

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults		
From: Sheetal Agarwal, Ph.D., RAC		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission		
DATE: 10/20/2014		NDA No. 202813 S007 SDN: 198	Original Supplement Submission Date: 02/27/2014	
NAME OF DRUG: QNASL  BDP (beclomethasone dipropionate) HFA (hydrofluoroalkane) Nasal Aerosol		PRIORITY CONSIDERATION: S	Date of informal/Formal Consult:	
NAME OF THE SPONSOR: Teva				
TYPE OF SUBMISSION: PREA PMR supplement				
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> PRE-IND  <input type="checkbox"/> ANIMAL to HUMAN SCALING  <input type="checkbox"/> IN-VITRO METABOLISM  <input type="checkbox"/> PROTOCOL  <input type="checkbox"/> PHASE II PROTOCOL  <input type="checkbox"/> PHASE III PROTOCOL  <input type="checkbox"/> DOSING REGIMEN CONSULT  <input type="checkbox"/> PK/PD- POPPK ISSUES  <input checked="" type="checkbox"/> PHASE IV RELATED         </div> <div style="width: 33%;"> <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE  <input type="checkbox"/> BIOAVAILABILITY STUDIES  <input type="checkbox"/> IN-VIVO WAIVER REQUEST  <input type="checkbox"/> SUPAC RELATED  <input type="checkbox"/> CMC RELATED  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS  <input type="checkbox"/> Meeting package (eop2/Pre-NDA/CMC/Pharmacometrics/Others)         </div> <div style="width: 33%;"> <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> ANNUAL REPORTS  <input type="checkbox"/> FAX SUBMISSION  <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):            Labeling supplement incorporating HPA axis study data from a post marketing study into a label         </div> </div>				
REVIEW ACTION				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NAI (No action indicated)  <input type="checkbox"/> E-mail comments to:  <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox  <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others            (Check as appropriate and attach e-mail)         </div> <div style="width: 33%;"> <input type="checkbox"/> Oral communication with            Name: [      ]  <input type="checkbox"/> Comments communicated in            meeting/Telecon. see meeting minutes            dated: [      ]         </div> <div style="width: 33%;"> <input checked="" type="checkbox"/> Formal Review/Memo (attached)  <input checked="" type="checkbox"/> See comments below  <input type="checkbox"/> See submission cover letter  <input type="checkbox"/> OTHER (SPECIFY BELOW):            [      ]         </div> </div>				
REVIEW COMMENT(S) <input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR				

**COMMENTS:** The results and conclusions within the HPA axis study report for study BDP-AR-307 are acceptable. The sponsor submitted a labeling supplement to add the HPA axis data to the approved label, PD data from the completed study was added to Section 12.2 and PK data from the completed study was added to Section 12.3. Many edits were made to the sponsor's proposed labeling language, discussion for which is pending with the sponsor at the time of writing this review. As such, the reader is referred to the final approved label for the final agreed upon recommendations.

## **BACKGROUND**

NDA 202813 for BDP nasal aerosol (QNASL) has been approved by the FDA since March 2012 and is currently available for adolescent and adult patient use. BDP nasal aerosol is indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The Reference ID: 3646947

original approval letter included 5 pediatric assessments (DARRTS dated 03/23/2012), from which 4 studies including the HPA axis study in children 6-11 years of age, were waived later and 1 new study was added (DARRTS dated 12/05/2012). The current status of pediatric studies with Qnasl is provided in the table below.

### **Current status of Qnasl pediatric studies as provided by the sponsor in this submission**

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

### **CURRENT SUBMISSION**

In the current submission, the sponsor is seeking approval for a new indication, i.e., for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis (SAR & PAR) in patients 4 years of age and older. This request is based on the completed study BDP-AR-306. In addition, the sponsor is proposing to add PK and PD data from completed HPA axis study, BDP-AR-307 in the approved labeling. As noted above, the HPA axis study although originally included as a PMR, was waived later based on then available information, however since the study was already initiated when the sponsor received the waiver, the sponsor decided to complete it. This review will focus on the completed HPA axis study and proposed labeling based on HPA axis study data.

### **REVIEW OF THE HPA AXIS STUDY**

A synopsis of the study report is attached at the end of this report.

