

1.1.1.9. 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 0.20 L in FEV₁ 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 0.48 liters.

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 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 320 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 160 mcg/day was compared to placebo. Finally, if the first two comparisons were statistically significant, then ciclesonide 80 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, e.g., albuterol was taken within 4 hours of spirometry, 3) the subject was 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 with Kaplan-Meier time to event analyses and the log-rank test. The rates of withdrawal were also compared using Fisher's exact test. Asthma Severity Scores, AM PEF, and albuterol use were analyzed during the first week of randomized treatment. 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 (12-17 vs 18-64, and >64 years), gender, race (white vs non-white), previous therapy (Stratum 1 vs Stratum 2) baseline FEV₁ (above and below 70% predicted), and pooled center.

Patient Reported Outcomes

Patient reported outcomes were assessed using the Asthma Quality of Life Questionnaire (AQLQ). The Asthma Quality of Life Questionnaire is made up of 32 questions categorized as belonging to one of four domains (activity limitations, symptoms, emotional function, and exposure to environmental stimuli). Each question has a response range of 1 ("totally limited", "A very great deal of distress" or "All of the time") to 7 ("not at all limited", "None", or "None of the Time") depending on the form of the question. In the domain of activity limitation, a category 8 ("Activity not done") could be a response in the follow-up questionnaires. The overall score was the mean of the 32 questions and separate means were calculated for each of the four domains. For any individual subject, at least half of the questions had to have been answered to calculate either the overall or domain score. 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.

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 created 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 all dependent on age and sex, and each is listed in the study report (*Appendix A.4.1.Laboratory Normal Ranges, pg 672-702: clinstat\321\study321a.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 (1 µg) 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 criteria see 1.1.1.4. Study Population, pg. 62*); and 24-hour urinary free cortisol and free cortisol corrected for creatinine.

1.1.2. Results

1.1.2.1. Study Population

Disposition

Of the 1082 subjects screened, 526 were randomized: placebo = 134, ciclesonide 80 mcg = 133, ciclesonide 160 = 128, and ciclesonide 320 = 131. The percentage of completers was comparable in the active treatment groups (82-85%) but was only 64% in the placebo-treated subjects. As shown in Table 16, drop-out in the placebo-treated subjects was particularly notable for “lack of efficacy” (29.9%) and “adverse event” (16.4%). Of the adverse events, all but 7 (2 placebo, 3 ciclesonide-160, and 2 ciclesonide-320) were due to asthma exacerbations (*see Adverse Events, pg. 76*). All but 1 asthma exacerbation in the placebo group was also designated “lack of efficacy”. (*Listing 3, pg 1590 and Listing 29, pg 4774 – clinstat\321\study_321a.pdf.*)

Table 16. Disposition of Subjects in Study 321

	Placebo	Ciclesonide			Total
Dose of ciclesonide, µg/day	0	80	160	320	N/A
Randomized Subjects, n	134	133	128	131	526
Completed study, n (%)	86 (64.2)	112 (84.2)	105 (82.0)	112 (85.5)	415 (78.9)
Discontinued from study, n (%)	48 (35.8)	21 (15.8)	23 (18.0)	19 (14.5)	111 (21.1)
Reason for Discontinuation, n (%)					
Lack of efficacy	40 (29.9)	18 (13.5)	12 (9.4)	8 (6.1)	78 (14.8)
Adverse event	22 (16.4)	5 (3.8)	9 (7.0)	5 (3.8)	41 (7.8)
Consent withdrawn	4 (3.0)	3 (2.3)	3 (2.3)	4 (3.1)	14 (2.7)
Loss to follow-up	1 (0.7)	0	2 (1.6)	1 (0.8)	4 (0.8)
Protocol violation	2 (1.5)	0	2 (1.6)	3 (2.3)	7 (1.3)
Death	0	0	0	0	0
Poor compliance	0	0	0	0	0
Other	2 (1.5)	2 (1.5)	1 (0.8)	3 (2.3)	8 (1.5)

Seven patients were withdrawn from the study due to protocol violations. All were included in the ITT population except 1 patient who was enrolled in study 321 twice and 1 patient who was enrolled in both study 321 and study 323. This resulted in an ITT population of 524 (134 on placebo, 133 on ciclesonide-80, 128 on ciclesonide-160, and 131 on ciclesonide-320) subjects and a safety population of 526.

Compliance, as determined from the diary records was high. By this measure, compliance was >90% in at least 95% of the subjects in all of the treatment groups.

Demographics

The ITT population consisted of 290 (55.3%) subjects in Stratum 1 (subjects previously treated with ICS) and 234 (44.7%) in Stratum 2 (subjects previously treated only with bronchodilators). There were 213 (40.6%) males and 311 (59.4%) females, the mean age was 36.6 years with a range of 12-72, and 87% of subjects were Caucasian. The distribution of these characteristics was comparable across the treatment groups (Table 17)

Table 17. Demographics and Clinical Variables for the ITT Population Enrolled in Study 321

	Placebo	Ciclesonide			Total
Dose of ciclesonide, µg/day	0	80	160	320	N/A
n	133	133	127	131	524
Stratum 1*, n(%)	74 (55.6)	75 (56.4)	70 (55.1)	71 (54.2)	290 (55.3)
Stratum 2, n(%)	59 (44.4)	58 (43.6)	57 (44.9)	60 (45.8)	234 (44.7)
Gender: Male, n(%)	50 (37.6)	55 (41.4)	55 (43.3)	53 (40.5)	213 (40.6)
Female, n(%)	83 (62.4)	78 (58.6)	72 (56.7)	78 (59.5)	311 (59.4)
Mean Age (years)	37.0	35.7	36.8	37.1	36.6 (14.4)
Range	12-67	12-70	12-72	12-72	12 - 72

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

The mean duration of asthma prior to enrollment was 18.6 ± 13.71 years with a range of 0.4 to 63.0 years. Prior to enrollment 99.6% of the subjects were using short acting β-agonists, 55.4% were taking ICS, and 8.2% used leukotriene receptor antagonists. Three patients took methylxanthines, and none used cromolyn.

Comparing the two strata based on prior asthma medication, the subjects who had been on maintenance ICS (Stratum 1) were older, however more of them had had asthma for less than 5 years than the patients in Stratum 2. The distribution between genders was markedly different in Stratum 1 with males making up only 33.4% of the subjects. In Stratum 2 the distribution between genders was similar (49.6% males, 50.4% females). The mean FEV₁ after 5 to 28 days of placebo treatment was larger in the Stratum 2 subjects (2.67 ± 0.62 Liters compared to 2.27 ± 0.54 Liters in the Stratum 1 subjects). In Stratum 1 there were 26 (8.9%) subjects with an FEV₁% at randomization of less than 60% predicted. In Stratum 2 there were 4 (1.7%) subjects with an FEV₁% of less than 60% predicted. These results are summarized in Table 18.

