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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Indication(s): [REDACTED] (b) (4)

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1. EXECUTIVE SUMMARY

Teva proposes a new beclomethasone dipropionate (BDP) hydrofluoroalkane (HFA) product with a new nasal actuator for the treatment of allergic rhinitis (AR). The applicant conducted two studies, BDP-AR-301 and BDP-AR-302 to evaluate the efficacy and safety of BDP HFA 320 mcg/day applied in a nasal aerosol in subjects with seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). Study BDP-AR-301 was conducted in patients with SAR and Study BDP-AR-302 was conducted in patients with PAR. Both studies recruited patients 12 years of age and older. The applicant also submitted the results from their long-term efficacy and safety study, Study BDP-AR-303.

I identified no statistical issues during the course of my review. The applicant did not conduct any missing data imputations for these studies. The amount of missing data in each study was predicted to be low and the maximum likelihood method chosen to analyze the endpoints was valid for missing-at-random data. The most common reason for early dropout in Study BDP-AR-301 was protocol violation/non-compliance; 0 patients in the BDP HFA group and 3 (2%) patients in the placebo group. The most common reason for early dropout in Study BDP-AR-302 was withdrawal of consent; this study had 6 (3%) patients in each group. Given that the percentage of dropouts was low, the impact of missing data in this application is inconsequential. Studies BDP-AR-301 and BDP-AR-302 controlled the type I error using a fixed sequential step down test to test the primary and secondary endpoints.

Based on my statistical review of the two key efficacy studies, there is evidence to support the claim of efficacy of BDP HFA nasal aerosol at a dose of 320 mcg/day in the treatment of patients 12 years of age or older with seasonal allergic rhinitis or perennial allergic rhinitis. In both studies there is evidence that BDP HFA nasal aerosol is effective in decreasing rTNSS and iTNSS compared to placebo. The evidence was supported by the results in Study BDP-AR-303. Only Study BDP-AR-301 evaluated the reflective ocular symptom scores. Although the study concludes that there is a significant treatment difference in decreasing reflective ocular symptom scores in favor of BDP HFA nasal aerosol, this evidence was not replicated. Therefore, I recommend including the results from the analyses of rTNSS and iTNSS scores from Studies BDP-AR-301 and BDP-AR-302 in the label. There are inconsistent results for RQLQ between the two key efficacy studies. Therefore, there is weak evidence to support inclusion of RQLQ in the label.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Teva is currently marketing QVAR[®] 40 mcg and 80 mcg (beclomethasone dipropionate [BDP]) Inhalation Aerosol which is indicated in the maintenance treatment of asthma as a prophylactic therapy in patients 5 years of age and older, where BDP is anti-inflammatory corticosteroid. QVAR utilizes a hydrofluoroalkane (HFA) propellant. The QVAR formulation has been approved in the United States since September 2000 in a metered-dose inhaler device. The purpose of this submission is to obtain approval of marketing, BDP HFA Nasal Aerosol to be used in patients 12 years of age and older with allergic rhinitis (AR).

Allergic rhinitis is an allergen-induced inflammatory condition that can cause sneezing, runny nose, nasal itching and nasal congestion. People who have AR can also have asthma. The applicant has developed a new BDP HFA Nasal Aerosol product that, according to them, utilizes the same chemical formulation and concentrations as the orally inhaled BDP HFA formulation (QVAR Inhalation Aerosol) with a new nasal actuator for the treatment of AR. The approach is to insert already available canisters into the newly developed plastic nasal actuators.

Teva is requesting approval for dosage strength of 320 mcg once daily.

2.1.2 History of Drug Development

A pre-IND meeting was held on April 2, 2008. IND 101,639 was submitted on January 20, 2009. An end-of-phase 2 meeting was held on September 9, 2009 to discuss the Phase 3 clinical questions for the registration of BDP HFA Nasal Aerosol. The applicant suggested that a dose of 320 mcg/day was the lowest safe and effective dose. The division agreed that 320 mcg/day was the lowest effective dose; however, the division notes that this dose may not be optimal to carry forward as a single dose into the Phase 3 studies. The division suggested to either increase the daily dosage or to modify the dose frequency to twice a day. A pre-NDA meeting was held on October 18, 2010 where the division stated

- While in general your approach appears reasonable, we have the following comments with regard to your Safety Statistical Analysis Plan:
 - a. Submit safety data for subjects treated with all doses, not just those with 320 mcg BDP HFA (refer to section 2.2 on page 17 of the Briefing Package);
- The Agency clarified that each clinical study in their allergic rhinitis program will be reviewed both individually and as part of the integrated summary of safety (ISS). Thus, the pooled analyses should include not only the 320 mcg dose but all the doses used in study BDP-AR-201. Teva stated that they have concerns over pooling of adverse event data from studies of different lengths. The Agency stated that one way to alleviate this concern would be to present the safety data according to dose and length of exposure in the ISS. The Agency stressed that AEs from all doses will need to be provided.

b. Submit all adverse events (AEs) that occurred in the studies, not just “treatment emergent” AEs. Subsequent sub-grouping AEs into those that are treatment emergent is acceptable (refer to section 2.7 on page 18 of the Briefing Package);

- We agree with you that integrating statistical analyses for disparate studies is not likely to provide useful information. While both the Summary of Clinical Efficacy and Integrated Summary of Efficacy are required components of this submission, there is no need for them to be markedly different.
- Provision of SAS programs for primary and secondary analyses, plus those for tables concerning patient demographics, baseline characteristics, and disposition by treatment will be sufficient. We also note that inclusion of programs employed for any additional calculations or for construction of your analysis datasets may facilitate review of your submission by resolving any ambiguities in documentation. Be sure to document what each program does, how it is called, and any dependencies, e.g., order in which programs should be run.

