

HPA-axis Evaluation

Blood was collected at 15 centers for cosyntropin stimulation testing. While the basal and post-stimulation cortisol levels at baseline in the ciclesonide subjects were higher than those measured in subjects taking QVAR the differences were small. Similarly, both basal and peak values increased over the year's follow-up in the ciclesonide group while both values for the QVAR group fell slightly. However, all of the 95% confidence limits for change in cortisol included zero (Table 66).

Table 66. Results of Cosyntropin Stimulation in Study 323/324LT

	Baseline		End of Study		Change from Baseline*
	N	Mean	N	Mean	
Pre-stimulation serum cortisol (µg/dL)					
Ciclesonide	48	14.6	43	15.1	1.0 (-1.0, 3.0)
QVAR	22	12.7	18	12.3	-0.2 (-4.1, 3.8)
Post-stimulation peak serum cortisol (µg/dL)					
Ciclesonide	48	23.5	44	25.1	1.8 (-0.0, 3.7)
QVAR	22	21.5	18	20.3	-0.5 (-3.9, 2.9)

* Difference between value at end-of-study and baseline

Defining normal HPA-axis function as a post-stimulation cortisol of at least 18 µg/dL, a basal level of >5µg/dL, and a degree of stimulation (peak-basal) > 7 µg/dL in females taking contraceptive, there were two subjects in each treatment group who shifted from normal to abnormal because of low peak values (ciclesonide peak: 5 and 17 µg/dL . QVAR peak: 12 and 17 µg/dL [Table 67]). One of the ciclesonide subjects also had a basal level <5µg/dL. This subject had been started on oral corticosteroids 10 days prior to cosyntropin stimulation. Four females (3 on ciclesonide and 1 on QVAR) had a low degree of stimulation. The total incidence of normal values at the beginning of the study and abnormal values at the end was 5 (10.2%) in the ciclesonide group and 3 in the (13.6%) QVAR group.

Table 67. Shift in HPA-axis Functioning in Study 323/324LT

	Number (%) of Subjects	
	Ciclesonide n=49	QVAR n=22
Normal baseline/normal end of study	31 (63.3)	9 (40.9)
Normal baseline/non-normal end of study	5 (10.2)	3 (13.6)
Non-normal baseline/normal end of study	7 (14.3)	3 (13.6)
Non-normal baseline/non-normal end of study	0	3 (13.6)
Missing	6 (12.2)	4 (18.2)

As in the previous studies the urinary cortisol were presented without any assessment of the quality of the specimen. The results presented show no change over the duration of the study.

1.5.2.3. Pulmonary function

Results from spirometry were available for 281 (188 ciclesonide and 93 QVAR) subjects. The baseline value (2.11 L) and the change from baseline (110 mL) was the same in both treatment groups.

1.5.3. Discussion and Conclusions

Subjects were randomized in a 2:1 ratio ciclesonide:QVAR, and they were well balanced for demographic and pulmonary function variables at baseline. The completion rate was equivalent in the two treatment groups (>66%), however, almost twice as many subjects withdrew from the ciclesonide arm for "consent withdrawn" than from the QVAR group. On the other hand, adverse events and lack of efficacy were somewhat more frequent in the QVAR group. The overall incidence of adverse events was similar in the two treatment groups (74% for ciclesonide and 79% for QVAR) and the most frequent events occurred in the respiratory tract and/or were infectious manifestations. As in the pivotal trials, the incidence of oral candidiasis was low in the ciclesonide-treated subjects (3.0% compared to 10.4% in the QVAR subjects). On the other hand, sinusitis NOS, occurred more than twice as frequently in the ciclesonide subjects. Headaches were more frequent in the QVAR subjects (15.6% vs 9.6% for ciclesonide), however the incidence of musculoskeletal complaints was similar in the two groups. There were 12 serious AEs in the ciclesonide group compared with 2 in the QVAR group. However, only 2 in each treatment group were likely to have been related to treatment (ciclesonide - 1 case each of pneumonia and mental depression; QVAR - 1 case each of asthma and abdominal pain). One subject treated with ciclesonide was found dead at home. The death certificate attributed the death to a myocardial infarction. However, there was no autopsy, and there is no way to assign attribution or to rule out an effect of study drug treatment.

The development of cataracts was not as frequent in this follow-up as in the pivotal trials. Using the applicant's summary, 14 (7.1%) of the ciclesonide and 8 (8.4%) of the QVAR subjects had worsening eye involvement. All of the subcapsular cataracts seen in this one year follow-up were in the subjects treated with ciclesonide.

Laboratory abnormalities were infrequent and mild. However, as in the prior studies, there appeared to be a higher incidence of abnormal liver transaminases in the ciclesonide-treated subjects (6.7%) compared with the QVAR-treated subjects (3.8%). Elevations of eosinophil counts occurred with similar frequency in both treatment groups.

Cosyntropin stimulation tests to assess the HPA-axis were completed at baseline and at the end of the study in 43 ciclesonide and 18 QVAR subjects. There were minimal changes during the trial in both treatment groups. A higher percentage of ciclesonide subjects had normal HPA-axis function at baseline and follow up (ciclesonide 63.3% and QVAR 40.9%). A higher percentage of QVAR subjects went from normal to abnormal during the trial (13.6% QVAR and 10.2% ciclesonide). However there was also a substantially higher

percentage of subjects in the QVAR group that had abnormal cosyntropin results at the beginning of the study (27.2% QVAR and 14.3% ciclesonide).

Pulmonary function showed a small improvement which was identical in the two treatment-groups.

1.6. Study 325

A phase III double-blind, parallel-group, multicenter, placebo-controlled study of ciclesonide MDI 640 mcg/day and 1280 mcg/day administered twice daily for 12 weeks to determine the effectiveness of ciclesonide to reduce oral corticosteroid (OCS) use in oral corticosteroid-dependent patients with severe persistent asthma.

1.6.1. Protocol

1.6.1.1. Administrative

Enrollment: July 26, 2001 – March 17, 2003

Clinical Director: _____

b(4)

Sites: 41 clinics in the United States and 19 in South Africa

1.6.1.2. Objective/Rationale

To compare the oral steroid-sparing effects of ciclesonide MDI at 320 mcg/day BID (80 mcg x 8 puffs) and 640 mcg/day BID (160 mcg x 8 puffs) with placebo in chronic oral corticosteroid-dependent patients with severe persistent asthma.

1.6.1.3. Study Design

This study consisted of a 2 to 4-week screening/run-in period during which time the investigator determined the lowest effective OCS dose for each subject. The lowest OCS dose was based on either a documented history of a failed attempt to lower the OCS dose within the previous 2 months or the investigator systematically lowered the OCS dose until the subject became symptomatic. The OCS dose was then increased to regain control of the asthma symptoms and this dose was maintained for at least 7 days prior to randomization. Subjects were randomized to one of the following regimens:

Placebo taken as 4 puffs BID

Ciclesonide 640 mcg/day ex-actuator, taken as 80 mcg x 4 puffs BID

Ciclesonide 1280 mcg/day, taken as 160 mcg x 4 puffs BID

The primary efficacy variable was the percent change from baseline to end of study in the oral prednisone dose.

1.6.1.4. Study Population

Inclusion Criteria

- Subjects 12 years old and above with a history of persistent asthma for at least 12 months.
- Prior Treatment:

- OCS at least every other day for 5 of the prior 6 months.
- ICS for the prior 6 months with a stable dose for the month prior to enrollment. This could be fluticasone, budesonide, beclomethasone, flunisolide or trimacinolone.
- Requirement for on demand β -agonists for the 2 weeks prior to enrollment.
- Pulmonary function:
 - FEV₁ between 40 and 80 % predicted
 - Reversibility of FEV₁ after albuterol of at least 12%. Historical documentation within 1 year acceptable.

Exclusion Criteria

- Any concurrent serious disease or pregnancy
- Asthma severity:
 - History of life-threatening asthma (intubation, respiratory arrest, or seizures) within 2 years.
 - 3 or more in-patient hospitalizations for 6 months or 1 in-patient hospitalization 1 month prior.
- Concomitant asthma medication:
 - Zafirlukast and zileuton not allowed: Montelukast allowed
 - Immunosuppressive therapy not allowed within 3 months of enrollment
 - Immunotherapy allowed if started more than 3 months prior to enrollment.

1.6.1.5. Medication

Run-in Determination of Lowest Effective Dose (LEF) of OCS

If the subject did not have a documented history of a failed attempt to lower their OCS dose, then they were to have the lowest dose determined within 1 month of randomization. All subjects were switched to prednisone as the maintenance OCS. At the first post-screening visit (2A) they were instructed to decrease the prednisone dose according to a pre-specified amount depending upon the maintenance dose. The subjects returned to the clinic in 1 week and were told to further reduce the dose of prednisone if all of the following conditions were met:

- FEV₁ \geq 80% of the actual FEV₁ at visit 2A & \geq 40% predicted
- No increase in asthma symptoms
- No increase in the number of nighttime awakenings
- No increase in the amount of albuterol used

If all of the above criteria were not met, the subject was told to increase the prednisone back to the previous level and that was declared the LEF. Asymptomatic subjects were instructed to decrease the prednisone again and return to the clinic in 1 week. These procedures were

repeated for up to 4 weeks. If an LEF had not been determined by that time or if the LEF was < 5 mg/day (< 10 mg every other day) the subject was characterized as a screen failure.

Tapering prednisone during the double-blind period

At weekly visits after randomization the subjects were evaluated for the ability to decrease the dose of prednisone on the basis of the following criteria:

FEV₁ \geq 80% of the actual FEV₁ at visit 2A & \geq 40% predicted

AM PEF \geq 80% of baseline mean AM PEF on all days since last visit

Mean nighttime awakenings \leq 50% increase over the baseline period

Albuterol use never $>$ 4 puffs/day above the baseline mean for 2 consecutive days or $>$ 12 puffs/day

No prednisone burst required since last visit

If all of the above criteria were met the subject was instructed to decrease the dose according to the schedule. If all of the criteria were not met, the investigator could either maintain the current dose, increase the dose by up to 10 mg / day according to the schedule, or give a 7-10 day burst of prednisone if symptoms were severe. If a subject required a second burst, they had to be discontinued from the study.

Other study procedures

Spirometry was performed at all visits. Diary symptoms were reviewed and adverse events elicited at all visits. Symptoms were classified as described in study 321 (pg 66 of this review). Serum was obtained for low-dose cosyntropin stimulation at baseline and week 12. Oropharyngeal exam was performed at baseline and end-of-study. If signs or symptoms of infection were present then a sample was sent for culture.

Reviewer: No ophthalmologic exam was performed other than that included in the routine physical exam.

1.6.1.6. Analysis

The primary efficacy endpoint was the percent change from baseline to end of study in prednisone dose in the ITT population. If the subject discontinued from the study due to an exacerbation of asthma, or due to lack of efficacy, the end-of-study prednisone dose was to be analyzed as 10 mg more than the prednisone dose at the time of the exacerbation. If the subject was withdrawn from the study for any reason other than efficacy, then the last post-randomization dose was to be carried forward.

Secondary endpoints included other measures of decreased prednisone dosage (percentage of subjects eliminating OCS use, percentage of patients with prednisone dose reduction below 5 mg QD, change from baseline to end of study in prednisone dose), baseline to end-of-study changes in pulmonary function (FEV₁, AM and PM PEF) and changes in symptoms (Asthma Severity Score, albuterol use, nighttime awakenings).

The primary endpoint was analyzed using analysis of covariance of the percent change from baseline to end of study in prednisone dose. The model included factors for treatment and pooled center, and covariates; gender, previous ICS, baseline prednisone dose, baseline FEV₁, and age. The baseline prednisone dose was the LEF as described above in 1.6.1.5. A step-down procedure was used whereby the 1280 mcg dose of ciclesonide was compared to

placebo and only after that was found to be significant, was the lower dose of ciclesonide compared to placebo. Subgroup analyses were performed for age, gender, race, previous ICS therapy (fluticasone/Advair vs any other ICS), baseline FEV₁ percent predicted, country of center.

1.6.2. Results

1.6.2.1. Study Population

Of 241 subjects screened, 141 were randomized (45 on placebo, 47 on ciclesonide-320 BID, and 49 on ciclesonide-640 BID). The disposition of the subjects is shown in Table 68. The overall withdrawal rate was lower in the active treatment groups (13.5%) compared to 31.1% of the placebo subjects. The most common reason for withdrawal was adverse events (23 [16.3%] overall) and lack of efficacy (22 [15.6%] overall). Most subjects who withdrew due to an “asthma exacerbation” were also categorized as withdrawing due to a “lack of efficacy”. However, the concordance was not complete. If each subject is categorized as withdrawing due to poor asthma control if they are categorized as either lack of efficacy or asthma exacerbation, then 13 (28.9%), 6 (12.8%), 4 (8.2%) of the placebo, ciclesonide-320 BID and ciclesonide-640 BID subjects withdrew because of worsening asthma. Diary-recorded compliance with the protocol was > 93% in all of the treatment groups. All of the 141 enrolled subjects were included in the safety population. One subject withdrew after the first dose of study medication because of non-serious bronchospasm. There were no follow-up measurements so the subject was not included in the ITT population.

Table 68. Disposition of subjects in study 325

	Placebo	Ciclesonide		Total
Drug dose, mcg	0	320 BID	640 BID	N/A
Randomized Subjects, n	45	47	49	141
Completed study, n(%)	31 (68.9)	39 (83.0)	44 (89.8)	114 (80.9)
Discontinued from study, n(%)	14 (31.1)	8 (17.0)	5 (10.2)	27 (19.1)
Reason for Discontinuation, n(%)				
Lack of efficacy	13 (28.9)	6 (12.8)	3 (6.1)	22 (15.6)
Adverse event	12 (26.7)	7 (14.9)	4 (8.2)	23 (15.6)
Consent withdrawn	0	4 (8.5)	5 (5.2)	5 (3.5)
Loss to follow-up	0	0	0	0
Protocol violation	0	0	0	0
Death	0	0	0	0
Poor compliance	0	0	0	0
Other	1 (2.2)	0	0	1 (0.7)

The demographic characteristics of the population are shown in table 69. There were substantially more women (68.6%) than men (31.4%), the mean age was 48.3 years, and more than 40% of the subjects were non-Caucasian. Clinical centers in South Africa

supplied more than 40% of the subjects, and 70.8% of these were non-Caucasian. The clinics in the United States had non-Caucasian populations of 34%. The mean duration of asthma was 24 years and the mean FEV₁% was 56%.

Table 69. Demographic and Clinical Characteristics of Subjects in Study 325

	Dose	Placebo	Ciclesonide		All
		0	320 mcg BID	640 mcg BID	N/A
Characteristic	N	45	47	49	141
Gender n(%)	Male Female	11 (24.4) 34 (75.6)	15 (31.9) 32 (68.1)	18 (37.5) 30 (62.5)	44 (31.4) 96 (68.6)
Age, years	Mean (SD) Range	48.3 (14.1) 12 – 73	48.3 (14.7) 13 – 74	48.3 (13.2) 17 – 70	48.3 (13.5) 13 – 74
Race, n(%)	White Black Asian Multiracial Other	23 (51.1) 7 (15.6) 3 (6.7) 10 (22.2) 2 (4.4)	29 (61.7) 6 (12.8) 4 (8.5) 7 (14.9) 1 (2.1)	26 (54.2) 11 (22.9) 4 (8.3) 7 (14.6) 0	78 (55.7) 17 (17.9) 11 (7.9) 24 (17.1) 3 (2.1)
Duration of Asthma (years)	Mean (SD) Range	26.8 (18.3) 1.7 – 62.8	21.6 (15.5) 1.8 – 64.1	22.5 (12.3) 1.8 – 50.0	23.6 (15.5) 1.7 – 64.1
Prednisone dose (Mg/day)	Mean (SD) Range	12.0 (6.5) 5- 25	13.6 (7.5) 5 -30	11.5 (6.6) 5- 30	12.4 (6.9) 5 -30
FEV₁, (L)	Mean (SD) Range	1.62 (0.43) 0.79 – 2.50	1.58 (0.55) 0.76 – 75.2	1.71 (0.51) 0.98 – 3.12	1.64 (0.50) 0.6 – 3.57
FEV₁, (% predicted)	Mean (SD) Range	56.4(10.6) 41.7 – 77.4	52.1 (10.0) 37.5 – 75.2	57.2 (13.0) 36.4 – 84.8	55.2 (11.5) 36.4 – 84.8

During the trial all subjects took short-acting β-agonists. There were 90 (63.8%) subjects who also took long-acting β-agonists, 61 (43.6%) who took xanthines and 55 (39%) who took leukotriene receptor antagonists.

1.6.3. Efficacy Outcomes

The primary outcome variable was the percent change from baseline in the daily use of OCS. At baseline the mean dose of prednisone was 12, 13.6, and 11.5 mg/day in the placebo, ciclesonide-320 BID, and ciclesonide-640 BID subjects respectively (Table 70). During the 12 week treatment period prednisone use increased by 4.21 % in the placebo subjects and decreased -47.4% and -62.4 % in the 320 mcg BID and 640 mcg BID ciclesonide groups respectively. The difference in the response between active treatment and placebo was significant for both active treatment groups (p-value = 0.003 and 0.001 for ciclesonide- 320 BID and ciclesonide-640 mg BID respectively.) The difference between the two ciclesonide

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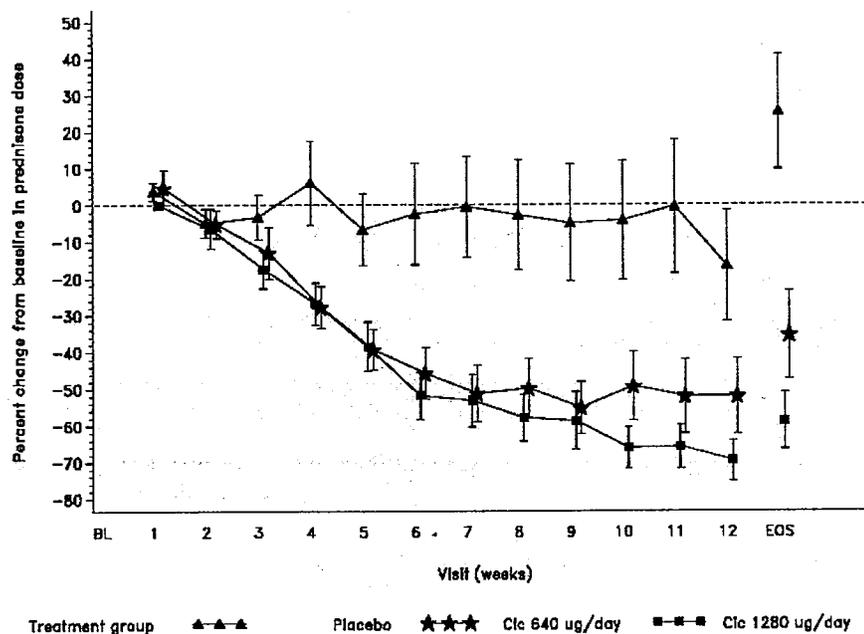
treatment group responses was not significant (-15.1 %, p-value = 0.27). The absolute change in prednisone dose was a secondary outcome and the results are displayed in the bottom half of Table 70. The results parallel those of the percent changes.

Table 70. Change in Prednisone Dose with Treatment in Study 325

	N	Baseline Mean Mg/day	Percent Change from Baseline LS Mean (SE)	Difference from Placebo LS Mean (SE)	95% CI
Placebo	45	12.0	4.21 (10.33)		
Ciclesonide-320 BID	47	13.6	-47.4 (10.10)	-51.6 (13.79)	-78.9, -24.3
Ciclesonide-640 BID	48	11.5	-62.54 (9.79)	-66.7 (13.81)	-94.1, -43.1
			Absolute Change from Baseline (mg/day)		
Placebo	45	12.0	0.72 (1.46)		
Ciclesonide-320 BID	47	13.6	-5.97 (1.43)	-6.7 (1.94)	-10.5, -2.8
Ciclesonide-640 BID	48	11.5	-8.00 (1.38)	-8.72 (1.95)	-12.6, -4.9

Figure 7. depicts the responses graphically. Subjects in both active treatment groups showed a gradual decrease in prednisone usage which was significant by 4 weeks of treatment.

Figure 7. Change in Prednisone Dose with Treatment in Study 325



The degree of prednisone dose reduction was comparable for both ciclesonide doses (Table 71).

Table 71. Categorical Description of Decrease in Prednisone Dose by Treatment Group in Study 325.

		Placebo	Ciclesonide	
Dose of ciclesonide		0	320 mcg BID	640 mcg BID
Randomized Subjects		45	47	48
Percent reduction in baseline prednisone dose	100%	5 (11.1)	14 (29.8)	15 (31.3)
	50-100%	10 (22.2)	16 (34.0)	22 (45.8)
	0-50%	3 (6.7)	5 (10.6)	4 (8.3)
	no change	3 (6.7)	1 (2.1)	2 (4.2)
	increase	24 (53.3)	11 (23.4)	5 (10.4)

Pulmonary function was analyzed as a secondary outcome variable. The FEV₁, AM PEF, and Daily albuterol use all deteriorated in the placebo subjects and improved slightly in the subjects receiving active treatment (Table 72). The Asthma Severity Score improved in the placebo and ciclesonide-1280 subjects, but it deteriorated slightly in the ciclesonide- 640 subjects.