Table 18. Clinical Characteristics of Subjects Based on Prior Asthma Treatment

	Stratum 1 * (N=290)	Stratum 2** (N=234)
Age, years (Mean [SD])	39.2 (14.5)	33.5 (13.7)
Range	12-71	12-72
Gender: Male, n (%)	97 (33.4)	116 (49.64)
Female, n (%)	193 (66.6)	118 (50.4)
Duration of Asthma, n (%)		
< 2 years	20 (6.9)	11 (4.7)
2-5 years	38 (13.1)	19 (8.1)
> 5 years	232 (80.0)	204 (87.2)
FEV ₁ at screening, L (Mean [SD])	2.70 (0.64)	2.71 (0.61)
FEV ₁ at randomization, L (Mean [SD])	2.27 (0.54)	2.67 (0.62)
FEV1 % predicted at randomization, %	68.5	73.3
Range FEV1 % predicted	38.0 – 88.1	53.1 – 95

** Stratum 1 = subjects treated with ICS prior to enrollment, ** Stratum 2 = subjects treated with bronchodilators only prior to enrollment.*

In addition to ICS, the stratum 1 subjects were treated with long-acting β-agonists and leukotriene inhibitors more frequently than the stratum 2 subjects. Salmeterol had been taken by over 40% of the stratum 1 subjects but only 5.6% of the stratum 2 subjects. Leukotriene inhibitors had been taken by approximately 15% of the stratum 1 subjects while only 1 (0.4%) of the stratum 2 subjects were treated with them. Almost all of the subjects took short-acting β-agonists. For the most part, stratum 2 subjects had been managed on short-acting β-agonists alone while the stratum 2 subjects had received ICS, frequently with other controller medications.

Reviewer: The distribution of medication within strata prior to enrollment is taken from the dataset "... \crt\datasets\321\CONDRUG.xpt". The data in Table 18 and the percentage of subjects with FEV1% less than 60% are taken from the End-of-text tables 12-12, 12-13 (pg 186-188), 12-21, and 12-22 (pg 208-210) [... \clinstat\321\study321.pdf and ... \crt\datasets\321\effpft.xpt].

1.1.2.2. Efficacy Outcomes

The primary efficacy variable in this study was change from baseline to end of study (Week12-LOCF) in the pre-dose AM FEV₁ (L). The ITT population was made up of 524 subjects: 133 in the placebo group, 133 in the ciclesonide-80 group, 127 in the ciclesonide-160 group, and 131 in the ciclesonide-320 group. The baseline pulmonary function was comparable in all of the treatment groups (Table 19).

Table 19. Baseline Pulmonary Function Study 321

Dose of ciclesonide	µg/day	Placebo	Ciclesonide (dose/day)		
		0-	80	160	320
N		133	133	127	131
FEV ₁ (L)	Mean (SD)	2.46 (0.69)	2.44 (0.57)	2.46 (0.56)	2.45 (0.61)
	Range	1.13-4.15	1.46-3.93	1.29-3.69	1.30-4.28
FEV ₁ % predicted (%)	Mean (SD)	71.1 (8.4)	70.3 (8.0)	71.7 (8.1)	70.8 (8.2)
	Range	47.0-86.5	55.5-90.2	54.3-85.4	47.0-94.8

Over the 12-week period, the FEV₁ increased by 200 ml in the placebo group, 320 ml in the ciclesonide-80 group, 260 ml in the ciclesonide-160 group, and 350 ml in the ciclesonide-320 group. The difference between placebo and ciclesonide-treated subjects was 150 mls for the high-dose ciclesonide subjects (p=0.0014) but it was only 70 ml for the comparison between placebo and ciclesonide-160 (p=0.1645) (Table 20).

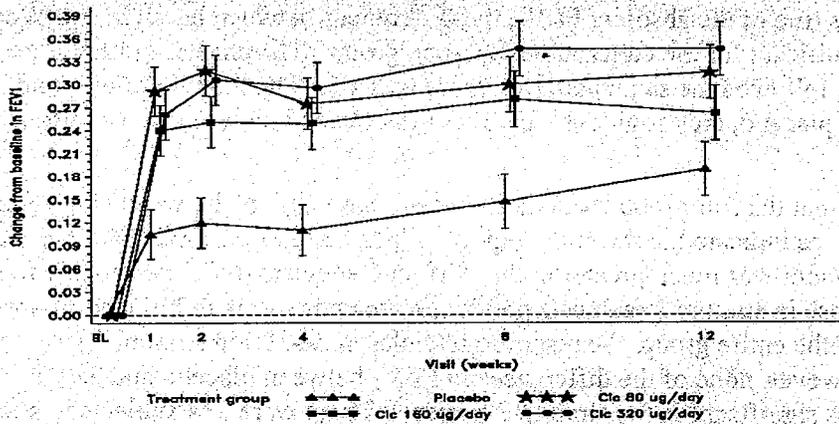
Reviewer comment: Using the step-down procedure defined a priori in the protocol to address multiplicity, only the ciclesonide 320 mcg dose achieved statistical significance. If a Bonferroni method had been used (p = 0.05/3), the 160 mcg dose would also not have achieved statistical significance.

Table 20. Change in FEV₁: Baseline – Week 12 (LOCF)

	LS mean difference (mL)	95% Confidence Interval	p-value
Difference between baseline and Week 12 (LOCF) pre-dose AM FEV ₁			
Placebo	200	0.13, 0.27	
Ciclesonide-80	320	0.25, 0.39	
Ciclesonide-160	260	0.19, 0.33	
Ciclesonide-320	350	0.28, 0.42	
Change from Baseline to Week 12 (LOCF) in Pre-dose FEV ₁ comparing ciclesonide and placebo treatment			
Ciclesonide-80-placebo	120	30, 210	
Ciclesonide-160-placebo	70	-30, 160	0.1645
Ciclesonide-320-placebo	150	60, 250	0.0014

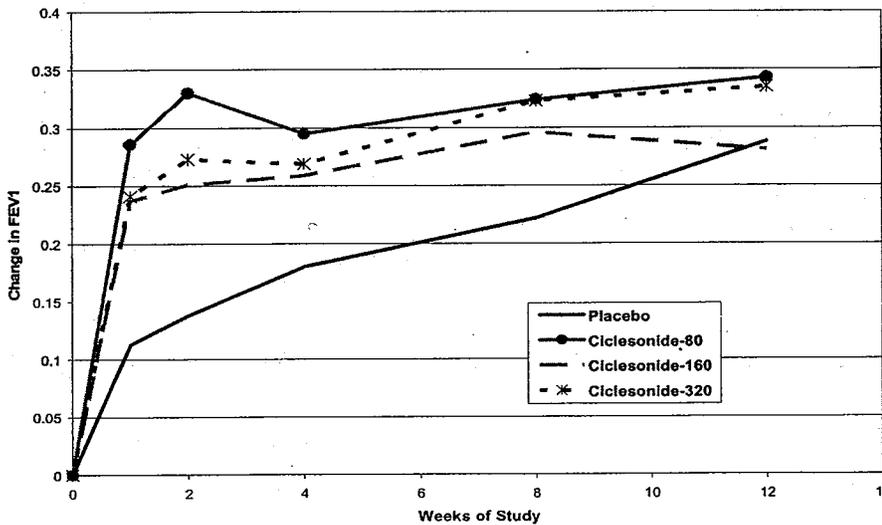
The results of the LOCF analysis are depicted graphically in Figure 2.

Figure 2. Change in FEV1 with Treatment in Study 321



Reviewer: Note that the Week 12 values reported by the Applicant includes measurements from earlier time points carried forward (LOCF). The actual number of subjects at Week 12 were: Placebo n = 86, ciclesonide-80 n = 112, ciclesonide-160 n = 105 and ciclesonide-320 n = 112. In a completer analysis the mean change from baseline in Pre-dose FEV₁ (mL) at Week 12 was 288, 343, 281, and 335 mL in the placebo, and the ciclesonide-80, 160, and 320 mcg groups respectively. Compared to placebo the change from baseline was 55, -7, and 47 mL in the ciclesonide-80, ciclesonide-160 and ciclesonide 320 mcg groups respectively. When the data were analyzed without LOCF, the response differential between placebo and ciclesonide treatment was not maintained throughout the 12-week treatment period Figure 2. (Source: End-of-Text Table 12-38 [...\clinstat\321\study321.pdf, pg 241])

Figure 3. Non-LOCF Analysis of Results from Study 321*



*(Source:crt\datasets\321\effpft.xpt)

At Week 12 the (LOCF) FEV₁, as a percent of baseline, increased by 8.66%, 13.44%, 11.2%, and 15.28% in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively. As was true of the absolute FEV₁, the differences between baseline and Week 12 (LOCF) were significant for the ciclesonide 320 mcg group. The change in FEV₁, as a percent of predicted, followed the same pattern. There was a 5.39%, 8.83%, 7.66%, and 9.7% increase in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively.