The post meeting comments from the division were

We have concerns with the design of your proposed nasal inhaler because it resembles and performs in a similar manner as other oral inhalers frequently used by patients with respiratory diseases. As such there is the potential that it may be confused as an oral inhaler, which may result in an incorrect route of administration and drug medication errors. You will need to address this issue in the NDA for your proposed beclomethasone nasal aerosol spray including consideration of conducting usability and labeling comprehension studies to evaluate patients’ ability to use the inhaler correctly with the proposed labels and content of labeling.

2.1.3 Specific Studies Reviewed

The applicant submitted one phase 2 dose-range-finding study (BDP-AR-201), two phase 3 efficacy studies (BDP-AR-301 and BDP-AR-302) and a long-term efficacy and safety study (BDP-AR-303). I will refer to the Studies BDP-AR-201, BDP-AR-301, BDP-AR-302 and BDP-AR-303 as 201, 301, 302 and 303 respectively. The focus of my review is on the two efficacy studies (Studies 301 and 302). I have also included in this review my evaluation of the long-term efficacy and safety study (Study 303). All three studies were phase 3, randomized, double-blind, placebo-controlled, parallel group, multi-center in patients 12 years of age and older. All three studies were conducted in the United States (US). Study 301 was conducted in patients with seasonal allergic rhinitis (SAR); Studies 302 and 303 were conducted in patients with perennial allergic rhinitis (PAR).

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location [\\CDSESUB1\EVSPROD\NDA202813\202813.enx](#). The information needed for this review was contained in modules 1, 2.5, 2.7.3i, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoint analyses. I was able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The summary of the study designs and endpoints are given in Table 1. All three studies are Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center, outpatient studies in male and female subjects 12 years of age and older. Study 301 was 2 weeks in duration, Study 302 was 6 weeks and Study 303 was 52 weeks. The design and efficacy endpoints are explained in detail in the following paragraphs.

Table 1 Summary of Study Design.

Study ID	Indication	Length of the Study	Treatment Arms (Per Nostril, Q.D.)	Number of Patients	Primary Efficacy Endpoints
301	SAR	RI: 7-10 days TP: 2 weeks	BDP HFA 320 mcg/day, 2 actuations/nostril	169	Change from baseline in the average AM and PM daily rTNSS
			Placebo, 2 actuations/nostril	171	
302	PAR	RI: 7-21 days TP: 6 weeks	BDP HFA 320 mcg/day, 2 actuations/nostril	236	Change from baseline in the average AM and PM daily rTNSS
			Placebo, 2 actuations/nostril	238	
303	PAR	RI: 7-21 days TP: 30 weeks 52 weeks	BDP HFA 320 mcg/day, 2 actuations/nostril	418	Change from baseline in weekly averages of 24-hour rTNSS over the first 30 weeks of Treatment
			Placebo, 2 actuations/nostril	111	

- RI: Run-in period, TP: Treatment period

Studies 301 and 302 are similar in design. Both studies were designed to assess the efficacy and safety of BDP HFA nasal aerosol by applying 2 actuations per nostril each containing 80 mcg per actuation for a total daily dose of 320mcg/day, in patients with SAR or PAR. Each study consisted of a run-in period and a treatment period. Study 303 is also of similar design.

Study 301 had

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). Subjects who discontinued the study prematurely had a Termination Visit (TdV) conducted. The study was conducted during the 2009-2010 mountain cedar pollen season in Texas, USA.

Study 302 had

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). Subjects who discontinued the study prematurely had a Termination Visit (TdV) conducted. All TV2 procedures were to be performed at the Termination Visit (TdV).

In the run-in period for each study patients self-administered a placebo nasal aerosol once daily (B.I.D.) in the morning. The patients were instructed to assess and record their reflective and instantaneous nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) and in Study 301, their reflective and instantaneous non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) twice daily using the following scale:

- 0=absent (no sign/symptom present)
- 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; cause interference with activities of daily living and/or sleeping).

Following the run-in period, patients in Studies 301 and 302 were randomized in a 1:1 ratio to receive BDP HFA 320 mcg/day or placebo. The treatment period in each study was from the randomization visit to the final treatment visit where patients self-administered the double-blind study medication once daily in the morning. The patients assessed and recorded their reflective and instantaneous nasal symptoms and their reflective and instantaneous non-nasal symptoms (Study 301 only) using the same scale as above. Patients received the study medication for the duration of the respective studies' treatment period.

