CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDAs: 22-004	**Date of Submission:** December 21, 2005
Generic Name	Ciclesonide
Brand Name:	N/A
Formulations:	Nasal Spray
Route of Administration:	Nasal
Indication:	Seasonal and Perennial Rhinitis
Type of Submission:	**Drug Interaction Report/Addendum**
Sponsor:	Altana Florham Park, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

Background

This is an addendum to the OCP review dated August 28, 2006 to report ketoconazole drug interaction data with ciclesonide (Study # BY9010/CP-036). This study was conducted with ciclesonide inhalation aerosol but was submitted in this NDA for ciclesonide nasal spray. Therefore, the study was inadvertently not included in the original review dated August 28, 2006.

Study Objective:

The primary objective of this study is to investigate the effect of ketoconazole on the PK of ciclesonide and its active metabolite, RM1 in healthy subject.

Study design:

This was two-period repeated dose study in 14 healthy subjects as follows:

Treatment A: Inhaled ciclesonide 320 mcg QD (2 puffs of 160 mcg) x 7 days alone
Treatment B: Inhaled ciclesonide 320 mcg QD (2 puffs of 160 mcg) coadministred with 400 mg ketoconazole QD x 7 days

There was no washout period between treatments in periods 1 and 2. On Day 7 of each treatment period serial PK blood samples were collected over 24 hours for PK analysis of ciclesonide, RM1 metabolite, and ketoconazole (Day 7 on treatment 2). In addition, pre-dose blood samples were collected on Day 2, Day 4, and Day 6 for the determination of trough concentration.

Results:

Ketoconazole had no effect on the PK of ciclesonide (**Table 1 and Figure 1**). However, the Cmax and AUC of RM1 metabolite increased by approximately 2.2 and 3.7 fold after ketoconazole, respectively (**Table 2 and Figures 2 and 3**).

Table 1. Ciclesonide PK Parameters With and Without Ketoconazole (Study CP-036)

Pharmacokinetic parameter estimates	Period 1 Ciclesonide 320 µg od		Period 2 Ciclesonide 320 µg od Ketoconazole 400 mg od	
	n	Mean ± SEM	n	Mean ± SEM
AUC_{tau} (h*µg/L)	14	1.338 ± 0.067	14	1.306 ± 0.064
C_{max} (µg/L)	14	2.382 ± 0.157	14	2.069 ± 0.14
$t_{1/2}$ (h)	14	13.96 ± 3.09	14	14.31 ± 1.78
t_{max} (h)	14	0.25 ± 0.00	14	0.25 ± 0.00

Figure 1. Ciclesonide Plasma-Concentration Time Profiles Without (Period 1) and With (Period 2) Ketoconazole (Study CP-036)

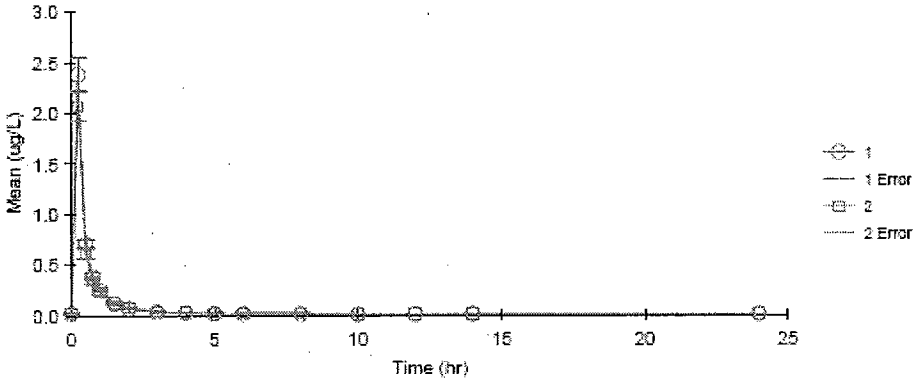


Table 2. RM1 PK Parameters With and Without Ketoconazole (Study CP-036)

Pharmacokinetic parameter estimates	Period 1 Ciclesonide 320 µg od		Period 2 Ciclesonide 320 µg od Ketoconazole 400 mg od	
	n	Mean ± SEM	n	Mean ± SEM
AUC_{tau} (h*µg/L)	14	3.022 ± 0.134	14	11.129 ± 0.75
C_{max} (µg/L)	14	0.645 ± 0.032	14	1.406 ± 0.076
$t_{1/2}$ (h)	14	9.08 ± 0.62	14	7.07 ± 0.36
t_{max} (h)	14	0.70 ± 0.10	14	1.45 ± 0.20

Figure 2. Individual RM1 AUC Alone and With Ketoconazole (Study CP-036)

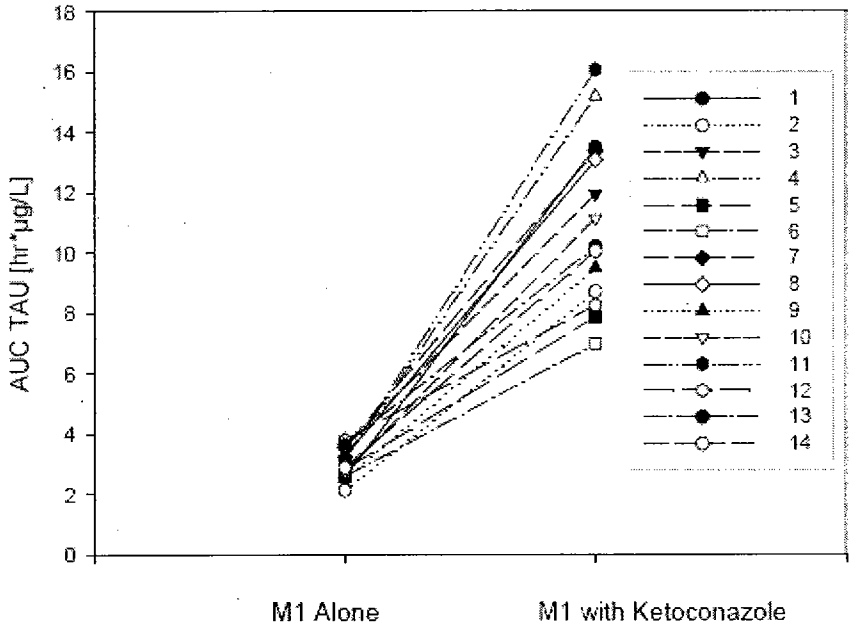
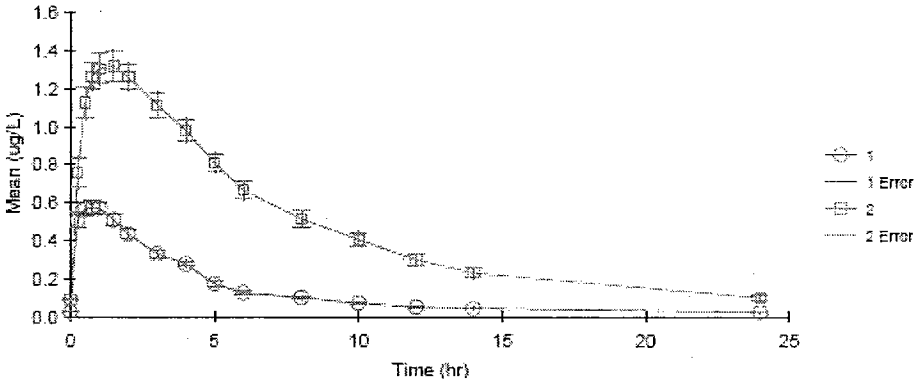
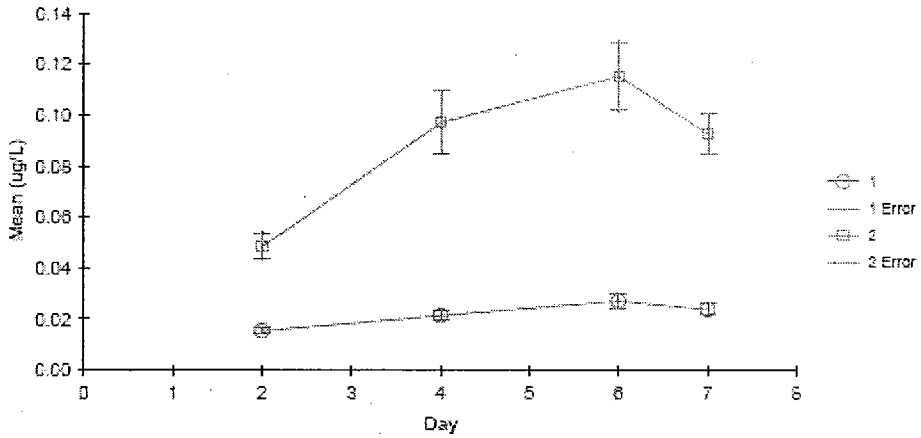


Figure 3. RM1 Plasma-Concentration Time Profiles Without (Period 1) and With (Period 2) Ketoconazole (Study CP-036)



Steady state level was reached by Day 6 as confirmed by the trough concentrations of RM1 on Days 2, 4, 6, and 7 (**Figure 4**).