The primary objective of the study BDP-AR-307 was to evaluate the effect of 6 weeks of treatment with budesonide (BDP) nasal aerosol versus placebo on HPA-axis function, as assessed by 24-hour serum cortisol weighted mean, in subjects 6 to 11 years of age with PAR. Blood samples for BDP and 17-BMP (active major metabolite of BDP) were obtained at pre-dose (within 30 minutes prior to dose administration) and at 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 3, 6, 12, and 24 hours after dose administration. Plasma concentrations of BDP and 17-BMP were simultaneously determined using a validated LC-MS/MS method. The lower-limit-of-quantitation (LLOQ) of the assay was 10 pg/mL for BDP and 20 pg/mL for 17-BMP.

Results of the primary endpoint of the study showed that BDP nasal aerosol 80 mcg/day was non-inferior to placebo for effects on the 24-hour serum cortisol weighted mean after 42 days of treatment. For the PP population, the geometric mean ratio for BDP nasal aerosol 80 mcg/day to placebo was 0.91 (95% CI: 0.81, 1.03).

**Table 12: Summary of Primary Analysis: Logarithmically-Transformed Serum Cortisol (mcg/dL) Weighted Mean (PP Population)**

Statistic	BDP nasal aerosol 80 mcg/day N=66	Placebo N=31
Baseline geometric mean (SE)	5.97 (1.039)	6.47 (1.039)
Week 6 geometric mean (SE)	6.19 (1.043)	7.13 (1.048)
Week 6/Baseline geometric mean ratio (SE)	1.04 (1.037)	1.10 (1.053)
Ratio of BDP nasal aerosol to Placebo 95% CI	0.91 (0.81, 1.03)	

Source: Page 65/419 of the PK study report

The sponsor also evaluated steady state PK parameters for BDP and 17-BMP. When administered as BDP nasal aerosol 80 mcg/day, the mean AUC<sub>0-24</sub> was 619.06 h\*pg/mL, the mean C<sub>max</sub> was 142.68 pg/mL, the median t<sub>max</sub> was 1.00 hours, the mean λ<sub>z</sub> was 0.31 hours<sup>-1</sup> and the mean t<sub>1/2</sub> was 3.1 hours. The results for BDP were lower for the mean AUC<sub>0-24</sub> (200.80 h\*pg/mL) and mean C<sub>max</sub> (44.65 pg/mL). The median t<sub>max</sub> (0.25 hours) for BDP was shorter than for 17-BMP. The λ<sub>z</sub> and t<sub>1/2</sub> for BDP were not calculable in any of the subjects.

**Reviewer's comments:**

*The sponsor did not include a positive control arm in this study to validate the assay sensitivity. However, as rationalized by the sponsor, there are ethical concerns with the inclusion of a positive control arm such as administration of dexamethasone, an oral corticosteroid to suppress HPA axis in healthy children. The reviewer finds this rationale reasonable. In addition, the sponsor previously conducted another HPA axis study in adolescents and adults 12-45 years of age (study BDP-AR-304, results of which are included in approved labeling). This study demonstrated that 7 days of prednisone (10 mg/day) treatment resulted in a marked suppression of HPA axis function, thus validating the patient selection and assay methodologies in a similarly designed study. In addition, the study design along with the primary endpoint assessed (i.e., serum cortisol) was robust with a significant number of subjects in each group. As such, the study design and the data are considered acceptable. The data show that baseline geometric mean serum cortisol weighted mean values were similar in the QNASL Nasal Aerosol 80 mcg once daily and placebo treatment groups (5.97 and 6.47 mcg/dL, respectively). The new HPA axis data will be added to section 12.2 of the approved QNASL labeling.*

## STUDY SYNOPSIS FOR HPA AXIS STUDY

<b>Name of Sponsor/Company:</b> Teva Branded Pharmaceutical Products R&D, Inc. Global Respiratory Research and Development 41 Moores Road, Frazer, PA 19355, USA	<b>Individual Study Table Referring to Part of the Dossier</b>	<i>(For National Authority Use only)</i>
<b>Name of Finished Product:</b> BDP Nasal Aerosol	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Beclomethasone dipropionate	<b>Page:</b>	