The primary efficacy endpoint in Studies 301 and 302 was the average AM and PM subject-reported reflective Total Nasal Symptom Score (rTNSS) over the treatment period in the intent-to-treat (ITT) population. The ITT population was defined as all randomized subjects who received at least one dose of randomized study medication and had at least one post-baseline assessment. The secondary efficacy endpoints for Studies 301 and 302 were the average AM and PM subject-reported instantaneous Total Nasal Symptom Score (iTNSS) over the treatment period in the ITT population, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and the average AM and PM subject-reported reflective ocular symptom score (rTOSS), Study 301 only.

RTNSS was defined as the sum of the four nasal symptoms: rhinorrhea (runny nose), nasal congestion, nasal itching, and sneezing, scored using the scale above evaluated over the past 12 hours prior to recording of the score. Instantaneous Total Nasal Symptom Score is defined as the evaluation of the TNSS over the last 10 minutes. The RQLQ is defined as a disease-specific quality of life questionnaire developed to measure the functional problems (physical, emotional

and social), through 28 items in 7 domains. The RQLQ is measured on a 7-point scale, where 0=least severe and 6=extremely severe. The population for RQLQ is based on subjects 18 years of age or older with impaired quality of life at baseline with a RQLQ score of 3.0 or greater at the time of randomization. The rTOSS was defined as the sum of the individual non-nasal symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness, scored using the same scale as TNSS.

The primary efficacy endpoint for Study 303 was change from baseline in weekly averages of 24-hour rTNSS over the first 30 weeks of treatment. Of note, the TNSS was recorded once daily in the morning prior to administration of study medication or starting any activity; this is different from how it was recorded in Studies 301 and 302 (i.e. recorded twice daily every 12 hours). The secondary efficacy endpoints for Study 303 were subject-reported iTNSS over the first 30 weeks of the treatment period, subject-reported 24-hour rTNSS over the 52 weeks of the treatment period, subject-reported iTNSS over the 52-week of the treatment period and the RQLQ at 30 weeks and 52 weeks of the treatment period.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Studies 301 and 302 were conducted in adolescents and adults 12 years of age and older. All patients had at least a 2-year history of SAR (Study 301) or PAR (Study 302). The summary of the patient disposition in all three studies is given in Table 2. The main reason for discontinuation in Study 301 was protocol violation/non-compliance, about 1%. Study 302 had about 1% of the patients with protocol violations and Study 303 had about 2% of the patients with protocol violations. The main reason for discontinuation in Study 302 was patients withdrawing consent, about 3%. Study 303 had the largest proportion of patients who withdrew consent, about 11%.

Table 2 Summary of patient disposition

	Study 301		Study 302		Study 303	
	BDP HFA 320 mcg/day	Placebo	BDP HFA 320 mcg/day	Placebo	BDP HFA 320 mcg/day	Placebo
Randomized	169	171	236	238	418	111
ITT	167	171	232	234	414	110
Completed	165	167	221	216	335	85
PP	160	160	215	220	358	95
Discontinued	2 (1%)	4 (2%)	15 (6%)	22 (9%)	83 (20%)	26 (23%)
Adverse Event	1	0	1	7	17	3
Withdrew Consent	1	0	6	6	44	13
Sponsor Requested Withdrawal	0	0	0	0	3	1
Pregnancy	0	0	1	0	1	2
Lost to Follow Up/Failure to Return	0	1	5	2	11	2
Protocol Violation/Non- Compliance	0	3	1	1	4	5
Other	0	0	1	6	3	0

The demographic and baseline characteristics in the three studies are summarized in Table 3 for the ITT population. The patients' mean age was about 36 to 39 years in the three studies. In all three studies, most patients were women (57% ~ 69%), Caucasian (70%~ 88%) and not Hispanic or Latino (69% ~ 89%). There were no noticeable imbalances of the demographics and baseline characteristics between the treatment groups across all three studies on gender, age, race and ethnicity.

The primary and secondary efficacy analyses were conducted on the ITT population. The applicant also conducted the primary and secondary analyses on the per-protocol (PP) population, and the RQLQ analyses were conducted on the RQLQ population. The PP population was a subset of the ITT population and included all data from subjects in the ITT population obtained prior to experiencing major protocol deviations. 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 or greater, were aged 18 years or more and who understood English.