Figure 4. Mean RM1 Trough Concentration of RM1 Without (Period 1) and with (Period 2) Ketoconazole (Study CP-036)



Conclusion:

Based on the data from this study it can be concluded that the PK of the parent drug, ciclesonide, was essentially unaffected by ketoconazole. However, the exposure (Cmax and AUC) to ciclesonide metabolite, RM1, was increased by approximately 2.2 and 3.7 fold when co-administered with ketoconazole. This information should be included in the labeling for ciclesonide nasal spray.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 2
Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

---

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

/s/

Sayed Al-Habet
9/8/2006 09:53:30 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
9/8/2006 10:03:43 AM
BIOPHARMACEUTICS
I concur.

Clinical Pharmacology Review

NDAs: 22-004 **Date of Submission: December 21**, 2005

Generic Name	Ciclesonide
Brand Name:	N/A
Formulations:	Nasal Spray
Route of Administration:	Nasal
Indication:	Seasonal and Perennial Rhinitis
Type of Submission:	New NDA
Sponsor:	Altana Florham Park, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation:

From the clinical pharmacology perspective, this NDA is acceptable.

1.2 Phase 4 Commitment

From the clinical pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Clinical Pharmacology Findings:

Ciclesonide is a new pro-drug non-halogenated glucocorticoid that is required to be activated by esterases to its biologically active metabolite (RMI or M1). This metabolite exhibits approximately 100-fold greater affinity for the glucocorticoid receptor than the parent drug. The sponsor formulated this drug as nasal spray for the treatment of symptoms associated with allergic rhinitis in adult and children.

All clinical pharmacology studies conducted with orally inhaled ciclesonide along with other supportive studies such as metabolism and *in vitro* studies were reviewed by the Office of Clinical Pharmacology (OCP). Therefore, the focus of this review is on studies using nasal spray (OCP review by Dr. Sandra Suarez-Sharp dated September 20, 2004).

The sponsor conducted several studies following intranasal administration in adults and children. The two main studies are Study 202/2003 (TBN-CL-001) and 61/2005 (TBN-15-001). The former study was a repeat dose for 14 days in healthy subjects and in patients and the second study was in Japanese subjects for 7 days. The doses in both studies ranged from 50 mcg to 800 mcg per day.

In all of these studies, ciclesonide and its active metabolite, RMI were virtually undetected in the plasma. In most of the plasma samples the levels were below the lower limit of quantification (LLOQ) for ciclesonide (<25 pg/ml) or RMI (<10 pg/ml). The highest concentration detected in this NDA was 48.9 pg/ml for ciclesonide and 64.5 pg/ml for RMI. Across study comparison reveals that the observed plasma levels of ciclesonide and RMI after oral inhalation were approximately 10 to 30 fold higher than after intranasal administration at the same dose or dose corrected values.

In addition to the PK studies, the sponsor conducted five Phase II/III studies to investigate the effect of ciclesonide on HPA-axis (cortisol suppression). The doses in these studies ranged from 25 mcg to 200 mcg daily up to 42 to 85 days (Studies # 403, 404, 405, 408, and 409). Overall, in all these studies the intranasal ciclesonide did not show significant change in plasma or urine cortisol levels from baseline at all tested doses.

Reviewer's Overall Comments:

Since the absorption following intranasal administration was negligible, the effect on HPA axis was also negligible. The recommended dose is 200 mcg which is sufficiently low relative to other tested high doses in this NDA not to raise a major concern and also considering the negligible absorption after intranasal administration. Furthermore, the effect of orally inhaled ciclesonide on HPA axes was noticeable but not substantial considering the higher systemic exposure than from intranasal administration. Thus, the HPA axis effect of ciclesonide after intranasal administration is of little concern

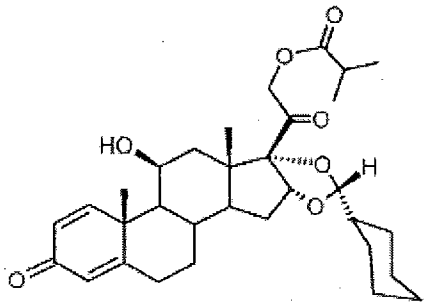
Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 2
Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

2. Clinical Pharmacology review (Question Based Review)

2.1 General Attributes/Background:

Ciclesonide, a novel non-halogenated glucocorticoid was originally developed as oral inhalation therapy via meter dose inhaler for the treatment of asthma



The current sponsor, Altana Pharma has developed nasal spray for the treatment of nasal symptoms associated with seasonal and perennial rhinitis in adults and children 2 years of age or older. The drug will be available as spray of 50 mcg per spray. The proposed dose is 200 mcg per day as 2 sprays in each nostril once daily.

Ciclesonide is considered a pro-drug since it is cleaved by the intracellular esterases at carbon 21 to a biologically active metabolite (RM1 or M1) which exhibits over 100-fold greater affinity to glucocorticoid receptor than the parent drug.

The development of ciclesonide started with the use of an epimeric mixture of R- and S-ciclesonide. However, according to the sponsor, further clinical development was continued with the R-epimer. This is because the major metabolite (RM1) of the R-epimer has 6-8-fold higher affinity to the cortisol receptor when compared to the M1-metabolite of S-epimer. In addition, there was no inter-conversion from R to S ciclesonide *in vivo*. The parent drug appears to have only 1/100 of the binding affinity to the glucocorticoid receptor as compared to its major circulating metabolite, RM1.

From the clinical pharmacology and PK perspective, the parent drug and its metabolite, RMI are virtually undetectable in the plasma following intranasal administration. Thus, according to the sponsor, it is designed to act locally.

2.2 General Clinical Pharmacology

2.2.1 What is the Proposed Indication and Dosage?

Ciclesonide will be available as nasal spray for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

Each actuation of the pump delivers 50 mcg of ciclesonide. For adults and children (Years of age and older), the recommended dose is 2 sprays in each nostril once daily for a total daily dose of 200 mcg. [redacted] The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

2.3 Intrinsic factors

All intrinsic factors such as age, gender, weight, and diseases have been reviewed by the office of clinical pharmacology in the original NDA for oral inhalation.

2.4 Extrinsic factor

All extrinsic factors such as drug-drug interactions have been reviewed by the office of clinical pharmacology in the original NDA for oral inhalation. Other extrinsic factor that may affect the performance of the product is the variation among patients in the use of the device/spray.

2.5 General Biopharmaceutics

Ciclesonide nasal spray comprises a white plastic manual spray pump fitted to an amber glass bottle. As stated earlier, the pump delivers a metered dose of 50 mcg of the drug per actuation. Each actuation volume is 70 microliter (mcL).

The formulation consists of a hypotonic aqueous suspension of ciclesonide containing several in ingredients (**Table 2.4.1**):

Table 2.4.1 . Composition of Drug Product

Ingredient	Amount					Function
	mg/actuation[1]	mg/mL	wt %[2]	mg/bottle[3]	120 puff presentation	
Drug Substance:						
Ciclesonide,	0.050					Active ingredient
Excipients:						
Microcrystalline Cellulose and						
Hydroxypropyl Methylcellulose USP						
Potassium Sorbate NF						
Edetate Disodium USP						
Hydrochloric Acid NF q.s. ad	pH 4.5 ± 0.2	pH 4.5 ± 0.2	pH 4.5 ± 0.2	pH 4.5 ± 0.2	pH 4.5 ± 0.2	pH adjustment
Purified Water USP q.s. ad						
	-	-	-	-	-	

Only one formulation has been developed and tested throughout the development program. No change in formulation has been made. Therefore, no bioequivalence study has been conducted in this NDA.