The applicant states that the sub-group analysis shows no “interaction” between strata and treatment. However, as indicated in the study report (... \clinstat\321\study321.pdf, pg. 409), the response to treatment was much greater in the stratum 1 subjects (those previously treated with ICS) than in those in stratum 2 (subjects previously treated only with bronchodilators). As in the analysis of the entire group, the response to ciclesonide-320 in stratum 1 subjects was significant. However, none of the differences in FEV₁ between placebo and active treatment groups was significant in the stratum 2 subjects. There were 234 subjects in stratum 2 and 290 in stratum 1 so the difference in statistical analysis is not due to smaller numbers in stratum 2. In absolute terms, the increase in FEV₁ after ciclesonide-320 in the stratum 1 subjects was 244 mL greater than placebo while it was 36 mL larger than placebo in the stratum 2 subjects (Table 21 and 22). (Table 21 and 22 are taken from Dr. Ted Guo’s biostatistical review, pg 60).

Table 21. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Controller (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1540	0.0627	2.46	0.0147	0.0059	0.3022
100mcg2PfsQD vs Placebo	0.1074	0.0636	1.69	0.0924	-0.0429	0.2577
200mcg2PfsQD vs Placebo	0.2442	0.0633	3.86	0.0001	0.0947	0.3937

Table 22. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Reliever (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0719	0.0753	0.96	0.3404	-0.1062	0.2501
100mcg2PfsQD vs Placebo	0.0223	0.0758	0.29	0.7694	-0.1572	0.2017
200mcg2PfsQD vs Placebo	0.0358	0.0750	0.48	0.6331	-0.1416	0.2133

The finding that response to ciclesonide is dependent upon prior asthma treatment, is also supported by the fact that the drop-out rate was dose dependent in stratum 1 subjects but not in stratum 2 (See *Withdrawals*, pg. 74).

The baseline values for the secondary outcome variables were similar in all of the treatment groups (Table 6.)

Table 23. Baseline Values for Secondary Efficacy Variables for Subjects Enrolled in Study 321

		Ciclesonide			
		Placebo	80	160	320
Dose ciclesonide	µg/day	0	80	160	320
n		133	133	127	131
AM PEF (L/min)	Mean (SD)	364 (90)	358 (93)	364 (89)	365 (91)
	Range	192-667	163-603	170-670	166-717
Asthma Severity Score	Mean (SD)	2.65 (1.49)	2.64 (1.37)	2.50 (1.48)	2.70 (1.48)
	Range	0.0-7.0	0.0-6.1	0.0-7.0	0.0-6.1
Daily albuterol use (puffs/ day)	Mean (SD)	3.1 (2.5)	3.4 (2.7)	3.0 (2.2)	3.3 (2.4)
	Range	0.0-16.3	0.0-13.4	0.0-8.9	0.0-12.0
Nighttime awakenings	Mean (SD)	0.3 (0.5)	0.4 (0.7)	0.2 (0.4)	0.3 (0.5)
	Range	0.0-2.7	0.0-6.6	0.0-1.4	0.0-2.6

The changes in the secondary outcome variables mirrored the changes in FEV₁ (Table 24) except that there was a more consistent dose ordering.

Table 24. Secondary Outcome Variables Using LOCF Analysis in Study 321

	Ciclesonide*		
	80 mcg	160 mcg	320 mcg
Daily dose of ciclesonide	80 mcg	160 mcg	320 mcg
AM PEF (L/min)	13.4 / 15.6	16.7/ 18.9	22.3 / 24.5
AM PEF variability (%)	-0.96 / -1.22	-1.32 / -1.59	-2.48 / -2.75
Daily albuterol use (puffs/day)	-0.91 / -1.52	-0.99 / -1.60	-1.27 / -1.88
Total Asthma Severity Score	-0.52 / -0.38	-0.69 / -0.55	-0.82 / -0.68
Nighttime awakenings	-0.07 / -0.11	-0.19 / -0.23	-0.14 / -0.17

* 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 mean AM PEF fell slightly in the placebo-treated subjects and increased in all of the ciclesonide-treated patients (-2.8, 13.4, 16.7, and 22.3 L/min change from baseline in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively.) The difference from placebo in the active treatment groups was 15.6 L/min for ciclesonide-80, 18.9 L/min for ciclesonide-160, and 24.5 L/min for ciclesonide-320.

Over the course of the study, the mean Asthma Severity Score fell in all the treatment groups (-0.14, -0.52, -0.69, and -0.82 in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively). The difference between placebo and active treatment was -0.38 for ciclesonide-80, -0.55 for ciclesonide-160, and -0.68 for ciclesonide-320.

Daily albuterol use increased in the placebo-treated subjects and decreased in the ciclesonide treated subjects. The change between baseline and Week 12 (LOCF) was 0.60, -0.91, -0.99,

and -1.27 puffs per day in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively. The difference between placebo and active treatment was -1.52 for ciclesonide-80, -1.60 for ciclesonide-160, and -1.88 for ciclesonide-320.

Both AM and PM PEF variability decreased in a dose dependent manner in the ciclesonide-treated subjects and increased in the placebo-treated subjects. The decreases were -0.96 for the ciclesonide-80 group, -1.32 for the ciclesonide-160 group, and -2.48% for the ciclesonide-320 group. The number of nighttime awakenings increased in the placebo subjects and decreased in the ciclesonide-treated subjects. The increase in the placebo group was 0.04 awakenings per night, whereas, the decrease was -0.07 in the ciclesonide-80 group, -0.19 in the ciclesonide-160 group, and -0.14 for the ciclesonide-320 group. This corresponds to a difference between placebo and the maximally improved ciclesonide group (160 mcg) of 1 awakening every 4.3 nights.

Analysis of Withdrawals

In a time-to-event analysis the withdrawal rate for any cause was higher for the placebo subjects than for the ciclesonide-treated subjects. The percentage of subjects withdrawing for any reason was 35.3%, 15.8%, 17.3%, and 14.5% in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively. Discontinuation for lack of efficacy showed the same pattern, but there was more of a dose-response. The withdrawal rate for lack of efficacy was 30.1%, 13.55%, 9.4%, and 6.1% in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively. Including the placebo subject who withdrew due to an "asthma exacerbation" but who was not classified as a "lack of efficacy" only strengthens the relationship between drop-out and dose. The drop-out rate was dose-dependent in stratum 1 subjects but not those in stratum 2. In stratum 1 (subjects previously treated with ICS), 47.3%, 24.0%, 18.6%, and 16.9% of the subjects withdrew prematurely in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively. In stratum 2 (subjects previously treated with bronchodilators only) there was no dose ordering in the drop-out rate. The incidence was 20.3%, 5.2%, 15.8%, and 11.7% in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively.