Table 3 Demographics and baseline characteristics (ITT population)

		Study 301		Study 302		Study 303	
		BDP HFA 320 mcg/day	Placebo	BDP HFA 320 mcg/day	Placebo	BDP HFA 320 mcg/day	Placebo
Gender, n (%)	Male	54 (32)	74 (43)	74 (32)	73 (31)	128 (31)	44 (40)
	Female	113 (68)	97 (57)	158 (68)	161 (69)	286 (69)	66 (60)
Age (years)	Mean (SD)	39.3 (13)	38 (13)	36.8 (15)	37.2 (14)	37.4 (14)	35.7 (13)
Race	White	142 (85)	142 (83)	186 (80)	185(79)	341 (82)	97 (88)
	African American	23 (14)	26 (15)	40 (17)	40 (17)	63 (15)	14 (13)
	Asian	3 (2)	3 (2)	6 (3)	5(2)	13 (3)	1 (1)
	American Indian or Alaskan Native	1 (1)	1 (1)	1 (1)	2 (1)	7 (2)	2 (2)
	Native Hawaiian, other Pacific Islander	0	1 (1)	0	0	3 (1)	0
	Other	0	0	1 (1)	6 (3)	1 (1)	0
Ethnicity, n (%)	Hispanic or Latino	52 (31)	49 (29)	26 (11)	30 (13)	45 (11)	12 (11)
	Not Hispanic, not Latino	115 (69)	122 (71)	206 (89)	204 (87)	369 (89)	98 (89)

3.2.3 Statistical Methodologies

The primary statistical objective of Studies 301 and 302 was to demonstrate the efficacy of BDP HFA, applied as a nasal aerosol, in subjects with SAR and PAR, respectively.

The summary of the statistical methods used for the primary and secondary analysis is given in Table 4.

Table 4 Summary of Analysis Methods

Study ID	Measure of Interest	Analysis Method	Adjustments
301	rTNSS	repeated measures ANCOVA model	Fixed sequential step-down approach
	iTNSS	repeated measures ANCOVA model	Fixed sequential step-down approach
	RQLQ	ANCOVA	Fixed sequential step-down approach
	rTOSS	repeated measures ANCOVA model	Fixed sequential step-down approach
302	rTNSS	repeated measures ANCOVA model	Fixed sequential step-down approach
	iTNSS	repeated measures ANCOVA model	Fixed sequential step-down approach
	RQLQ	ANCOVA	Fixed sequential step-down approach
303	rTNSS	repeated measures ANCOVA model	No multiplicity adjustments were made for the pre-planned multiple comparisons
	iTNSS	repeated measures ANCOVA model	No multiplicity adjustments were made for the pre-planned multiple comparisons
	RQLQ	ANCOVA	No multiplicity adjustments were made for the pre-planned multiple comparisons

All three studies consisted of a treatment arm of 320mcg/day vs. placebo. The primary analysis for the change from baseline in the average AM and PM daily subject-reported rTNSS over the treatment period in Studies 301 and 302 is summarized as follows:

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. Day was treated as an unordered categorical variable. A first-order autoregressive structure was used to model intrasubject correlation, and in conjunction with treating subject as a random effect, this yielded a correlation structure in which observations from the same subject were considered to be correlated, with observations closer in time being more correlated. Baseline was defined as the average AM and PM subject-reported rTNSS over the 4 days prior to randomization. Estimated treatment differences and 95% confidence intervals (CI) for the treatment differences were calculated.

The secondary efficacy analyses in Studies 301 and 302 of the change from baseline in the average AM and PM subject-reported iTNSS over the treatment period and the change from baseline in the average AM and PM subject-reported ocular symptom score over the treatment period (study 301 only) were analyzed in a similar fashion to the primary endpoint. The analyses were performed using the ITT Population with supportive analyses performed using the PP Population.

The change from baseline in RQLQ at Week 2 (Study 301) or Week 6 (Study 302) for subjects with impaired quality of life at Baseline was analyzed using an ANCOVA with factors for

treatment, Baseline (RV), and center. This pre-specified subset analysis is reasonable for this application given that the exclusion of patients were not based on post-randomization characteristics that are likely affected by the treatment assignment. However, such restriction will not allow one to give a claim of RQLQ benefit to the general SAR/PAR population. Therefore, change from baseline in RQLQ was re-analyzed in the ITT population with supportive analyses performed using the PP population.

In Study 303, the analyses of the efficacy endpoints were as follows:

Separate models were used to analyze the TNSS data (both rTNSS and iTNSS) over the first 30 weeks and over the entire 52 weeks of the Treatment Period. The analyses for the TNSS over the first 30 weeks of the Treatment Period were conducted using the ITT population (first 30 weeks only). The analyses for the TNSS over the 52 weeks of the Treatment Period were conducted using the ITT population (entire 52 weeks). The primary analysis was based on all subjects in the ITT population (based on data from the first 30 weeks only). The primary efficacy endpoint was the change from Baseline in weekly averages of subject-reported 24-hour rTNSS over the first 30 weeks of the Treatment Period. The primary endpoint was analyzed using a repeated measures analysis of covariance (ANCOVA) with covariate adjustment for baseline, week, treatment, and the treatment-by-week interaction using the ITT analysis set. Week was treated as an unordered categorical variable. A first-order autoregressive structure was used to model intra-subject correlation, and in conjunction with treating subject as a random effect, this yielded a correlation structure in which observations from the same subject were considered to be correlated, with observations closer in time being more correlated. Baseline was defined as the average subject-reported 24-hour rTNSS over the last 7 days prior to randomization. Estimated treatment differences and 95% confidence intervals (CI) for the treatment differences were calculated. Supportive analyses were performed using the PP population.

