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: 09/08/2014	NDA No. 202129, S005	Original Supplement Submission Date: 12/23/2013	

NAME OF DRUG: Zetonna (Ciclesonide nasal aerosol) Treatment of symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older 1 actuation per nostril daily (74 mcg/day)	PRIORITY CONSIDERATION: S	Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Originally Nycomed, now Takeda GmbH / Sunovion Pharmaceuticals

TYPE OF SUBMISSION: PREA PMR supplement

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ Meeting package (eop2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER (SPECIFY BELOW): Labeling supplement incorporating HPA axis study data from a post marketing study
☒ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒☐See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in	☐☐See submission cover letter
☐Micro ☐Pharmacometrics ☐Others	meeting/Telecon. see meeting minutes	☐ OTHER (SPECIFY BELOW):
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)
☐ NEED TO BE COMMUNICATED TO THE SPONSOR ☐ HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS: The results and conclusions within the HPA axis study report for study 060-308 are acceptable. The sponsor submitted a labeling supplement to add the HPA axis data to the approved label. The following language proposed by the sponsor to be added to section 12.2 (Pharmacodynamics) seems reasonable except for suggested deletion of the last sentence indicated as crossed out:

In a 6-week, randomized, double-blind, placebo-controlled, parallel-group trial in patients 6 to 11 years of age with perennial allergic rhinitis, a daily dose of 74 mcg of ZETONNA (b) (4) *was compared to placebo nasal aerosol. Adrenal function was assessed by 24-hr serum cortisol AUC before and after the treatment. At the end of 6 weeks of treatment, the LS means (SE) change from baseline in serum cortisol* $AUC_{(0-24)}$ *was 5.9 (5.6) mcg•hour/dL and 1.7 (5.2) mcg•hour/dL for placebo and ZETONNA* (b) (4)*, respectively . The LS means difference from placebo for the change from baseline in serum cortisol* $AUC_{(0-24)}$ *was 7.6 mcg•hour/dL (95% CI: -7.4, 22.6).* (b) (4)

BACKGROUND

NDA 202-129 for Zetonna (ciclesonide) Nasal Aerosol was approved on January 20, 2012 with a number of pediatric and post marketing studies included in its approval letter (see table below). The sponsor submitted study reports for studies in children 6-11 years of age, i.e., studies listed as 1864-1, 1864-2, 1864-3 and 1864-7 in the approval letter under 3 different supplements: **S004:** To provide long term ocular safety data in the label; **S005:** To provide data on patients 6-11 years of age in PAR and HPA axis data and **S006:** To provide data on patients 6-11 years of age in SAR. This review will cover the HPA axis study 1864-1, study number 060-308, submitted in **S005**.

Pediatric studies included in the approval letter for NDA 202-129	
1864-1	Conduct a 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally the steady-state PK profile after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.
1864-2	Conduct a 2-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied.
1864-3	Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied.
1864-4	Conduct a 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age.
1864-5	Conduct a 12-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. The primary efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data.
1864-6	Conduct a 6-week double blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.
Post-marketing requirements included in the approval letter for NDA 202-129	
1864-7	Conduct a randomized clinical trial in adolescent (age 12 years and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of ciclesonide nasal aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS (ciclesonide) Nasal Spray.

REVIEW OF THE HPA AXIS STUDY 060-308

The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety study of the effects of ciclesonide nasal aerosol (74 mcg) on the HPA axis when administered once daily to male and premenarchal female subjects 6 to 11 years of age with a diagnosis of PAR. Study synopsis is attached at the end of this review.

The effects of ciclesonide on the HPA axis were assessed primarily based on changes in serum cortisol levels from predose to the end of the 6-week treatment period. Additionally, the effects of ciclesonide on the HPA axis were assessed based on changes in 24-hour urinary free cortisol levels from pre-dose to the end of the 6-week treatment period. Subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment arms in a double-blind manner as follows:

· Treatment A: Ciclesonide nasal aerosol 74 mcg administered once daily (1 actuation of 37 mcg per nostril) for 6 weeks

· Treatment B: Placebo nasal aerosol administered once daily (1 actuation per nostril) for 6 weeks

The 74 mcg dose of ciclesonide is the marketed dose for adolescents and adults and would be expected to be the highest dose used in pediatric patients 6-11 years of age with PAR and SAR. The 74 mcg dose was expected to be effective in pediatric patients based on the pivotal clinical SAR and PAR studies (060-622, 060-633, and 060-634) in adolescents and adults 12 years of age and older and have a favorable risk/benefit profile.