Table 72. Secondary Efficacy Variables in Study 325

	Placebo	Ciclesonide*	
Dose ciclesonide, mcg/day	0	320 BID	640 BID
n	45	47	48
FEV ₁ (L)	-0.13	0.04 / 0.17	0.04 / 0.17
AM PEF (L/min)	-0.70	4.32 / 5.02	15.97 / 16.67
Daily albuterol use (puffs/day)	0.32	-0.07 / -0.39	-0.08 / -0.40
Total Asthma Severity Score	-0.24	.010 / 0.30	-0.31 / -0.07

** Two values are listed: 1) the difference between baseline and Week12 value and 2) the difference between placebo and ciclesonide for the baseline-Week12 change.*

1.6.4. Safety Outcomes

The mean exposure to study medication was 79.8 days with a range of 1 to 93 days. The exposure was greater in the active treatment groups than in the placebo subjects (72.7, 79.6, and 80.0 days in the placebo, ciclesonide-640, and ciclesonide-1280 subjects respectively).

1.6.4.1. Adverse Events

The overall incidence of adverse events was relatively high with more than 80% of the subjects reporting at least 1 event (Table 73). The most common organ involvement was the respiratory tract with 71.1%, 59.6%, and 49.0% of the subjects in the placebo, ciclesonide-640, ciclesonide-1280 groups reporting events respectively. The high rate in the placebo group is primarily due to asthma exacerbations, however, pharyngitis and rhinitis were also common in the placebo subjects. Infections and infestations were the next most frequent type of AE and the ciclesonide-1280 group had more cases of sinusitis and oral candidiasis than the placebo subjects. The incidence of oral candidiasis was dose-related as 0, 3 (6.4%), and 6 (12.2%) subjects in the placebo, ciclesonide-640, ciclesonide-1280 groups reporting events respectively. The incidence of most of the other AEs was distributed across the treatment groups with the exception of GI complaints which were more common in the placebo-treated subjects.

Table 73. Adverse Events Occurring in > 3% of Subjects Enrolled in Study 325

	Number (%) Subjects			
	Placebo	Ciclesonide		
Dose of ciclesonide, mcg	0	320 BID	640 BID	Total
n	45	47	49	96
Patients with treatment-emergent adverse events	40 (88.9)	40 (85.1)	39 (79.6)	79 (82.3)
Respiratory & Thoracic	32 (71.1)	28 (59.6)	24 (49.0)	52 (54.2)
Nasopharyngitis	8 (8.9)	3 (6.4)	6 (12.2)	9 (9.4)
Pharyngitis	6 (13.3)	3 (6.4)	2 (4.1)	5 (5.2)
Asthma aggravated	28 (62.2)	19 (40.4)	14 (28.6)	33 (34.4)
Bronchitis NOS	2 (4.4)	1 (2.1)	2 (4.1)	3 (3.1)
Nasal congestion	1 (2.2)	2 (4.3)	0	2 (2.1)
Rhinitis NOS	4 (8.8)	1 (2.1)	1 (2.0)	2 (2.0)
Hoarseness	1 (2.2)	3 (6.4)	0	3 (3.1)
Epistaxis	2 (4.4)	1 (2.1)	0	3 (3.1)
Infections	17 (37.8)	21 (44.7)	23 (46.9)	44 (45.8)
Upper Respiratory	9 (20.0)	9 (19.1)	9 (18.4)	18 (18.8)
Sinusitis	2 (4.4)	5 (10.6)	6 (12.2)	11 (11.5)
Influenza	0	1 (2.1)	2 (4.1)	3 (3.1)
Oral candidiasis	0	3 (6.4)	6 (12.2)	9 (9.4)
Pneumonia	0	3 (6.4)	0	3 (3.1)
Lower Respiratory	1 (2.2)	0	2 (4.1)	2 (2.1)
Cellulitis	2 (4.4)	1 (2.1)	0	1 (1.0)
Nervous System	6 (13.3)	10 (21.3)	10 (20.4)	20 (20.8)
Headache	6 (13.3)	8 (17.0)	6 (12.2)	13 (13.5)
Dizziness	2 (4.4)	3 (6.4)	2 (4.1)	5 (5.2)
Tremor	2 (4.4)	0	0	0

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	Number (%) Subjects			
	Placebo	Ciclesonide		
Dose of ciclesonide, mcg	0	320 BID	640 BID	All
Musculoskeletal	10 (22.2)	11 (23.4)	14 (28.6)	25 (26.0)
Back, neck, or limb pain	7 (15.4)	7 (14.9)	3 (6.1)	10 (10.4)
Arthralgia	1 (2.2)	0	7 (14.3)	7 (7.3)
Myalgia	2 (4.4)	1 (2.1)	1 (2.0)	2 (2.1)
Gastrointestinal	15 (33.3)	10 (21.3)	8 (16.3)	18 (18.8)
Diarrhea	2 (4.4)	2 (4.3)	0	2 (2.1)
Nausea	2 (4.4)	1 (2.1)	1 (2.0)	2 (2.1)
Gastroenteritis	1 (2.2)	2 (4.3)	2 (4.1)	4 (4.2)
Dyspepsia	2 (4.4)	3 (6.4)	0	3 (3.1)
Vomiting	6 (13.3)	0	2 (4.1)	2 (2.1)
Abdominal pain	2 (4.4)	0	1 (2.0)	1 (1.0)
Dry mouth	2 (4.4)	0	0	0
Toothache	2 (4.4)	0	0	0
General Disorders	5 (11.1)	5 (10.6)	8 (16.3)	13 (13.5)
Fatigue	2 (4.4)	3 (6.4)	4 (8.2)	7 (7.3)
Pain	1 (2.2)	2 (4.3)	1 (2.0)	3 (3.1)
Pyrexia	1 (2.2)	0	2 (4.1)	2 (2.1)
Skin and Subcu. tissue	6 (13.3)	3 (6.4)	6 (12.2)	9 (9.4)
Dermatitis	2 (4.4)	0	0	0
Pruritis	2 (4.4)	0	0	0
Eye Disorders	2 (4.4)	2 (4.3)	4 (8.2)	6 (6.3)
Conjunctivitis	0	1 (2.1)	2 (4.1)	3 (3.1)
Cardiac Disorders	4 (8.9)	0	0	0

Serious and Important Adverse Events

There were 8 serious adverse events but no deaths (Table 74). Five of the 8 serious AEs were due to asthma exacerbations, and three of these occurred in subjects receiving ciclesonide-320 BID. There was 1 additional serious AE in each of the treatment groups: placebo – cellulitis; ciclesonide-320 BID – pneumonia, and ciclesonide-640 BID – contusion after a fall. Other AE-related changes in management were distributed more-or-less evenly across the treatment groups.

Table 74. Other Clinically Relevant Adverse Events Reported in Study 325.

	Placebo		Ciclesonide	
	0	320 BID	640 BID	Total
Dose of ciclesonide, mcg				
n	45	47	49	96
All treatment-related AEs, n(%)	40 (88.9)	40 (85.1)	39 (79.6)	79 (82.3)
Serious treatment-related AEs, n(%)	2 (4.4)	4 (8.5)	2 (4.1)	6 (6.3)
Subjects with other significant AEs, n(%)	60 (44.4)	66 (49.6)	60 (46.9)	49 (37.4)
AE resulting in: n, (%)				
Discontinuation from study	22 (16.4)	5 (3.8)	9 (7)	5 (3.8)
Therapy temporarily interrupted	0	0	2 (1.6)	0
Other intervention	9 (6.7)	9 (6.8)	5 (3.9)	3 (2.3)
Treatment with counter active measure	56 (41.8)	66 (49.6)	57 (44.5)	49 (37.4)
Important laboratory abnormality	2 (1.5)	0	1 (0.8)	1 (0.8)

Adverse Events Leading to Withdrawal

The withdrawal rate due to adverse events was higher in the placebo than in the active treatment groups: 12 (26.7%), 7 (14.9%), and 4 (8.2%) in the placebo, ciclesonide-320 BID, and ciclesonide-640 BID groups. However all of these AEs were due to asthma aggravation or bronchospasm except for the case of pneumonia in the ciclesonide-320 BID group.

Abnormal Laboratory Values

There were no notable changes in any of the parameters of any of the liver function tests when comparing the baseline to end-of-study value.

Eosinophilia ($>1 \times 10^3$ cell/ μ L) was reported in 2 subjects in each of the ciclesonide treatment groups (Table 75). One subject in each of these groups had an abnormal value at the beginning of the study, but in all of the cases the end-of-study value was substantially higher (>0.77 cell/ μ L) than at baseline. There were no adverse events ascribed to eosinophilia. The

Table 75. Eosinophil Counts (cells/ μ L) for Subjects with End of Study Values $> 1.0 \times 10^3$.

Ciclesonide dose	Baseline	End of study
320 mcg BID	0.94	3.22
	0.27	1.04
640 mcg BID	2.06	3.27
	0.09	1.54

PCA value (increase of 0.37×10^3 cells/mL over baseline) was reached in approximately equal proportions in the three treatment groups: 7, 9.5, and 7.0% in the placebo ciclesonide-320 BID and ciclesonide-640 BID subjects.

Hyperglycemia (150 mg/dL) was reported as an adverse event in one placebo subject and was defined as clinically noteworthy ($> 2x$ ULN or 256 mg/dL) in one ciclesonide-320 BID subject.

HPA axis Evaluation

Cosyntropin stimulation testing was performed on 138 subjects prior to the start of double-blind treatment. Of these, 100 had baseline and end-of-study pre-stimulation values and 112 had baseline and end-of-study post-stimulation values available for analysis (Table 76). As expected in subjects who have been on maintenance oral corticosteroid therapy, the mean basal values for all the treatment groups were low, with the mean in both ciclesonide groups being below the minimum normal value. Similarly, the mean peak values were all below the lower limits of normal (18 mcg/dL). Between the baseline and end-of-study, the values of the pre-stimulation cortisol increased in all of the treatment groups with the ciclesonide-treated subjects showing greater increases than the placebo-treated subjects. The post-stimulation values fell in the placebo subjects during the study while they increased in both of the ciclesonide treatment groups.

Table 76. Low-dose Cosyntropin Stimulation Test in Subjects Enrolled in Study 325

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Pre-stimulation serum cortisol (μ g/dL)				
Placebo	32	6.04	1.33 (1.01)	
Ciclesonide-320 BID	36	4.89	3.58 (0.97)	2.25 (1.37)
Ciclesonide-640 BID	32	4.71	2.34 (1.01)	1.01 (0.48)
Peak post- stimulation serum cortisol				
Placebo	35	12.48	-0.16 (1.39)	
Ciclesonide-320 BID	37	12.24	5.28 (1.33)	3.43 (1.88)
Ciclesonide-640 BID	40	12.96	3.55 (1.30)	3.70 (1.89)

* LS Mean (SE)

The HPA-axis evaluation was complete (basal and peak levels at both baseline and end-of-study) in 97 subjects (Table 77). In the majority of these subjects, the cortisol values were low in each treatment group at both time periods. More subjects in the placebo group were normal at baseline, but more subjects increased from low to normal in the ciclesonide treatment groups. This resulted in a somewhat higher percentage of subjects in the ciclesonide-320 BID group (47.9%) with normal basal values at the end of the study than in the placebo (36.3%) or the ciclesonide-640 BID (34.6%) groups.

Table 77. Shifts in HPA-axis Function During Study 325

	Placebo	Ciclesonide	
		320 BID	640 BID
Dose of ciclesonide, mcg	0	320 BID	640 BID
N	45	45	48
Subjects with complete evaluation	33	34	30
Normal baseline/normal end of study	8 (24.2%)	6 (17.6)	6 (20.0%)
Normal baseline/Low end of study	2 (6.0%)	2 (5.9%)	1 (2.1%)
Low baseline/normal end of study	4 (12.1%)	10 (30.3%)	7 (14.6%)
Low baseline/Low end of study	19 (57.6%)	16 (47.1%)	16 (53.3%)

1.6.5. Discussion and Conclusions

This 12-week study designed to compare placebo with ciclesonide at 320 mcg BID and 640 mcg BID was conducted in subjects with severe (mean FEV1 = 55%), corticosteroid dependent asthma (mean dose of prednisone at randomization – 12,4 mg/day). Subjects were required to be on oral corticosteroids and ICS at least 6 months prior to screening, and to need inhaled β-agonists for asthma control. After randomization, protocol -driven procedures were used to find and maintain the lowest tolerable OCS dose. By the end of the study, the placebo subjects had increased their prednisone dose by 4.2 % while the active treatment subjects had decreased the dose of prednisone by 47.4 and 62.5 % in the ciclesonide-320 BID and ciclesonide-640 BID group respectively. In the placebo group, 11.1% of the subjects discontinued the use of prednisone entirely, while the percentages were 29.8% and 31.3% in the ciclesonide-320 BID and ciclesonide-640 BID groups respectively. At the same time, daily albuterol use increased in the placebo subjects while it decreased in both active treatment groups. As would be expected, the withdrawal rate, which was almost exclusively related to lack of efficacy, was higher in the placebo than the actively treated subjects.

Adverse events were common with 82.3% of the entire group registering at least one AE. However, the incidence was as high or higher in the placebo subjects as in the active treatment groups for most of the categories. The only notable exception to this generalization

was sinusitis and oral candidiasis. There was a clear dose response for both of these AEs with 12.2% of the ciclesonide-640 BID subjects reporting each of these events. Serious AEs were infrequent and there were no deaths. Laboratory abnormalities were infrequent and mild. As compared with the pivotal studies, where the subjects had not been taking oral corticosteroids previously, there were no notable changes in liver function. The only notable laboratory values were eosinophilia which occurred in 2 subjects in each of the active treatment groups.

As expected in a cohort of individuals on maintenance OCS, the baseline, pre-stimulation serum cortisol levels were low, and more than half of the values were below the lower limits of normal. Most of these remained abnormally low at the end of the study, however, more of the subjects had an increase basal cortisol level than had a decrease. There were no marked differences among the treatment groups.

1.7. Study # 102

A randomized, Double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose study of the potential effects of ciclesonide and fluticasone propionate (FP) on HPA-axis in adult asthma patients.

1.7.1. Protocol

1.7.1.1. Administrative

b(4)

Enrollment: February 15, 2001 – August 13, 2001

Clinical Director: _____

Sites: 20 U. S. centers

1.7.1.2. Objective/Rationale

To evaluate the potential effects of inhaled ciclesonide and fluticasone propionate on the HPA-axis function in asthmatic adults.

1.7.1.3. Overall design

This was a 12-week randomized, double-blind trial in subjects > 18 years of age with mild-to-moderate persistent asthma who were not taking corticosteroids and who had normal HPA-axis function at screening. Subjects were randomized to one of the following regimens:

Ciclesonide 320 µg (ex-actuator) QD (in the evening)

Ciclesonide 320 µg (ex-actuator) BID

Fluticasone propionate 440 µg BID

Compliance was ascertained through the subject diaries and by weighing the canisters before they were dispensed and again after they were returned. Subjects were asked to list puffs of medication discharged but not inhaled as well as those inhaled. Albuterol MDI was used for rescue therapy. Subjects were seen at 2, 4, 6, 8, 10, and 12 weeks after the initiation of therapy. HPA-axis was evaluated at 6 and 12 weeks.

1.7.1.4. Study Population

To be eligible, subjects had to be at least 18 years old, to have had mild to moderate asthma for at least 6 months, to require β -agonists at least two times a week, and to have an FEV₁ \geq 70% predicted. In addition, they had to have a normal HPA-axis as defined by a pre-cosyntropin stimulation serum cortisol \geq 5 μ g/dL, and a post-cosyntropin stimulation serum cortisol of at least 18 μ g/dL. Females on oral contraceptives and those taking hormone replacement therapy also had to have an increase in their post-stimulation peak cortisol of \geq 7 μ g/dL. Exclusion criteria included the presence of oral candidiasis within 30 days of enrollment, the use of systemic steroids within 6 months and intranasal steroids within 2 months of enrollment.

1.7.1.5. Study Procedures

Subjects were permitted to take albuterol, leukotriene receptor antagonists, cromones and short acting xanthines during the study. Atrovent, Serevent, Singulair, and sustained-release theophylline were withheld. Outcome measures were as follows:

- Serum cortisol before and after low (1 mcg) and high (250 mcg) -dose cosyntropin stimulation at baseline, 6, and 9 weeks.
- 24-hour urine cortisol (corrected for creatinine) collected at baseline, 6, and 12 weeks.
- Spirometry (FEV₁, FVC, FEF₂₅₋₇₅) at all visits.
- Adverse events, physical exam, laboratory safety exam.

1.7.1.6. Analysis Plan

The results were analyzed for an ITT population (all subjects who received at least 1 dose of study medication) and a per-protocol (PP) population. Subjects were excluded from the PP population for the following reasons:

- Abnormal HPA-axis function at screening (*see 1.7.1.4 above*),
- Deviation from the protocol -specified cortisol collection times,
- Ingestion of systemic corticosteroids or other forbidden medications,
- Failure to take the study medication for 5 consecutive days or $>$ 30% of the total days.

There were no exclusion criteria for the 24-hour urine collections and no separate urine cortisol population in the original application. In response to a request from the Agency the applicant re-analyzed the data after removing all of the subjects who had significant protocol violations that were related to incorrect dosage of study medication, significantly poor compliance, or ingestion of additional, non-approved corticosteroid. In addition to these criteria, the 24 hour urine values were reanalyzed after removal of any subject with a urine volume of $<$ 500 mL, a 24-hour creatinine excretion outside of the normal range, or a collection that was $<$ 22 hours or $>$ 26 hours long. (... \N21678\N_000\2004-08-04\hbio\study102\....pdf)

The primary statistical analysis compared ciclesonide-320 mcg once daily to fluticasone-440 mcg BID. If that comparison was significant then ciclesonide-320 mcg BID was compared

to fluticasone-440 mcg BID. The analytic technique was the ANCOVA with baseline pulmonary function age gender and baseline cortisol values as covariates.

1.7.2. Results

1.7.2.1. Study Population

Of 243 subjects screened, 164 were randomized (41 on placebo, 40 on ciclesonide-320 QD, 42 on ciclesonide-320 BID, and 41 on fluticasone-440 BID). Of the 164 randomized 148 (90.2%) completed the study. More subjects dropped out of the placebo and fluticasone groups (12.2% each) than the ciclesonide groups (7.5 and 7.1% in the ciclesonide-320 QD and ciclesonide-320 BID groups respectively). The most common reason for withdrawal was adverse events and this was more common in the placebo subjects (7.3%) than in the other groups (2.5%, 0, 4.9% in the ciclesonide-320 QD, ciclesonide-320 BID and fluticasone groups respectively). Protocol deviations occurred in 3 (7.3%), 5 (12.5%), 5 (11.9%), and 6 (14.6%) of the placebo, ciclesonide-320 QD ciclesonide-320 BID, and fluticasone subjects respectively.

Compliance with the treatment regimen was assessed by measuring the weight of the medication canisters. The incidence of a $\geq 90\%$ compliance by this measure was $>70\%$ for the placebo and ciclesonide- treated subjects. On the other hand, a $\geq 90\%$ compliance was found in only 56.1% of the fluticasone subjects.

The treatment groups were well balanced in terms of age, gender, and racial makeup (Table 78). The mean age was 37 years, there were 48% males and 52% females, and 85% of the entire population was Caucasian. The baseline FEV₁ and FEV₁% were mildly abnormal and also similar in the four treatment groups.

Table 78. Demographic Variables for Subjects in Study 102

		Placebo	Ciclesonide		FP	Total
	Dose (mcg)	0	320 QD	320 BID	440 BID	N/A
	n	41	40	42	41	164
Age, years	Mean (SD)	36.3 ± 12.2	36.9 ± 11.5	38.2 ± 12.7	36.4 ± 11.1	37.0 ± 11.8
	Range	18 - 78	18 - 60	18 - 72	18 - 68	18 - 78
Sex, n(%)	Male	16 (39.0)	23 (57.5)	20 (47.6)	20 (48.8)	79 (48.2)
	Female	12 (61.0)	17 (42.5)	22 (52.4)	21 (51.2)	85 (51.8)
Race, n(%)	White	35 (85.4)	35 (87.5)	37 (88.1)	33 (80.5)	140 (85.4)
	Black	5 (12.2)	3 (7.5)	4 (9.5)	4 (9.8)	16 (9.8)
	Asian	0	0	1 (2.4)	1 (2.4)	2 (1.2)
	Other	1 (2.4)	2 (5.0)	0	3 (7.3)	6 (3.7)
FEV₁, L	Mean (SD)	2.9 (0.61)	3.2 (0.76)	2.9 (0.68)	3.0 (0.73)	
	Range	1.4 - 4.2	1.9 - 4.9	1.5 - 4.6	1.0 - 4.6	
FEV₁%, %	Mean (SD)	81.7 (12.7)	84.2 (11.0)	82.3 (11.2)	81.7 (12.6)	
	Range	41.6-108.3	62.8-105.7	47.1-104.4	51.1-102.5	

1.7.2.2. HPA-axis Evaluation

HPA-axis function was normal in all but one of the subjects at baseline. One subject in the ciclesonide 320 BID group was a female on oral contraceptives who had a degree of cortisol stimulation (peak – baseline) of 0 µg/dL. The pre-stimulation and peak cortisol levels were normal at baseline in all of the subjects (Table 79).