The change from Baseline for the secondary endpoints was analyzed in a similar fashion to the primary endpoint.

According to the applicant:

No imputation for missing data was performed as the extent of missing data was predicted to be low and the chosen analysis as a maximum likelihood method was valid for missing-at-random missingness. If any of the component symptom scores were missing for a particular time point, then the rTNSS score for that time point was also considered missing.

In Studies 301 and 302

A fixed sequence step-down multiplicity procedure will be implemented to test the primary and secondary endpoints while controlling the family-wise error rate at 5%. If the resulting two-sided p-value from the primary endpoint comparison is less than 0.05, then the next comparison(s) of interest will be interpreted inferentially. This process continues until either all comparisons of interest are interpreted inferentially, or until the point at which the resulting two-sided p-value for a comparison(s) of interest is greater than 0.05. At the point where $p > 0.05$, no further comparisons will be interpreted inferentially.

For Study 303

no multiplicity adjustments will be made for the pre-planned multiple comparisons.

However, the applicant stated that a fixed sequential step down test was implemented to test the primary and key secondary endpoints while controlling the type I error rate at 0.05.

The applicant conducted subgroup analyses for the primary and secondary efficacy endpoints based on gender, age (12-17 years, 18-64 years, 65 years and older) and race (white, black, other). Estimated treatment differences and 95% CI for the treatment differences were calculated for each subgroup. The subgroup analyses were performed using the ITT analysis population, except for RQLQ which used the RQLQ analysis population.

3.2.4 Results and Conclusions

Table 5 below summarizes the primary and secondary efficacy analysis results for patients with SAR in Study 301 for the ITT population (RQLQ results for the RQLQ population). The applicant states that a difference of 0.55 units in TNSS has been viewed to be a clinically meaningful effect. The clinically meaningful threshold for RQLQ is 0.5. For the primary efficacy endpoint, average AM and PM rTNSS over the 2-week treatment period, there was a statistically significant difference between the BDP HFA 320 mcg/day group and the placebo group. The BDP HFA 320 mcg/day group had a significantly greater decrease from baseline than the placebo group. The applicant also conducted the primary analysis on the PP population. The same conclusion was drawn from the PP analysis as from the ITT analysis; the LS mean treatment difference between BDP HFA 320 mcg/day and placebo group was -0.90 (95% CI: -1.3, -0.5; $p < 0.001$).

The results for the secondary efficacy endpoint, average AM and PM iTNSS over the 2-week treatment period were consistent with the primary efficacy results, with a statistically significant treatment difference between the BDP HFA 320 mcg/day group and the placebo group in the ITT analysis. The analysis was also conducted on the PP population. The same conclusion was drawn from the PP analysis as from the ITT analysis; the LS mean treatment difference between BDP HFA 320 mcg/day and placebo group was -0.87 (95% CI: -1.3, -0.4; $p < 0.001$).

The RQLQ at week 2 showed a statistically significant treatment difference between the BDP HFA 320 mcg/day group and the placebo group in the RQLQ population. However, the LS mean treatment difference, -0.48, was below the RQLQ threshold of 0.5 suggesting that the difference is not clinically meaningful. Of note, this analysis was based on patients with impaired quality of life at Baseline. The analysis was also conducted on the ITT and PP populations. The same conclusion was drawn from both populations as from the RQLQ population. The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the ITT population was -0.40 (95% CI: -0.7, -0.1; $p = 0.008$). The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the PP population was -0.40 (95% CI: -0.7, -0.1; $p = 0.009$).

The change in the average AM and PM reflective ocular symptom scores for the ITT population were significantly greater with BDP HFA 320 mcg/day compared with placebo as seen in Table 5. This is consistent with the primary efficacy results. The analysis was also conducted in the PP population. The same conclusion was drawn from the PP analysis as from the ITT analysis; the

LS mean treatment difference between BDP HFA 320 mcg/day and placebo group was -0.54 (95% CI: -0.9, -0.2; p=0.003).

Table 5 SAR Study 301 Efficacy Results-2 Weeks (ITT Population)

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 (1.81)	-0.8 (0.15)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (RQLQ Population)*						
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 Score (rTOSS)						
BDP HFA 320 mcg/day	167	6.7 (1.50)	6.6 (1.46)	-0.56	-0.9, -0.2	0.002
Placebo	171	6.6 (1.46)	-0.7 (0.12)			

Source: Clinical Study Report - Protocol Number BDP-AR-301 Table 11-14, pages 56-61

*RQLQ analysis was based on select patients with impaired quality of life at Baseline. The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the ITT population was -0.40 (95% CI: -0.7, -0.1; p=0.008)

Table 6 below summarizes the primary and secondary efficacy analysis results for patients with PAR in study 302 for the ITT population (RQLQ results for the RQLQ population). The primary efficacy endpoint, change from baseline in the average AM and PM daily rTNSS over the 6-week treatment period, showed a statistically significant difference between the BDP HFA 320 mcg/day group and the placebo group in favor of BDP HFA 320 mcg/day. The BDP HFA 320 mcg/day group had a significantly greater decrease from baseline than the placebo group. The applicant also conducted the primary analysis on the PP population. The same conclusion was drawn from the PP analysis as from the ITT analysis; the LS mean treatment difference between BDP HFA 320 mcg/day and placebo group was -0.70 (95% CI: -1.1, -0.3; p<0.001).