2.6 Analytical Section

The analytical method used in the determination of ciclesonide and its metabolite, RMI was LC/MS/MS. The lower limit of quantification (LLOQ) is 25 pg/ml and 10 pg/ml for ciclesonide and RMI, respectively. This method has been reviewed by OCP in more detail in the original

2.7 Summary of Clinical Pharmacology Studies:

The sponsor crossed referenced several studies from the original for oral inhalation. These studies have already been reviewed by the Office of Clinical pharmacology. Therefore, the focus will be only on the intranasal studies. Two phase I studies were conducted to determine the PK and PD of intranasal ciclesonide. The first study (# 202/2003 (TBC-CL-001) was in healthy subjects and patients with seasonal allergic rhinitis who received nasal administration daily over 14 days. The second study (61/2005 (TBN-15-001) was an escalating dose ranging (from 50 to 800 mcg/day) study in healthy Japanese subjects over 7 days.

Furthermore, two additional Phase III clinical studies containing PK and pharmacodynamic (PD) information are 149/2005 (M1-403) and 144/2005 (M1-405). These studies were conducted in pediatric patients to determine the safety and pharmacodynamics of the nasal route. In all these studies, the serum levels were close or below the limits of quantification (LLOQ) for ciclesonide (<25 pg/ml) and RMI (<10 pg/ml).

2.7.1 Study 202/2003 (TBN-CL-001):

Objectives: The primary objective of this study was to evaluate the safety and PK and PD of repeated intranasal doses of ciclesonide (50-800 mcg/day) given for 14 days to healthy volunteers and asymptomatic patients with SAR.

Design: This was placebo-controlled and double-blinded study in 40 healthy subjects as follows:

Group A (n=8): 50 mcg QD (n=6) or Placebo (n=2) x 14 days
Group B (n=8): 100 mcg QD (n=6) or placebo (n=2) x 14 days
Group C (n=8): 200 mcg QD (n=6) or placebo (n=2) x 14 days
Group D (n=8): 400 mcg QD (n=6) or placebo (n=2) x 14 days
Group E (n=8): 400 mcg BID (n=6) or placebo (n=2) x 14 days
Group F (**n=8 SAR patients**): 400 mcg BID (n=6) or placebo (n=2) x 14 days

Blood samples were collected at appropriate intervals over 24 hours on Days 1 and 14 and before the morning doses on Days 11, 12, and 13 for PK and PD (cortisol) profiles.

Results:

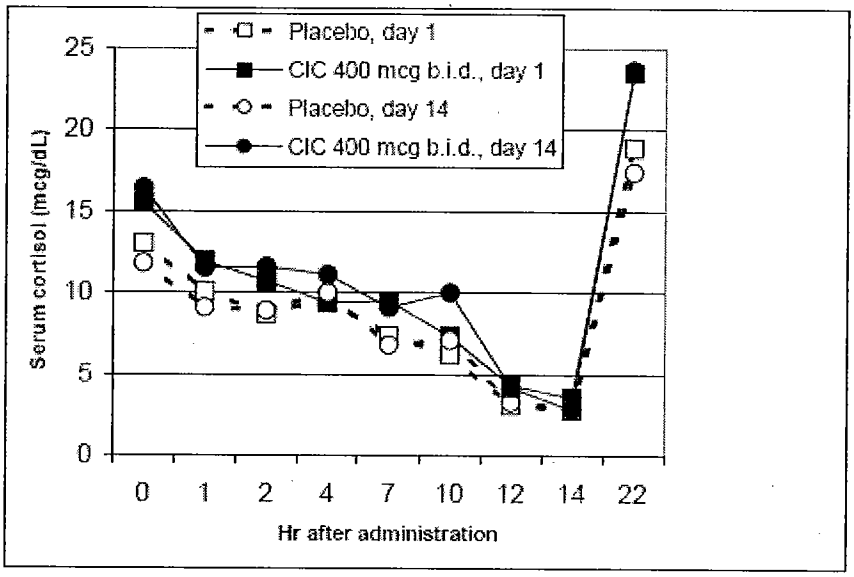
Most of the blood samples were below or close to the LLOQ of 25 pg/ml, for the parent drug, ciclesonide, and 10 pg/ml for its metabolite, RM1. Since there was no detectable concentration for either ciclesonide or RMI at 200 mcg dose, it was not necessary to analyze the samples collected at 50 and 100 mcg doses. The maximum concentrations of ciclesonide that were detected in this study were [redacted] in one subject after 400 mcg QD and 400 mcg BID arms, respectively (**Table 2.7.1.1**). The maximum concentration of RMI that was detected in one subject following 400 mcg QD dose was [redacted]

Table 2.7.1.1. Number of Subjects with Detectable Serum Levels for the Parent drug, Ciclesonide, and RM1 metabolite (Study # 202/2003-TBN-CL-001).

Ciclesonide Dose	Number of subjects		Highest recorded concentration	
	Ciclesonide	RMI	Ciclesonide	RMI
200 mcg; 1x daily	0/6	0/6	<25	<10
400 mcg, 1x daily	1/6	4/6	[redacted]	
400 mcg, 2x daily	1/6	6/6		
400 mcg, 2x daily (SAR patients)	0/6	3/6		

There was no difference among treatments with respect to serum cortisol levels (**Figure 2.7.1.1**). Over 14 days, the decline in cortisol level in all treatments with ciclesonide was comparable to that of the placebo arm.

Figure 2.7.1.1. Cortisol Serum Concentration-Time Profiles over 14 days in all treatments (Study # 202/2003-TBN-CL-001).



Conclusions:

Based on this data, ciclesonide and its metabolite, RMI was undetectable in the plasma up a dose of 400 mg BID for 14 days. This indicates that ciclesonide is not absorbed via nasal cavity. This is also evident by the lack of effect on HPA axis following nasal administration asthere was no effect on cortisol level over 14 days. The serum cortisol levels following all intranasal treatments were similar to that of the placebo (**Figure 2.7.1.1**).

2.7.2 Study # 61/2005 (TBN-15-001) (Japanese Subjects):

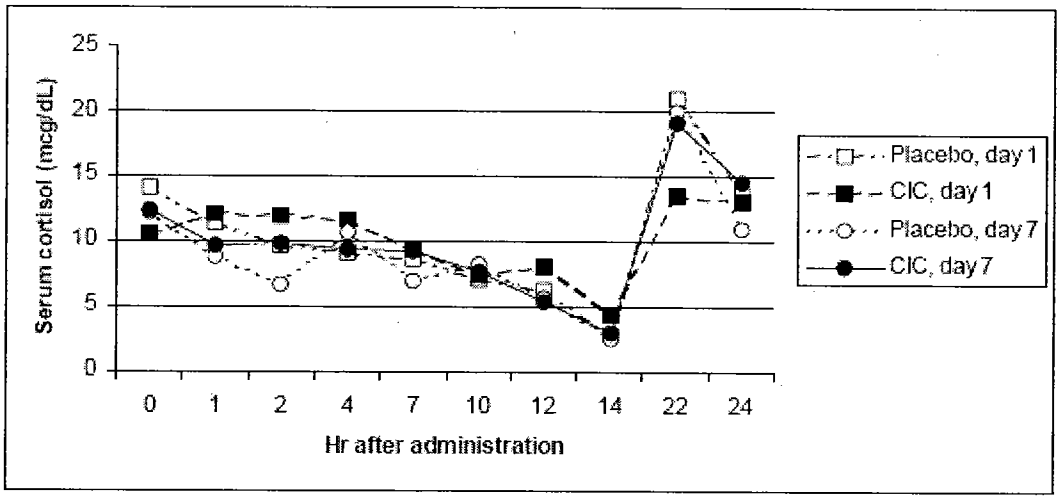
Objectives: The primary objective of this study is to evaluate the safety and PK/PD of intranasal ciclesonide following a single or repeated doses ranging from 50 to 800 mcg over 7 days in Japanese subjects.

Design: This was a placebo-controlled and double-blind study in 33 healthy male Japanese subjects administered as 50, 200, 800 mcg as single dose then 400 mcg BID x 7 days. At each dose level 6 subjects received the active treatment and 2 subjects received placebo. Blood samples were collected on Day 1 and Day 7.