Time of Onset Analysis

An analysis of the changes in AM PEF, Asthma Severity Score, and albuterol use during the first week of therapy was undertaken to determine the onset of action of ciclesonide. In the ciclesonide-320 group, improvement in AM PEF was seen at day 3, and improvement was seen at 5 and 7 days in the ciclesonide-160 and ciclesonide-80 groups respectively. Asthma Severity Score and albuterol use had improved by day 1 in all treatment groups, with an improvement over placebo of approximately 0.3 points for the Asthma Severity Score and 0.8 puffs/day of albuterol use in the ciclesonide 320 group.

Patient Reported Outcomes

Of the 526 subjects enrolled in the study, the overall AQLQ score was available for 517 subjects. Of these, 98 withdrew early (39 in placebo, 19 in ciclesonide-80, 19 in ciclesonide-160, and 16 in ciclesonide-320 group) so that the last AQLQ was administered after approximately 4 weeks of therapy. In the LOCF analysis the improvement in the overall score (mean of 32 questions) compared to placebo over the 12-week study was clinically significant (difference from placebo > 0.5) in the ciclesonide-320 group only (Table 25). The

ciclesonide-320 group also had a clinically significant improvement compared to placebo (> 0.5) in the Symptoms, Activity Limitation, and Emotional Function domains but not in the Environmental Stimuli domain (difference from placebo = 0.45).

Table 25. Results of AQLQ in Study 321

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Overall Score				
Placebo	125	4.77	0.15 (0.09)	---
Ciclesonide-80	130	4.44	0.46 (0.08)	0.31 (0.12)
Ciclesonide-160	124	4.84	0.59 (0.09)	0.44 (0.12)
Ciclesonide=320	128	4.65	0.81 (0.08)	0.66 (0.12)
Symptoms				
Placebo	126	4.56	0.08 (0.09)	---
Ciclesonide-80	130	4.35	0.55 (0.09)	0.46 (0.13)
Ciclesonide-160	124	4.66	0.68 (0.09)	0.60 (0.13)
Ciclesonide=320	128	4.50	0.87 (0.09)	0.79 (0.13)
Activity Limitation				
Placebo	124	5.10	0.22 (0.09)	---
Ciclesonide-80	127	4.71	0.41 (0.09)	0.19 (0.12)
Ciclesonide-160	121	5.07	0.49 (0.09)	0.27 (0.12)
Ciclesonide=320	124	4.93	0.74 (0.09)	0.51 (0.12)
Emotional Function				
Placebo	126	4.64	0.06 (0.10)	---
Ciclesonide-80	130	4.22	0.41 (0.10)	0.35 (0.14)
Ciclesonide-160	124	4.75	0.66 (0.10)	0.61 (0.14)
Ciclesonide-320	128	4.59	0.80 (0.10)	0.75 (0.14)
Exposure to Environmental Stimuli				
Placebo	126	4.68	0.29 (0.09)	---
Ciclesonide-80	130	4.29	0.48 (0.09)	0.19 (0.13)
Ciclesonide-160	124	4.76	0.50 (0.09)	0.21 (0.13)
Ciclesonide=320	128	4.39	0.74 (0.09)	0.45 (0.13)

* LS (SE)

1.1.2.3. Safety Outcomes

Extent of exposure

The safety population consisted of the 526 subjects originally enrolled in the study. The mean time on study medication was 61.4, 75.0, 74.5, and 77.5 days in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. The median exposure was 83.0, 84.0, 84.0, and 84.0 days respectively.

Adverse Events

Overall, 279/392 (53.0%) of subjects reported adverse events. As shown in Table 26, the incidence was comparable in all of the treatment groups (Placebo, 53.7%; ciclesonide-80, 57.1%; ciclesonide-160, 50.8%; and ciclesonide-320, 50.4%). The most common organ involvement was the respiratory tract with 32.8%, 23.3%, 23.4%, and 19.8% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups reporting events respectively. The high rate in the placebo group is primarily due to asthma exacerbations and if these are removed, then the remaining respiratory AEs are almost identical in the four treatment groups; 17.2%, 18.8%, 18.0%, 17.6% of subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups reporting events respectively.

Table 26. Adverse Events Occurring in > 3% of Subjects Enrolled in Study 321

	Number (%) Subjects				
	Placebo	Ciclesonide			
Mcg/ day ciclesonide	0	80	160	320	All
n	134	133	128	131	392
Total patients	72(53.7)	76 (57.1)	65 (50.8)	66 (50.4)	207 (52.8)
Respiratory & Thoracic	44 (32.8)	31 (23.3)	30 (23.4)	26 (19.8)	87 (22.2)
Nasopharyngitis	6 (4.5)	11 (8.3)	10 (7.8)	8 (6.1)	29 (7.4)
Pharyngitis	6 (4.5)	5 (3.8)	6 (4.7)	5 (3.8)	16 (4.1)
Asthma aggravated	21 (15.7)	6 (4.5)	7 (5.5)	3 (2.3)	16 (4.1)
Bronchitis NOS	2 (1.5)	2 (1.5)	2 (1.6)	5 (3.8)	9 (2.3)
Nasal congestion	1 (0.7)	2 (1.5)	4 (3.1)	2 (1.5)	8 (2.0)
Rhinitis NOS	4 (3.0)	4 (3.0)	3 (2.3)	1 (0.8)	8 (2.0)
Infections	23 (17.2)	26 (19.5)	20 (15.6)	26 (19.8)	72 (18.4)
Upper Respiratory	10 (7.5)	11 (8.3)	8 (6.3)	7 (5.3)	26 (6.6)
Sinusitis	3 (2.2)	4 (3.0)	5 (3.9)	4 (3.1)	13 (3.3)
Influenza	0	0	0	5 (3.8)	5 (1.3)
Nervous System	11 (8.2)	9 (6.8)	15 (11.7)	12 (9.2)	36 (9.2)
Headache	7 (5.2)	6 (4.5)	8 (6.3)	8 (6.1)	22 (5.6)
Musculoskeletal	5 (3.7)	14 (10.5)	11 (8.6)	7 (5.3)	32 (8.2)
Back pain	2 (1.5)	5 (3.8)	2 (1.6)	3 (2.3)	10 (2.6)

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	Number (%) Subjects				
	Placebo	Ciclesonide			
Mcg/day ciclesonide	0	80	160	320	All
Gastrointestinal	8 (6.0)	9 (6.8)	6 (4.7)	11 (8.4)	26 (6.6)
Diarrhea	0	5 (3.8)	2 (1.6)	1 (0.8)	8 (2.0)
Nausea	0	1 (0.8)	4 (3.1)	1 (0.8)	6 (1.5)
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)

The second most frequently reported AE was infections. This occurred in 17.2%, 19.5%, 15.6%, and 19.8% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. Upper respiratory tract infection and sinusitis were similarly distributed across the treatment groups. However, influenza was reported in only the ciclesonide-320 group (3.8%). If "influenza-like illness" is combined with influenza, there appears to be a slight overrepresentation in the active treatment groups (placebo, 1 (0.7%), ciclesonide-80, 4 (3.0%), ciclesonide-160, 2 (1.6%), and ciclesonide-320, 5 (3.8%). Oral candidiasis was reported infrequently with only 2 (1.5%) subjects each in the ciclesonide-80 and ciclesonide-320 groups.

There appeared to be more musculoskeletal and connective tissue disorders in the active treatment groups than in the placebo-treated patients, although there was no dose ordering. There were 5 (3.7%), 14 (10.5%), 11 (8.6%), and 7 (5.3%) subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively, who reported these events. There were 3 cases each of arthralgia and 2 each of myalgia in the ciclesonide-80 and ciclesonide-160 groups. There was 1 case of myalgia in the ciclesonide-320 subjects and no case of myalgia or arthralgia was reported in a placebo subject.