The results for the secondary efficacy endpoint, the change from baseline in the average AM and PM iTNSS over the 6-week treatment period were consistent with the primary efficacy results. There was a statistically significant treatment difference between the BDP HFA 320 mcg/day group and the placebo group in the ITT analysis in favor of the BDP HFA 320 mcg/day group. The analysis was also conducted on the PP population. The same conclusion was drawn from the PP analysis as from the ITT analysis; the LS mean treatment difference between BDP HFA 320 mcg/day and placebo group was -0.65 (95% CI: -1.0, -0.3; p<0.001).

The RQLQ at week 6 showed a statistically significant treatment difference between the BDP HFA 320 mcg/day group and the placebo group in favor of BDP HFA 320 mcg/day in the RQLQ

population. The analysis was also conducted on the ITT and PP populations. The same conclusion was drawn from both populations as from the RQLQ population. The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the ITT population was -0.56 (95% CI: -0.8, -0.3; p<0.001). The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the PP population was -0.50 (95% CI: -0.7, -0.2; p>0.001).

Table 6 PAR Study 302 Efficacy Results -6 Weeks (ITT Population)

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 320mcg/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 320mcg/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) (RQLQ Population)*						
BDP HFA 320mcg/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)			

Source: Clinical Study Report - Protocol Number BDP-AR-302 Table 11-13, pages 64-67

*RQLQ analysis was based on select patients with impaired quality of life at Baseline. The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the ITT population was -0.56 (95% CI: -0.8, -0.3; p<0.001)

Table 7 below summarizes the primary and secondary efficacy analysis results for patients with PAR in study 303 for the ITT population (RQLQ results for the RQLQ population). The primary efficacy endpoint, change from baseline in the 24-hour rTNSS over the first 30 weeks of the treatment period, showed a statistically significant difference between the BDP HFA 320 mcg/day group and the placebo group in favor of BDP HFA 320 mcg/day. The BDP HFA 320 mcg/day group had a significantly greater decrease from baseline than the placebo group. The results for the secondary efficacy endpoints (i.e. iTNSS and rTNSS at 30 weeks and 52 weeks) were consistent with the primary efficacy results. This study supports the efficacy of BDP HFA 320 mcg/day demonstrated in Studies 301 and 302.

Table 7 PAR Study 303 Efficacy Results- 30 Weeks and 52 Weeks (ITT Population)

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 320mcg/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 320mcg/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 320mcg/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 320mcg/day	414	7.7 (2.16)	-3.1 (0.11)	-1.10	-1.6, -0.6	<0.001
Placebo	110	8.0 (2.27)	-2.0 (0.22)			
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ 30 Week Treatment) (RQLQ Population)*						
BDP HFA 320mcg/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) (RQLQ Population)*						
BDP HFA 320mcg/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)			

Source: Clinical Study Report - Protocol Number BDP-AR-303 Tables 13-17, page 77-85

*RQLQ analysis was based on select patients with impaired quality of life at Baseline. The LS mean treatment difference between BDP HFA 320 mcg/day and placebo group for the ITT population at 30 weeks was -0.24 (95% CI: -0.5, 0.0; p=0.100) and at 52 weeks was -0.27 (95% CI: -0.7, 0.1; p=0.198)

3.3 Evaluation of Safety

The evaluation of safety was conducted by Dr. Xu Wang. Reader is referred to Dr. Xu Wang's review for this section.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on the primary efficacy endpoint (rTNSS) was performed by gender, age, and race in all three studies. The subgroup analyses were performed using the ITT population.

4.1 Gender, Race, and Age

Table 8 summarizes the subgroup analysis by gender for Study 201 in patients with SAR, BDP HFA 320 mcg. I have included this table to compare it to the subgroup analysis by gender in Study 301. Table 9 summarizes the subgroup analysis by gender for Studies 301 and 302, patients with SAR and PAR respectively. In Studies 301 and 302 there was a greater effect in the LS mean for rTNSS with BDP HFA 320 mcg/day than with placebo for both males and females.

Results for the secondary efficacy endpoints by gender were similar to that of the primary efficacy endpoint.

In Study 201, there was a statistically significant difference between the BDP HFA 320 mcg/day group and the placebo groups for females, but not for males. Study 301 concludes results in the opposite direction; here there was a statistically significant difference between the BDP HFA 320 mcg/day group and the placebo groups for males, but not for females. I looked at the interaction between gender and treatment group in both Studies 201 and 301. The interaction between gender and treatment in Study 201 is not significant, p-value=0.3560. However, there was a significant interaction between gender and treatment in Study 301, p-value=0.0009. The applicant states that the difference in these two studies is most likely due to chance.