<b>Title of Study:</b> A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 6-Week Study Designed to Investigate the Effects of BDP Nasal Aerosol on the Hypothalamic-Pituitary-Adrenal (HPA)-Axis in Pediatric Subjects (6 to 11 Years of Age) with Perennial Allergic Rhinitis (PAR) (BDP-AR-307)	
<b>Investigators and Study Centers:</b> 6 centers in the US participated in the study	
<b>Publication (reference):</b> None	
<b>Study Period:</b> First Subject Screened: 08-Oct-2012 First Subject Dosed: 20-Oct-2012 Last Subject Dosed: 05-Jan-2013 Last Subject Visit: 21-Feb-2013	<b>Phase of Development:</b> 3
<b>Objectives:</b>  <b>Primary Objective:</b> To compare the effect of 6 weeks of treatment with beclomethasone dipropionate (BDP) nasal aerosol versus placebo on HPA-axis function, as assessed by 24-hour serum cortisol weighted mean, in subjects 6 to 11 years of age with PAR.  <b>Secondary Objectives:</b> To evaluate the safety and tolerability of BDP nasal aerosol in subjects 6 to 11 years of age with PAR	
<b>Methodology:</b>  This was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group study in male and female pediatric subjects 6 to 11 years of age with PAR. Each subject participated in the study for approximately 9 weeks. The study consisted of 3 periods: Run-in Period (7-21 days from Screening Visit 1 [SV1] to Randomization Visit [RV]), Treatment Period (42 days from Randomization Visit [RV] to the Post Treatment Visit [PTV]), and a follow-up period (6 ±2 days from the Post Treatment Visit [PTV] to Final Visit [FV]). Each subject completed three screening visits (SV1, SV2 and SV3), five treatment visits (RV, TV1, TV2, TV3, PTV), and a Final Visit (FV). There were two domiciled inpatient visits at the clinic during the study; a 2-day/2-night inpatient visit at the end of the Run-in period (comprising SV2, SV3 and RV visits) and a 2-day/2-night inpatient visit at the end of the Treatment Period (comprising TV2, TV3 and PTV visits).  During the Run-in Period, subjects (either on their own or with assistance from parents/guardians/caregivers, as needed) administered a single-blind placebo nasal aerosol once daily in the morning. Subjects (with parents/guardians/caregivers) were domiciled before randomization on SV2 through RV (Day -2 through Day 1) for pharmacodynamic measurements of HPA-axis function.	

During the Treatment Period (RV through PTV), subjects were randomly assigned to either BDP nasal aerosol (80 mcg/day) or placebo nasal aerosol in a 2:1 ratio. Subjects (either on their own or with assistance from parents/guardians/caregivers, as needed) administered the double-blinded nasal aerosol (BDP nasal aerosol or placebo) once daily in the morning for 6 weeks (42 days). Adherence to treatment was confirmed by use of video adherence monitoring for each dose administration. Subjects were domiciled at the end of the Treatment Period (TV2 through PTV, Day 41 through Day 43) for pharmacodynamic measurements of HPA-axis function and pharmacokinetic (PK) measurements of BDP and beclomethasone-17 monopropionate (17-BMP).

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

**Number of Subjects (Planned and Actual):**

*Planned:* Screened: 135; Enrolled: 110 subjects; Randomized: 99; Completed: 90

*Actual:* Screened: 110 subjects; Enrolled: 106 subjects; Randomized: 99 subjects; Completed: 97 subjects

**Diagnosis and Main Criteria for Inclusion:** The study population defined in the protocol consisted of male or female pediatric subjects in general good health, 6 to 11 years of age inclusive, with a documented history of PAR to a relevant perennial allergen for a minimum of 12 months immediately preceding the study. The PAR had to have been of sufficient severity to have required treatment and to be expected to require treatment throughout the entire study. Subjects had a positive skin prick test to at least one allergen known to induce PAR.

**Test Product, Dose and Mode of Administration, Batch (Lot) Number:**

**Product:** BDP Nasal Aerosol (40 mcg/actuation) – Lot number 110232

**Manufacturer:** Teva Pharmaceuticals, Ireland (b) (4)  
3M Drug Delivery Systems, USA (b) (4)  
(b) (4)

**Mode of Administration:** intranasal aerosol (spray)

**Dose:** 1 actuation/nostril once daily (total of 2 actuations, once daily)

**Duration of Treatment:** 6 weeks



**Reference Therapy, Dose and Mode of Administration, Batch (Lot) Number:**

**Product:** Placebo Nasal Aerosol – Lot number 110241

**Manufacturer:** Teva Pharmaceuticals, Ireland

3M Drug Delivery Systems, USA

(b) (4)

(b) (4)

**Mode of Administration:** intranasal aerosol (spray)

**Dose:** 1 actuation/nostril once daily (total of 2 actuations, once daily)

**Criteria for Evaluation:**

Pharmacodynamic:

24-hour serum cortisol weighted mean for BDP nasal aerosol and placebo after 42 days of treatment

Safety:

Spontaneous and elicited AEs, physical examinations, ENT examinations, vital signs, and clinical laboratory evaluations (serum chemistry and hematology).

