30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

30
LOT 3 090403 090404 090405

Reviewer's Comments

The in vitro BE analysis shows that there are no differences in the *in vitro* performance (single actuation content through actuation life, droplet size distribution by laser diffraction, particle/droplet size distribution by cascade impactor, spray patten, plume geometry, priming and repriming in various orientations) of canisters containing 100 or 120 actuations.

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

/s/

SANDRA SUAREZ
02/05/2012

ANGELICA DORANTES
02/07/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202-813	Brand Name	TRADENAME
OCP Division (I, II, III, IV, V)	II	Generic Name	Beclomethasone Dipropionate (BDP) HFA Nasal Aerosol
Medical Division	DPARP	Drug Class	Corticosteroid (allergy medicine)
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	BDP HFA nasal aerosol is a corticosteroid indicated for the (b) (4)
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	BDP HFA nasal aerosol is a non-aqueous nasal spray solution.
Pharmacometrics Reviewer		Dosing Regimen	The recommended dose of BDP HFA nasal aerosol is 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).
Date of Submission	May 24, 2011	Route of Administration	Nasal spray
Estimated Due Date of OCP Review		Sponsor	Teva Respiratory, LLC
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	March 24, 2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	3		Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports
Tabular Listing of All Human Studies	X	2		
HPK Summary	X	2		
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		RPT02138 (validation), XLB RPT02256 (Study BDP-AR-101), XLB RPT02532, (Study BDP-AR 304)
I. Clinical Pharmacology	X	2		
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

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Pharmacokinetics (e.g., Phase I) -	<input checked="" type="checkbox"/>	2		
Healthy Volunteers-				
single dose:	X	1		Study # BDP-AR-101
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		Study # BDP-AR-304
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Study # BDP-AR-101
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	1		HPA Axis Study # BDP-AR-304
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	<input checked="" type="checkbox"/>	1		
solution as reference:				
alternate formulation as reference:	X	1		Study # BDP-AR-101: alternate route of dosing (inhalation vs. intranasal)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Waiver requested for 0-<2 year old, Deferral requested for 2-11 year old
Literature References	X			
Total Number of Studies	<input checked="" type="checkbox"/>	3		Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Referred to NDA 20-911
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			505(b)(2)
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Study BDP-AR-201 determined relationship between efficacy and dose at 80, 160 and 320 mcg/day.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requested waiver for 0 to <2 years of age, and deferral for 2 to 11 years of age.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

Background:

This NDA filing review is for Beclomethasone Dipropionate (BDP) nasal aerosol submitted under 505(b)(2) of the FDC Act. BDP is a synthetic corticosteroid chemically related to dexamethasone. BDP is a prodrug which undergoes rapid and extensive conversion to its main active metabolite, beclomethasone-17-monopropionate (17-BMP) during absorption. Corticosteroids are reported to have multiple anti-inflammatory effects, inhibiting both inflammatory cells and the release of inflammatory mediators. BDP has been previously formulated and developed as an aqueous nasal spray (Vancenase AQ, Beconase AQ) for the treatment of allergic rhinitis (AR). Both of these products were also marketed as chlorofluorocarbon (CFC) metered-dose inhaler (MDI) nasal aerosols prior to being withdrawn from the market with the phase out of CFC-containing nasal products.

Sponsor has developed a new BDP hydrofluoroalkane (HFA) product (BDP HFA nasal aerosol) utilizing the same chemical formulation and concentrations as the orally inhaled BDP HFA formulation (QVAR, BDP HFA inhalation aerosol, NDA 20-911, approved and marketed since September 2000 for the maintenance treatment of asthma in patients 5 years of age and older) with a new nasal actuator for use by the intranasal route for the treatment of AR.

Clinical Pharmacology Studies:

Sponsor has conducted two clinical pharmacology studies with BDP HFA nasal aerosol - one PK study in healthy subjects (BDP-AR-101) and one PD (HPA Axis) study in subjects with perennial allergic rhinitis (PAR) (BDP-AR-304).

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Study BDP-AR-101: This study determined PK parameters for BDP and 17-BMP following a single dose intranasal administration of BDP HFA at 80 mcg or 320 mcg. Results suggested dose proportionality in systemic exposures of BDP and 17-BMP between the 80 mcg and 320 mcg doses of BDP HFA nasal aerosol.

This study also compared the PK parameters for the intranasal doses (80 mcg and 320 mcg) with an orally inhaled dose (320 mcg) of QVAR inhalation aerosol. The systemic bioavailability of BDP HFA nasal aerosol 320 mcg was 27.5% of that of orally inhaled BDP HFA 320 mcg based on the plasma concentrations of 17-BMP, and was 12.7% of that of orally inhaled BDP 320 mcg based on the plasma concentrations of BDP. Further, the systemic bioavailability of BDP HFA nasal aerosol 80 mcg was 7.1% of that of orally inhaled BDP HFA 320 mcg based on the plasma concentrations of 17-BMP, and was 3.4% of that of orally inhaled BDP 320 mcg based on the plasma concentrations of BDP.

Study BDP-AR-304: This study compared the effects of 6 weeks of treatment with BDP HFA nasal aerosol (320 mcg/day) with the effects of 6 weeks of treatment with placebo, or with the effects of 7 days of treatment with active control prednisone (10 mg/day) on hypothalamic-pituitary adrenal (HPA)-axis function as assessed by 24-hour serum cortisol measurements. Prednisone treatment resulted in a substantial reduction in HPA-axis function as compared to placebo nasal aerosol treatment while BDP HFA 320 mcg/day was not associated with HPA-axis suppression relative to placebo in adult and adolescent subjects (≥ 12 years of age) with PAR. PK results obtained at the end of the 6-week treatment period showed low systemic exposure of BDP and 17-BMP following intranasal administration and the results were similar to those obtained in Study BDP-AR-101.

This NDA is fileable from a clinical pharmacology perspective.

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

None

Arun Agrawal, PhD

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni, PhD

Team Leader/Supervisor

Date

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

/s/

ARUN K AGRAWAL
07/01/2011

SURESH DODDAPANENI
07/01/2011