Headaches and gastrointestinal complaints occurred with approximately equal frequency in all of the treatment groups.

Serious and Important Adverse Events

There were no deaths reported in the study. There were 5 serious adverse events reported. In the ciclesonide-80 group there was one case each of appendicitis and anaphylaxis. The episode of anaphylaxis occurred in a 31 year old female after ingestion of walnuts. The subject self-medicated with prednisone and diphenhydramine and did not seek medical attention. The event resolved without sequelae on the same day, and the study medication was not changed due to the event. The subject was withdrawn from the study approximately 1 month later due to aggravation of asthma (non-serious AE). In the ciclesonide-160 group there was one gun shot wound and one case of status asthmaticus. In the ciclesonide-320 group there was one case of severe pedal edema. As seems appropriate, none of these events was considered to be related to the drug by the applicant. The case of status asthmaticus was included in the list of subjects who discontinued the study due to exacerbation of asthma.

A total of 41 subjects were withdrawn due to adverse events: 22 in the placebo group and 19 in the ciclesonide treated subjects (Table 27). The most common reason for withdrawal was aggravation of asthma. Only seven subjects withdrew for an AE not related to worsening asthma. In the placebo group there was 1 case each of upper respiratory tract infection and

cough. In the ciclesonide-160 group there was 1 case each of paresthesia, lethargy, and abnormal liver enzymes. In the ciclesonide-320 group there was 1 case each of sinobronchitis and oral candidiasis.

The percentage of patients who had "other significant AEs" was somewhat lower in the ciclesonide-320 subjects than in the other treatment groups- 37.4% compared with 44.8% in the placebo subjects and 49.6% and 46.9% in the ciclesonide-80 and ciclesonide-160 treated subjects. The incidence of AE that were treated with counteractive medication was also slightly lower in the ciclesonide-320 group (Table 27)

Table 27. Other Adverse Events Reported in Study 321

	Placebo	Ciclesonide		
		80 mcg	160 mcg	320 mcg
Daily dose of ciclesonide, mcg	0	80 mcg	160 mcg	320 mcg
Subjects with other significant AEs, n (%)	60 (44.4)	66 (49.6)	60 (46.9)	49 (37.4)
AE (n [%]) resulted in:				
Discontinued 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)
Treated with counter active measure	56 (41.8)	66 (49.6)	57 (44.5)	49 (37.4)
Important laboratory abnormality, n (%)	2 (1.5)	0	1 (0.8)	1 (0.8)

Laboratory Abnormalities

PCA values (a laboratory value that was above the laboratory normal and had increased by a pre-specified amount over the course of the study) for liver enzymes were recorded in 3.9%, 2.3%, 6.0% and 2.4% of the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 subjects respectively. In the placebo-treated subjects, 4 of the 5 (80%) abnormal values were obtained in subjects who had an abnormal value at baseline whereas in the ciclesonide-treated subjects 2 of 13 (15.4%) abnormal values were obtained in subjects who had an abnormal value at baseline. The alkaline phosphatase reached the PCA level in 3.1% of the placebo subjects, but in none of the ciclesonide-treated subjects. The individual End-of-study values and changes during the study for subjects with liver enzymes in the PCA range are shown in Table 28.

Table 28. End-of-Study (ES) Values and Changes in Liver Function Tests in Subjects Who Had Both an Abnormal Value for the Variable and for Whom the Value had Increased a Pre-specified Amount (PCA)[†] During the 12-week Treatment Period

	Placebo		Ciclesonide-80		Ciclesonide-160		Ciclesonide-320	
	ES	Increase	ES	Increase	ES	Increase	ES	Increase
SGPT (U/L)	134*	34	89*	42	82	46	63	32
	86*	28			96	71	49	18
					68	45		
					44	30		
SGOT (U/L)	101*	25	50	25	63	38	45	26
	95*	49			136	116		
					65	33		
SGGT	154	138	115*	35	---	---	---	---
Alk p'tase (U/L)	131	47	---	---	---	---	---	---
	122	33						
	154	128						
	426	61						
Total Bili (µmol/L)	53*	22	29	15	22	10	---	---
			26	11				

[†] The increase required for a value to be categorized as PCA was as follows: SGPT = 28 U/L, SGOT = 29 U/L, SGGT = 29 U/L, and alkaline phosphatase 28 = U/L ; Total Bilirubin = 10 µmol/L

* Abnormal at baseline

Four of the subjects with abnormal enzyme levels at the end of the study (placebo (n =2), ciclesonide-160 (n =1), and ciclesonide-320 (n=1)) were also reported as adverse events. The PCA levels were reached in less than 3% of the subjects for all of the other chemistries

Reviewer: The applicant did not include one of the subjects with a laboratory -defined AE (SGGT = 137 U/L) in the PCA list. Review of this subject's data (ID 186-04 ... \crt\datasets\321\labfin3.xpt) showed that the baseline value, obtained 14 days prior to enrollment, was 124 U/L. However a repeat on the day after initiation of therapy showed a value of 104 U/L. The requisite increase of 29 U/L to define a PCA is only obtained if the lower value is used as the baseline.

One subject in the ciclesonide-160 group had a prior diagnosis of diabetes, and he had a random glucose of 244 mg/dL at the end of the study. This was above the “clinically noteworthy” level of 230 mg/dL.

One subject had what the applicant pre-defined as a “clinically noteworthy” abnormal eosinophil count of $1.3 \times 10^3/\mu\text{l}$. The absolute eosinophils counts reached the PCA level ($> 0.57 \times 10^3 \text{ cells/mm}^3$ and an increase of $0.37 \times 10^3 \text{ cells/mm}^3$) in 0.8%, 0%, 2.7%, and 4.1% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups who reported these events respectively. The shift tables indicated that there were more increases in eosinophil counts than decreases in all of the treatment groups, but the disproportion was not more prominent in the high-dose ciclesonide groups than in placebo-treated subjects.

HPA-axis Evaluation

All 118 subjects enrolled in the 8 sites that participated in the cortisol HPA-axis studies had baseline blood drawn for cortisol. Of these, 109 had follow-up studies and these 109 make up the cortisol population (Table 29). The peak serum cortisol after stimulation with 1 µg cosyntropin did not differ among the treatment groups at baseline. After 12 weeks of treatment the peak cortisol fell slightly in the placebo subjects, increased slightly in the ciclesonide-80 and 160 groups and fell in the ciclesonide-320 group. None of the changes in the ciclesonide-treated subjects differed from the response in placebo-treated subjects. Similarly, the degree of stimulation (peak – baseline cortisol), was similar in the treatment groups at the beginning of the study. The degree of stimulation dropped less in the ciclesonide treated subjects than in the placebo subjects.

Table 29. Evaluation of HPA-Axis in Study 321

	N (total)	N (early withdrawal)	Baseline Mean LS Mean	Change from Baseline LS means (SE)	Difference from Placebo LS means (SE)
Peak post-stimulation serum cortisol, mcg/dL					
Placebo	27	7	27.30	-0.38 (1.27)	
Ciclesonide-80	30	2	27.70	0.75 (1.12)	1.13 (1.37)
Ciclesonide-160	27	1	29.41	0.95 (1.27)	1.33 (1.40)
Ciclesonide-320	25	2	25.40	-0.54 (1.31)	-0.16 (1.43)
Degree of stimulation (peak-baseline), mcg/dL					
Placebo	27	7	12.41	-1.03 (1.26)	
Ciclesonide-80	30	2	11.63	0.34 (1.10)	1.37 (1.36)
Ciclesonide-160	27	1	11.56	-0.12 (1.25)	0.91 (1.38)
Ciclesonide-320	25	2	11.56	-0.44 (1.30)	0.59 (1.41)

Reviewer: Looking at graphs of the actual peak and change in peak values, there appears to be a shift down (fewer high outliers in the ciclesonide-320 group) in the values with treatment. There is no suggestion of a significant change in the mean, however a small effect on HPA axis function cannot be ruled out.