At Visit 4 (pre-dose), a single blood sample was collected approximately 30 minutes before the first double-blind treatment dose was administered, which served as a stable drug-free control sample for all subjects. At Visit 7 (last dose), serial blood samples for steady-state serum concentrations of ciclesonide and des-ciclesonide were collected starting in the morning of Day 42 (- 1 to + 3) immediately prior to administration of the last study medication dose (i.e., at the same time as the predose cortisol sample), and after dosing at 30, 60, 90 minutes and 2, 4, 8, 12, 16, and 24 hours. Systemic levels of ciclesonide and desciclesonide were quantified by a validated bioanalytical method employing a sensitive assay with an LLOQ of 1.0 pg/mL for both ciclesonide and des-ciclesonide.

Change from baseline (Visit 4) to end of study (Visit 7) in serum cortisol $AUC_{(0-24)}$ is summarized by treatment group in table 1, and serum cortisol concentrations by treatment group are displayed for the per protocol population in Figure 1. In addition, change from baseline in 24-hour urinary free cortisol excretion, corrected for urine creatinine, is summarized in Table 2.

PK data from the study are summarized in Table 3.

Reviewer's comments: At the end of 6 weeks of treatment, the LS means (SE) change from baseline in serum cortisol AUC(0-24) was 5.9 (5.6) mcg•hour/dL and 1.7 (5.2) mcg•hour/dL for placebo and ZETONNA Nasal Aerosol, respectively. The LS mean difference in serum cortisol $AUC_{(0-24)}$ change from baseline for the per protocol population was 7.6 mcg•hour/dL (95% CI: -7.4, 22.6) for ciclesonide nasal aerosol 74 mcg vs placebo. The data indicates that ZETONNA Nasal Aerosol had no suppressive effect on the HPA axis in this age group. In addition, the sponsor analyzed change from baseline in urinary cortisol as well, which demonstrated no difference between ciclesonide nasal aerosol and placebo on HPA axis function after 6 weeks of once daily treatment

The sponsor did not include a positive control arm in this study to validate the assay sensitivity as recommended to them when the protocol was reviewed in its preliminary stage by the Agency included in a Type C meeting package (meeting held on 09/28/2011, meeting minutes in DARRTS dated 10/28/2011). However as rationalized by the sponsor, there would be ethical concerns with the inclusion of a positive control arm such as administration of dexamethasone, an oral corticosterioid to suppress HPA axis in healthy children, this seems reasonable. In addition, the sponsor had conducted another HPA axis study prior to this study (study 060-610, results of which are included in approved labeling) demonstrating that dexamethasone did suppress HPA axis activity in patients 12-73 years of age while daily doses of 148 mcg and 282 mcg of ZETONNA Nasal Aerosol did not. In addition, the study design seems robust with a significant number of subjects in each group as well as robust end points such as measurement of changes in serum cortisol. As such, the study design is considered acceptable.

In terms of PK data, both parent (ciclesonide) and active metabolite (des-ciclesonide) were characterized as shown in Table 3. Mean C_{max} of des-ciclesonide was ~2.5-fold higher than the mean C_{max} of ciclesonide.