Results:

Similar to the previous study, neither Ciclesonide nor its metabolite, RM1 was detected with confidence following any of the doses on either Day 1 or Day 7. In a few subjects, RMI level was just above the LLOQ of 10 pg/ml [redacted]. Furthermore, the conclusions in reference to the effect on the HPA axis and the serum cortisol level were similar to the previous study (**Figure 2.7.2.1**).

Figure 2.7.2.1. Cortisol Serum Concentration-Time Profiles over 14 days in all treatments (Study # 61/2005 (TBN-15-001)



Conclusions:

The data from this study further confirm the negligible systemic absorption following intranasal administration of ciclesonide. As shown in the previous study, the effect on HPA axis was also negligible.

2.7.3 Effect on HPA Axis (Cortisol Suppression):

The sponsor conducted five Phase II clinical studies in patients with allergic rhinitis with intranasal route as follows:

1) Study # 144/2005 (MI-405) was in pediatric patients with PAR ages from 2 to 5 years
2) Study # 149/2005 (MI-403) was conducted in older children aged 6 to 11 years of age.
3) Study # 146/2005 (MI-404) was conducted in adolescent and adult patients with PAR 12 years and older with PAR.
4) Studies # 147/2005 (MI-408) and 148/2005 (MI-409) were conducted in adult patients with allergic rhinitis.

Study Designs/Dose:

- Study # 403: 25, 100, and 200 mcg QD x 85 days in patients with PAR
- Study # 404: 200 mcg QD x 48 weeks in patients with PAR 12 years and older
- Study # 405: 25, 100, and 200 mcg QD x 6 weeks in patients with PAR 2-5 years of age

- Study # 408: 200 mcg QD plus orally inhaled Beclomethasone Dipropionate (HFA-BDP) 400 mcg BID or placebo X 43 days. On the last day of treatment day, all patients received 2 mg tablet of dexamethasone. The objective of this study was to investigate the potential additive inhibitory effects on HPA-axis with nasal ciclesonide.

- Study # 409: 200 mcg QD plus orally inhaled Fluticasone Propionate/Salmeterol (FP/SAL) 500/50 mcg BID or placebo X 43 days. On the last day of treatment, all patients received 2 mg tablet of dexamethasone. The objective of this study was to investigate the potential additive inhibitory effects on HPA-axis with nasal ciclesonide.

In all of these studies, blood and urine samples were collected at appropriate time points. For detail on the study designs, please see the Medical Officer's review.

Results of HPA-Axis/Pharmacodynamic Studies:

- Overall, treatment with intra-nasal ciclesonide at all doses did not significantly change plasma or urine cortisol levels from baseline (**Tables 2.7.3.1-2.7.3.5**).

Table 2.7.3.1 Mean Plasma Cortisol Level (mcg/dL) (Study # MI-403).

Treatment	N	Mean (SD)		LS Mean (SE) for Difference from Baseline	Estimated Difference from Placebo (95% CI)[1]
		Baseline	Endpoint		
Placebo	47	10.8 (5.3)	10.7 (3.6)	0.39	--
Cic 25 mcg	51	10.1 (3.8)	10.2 (4.7)	0.01	-0.38 (-2.1, 1.3)
Cic 100 mcg	61	9.6 (4.6)	10.4 (4.8)	0.51	0.12 (–1.5, 1.7)
Cic 200 mcg	45	10.2 (4.8)	10.8 (4.3)	0.74	0.35 (–1.4, 2.1)

[1] Treatment differences represent ciclesonide – placebo and are estimated based on an ANCOVA model

Table 2.7.3.2 Mean Urinary Excretion of Cortisol (Study # MI-403).

Treatment	N	Mean (SD)		LS Mean (SE) for Difference from Baseline	Estimated Difference from Placebo (95% CI)[1]
		Baseline	Endpoint		
Placebo	33	22.8 (8.6)	23.7 (9.2)	0.10	--
Cic 25 mcg	32	23.0 (8.2)	21.2 (10.0)	-2.32	-2.42 (-7.2, 2.4)
Cic 100 mcg	44	24.3 (11.0)	24.7 (12.1)	0.78	0.68 (-3.8, 5.2)
Cic 200 mcg	35	24.2 (12.2)	24.2 (8.8)	0.52	0.42 (-4.3, 5.2)

[1] Treatment differences represent ciclesonide – placebo and are estimated based on an ANCOVA model

Table 2.7.3.3 Mean Plasma Cortisol Levels and Urinary Excretion of Cortisol (Study # MI-404).

	Treatment	N	Mean (SD),[1]		Change from Baseline, LS Mean (SE)[3]	Treatment Difference (95% CI)[3]
			Baseline	Endpoint[2]		
Plasma	Placebo	93	14.5 (7.3)	14.2 (6.3)	-0.4 (0.6)	0.7
	200 mcg	193	14.3 (7.3)	13.3 (6.3)	-1.1 (0.4)	(-0.6, 2.0)
Urine	Placebo	92	27.8 (14.7)	27.3 (15.3)	1.2 (2.5)	-1.0
	200 mcg	174	26.3 (14.5)	27.8 (26.5)	2.3 (1.9)	(-6.7, 4.7)

[1] Plasma cortisol expressed as mcg/dL; urine cortisol as mcg/day (not corrected for creatinine)
[2] Endpoint refers to the last assessment conducted on a patient after completion of the baseline period.
[3] Treatment differences are placebo – ciclesonide and are estimated based on an ANCOVA model

The data from study 405 did not show any effect on plasma cortisol levels in pediatric patients (**Table 2.7.3.4**). The drop in mean cortisol level from 9.7 to 8.8 mcg/dL is considered small. For urinary excretion, however, two sets of data are reported, one for creatinine corrected and the other for uncorrected (**Table 2.7.3.5**). For uncorrected urinary cortisol excretion data the mean change for all treatments was approximately -3.5 and was independent of dose. However, for the mean change from the baseline for the creatinine corrected data was slightly greater being -13.5, -14.0 and -6.9 for 25, 100, and 200 mcg doses, respectively. Also, it does not appear to be a consistent dose dependent trend.

It should be noted, according to the Division of Scientific Investigations (DSI) inspection report, the data from study 405 is unreliable. It was recommended that that the data from this study to be excluded from the analysis (DSI Report dated August 15, 2006). Therefore, for the final conclusions and assessment of the data from study # 405 please see the Medical Officer's review.

Table 2.7.3.4 Mean Plasma Cortisol Levels (mcg/dL) in Patients 2 to 5 years of Age (Study # MI-405).

Treatment	N	Mean (SD)		LS Mean Change from Baseline	Estimated Difference from Placebo (95% CI)[1]
		Baseline	Day 42		
Placebo	30	10.5 (4.7)	10.2 (3.6)	-0.03	--
25 mcg	28	10.3 (3.3)	10.0 (3.7)	-0.15	-0.12 (-1.8, 1.6)
100 mcg	27	9.6 (4.2)	9.4 (4.5)	-0.39	-0.36 (-2.1, 1.4)
200 mcg	28	9.7 (3.7)	8.8 (2.7)	-1.07	-1.04 (-2.7, 0.7)

[1] Treatment differences are ciclesonide – placebo; estimates based on an ANCOVA model

Table 2.7.3.5 Mean Free-Cortisol Excretion Corrected and Uncorrected for Ceatinine (mcg/g) in Patients 2 to 5 years of Age (Study # MI-405).

Visit	Ciclesonide			Placebo
	200 mcg	100 mcg	25 mcg	
Baseline				
N	22	15	16	18
Uncorrected Mean (SD)[1]	11.8 (10.2)	8.8 (4.4)	12.6 (8.6)	8.6 (3.7)
Corrected Mean (SD)[2]	47.4 (41.8)	31.7 (11.9)	43.2 (17.7)	36.3 (18.0)
Endpoint				
N	22	15	16	18
Uncorrected LS Mean Change[1]	-3.55	-3.47	-3.27	-1.51
Corrected LS Mean Change[2]	-6.9	-14.0	-13.5	-6.8
Uncorrected Diff from Placebo (95% CI)[1,3]	-2.04 (-4.4, 0.3)	-1.96 (-4.5, 0.6)	-1.76 (-4.3, 0.8)	-
Corrected Diff from Placebo (95% CI)[2,3]	-0.1 (-7.9, 7.7)	-7.3 (-15.7, 1.2)	-6.8 (-15.1, 1.5)	-

1. Uncorrected for creatinine (mcg / D)
2. Correct for creatinine (mcg / g)
3. Based on ANCOVA model with factors for age, gender, baseline cortisol and treatment.