Table 79. Results of Baseline Cosyntropin Stimulation in Study 102

		Placebo	Ciclesonide		FP
	Dose (mcg)	0	320 QD	320 BID	440 BID
Cortisol	n	41	40	42	41
Pre-stimulation, mcg/dL	Mean (SD)	15.6 (4.8)	13.5 (4.5)	13.5 (5.2)	13.7 (5.4)
	Range	6-29	5-23	7-31	5-30
Low-dose peak, mcg/dL	Mean (SD)	25.1 (5.2)	23.6 (4.4)	23.4 (5.1)	24.6 (5.0)
	Range	18-44	18-34	18-43	19-42
High-dose peak, mcg/dL	Mean (SD)	30.6 (5.4)	29.2 (4.7)	29.1 (4.6)	30.1 (5.6)
	Range	19-46	22-39	21-46	22-50

Follow-up cortisol measurements were available for 159 of the subjects. Of these, 148 follow-up samples were collected at the 84 ±2 day time point. The remaining 11 subjects had their end-of-study sample collected prior to the end of the 12- week follow-up and the last available value was carried forward. The peak post low-dose stimulation serum cortisol showed little change over the course of the study, although there was a greater fall in the mean value for the fluticasone-440 BID group (Table 80). According to the applicant's analysis the change from baseline was significant only in the fluticasone-440 BID group (95% CI = -3.8, -0.74). However, the comparison between fluticasone-440 BID and placebo

Table 80. Peak Serum Cortisol after Low-dose Cosyntropin Stimulation in the ITT Population*

	Placebo	Ciclesonide			FP
Dose, mcg	0	320 QD	320 BID	Total	440 BID
N	39	39	41	80	40
Baseline, mcg/dL	25.2 (5.3)	23.7 (4.4)	23.3 (5.2)	23.5 (4.8)	24.6 (5.1)
End-of-Study, mcg/dL	24.7 (7.1)	24.5 (5.6)	23.3 (4.5)	23.9 (5.1)	22.1 (6.3)
Change from Baseline, mcg/dL	-0.5 (4.9)	0.8 (5.4)	0.0 (6.1)	0.4 (5.8)	-2.5 (3.9)

* Results as mean (SE) µg/dL

did not reach statistical significance (p=0.085). The difference between fluticasone 440 BID and ciclesonide 320 QD was significant, but not the comparison fluticasone-440 BID and ciclesonide 320 BID (Table 81). In fact the two most extreme values for change in peak value over the study (-24 and -16 µg/dL) were seen in the ciclesonide 320 BID subjects.

Table 81. Comparison Among Treatment Regimens for the Difference Between Baseline and End-of-Study Value for Peak, Post-low Dose Cosyntropin Serum Cortisol.

	Difference Baseline-End of Study (mcg/dL)	95% CI
Cicles320-FP880	2.88	0.73, 5.04
Cicles640-FP880	1.78	-0.34, 3.91
Placebo-cicles320	-0.98	-3.18, 1.23
Placebo-cicles640	0.12	-2.04, 2.29
Placebo-FP 880	1.91	-0.27, 4.08
Cicles320-cicles640	1.10	-1.04, 3.24

The per protocol analysis was performed in 140 of the subjects (36, 34, 36, and 34 in the placebo, ciclesonide 320 QD, ciclesonide 320 BID, and FP 440 BID groups respectively). The results were very similar to those in the ITT population, however, in this calculation the difference in post stimulation cortisol between FP 440 BID and ciclesonide 320 BID was larger (2.59 mcg/dL [95% CI = 0.35, 4.83]).

There were 29 females who took oral contraceptives concurrently with the study drug (n=8, 7, 8, and 6 in the placebo, ciclesonide 320 QD, ciclesonide 320 BID, and fluticasone 440 BID groups respectively). These women had peak, post-stimulation serum cortisol levels that were higher than the other subjects at baseline and the change with treatment showed a great deal of variability (Table 82)

Table 82. Peak Post Cosyntropin Stimulation Serum Cortisol in Women Taking OCT* Compared with Other Subjects in Study 102

		Placebo	Ciclesonide		FP
	Dose, (mcg)	0	320 QD	320 BID	440 BID
	n	39	39	41	40
Baseline	On OCT*, n	8	7	8	6
	Mean (SD), µg/dL	30.6 (7.7)	26.4 (6.2)	25.4 (7.9)	32.0 (7.2)
	All Others, n	31	32	33	34
	Mean (SD), µg/dL	23.8 (3.3)	23.1 (3.8)	22.8 (4.3)	23.3 (3.4)
Change	On OCT, :n	8	7	8	6

with Treatment	Mean (SD) µg/dL	-0.9 (9.9)	4.4 (9.8)	-2.5 (11.2)	0.2 (5.6)
	All Others, n	31	32	33	34
	Mean (SD) µg/dL	-0.4 (2.7)	0.0 (3.7)	0.6 (4.1)	-3.0 (3.4)

** Taking oral contraceptives at the time of the study*

According to this post hoc sub-set analysis, ciclesonide at both doses does not cause higher HPA-axis suppression than FP (Table 83).

Table 83. Comparison Among Treatment Regimens for the Difference Between Baseline and End-of-Study Value for Peak, Post-low Dose Cosyntropin Stimulation Serum Cortisol Excluding Females Taking Oral Contraceptives.

	Difference Baseline-End of Study (µg/dL)	95% CI
Cicles 320 QD-FP 440 BID	2.87	1.33, 4.41
Cicles 320 BID-FP 440 BID	3.21	1.68, 4.74
Placebo-cicles-320 QD	-0.23	-1.88, 1.41
Placebo-cicles-320 BID	-0.57	-2.20, 1.06
Placebo-FP 440 BID	2.64	1.05, 4.23
Cicles-320 QD-cicles-320 BID	1.10	-1.04, 3.24

The results of the high-dose cosyntropin stimulation were similar to the results for the low dose stimulation test. The adjusted mean change from baseline of high-dose peak cortisol levels were 0.79, 1.01, -1.08, and -2.60 mcg/dL for the placebo, ciclesonide 320 QD, ciclesonide 320 BID and fluticasone 440 BID groups. The comparison with placebo was significant for fluticasone only (3.30, 95% CI [1.15, 5.61]).

At the end of the 12-week study one of the indices of HPA-axis function was abnormal in 2 (5.1%), 9 (11.3%), and 10 (25%) of the placebo, ciclesonide, and fluticasone-treated subjects respectively (Table 84). None of the placebo or ciclesonide-treated subjects had an abnormal basal (pre-stimulation value) while 3 (7.5%) of the FP subjects were abnormal. The peak serum cortisol was abnormal in 2 (5.1%), 1 (2.6%), 5 (12.2%), and 8 (20.0%) of the placebo, ciclesonide-320 QD, ciclesonide-320 BID and FP 440 BID subjects respectively.

Table 84. Subjects with Abnormal Low-dose Consyntropin Tests in Study 102

	Placebo	Ciclesonide			FP
Dose	0	320 QD	320 BID	Total	440 BID
N	39	39	41	80	40
Non-normal prestimulation (<5 µg/dL), n(%)	0	0	0	0	3 (7.5)
Abnormal Basal Values, Mcg/dL	---	---	---	---	4 2 1
Non-normal peak (<18 µg/dL), n(%)	2 (5.1)	1 (2.6)	5 (12.2)	6 (7.5)	8 (20.0)
Abnormal Peak Values after low dose stimulation, Mcg/dL	17 9	16	17, 17 16,16 15		17, 17, 17, 17 16 15 10

In the per-protocol population for the 24-hour urine collections there were 94 subjects (23 in the placebo, 26 in the ciclesonide-320, 25 in the ciclesonide 640, and 20 in the fluticasone 880 group). The geometric mean ratio of the uncorrected free cortisol and the 90% confidence intervals of the ratios are shown in Table 85. The subjects treated with ciclesonide 320 mcg daily had less suppression than the placebo subjects; the ciclesonide-640 and flutiasonce-880 subjects had more suppression than the placebo subjects. However, the ratios for the high-dose ciclesonide and fluticasone subjects were of the same order of magnitude.

Table 85. Geometric Mean Urine Free Cortisol in the Per-protocol Population in Study 102

Comparator Drugs	Ratio of Geometric Mean Free Cortisol	90% Confidence Interval
Ciclesonide 320 mcg/day vs placebo	1.24	0.96, 1.60
Ciclesonide 640 mcg/day vs placebo	0.99	0.76, 1.30
Fluticasone 880 mcg/day vs placebo	0.83	0.63, 1.09

One subject in the fluticasone-440 BID group was withdrawn from the study due to a low basal cortisol. This was a 36 year old male with a baseline pre and post-stimulation cortisol of 11 and 22µg/dL respectively. On day 43 the values were 1 and 15 µg/dL and the subject was withdrawn from the study. On day 71 the pre-stimulation value was 0 and on day 102 it

was 10. There were no follow-up post-stimulation values. One subject in the ciclesonide 320 BID group had elevated cortisol levels. At week 6 the pre and post-stimulation values were 37 and 51 µg/dL respectively. By the 12-week measurement the values were back to the baseline value of 12 and 34 µg/dL.

1.7.2.3. Pulmonary Function

The changes in FEV₁ over the 12 week treatment period were small and approached clinical significance only for fluticasone (-30, 80, 50, and 170 mL for placebo, ciclesonide 320 QD, ciclesonide 320 BID, and FP 440 BID respectively).

1.7.2.4. Safety

Assessing exposure by patient diary resulted in >90% of the subjects in all of the groups claiming to have taken > 90% of the medication. However, assessed by the weight of the medication canisters, 73.2%, 45.0%, 64.2%, and 46.4% of the subjects in the placebo, ciclesonide-320 QD, ciclesonide-320 BID, and fluticasone 440 BID groups received >90% of the prescribed medication. By canister weight >90% of the subjects received >80% of the medication except for the FP group. Only 75.7% of the subjects received >80% of the FP doses.

Adverse Events

An adverse event was reported by 35 (85.4%), 53 (64.6%), and 32 (78.0%) of the placebo, ciclesonide, and fluticasone-treated subjects respectively (Table 86). While there were more subjects treated with ciclesonide who complained of throat pain (13.4%) compared with 12.5% on placebo and 1 (2.4%) on fluticasone, there were substantially more subjects in the fluticasone group with oral candidiasis and upper respiratory tract infections. Only 2 of the 80 subjects treated with ciclesonide developed oral candidiasis compared with 9 (22%) of the fluticasone-treated subjects. Similarly, 5 (12.2%) of the fluticasone subjects complained of an upper respiratory tract infection compared with 2(2.4%) of the ciclesonide subjects. Headache was more common in the fluticasone subjects (17.1%) than the ciclesonide subjects (13.4%), but it was less frequent than in the placebo subjects (19.5%). On the other hand asthma aggravation was notable only in the placebo subjects (5 [12.2%]) compared with 1.2% of the ciclesonide subjects and 2.4% of the fluticasone subjects.

Table 86. Adverse Events Reported by Subjects Enrolled in Study 102*

Dose (mcg)	Placebo	Ciclesonide			FP
		320 QD	320 BID	Total	
n	39	39	41	80	40
All AEs	35 (85.4)	25 (62.5)	28 (66.7)	53 (64.6)	32 (78.0)
Headache	8 (19.5)	5 (12.5)	6 (14.3)	11 (13.4)	7 (17.1)
Throat pain	5 (12.5)	5 (12.5)	6 (14.3)	11 (13.4)	1 (2.4)
Back pain	1 (2.4)	4 (10.0)	2 (4.8)	6 (7.3)	3 (7.3)

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	Placebo	Ciclesonide			FP
		320 QD	320 BID	Total	
Dose, mcg	0	320 QD	320 BID	Total	440 BID
Sinusitis	0	4 (10.0)	2 (4.8)	6 (7.3)	0
Nasopharyngitis	4 (9.8)	2 (5.0)	3 (7.1)	5 (6.1)	4 (9.8)
Dyspepsia	2 (4.9)	3 (7.5)	1 (2.4)	4 (4.9)	0
Arthralgia	2 (4.9)	0	3 (7.1)	3 (3.7)	1 (2.4)
Nausea	3 (7.3)	1 (2.5)	1 (2.4)	2 (2.4)	2 (4.9)
Ear pain	3 (7.3)	0	2 (4.8)	2 (2.4)	0
Hoarseness	0	2 (5.0)	0	2 (2.4)	3 (7.3)
Myalgia	3 (7.3)	1 (2.5)	1 (2.4)	2 (2.4)	0
Oral Candidiasis	0	1 (2.5)	1 (2.4)	2 (2.4)	9 (22.0)
URI	2 (4.9)	1 (2.5)	1 (2.4)	2 (2.4)	5 (12.2)
Asthma aggravated	5 (12.2)	0	1 (2.4)	1 (1.2)	1 (2.4)

* All but dose and n are n (%)

There were no deaths reported. Of the adverse events reported, the intensity was classified as severe in 4(9.8%), 7 (17.5%), 5 (11.9%) and 4 (9.8%) of the placebo, ciclesonide-320 QD, ciclesonide-320 BID and fluticasone-440 BID subjects. One serious AE was reported in a 45 year-old female who had taken ciclesonide 320 BID who develop ischemic colitis 16 days after completion of the protocol. The event resolved after 5 days in the hospital.

Laboratory other than HPA-axis

Abnormal results of liver function tests were unusual and distributed evenly across the treatment groups. One patient in the ciclesonide-320 BID group had an elevation of ALT (33 U/L at baseline to 71 U/L at 12 weeks) that was reported as an adverse event. Two patients in the fluticasone-440 BID group had elevations of ALT that reached the PCA level (above normal value for the laboratory and an increase of at least 28 U/L). The baseline and peak values were 34 and 30 U/L and 68 U/L. Two patients in the ciclesonide-320 QD group had values for bilirubin that reached the PCA level. These values were 17 and 9 µmol/L at baseline and 27 and 22 µmol/L at 12 weeks. The shift tables were unremarkable.

There were no remarkable hematology values.

1.7.3. Discussion and Conclusions

This 12 week study compared the effect of ciclesonide, and fluticasone on the on HPA axis function in subjects with mild to moderate asthma. All subjects had normal pre- and post-cosyntropin stimulation serum cortisol levels at baseline. After 12 weeks of treatment, a higher percentage of the fluticasone-treated subjects (25%) had abnormal values for HPA function than subjects treated with placebo (5.1%), ciclesonide-320 QD (5.1%) or ciclesonide-320 BID (17.1%). The mean decrease in the post-stimulation cortisol was

statistically greater in the fluticasone group, however the absolute difference was small (2.88 µg/dL between fluticasone-440 BID and ciclesonide-320 QD). The differences between fluticasone 440 BID and ciclesonide 320 BID were not statistically significant. In addition, these differences in apparent HPA-axis suppression must be assessed jointly with the results of the efficacy testing. Fluticasone at 440 mcg BID produced an improvement in FEV₁ that was more than double the response after treatment with either dose of ciclesonide. The change in FEV₁ over the 12 weeks was -30, 80, 50, and 170 mL for placebo, ciclesonide 320 QD, ciclesonide 320 BID, and FP 440 BID respectively. While FEV₁ was not a primary outcome variable in this study, the results are consistent with the results of the efficacy trials. As in the pivotal trials, ciclesonide did not significantly improve pulmonary function in these mild to moderate asthmatics who had not been previously treated with ICS.

Adverse events were mild and similar to those seen in the other studies. Again, there were very few candida infections in the ciclesonide-treated subjects compared with an incidence of 22% in the fluticasone-treated subjects. The routine laboratory tests were unremarkable.

1.8. Study FK1 103

Effect of inhaled ciclesonide on hypersensitivity to AMP in subjects with bronchial asthma.

1.8.1. Protocol

1.8.1.1. Administrative

Enrollment: July 3, 1998 – December 12, 1998

Clinical Director: H. Magnussen, MD

Sites: 1 site in Germany. This protocol was sponsored by Byk Gulden Pharmaceuticals

1.8.1.2. Objective/Rationale

To compare the effect of 2 weeks treatment with ciclesonide and budesonide (each given as 400 [ex-valve] in the morning) on hypersensitivity to adenosine monophosphate (AMP) in subjects with mild to moderate allergic asthma. Information would also be obtained on safety and efficacy.

1.8.1.3. Study Design

This was a blind co-investigator randomized crossover study to compare the effects of two inhaled corticosteroids. After a baseline period of 3 to 14 days subjects were treated for two weeks with one of the following

Ciclesonide 400 µg/day (200 µg x 2 puffs Q AM via MDI) (320 mcg ex-actuator)

Budesonide 400 µg/day (200 µg x 2 puffs Q AM via Turbohaler™)

After the first treatment period there was a 3 to 8-week washout period and then a second two-week treatment period with the alternative medication. The AMP challenge and physiologic testing was performed immediately prior to and at the end of the treatment period. Because of the differences in the delivery systems, the blind was maintained by having the technician who performed the testing blinded as to the treatment regimen.

1.8.2.2. Efficacy

For the PC₂₀FEV₁ the baseline values for the two treatments were comparable (3.39 mg/mL for ciclesonide and 4.58 for budesonide). At the end of the two-week treatment period the PC₂₀FEV₁ had increased to 19.99 mg/mL (95% C.I. = 2.98, 8.36) for ciclesonide and to 32.48 mg/mL (95% C.I. = 4.0, 12.17) for budesonide. The change with treatment was significant for both treatment groups (p < 0.05) and there was no difference between the two groups. The improvement in doubling doses was 2.36 for ciclesonide and 2.82 for budesonide. The changes are depicted graphically in Figures 6 and 7. As can be seen in Figure 7, one subject in each group did not respond to treatment.

Figure 8. Response in PC₂₀FEV₁ (AMP) After Two Weeks of Treatment with 400 µg/day Ciclesonide or Budesonide.

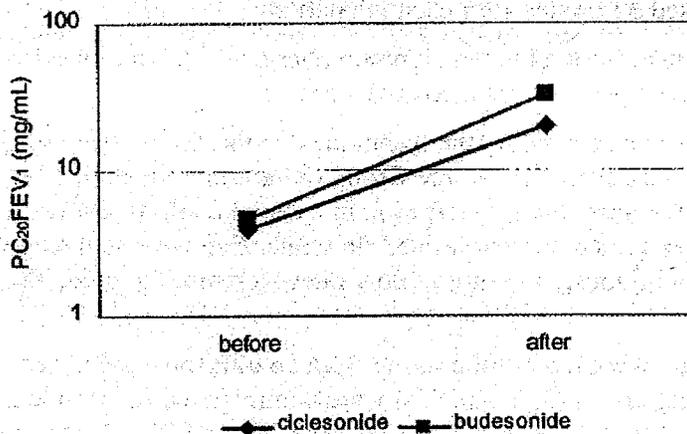
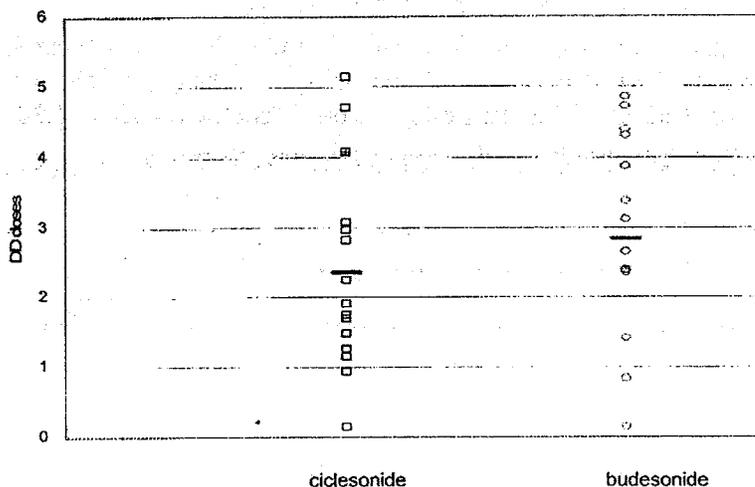


Figure 9. Change in Doubling Dose for PC₂₀FEV₁ (AMP) After Two Weeks of Treatment with Ciclesonide or Budesonide.



1.8.1.4. Study Population

The subjects adult asthmatics, 18-45 years of age. They were excluded if they had taken ICS (>1 mg/day) within 6 months or up to 1 mg/day within 2 months. The FEV₁ had to be > 60% predicted and they had to have had a positive response to AMP (PC₂₀ FEV₁ < 60 mg/ml). In addition they had to have a positive prick test, be non-smokers, and not be pregnant.

1.8.1.5. Study Procedures

The AMP challenge was started with 5 slow inspirations from functional residual capacity of a 0.39 mg/ml solution. The total output was 75 µL per five nebulizations. Doubling concentrations were inhaled unless the FEV₁ fell by more than 10%. The challenge was terminated if the FEV₁ fell by 20% or a concentration of 400 mg/ml was reached. Lung function was assessed 3 minutes after each inhalation.

Skin prick tests were performed to ten common allergens. A 3 mm weal was considered positive, and histamine was used as a positive control.

Nitric oxide (NO) was measured by the technique of Silkoff et al (Silkoff, 1997) and the recommendations of the ERS Task Force Group (Kharitonov S, et al, 1997). After a forced expiration through the nose, the subjects took in a deep breath of NO-free air through the mouth. They then expired at predetermined flow rates that were set using varying expiratory resistances. The continuously monitored flow rates were used to guide the subject's respiratory pattern.

Sputum was induced using hypertonic saline from an ultrasonic nebulizer. Three inhalations of increasing concentrations (3, 4, and 5%) were administered for 10 minutes each unless the FEV₁ fell more than 10%. If the FEV₁ fell between 10 and 20% the concentration of the subsequent saline inhalation was not increased. If the FEV₁ fell by >20% the induction was terminated. Sputum was collected after each inhalation for differential cell counts. Spirometry and adverse events were elicited at each visit.

1.8.1.6. Analysis Plan

The primary outcome measure was the change in PC₂₀ FEV₁ (AMP) between start and end of treatment period in the ITT population. The changes in the per-protocol population were also measured. It was estimated that 12 subjects would provide a power of 80% to detect differences between treatments in the order of a factor of 8.

1.8.2. Results

1.8.2.1. Study Population

Eighteen subjects were screened and 15 completed all of the assessments. Four subjects were excluded from the per-protocol analysis because they took forbidden medications during the treatment period. There were 7 females and 8 males age 20 – 48 years of age (median=33 years). They all had at least 1 positive skin test and all were healthy except for concomitant rhinitis in some. The baseline FEV₁ was 3.51 L or 99% predicted. The PC₂₀FEV₁ (AMP) was 5.14 mg/mL

The FEV₁ was available at all time points for only 7 subjects. The baseline FEV₁ increased from 3.54L to 3.69 L in the ciclesonide subjects and from 3.26 to 3.52 in the budesonide subjects.