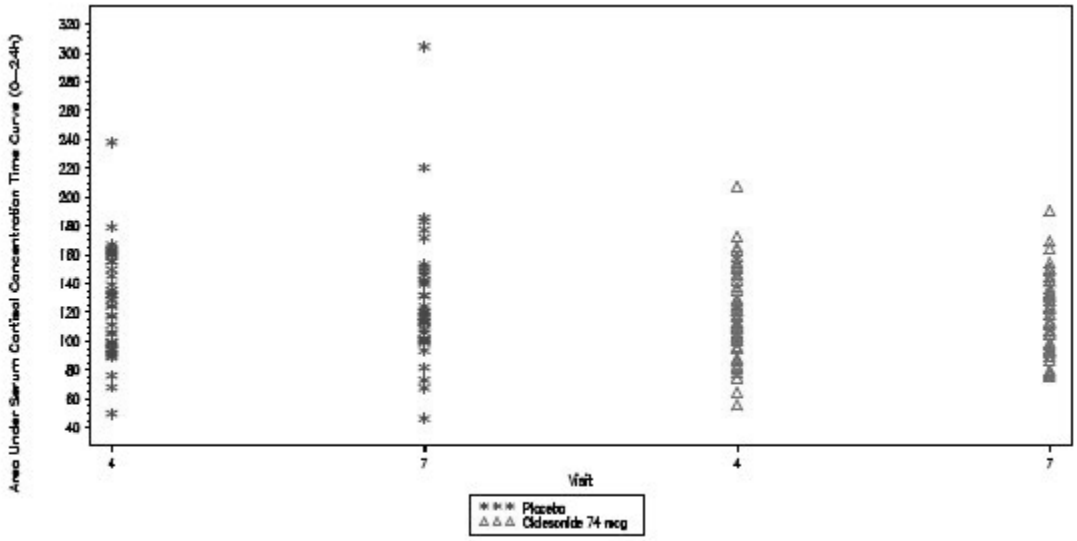
The proposed language by the sponsor is proposed to be edited as shown in the COMMENTS section of this review.

Table 1: Change from Baseline in Serum Cortisol $AUC_{(0-24)}$ (mcg•hour/dL) (PP Population)

	Placebo (N = 39)		Ciclesonide 74 mcg (N = 46)	
	Value	Change from baseline	Value	Change from baseline
Baseline (Visit 4)				
n	39		46	
Mean (SD)	125.6 (36.6)		118.5 (31.2)	
Median	124.6		114.3	
Min, Max	50, 238		56, 208	
25^{th}, 75^{th} percentiles	96.9, 155.5		95.7, 142.4	
10^{th}, 90^{th} percentiles	88.7, 164.4		81.7, 158.7	
End of Treatment (Visit 7)				
n	39	39	46	46
Mean (SD)	127.9 (44.9)	2.3 (51.7)	118.9 (26.2)	0.4 (29.7)
Median	117.2	-2.3	118.5	2.7
Min, Max	46, 304	-115, 229	76, 191	-68, 64
25^{th}, 75^{th} percentiles	101.3, 146.1	-17.8, 12.7	97.7, 134.3	-19.9, 18.4
10^{th}, 90^{th} percentiles	81.5, 183.0	-46.9, 47.3	86.7, 150.5	-42.1, 37.6
LS Mean (SE)		5.9 (5.6)		-1.7 (5.2)
Diff Placebo LS Mean (SE)				7.6 (7.5)
95% CI				(-7.4, 22.6)

Reference: Table 14.2.1.1

Figure 1: Vertical Scatter Plot: Serum Cortisol $AUC_{(0-24)}$ (mcg•hour/dL) (PP Population)



Reference: Figure 14.2.5

Table 2: Change from Baseline in Urinary Free Cortisol-Corrected for Urine Creatinine (mcg/g) (PP Population)

	Placebo (N = 39)		Ciclesonide Nasal Aerosol 74 mcg (N = 46)	
	Value	Change from baseline	Value	Change from baseline
Baseline (Visit 4)				
n	39		45	
Mean (SD)	27.6 (17.4)		26.1 (13.10)	
Median	21.0		22.0	
Min, Max	11, 103		8, 62	
25th, 75th percentiles	16.9, 35.1		16.6, 32.7	
10th, 90th percentiles	13.1, 51.0		10.5, 41.9	
End of Treatment (Visit 7)				
n	39	39	46	45
Mean (SD)	27.3 (11.5)	-0.3 (17.0)	28.1 (25.8)	2.2 (20.5)
Median	25.7	1.9	20.6	-1.8
Min, Max	11, 65	-75, 31	8, 179	-16, 120
25th, 75th percentiles	19.7, 33.6	-4.2, 6.2	16.4, 30.8	-4.5, 4.5
10th, 90th percentiles	14.8, 43.9	-23.7, 17.4	12.9, 42.9	-13.3, 13.5
LS Mean (SE)		1.4 (2.9)		3.3 (2.7)
Diff Placebo LSM (SE)				-1.9 (3.9)
95% CI				(-9.6, 5.9)

Reference: Table 14.2.3.1

Table 3: Mean (SD) Pharmacokinetic Parameters (PK Population)