- Studies 408 and 409 did not show substantial additive inhibitory effects on HPA-Axis for intra-nasal ciclesonide compared to placebo when administered either with orally inhaled Beclomethasone Dipropionate (HFA-BDP) or orally inhaled Fluticasone Propionate/Salmeterol (FP/SAL) in patients with perennial allergic rhinitis (**Table 2.7.3.6-9**). In these studies, dexamethsone was used as positive control. However, for the final conclusions and analysis of the data from these clinical studies please see the Medical officer's review

Table 2.7.3.6 Effect of HFA-BDP, Ciclesonide and Dexamethasone on Plasma Cortisol $AUC_{0\text{-}24h}$ (mcg.h/ml) (Study # MI-408).

Interval (Description) [n/N][1]	Placebo + HFA-BDP		Ciclesonide + HFA-BDP		Estimated Treatment Difference (95% CI)[2]
	Baseline, mcg·h/dL (SD)	LS Mean Change (SE)	Baseline, mcg·h/dL (SD)	LS Mean Change (SE)	
Visit S1-B1, (Run-in Period) [47/50]	202.8 (53.7)[2]	-65.6 (5.7)	197.4 (62.0)	-70.0 (5.5)	4.4 (-11.4, 20.1)
Visit B1-T2 (Run-in-42 days co-treatment) [46/48]	135.5 (50.7)	1.0 (7.0)	125.5 (46.1)	8.5 (6.9)	-7.5 (-27.2, 12.1)
Visit T2-T3 (dexamethasone challenge) [46/48]	135.5 (62.4)	-62.7 (4.1)	135.0 (59.0)	-67.5 (4.0)	4.8 (-6.6, 16.1)

[1] Patient numbers for placebo and ciclesonide groups, respectively.
[2] Treatment differences are expressed as placebo (mean change) minus ciclesonide (mean change) and are estimated from an ANCOVA model.

Table 2.7.3.7 Effect of HFA-BDP, Ciclesonide and Dexamethasone on 24 hour Urinary Free Cortisol (Study # MI-408).

Interval (Description) [n/N][1]	Placebo + HFA-BDP		Ciclesonide + HFA-BDP		Estimated Treatment Difference (95% CI)[2]
	Baseline, mcg/g (SD)	LS Mean Change (SE)	Baseline, mcg/g (SD)	LS Mean Change (SE)	
Visit S1-B1, (Run-in Period) [52/46]	57.6 (41.9)	-15.9 (2.4)	46.4 (23.8)	-19.9 (2.5)	4.0 (-2.9, 11.0)
Visit B1-T2 (Run-in-42 days co-treatment) [49/41]	37.3 (22.6)	-10.8 (2.2)	30.2 (12.7)	-15.1 (2.4)	4.4 (-2.1, 10.8)
Visit T2-T3 (dexamethasone challenge) [50/43]	24.1 (17.4)	5.2 (1.7)	18.9 (12.5)	-4.4 (1.8) -	-0.8 (-5.8, 4.2)

[1] Patient numbers for placebo and ciclesonide groups, respectively.
[2] Treatment differences are expressed as placebo (mean change) minus ciclesonide (mean change) and are estimated from an ANCOVA model.

Table 2.7.3.8 Effect of Fluticasoe/salmeterol (FP/SAL), Ciclesonide and Dexamethasone on Plasma Cortisol $AUC_{0\text{-}24h}$ (mcg.h/ml) (Study # MI-409).

Interval (Description) [n/N][1]	Placebo + FP/SAL		Ciclesonide + FP/SAL		Estimated Treatment Difference (95% CI)[2]
	Baseline, mcg·h/dL (SD)	LS Mean Change (SE)	Baseline, mcg·h/dL (SD)	LS Mean Change (SE)	
Visit S1-B1, (Run-in Period) [70/69]	188.0 (61.0)	-44.4 (5.0)	193.3 (60.2)	-63.0 (5.0)	18.6 (4.6, 32.6)
Visit B1-T2 (Run-in-42 days co-treatment) [62/66]	142.0 (54.5)	-15.7 (7.1)	129.7 (52.9)	-12.7 (6.9)	-2.9 (-22.6, 16.8)
Visit T2-T3 (additional challenge with dexamethasone) [61/66]	125.6 (55.6)	-74.8 (3.0)	118.0 (82.8)	-71.7 (2.8)	-3.1 (-11.2, 5.0)

[1] Patient numbers for placebo and ciclesonide groups, respectively.
[2] Treatment differences are expressed as placebo (mean change) minus ciclesonide (mean change) and are estimated from an ANCOVA model.

Table 2.7.3.9 Effect of Fluticasoe/salmeterol (FP/SAL), Ciclesonide and Dexamethasone on 24 h Urinary Free Cortisol excretion (Study # MI-409).

Interval (Description) [n/N][1]	Placebo + FP/SAL		Ciclesonide + FP/SAL		Estimated Treatment Difference (95% CI)[2]
	Baseline, mcg/g (SD)	LS Mean Change (SE)	Baseline, mcg/g (SD)	LS Mean Change (SE)	
Visit S1-B1, (Run-in Period) [54/54]	48.0 (31.0)	-19.3 (2.2)	43.4 (24.3)	-15.1 (2.2)	-4.2 (-10.4, 2.0)
Visit B1-T2 (Run-in-42 days co-treatment) [49/55]	28.1 (17.4)	-9.0 (2.1)	30.2 (20.5)	-5.6 (1.9)	-3.4 (-9.1, 2.2)
Visit T2-T3 (dexamethasone challenge) [58/58]	21.1 (14.7)	-10.6 (1.2)	24.4 (17.4)	-7.1 (1.2)	-3.5 (-6.9, -0.1)

[1] Patient numbers for placebo and ciclesonide groups, respectively.
[2] Treatment differences are expressed as placebo (mean change) minus ciclesonide (mean change) and are estimated from an ANCOVA model.

- As show in the PK studies, ciclesonide and its major metabolite, RMI, were hardly detected in plasma in all the Phase II/III studies (**Tables 2.7.3.10 and 2.7.3.11**). The highest detectable concentration in this set of studies was [redacted] in one patient following 25 mcg dose (**Table 2.7.3.11**). By contrast, at a dose of 200 mcg, the highest detectable concentration in one subject was only [redacted] The level of the ciclesonide and RMI in most of the samples were below the lower limit of quantification (LLOQ).

Table 2.7.3.10 Serum Levels of RMI in Pediatric Patients (ages 6-11) Treated With Ciclesonide (Study # MI-403).

Ciclesonide Dose	Number of subjects with levels above LLOQ	Highest recorded concentration
	RM1	RM1
25 mcg	0/19	<10
100 mcg	1/20	[redacted]
200 mcg	8/16	[redacted]

- Serum levels of RM1 was slightly higher that LLOQ in 38 of 189 samples. The highest observed level was [redacted] **Table 2.7.3.11**). Therefore, there was no sufficient number of detectable values to allow for PK/PD analysis.

Table 2.7.3.11 Serum Levels of RMI in Pediatric Patients (ages 2-5) Treated With Ciclesonide (Study # MI-405).

Dose	Number of subjects with levels above LLOQ	Highest recorded concentration
25 mcg	4/32	
100 mcg	8/32	
200 mcg	13/32	

- There was not relationship between the detectable levels of RMI and the changes in 24 hour urinary excretion (**Table 3.12**). As show in the table, only a few subjects had a detectable level of RMI at 2 and 5 hours after treatments.

Table 2.7.3.12. Urine Cortisol Change from the Baseline Versus Plasma Levels of Metabolites M1 Detected (Study # MI-405).