For the expired NO testing the flow rates ranged from 18-207 ml/s. At baseline the corresponding exhaled NO values ranged from 27-166 ppb for ciclesonide and 23-143 ppb for budesonide. At the end of the study the values had fallen to 15 – 80 ppb for ciclesonide and to 16 – 94 ppb for budesonide.

At baseline the mean sputum eosinophil counts were 11.8 and 12.5 cells / mm³ (median = 6.7 and 6.32) for ciclesonide and budesonide respectively. After two weeks of treatment the mean eosinophil counts were 7.3 and 9.1 cells / mm³ (median = 5.5 and 3.2) for ciclesonide and budesonide respectively.

1.8.2.3. Safety

Adverse events were reported in 11/15 (73%) subjects during treatment with ciclesonide and in 4/16 (25%) subjects treated with budesonide. The applicant attributed the difference in the adverse event rate to the pollen season. The adverse events are listed in table 87.

Table 87. Adverse Events Reported During a 2-week Treatment Period with Ciclesonide or Budesonide

Body system	Adverse events reported	ciclesonide (n=15 patients)	budesonide (n=16 patients)
body as a whole	flu syndrome	n=1	n=1
cardiovascular system	migraine		n=1
nervous system	headache	n=3	n=1
	dry mouth	n=1	
digestive system	sore throat	n=2	
respiratory system	dyspnea	n=1	
	asthma	n=1	
	rhinitis	n=3	
	sputum increased	n=1	n=1
special senses	conjunctivitis	n=1	

1.8.3. Discussion and Conclusions

This crossover study described the physiologic responses to 2 weeks of treatment with ciclesonide and budesonide, both at 400 µg/day (ex-valve). Both drugs increased the PC₂₀ FEV₁ (AMP), increased the FEV₁, decreased exhaled NO, and decreased the eosinophils in induced sputum. Small differences between the treatment groups were not clinically significant. There were almost 3 times as many adverse events in the ciclesonide group than in those treated with budesonide. The adverse events were the same ones seen frequently in this patient population.

1.9. Study #341

A phase III double-blind, placebo-controlled, parallel-group, multicenter, efficacy, safety and dose response study of ciclesonide metered dose inhaler 50 mcg/day, 100 mcg/day, and 200 mcg/day ex-valve (40 mcg, 80 mcg, and 160 mcg/day ex-actuator) administered once daily for 12 weeks in the treatment of children with persistent asthma.

1.9.1. Protocol

1.9.1.1. Administrative

Enrollment: May 22, 2001 – February 10, 2003

Clinical Director: _____

b(4)

Sites: 46 sites in the United States and 21 sites in Mexico

1.9.1.2. Objective/Rationale

To compare the efficacy, safety, and dose response of once-daily administration of 3 doses of ciclesonide MDI, 50 mcg/day ex-valve (40 mcg/day ex-actuator), 100 mcg/day ex-valve (80 mcg ex-actuator), and 200 mcg/day ex-valve (160 mcg/day ex-actuator), to placebo in children with mild, moderate, or severe persistent asthma.

1.9.1.3. Study Design

The design of this study is similar to the design of study 321 except for the age of the subjects, the pulmonary function inclusion criteria, and doses of ciclesonide used. Briefly, subjects 4-11 years of age with mild to severe asthma who met screening criteria were treated in a single blind fashion with placebo for 5 to 21 days prior to randomization. Randomization was carried out within each of two strata based on asthma therapy for the last 30 days prior to screening. Stratum I subjects had been treated with any combination of inhaled corticosteroids (ICS), leukotriene inhibitors, and/or cromones. Stratum II subjects had been treated with any combination of short and long acting β -adrenergic agonists and/or theophylline, but not with inhaled corticosteroids or leukotriene inhibitors.

The study included 526 patients randomized to receive one of the following regimens:

Placebo once daily, taken as 1 puff in the morning,
Ciclesonide 40 mcg once-daily, taken as 1 puff (40 mcg/puff) in the morning
Ciclesonide 80 mcg once-daily, taken as 1 puff (80 mcg/puff) in the morning
Ciclesonide 160 mcg once-daily, taken as 1 puff (160 mcg/puff) in the morning

All medications were formulated as HFA-134a multi-dose inhalers (MDI). Albuterol MDIs were provided for rescue. Outcome variables included pulmonary function, symptoms, and adverse events. Eight centers collected serum cortisol after cosyntropin stimulation, urine for 24-hour free cortisol excretion, and blood for PK analysis.

1.9.1.4. Study Population

Patients were stratified on the basis of asthma treatment for the last 30 days prior to screening

- Stratum 1- any combination of the following:

- Inhaled corticosteroids (dose not to exceed 200 mcg/day fluticasone DPI, 440 mcg/day fluticasone pMDI, 250/50 bid for fluticasone/salmeterol combination DPI, or 800 mcg/day budesonide, 400 mcg/day beclomethasone, 1000 mcg/day flunisolide, or 1200 mcg/day triamcinolone).
- Leukotriene receptor antagonists
- Cromones
- Stratum 2 – any combination of the following:
 - Short acting β -agonists
 - Long acting β -agonists
 - Methylxanthines

Inclusion criteria

- 4-11 years of age
- Diagnosis of mild, moderate, or severe persistent asthma for at least 6 months
- FEV₁ at screening:
 - Stratum 1: 40-100% predicted
 - Stratum 2: 40-85% predicted
- FEV₁ at randomization (after 5-21 days placebo treatment) of 40 – 90% predicted AND:
 - Stratum 1: FEV₁ at least 10% less than FEV₁ recorded at screening
 - Stratum 2:
 - Asthma severity score ≥ 3 for 3/7 days prior to randomization (see 1.1.1.10 Statistical analysis, pg. 65) OR
 - PEF variability $\geq 20\%$ for 3/7 days prior to randomization OR
 - Albuterol use ≥ 2 puffs/day for 3/7 days prior to randomization.
- Reversibility of FEV₁ by at least 12% following 2 inhalations of albuterol demonstrated within 1 year of screening
- Normal HPA-axis function for those participating in HPA axis evaluation
 - AM cortisol ≥ 5 mcg/dL preceding low-dose (1 mcg) cosyntropin stimulation
 - Serum cortisol ≥ 18 mcg/dL at one or more of the following time points following low-dose cosyntropin stimulation: 20, 30, or 60 minutes

Exclusion criteria

- Severe asthma
 - History of life-threatening asthma as evidenced by intubation, respiratory arrest or PCO₂ >45 mm Hg
 - Two or more hospitalizations for asthma in the year prior to screening
- Asthma therapy and concomitant medications:

- Parenteral corticosteroids within 1 months of screening
- Use of inhaled corticosteroids in doses greater than those described in inclusion criteria
- Began immunotherapy within 30 days of screening
- Other serious medical conditions

1.9.1.5. Study Procedures

At baseline, subjects were provided with diary cards and instructed in their use. After randomization and initiation of therapy, subjects were seen in the clinic at 1, 2, 4, 8, and 12 weeks. Review of the diary cards, elicitation of adverse events, spirometry and oropharyngeal examination for candidiasis were performed at all visits. Compliance was obtained from the diary entries for the number of puffs of study medication taken per day. The Pediatric Asthma Quality of Life Questionnaire (AQLQ) was administered to subjects \geq 7 years of age at baseline, 4, and 12 weeks. Hematology and chemistry blood work were performed at baseline and 12 weeks. In 8 centers blood and urine were collected for cortisol at baseline and 12 weeks, and blood was obtained for PK analysis at baseline and 4 weeks.

Throughout the double-blind treatment period subjects were advised to contact the investigator for any of the following events:

- Clinical exacerbation defined by the patient feeling worse
- Morning PEF measurements on any 2 consecutive days below 80% of the PEF recorded at screening (The patient was instructed to come to the office if the PEF was below 70% of baseline on any 2 consecutive days.)
- Albuterol use of more than eight actuations per day on more than 3 consecutive days

Continued participation in the study for a subject with any of the above complaints was at the discretion of the investigator. Patients could also be discontinued for the development of other serious medical conditions, pregnancy, or an asthma exacerbation requiring non-study medications.

Throughout the study, subjects were allowed to take albuterol for their asthma as needed. They were also permitted to use low dose hydrocortisone (\leq 1%) cream or ointment; intranasal or ocular cromolyn; antihistamines, and decongestants to treat allergic rhinitis; and maintenance immunotherapy as long as the dose had not changed within 30 days of screening. Patients enrolled at centers that did not collect urine or serum for cortisol testing were permitted to use intranasal corticosteroids.

1.9.1.6. Efficacy Parameters

The primary efficacy endpoint was the change from baseline to end-of-study in the AM FEV₁ % predicted in the intent-to-treat (ITT) population. Testing was performed between 7 AM and 9 AM, at least 6 hours after the last dose of albuterol, and before the daily dose of study medication. If the subject withdrew prematurely, the last available post-randomization measurement was carried forward. The secondary efficacy variables included change from baseline in FEV₁ (in liters and as percent predicted) at weeks 1, 2, 4, 8, and 12 weeks; change

from baseline in FVC and FEF_{25-75%} at weeks 1, 2, 4, 8, & 12; and percent change from baseline in FEV₁ at weeks 1, 2, 4, 8, and 12 weeks. Diary variables included AM and PM PEF (liters/min); peak flow variability of AM and PM PEF; total asthma severity rating scores (AM + PM); albuterol use as puffs/day; and number of nighttime awakenings.

The Pediatric Asthma Quality of Life Questionnaire (AQLQ) of Juniper and Guyatt (Juniper, 1996) was administered (without the presence of a parent or guardian) to subjects 7-11 years of age at baseline and at weeks 4 and 12. The questionnaire was filled out at the beginning of the visit before any other testing or any contact with medical personnel. The validated questionnaires were provided in English and Spanish in the United States and Mexico respectively.

1.9.1.7. PK data

At selected centers blood was collected for PK measurements at baseline and Week 4 of treatment. The results are submitted separately.

1.9.1.8. Safety Evaluations

Physical examination including vital signs and oropharyngeal examination, and adverse event queries were performed at all visits. Blood was collected for hematology and chemistry at baseline and end-of-study. Safety was evaluated with serum cortisol before and after cosyntropin stimulation as well as 24-hour urine collections for cortisol at screening and at end of study in subjects enrolled in 8 of the clinical centers.

1.9.1.9. Statistical Plan

Power Calculation

A sample size of 125 patients in each treatment group was calculated to have a 90% power to detect a difference of 6 percentage points in FEV₁ percent predicted between baseline and 12 weeks with a 2-sided significance level of $\alpha=0.05$. This assumes a common standard deviation of the measurement of 14.5 percent.

Efficacy

Demographic and clinical variables were summarized by treatment group and for each stratum within the treatment groups.

The primary efficacy analysis (ITT population) used an analysis of covariance (ANCOVA) of the change in FEV₁ percent predicted, between baseline and week 12. The model included factors for treatment, pooled center, previous therapy (Stratum 1 or 2), baseline FEV₁, age, and gender. The efficacy of ciclesonide was assessed by pair-wise comparisons of each ciclesonide dose against placebo. A step-down procedure was utilized to address the issue of multiplicity. Ciclesonide 160 mcg/day was first compared to placebo and the difference was tested at the $\alpha=0.05$ level of significance. If that comparison was statistically significant then ciclesonide 80 mcg/day was compared to placebo. Finally, if the first two comparisons were statistically significant, then ciclesonide 40 mcg/day was compared to placebo.

A second analysis was performed using a per-protocol (PP) population. In this analysis subjects with significant protocol violations were excluded. These violations included: (1) failure to meet enrollment criteria because the pulmonary function variables were out of range, (2) pulmonary function not measured correctly, [eg albuterol taken within 4 hours of testing], (3) subject treated for less than 7 days, (4) the subject received forbidden medications, and (5) the end of study measurement was obtained more than 5 days after the last dose of study medication.

Secondary efficacy variables were considered supportive and no correction was made for multiplicity. The ANCOVA analysis for percentage symptom-free days included covariates for treatment, pooled center, previous therapy, baseline daily Total Asthma Severity Rating Score, age, and gender. For the percent of nighttime awakenings, the covariates were treatment, pooled center, previous therapy, baseline number of awakenings, age, and gender.

The diary variables were analyzed as an average of the last 7 non-missing values prior to the relevant visit. In addition, the percent of symptom-free days and percent of nights a patient had a nighttime awakening were recorded for the entire treatment period.

Asthma Severity Score

0 = No symptoms

1 = Occasional wheezing, cough, or shortness of breath, but no interference with daily activities or sleep

2 = Occasional wheezing, cough, or shortness of breath which interfere with daily activities or sleep

3 = Frequent or continuous wheezing, cough, or shortness of breath which interfere with daily activities or sleep

4 = Symptoms which prevent the patients from engaging in daily activities or sleep

Total withdrawals and those for asthma symptoms, were compared. Asthma Severity Scores, AM PEF, and albuterol use were analyzed during the first week of randomized treatment in order to detect an early onset of action. An effect was said to have been demonstrated if there was a statistically significant difference between ciclesonide dose groups and placebo. No adjustment was made for multiple comparisons.

Subgroup summaries were performed for age (4- <6 vs 6- <12), gender, race (white vs non-white), previous therapy (Stratum 1 vs Stratum 2) baseline FEV₁ (above and below 70% predicted), and pooled center, asthma severity, and country.

Safety

Frequency tables were prepared for adverse events. Mean laboratory values were summarized by treatment group at baseline and at the end of follow-up. Normal values were defined by the central laboratory. Clinically noteworthy abnormalities (predetermined by the applicant) were tabulated, and the number of subjects in each shift category (moves from normal to high, normal to low, etc) was listed. Finally the applicant defined a predefined change abnormal (PCA) value. To be abnormal by this criterion the variable had to be both above the laboratory defined normal value and to have increased by a pre-specified amount.

The PCA values were obtained from 5,116 patients treated in clinical trials (Thompson, 1986). The limit was that value above or below which 1% of the subjects fell after placebo treatment. The normal range, critical increase, and clinically noteworthy values were variable-age- and sex -dependent and each is listed in the study report (*Appendix A.4.1 Laboratory Normal Ranges, pg 672 [clinstat\341\study341a.pdf]*).

The HPA-axis was evaluated in all of the patients enrolled in the 8 preselected centers that participated in this part of the study. No attempt was made to define an *a priori* "cortisol population." In regard to the 24-hour urine samples, the applicant stated that the quality of the collection was assured by (1) recording the volume of the sample and the instructions to the patients which included the request to note if any void was not collected; (2) analyzing the data with and without correction for creatinine; and (3) the confirmatory blood cortisol measurements. The primary comparison was between baseline and Week 12 measurements for the peak serum cortisol after low-dose cosyntropin stimulation; degree of stimulation (peak - pre-stimulation) in serum cortisol; serum cortisol level measured 15 minutes prior to cosyntropin stimulation; the percentage of patients with "non-normal" HPA-axis function (*For normality criteria see 1.9.1.4. Study Population, pg. 155*); and 24-hour urinary free cortisol and free cortisol corrected for creatinine.

Patient Reported Outcomes

The Pediatric Asthma Quality of Life Questionnaire is made up of 23 questions categorized as belonging to one of three domains (activity limitations, symptoms, and emotional function). Each question had a response range of 1 (maximum impairment) to 7 (no impairment). A mean score was calculated for each domain and for the overall questionnaire. Analysis endpoints were defined as the change from baseline at weeks 4 and 12. The minimally important difference in scores was taken from the literature as 0.5. The test was administered to each child before any of the other tests and the parent or guardian was not present at the time of testing.

1.9.2. Results

1.9.2.1. Study Population

Disposition

Of the 1109 subjects screened, 514 were randomized: Placebo n = 131, ciclesonide 40 mcg n = 126, ciclesonide 80 mcg n = 135, and ciclesonide 160 mcg n = 122. More than 80% of subjects in all the treatment groups completed the study. As shown in Table 88, lack of efficacy and adverse events were the most common cause of early withdrawal. However, most of the adverse events were for an "asthma aggravation". If subjects with either an asthma-exacerbation AE or a lack-of-efficacy withdrawal are combined, then the incidence of withdrawal due to poor asthma control was only slightly lower in the high-dose ciclesonide group than in the placebo group (14 [10.7%], 13 [10.3%], 10 [7.4%], 10 [8.2%] in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively) (*See discussion of Adverse Events, pg. 167*).

Table 88. Disposition of Subjects in Study 341

	Placebo	Ciclesonide			Total
Mcg/day ciclesonide	0	40	80	160	N/A
Randomized Subjects, n	131	126	135	122	514
Completed study, n (%)	107 (81.7)	103 (81.7)	117 (86.7)	104 (85.2)	431 (83.9)
Discontinued from study, n (%)	24 (18.3)	23 (18.3)	18 (13.3)	18 (14.8)	83 (16.1)
Reason for Discontinuation, n(%)					
Lack of efficacy	14 (10.7)	10 (7.9)	8 (5.9)	9 (7.4)	41 (8.0)
Adverse event	15 (11.5)	14 (11.1)	11 (8.1)	9 (7.4)	49 (9.5)
Consent withdrawn	3 (2.3)	6 (4.8)	2 (1.5)	3 (2.5)	14 (2.7)
Loss to follow-up	1 (0.8)	1 (0.8)	2 (1.5)	1 (0.8)	5 (1.0)
Protocol violation	5 (3.8)	4 (3.2)	4 (3.0)	2 (1.6)	15 (2.9)
Death	0	0	0	0	0
Poor compliance	0	1 (0.8)	0	1 (0.8)	2 (0.9)
Other	0	0	0	1 (0.8)	1 (0.2)

Of the 514 subjects enrolled, 10 were not included in the ITT population because of protocol violations; 4 because no study drug was taken and 6 because they did not have a baseline and/or follow-up FEV1. This resulted in an ITT population of 504 (127 placebo subjects, 124 ciclesonide-40 subjects, 134 ciclesonide-80 subjects, and 119 ciclesonide-160 subjects). The 4 subjects who never received drug (3 in ciclesonide-160 group and 1 in the placebo group) were excluded from the safety population as well.

Demographics

The ITT population consisted of 300 (59.5%) subjects in Stratum 1 (previously treated with ICS) and 204 (40.5%) in Stratum 2 (treated with bronchodilators only). There were 306 (60.7%) males and 204 (40.5%) females, and the mean age was 8.1 years with a range of 4-11 years. Due to the study sites in Mexico there was a large number of subjects who were classified as of Hispanic origin (Table 89).

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Table 89. Demographics and Clinical Variables for the ITT Population Enrolled in Study 341

		Ciclesonide				Total
		Placebo	40	80	160	
Mcg/day ciclesonide		0	40	80	160	N/A
n		127	124	134	119	504
Stratum 1*	N (%)	73 (57.5)	75 (60.5)	85 (63.4)	67 (56.3)	300 (59.5)
Stratum 2		54 (42.5)	49 (39.5)	49 (36.6)	52 (43.8)	204 (40.5)
Gender, n(%)	Male	83 (65.4)	78 (62.9)	83 (61.9)	62 (52.1)	306 (60.7)
	Female	44 (34.6)	46 (37.1)	51 (38.1)	57 (47.9)	198 (39.3)
Age, years	Mean (SD)	8.3 (2.1)	8.2 (2.2)	8.0 (2.1)	8.0 (1.9)	8.1 (2.1)
	Range	4-11	4-11	4-11	4-11	4-11
Race	White	56 (44.1)	54 (43.5)	58 (43.3)	44 (37.0)	212 (42.1)
	Black	12 (9.4)	18 (14.5)	14 (10.4)	21 (17.6)	65 (12.9)
	Asian	0	2 (1.6)	1 (0.7)	2 (1.7)	5 (1.0)
	Other	59 (46.4)	50 (40.3)	61 (45.5)	52 (43.7)	222 (44.1)
Hispanic Origin		56 (44.1)	51 (41.1)	64 (47.8)	50 (42.0)	221 (43.8)
Country	Mexico	47 (37.0)	43 (34.7)	50 (37.3)	42 (35.3)	182 (36.1)
	USA	80 (63.0)	81 (65.3)	84 (62.7)	77 (64.7)	322 (63.9)
Duration	Mean (SD)	4.6 (2.9)	4.4 (2.8)	4.1 (2.6)	4.3 (2.8)	4.3 (2.8)
	Range	0.5-11.3	0.3-11.3	0.2-10.6	0.5-11.2	0.2-11.3

* Stratum 1 = prior treatment with ICS, Stratum 2 = prior treatment with bronchodilators only.

The mean duration of asthma prior to enrollment was 4.3 ± 2.8 years with a range of 0.2 to 2.8 years. Prior to enrollment 99.0% of the subjects were using short acting β-agonists, 55.1% were taking ICS, and 24.3% used leukotriene receptor antagonists. Long-acting β-agonists were taken by 16.6%, 8% in combination with ICS.

Comparing the two strata based on prior asthma medication (Table 90), the age and age distribution were similar in the two groups. In all, 76 were below the age of 6 (49 in Stratum 1 and 27 in Stratum 2). There were, however, more males and fewer Hispanics and Mexicans in the group that had previously received treatment with corticosteroids. The stratum 1 subjects had slightly more severe disease though the duration of disease was approximately the same in the two groups. The mean FEV₁ was higher in the Stratum 2 subjects (1.34 ± 0.46 Liters compared to 1.24 ± 0.43 Liters in the Stratum 1 subjects).