	Des-Ciclesonide	Ciclesonide
$AUC_{(0-24)}$ (ng*hr/mL)	0.261 (0.139)	0.038 (0.034) $AUC_{(0-last)}$ was calculated instead of $AUC_{(0-24)}$, as because in 35 subjects out of 41, the last measurable concentration occurred prior to 24 hours.
C_{max} (ng/mL)	0.029 (0.0169)	0.012 (0.009)
t_{max} (hour)	2.200 (1.330)	1.146 (0.700)
$t_{1/2}$ (hour)	11.727 (5.864)	ND

STUDY SYNOPSIS FOR HPA AXIS STUDY 060-308

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Ciclesonide	**Page:**	
Title of Study: A 6-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Safety Study of the Potential Inhibitory Effects of Ciclesonide Nasal Aerosol on The Hypothalamic-Pituitary-Adrenal Axis in Subjects 6-11 Years of Age with Perennial Allergic Rhinitis		
Principal Investigator: **Investigators:** 7 Investigators at 7 sites in the United States; a complete list is provided in Appendix 16.1.4.		
Study center(s): This was a multicenter study; see Appendix 16.1.4 for a complete list.		
Publications (reference): none		
Studied period (years): First subject first visit: 12 July 2011 Last subject last visit: 21 November 2011	**Phase of development:** 3b	

Objectives:

Primary:

- The primary objective of this study was to evaluate the effect of ciclesonide on the hypothalamic-pituitary-adrenal (HPA) axis as measured by serum cortisol area under the concentration-time curve (AUC) over 24 hours when ciclesonide nasal aerosol 74 mcg was administered once daily to subjects 6 to 11 years of age with perennial allergic rhinitis (PAR) compared with placebo.

Secondary:

- Further evaluate the effect of ciclesonide on the HPA axis as measured by 24-hour urinary free cortisol.
- Evaluate the safety and tolerability of ciclesonide
- Characterize the pharmacokinetic (PK) profile after 6 weeks of steady-state treatment and the relationship between study drug exposure and change in cortisol exposure from baseline.
- Assess the efficacy of ciclesonide
- Assess the accuracy of the dose counter affixed to the study medication device.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety study of the effects of ciclesonide nasal aerosol (74 mcg) on the HPA axis when administered once daily to male and premenarchal female subjects 6 to 11 years of age with a diagnosis of PAR.

The total duration of subject participation was approximately 3 months (including the 3- to 30-day screening period, the 7- to 10-day single-blind placebo run-in period, the 6-week double-blind treatment period, and the 7- to 10-day follow-up period).

Subjects were domiciled during two 24- to 36-hour time periods for sample collection for serum and urinary free cortisol measurements, as well as PK evaluations (single [predose] time point during the first domiciled period, and 24-hour sampling during the second domiciled period). Depending on the investigational site capabilities, 2 different but affiliated types of clinical sites may have been utilized: a clinic for visits that occurred during regular office hours (clinic site) and a facility where subjects were domiciled overnight (overnight site). If 2 locations were required, the subject went to each site, and the site's principal Investigator (or designee) oversaw all study procedures for both locations.

Study medication was administered once daily (in the morning, between 06:00 AM to 12:00 PM local time) for 6 weeks during the double-blind treatment period. The subjects' parents/legal guardians were contacted by the call center each day (with the exception of clinic visit days) to initiate the videophone and administer the double-blind study medication dose.

The call center observed the administration of the study medication dose via the videophone. On clinic visit days at Week 2, Week 4, and Week 6, the subject or parent/legal guardian was instructed to withhold the dose of double-blind study medication and administer the subject's dose of study medication at the clinical site; the investigator (or designee) recorded in the electronic case report form (eCRF) the date and time of dosing. The last dose of double-blind study medication was administered at the clinical site on Day 42 (- 1 to + 3) at Visit 7.

During the 6-week double-blind treatment period, subjects or their parent/legal guardian assessed and recorded their reflective and instantaneous total nasal symptom score (TNSS) twice daily (am and pm) on a scale of 0 (no signs/symptom evident) to 3 (severe signs/symptoms that are hard to tolerate). Scores were recorded in the Allergic Rhinitis Assessment Diary each day during the Double-blind Treatment period up to and including the morning of Day 42 (- 1 to + 3) (Visit 7). Subjects or their parents/legal guardians also recorded the number of actuations of study medication administered per day, the date and time of dosing, the number (if any) of extra non-nasal actuations per day, and any rescue medication that was taken in the Allergic Rhinitis Assessment Diary. The Allergic Rhinitis Assessment Diary was collected and reviewed by the investigator (or designee) at each study visit during the Double-blind Treatment period.