Defining normal HPA function as a basal cortisol of at least 5 mcg/dL and a post-stimulation serum cortisol of at least 18 mcg/dL, three subjects in the placebo group were normal at baseline and abnormal at the end of the study. In all of these cases the peak cortisol was less than 18, but more than 12 mcg/dL.

Measurements of urinary free cortisol were attempted on all of the subjects enrolled at the 8 participating sites. Results are available for the same subjects who had the serum cortisol measurements with the exception of three subjects, (one in the ciclesonide-80 group and 2 in the ciclesonide-160 group) who had no follow-up urine collections. In addition, there is one

subject in the ciclesonide-320 group who was included in the summary of 24-hour urinary cortisol who is not included in the serum measurements. No explanation is provided for these discrepancies. Urine volumes are not listed. The free urinary cortisol increased by 0.37 mcg/day in the ciclesonide-320 group while it fell by 5.91 mcg/day in the placebo group. Values for ciclesonide-80 and ciclesonide-160 were intermediary. However, there was no difference in the change in 24-hour cortisol corrected for creatinine. (range -0.0026 to -0.0003 mcg/mg creatinine/day).

Other Safety Data

There were no clinically important changes in vital signs in any of the treatment groups. No ophthalmologic examinations were performed in this study.

1.1.3. Discussion and Conclusions

This 12 week trial compared the results of pulmonary function, symptoms, adverse events and measures of HPA-axis function in adults and adolescents with mild to moderate persistent asthma. The primary outcome variable, change in pre-dose AM FEV₁ from baseline to Week 12 (end of study) improved significantly in only the ciclesonide-320 treatment group, and efficacy appeared to differ between strata determined on the basis of prior asthma therapy. Subjects who had been treated with ICS prior to enrollment showed a significant response to treatment with ciclesonide-320 whereas subjects who had been treated with short-acting bronchodilators only did not. In addition, the withdrawal rate (most of which was due to lack of efficacy) was dose dependent in subjects previously treated with ICS but not in subjects treated with bronchodilators only prior to enrollment. Of note, the subjects in Stratum 1 had poorer pulmonary function than those in stratum 2, and some in stratum 1 would be characterized as severe (FEV₁% less than 60%) by the national Asthma Education and Prevention Program (NAEEP) guidelines. This suggests that severity of disease as well as prior ICS therapy is also a determinant of the response to ciclesonide treatment in the dose regimens used in this study.

The applicant submitted an analysis of pulmonary function and symptoms occurring in the first week of therapy. The *a priori* assumption was that the first statistically significant difference from placebo for a variable would define the time-point for the onset of action. However, without a correction for multiple comparisons, this statistical analysis is not robust. In addition, even using the criterion of statistical significance, the results showed different times for the first effect of the three variables measured (PEF did not improve for 3 – 5 days depending on the dose). Therefore, it is inappropriate to make a claim of _____

b(4)

The results of the AQLQ showed a clinically meaningful improvement (>0.5) in the overall score and in 3 of the 4 domains scores for the ciclesonide-320 group compared to the changes seen in the placebo-treated subjects.

The overall adverse event rate was comparable among all of the treatment groups. Respiratory AEs were more common in the placebo-treated subjects due to the increased number of asthma exacerbations. Musculoskeletal complaints were more common in the ciclesonide-treated subjects (8.2%) than in placebo (3.7%) but there was no distinctive pattern of complaints. Most of the events were mild to moderate and none of the serious

events was directly related to drug treatment. Only 7 withdrawals were not due to poor asthma control as defined by a "Lack of Efficacy" or "Asthma exacerbation AE". There were very few reports of oral candidiasis in any of the treatment groups. No ophthalmologic examinations were performed.

Laboratory abnormalities were infrequent, and mild. There was a suggestion of more abnormal liver enzymes at the end of the study in the high-dose ciclesonide groups, but the overall numbers were small. Four ciclesonide-160 and 2 ciclesonide-320 subjects had an increase in SGOT from normal at baseline to abnormal at the end of the study compared with no subject in the placebo and ciclesonide-80 groups. There were more abnormal eosinophil counts in the high dose ciclesonide groups than in the placebo or ciclesonide-80 group. Although there tended to be more increases in eosinophil counts than decreases, this shift was not dose dependent.

There were no changes in the baseline or post-stimulation serum cortisol levels. Only one subject (in the ciclesonide-160 treatment group) who had a normal HPA axis evaluation at baseline had an abnormal result at the end of the study, and this was a female on oral hormone replacement therapy whose only abnormality was the failure to increase her serum cortisol level more than 7 mcg/dL after cosyntropin stimulation. The 24-hour urinary cortisol measurements were not accompanied by any assessment of the adequacy of the samples. Since the correction for creatinine can not account for the diurnal fluctuation in cortisol production it is inappropriate to correct urine cortisol for creatinine. Therefore, these results can not be used as supportive evidence for a lack of effect of ciclesonide on the HPA-axis.

In summary, significant increases in pre-dose AM FEV₁ were shown after 12 weeks (end of study) of treatment with ciclesonide 320, mcg QD compared to placebo. When efficacy was analyzed by strata, only the subjects previously maintained on ICS (Stratum 1) showed efficacy.

Adverse events were mild to moderate in intensity and oral candidiasis was uncommon in all of the subjects (1.5% each, in the ciclesonide-80 and ciclesonide-320 groups). Assessment of HPA-axis function using the low dose (1 µg) Cosyntropin test showed no change in function in the actively treated subjects over the 12- week period. Only one of the actively treated subjects who had a normal HPA-axis function at the beginning of the study had an abnormal result at the end of the study. The abnormality was due entirely to a failure to increase the serum cortisol by ≥ 7 mcg/dL after low-dose cosyntropin stimulation. Given the high basal cortisol (43 mcg/dL) the failure to respond to stimulation may not be abnormal.

1.2. Study # 322

A Phase III double-blind, placebo-controlled, parallel-group, multicenter efficacy, safety and dose response study of ciclesonide metered dose inhaler 100 mcg/day, 200 mcg/day, and 400 mcg/day (ex-valve) administered once daily for 12 weeks in the treatment of mild to moderate persistent asthma in adolescents and adults.

1.2.1. Protocol

1.2.1.1. Administrative

Enrollment: July 19, 2001 – October 30, 2002

Appendix

NDA # 21-658, Ciclesonide (Alvesco™)

Clinical Director: _____

b(4)

Sites: 40 clinics in the United States

1.2.1.2. Objective/Rationale

To compare the efficacy, safety and dose response of once-daily administration of 3 doses of ciclesonide (100, 200, and 400 mcg/ day ex-valve: 80, 160, 320 mcg/day ex-actuator) metered dose inhaler with placebo in patients with mild to moderate persistent asthma. A secondary objective was to describe the pharmacokinetic profile of ciclesonide and its main metabolite.

1.2.1.3. Study Design

The study design was identical to that of Study 321 (*1.1.1.3. Overall Design, pg. 61*).