Reviewer: the above data were taken from End-of-text Tables 12 (pg 245),-13(pg 248), 12-21, and Text Table 12 (pg 113)/,,\clinstat\341\study341.pdf]. The severity was recalculated from the SAS transport files[... \crt\datasets\341\effpft.xpt] using a FEV₁% predicted < 60% to define severe, 60-<80% to be moderate, and ≥80% to define mild. The numbers reported for mild, moderate, and severe in n Table T-12 and T13 suggest that lower values were taken for cutoffs between mild and moderate and between moderate and severe.

Table 90. Clinical Characteristic of Subjects Based on Prior Treatment for Subjects Enrolled in Study 341

	Stratum 1 (On ICS)	Stratum 2 (Bronchodilators Only)
Total N	300	204
Age, years (Mean [SD])	8.1 (2.1)	8.2 (2.1)
Range	4-11	4-11
Gender: Male, n(%)	195 (65.0)	111 (54.4)
Female	105 (35.0)	93 (45.6)
Hispanic, n(%)	115 (38.8)	106 (52.0)
Mexico, n(%)	95 (31.7)	87 (42.6)
Duration of Asthma, n(%)		
< 0.5 years	1 (0.3)	3 (1.5)
0.5 - <2 years	82 (27.3)	46 (22.5)
2 - <5 years	109 (36.3)	69 (33.8)
≥5 years	108 (36.0)	86 (42.4)
Asthma severity, n(%)		
Mild	45 (15.0)	56 (27.4)
Moderate	166 (55.3)	115 (56.4)
Severe	89 (29.7)	33 (16.2)
FEV ₁ (Liters), Mean (SD)	1.24 (0.43)	1.34 (0.47)
% predicted	65.7	71.1

Comparing the subjects enrolled in the United States to those enrolled in Mexico, the Mexican children were 0.6 years younger and 7 cms shorter than those from the United States, but they had a duration of asthma that was almost two years shorter (Mexico 3.16 years and US 4.97 years). The FEV₁ was 1.10 (65.8% predicted) and 1.38 L (70.0% predicted), in the Mexican and US children respectively. The distribution of asthma severity was similar in the two groups although there were slightly more severe subjects in the children from Mexico (29.1% vs 21.4% in the US). Despite this, 52.2% of the Mexican children were treated with corticosteroids compared with 64% of the children in the US. Additionally, there was a higher prevalence of leukotriene inhibitor and long-acting β -agonist use in the United States than in Mexico. In contrast to the adult populations (Studies 321 – 326) 24.3 % of the children received leukotriene inhibitors (34.2% in the United States and 9.3% in Mexico). The use of long-acting β -agonists was less skewed, but was still more prevalent in the subjects from the United States than in Mexico (18.6% in the United States and 6.6% in Mexico). Twenty-seven (8.4%) of the children enrolled in the United States were taking both a long-acting β -agonist and a leukotriene inhibitor compared with none in the Mexican subjects. Over 90% of the subjects receiving either a long-acting β -agonist or a leukotriene inhibitor were in Stratum 1.

Reviewer: The distribution of medication within strata prior to enrollment is taken from the dataset "crt\Study_341_CONDRUG.xpt".

Despite the many differences among the sub-groups based on strata or country of origin, the distribution of the demographic characteristics was roughly even across the treatment groups.

1.9.2.2. Efficacy Outcomes

The primary efficacy variable in this study was change from baseline to end -of -study in the pre-dose AM FEV₁ percent predicted. The ITT population was made up of 504 individuals: placebo = 127; ciclesonide-40=124; ciclesonide-80 = 134; and ciclesonide-160 =119. The baseline pulmonary function was comparable in all of the treatment groups (Table 91).

Table 91. Baseline Pulmonary Function Study 341

		Placebo	Ciclesonide (dose/day)		
		n=127	40 (n=124)	80 (n=134)	160 (n=119)
FEV1 % predicted (%)	Mean (SD)	68.1 (11.1)	68.6 (11.8)	67.9 (12.1)	67.0 (13.3)
	Range	40.2-88.0	40.7-93.4	41.8-89.9	32.5-90.5
FEV1 (L)	Mean (SD)	1.33 (0.46)	1.31(0.43)	1.25 (0.45)	1.24 (0.44)
	Range	0.47-2.51	0.52-2.49	0.56-2.73	0.40-2.73

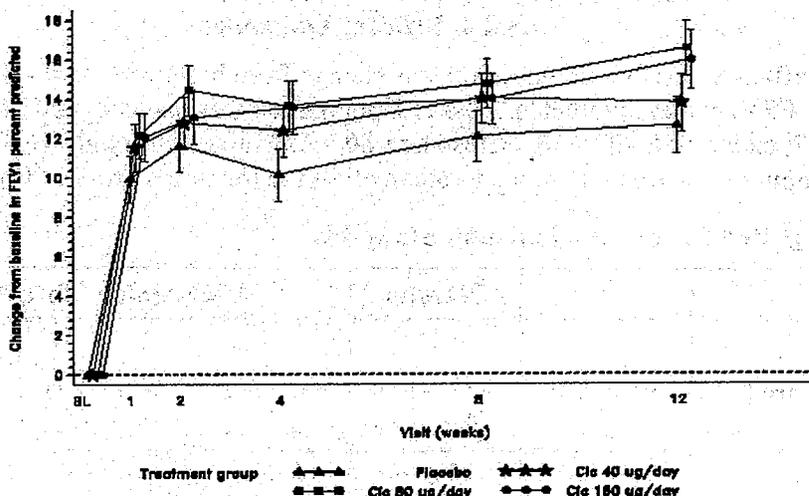
Over the 12-week treatment period the FEV₁ % predicted increased by 12.61% in the placebo group, 13.76% in the ciclesonide-40 group, 16.54% in the ciclesonide-80 group, and 15.95% in the ciclesonide-160 group (Table 92). The difference between placebo and ciclesonide-160 was 3.34% and was not statistically significant (p=0.1005). Following the step-down procedures, no other comparison is statistically significant. If a Bonfoerroni correction (p=[0.05]/3) had been applied, the 80 and 40 mcg doses would also not have been statistically different from placebo.

Table 92. Change in FEV1% Baseline - Week 12 (LOCF) in Study 341

	LS Mean Difference (%)	95% Confidence Interval	p-value
Difference between baseline and Week 12 (LOCF) pre-dose AM FEV₁% predicted			
Placebo	12.61	9.76, 15.46	
Ciclesonide-40	13.76	10.90, 16.63	
Ciclesonide-80	16.54	13.78, 19.30	
Ciclesonide-160	15.95	13.05, 18.85	
Change in FEV₁ Baseline - Week 12 (LOCF) ciclesonide vs. placebo			
Ciclesonide-40-placebo	1.15	-2.77, 5.07	0.56
Ciclesonide-80-placebo	3.93	0.07, 7.78	0.046
Ciclesonide-160-placebo	3.34	-0.65, 7.33	0.10054

The change in FEV₁% with treatment is shown in Figure 10.

Figure 10. Response of FEV₁ % Predicted to Treatment Study 341



In the per-protocol population the increase in FEV₁% in both the ciclesonide-80 (n = 117) and ciclesonide-160 (n = 109) subjects was 5.6% compared with placebo (p > 0.01).

It is important to note that the change in FEV₁ and FEV₁% differed depending on the country in which the subject was enrolled. Of the 182 Mexican children enrolled, the FEV₁ increased 488 ml over the course of the study compared to 190 ml for the 322 children enrolled in the United States. The FEV₁% predicted increased 27.5% in the Mexicans and 8.4% in the children enrolled in the United States. In both groups the difference between placebo and ciclesonide treatment was very small. For the FEV₁% predicted in the Mexican children the difference was 1.8, 8.5, and 4.6% in the ciclesonide-40, ciclesonide-80, and the ciclesonide-160 groups while in the children enrolled in the United States the difference from placebo was 0.8, 1.1, and 3.6% in the ciclesonide-40, ciclesonide-80 and ciclesonide-160 subjects respectively.

Reviewer: The above numbers are taken from datasheet [crt\databases\341\effpft.xpt].

For the entire group at Week 12 (LOCF), the absolute FEV₁ (L) increase was 240, 280, 320, and 290 ml in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. The differences (ml [% predicted]) between active treatment and placebo were small (30 ml [1.09%], 80 ml [6.04%], and 50 ml [5.80%]) in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively.

Most of the other secondary outcome variables followed the same pattern in that the change in the ciclesonide-160 group was less than that seen in the ciclesonide-80 group. The baseline values for the other secondary outcome variables were similar in all of the treatment groups (Table 93).

Table 93. Baseline Values for Secondary Efficacy Variables in Study 341

		Placebo	Ciclesonide		
Mcg/day ciclesonide		0	40	80	160
N		126	122	129	117
AM PEF (L/min)	Mean (SD)	207 (67)	205 (62)	194 (66)	204 (64)
	Range	74-371	84-361	69-406	76-373
Asthma Severity Score	Mean (SD)	2.26 (1.86)	2.08 (1.68)	2.12 (1.84)	2.25 (1.74)
	Range	0.0-8.0	0.0-5.7	0.0-8.0	0.0-8.0
Daily albuterol use (puffs/ day)	Mean (SD)	1.6 (1.7)	1.7 (1.6)	2.0 (2.4)	2.3 (1.7)
	Range	0.0-8.3	0.0-8.6	0.0-18.0*	0.0-8.0
Nighttime awakenings	Mean (SD)	0.3 (0.8)	0.3 (0.7)	0.4 (0.7)	0.3 (0.5)
	Range	0.0-5.4	0.0-68	0.0-3.6	0.0-3.1

* If 1 subject with a extreme value is removed the maximum was 10.3 puffs/day

The mean AM PEF increased in all of the subjects (8.96, 13.23, 25.3, and 18.7 L/min change from baseline in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups respectively.) The difference from placebo in the active treatment groups was 4.3 L/min for ciclesonide-40, 16.3 L/min for ciclesonide-80, and 9.7 L/min for ciclesonide-160. Both AM and PM PEF variability decreased in all of subjects. However, compared to placebo it increased in the ciclesonide-40 group. For AM PEF variability compared to placebo, the changes were 0.14 for the ciclesonide-40 group, -0.17 for the ciclesonide-80 group, and -1.17% for the ciclesonide-160 group.

Daily albuterol use decreased in all of the subjects (Table 94). The change between baseline and Week 12 was -0.12, -0.35, -0.94, and -0.88 puffs per day in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups respectively. The difference between placebo and active treatment was -0.23 for ciclesonide-40, -0.82 for ciclesonide-80, and -0.76 for ciclesonide-160.

Table 94. Secondary Outcome Variables Given as Change from Baseline / Baseline-Week 12 Difference from Placebo in Study 341

	Ciclesonide*		
	40 mcg	80 mcg	160 mcg
AM PEF (L/min)	13.23 / 4.3	25.3 / 16.3	18.7 / 9.7
AM PEF variability (%)	-3.41 / -0.14	-3.71 / -0.17	-4.72 / -1.17
Daily albuterol use (puffs/day)	-0.35 / -0.23	-0.94 / -0.82	-0.88 / -0.76
Total Asthma Severity Score	-0.66 / 0.14	-1.25 / -0.73	-1.12 / -0.60
Nighttime awakenings	0.06 / 0.06	-0.21 / -0.21	-0.05 / -0.05

* Two values are listed: 1) the difference between baseline and Week12 value and 2) the difference between placebo and ciclesonide for the baseline-Week12 change.

Over the course of the study, the mean Asthma Severity Score fell in all the treatment groups (-0.52, -0.66, -1.25, and -1.12 in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups respectively). The difference between placebo and active treatment was -0.14 for ciclesonide-40, -0.73 for ciclesonide-80, and -0.60 for ciclesonide-160

The number of nighttime awakenings did not change in the placebo subjects, increased in the ciclesonide-40 subjects, and decreased in the ciclesonide-80 and 160-treated subjects. The change compared to placebo was 0.06 in the ciclesonide-40 group, -0.21 for the ciclesonide-80, and -0.05 for the ciclesonide-160 group. This is equivalent to a difference between placebo and active treatment of one awakening every 5 nights for the maximal response (the ciclesonide-80 group).

The drop-out rates were similar in all of the treatment groups. The all-cause rate was 15.7, 16.9, 12.7, and 12.6% for the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. The dropout rate due to lack of efficacy was 11, 8.1, 6.0, and 7.6 percent in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively.

Patient Reported Outcomes

The overall pediatric AQLQ score was available for 379 subjects 7 – 11 years of age (Table 95). Compared to placebo, the improvement in the overall score (mean of 32 questions) over the 12 -week study and for the three component domains (Symptoms, Activity Limitation, and Emotional Function) did not reach a clinically significant improvement (>0.5) for any of the ciclesonide doses.

Table 95. Results of Pediatric AQLQ in Study 341

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Overall Score				
Placebo	97	5.43	0.48 (0.10)	---
Ciclesonide-40	92	5.28	0.60 (0.10)	0.13 (0.14)
Ciclesonide-80	94	5.14	0.77 (0.10)	0.29 (0.14)
Ciclesonide=160	88	4.89	0.70 (0.11)	0.22 (0.14)
Symptoms				
Placebo	98	5.29	0.47 (0.11)	---
Ciclesonide-40	92	5.10	0.60 (0.12)	0.13 (0.16)
Ciclesonide-80	94	5.04	0.80 (0.12)	0.32 (0.16)
Ciclesonide=160	88	4.73	0.74 (0.12)	0.26 (0.17)

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Activity Limitation				
Placebo	98	5.28	0.53 (0.10)	---
Ciclesonide-40	92	5.29	0.55 (0.11)	0.02 (0.14)
Ciclesonide-80	94	5.18	0.80 (0.10)	0.27 (0.14)
Ciclesonide=160	88	4.90	0.66 (0.11)	0.13 (0.15)
Emotional Function				
Placebo	97	5.64	0.51 (0.10)	---
Ciclesonide-40	92	5.49	0.62 (0.11)	0.12 (0.14)
Ciclesonide-80	94	5.24	0.74 (0.10)	0.23 (0.14)
Ciclesonide=160	88	5.09	0.67 (0.11)	0.16 (0.14)

* Least squares mean (SE)

1.9.2.3. Safety Outcomes

Extent of Exposure

The safety population is made up of the 510 subjects who received at least one dose of study drug. The mean exposure to study drug was 77.9, 76.8, 79.0, and 81.0 days in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. The median exposure was 84 days in all of the treatment groups.

Adverse Events

Overall, 337 (66.1%) subjects reported adverse events. As shown in Table 96, the incidence was highest in the ciclesonide-160 group followed by placebo and the other active treatments (placebo, 67.7%; ciclesonide-40, 64.3%; ciclesonide-80, 61.5%; and ciclesonide-160, 71.4%.) The most common site of involvement was the respiratory tract with 45.4, 41.3, 37.0, and 42.0% of the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups reporting events respectively. The incidence of asthma exacerbation was only marginally higher in the placebo than the active treatment groups (21.5, 14.3, 15.6, 16.0% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups). The incidence of oropharyngeal adverse events was similar across the treatment groups with 6.9, 6.3, 8.1, and 6.7% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups reporting events respectively. No case of candidiasis was reported in any of the subjects.

Table 96. Adverse Events Occurring in > 3% of Subjects Enrolled in Study 341

	Number (%) Subjects				
	Placebo	Ciclesonide			
Mcg/ day ciclesonide	0	40	80	160	All
N	130	126	135	119	380
Patients with treatment-emergent adverse events	88 (67.7)	81 (64.3)	83 (61.5)	85 (71.4)	249 (65.5)
Respiratory & Thoracic	59 (45.4)	52 (41.3)	50 (37.0)	50 (42.0)	152 (40.0)
Nasopharyngitis	15 (11.5)	11 (8.7)	17 (12.6)	13 (10.9)	41 (10.8)
Pharyngitis	9 (6.9)	8 (6.3)	11 (8.1)	8 (6.7)	27 (7.1)
Asthma aggravated	28 (21.5)	18 (14.3)	21 (15.6)	19 (16.0)	58 (15.3)
Cough	4 (3.1)	4 (3.2)	5 (3.7)	4 (3.4)	13 (3.4)
Nasal congestion	3 (2.3)	2 (1.6)	2 (1.5)	4 (3.4)	8 (2.1)
Rhinitis NOS	5 (3.8)	6 (4.8)	4 (3.0)	2 (1.7)	12 (3.2)
Epistaxis	1 (0.8)	3 (2.4)	5 (3.7)	2 (1.7)	10 (2.6)
Rhinorrhea	1 (0.8)	1 (0.8)	4 (3.0)	1 (0.8)	6 (1.6)
Infections	33 (25.4)	29 (23.0)	33 (24.4)	33 (27.7)	95 (25.0)
Upper Respiratory	10 (7.7)	6 (4.8)	6 (4.4)	6 (5.0)	18 (4.7)
Sinusitis	10 (7.7)	14 (11.1)	16 (11.9)	9 (7.6)	39 (10.3)
Tonsillitis	1 (0.8)	1 (0.8)	0	4 (3.4)	5 (1.3)
Nervous System	19 (14.6)	13 (10.3)	18 (13.3)	16 (13.4)	47 (12.4)
Headache	17 (13.1)	13 (10.3)	18 (13.3)	15 (12.6)	46 (12.1)
Musculoskeletal	10 (7.7)	2 (1.6)	4 (3.0)	2 (1.7)	8 (2.1)
Arthralgia	4 (3.1)	0	0	0	0
Gastrointestinal	17 (13.1)	12 (9.5)	15 (11.1)	14 (11.8)	41 (10.8)
Diarrhea	2 (1.5)	6 (4.8)	1 (0.7)	2 (1.7)	9 (2.4)
Vomiting	8 (6.2)	6 (4.8)	3 (2.2)	2 (1.7)	11 (2.9)
Upper abdominal pain	6 (4.6)	0	4 (3.0)	1 (0.8)	5 (1.3)
General Disorders	4 (3.0)	7 (5.3)	7 (5.5)	5 (3.8)	19 (4.8)
Influenza-like illness	1 (0.7)	4 (3.0)	2 (1.6)	0	6 (1.5)
Skin & Subcu. Tissue	6 (4.6)	7 (5.8)	4 (3.0)	7 (5.9)	18 (4.7)
Rash	1 (0.8)	5 (4.0)	1 (0.7)	2 (1.7)	8 (2.1)
Ear & Labyrinth	1 (0.8)	2 (1.6)	5 (3.7)	2 (1.7)	9 (2.4)
Ear pain	1 (0.8)	2 (1.6)	4 (3.0)	2 (1.7)	8 (2.1)

The second most frequently reported AE was infections. This occurred in 25.4%, 23.0%, 24.4%, and 27.7% of the subjects in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups respectively. Upper respiratory tract infection was slightly more common in the placebo patients (7.7% vs 4.7% ciclesonide).

In general, the adverse events were evenly distributed across the treatment groups. There were a few more musculoskeletal and connective tissue disorders in the placebo subjects than in the active treatment groups, however, the absolute numbers were small.

Ophthalmologic Examination

Of the safety population, 459 subjects had both baseline and follow-up ophthalmologic examination. Two subjects had worsening lenticular opacities over the course of the study. One placebo subject developed a trace posterior cataract in one eye and had a trace cortical cataract increase to 1+ in the other eye. One ciclesonide-160 subject had no cataracts at baseline and a trace cortical cataract in both eyes at follow-up. Three subjects had cataracts that improved: 2 placebo subjects and 1 ciclesonide-160 subject had bilateral trace cataracts at baseline and none at follow-up. This includes the trace posterior subcapsular cataract in the ciclesonide-160 subject.

Serious and Important Adverse Events

There were no deaths reported. There were 4 serious adverse events reported - 3 cases of aggravated asthma (2 in the placebo group and 1 in the ciclesonide-40 group) and one case of a posterior subcapsular cataract in a placebo subject.

A total of 49 subjects were withdrawn due to adverse events: 15 (11.5%) in the placebo group and 34 (8.9%) in the ciclesonide- treated subjects (Table 97). The most common reason for withdrawal was aggravation of asthma. Only 4 subjects withdrew for an AE not related to worsening asthma – one was a case of pneumonia in the placebo group, 1 case each of sinusitis and viral infection in the ciclesonide-40 group, and 1 case of a “behavior problem” in the ciclesonide-80 group. One placebo subject who withdrew with an asthma exacerbation also had a viral infection and a subject in the ciclesonide-40 group with an asthma exacerbation had sinusitis. All of the adverse events leading to withdrawal of subjects receiving ciclesonide-160 were due to an asthma exacerbation. The percentage of patients who had “other significant AEs” was comparable in all of the treatment groups.

Table 97. Other Adverse Events Reported in Study 341.

	Placebo	Ciclesonide		
		40 mcg	80 mcg	160 mcg
Daily dose of ciclesonide, mcg	0	40 mcg	80 mcg	160 mcg
Subjects with other significant AEs, n(%)	75 (57.7)	66 (52.4)	70 (51.9)	70 (58.8)
AE resulted in: n (%)				
Discontinued from study	15 (11.5)	14 (11.1)	11 (8.1)	9 (7.6)
Therapy temporarily interrupted	0	2 (1.6)	2 (1.5)	1 (0.8)
Other intervention	8 (6.2)	4 (3.2)	4 (3.0)	9 (7.6)
Treated with counter active measure	74 (56.9)	65 (51.6)	69 (51.1)	70 (58.8)
Important laboratory abnormality, n(%)	1 (0.8)	0	1 (0.7)	1 (0.3)

Laboratory Abnormalities

Tests of liver function were unremarkable except for the alkaline phosphatase. At the start of the study 13.7% of the children had elevated levels (>325 U/L for age 7 – 10 years) and the same percentage had elevated levels at the end of the study. The distribution of elevated alkaline phosphatase values at both baseline and end-of-study was uniform across the treatment groups, and the proportion was the same in the children enrolled in Mexico and those enrolled in the United States. The PCA value (above normal at end of study and increased by 28 U/L during the course of the study) was reached in 9/116 (7.8%) of the placebo subjects, 2/111 (1.8%) of the ciclesonide-40 subjects, 11/129 (8.5%) of the ciclesonide-80 subjects, and 4/112 (3.6%) of the ciclesonide-160 subjects.