Dose		Pre-drug		Hour 2		Hour 5	
		BLQ	Detectable	BLQ	Detectable	BLQ	Detectable
Placebo	N	27		26		26	
	Mean	0.09		0.04		0.04	
	SD	4.36		4.44		4.44	
CIC 25 mcg	N	23		22		22	
	Mean	-3.9		-2.6		-3.7	
	SD	8.76		6.88		8.87	
CIC 100 mcg	N	23		22		22	
	Mean	-1.7		-1.9		-1.4	
	SD	5.19		5.35		4.46	
CIC 200 mcg	N	24		14		19	
	Mean	-4.5		-6.8		-5.7	
	SD	9.82		12.2		10.7	

CIC: Ciclesonide; BLQ: Below LLOQ (lower limit of quantitation)

2.7.4. Overall Summary of the Clinical pharmacology Data (Cross Studies Analysis):

Unlike orally inhaled route, intranasal ciclesonide has a low systemic availability and hence low effect on HPA axis. Ciclesonide is a pro-drug that become active only upon conversion to its active metabolite, RMI. Although RMI is further metabolized, according to the sponsor none of these metabolites has appreciable activity in comparison with RMI.

When administered intranasally, ciclesonide shows negligible absorption into the systemic circulation. In 3 separate studies adult and children following doses ranging from 25 to 800 mcg for up to 84 days, ciclesonide and RM1 were hardly detected in the plasma. The highest C_{max} value recorded for RMI in all studies was [redacted] The LLOQ of the assay is 25 pg/ml. Therefore, there was no adequate PK data or plasma profiles for either the parent or the metabolite as the majority of the samples were below LLOQ (**Table 2.7.4.1**)

Table 2.7.4.1. RMI Levels detected Across Studies Following Repeated Intranasal Administration of Ciclesonide.

Report no. (Study code)	Subjects	Daily Dose (mcg)	Number of days	Percent of subjects with detectable RM1 levels	Median Cmax (pg/mL) value[1]
202/2003 (TBN-CL-001)	Healthy	200	14	0%	< 10
	Healthy	400	14	67%	11.5
	Healthy	800	14	83%	17.0
	Adult SAR	800	14	50%	< 12.9
149/2005 (M1-403)	Pediatric PAR, 6-11 yr	25	84	0%	< 10
	Pediatric PAR, 6-11 yr	100	84	5%	< 10
	Pediatric PAR, 6-11 yr	200	84	50%	< 10.3
144/2005 (M1-405)	Pediatric PAR, 2-5 yr	25	42	13%	< 10
	Pediatric PAR, 2-5 yr	100	42	22%	< 10
	Pediatric PAR, 2-5 yr	200	42	41%	< 10

1 Calculation of median values is based on all C_{max} values including C_{max} values of < LLOQ (10 pg/mL)

Compared to orally inhaled ciclesonide at the same dose levels, the plasma concentrations of both the parent and the metabolite were negligible or almost zero in adults and children (**Tables 2.7.4.2 and 2.7.4.3 and Figure 2.7.4.1**). From this analysis, it can be concluded that overall the levels of the parent or RMI metabolite after oral inhalation is approximately 10 to 30 fold higher than after intranasal administration at the same dose or dose corrected data in adult and children.

Table 2.7.4.2. Mean RMI Cmax Values at Steady State and percent of Subject/Patients With Detectable RMI Levels After Intranasal and Inhaled Ciclesonide in Adults (Across Studies Analysis).

Route	Report no. (Study code)	Subjects	PK sampling[3]	Daily Dose (mcg)	Number (percent) of subjects with detectable RMI levels	Mean of Cmax (pg/mL) values above LLOQ[1]	Highest Cmax (pg/mL) recorded in any subject sampled
Oral inhalation	2/2004 (DMPK/USA/2003-0019)	Asthma adults (Study XRP1526 B-321)[2]	Sparse	100	28/28 (100%)	104.8	246.9
				200	27/27 (100%)	148.6	309.7
				400	26/26 (100%)	272.2	651.0
		Asthma adults (Study XRP1526 B-322)[2]	Sparse	100	18/18 (100%)	88.8	169.1
				200	18/18 (100%)	132.3	231.5
				400	17/17 (100%)	223.6	423.1
	211/2000 (FHP027)	Healthy adults	Extensive	400	18/18 (100%)	369.1	498.8
	178/2005 (CP-036)	Healthy adults	Extensive	400	14/14 (100%)	645.4	818.0
Intranasal	202/2003 (TBN-CL-001)	Healthy adults	Extensive	200	0/6 (0%)	< 10	<10
				400	4/6 (67%)	11.5	29.1

[1] Excludes all values below the LLOQ (10 pg/mL)

[2] This study report is not included in the current submission. The pharmacokinetic data are provided in [2/2004 [redacted] USA/2003-0019)]

[3] PK sampling approaches: sparse, 3 samples available; extensive: full (multiple) PK sampling profile (8 – 12 time points per day) available

Table 2.7.4.3. Mean RMI Cmax Values at Steady State and percent of Subject/Patients With Detectable RMI Levels After Intranasal and Inhaled Ciclesonide in Children (Across Studies Analysis).

Route	Report no. (Study code)	Subjects	PK sam-pling[1]	Daily Dose (mcg)	Number (percent) of subjects with detectable RMI levels	Mean C_{max} (pg/mL) values above LLOQ [2]	Highest C_{max} (pg/mL) value recorded in any subject sampled
Oral inhalation	2/2004 (DMPK/ USA /2003-0019)	Pediatric asthma, 4-11 yr (XRP1526B/ 341)[2,3]	sparse	50	4/7 (57 %)	65.2	103.2
				100	8/8 (100 %)	137.8	237.2
				200	9/9 (100 %)	180.9	356.7
		Pediatric asthma, 4-11 yr (XRP1526B/ 342)[2,3]	sparse	50	3/3 (100%)	72.8	145.6
				100	5/5 (100 %)	80.6	172.9
				200	5/5 (100%)	110.3	288.4
Intranasal	149/2005 (MI-403)	Pediatric PAR, 6-11 yr	sparse	25	0/19 (0%)	< 10	<10
				100	1/19 (5%)	13.1	13.1
				200	8/16 (50%)	19.9.	44.9
	144/2005 (MI-405)	Pediatric PAR, 2-5 yr	sparse	25	4/32 (13%)	26.4	64.5
				100	7/32 (22%)	17.4	36.1
				200	13/32 (41%)	19.8	39.1

[1] Mean maximal C_{max} values. Excludes all values below the LLOQ (10 pg/mL)
[2]Sparse PK sampling approach: 3 samples available for each patient
[3]This study report is not included in the current submission. The pharmacokinetic data are provided in [2/2004 USA/2003-0019)]

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 18

Figure 2.7.4.2. RMI Cmax Values in Healthy and asthmatic Adults (Across Studies Analysis, Excluding Values Below LLOQ).