Pharmacokinetics:

Steady-state plasma concentration vs. time profiles of 17-BMP and BDP were obtained from analysis of plasma samples collected over a 24-hour post-dose period on Day 42, after 6 weeks of treatment with BDP nasal aerosol 80 mcg/day. Plasma concentrations of BDP and 17-BMP were determined using a validated high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation of 10 pg/mL for BDP and 20 pg/mL for 17-BMP. The following endpoints were measured for both BDP and 17-BMP.

- Area under the plasma concentration-time curve from time zero (time of dosing) to the time of the last measurable analyte concentration ( $AUC_{0-t}$ )
- Area under the plasma concentration-time curve from time zero (time of dosing) to 24 hours post-dose ( $AUC_{0-24}$ )
- Observed maximum plasma concentration ( $C_{max}$ )
- Time to observed maximum plasma concentration ( $t_{max}$ )
- Terminal elimination rate constant ( $\lambda_z$ )
- Apparent terminal elimination half-life ( $t_{1/2}$ )

### Statistical Methods:

Sample size: The standard deviation of the logarithmically transformed data on the change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean was assumed to be 0.30. Using this standard deviation, 90 subjects (approximately 60 and 30 subjects in the BDP nasal aerosol and placebo groups, respectively) would yield approximately 90% power to demonstrate non-inferiority between BDP nasal aerosol and placebo, if there were no true differences between treatment groups. Non-inferiority was to be demonstrated if the lower limit of the 2-sided 95% CI for the geometric mean ratio of BDP nasal aerosol to placebo was greater than 0.80 following 6 weeks of therapy.

Four populations were defined for the study. The safety population, used for all safety analyses, included all randomized subjects who received at least one dose of randomized study medication, with treatment assignment based upon the treatment subjects actually received. The Intent-to-Treat (ITT) population included all randomized subjects, with treatment assignment based upon the treatment to which subjects were randomized regardless of which treatment they actually received. The Full Analysis Set included all subjects in the ITT population who received at least one dose of study medication and had at least one post-baseline assessment and was used for supportive analyses of pharmacodynamic and pharmacokinetic endpoints. The Per-Protocol (PP) population included all data from randomized subjects obtained prior to experiencing major protocol deviations and was used for primary analyses of pharmacodynamic and pharmacokinetic endpoints.

### Pharmacodynamics:

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

### Safety:

Data were summarized by incidence, means, changes and shifts depending on measure.

#### Pharmacokinetics:

PK parameters were calculated for 17-BMP and BDP from the corresponding plasma concentration-time data using non-compartmental PK methods. The PK parameters calculated, as data permitted, included  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-24}$ ,  $\lambda_z$ , and  $t_{1/2}$ . Plasma concentration-versus-time data and PK parameter estimates for 17-BMP and BDP were summarized by descriptive statistics

### **SUMMARY OF RESULTS**

#### Disposition, Demography and Compliance

A total of 99 subjects were randomized and received study treatment (67 to BDP nasal aerosol 80 mcg/day and 32 to placebo). Two subjects, one in each treatment group, were discontinued prematurely due to protocol violations (both subjects had attention deficit and hyperactivity disorder [ADHD] and were receiving prohibited medication for this condition). Hence, 97 randomized subjects (66 treated with BDP nasal aerosol 80 mcg/day and 31 treated with placebo) completed the study.

The mean age of study subjects was 9.0 years and ranged from 6 to 11 years. The majority of subjects in both groups were white (74%) and not Hispanic or Latino (73%). There were more males in the BDP nasal aerosol 80 mcg/day group than in the placebo group (53% compared with 35%). With the exception of gender, demographic characteristics were generally comparable in the two treatment groups.

Mean adherence rates with the study treatment based on video adherence monitoring was at least 97% in each treatment group. Adherence was at least 80% in all subjects except two: one subject treated with BDP nasal aerosol 80 mcg/day had an adherence rate <60% (this subject was excluded from the PP population and the Full Analysis Set) and one subject treated with placebo had adherence between 60% and 80%.

#### Pharmacodynamics:

The primary endpoint was the change from Baseline (expressed as a ratio) in the 24-hour serum cortisol weighted mean for BDP nasal aerosol 80 mcg/day and placebo after 42 days of treatment. The primary population for analysis was the PP population.