1.2.2. Results

1.2.2.1. Study Population

Disposition

Of the 1070 subjects screened, 489 were randomized (placebo = 118, ciclesonide 80 mcg = 124, ciclesonide 160 = 123, and ciclesonide 320 = 124). The percentage of completers was comparable in the active treatment groups (82-89%) but was only 69.5% in the placebo-treated subjects. Drop-out in the placebo-treated subjects was particularly notable for “lack of efficacy” (19.5%) and “adverse event” (14.4%) (Table 30). All of the randomized subjects were included in the ITT population except for two who had no follow-up spirometry, both of whom were randomized to placebo. This resulted in a safety population of 489 and an ITT population of 487 subjects.

Table 30. Disposition of Subjects in Study 322

	Placebo	Ciclesonide			Total
Ciclesonide dose, mcg/day	0	80	160	320	N/A
Randomized Subjects, n	118	124	123	124	489
Completed study, n (%)	82 (69.5)	109 (87.9)	110 (89.4)	102 (82.3)	403 (82.4)
Discontinued from study, (n%)	36 (30.5)	15 (12.1)	13 (10.6)	22 (17.7)	46 (9.4)
Reason for Discontinuation, n (%)					
Lack of efficacy	23 (19.5)	7 (5.6)	7 (5.7)	9 (7.3)	46 (9.4)
Adverse event	17 (14.4)	6 (4.8)	5 (4.1)	6 (4.8)	34 (7.0)
Consent withdrawn	10 (8.5)	5 (4.0)	2 (1.6)	3 (2.4)	20 (4.1)
Protocol violation	3 (2.5)	2 (1.6)	1 (0.8)	6 (4.8)	12 (2.5)
Loss to follow-up	1 (0.8)	1 (0.8)	0	1 (0.8)	3 (0.6)
Poor compliance	0	2 (1.6)	0	0	2 (0.4)
Death	0	0	0	0	0
Other	2 (1.7)	0	0	4 (3.2)	6 (1.2)

Most of the adverse events were also related to lack of efficacy. An asthma exacerbation was the adverse event in all but 7 subjects: 1 each in the placebo and ciclesonide-80 groups, 3 in the ciclesonide-160 group, and 2 in the ciclesonide-320 group (*see adverse events below*).

Most of the protocol violations were not related to the response to therapy. There were 3 pregnancies, and 6 patients had pulmonary function parameters that were outside of the inclusion criteria. One patient (male) in the ciclesonide-80 group took oral prednisone during the study. He is listed as being withdrawn due to a protocol violation and a worsening adverse event, but he is not included in the "lack of efficacy" category despite the fact that "Asthma exacerbation" is the only adverse event on the listing (*Appendix C.3.2, Listing 29, pg 4452 of Appendices-clinstat\322\study322a.pdf*) Another patient took Pulmicort during the study and 2 patients were non compliant with the study visits. Diary-recorded compliance was high in all treatment groups.

Demographics

The ITT population consisted of 268 (55.0%) subjects in Stratum 1 (previously treated with ICS) and 219 (45.0%) in Stratum 2 (no prior treatment with ICS) (Table 31). There were 200 (41.1%) males and 287 (58.9%) females, the mean age was 36.5 years with a range of 11-79, and 87% were Caucasian. The distribution of these characteristics was comparable in all of the treatment groups.

Table 31. Demographics of Subjects Enrolled in Study 322

	Placebo	Ciclesonide			Total
Dose of ciclesonide, µg/day	0	80	160	320	N/A
n	116	124	123	124	487
Stratum 1*, n (%)	61 (52.6)	67 (54.0)	69 (56.1)	71 (57.3)	268 (55.0)
Stratum 2, n (%)	55 (47.4)	57 (46.0)	54 (43.9)	53 (42.7)	219 (45.0)
Gender, n (%)					
Male	49 (42.2)	50 (40.3)	42 (34.1)	59 (47.6)	200 (41.1)
Female	67 (57.8)	74 (59.7)	81 (65.9)	65 (52.4)	287 (58.9)
Age (years)					
Mean (SD)	36.7 (16.0)	36.8 (14.8)	35.9 (13.2)	36.5 (13.9)	36.5 (14.5)
Range	12-79	12-70	12-70	11-75	11 - 79

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

The mean duration of asthma prior to enrollment was 18.9 ± 13.7 years with a range of 0.4 to 64.4 years. Prior to enrollment all of the subjects were using short acting β -agonists, 49.9% were taking ICS, and 8.6% used leukotriene receptor antagonists. Three subjects took xanthines, and none used cromolyn prior to enrollment.

Comparing the two strata, the subjects who had been on maintenance ICS (Stratum 1) were 6 years older on average than those who had not received ICS within 30 days of enrollment (Table 32). At the screening visit, the mean FEV₁ was 110 mL larger in the subjects who were receiving ICS at the time of enrollment. After the placebo run-in the FEV₁ in the subjects in Stratum 1 fell by 420 mL to a level that was 310 mL less than the FEV₁ of the subjects in Stratum 2 (2.28 ± 0.49 Liters and 2.59 ± 0.62 Liters respectively). In Stratum 1 there were 38 (14.1%) subjects with an FEV₁% less than 60% predicted. In Stratum 2 there were 3 (1.4%) with an FEV₁% less than 60%. These results are summarized in Table 32.

Reviewer: the above data was taken from End-of-text tables 12-12, 12-13, 12-21, and 12-22.pg 184-188 of study report... \:clinstat\322\study322.pdf and ... \crt\datasets\322\effpft.xpt.

Table 32. Clinical Characteristics of Subjects based on Prior Treatment

	Stratum 1 * (N=268)	Stratum 2 ** (N=219)
Age, years (Mean, SD)	39.2 (14.2)	33.1 (14.1)
Range	12-75	11-79
Gender: Male, n (%)	101 (37.7)	99 (45.2)
Female	167 (62.3)	120 (54.8)
Duration of Asthma, n (%)		
< 2 years	14 (5.2)	5 (2.3)
2-5 years	22 (8.2)	20 (9.1)
> 5 years	232 (86.6)	194 (88.6)
FEV ₁ , L at enrollment (mean [SD])	2.70 (0.61)	2.59 (0.62)
FEV ₁ , L at randomization (mean [SD])	2.28 (0.49)	2.59 (0.62)
FEV ₁ % predicted at randomization	68.7 (8.7)	73.2 (7.7)
Range FEV ₁ %	28.9 – 88.1	54.8 – 90.5

** Stratum 1 = subjects treated with ICS prior to enrollment, ** Stratum 2 = subjects treated with bronchodilators only prior to enrollment*

In addition to the differences in age and function between the two strata, there was a difference in FEV₁ among the treatment groups in stratum 2. The FEV₁ at screening (visit #2) was highest in the ciclesonide-320 group (2.82 L) compared to 2.54, 2.57, 2.43, and 2.82 liters in the placebo, clicesonide-80, and ciclesonide-160, groups respectively. After 5 to 28 days of placebo treatment the values were essentially unchanged.

There was a broad range of reversibility in the FEV₁ ranging from 0 to 197%. One subject in stratum 1 who was treated with ciclesonide-80 had a reversibility of 120%. This subject was considered as having a protocol violation because the visit 3 FEV₁ was 29% (below the inclusion criteria).

Reviewer: One ciclesonide-320 treated-subject in stratum 2 had a reversibility of 197%. Since the baseline FEV₁ was 3.02 liters, a close to 200% increase is unlikely to be a valid measurement, although the subject is not identified as a protocol violation in the application.