Table 8 SAR Study 201: Summary of Primary Efficacy Endpoint by Gender (ITT Population)

Category	Females N=154		Males N=91	
	BDP HFA	Placebo	BDP HFA	Placebo
Baseline mean (SD)	9.2 (1.74)	9.0 (1.47)	9.2 (1.53)	9.0 (1.48)
Overall LS mean (SE) change from Baseline ¹	-2.44 (0.22)	-1.51 (0.23)	-1.79 (0.31)	-1.70 (0.28)
LS mean treatment difference from placebo (95% CI)	-0.93 (-1.6, -0.3)		-0.09 (-0.9, 0.7)	

Source: Study 201, Study Report Section 11.4.2.8

¹Change over the 2-week Treatment Period

Table 9 Studies 301 and 302: Summary of Primary Efficacy Endpoint by Gender (ITT Population)

Category	BDP-AR-301				BDP-AR-302			
	Females N=210		Males N=128		Females N=319		Males N=147	
	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo
Baseline mean (SD)	9.5 (1.50)	9.9 (1.40)	9.8 (1.54)	9.1 (1.61)	8.8 (1.71)	9.1 (1.76)	9.0 (1.68)	8.9 (1.67)
Overall LS mean (SE) change from Baseline ¹	-1.61 (0.19)	-1.29 (0.20)	-2.72 (0.28)	-0.70 (0.24)	-2.68 (0.17)	-1.76 (0.17)	-2.00 (0.24)	-1.33 (0.24)
LS mean treatment difference from placebo (95% CI)	-0.32 (-0.9, 0.2)		-2.03 (-2.8, -1.3)		-0.92 (-1.4, -0.5)		-0.66 (-1.3, -0.0)	

Source: Study 301, Study Report Section 11.4.2.8 and Study 302, Study Report Section 11.4.2.8

¹Change over the 2-week Treatment Period in Study 301, Change over the 6-week Treatment Period in Study 302

In both studies (301 and 302) about 89% of the patients were 18 to 64 years of age. In general, the results for the two phase 3 studies for the primary efficacy endpoint between the BDP HFA 320 mcg/day group and the placebo group across subgroups by age were consistent with the overall treatment results. Because of the small number of patients were between the ages of 12 and 17, as well as over 65, any claims of disparity in terms of patient's age are essentially unsupported. The results by age for the primary efficacy endpoint are summarized in Table 10 for Studies 301 and 302. Results for the secondary efficacy endpoints by age were similar to that of the primary efficacy endpoint in each of the studies.

Table 10 Studies 301 and 302: Summary of Primary Efficacy Endpoint by Age (ITT Population)

Category	BDP-AR-301						BDP-AR-302					
	12-17 years N=28		18-64 years N=301		≥65 years N=9		12-17 years N=47		18-64 years N=409		≥65 years N=10	
	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo
Baseline mean (SD)	10.0 (1.31)	9.4 (1.84)	9.6 (1.54)	9.5 (1.54)	9.4 (1.20)	9.8 (0.86)	8.7 (1.48)	8.5 (1.61)	8.9 (1.73)	9.1 (1.73)	8.0 (1.33)	8.1 (1.77)
Overall LS mean (SE) change from Baseline ¹	-1.32 (0.42)	-0.64 (0.42)	-1.99 (0.17)	-1.08 (0.17)	-3.18 (1.16)	-0.70 (1.31)	-1.70 (0.39)	-0.63 (0.42)	-2.52 (0.15)	-1.74 (0.15)	-3.80 (0.66)	-1.40 (0.81)
LS mean treatment difference from placebo (95% CI)	-0.68 (-1.9, 0.5)		-0.92 (-1.4, -0.5)		-2.49 (-6.0, 1.0)		-1.07 (-2.2, 0.1)		-0.77 (-1.2, -0.4)		-2.41 (-4.5, -0.3)	

Source: Study 301, Study Report Section 11.4.2.8 and Study 302, Study Report Section 11.4.2.8.

¹Change over the 2-week Treatment Period in Study 301, Change over the 6-week Treatment Period in Study 302

The patients randomized in the study were mainly Caucasians (about 80%) and Blacks (about 15%), the rest of the subgroups are grouped into the “Other” category. The results by race for the primary efficacy endpoint are summarized in Table 11 for Studies 301 and 302. Results for the secondary efficacy endpoints by race were similar to that of the primary efficacy endpoint in each of the studies.