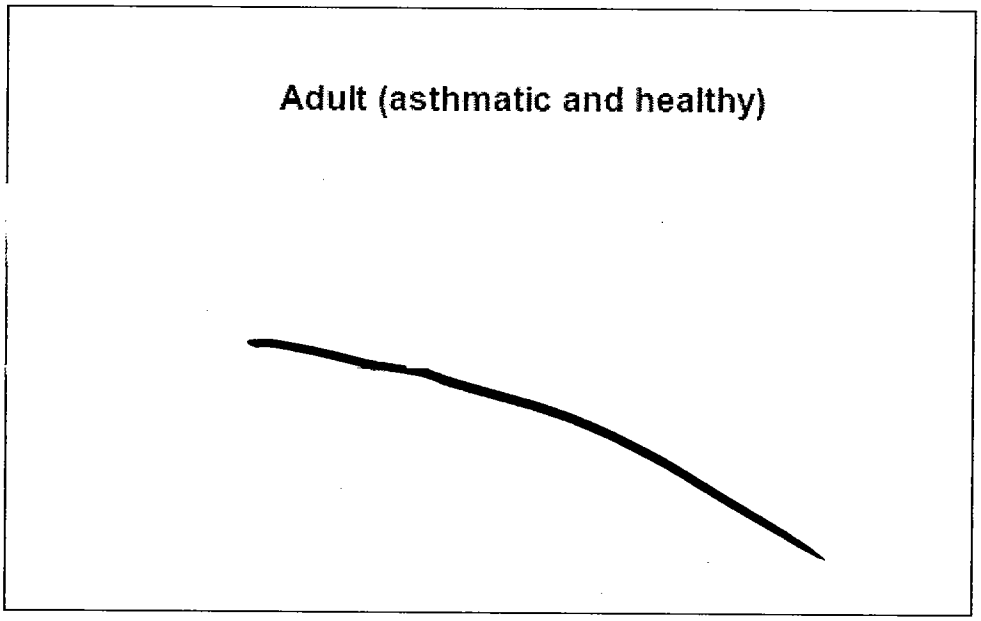
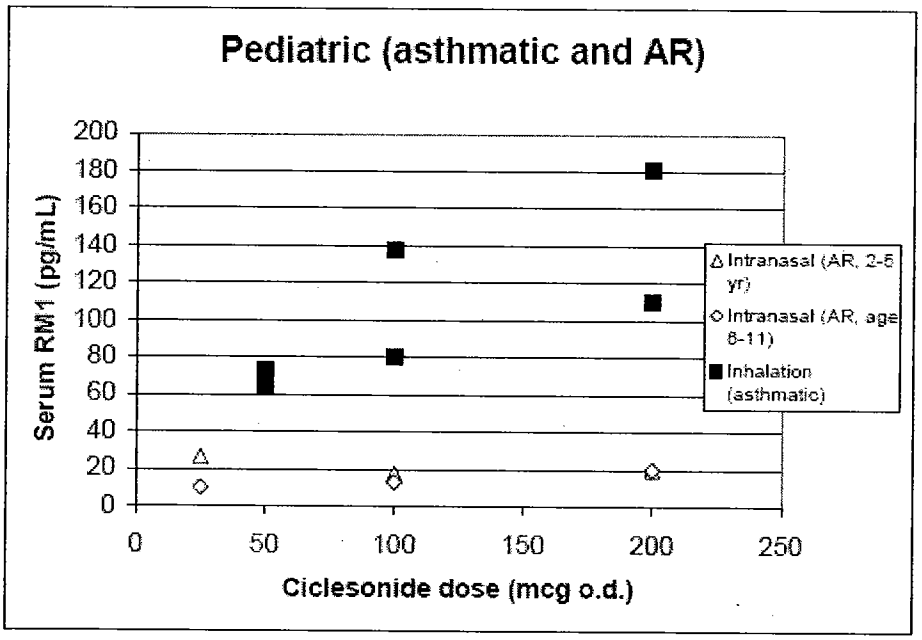


Figure 2.7.4.3. Mean RMI Cmax Values in Pediatric Patients Following intranasal and Inhalation Routes (Across Studies Analysis, Excluding Values Below LLOQ).



In terms of the effect on HPA axis, cross study comparisons shows a consistent trend for intranasal ciclesonide. Overall, there was little or no effect on plasma cortisol or urinary cortisol levels following intranasal ciclesonide compared to placebo (**Tables 2.7.4.4-2.7.4.6**). However, following oral inhalation, there was noticeable effect on both plasma and urinary cortisol suppression (**Tables 2.7.4.6-2.7.4.8**).

It is noteworthy that fluticasone propionate showed marked suppression of cortisole level. This would act as a positive control to validate the data in reference to intranasal route (**Table 2.7.4.7**). Additionally, according to the sponsor, orally (by mouth, not inhalation) and intravenously administered ciclesonide at doses ranging from 100 to 10,000 mcg did not significantly change serum cortisol levels (**Table 2.7.4.8**). However, the data from these referenced studies shown in **Table 2.7.4.8** was not reviewed to confirm the sponsor's conclusions.

It is of interest, that 800 mcg IV dose did not show suppression of cortisol (**Table 2.7.4.8**). If this data is true, then there should be no concern about 200 mcg dose given once or twice daily intranasally.

Table 2.7.4.4. Effect of Intranasaly Administered Ciclesonide on Serum/Plasma Cortisol Levels in Healthy Adults (Phase I studies).

Study/ Report Number	Daily ciclesonide doses (mcg)	No. of days	N	Cortisol in plasma or serum; assessment	Cortisol in plasma; diff. vs. placebo	Urinary cortisol (24 h collection period); diff. vs. placebo;
202/2003 (TBN-CL-001)	50, 100, 200, 400, 800[1] placebo	14	6[2]	24 h concentration profiles	Similar to placebo, no dose dependence	No apparent effect
61/2005 (TBN-15-001)	50, 200, 800	1	8[2]	24 h concentration profiles	Similar to placebo, no dose dependence	No apparent effect
	800	7	9[3]	24 h concentration profiles	Similar to placebo, no dose dependence	No apparent effect

[1] Two cohorts received this dose: 8 healthy subjects, then 8 subjects with allergic rhinits
[2] Per cohort; in each cohort, 6 subjects received ciclesonide and 2 placebo.
[3] n = 6, ciclesonide, n = 3 for placebo

Table 2.7.4.5. Effect of Intranasaly Administered Ciclesonide on Morning Serum/Plasma Cortisol (mcg/dl) in Allergic Rhinitis Patients (Phase III studies).

Study	Daily dose (mcg)	No. of Days on treatment	N	Morning plasma cortisol concentration		
				Baseline Mean (SD)[1]	LS Mean Change from Baseline [1]	Estimated Difference from Placebo (95% CI)[2, 3]
149/2005 (M1-403)	Placebo	84	47	10.8 (5.3)	0.39	--
144/2005 (M1-405)	Placebo	42	30	10.5 (4.7)	-0.03	--
146/2005 (M1-404)	Placebo	337	93	14.5 (7.3)	-0.4	--
149/2005 (M1-403)	25	84	51	10.1 (3.8)	0.01	-0.38 (-2.1, 1.3)
144/2005 (M1-405)	25	42	28	10.3 (3.3)	-0.15	-0.12 (-1.8, 1.6)
149/2005 (M1-403)	100	84	61	9.6 (4.6)	0.51	0.12 (-1.5, 1.7)
144/2005 (M1-405)	100	42	27	9.6 (4.2)	-0.39	-0.36 (-2.1, 1.4)
149/2005 (M1-403)	200	84	45	10.2 (4.8)	0.74	0.35 (-1.4, 2.1)
144/2005 (M1-405)	200	42	28	9.7 (3.7)	-1.07	-1.04 (-2.7, 0.7)
146/2005 (M1-404)	200	337	193	14.3 (7.3)	-1.1	-0.7 (-2.0, 0.6)

[1] Value on last day of treatment values used for calculation if patient terminated early from study
[2] Based on ANCOVA
[3] Differences presented here calculated as ciclesonide minus placebo (note: M1-404 report presented difference for placebo minus ciclesonide)

Appears This Way
On Original

Table 2.7.4.6. Effect of Intranasaly Administered Ciclesonide on 24 hour Urinary Free Cortisol Levels in Allergic Rhinitis Patients (Phase III studies).

Study	Daily dose (mcg)	No. of Days on treat-ment	N	24 –h Urinary free cortisol[1]		
				Baseline Mean (SD)	LS Mean Change from Baseline [2]	Estimated Difference from Placebo (95% CI)[3,4]
149/2005 (M1-403)	Placebo	84	33	22.8 (8.6)	0.1	--
144/2005 (M1-405)	Placebo	42	18	36.3 (18.0)	-6.8	--
146/2005 (M1-404)	Placebo	337	92	27.8 (14.7)	1.2	--
149/2005 (M1-403)	25	84	32	23.0 (8.2)	-2.3	-2.42 (-7.2, 2.4)
144/2005 (M1-405)	25	42	16	43.2 (17.7)	-13.5	-6.8 (-15.1, 1.5)
149/2005 (M1-403)	100	84	44	24.3 (11.0)	0.8	0.68 (-3.8, 5.2)
144/2005 (M1-405)	100	42	15	31.7 (11.9)	-14.0	-7.3 (-15.7, 1.2)
149/2005 (M1-403)	200	84	35	24.2 (12.2)	0.5	0.42 (-4.3, 5.2)
144/2005 (M1-405)	200	42	22	47.4 (41.8)	-6.9	-0.1 (-7.9, 7.7)
146/2005 (M1-404)	200	337	174	26.3 (14.5)	2.3	1.0 (-4.7, 6.7)

[1] Studies 149/2005 (M1-403 and 144/2005 (M1-405) corrected for creatinine; Study 146/2005 (M1-404) not corrected.
[2] Value on last day of treatment values used for calculation if patient terminated early from study
[3] Based on ANCOVA
[4] Differences presented here calculated as ciclesonide minus placebo (note: M1-404 report presented difference for placebo minus ciclesonide)

Appears This Way
On Original

Table 2.7.4.6. Effect of Intranasally Administered Ciclesonide on 24 hour Urinary Free Cortisol Levels in Allergic Rhinitis Patients (Phase III studies).