The absolute eosinophil count was elevated ($> 0.57 \times 10^3$ cells/mL) at baseline in 16.1, 11.8, 15.4, and 18.9% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively. In all of the treatment groups more subjects had an increase than a decrease in eosinophil count over the course of the study. At the end of the study, the PCA value (above normal and increased by 0.37×10^3 cells/mL over the course of the study) was reached in 7/118 (5.9%) of the placebo, 7/110 (6.4%) of the ciclesonide-40, 10/123 (8.1%) of the ciclesonide-80, and 7/106 (6.6%) of the ciclesonide-160 subject respectively. Of note, 34.5% of the subjects with eosinophil counts were enrolled in Mexico. These subjects had higher eosinophil counts at the end of the study and a greater change in eosinophil count over the course of the study than did the children enrolled in the USA. A clinically noteworthy value was defined prospectively by the applicant as $>1.0 \times 10^3$ cells/uL. This value was reached by 7 placebo, 6 ciclesonide-40, one ciclesonide-80 and 4 ciclesonide-160 subjects. Of those with clinically noteworthy values, 4 (57.1%), 4 (66.7%), 0, and 2 (50%) of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects were enrolled in Mexico.

Two subjects had abnormal laboratory values reported as adverse events. One placebo patient had an elevated 24-hour urinary free cortisol and one ciclesonide-80 subjects had a decreased 24-hour urine cortisol (*See HPA-axis evaluation, below*).

HPA-axis Evaluation

Blood for cortisol determination was available at both baseline and follow-up for 32 subjects recruited at 5 pre-selected centers (all in the United States). (Table 98). The peak serum cortisol after stimulation with 1 μ g cosyntropin did not differ among the treatment groups at baseline. After 12 weeks of treatment the peak cortisol fell slightly in the placebo and ciclesonide-80 subjects, and increased slightly in the ciclesonide-40 and ciclesonide-160 groups. No statistics were provided for this data because of the small number of subjects. The degree of stimulation (peak – baseline cortisol), was similar in the treatment groups at the beginning of the study and fell in all treatment groups.

Table 98. Evaluation of HPA-axis in Study 341

	N (total)	N (early withdrawal)	Baseline Mean	Change from Baseline*	Difference from Placebo
Peak post-stimulation serum cortisol, mcg/dL					
Placebo	7	2	21.29	-2.35 (1.76)	
Ciclesonide-40	6	2	22.83	0.62 (1.77)	-2.97
Ciclesonide-80	10	0	24.10	-0.40 (1.28)	-1.95
Ciclesonide-160	9	1	23.56	1.44 (1.57)	-0.91
Degree of stimulation (peak-baseline), mcg/dL					
Placebo	7	2	10.57	-5.82 (2.37)	
Ciclesonide-40	6	2	12.50	-5.65 (2.39)	0.17
Ciclesonide-80	10	0	11.80	-5.59 (1.73)	0.23
Ciclesonide-160	9	1	10.78	-3.22 (2.12)	2.43

* LS Mean (SE)

Defining normal HPA function as a baseline cortisol of at least 5 µg/dL and a post-stimulation serum cortisol of at least 18 µg/dL, two subjects in the ciclesonide-80 group were abnormal at baseline due to a low post stimulation cortisol (17 and 16 mcg/dL). One of these subjects was normal at 12 weeks, but the subject with the peak of 17 mcg/dL had the same value at the end of the study. This was the same subject that had the low urinary cortisol. Only one subject in the placebo group was normal at baseline and abnormal at 12 weeks due to a post-stimulation peak of 8 mcg/dL.

Measurements of urinary free cortisol are reported for 33 of the subjects for whom the blood cortisol measurements were available. Urine volumes are not listed. The free urinary cortisol was higher at baseline and decreased more in the placebo subjects (10.23 baseline, -2.51 fall) than in the other treatment groups. In the ciclesonide-40 group the urinary free cortisol actually rose by 4.52 mcg/day. In the ciclesonide-80 and ciclesonide-160 groups, both the urinary free cortisol and urinary free cortisol corrected for creatinine fell over the course of the trial.

Vital Signs and Physical Examination

At baseline approximately half of the subjects had abnormal systolic blood pressure readings and one quarter had abnormal diastolic blood pressure readings. The incidence was the same in placebo and ciclesonide-treated subjects and it was unchanged at the end of the study. The heart rate was abnormal in 14.6, and 14.2% of the placebo and ciclesonide subjects respectively at the beginning of the study, and the incidence dropped to 8.5 and 9.7% at the end of the study. The physical examination was unremarkable for any changes other than those associated with adverse events.

1.9.3. Discussion and Conclusions

In this pivotal 12-week trial, 514 subjects age 4 – 11 years with asthma were treated with placebo, ciclesonide 40 mcg QD, ciclesonide 80 mcg QD, or ciclesonide 160 mcg QD. This study failed to show efficacy as there was no significant difference between the placebo and ciclesonide-160-treated children in the primary outcome variable, FEV₁% predicted. The secondary outcome measures also showed greater improvement in the ciclesonide-80 group (except for the AM PEF variability) than the ciclesonide-160 group. The pediatric AQLQ did not show a clinically meaningful improvement in the Overall score, or any of the three domains for any ciclesonide group.

Adverse events were somewhat more common (65.5%) in children taking ciclesonide than in the adult population, but the distribution was similar. The most frequently affected system was the respiratory tract (40%) and the next most frequent was infectious processes (25%). Of note, no case of oropharyngeal candidiasis was reported. In the respiratory tract asthma aggravation was listed in 21.5% of the placebo- and 15.3% of the ciclesonide-treated subjects. The incidence of infections was almost identical in the placebo (25.4%) and ciclesonide (25.0%) treated subjects. Musculoskeletal and gastrointestinal complaints were more common in the placebo-treated subjects. The incidence of cataracts was low and similar in all of the treatment groups. The only posterior subcapsular cataract developed in a placebo subject. The alkaline phosphatase was elevated in 13.7% of the children at baseline and a similar number at the end of the study. The elevations were mild, and distributed evenly among the treatment groups and between Mexican and US children. Eosinophil counts, on the other hand, were elevated more frequently in the Mexican children. While only 35% of the enrollment was Mexican more than 50% of subjects with an eosinophil value $> 1.0 \times 10^3$ cells/ μ L were Mexican. . On the other hand the elevation in eosinophils count was not treatment related.

There were only minor changes in the post cosyntropin stimulation cortisol measurements. On average the values fell more in the placebo-treated subjects than in the active treatment groups. No subject in an active treatment group went from normal to abnormal HPA-axis function over the course of the study.

1.10. Study #342

A phase III double-blind, placebo-controlled, parallel-group, multicenter, efficacy, safety and dose response study of ciclesonide metered dose inhaler 50 mcg/day, 100 mcg/day, and 200 mcg/day ex-valve (40 mcg, 80 mcg, and 160 mcg/day ex-actuator) administered once daily for 12 weeks in the treatment of children with persistent asthma.

1.10.1. Protocol

1.10.1.1. Administrative

Enrollment: June 13, 2001 – January 25, 2003

Clinical Director: _____

Sites: 54 in the United States and 10 in Poland

b(4)

1.10.1.2. Objectives/Rationale

To compare the efficacy, safety and dose response of once-daily administration of 3 doses of ciclesonide (5, 100, and 200 mcg/ day ex-valve: 40, 80, 160 mcg/day ex-actuator) metered dose inhaler with placebo in patients with mild to severe persistent asthma. A secondary objective was to describe the pharmacokinetic profile of ciclesonide and its main metabolite.

1.10.1.3. Study Design

The study design was identical to that of Study 341 (1.9.1.3. Study Design, pg. 154).

1.10.2. Results

1.10.2.1. Study Population

Disposition

Of the 913 subjects screened, 517 were randomized; Placebo n = 127, ciclesonide-40, n = 130, ciclesonide-80 n = 126, and ciclesonide-160, n = 134. Seventy-eight percent (78.7%) of the placebo subjects and 339/390 (86.9%) of the ciclesonide subjects completed the study. Drop-out for lack of efficacy and adverse events were substantially higher in the placebo (14.2 and 15.0%, respectively) than in the ciclesonide-treated subjects (8.1% for both indications) (Table 99). All but 2 of the randomized subjects who never received study medication were included in the safety population. This resulted in a safety population of 515. One subjects had no post baseline FEV1 and so the ITT population consisted of 514 subjects.

Table 99. Disposition of Subjects in Study 342

	Placebo	Ciclesonide			Total
Mcg/day	0	40	80	160	N/A
Randomized Subjects, n	127	130	126	134	517
Completed study, n (%)	100 (78.7)	109 (83.8)	109 (86.5)	121 (90.3)	439 (84.9)
Discontinued from study, n(%)	27 (21.3)	21 (16.2)	17 (13.5)	13 (9.7)	78 (15.1)
Reason for Discontinuation, n(%)					
Lack of efficacy	18 (14.2)	11 (8.7)	8 (6.3)	5 (3.7)	42 (8.1)
Adverse event	19 (15.0)	8 (6.2)	8 (6.3)	7 (5.2)	42 (8.1)
Consent withdrawn	5 (3.9)	6 (4.6)	3 (2.4)	1 (0.7)	15 (2.9)
Protocol violation	3 (2.4)	3 (2.3)	4 (3.2)	4(3.0)	14 (2.7)
Loss to follow-up	0	1 (0.8)	1 (0.8)	1 (0.7)	3 (0.6)
Poor compliance	0	0	1 (0.8)	0	1 (0.2)
Death	0	0	0	0	0
Other	0	1 (0.8)	1 (0.8)	0	2 (0.4)

Most of the adverse events were also related to lack of efficacy. An asthma exacerbation was the adverse event in all but 4 subjects (*see Adverse Events, pg. 181*). Five subjects (placebo n =2, ciclesonide-80 n =1, and ciclesonide-160 n =2) took prohibited corticosteroids for non-asthma indications and were kept in the ITT population (*Table 4 of study report. Pg 100 [clinstat\342\study342.pdf]*). Diary-recorded compliance was >90% in > 97% of the subjects in all of the treatment groups.

Demographics

The ITT population consisted of 346 (67.3%) subjects in Stratum 1 (previously treated with ICS) and 168 (32.7%) in Stratum 2 (no prior treatment with ICS) (Table 100). There were 346 (67.3%) males and 168 (32.7%) females, the mean age was 8.3 years with a range of 4-11 years, and 81.5% were Caucasian. The distribution of these characteristics was comparable in all of the treatment groups. Twelve percent of the subjects were Hispanic and 38.3% were enrolled in Poland. The mean duration of asthma prior to enrollment was 4.4 ± 2.8 years with a range of 0.4 to 12.1 years. Prior to enrollment, all of the subjects were using short acting β-agonists, 59.4% were taking ICS, 25 % used leukotriene receptor antagonists, 14.9% took long-acting β-agonists, 8.2% took cromones and 4 patients took xanthines. (Source: Text Table 9 [...\clinstat\342\study342.pdf, pg. 108] *There is no explanation for why the percentage taking ICS is not the same as the percentage in Stratum 1*) Most of the subjects taking either leukotriene receptor antagonists or long acting β-agonists were in.

Table 100. Demographics for Subjects Enrolled in Study 342

Mcg/day		Placebo	Ciclesonide			Total
		0	40	80	160	N/A
n		127	128	125	134	514
Stratum 1*, n (%)		87 (68.5)	82 (64.1)	84 (67.2)	93 (69.4)	346 (67.3)
Stratum 2, n (%)		40 (31.5)	46 (35.9)	41 (32.8)	41 (30.6)	168 (32.7)
Gender, n (%)	Male	86 (67.7)	84 (62.1)	86 (68.8)	92 (68.7)	346 (67.3)
	Female	41 (32.3)	46 (35.9)	39 (31.2)	42 (31.3)	168 (32.7)
Age, years	Mean (SD)	8.1 (2.1)	8.1 (2.1)	8.4 (2.1)	8.6 (1.9)	8.3 (2.1)
	Range	4-11	4-11	4-11	4-11	4-11
Race, n (%)	White	107 (84.3)	102 (79.7)	99 (79.2)	111 (82.8)	419 (81.5)
	Black	11 (8.7)	16 (12.5)	15 (12.0)	12 (9.0)	54 (10.5)
	Asian	3 (2.4)	2 (1.6)	0	1 (0.7)	6 (1.2)
	Other	6 (4.7)	8 (6.2)	11 (8.8)	10 (7.4)	35 (6.8)
Hispanic Origin, n (%)		18 (14.2)	14 (10.9)	15 (12.0)	14 (10.4)	61 (11.9)
Country, n (%)	Poland	47 (37.0)	51 (39.5)	50 (40.0)	49 (36.6)	197 (38.3)
	USA	80 (63.0)	78 (6.5)	75 (60.0)	85 (63.4)	318 (61.7)
Duration, years	Mean (SD)	4.4 (2.9)	4.3 (2.8)	4.6 (2.9)	4.5 (2.7)	4.4 (2.8)
	Range	0.5-11.5	0.5-11.1	0.4-11.1	0.6-12.1	0.4-12.1

* Stratum 1 subjects previously treated with ICS, stratum 2 = subjects not treated with ICS within 30 days of enrollment.

Stratum 1. In Stratum 2 there were two subjects who took leukotriene receptor antagonists and 7 who took long-acting β -agonists prior to enrollment

Comparing the two strata, the group that had been on maintenance ICS (Stratum 1) contained more males (70.2%) vs 61.3% in Stratum 2, contained more subjects from Poland (41.6%) vs 31.5% for Stratum 2, and had a more severe disease (Table 101). In addition, 34 (9.8%) of the subjects in stratum 1 were Hispanic while 16.1% of the subjects in stratum 2 described themselves as Hispanic. The distribution of these demographic and functional variables was uniform across the treatment groups.

Reviewer: the above data is taken from End-of-Text tables 12-12, 13, 21, 22, 27 and 29, pg. 243-278 of study report (... \clinstat\342\study342.pdf)

Table 101. Clinical Characteristics by Stratum in Study 342

	Stratum 1 (On ICS)	Stratum 2 (Bronchodilators Only)
Age, years (mean [SD])	8.3 (2.1)	8.3 (2.1)
Range	4-11	4-11
Gender: Male, n(%)	243 (70.2)	103 (61.3)
Female	103(29.8)	65 (38.7)
Duration of Asthma, n(%)		
< 0.5 years	2 (0.6)	1 (0.6)
0.5- <2 years	76 (22.0)	43 (25.6)
2 - <5	28 (37.0)	61 (36.3)
> 5 years	139 (40.2)	63 (37.5)
% predicted visit #2	68.1 (11.5)	70.3 (11.3)
FEV ₁ (L) visit #2*	1.55 (0.46)	1.45 (0.44)
FEV ₁ (L) visit #3*	1.29 (0.39)	1.37 (0.44)
Country, n(%)		
Poland	144 (41.6)	53 (31.5)
US	202 (58.4)	115 (68.5)
Asthma Severity, n(%)		
Mild	46 (13.3)	39 (23.2)
Moderate	216 (61.8)	99 (58.9)
Severe	86 (24.9)	30 (17.9)

* Mean (SD)

Comparing the subjects enrolled in the United States to those enrolled in Poland (Table 102), the Polish children were slightly younger on average (8.2 years vs 8.4 years for the US children) but a smaller percentage were less than 6 years of age (9.1% vs 12.3% for the US children). The Polish children had asthma for a shorter period of time (20.3% > 5 years vs 51.1% > 5 years for the US children). The FEV₁% predicted in the Polish children was lower (66.3% vs 71.4% for the US children) and more were on ICS prior to enrollment (73.1 vs 63.7% for the US children). Fewer of the Polish took leukotriene inhibitors prior to

enrollment (19.3% vs 29.3% of the US children) but more took a long acting β -agonist. Lastly all of the Hispanic children were enrolled in the US.

Reviewer: The distribution of medication within strata prior to enrollment is taken from the datasets (crt\datasets\342\condrug.xpt). The severity classification was created from the crt\datasets\342\effpft.xpt with an FEV1% <60 = severe, FEV1% 60 - <80 = moderate, and FEV1% \geq 80 = mild. This is in distinction to the Applicant's Table T-11 through T-15 on page 231 -245 (clinstat\342\study342.pdf) where the cutoffs are lower i.e. 60% FEV1% is considered mild disease.

Despite the many differences among the sub-groups based on strata or country of origin the distribution of the demographic characteristics was roughly even across the treatment groups.

Table 102. Demographic Variables by Country of Origin in Study 342

	Poland (N=197)	United States (N=317)
Age, n (%)		
4- <6	18 (9.1)	39 (12.3)
6- <12	179 (90.9)	278 (87.7)
Mean years (SD)	8.2 (1.9)	8.4 (2.1)
Gender: Male, n (%)	139 (70.6)	207 (65.3)
Female	58 (29.4)	110 (34.7)
Duration of Asthma, n (%)		
< 0.5 years	1 (0.5)	2 (0.6)
0.5- <2 years	80 (40.6)	39 (12.3)
2 - <5	76 (38.6)	113 (35.6)
> 5 years	40 (20.3)	162 (51.1)
FEV1 % predicted, Mean % (SD)	66.3 (9.6)	70.4 (12.2)
FEV ₁ ,Mean L (SD)	1.25 (0.34)	1.36 (0.44)
Stratum, n (%)		
1 (previous ICS)	144 (73.1)	202 (63.7)
2 (no previous ICS)	53 (26.9)	115 (36.3)
Asthma Severity, (%)		
Mild	17 (8.6)	68 (21.5)
Moderate	128 (65.0)	185 (58.4)
Severe	52 (26.4)	64 (20.2)

1.10.2.2. Efficacy Outcomes

The primary efficacy variable in this study was change from baseline to end of study in the pre-dose AM FEV₁ percent predicted. The ITT population was made up of 514 individuals:

placebo, 127; ciclesonide-40, 128; ciclesonide-80, 125; ciclesonide-160, 134. The baseline pulmonary function was comparable in all of the treatment groups (Table 103).

Table 103. Baseline Pulmonary Function Study 342

		Placebo	Ciclesonide (dose/day)		
		n=127	40 (n=124)	80 (n=134)	160 (n=119)
FEV1 % predicted (%)	Mean (SD)	69.01 (11.5)	68.4 (11.5)	68.7 (10.6)	69.2 (12.2)
	Range	35.7-99.6	41.0-92.5	39.7-90.3	31.9-105.4
FEV1 (L)	Mean (SD)	1.31 (0.40)	1.27 (0.41)	1.34 (0.41)	1.35 (0.42)
	Range	0.41-2.49	0.39-2.52	0.55-2.52	0.53-2.63

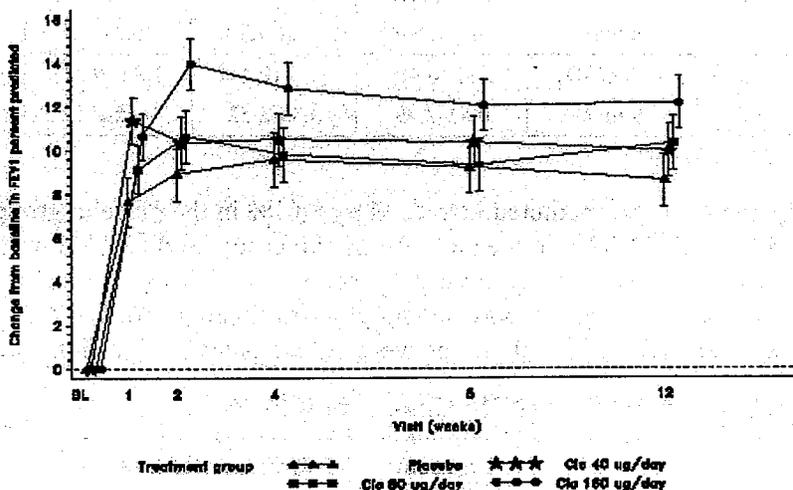
At End-of-study, the FEV₁ % predicted increased by 8.61% in the placebo group, 9.96% in the ciclesonide-40 group, 10.32% in the ciclesonide-80 group, and 12.15% in the ciclesonide-160 group. The difference between placebo and ciclesonide treated subjects of 3.55% for the ciclesonide-160 group was statistically significant (p=0.03). The response in the ciclesonide-80 and ciclesonide-40 groups were not statistically significant (Table 104).

Table 104. Baseline - Week 12 (LOCF) Change in FEV₁%

	LS mean difference (%)	95% Confidence Interval	p-value
Difference between baseline and Week 12 pre-dose AM FEV ₁ % predicted			
Placebo	8.61	6.21, 11.01	
Ciclesonide-40	9.96	7.58, 12.34	
Ciclesonide-80	10.32	7.90, 12.74	
Ciclesonide-160	12.15	9.79, 14.52	
(Baseline - Week 12) change in FEV ₁ comparing ciclesonide and placebo treatment			
Ciclesonide-40 - placebo	1.35	-1.84, 4.54	0.41
Ciclesonide-80 - placebo	1.71	-1.51, 4.93	0.30
Ciclesonide-160 - placebo	3.55	0.38, 6.71	0.03

The results for each time-period (LOCF) are shown graphically in figure 11.

Figure 11. FEV₁ % Predicted in Response to Treatment with Placebo of Ciclesonide in Children 4 – 11 Years of Age in Study 342.