Number of subjects (planned and analyzed): Planned: 80; Enrolled: 101; Randomized: 89; Completed: 88 (98.9%); Discontinued Early: 1 (1.1%)

Diagnosis and main criteria for inclusion: Male and premenarchal female subjects 6 to 11 years of age and ≥ 20 kg at the screening visit, with a history of PAR to a relevant perennial allergen for at least 1 year preceding the screening visit, and with a demonstrated sensitivity to at least 1 allergen known to induce PAR (house dust mites, animal dander, cockroaches, and molds) based on results of a standard skin-prick testing.

Test product, dose and mode of administration, batch number: Ciclesonide nasal aerosol, 1 actuation (ie, 37 mcg) in each nostril for a total dose of 74 mcg once daily (Lot # GMB079).

Duration of treatment: Each treatment (ciclesonide and placebo) was administered for 6 weeks.

Reference therapy, dose and mode of administration, batch number: Placebo nasal aerosol, 1 actuation in each nostril once daily (Lot # GKG021).

Criteria for evaluation:

Primary Endpoint:

The primary endpoint was the change in serum cortisol AUC from time 0 to 24 hours (AUC_{0-24}) from Baseline to the end of the 6-week treatment period.

Secondary Safety Endpoints:

- Change in 24-hour urinary free cortisol excretion (uncorrected and corrected for urine creatinine) from Baseline to the end of the 6-week treatment period
- Number and percentage of subjects experiencing AEs
- Number and percentage of subjects experiencing SAEs
- Number and percentage of subjects who discontinue due to AEs
- Number and percentage of subjects experiencing nasal AEs, including epistaxis, nasal ulceration, and nasal perforation.

Secondary Pharmacokinetic Endpoints: Steady-state pharmacokinetic (PK) parameters were calculated for ciclesonide and des-ciclesonide at Week 6 of the double-blind treatment period.

Secondary Efficacy Endpoint:

- Change from baseline in averaged daily subject-reported AM and PM rTNSS averaged over the 6-weeks of double-blind treatment

Secondary Dose Counter Endpoints:

- Ratio (percentage) of the number of correct advances of the dose indicator to the number of expected advances based on subject self-report of study medication administration plus extra non-nasal actuations
- Number and percentage of devices with actuation consistency, where actuation consistency is defined as a dose indicator count within ± 20% of the subject self-report of study medication administration

Other Endpoints:

- Number and percentage of subjects responding to each category per question in the dose indicator survey
- Ratio (percentage) of the number of correct advances of the dose indicator to the number of expected advances based on study medication canister weights
- Ratio (percentage) of the number of correct advances of the dose indicator to the number of expected advances based on number of days on treatment plus extra non-nasal actuations

SUMMARY – CONCLUSIONS

Safety Conclusions

Results of the primary safety analysis demonstrated that ciclesonide (administered as 74 mcg nasal aerosol) did not suppress serum cortisol levels, and as such support the overall safety profile of this formulation. Non-inferiority analyses were utilized to compare ciclesonide nasal aerosol 74 mcg with placebo, with a pre-specified non-inferiority margin of 35 mcg•hour/dL.

- For the primary endpoint, the least squares mean (LS mean) difference in serum cortisol $AUC_{(0-24)}$ change from baseline to the end of the 6-week treatment period for the PP population was 7.6 mcg•hour/dL (95% CI: -7.4, 22.6) for ciclesonide nasal aerosol 74 mcg vs placebo. Non-inferiority was demonstrated for ciclesonide nasal aerosol 74 mcg compared with placebo, as the upper bound of the 95% CI (22.6 mcg•hour/dL) was less than the non-inferiority margin of 35 mcg•hour/dL, thus indicating no suppression of the HPA axis after 6 weeks of treatment.