Total daily dose (mcg)	Dosing scheme	Study code (Report number)	No. of Days	N	24 –h cortisol, percent change from placebo[1], level of significance	Urine cortisol (24 h collection period); diff. vs. placebo; [2] level of significance
400	Single dose	117E/97 (FHP009)	1	12	-6%, NS	-1%, NS
500	250 b.i.d., 250 o.d. at last treatment day	117E/97 (FHP009)	7	12	+11%, NS	-2%, NS
800	800 in AM; 800 in p.m.; 400 b.i.d. AM and PM	151/98 (FHP013)	7	12	-2% to –7%, NS	Not assessed
1200	Single dose	117E/97 (FHP009)	1	12	-17%, significant	-4%, NS
1600	Single dose	172/97 (FHP015)	1	12	-4%, NS	No data
1600	800 b. i. d.	223/97 (FHP012)	7	11	--10%, NS	Not assessed
2000	1000 b.i. d. (o. d. on last treatment day)	117E/97 (FHP009)	7	12	-8%, NS	-4%, NS
3600	Single dose	117E/97 (FHP009)	1	12	-38%, significant	0%, NS

[1] Derived from point estimates for the ratio of respective treatments vs. placebo (using geometric mean values for each treatment arm); basis is cortisol concentration AUC calculations averaged for time (AUC/24h)

[2] Derived from point estimates for the ratio of respective treatments vs. placebo (using geometric mean values for each treatment arm) ; values not corrected for creatinine

Appears This Way
On Original

Table 2.7.4.7. Effect of Inhaled Ciclesonide and Fluticasone Propionate on Plasma Cortisol and 24 hour Urinary Cortisol Excretion (Across Studies Analysis)

Treat-ment (Total daily dose, mcg)	Dose adminis-tered[1]	Study code (Report number)	No. of Days	N[2]	Plasma cortisol, % change from placebo, ITT analysis	Cosyntropin stimulation, placebo comparison	Urinary free cortisol (24 h), de-crease from placebo, per protocol; e[3,4]
CIC (400)	400	49/2000 (FK1 107)	9	23	-11%, NS (per protocol)	Not done	-13%, NS
CIC (400)	400	65/2002 (XRP1526B–102)	84	37	Not done	NS	NS
CIC (800)	800	49/2000 (FK1 107)	9	23	-10%, NS (per protocol)	Not done	-9%, NS
CIC (800)	400 (b.i.d.)	65/2002 (XRP1526B–102)	84	39	Not done	NS	NS
CIC (800)	400 (b.i.d.)	71/2002 (XRP 1526B-103)	29	12	NS	NS	NS
CIC (1600)	800 (b.i.d.)	49/2000 (FK1 107)	9	23	-11%, NS (per protocol)	Not done	-16%, NS
CIC (1600)	800 b.i.d.	71/2002 (XRP 1526B-103)	29	12	NS	NS	NS
FP (1000)	500 (b.i.d)	49/2000 (FK1 107)	9	23	-29%, significant	Not done	-42%, significant
FP (1000)	500 (b.i.d.)	65/2002 (XRP1526B–102)	84	35	Not done	NS	Urinary cortisol reduced, significant
FP (1000)	500 (b.i.d.)	71/2002 (XRP 1526B-103)	29	12	NS	Not done	NS
FP (2000)	1000 (b.i.d.)	49/2000 (FK1 107)	9	23	-59%, significant	Not done	-67%, significant
FP (2000)	1000 (b.i.d.)	71/2002 (XRP 1526B-103)	29	12	-59%, significant	Not done	NS

[1] Once daily unless otherwise indicated; [2] N for primary comparison, where applicable; [3] Pair-wise comparisons of treatment vs. placebo based on differences in adjusted mean changes from baseline. Where percent changes are provided, they are derived from point estimates for the ratio of respective verum treatments vs. placebo (using geometric mean values); [4] Urinary cortisol excretion values based on excretion corrected for creatinine

CIC: ciclesonide; FP: fluticasone propionate; NS: Not statistically significant

Table 2.7.4.8. Effect of oral and intravenous Administration of Ciclesonide on Serum Cortisol levels and 24 hour Urinary Cortisol Excretion (Across Studies Analysis)

Study code (Report number)	Daily dose (mcg), route	No. of Days	N	Interval measured, serum/ plasma cortisol	Plasma cortisol, percent change from placebo, level of significance[1]	Urine cortisol (24 h collection period); change from placebo; level of significance[1]
187E/95 FHP005	100 – 6400 µg	1	2 x 8	24 h concentration profiles	-14% to +10% ; NS	-14% to +1% , NS
192/95 (FHP007)	6400, p.o.	1	6	Single time point (AM)	No placebo. No change from predose baseline.	No apparent effect
172/97 (FHP015)	10,000, p.o.	1	12[2]	24 h concnetration profile	-5% from placebo at baseline, 12 and 24 h, NS	No data.
172/97 (FHP015)	800, i.v.	1	12[2]	24 h concentration profile	0% , NS	No data
305/98 (FHP020)	4000 and 10,000 p.o.	1	5	12 h concentration profiles after morning dosing	-5% to -10%; NS	No data

[1] Where percent changes are provided they are derived from point estimates for the ratio of respective verum treatments vs. placebo (using geometric mean values)
[2] Per protocol analysis

Appears This Way
On Original

Conclusions:

Based on the integration of all data submitted to this NDA, the summary of the data submitted in the original [redacted] and the original clinical pharmacology review for [redacted] the following conclusions can be made:

- Ciclesonide and its active metabolite, RMI are negligibly detected in the plasma following all tested intranasal doses up 800 mcg.

- The levels observed after oral inhalation are approximately 10 to 30 fold higher than after nasal administration at the same dose or for dose corrected values.

- Since the drug and its metabolite are not significantly absorbed systemically there is little or no effect on HPA axis based on plasma or urinary excretion levels of cortisol.

- If orally administered dose of 10,000 mcg as well as 800 mcg intravenous administration did not significantly affect cortisol levels, then the 200 mcg intranasal dose would not be expected to have any effect on cortisol level. Furthermore, according to the original clinical pharmacology review on [redacted] the decrease in serum cortisol AUC at a dose of 800 mcg was 13%.

  However, it should be noted that the data for oral 10,000 mcg and 800 mcg IV administration were not submitted in the current NDA. Therefore, the latter conclusion depends on the validity of the oral and IV data and the study design in reference to cortisol level.

3.0 Labeling Comments:

The labeling comments will be incorporated directly into the sponsor's proposed label after the discussion with the review team

Appears This Way
On Original

8 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 19

4.2 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.3 Filing Memo:

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**222-004**	**Brand Name**	**N/A**
OCP (I, II, III)	**II**	**Generic Name**	**Ciclesonide**
Medical Division	**DPADP**	**Drug Class**	Glucocorticoid
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	**Indication(s)**	Seasonal and Perennial Rhinitis
OCPB Team Leader	**Emmanuel (Tayo) Fadiran, RP.h., Ph.D.**	**Dosage Form**	**Nasal Spray**
PM Reviewer		**Dosing Regimen**	**2 sprays (100 mcg) per nostril daily**
Date of Submission	**Dec 21, 2006**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review	**August 21, 2006**	**Sponsor**	**Altana**
PDUFA Due Date	**October 21, 2004**	**Priority Classification**	Standard
Division Due Date	Augest, 2006		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:	X	4		

Patients-				
single dose:	x	2		
multiple dose:		4		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	4		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	4		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		20		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time
QBR questions (key issues to be considered)		
Other comments or information not included above	**This is an extension of the original [redacted] for oral inhalation for the treatment of asthma. All PK related information in reference to oral inhalation, IV administration, drug-drug interactions studies and other relevant studies related to clinical pharmacology and PK were reviewed by OCP (See Dr. Sandra Suarez-Sharp dated September 20, 2004). Therefore, the focus of this NDA is on nasal route.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Sayed Al-Habet
8/28/2006 04:33:45 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
8/28/2006 04:38:36 PM
BIOPHARMACEUTICS
I concur.