It is important to note that the change in FEV₁ and FEV₁% differed depending upon the country in which the subjects were enrolled. Of the 197 children enrolled in Poland, the FEV₁ increased 400 ml over the course of the study compared to 194 ml for the 317 children enrolled in the United States. The FEV₁% predicted increased 18.85% in the Polish and 7.9% in the children enrolled in the United States. In both groups the difference between placebo and ciclesonide treatment was very small. For the Polish children the difference for the change in FEV₁% was 3.50, 1.64, and 6.37% in the ciclesonide-40, ciclesonide-80, and the ciclesonide-160 groups, respectively, while in the children enrolled in the United States the difference from placebo was 0.12, 1.45, and 1.36% in the ciclesonide-40, ciclesonide-80 and ciclesonide-160 subjects respectively.

Reviewer: The above numbers are taken from datasheet crt\databases\342\effpft.xpt

The absolute FEV₁ (L) increased by 200, 220, 240, and 280 ml in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively over the 12-week treatment period. The differences between active treatment and placebo were small (20, 40, and 80 ml in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively and the FEV₁% predicted was 1.82, 3.01, 6.32 for the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively.

The baseline values for the other secondary outcome variables were similar in all of the treatment groups (Table 105).

Table 105. Baseline Values for Secondary Efficacy Variables in Study 342

		Ciclesonide			
		Placebo	40	80	160
Mcg/day ciclesonide		0	40	80	160
N		126	122	129	117
AM PEF (L/min)	Mean (SD)	211 (58)	209 (64)	223 (64)	218 (66)
	Range	78.6-382.9	75.8-364.3	72.6-395.7	87.1-495.7
Asthma Severity Score	Mean (SD)	1.68 (1.47)	1.75 (1.47)	1.71 (1.43)	1.85 (1.43)
	Range	0.0-6.0	0.0-5.7	0.0-6.0	0.0-6.4
Daily albuterol use (puffs/ day)	Mean (SD)	1.2 (1.4)	1.5 (1.6)	1.3 (1.5)	1.51 (1.7)
	Range	0.0-6.0	0.0-7.4	0.0-8.7	0.0-10.0
Nighttime awakenings	Mean (SD)	0.25 (0.6)	0.20 (0.3)	0.25 (0.5)	0.3 (0.5)
	Range	0.0-4.7	0.0-68	0.0-2.4	0.0-2.6

The changes in the secondary outcome variables were all small when compared to placebo and there was not a consistent dose ordering (Table 106). The largest changes in AM PEF, AM PEF variability, asthma severity score, and nighttime awakening was in the ciclesonide-40 group.

Table 106. Secondary Outcome Variables (Change from Baseline / Baseline- Week 12 Difference from Placebo) in Study 342

	Ciclesonide*		
	40 mcg	80 mcg	160 mcg
AM PEF (L/min)	16.4 / 8.7	14.0 / 6.2	15.7 / 7.9
AM PEF variability (%)	-2.97 / -1.10	-2.34 / -0.47	-2.35 / -0.45
Daily albuterol use (puffs/day)	-0.28 / -0.31	-0.42 / -0.45	-0.20 / -0.23
Total Asthma Severity Score	-0.59 / -0.57	-0.50 / -0.47	-0.51 / -0.49
Nighttime awakenings	-0.12 / -0.12	-0.04 / -0.04	0.04 / 0.04

* Two values are listed: 1) the difference between baseline and Week12 value and 2) the difference between placebo and ciclesonide for the baseline-Week12 change.

The improvement in AM PEF compared to placebo was 8.7 L/min for ciclesonide-40, 6.2 L/min for ciclesonide-80, and 7.9 L/min for ciclesonide-160.

Over the course of the study the mean Asthma Severity Score fell in all the treatment groups. The difference between placebo and active treatment was -0.57 for ciclesonide-40, -0.47 for ciclesonide-80, and -0.49 for ciclesonide-160.

Daily albuterol increased (0.03 puffs/day) in the placebo- treated subjects but decreased in all of the active treatment groups. The difference between placebo and active treatment was - 0.31 for ciclesonide-40, -0.45 for ciclesonide-80, and -0.23 for ciclesonide-160.

The mean of both AM and PM PEF variability decreased in all of the treatment groups. For AM PEF variability compared to placebo, the changes were -1.10 for the ciclesonide-40 group, -0.47 for the ciclesonide-80 group, and -0.45% for the ciclesonide-160 group. The number of nighttime awakenings did not change in the placebo subjects, and decreased in the active treatment groups. The change compared to placebo was -0.12 in the ciclesonide-40 group, -0.04 for the ciclesonide-80, and -0.04 for the ciclesonide-160 group.

The drop-out rates were higher in the placebo subjects. The all-cause drop out rate was 21.3, 14.8, 12.8, and 9.7% for the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. The dropout rate due to lack of efficacy was 14.2, 8.6, 6.4, and 3.77 % in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively.

Patient Reported Outcomes

None of the active treatment groups had a clinically meaningful improvement (> 0.5) in the Overall Score or any of the individual domains compared to placebo at end-of-study (Table 107).

Table 107. Results of PAQLQ in Study 342

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Overall Score				
Placebo	95	5.62	0.05 (0.10)	---
Ciclesonide-40	98	5.38	0.42 (0.10)	0.37 (0.13)
Ciclesonide-80	100	5.59	0.31 (0.10)	0.27 (0.13)
Ciclesonide=160	110	5.47	0.41 (0.10)	0.36 (0.13)
Symptoms				
Placebo	95	5.46	-0.01 (0.12)	---
Ciclesonide-40	98	5.21	0.48 (0.12)	0.49 (0.15)
Ciclesonide-80	100	5.42	0.36 (0.11)	0.37 (0.15)
Ciclesonide=160	110	5.25	0.45 (0.11)	0.45 (0.15)
Activity Limitation				
Placebo	95	5.54	0.11(0.10)	---
Ciclesonide-40	98	5.36	0.34 (0.10)	0.23 (0.14)
Ciclesonide-80	100	5.52	0.38 (0.10)	0.27 (0.14)
Ciclesonide=160	110	5.43	0.46 (0.10)	0.35 (0.13)
Emotional Function				
Placebo	95	5.88	0.08 (0.11)	---
Ciclesonide-40	98	5.60	0.35 (0.11)	0.28 (0.14)
Ciclesonide-80	100	5.84	0.20 (0.10)	0.13 (0.14)

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Ciclesonide=160	110	5.78	0.31 (0.10)	0.24 (0.14)
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* *Least squares mean (SE)*

1.10.2.3. Safety Outcomes

Extent of Exposure

The safety population is made up of the 515 subjects who received at least one dose of study drug. The mean exposure to study drug was 73.5, 76.5, 78.0, and 80.5 days in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. The median exposure was 84 days in all of the treatment groups.

Adverse Events

Overall, 335/515 (65.0%) of subjects reported adverse events. As shown in Table 108, the incidence was highest in the placebo group (71.7%) followed by ciclesonide-160 (67.2%). The most common site of involvement was the respiratory tract, 42.5, 36.4, 34.4, and 40.3% in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups reporting events respectively. The incidence of asthma exacerbation was higher in the placebo than the active treatment groups (15.7, 9.3, 8.8, and 9.7% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups). The other respiratory events were distributed more or less evenly across the treatment groups. However, there were more cases of nasopharyngitis in the ciclesonide-160 and 80 mcg group. There was one case of oropharyngeal candidiasis in the ciclesonide-80 and 2 cases in the ciclesonide-160 treatment groups.

Table 108. Adverse Events Occurring in > 3% of Subjects Enrolled in Study 342

	Number (%) Subjects				
	Placebo	Ciclesonide			
Mcg/ day ciclesonide	0	40	80	160	All
N	127	129	125	134	388
Patients with treatment-emergent adverse events	91 (71.7)	77 (59.7)	77 (61.6)	90 (67.2)	244 (62.9)
Respiratory & Thoracic	54 (42.5)	47 (36.4)	43 (34.4)	54 (40.3)	144 (37.1)
Nasopharyngitis	11 (8.7)	7 (5.4)	17 (13.6)	20 (14.9)	44 (11.3)
Pharyngitis	13 (10.2)	13 (10.1)	9 (7.2)	15 (11.2)	37 (9.5)
Asthma aggravated	20 (15.7)	12 (9.3)	11 (8.8)	13 (9.7)	36 (9.3)
Rhinitis NOS	3 (2.4)	9 (7.0)	5 (4.0)	2 (1.5)	16 (4.1)
Bronchitis	4 (3.1)	4 (3.1)	4 (3.2)	3 (0.8)	11 (2.8)
Infections	46 (36.2)	35 (27.1)	33 (26.4)	35 (26.1)	103 (26.5)
Upper Respiratory	17 (13.4)	13 (10.1)	13 (10.4)	12 (9.0)	38 (9.8)
Sinusitis	7 (5.5)	4 (3.1)	3 (2.4)	8 (6.0)	15 (3.9)
Bronchitis, acute	0	4 (3.1)	2 (1.6)	2 (1.5)	8 (2.1)
Upper Respiratory, viral	3 (2.4)	5 (3.9)	2 (1.6)	1 (0.7)	8 (2.1)

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	Number (%) Subjects				
	Placebo	Ciclesonide			
Mg/ day ciclesonide	0	40	80	60	All
Influenza	2 (1.6)	0	0	4 (3.0)	4 (1.0)
Nervous System	9 (7.1)	7 (5.4)	8 (6.4)	14 (10.4)	29 (7.5)
Headache	9 (7.1)	7 (5.4)	7 (5.6)	13 (9.7)	27 (7.0)
Gastrointestinal	16 (12.6)	8 (6.2)	17 (13.6)	20 (14.9)	45 (11.6)
Vomiting	3 (2.4)	2 (1.6)	6 (4.8)	5 (3.7)	13 (3.4)
Upper abdominal pain	3 (2.4)	2 (1.6)	7 (5.6)	4 (3.0)	13 (3.4)
Apthous stomatitis	3 (2.4)	2 (1.6)	1 (0.8)	5 (3.7)	8 (2.1)
General Disorders	8 (6.3)	6 (4.7)	8 (6.4)	3 (2.2)	17 (4.4)
Pyrexia	7 (5.5)	6 (4.7)	5 (4.0)	1 (0.7)	12 (3.1)
Ear & Labyrinth	8 (6.3)	0	2 (1.6)	2 (1.5)	4 (1.0)
Ear pain	4 (3.1)	0	2 (1.6)	1 (0.7)	3 (0.8)

The second most frequently reported AE was infections. This occurred in 36.2%, 27.1%, 26.4%, and 26.1% of the subjects in the placebo, ciclesonide-40, ciclesonide-80, ciclesonide-160 groups respectively. Upper respiratory tract infection was slightly more common in the placebo patients (13.4% vs 9.8% ciclesonide).

In general, the adverse events were evenly distributed across the treatment groups. There was an excess of ear and labyrinth disorders in the placebo group (6.3% vs 1.0% in the ciclesonide subjects) but the absolute numbers were small.

Ophthalmologic Examination

Of the safety population, 478 subjects had both baseline and follow-up ophthalmologic examination. Two subjects had worsening lenticular opacities over the course of the study. In each case (one ciclesonide-40 and one ciclesonide-80 subject) the examination was normal at baseline and trace posterior subcapsular opacities were identified bilaterally at the end of the study. Six subjects had lenticular opacities at baseline and there was no change in any of them at end-of-study.

Serious and Important Adverse Events

There were no deaths reported, and there were 8 serious adverse events in 7 subjects. There were 3 cases of aggravated asthma (2 in placebo and one in ciclesonide-40 subjects). One of the placebo subjects with an asthma exacerbation also had pneumonia. In addition, there was one case each of head trauma, pneumonitis, and an anaphylactic reaction in subjects in the ciclesonide-40 group. An anaphylactic reaction occurred in a 5 year old male who developed hives, difficulty breathing and eyelid edema after handling peanuts. The episode resolved after the parent administered epinephrine and diphenhydramine. Study medication was not changed and the subject completed the protocol. One ciclesonide-160 subject had pericarditis. This was a 6 year old male enrolled in Poland. On study day 27 he was noted to

have rhinopharyngitis and on day 31 he was diagnosed with acute infective pericarditis. He was treated with antibiotics, diuretics and naproxen and the episode was considered to have resolved. Study medication was discontinued.

A total of 41 subjects were withdrawn due to adverse events: 19 in the placebo group and 23 in the ciclesonide- treated subjects (Table 109). The most common reason for withdrawal was aggravation of asthma. Only 5 subjects withdrew for an AE not related to worsening asthma. In the placebo group there was one case each of pneumonia, bronchitis, and viral upper respiratory infection. In the ciclesonide-160 group there was one case each of sinusitis and pericarditis. In addition, one placebo subject withdrew due to bronchopneumonia and asthma. The percentage of patients who had "other significant AEs" was comparable in all of the treatment groups.

Table 109. Other Adverse Events Reported in Study 342

	Placebo	Ciclesonide		
		40 mcg	80 mcg	160 mcg
Daily dose of ciclesonide	0	40 mcg	80 mcg	160 mcg
Subjects with other significant AEs, n (%)	79 (62.2)	73 (56.6)	69 (55.2)	70 (58.8)
AE (n [%]) resulted in:				
Discontinued from study	19 (15.0)	8 (6.2)	8 (6.4)	7 (5.2)
Therapy temporarily interrupted	0	0	0	1 (0.7)
Other intervention	12 (9.4)	4 (3.1)	2 (1.6)	4 (3.0)
Treated with counter active measure	74 (58.3)	72 (55.8)	67 (53.6)	74 (55.2)
Important laboratory abnormality, n (%)	2 (1.6)	0	0	1 (0.7)

Vital Signs

At baseline, systolic and diastolic blood pressure were abnormal in approximately 30% of the subjects, and the heart rate was abnormal in approximately 10%. The incidence was the same in the placebo and ciclesonide-treated subjects and it was unchanged at the end of the study. The incidence was 10.2 and 12.4% at the end of the study. The physical examination was unremarkable for any changes other than those associated with adverse events.

Significant Overdose

A 9-year-old male received 9 puffs of ciclesonide-80 on day 3. During the next 7 days he received 1 puff/day. An attack of asthma began on day 8 and study medication was discontinued on day 10.

Laboratory Abnormalities

Tests of liver function were generally unremarkable. The alkaline phosphatase reached the PCA level (>325 U/L [age 7 – 10 years] and increased by 28 U/L) in 8/115 (7.0%), 4/118 (3.4%), 3/114 (2.6%), and 4/125 (3.2%) of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively. In 6 of the placebo- treated subjects the alkaline phosphatase increased over the course of the study whereas it decreased in one subject. On the other hand, the alkaline phosphatase increased in 13 of the ciclesonide subjects and

decreased in 14. The transaminases reached the PCA level in less than 2% of the subjects in all of the treatment groups. However, one placebo subject had elevated transaminases that were reported as adverse events. The SGOT reached 77 U/L and SGPT 71 U/L.

An absolute eosinophil count of $>1.0 \times 10^3$ cells/uL was prospectively defined as “clinically noteworthy”. This level was reached at the end of the study in 6, 4, and 3, of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively. The PCA value ($> 0.57 \times 10^3$ cells/uL and an increase of 0.3710^3 cells/uL over the course of the study) was reached in 9/113 (8.0%) of the placebo, 6/115 (5.2%) of the ciclesonide-40, 5/110 (4.5%) of the ciclesonide-80, and 9/117 (7.7%) of the ciclesonide-160 subjects respectively.

Two subjects had abnormal laboratory values reported as adverse events in addition to the one placebo patient with abnormal transaminases. One placebo and one ciclesonide-160 subject had elevated triglycerides.

HPA-axis Evaluation

Blood for cortisol determination was available at both baseline and follow-up for 28 subjects recruited at 5 pre-selected centers (all in the United States) (Table 110). The peak serum cortisol after stimulation with 1 µg cosyntropin was slightly lower in the ciclesonide- 80 group than in the other treatment groups at baseline. After 12 weeks of treatment, the peak cortisol increased slightly in the placebo and ciclesonide-40 subjects, and fell slightly in the ciclesonide-80 and 160 groups. No statistics were provided for this data because of the small number of subjects. The degree of stimulation (peak – baseline cortisol), was similar in the treatment groups at the beginning of the study and fell in all treatment groups.

Table 110. Evaluation of HPA-axis in Study 342

	N (total)	N (early withdrawal)	Baseline*	Change from Baseline**	Difference from Placebo*
Peak post-stimulation serum cortisol, mcg/dL					
Placebo	8	0	28.63	2.70 (1.58)	
Ciclesonide-40	7	2	25.15	-2.75 (1.43)	5.45
Ciclesonide-80	6	0	19.83	0.01 (1.58)	2.69
Ciclesonide-160	7	0	22.43	-1.92 (1.39)	4.62
Degree of stimulation (peak-baseline), mcg/dL					
Placebo	8	0	14.13	2.96 (2.23)	
Ciclesonide-40	7	2	13.00	0.89 (2.02)	2.07
Ciclesonide-80	6	0	10.83	2.78 (2.23)	0.06
Ciclesonide-160	7	0	10.57	-3.49 (1.96)	6.45

* LS Mean ** LS Mean (SE)

Defining normal HPA function as a baseline cortisol of at least 5 mcg/dL and a post-simulation serum cortisol of at least 18 mcg/dL, two subjects (1 each in the ciclesonide-40 and ciclesonide-80 groups) were abnormal at baseline and normal at follow-up. One subject

in each of the active treatment groups was normal at baseline and abnormal at follow-up. Of those who became abnormal during the study, there were two ciclesonide-40 subjects who had a basal value of 4 mcg/dL. The post-stimulation cortisol was 22 and 19 mcg/dL. One ciclesonide-160 subject had an abnormal response due to a low post stimulation cortisol (11 µg/dL).

1.10.3. Discussion and Conclusions

In this pivotal 12-week trial, 514 subjects 4 – 11 years of age with asthma were treated with placebo, ciclesonide 40 mcg QD, ciclesonide 80 mcg QD, or ciclesonide 160 mcg QD. Compared with Study 341, the results of 342 showed a significant increase in FEV₁ % predicted, the primary outcome variable, for only the ciclesonide-160 dose. The secondary outcome variables did not follow the same pattern. The greatest improvement in AM PEF, AM PEF variability, asthma severity score, and nighttime awakenings was seen in the ciclesonide-40 group, and the greatest improvement in daily albuterol use was seen in the ciclesonide-80 group. The only variable that was dose-related was the drop-out rate which was 14.2% for the placebo patients, 3.8% for the ciclesonide-160 subjects, and intermediary for the ciclesonide-40 and 80 subjects.

The spectrum of adverse events was similar to that seen in all of the other studies with respiratory events being the most common and infections being the second most common. As compared with study 341 there were three cases of oropharyngeal candidiasis in subjects who received active treatment compared with none in the placebo group. Two active-treatment subjects also developed trace posterior subcapsular cataracts compared to none in the placebo group. One subject in the ciclesonide-160 group had an abnormal cortisol stimulation response at end-of-study.

1.11. Study #341LT

A multicenter, randomized, open-label, one-year long-term safety study of ciclesonide metered dose inhaler 50 µg/day to 200 µg/day (ex-valve: 40 to 160 µg/day ex-actuator). Administered once daily or fluticasone dry powder inhaler (Flovent® Rotadisk®) 50 µg or 100 µg administered twice daily for the treatment of children with persistent asthma.

1.11.1. Protocol

1.11.1.1. Administrative

Enrollment: September 19, 2001 – December 08, 2003

b(4)

Clinical Director: _____

Sites: 26 clinics in the United States

1.11.1.2. Objective

To establish the long-term (1 year) safety of ciclesonide metered-dose inhaler (MDI) at doses of 40 mcg to 160 mcg/day (ex-actuator) as compared to fluticasone dry powder inhaler (DPI) (Flovent® Rotadisk®) 50 mcg and 100 mcg/day BID (ex-actuator) in children with mild, moderate, or severe persistent asthma.

b(4)

1.11.1.3. Overall Design

This is a randomized, open label one year extension of pivotal study 341 in children 4 – 11 years of age. Subjects were enrolled within 4 weeks of the end of the pivotal trial. If patients were withdrawn prematurely from studies 341 due to an adverse event or an asthma exacerbation, they could still be enrolled in study 341LT if the event/exacerbation had resolved. In addition, screen failures from studies 341 were eligible to enroll in the follow-up study if the screen failure was based on a lack in fall in FEV₁ or failure to develop of symptoms during the placebo treatment period. Subjects with a “known history of posterior subcapsular cataract or significant lenticular opacities or glaucoma and abnormal laboratory examination” were excluded, as were subjects requiring >4 weeks corticosteroid treatment in the interim between exiting study 341 and enrollment into the long-term follow-up.

For the open label follow-up subjects were randomized in a 2:1 ratio (ciclesonide: fluticasone) and treated for at least 2 weeks:

Ciclesonide 160 mcg (80 mcg/puff x 2 puffs) QAM

Fluticasone DPI 100 mcg/day (50 mcg/puffs x 2 puffs) BID.

Subsequently the investigator could lower or raise the dose of ciclesonide between 40 and 160 mcg QD or fluticasone 50 – 100 mcg BID with the goal of finding the lowest dose that provided effective control of the patient’s asthma. Subjects could be treated with oral corticosteroids for exacerbations. Such treatment had to be limited to 2 courses not to exceed 7 days each. If the subject required a third course he/she had to be withdrawn. No other corticosteroid preparations were allowed during the study. However, β -agonists, theophylline, and cromolyn were permitted. Two courses of intranasal corticosteroids were permitted at centers that were not participating in the HPA-axis evaluation. The primary outcome variable was adverse events. Spirometry was performed but not qualified as an outcome variable.