- Consistent with the results of the primary endpoint, analysis of change from baseline to the end of the 6-week treatment period in urinary free cortisol, both corrected and uncorrected for urine creatinine, demonstrated no difference between ciclesonide nasal aerosol and placebo on HPA axis function after 6 weeks of once daily treatment.
- There were no deaths, other treatment-emergent serious adverse events, or TEAEs resulting in study discontinuation reported during the study.
- There were no treatment-emergent nasal ulcers or nasal septal perforations reported in either treatment group.
- Among all subjects who received ciclesonide nasal aerosol 74 mcg, 30 treatment-emergent adverse events (TEAEs) were reported for 20 (42.6%) subjects; 36 TEAEs were reported for 19 (45.2%) subjects who received placebo. The most frequently reported TEAE in ciclesonide-treated subjects was headache (6.4% of subjects), while the most frequently reported TEAE in the placebo treatment group was oropharyngeal pain (9.5% of subjects). Epistaxis (4.8% and 2.1% of subjects in the placebo and ciclesonide treatment groups, respectively) and excoriation (4.8% and 0% of subjects, respectively) were both reported infrequently, but in a slightly greater percentage of subjects in the placebo group than in the ciclesonide nasal aerosol group.
- A greater percentage of subjects in the placebo group reported TEAEs assessed as potentially related to study drug (14.3% of subjects) than in the ciclesonide nasal aerosol group (8.5% of subjects). The most frequently reported TEAEs assessed as potentially related to study medication were epistaxis (4.8% and 2.1% of subjects in the placebo and ciclesonide groups, respectively) and oropharyngeal pain (7.1% and 0% of subjects, respectively).
- All TEAEs reported by ciclesonide-treated subjects were mild or moderate in severity. One (2.4%) subject in the placebo treatment group reported a severe headache during the double-blind treatment period.
- There were no clinically significant changes from baseline in vital signs. There were no apparent patterns or trends of concern in laboratory parameters.

Pharmacokinetic, Efficacy, and Dose Indicator Conclusions

Investigation of the pharmacokinetics in subjects 6-11 years of age demonstrated the following:

- Mean serum des-ciclesonide C_{max} was approximately 2.5-fold higher than mean ciclesonide C_{max}. The median calculated half-life of des-ciclesonide was 9.59 hours.

Efficacy was assessed as a supportive measure of treatment compliance. Interpretation of the efficacy results was based on the 95% confidence intervals for the treatment difference from the ANCOVA models.

- Both treatments resulted in an improvement from baseline in rTNSS averaged over the 6-week double-blind treatment period; the LS mean change from baseline was -0.7 and -1.4 for the placebo and ciclesonide groups, respectively. Although the LS mean treatment group difference from placebo was not significant for the ciclesonide group (0.7; 95% CI: -0.1, 1.5), evidence for treatment compliance was observed.

Results of the dose indicator assessments demonstrated that the dose counter functioned effectively.

- Overall and for each 2-week treatment period (ie, Visits 4-5, Visit 5-6, and Visits 6-7), accuracy of the dose indicator based on the actuations reported was demonstrated, as the mean accuracy ratio ranged from 99.8% to 103.0% across treatments and treatment periods.

- The large majority of assessments of the dose indicator (91.1% of placebo devices and 89.4% of ciclesonide devices) were within the acceptable range of 20% of the reported value and therefore met the criteria for actuation consistency.
- Accuracy of the dose indicator based on canister weights was demonstrated, with overall accuracy ratios of 95.5% and 93.1% for the placebo and ciclesonide groups, respectively.
- Accuracy of the dose indicator based on expected number of days on treatment was demonstrated, with overall accuracy ratios of 101.0% and 99.6% for the placebo and ciclesonide groups, respectively.
- The dose indicator survey demonstrated that after 6 weeks of treatment, the majority of subjects felt that the dose indicator worked because the dose indicator 'clicked' (61.0% and 76.6% of subjects in the placebo and ciclesonide groups, respectively), found it easy to read and understand the dose indicator (70.7% and 74.5% of subjects, respectively), felt the dose indicator accurately reflected the number of doses remaining in the canister (61.0% and 76.6% of subjects, respectively), and were pleased with the dose indicator (68.3% and 80.9% of subjects, respectively).

CONCLUSIONS: The results of this study demonstrated that ciclesonide had no suppressive effect on the HPA axis. The safety profile of ciclesonide was similar to that of placebo in this population of pediatric subjects. The dose indicator functioned effectively with a high degree of accuracy.

Date of the Report: 28 August 2012

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

/s/

SHEETAL S AGARWAL
09/08/2014

SATJIT S BRAR
09/08/2014