Table 11 Studies 301 and 302: Summary of Primary Efficacy Endpoint by Race (ITT Population)

Category	BDP-AR-301						BDP-AR-302					
	White N=280		Black N=49		Other N=9		White N=366		Black N=78		Other N=22	
	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo	BDP HFA	Placebo
Baseline mean (SD)	9.6 (1.52)	9.5 (1.58)	9.7 (1.54)	9.6 (1.16)	10.2 (0.83)	10.3 (2.20)	8.8 (1.68)	9.0 (1.73)	9.3 (1.65)	9.0 (1.79)	9.3 (2.07)	8.9 (1.69)
Overall LS mean (SE) change from Baseline ¹	-2.02 (0.17)	-0.90 (0.17)	-1.54 (0.48)	-1.67 (0.45)	-2.06 (1.34)	-1.98 (1.19)	-2.53 (0.16)	-1.73 (0.16)	-2.36 (0.34)	-1.44 (0.34)	-1.58 (0.68)	-.73 (0.56)
LS mean treatment difference from placebo (95% CI)	-1.12 (-1.6, -0.7)		0.14 (-1.2, 1.4)		-0.09 (-3.6, 3.5)		-0.80 (-1.2, -0.4)		-0.91 (-1.9, 0.0)		-0.85 (-2.6, 0.9)	

Source: Study 301, Study Report Section 11.4.2.8 and Study 302, Study Report Section 11.4.2.8

¹Change over the 2-week Treatment Period in Study 301, Change over the 6-week Treatment Period in Study 302

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

There were no statistical issues identified during the course of my review. According to the applicant, in both studies

No imputation for missing data was performed as the extent of missing data was predicted to be low and the chosen analysis as a maximum likelihood method was valid for missing-at-random missingness. If any component symptom scores were missing for a particular timepoint, the TNSS score for that timepoint was also considered missing.

Of the 340 patients randomized in Study 301, only 2% dropped out. Protocol violation/ non-compliance were the most common reason for early termination in the placebo group. There was only one drop out due to AEs and one drop out due to withdrawal of consent in the BDP HFA 320 mcg/day group. Of the 474 patients randomized in Study 302, only 8% dropped out of the study. Withdrawal of consent were the overall common reason for early termination in both treatment groups; 6 (3%) patients in both the BDP HFA 320 mcg/day group and the placebo group. Therefore, missing data is not an issue with this application. In addition, I was able to replicate the results for the primary and key secondary endpoints generated by the applicant.

In patients with SAR (Study 301), the RQLQ is statistically significant, but it was below the RQLQ threshold of 0.5 to be considered clinically meaningful. In patients with PAR (Study 302), there is evidence that BDP HFA nasal aerosol is effective in improving the RQLQ compared to placebo, the observed effect is both statistically and clinically significant.

5.2. Comments on the Proposed Label

Based on review of the submitted data, I have some edits to the proposed label under Section 14.

14.1 Clinical Studies

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

5.3. Conclusions and Recommendations

Based on my statistical review of the two short term efficacy studies, there is evidence to support the claim of efficacy of BDP HFA nasal aerosol at a dose of 320 mcg/day in the treatment of patients 12 years of age or older with seasonal allergic rhinitis or perennial allergic rhinitis. In both studies there is evidence that BDP HFA nasal aerosol is effective in decreasing rTNSS and iTNSS compared to placebo. Only Study BDP-AR-301 evaluated the reflective ocular symptom scores. Although the study showed that BDP HFA nasal aerosol is effective in decreasing reflective ocular symptom scores, this evidence was not replicated. Therefore, I recommend including the results from the analyses of rTNSS and iTNSS scores from Studies BDP-AR-301 and BDP-AR-302 in the label. There are inconsistent results for RQLQ between the two studies. Therefore, there is weak evidence to support inclusion of RQLQ in the label.

6. APPENDICES

Applicant's repeated measures ANCOVA SAS code for the primary and secondary efficacy analysis for all three studies:

```
proc mixed data=;
class usubjid avisitn trtpn ;
model dychange=dybase trtpn avisitn trtpn*avisitn;
repeated avisitn / type=ar(1) sub=usubjid r;
random usubjid;
lsmeans trtpn / diff cl ;
ods output lsmeans=lsmeanmix;
ods output diffs=difffmix ;
run;
```

SAS code for RQLQ analysis for all three studies:

```
proc glm data=;
by avisitn;
class trtpn psiteid;
model dychange=dybase trtpn psiteid;
lsmeans trtpn / pdiff stderr cl ;
estimate trtpn 1 -1; **320mcg - Placebo **;
ods output diff=diffglm lsmeandiffcl=lsmeanglm
estimates=estimate;
run;
```

7. SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Kiya Hamilton, Ph.D.

Date: February 14, 2012

Statistical Team Leader: Joan Buenconsejo, Ph.D.

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

/s/

KIYA HAMILTON
02/14/2012

JOAN K BUENCONSEJO
02/14/2012

I concur with Dr. Hamilton's review and conclusion.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202813 Applicant: Teva Pharmaceutical Stamp Date: May 24, 2011

Drug Name: Belcomethasone Dipropionate Nasal Aerosol NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

This is a 505(b)(2) application. The applicant has identified 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) to support the approval of belcomethasone dipropionate nasal aerosol for the (b) (4). The applicant is also relying upon a few referenced studies described in different approved NDAs. The focus of my review is will be three of the phase III studies conducted by the applicant.

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Kiya Hamilton, Ph.D. 7/1/2011

 Reviewing Statistician Date

Joan Buenconsejo, Ph.D. 7/1/2011

 Supervisor/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/

KIYA HAMILTON
07/01/2011

JOAN K BUENCONSEJO
07/07/2011