1.11.2. Results

1.11.2.1. Subjects

All of the 193 screened subjects were randomized (129 to ciclesonide and 64 to fluticasone). Of the randomized subjects, 93 (72.1%) and 44 (68.8%) of the ciclesonide and fluticasone subjects respectively, completed the 1 year follow-up (Table 111). Combining “consent withdrawn” and “Lost-to-follow-up” suggested that a higher percentage of subjects in the fluticasone group withdrew for un-specified reasons (15 [23.4%]), compared with subjects treated with ciclesonide (22 [17.1%]). If the adverse events due to asthma exacerbation are added to the lack of efficacy withdrawals, a slightly higher percentage of subjects in the ciclesonide group (6 [6.5%]) withdrew due to poor asthma control than in the fluticasone group (2 [4.5%]). Diary-recorded compliance was high, but 92.2% of the ciclesonide subjects took \geq 90% of the medication while only 81.3% of the fluticasone subjects took \geq 90% of the medication.

Table 111. Disposition of subjects in study 341LT

	Number (%) Subjects		
	Ciclesonide n=129	Fluticasone n=64	Total n = 193
Completed Study	93 (72.1)	44 (68.8)	137 (71.0)
Reason for Discontinuation			
Consent withdrawn	12 (9.3)	13 (20.3)	25 (13.0)
Adverse Event	5 (3.9)	3 (4.7)	8 (4.1)
Lost to follow-up	10 (7.8)	2 (3.1)	12 (6.2)
Lack of Efficacy	5 (3.9)	2 (3.1)	7 (3.6)
Other	3 (2.3)	0	3 (1.6)
Protocol violation	4 (3.1)	2 (3.1)	6 (3.1)
Compliance	5 (3.9)	3 (4.7)	8 (4.1)
Death	1 (0.8)	0	1 (0.5)

As can be seen in Table 112, the demographic and clinical variables were evenly distributed between the two treatment groups. As in the pivotal trial, 61% were male and the mean age was 8.4 years. African-Americans made up 16.3% of the ciclesonide group and 23.4% of those treated with fluticasone. The pulmonary function variables were closely matched with a mean FEV₁ of 1.6 L which was approximately 81% of predicted and higher than that measured at the beginning of the pivotal trial (Mean FEV₁ in study 341 at baseline = 1.28 L).

Table 112. Demographic and Clinical Characteristics of Subjects in Study 341LT

		Ciclesonide n=129	Fluticasone n=64	Total n=293
Gender, n(%)	Male	81 (62.8)	37 (57.8)	118 (61.1)
	Female	48 (37.2)	27 (42.2)	75 (38.9)
Age, years	Mean (SD)	8.3 (2.2)	8.7 (2.1)	8.4 (2.2)
	Range	4-12	4-11	4-12
Race, n(%)	White	100 (77.5)	42 (65.6)	142 (73.6)
	Black	21 (16.3)	15 (23.4)	36 (18.7)
	Asian	0	1 (1.6)	1 (0.5)
	Other	8 (6.2)	6 (9.4)	14 (7.2)
Hispanic, n(%)		16 (12.4)	8 (12.5)	24 (12.4)
Duration of Asthma (years)	Mean (SD)	4.9 (2.7)	5.2 (3.0)	5.0 (2.8)
	Range	0.6-11.4	0.5 – 11.5	0.5-11.5
FEV₁ Liters	Mean (SD)	1.56 (0.48)	1.63 (0.50)	1.58 (0.49)
	Range	0.61-3.02	0.42-2.76	0.42-3.02
FEV₁ % predicted	Mean (SD)	81.4 (14.3)	79.9 (13.5)	80.9 (14.00)
	Range	46.0-167.4*	39.5-118.1	39.5-167.4

* The applicant attributed this wide range to an outlier that was due to an incorrect height measurement at the beginning of the study.

1.11.2.2. Safety results

After enrollment in study 341LT, The ciclesonide subjects were treated for a mean of 295.3 days (median 364, range 1-393) and the fluticasone subjects were treated for a mean of 289.6 days (median 363., range 4-379). The average daily dose of ciclesonide was 140.4 ± 30.1 mcg (range 48-160 mcg) and the average daily dose of fluticasone was 179.4 ± 32.2 mcg/day (range 104-200) The highest dose of study drug was prescribed for 75 (58.1%) of the ciclesonide subjects and 40 (62.5%) of the fluticasone subjects throughout the study.

The adverse event experience of the population is summarized in Table 113. There were 7 serious AEs (4 in the ciclesonide group and 3 in the fluticasone group). There was one death in the ciclesonide group (*see Serious Adverse Events below*), two cases of asthma exacerbation, and 1 case of trauma. In the fluticasone group there was one case each of atelectasis, status asthmaticus, and pneumonia. Other adverse events were distributed evenly between the two treatment groups.

Table 113. Summary of Adverse Events in Study 341LT

	Number (%) Subjects		
	Ciclesonide n=129	Fluticasone n=64	Total n=193
All adverse events	103 (79.8)	52 (81.3)	155 (80.3)
Serious Adverse Events	4 (3.1)	3 (4.7)	7 (3.6)
Deaths	1 (0.8)	0	1 (0.5)
Other Significant adverse events resulting in the following:	102 (79.1)	48 (75.0)	150 (77.7)
Discontinue medication	5 (3.9)	3 (4.7)	8 (4.1)
Interrupt therapy	1 (0.8)	0	1 (0.5)
Increase dose	2 (1.6)	1 (1.6)	3 (1.5)
Other intervention	19 (14.7)	4 (6.3)	23 (11.9)
Treated with medication	101 (78.3)	48 (75.0)	149 (77.2)
Medically important laboratory abnormalities	3 (2.3)	0	3 (1.5)

1.11.2.3. Adverse Events

At the end of the one-year follow-up, 155 (80.3%) of the subjects had reported at least 1 adverse event: 103 (79.8%) of the ciclesonide and 52 (81.3%) of the fluticasone subjects (Table 114). The most common treatment-emergent adverse events by system were infections/infestations with 68.8% of the fluticasone and 58.1% of the ciclesonide reporting these events. The incidence was higher in the fluticasone subjects despite the fact that the ciclesonide subjects reported more nasopharyngitis, sinusitis, ear infection, and viral upper respiratory infection. The fluticasone subjects had more upper respiratory tract infection

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(NOS), viral infection (NOS), pharyngitis, influenza, acute sinusitis, and tonsillitis. There were no cases of oropharyngeal candidiasis in the ciclesonide-treated subjects and only one in the fluticasone group.

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Respiratory tract AEs were the next most frequent with 44.2% of the ciclesonide subjects and 42.2% of the fluticasone subjects reporting AEs. There was a relatively large number of asthma exacerbations (29.5 and 21.9% in the ciclesonide and fluticasone groups respectively), however, the incidence was not markedly different between the two treatments. There were almost twice as many headaches and skin rash in the ciclesonide group compared with subjects treated with fluticasone.

Table 114. Adverse Events Reported in Study 341LT

	Number (%) Subjects	
	Ciclesonide n=129	Fluticasone n= 44
All adverse events	103 (79.8)	52 (81.3)
Infections and infestations	75 (58.1)	44 (68.8)
Nasopharyngitis	29 (22.5)	11 (17.2)
Sinusitis	20 (15.5)	9 (14.1)
Upper respiratory tract	19 (14.7)	14 (21.9)
Influenza	2 (1.6)	3 (4.7)
Upper respiratory tract, viral	11 (8.5)	14 (21.9)
Ear infection	14 (10.9)	3 (4.7)
Pharyngitis, streptococcal	11 (8.5)	3 (4.7)
Viral Infection	9 (7.0)	7 (10.9)
Otitis media	6 (4.7)	1 (1.6)
Pharyngitis	3 (2.3)	2 (3.1)
Sinusitis, acute	0	2 (3.1)
Tonsillitis	0	2 (3.1)
Respiratory manifestations	57 (44.2)	27 (42.2)
Asthma exacerbation	38 (29.5)	14 (21.9)
Cough	7 (5.4)	3 (4.7)
Nasal congestion	7 (5.4)	4 (6.3)
Pharyngolaryngeal pain	7 (5.4)	5 (7.8)
Bronchitis	4 (3.1)	1 (1.6)
Rhinitis, allergic	4 (3.1)	2 (3.1)
Epistaxis	3 (2.3)	2 (3.1)
Atelectasis	0	2 (3.1)
General Disorders	26 (20.2)	13 (20.3)
Pyrexia	18 (14.0)	9 (14.1)
Influenza-like illness	5 (3.9)	1 (1.6)
Pain, NOS	3 (2.3)	3 (4.7)
Nervous system	22 (17.1)	6 (9.4)
Headache	18 (14.0)	6 (9.4)

	Number (%) Subjects	
	Ciclesonide	Fluticasone
Musculoskeletal	7 (5.4)	4 (6.3)
Pain in extremity	2 (1.6)	2 (3.1)
Gastrointestinal	18 (14.0)	10 (15.6)
Upper abdominal pain	3 (2.3)	4 (6.3)
Tooth Ache	5 (3.9)	2 (3.1)
Vomiting	3 (2.3)	5 (7.8)
Ear Disorders	6 (4.7)	0
Ear pain	5 (3.9)	0
Skin	14 (10.9)	7 (10.9)
Rash	8 (6.2)	0
Psychiatric Disorders	4 (3.1)	3 (4.7)
Depression	1 (0.8)	2 (3.1)
Immune System Disorders	3 (2.3)	4 (6.3)
Hypersensitivity, NOS	2 (1.6)	3 (4.7)

Eye Involvement

There were 167 subjects with a slit lamp examination at baseline and at the end of the study. Lenticular opacities were detected in 5 subjects at baseline. Of the 162 subjects with a normal slit lamp examination at the beginning of the study, 3 in the ciclesonide group developed trace cataracts in one eye at the end of the study. Two of these cataracts were posterior subcapsular. In one subject, an 8 year-old female, the cataract was detected at the six month follow-up and was associated with color blindness and decreased visual acuity. The subject was withdrawn from the study. The 3 subjects who developed cataracts were re-examined by a second ophthalmologist after the study evaluation was completed, and none of the findings was confirmed. There were no cataracts in the fluticasone-treated subjects. Five subjects with cataracts at baseline, 3 (one on ciclesonide and two on fluticasone) had no change. Two ciclesonide-treated subjects had improvement from trace to 0 cataracts bilaterally.

Reviewer: The subjects were reexamined by a second ophthalmologist who did not know the results of the first examination. However, there was no pre-defined protocol for eye evaluation (they were instructed to dilate the pupil) and there is no description of a screening process or eligibility for the participating ophthalmologists. This type of re-examination is highly biased. To use the findings to support the conclusion that ciclesonide does not promote the development of cataracts all of the subjects would have had to be re-examined.

Deaths

One death was reported in a 12 year-old female receiving ciclesonide. The subject had a seizure at 2 or 3 years of age and another at 5 years of age. She was not taking preventive

medication at the time of enrollment into study 341/341lt. According to the DSI audit report, the subject also had encephalitis at the age of 5 years. The episode left her with serious disabilities that required special education classes for several years. The subject had asthma diagnosed in April of 2000 and was enrolled in study 341 on April 29, 2002. At the time of enrollment she was classified as mild-persistent asthma. She had a FEV₁ of 2.05 (63.5% predicted) and had been treated with albuterol and proventil only. For the 12-week pivotal study she was treated with ciclesonide-160 mcg/day and her FEV₁ fell to 1.61L by the end of the study on July 19, 2002. A course of antibiotics was prescribed during the last 4 days of the pivotal trial. She was enrolled in study 341lt immediately following completion of study 341, and ciclesonide- 160 mcg/day was continued. Repeat spirometry was recorded as an FEV₁ = 1.64L (50% predicted). Baseline laboratory values including cosyntropin stimulation were unremarkable. Between enrollment in the long-term follow-up study and her last clinic visit on August 30, 2002 the FEV₁ increased back to 2.08 L. At the time of the clinic visit she was described as stable with a PEF of 200-230 L/min. Eighteen days after the last clinic visit (day 61 of the long-term treatment protocol) she developed a viral URI and stayed out of school for the next two days. On _____ (Day -) she returned to school. During warm-up exercises for her physical education class she used an inhaler (bystanders did not notice any "marked asthma symptoms"), started a spritz, and then fell to the floor a few minutes later. She said "I can't see" and had difficulty breathing. She vomited, clenched her teeth and suffered seizure-like activity. She became apneic and unresponsive and a police officer who was on the scene initiated CPR immediately. The subject was, intubated, and ventilated, however ventricular fibrillation recurred and she could not be resuscitated after an attempt that lasted 1 hour and 20 minutes.

An autopsy was performed and no abnormal results were described. Specifically, "Sections of the large and small airways show no significant acute or chronic inflammation or changes of an acute asthmatic attack. The lungs show no acute or chronic inflammation, fibrosis, granulomas, infarction, thromboembolism, hemorrhage, or neoplasia. Congestion and edema are present." There was no evidence of aspiration. The heart was extensively sectioned and no abnormalities were found. The conducting system was normal and there was no sign of myocarditis. Histologic examination of the brain was normal and a toxicology screen was negative. The state medical examiner determined that the cause of death was most likely sudden cardiac arrhythmia of undetermined origin. The DSI audit of the site revealed no protocol deviations.

Reviewer: The above summary was taken from the sponsor's summary as well as from the data sheets for study 341 and 341LT and from s_216 submitted to IND 53391 which contained the final autopsy report. The DSI audit of the site was also reviewed..

Laboratory Values

Transaminase elevation was reported as an adverse event in one ciclesonide-treated subject. The maximum levels were 117 U/L for SGPT and 88 U/L for SGOT on day 88. The levels returned to normal after 6 days without change in study medication. Less than 2% of the liver enzymes reached the PCA level in either of the treatment groups except for the alkaline phosphatase which was both abnormal and had increased by 28 U/L during the study in 8/109 (7.3%) and 4/58 (6.9%) of the ciclesonide and fluticasone-treated subjects respectively. The

maximum abnormal values ranged from 325-458 U/L in the ciclesonide group and 305-383 U/L in the fluticasone group.

The eosinophil count was clinically noteworthy ($>1.0 \times 10^3$ cells/mm³) in 5 ciclesonide and 3 fluticasone-treated subjects. The values ranged from $1.12 \times 10^3 - 2.08 \times 10^3$ cells/mm³ in the ciclesonide group and $1.04 - 1.51 \times 10^3$ cells/mm³ in the fluticasone group. In all but one of these cases, the count was abnormal ($>0.57 \times 10^3$ cells/mm³) at baseline. The PCA values for eosinophil count were reached in 4/108 (3.7%) of the ciclesonide and 2/56 (3.6%) of the fluticasone-treated subjects. The shift tables showed that more subjects had a decrease in eosinophil count than an increase in both treatment groups.

The neutrophil counts and total white cell counts were recorded as having fallen to below the PCA level (1×10^3 cells/mcL) in 4/108 (3.7%) of the ciclesonide subjects, but no fluticasone subject. In two of the subjects both the neutrophils and total white count were low, in 2 subjects only the neutrophils count was low, and in 2 subjects only the total white count was low. The range of abnormal values was 0.77 – 1.27 for the neutrophils count and 3.98-4.31 for the total white count.

Other laboratory values that were reported as adverse events included a cholesterol level of 228 mg/dL (baseline=208 mg/dL) and a calcium level of 10.6 mg/dL (baseline 10.3 mg/dL) in one ciclesonide subject

Reviewer: A triglyceride level of 235 mg/dL is listed as an adverse event in Table 26 (pg 106 clinstat\341lt\study341lt.pdf sent in with the 120-day safety update. This event was reported on day 1 of the study and the value one year later was 76 mg/dL.

HPA-axis Function

Samples were collected for HPA-axis evaluation in 3 sites. There were 11 ciclesonide and 4 fluticasone-treated subjects who had results from both the baseline and at 12 months. In the ciclesonide subjects both the pre and post stimulation values increased whereas both values decreased for the fluticasone treated subjects (Table 115). However, the changes were small in both cases and based on a small number of subjects. Only 4 of the fluticasone subjects had measurements at 12 weeks.

Table 115. Serum Cortisol During Cosyntropin Stimulation Test in Study 341lt

	N (total)	N (early withdrawal)	Pre- stimulation*	Post- stimulation*
Baseline cortisol, mcg/ dL				
Ciclesonide	14	3	14.14 (5.3)	22.86 (3.1)
Fluticasone	9	5	12.56 (6.4)	23.22 (4.3)
End of Study cortisol, mcg/dL				
Ciclesonide	14	3	14.50 (4.6)	23.42 (3.8)
Fluticasone	9	5	11.67 (4.1)	21.67 (3.7)

* LS Means (SE)

Defining normal HPA-axis function as a baseline serum cortisol of ≥ 5 $\mu\text{g/dL}$ and a post-stimulation value of ≥ 18 $\mu\text{g/dL}$ one ciclesonide subject was abnormal at baseline and follow-up and one was abnormal only at baseline. In both cases the abnormality was in the post stimulation value which ranged from 14 – 17 mcg/dL . There were no abnormal values recorded in the fluticasone group.

1.11.2.4. Pulmonary function

Results from spirometry were available for 188 (124 ciclesonide, 64 fluticasone) subjects at baseline and follow-up. The baseline FEV_1 was 1.57 and 1.63 L in the ciclesonide and fluticasone-treated subjects respectively. The change in baseline was 190 and 230 ml in the ciclesonide and fluticasone subjects respectively.

1.11.3. Discussion and Conclusions

This was a 12-month open label follow-up safety study comparing treatment with varying doses of ciclesonide (40-160 mcg/day) with a similar treatment algorithm for fluticasone (50-100 mcg BID). Follow-up was not dramatically different in the two groups although more than 20% of the fluticasone group withdrew consent for unspecified reasons (compared with 9.3%) of the ciclesonide subjects. This finding may be influenced by the twice daily dosing of fluticasone which might have been less convenient for the subjects. On the other hand, the study was not blinded and it is impossible to assess investigator bias in retrospect. However, investigator enthusiasm for ciclesonide could explain differential drop-out. Withdrawal for lack of efficacy was slightly more common in the ciclesonide group. At some time during the year of follow-up approximately 80% of each treatment group reported an adverse event. The most common AEs were classified as infections. The fluticasone-treated subjects had more infections (68.8% compared with 58.1% for ciclesonide) and this was mostly due to upper respiratory tract NOS; influenza; upper respiratory tract viral; and viral infection. Oral candidiasis was very uncommon with only 1 case in a fluticasone-treated patient reported in the entire group. Respiratory events (44.2 and 42.2% ciclesonide and fluticasone respectively) and asthma exacerbations (29.5 and 21.5% ciclesonide and fluticasone respectively) were more common in the ciclesonide group.

Lenticular opacities developed in three (2 posterior subcapsular) of the ciclesonide-treated subjects but in no fluticasone-treated subject. The sponsor had the 3 subjects re-evaluated by a non-study ophthalmologist. It is stated in the study report that the new examiner was blinded as to the results of the first examination, however, it is not known exactly what he was told about why the examination was being performed. In addition, it is not clear if the examiner knew the study medication that the subject had been taking. The examiners were advised to dilate the pupil, but no other forms or procedures were specified. Even if the examiners were totally blinded as to all previous procedures and if they adhered to a specific study protocol, this type of selective re-examination is not useful in assessing this potential risk. The only way the information could be used is if all of the subjects were re-examined.

The single death in a 12 year-old child is disturbing. Her pulmonary function deteriorated during the pivotal trial, falling from the moderate to the severe range ($\text{FEV}_1 = 49.9\%$ predicted) just prior to enrollment in the follow-up study. During the first two months of the

follow-up trial her FEV₁ increased back to baseline prior to developing a URI which kept her out of school for two days. On the first day back to school she collapsed in gym class. A thorough autopsy failed to find any abnormalities and the presumed cause of death is a cardiac arrhythmia.

The HPA-axis evaluation was complete in very few subjects and showed no remarkable differences between baseline and end of study or between the treatment groups. In summary, the adverse event profile seen in the long term study was similar to that of the 12-week trials. However, the issue of cataracts remains to be settled and the occurrence of death in the 12-year old is disturbing.

1.12. Study #342LT

A multicenter, randomized, open-label, one-year long-term safety study of ciclesonide metered dose inhaler 50 mcg/day to 200 mcg/day (ex-valve: 40 to 160 mcg/day ex-actuator). Administered once daily or fluticasone dry powder inhaler (Flovent® Rotadisk®) 50 mcg or 100 mcg administered twice daily for the treatment of children with persistent asthma.

1.12.1. Protocol

1.12.1.1. Administrative

Enrollment: September 5, 2001 – December 08, 2003

Clinical Director: _____

Sites: 26 clinics in the United States

b(4)

1.12.1.2. Objective

To establish the long-term (1 year) safety of ciclesonide metered-dose inhaler (MDI) at doses of 40 mcg to 160 mcg/day (ex-actuator) as compared to fluticasone dry powder inhaler (DPI) (Flovent® Rotadisk®) 50 mcg and 100 mcg/day BID (ex-valve) in children with mild, moderate, or severe persistent asthma.

1.12.1.3. Overall Design

This long term study was of identical design to study 341LT (pg. 185).

1.12.2. Results

1.12.2.1. Subjects

Of the 192 subjects screened, 190 were randomized (128 to ciclesonide and 61 to fluticasone). Of the randomized subjects 96 (75.0%) and 45 (72.6%) of the ciclesonide and fluticasone subjects completed the 1 year follow-up respectively (Table 116). Combining "consent withdrawn" and "Lost-to-follow-up" suggested that a higher percentage of subjects in the fluticasone group withdrew for un-specified reasons (13 [20.9%]), compared with subjects treated with ciclesonide (14 [10.9%]). If the adverse events due to asthma exacerbation are added to the lack of efficacy withdrawals, all of the withdrawals due to lack of efficacy were in the ciclesonide group (13 [10.2%]). Diary-recorded compliance was high, but 90.0% of the ciclesonide subjects took \geq 90% of the medication while only 70.5% of the