Baseline geometric mean serum cortisol weighted mean values were similar in the BDP nasal aerosol 80 mcg/day and placebo treatment groups (5.97 and 6.47 mcg/dL, respectively). After 6 weeks of treatment the geometric mean values were 6.19 and 7.13 mcg/dL, respectively and there was a small increase from baseline values in both treatment groups. The ratio of Week 6/Baseline was 1.04 (95% CI: 0.96, 1.12) for BDP nasal aerosol 80 mcg/day and 1.10 (95% CI: 0.99, 1.22) for placebo. The geometric mean ratio for BDP nasal aerosol 80 mcg/day to placebo was 0.91 (95% CI: 0.81, 1.03). Thus, non-inferiority of BDP nasal aerosol 80 mcg/day to placebo was demonstrated since the lower limit of the two-sided 95% CI was greater than the predefined non-inferiority bound of 0.80. Identical results were seen for the Full Analysis Set as for the PP population.



#### Safety:

Of the 99 subjects included in the safety analyses, 35 (35%) experienced at least one treatment-emergent AE: 22 subjects (33%) in the BDP nasal aerosol 80 mcg/day group and 13 subjects (41%) in the placebo group. There were no appreciable differences in intensity of these events among the treatment groups and the majority of AEs were of mild or moderate intensity. Only 2 subjects (3%) in the BDP nasal aerosol 80 mcg/day group and 1 subject (3%) in the placebo group experienced AEs of severe intensity. The AEs of severe intensity were upper abdominal pain/ vomiting and allergic dermatitis in the BDP nasal aerosol 80 mcg/day group and nasal congestion in the placebo group. The most commonly reported AEs were epistaxis (reported in 5 subjects [7%] in the BDP nasal aerosol 80 mcg/day group and 1 subject [3%] in the placebo group) and pyrexia (reported by 5 subjects [7%] in the BDP nasal aerosol 80 mcg/day group and 1 subject [3%] in the placebo group). The only other AEs reported in more than 1 subject overall were upper abdominal pain, nasopharyngitis, otitis media, vomiting, oropharyngeal pain, upper respiratory tract infection, gastroenteritis and arthralgia. There were no appreciable differences between treatment groups with respect to the incidence of AEs. Only 3 subjects reported AEs considered to be treatment-related by the investigator. These were reported by 2 subjects (3%) in the BDP nasal aerosol 80 mcg/day group and 1 subject (3%) in the placebo group. Epistaxis (reported as treatment-related in 2 subjects [3%] in the BDP nasal aerosol 80 mcg group) was the only treatment-related AE reported in more than 1 subject.

No subjects died during the study and no SAEs were reported. There were no withdrawals due to treatment-emergent AEs.

There were no notable differences between BDP nasal aerosol 80 mcg/day and placebo in hematology and blood chemistry results. No relevant treatment-related findings were observed for vital signs or ENT or physical examinations.

#### Pharmacokinetics:

For the PP population (BDP nasal aerosol 80 mcg/day group), the mean  $AUC_{0-1}$  for 17-BMP was 573.81 h\*pg/mL, the mean  $AUC_{0-24}$  was 619.06 h\*pg/mL, the mean  $C_{max}$  was 142.68 pg/mL, the median  $t_{max}$  was 1.00 hours, the mean  $\lambda_z$  was 0.31 1/hours and the mean  $t_{1/2}$  was 3.1 hours. The highest observed maximum concentration of 17-BMP in any individual subject was 349 pg/mL. The results for BDP were lower for the mean  $AUC_{0-1}$  (45.60 h\*pg/mL), the mean  $AUC_{0-24}$  (200.80 h\*pg/mL) and mean  $C_{max}$  (44.65 pg/mL). The median  $t_{max}$  (0.25 hours) for BDP was shorter than for 17-BMP. The  $\lambda_z$  and  $t_{1/2}$  for BDP were not calculable in any of the subjects.

The PK results showed that pediatric subjects treated with BDP nasal aerosol 80 mcg/day for 6 weeks were systemically exposed to BDP and its active metabolite, 17-BMP. Following repeated once daily administration of the BDP nasal aerosol, there was no apparent accumulation of 17-BMP or BDP, primarily due to the short plasma elimination half-lives relative to the dosing frequency.

#### **CONCLUSIONS:**

This study demonstrated that BDP nasal aerosol 80 mcg/day was not associated with HPA-axis suppression relative to placebo in pediatric subjects (6 to 11 years of age) with PAR. Patient adherence (compliance) data and PK results confirmed adherence with BDP nasal aerosol 80 mcg/day treatment. Additionally, BDP nasal aerosol 80 mcg/day administered to pediatric subjects with PAR for 6 weeks was well tolerated and showed no meaningful differences compared with placebo in the incidence of AEs or in other safety assessments.

Date of the Report: 18-Jul-2013 (Draft 7)

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/s/  
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SHEETAL S AGARWAL  
10/22/2014

SATJIT S BRAR  
10/22/2014