1.2.2.2. Efficacy Outcomes

The primary efficacy variable in this study was change from baseline to end of study [Week 12 (LOCF)] in AM pre-dose FEV₁ (L). The ITT population was made up of 487 individuals (placebo n =116, ciclesonide-80 n=124, ciclesonide-160 n =123, ciclesonide-320 n= 124). The baseline pulmonary function was comparable in all of the treatment groups (Table 33).

Table 33. Baseline Pulmonary Function Study 322

Dose of ciclesonide	mcg/day	Placebo	Ciclesonide		
		0	80 mcg	160 mcg	320 mcg
N		116	124	123	124
FEV ₁ (L)	Mean (SD)	2.43 (0.59)	2.40 (0.60)	2.51 (0.61)	2.41 (0.57)
	Range	1.3 - 4.1	1.1 - 4.3	1.3 - 4.1	1.1 - 4.3
FEV ₁ % predicted (%)	Mean (SD)	71.8 (8.5)	71.4 (9.6)	70.1 (8.2)	71.0 (8.4)
	Range	47.7 - 91.1	28.9 - 88.1	49.2 - 87.3	49.2 - 87.3

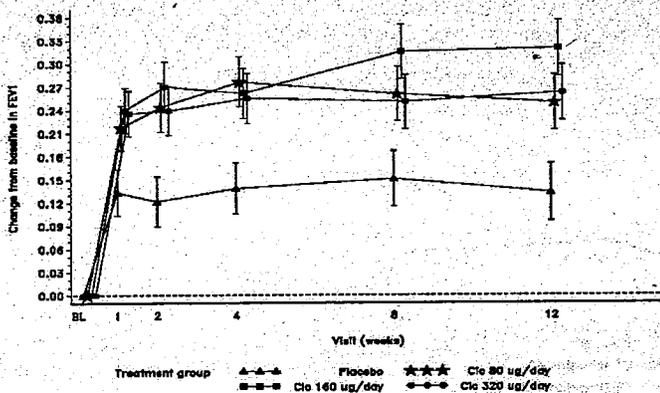
Over the 12-week period the FEV₁ increased by 130 ml in the placebo group, 250 ml in the ciclesonide-80 group, 320 ml in the ciclesonide 160 group, and 250 ml in the ciclesonide-320 group. The difference between placebo and ciclesonide treated subjects was 120 mL for the ciclesonide-80 subjects (p=0.0224), 190 mL for the ciclesonide-160 subjects (p=0.0003), and 120 ml for the ciclesonide-320 (p=0.173) (Table 34).

Table 34. Change in FEV₁ in Study 322: Baseline-Week 12 (LOCF)

	LS mean difference (mL)	95% Confidence Interval	p-value
Difference between baseline and 12-week pre-dose AM FEV ₁			
Placebo-baseline	130	60, 210	
Ciclesonide-80-baseline	250	180, 320	
Ciclesonide-160-baseline	320	250, 390	
Ciclesonide-320-baseline	250	180, 330	
(Baseline-12-week) change in FEV ₁ comparing ciclesonide and placebo treatment			
Ciclesonide-80-placebo	120	20, 220	0.0224
Ciclesonide-160-placebo	190	90, 290	0.0003
Ciclesonide-320-placebo	120	20, 220	0.0173

The difference in the response among the active treatment groups was not significant. The response to therapy is depicted graphically in figure 4.

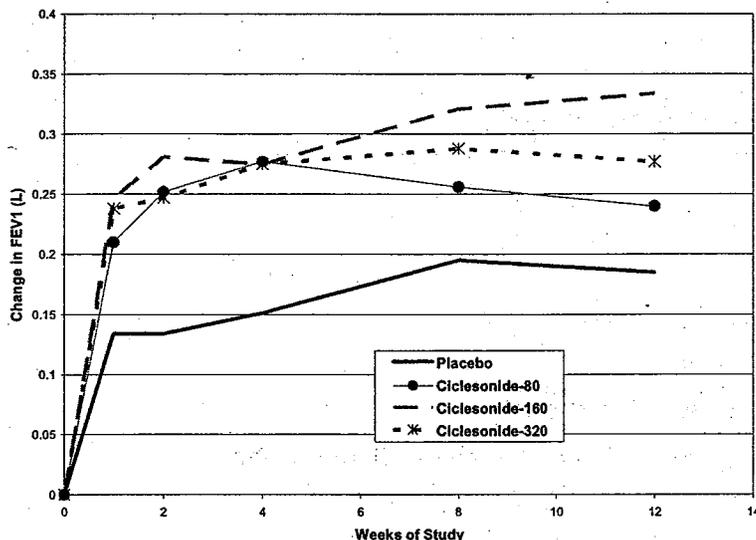
Figure 4. Change in FEV₁ with Treatment in study 322



A significant change from placebo was seen after one week of treatment in all active treatment groups (ciclesonide-80, 60 ± 40 ml, $p=0.037$; ciclesonide-160, 110 ± 40 , $p=0.0078$, ciclesonide-320, 90 ± 40 ml, $p=0.021$) using the LOCF analysis.

Reviewer: Note that the Week 12 values reported by the Applicant includes measurements from earlier time points carried forward (LOCF). The actual number of subjects at Week 12 were: Placebo $n = 82$, ciclesonide-80 $n = 109$, ciclesonide-160 $n = 110$ and ciclesonide-320 $n = 102$. In the completer analysis the mean change from baseline in Pre-dose FEV₁ (mL) at Week 12 was 185, 240, 334, and 278 mL in the placebo, and the ciclesonide-80, 160, and 320 mcg groups respectively. Compared to placebo the change from baseline was 55, 149, and 93 mL in the ciclesonide-80, ciclesonide-160 and ciclesonide 320 mcg groups respectively. When the data were analyzed without LOCF, the response differential between placebo and ciclesonide treatment was maintained throughout the 12-week treatment period in the ciclesonide -160 group only Figure 2. (Source: End-of-Text Table 12-38 [...\clinstat\322\study321.pdf, pg 239])

Figure 5. Non-LOCF Analysis of Results from Study 322*



*(Source: crt\datasets\322\effpft.xpt)

The applicant states that the sub-group analysis shows no “interaction” between strata and treatment. However, as indicated on page 406 of the study report (Table 12-154, clinstat\322\study3221.pdf), the response to treatment was much greater in the stratum 1 subjects (those previously treated with ICS) than in those in stratum 2 (subjects previously treated only with bronchodilators). In this study, the response to all doses of ciclesonide was significant in stratum 1 subjects. However, none of the differences in FEV₁ between placebo and active treatment groups was significant in the stratum 2 subjects. There were 219 subjects in stratum 2 and 268 in stratum 1 so the difference in statistical analysis is not due to smaller numbers in stratum 2. In absolute terms compared to placebo (LOCF), the increase in stratum 1 subjects after ciclesonide-320 was 133 ml and the increase in stratum 2 subjects was 78 mL (Table 35 and 36). (Table 35 and 36 are taken from Dr. Ted Guo’s biostatistical review, pg. 62).

Table 35. ANOVA on FEV₁ Change at Week 12 (Visit 8) from Baseline for Stratum 1: Controller (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1901	0.0678	2.81	0.0054	0.0303	0.3499
100mcg2PfsQD vs Placebo	0.2211	0.0671	3.29	0.0011	0.0628	0.3794
200mcg2PfsQD vs Placebo	0.1326	0.0666	1.99	0.0478	-0.0245	0.2897

Table 36. ANOVA on FEV₁ Change at Week 12 (Visit 8) from Baseline for Stratum 2: Reliever (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	-0.0078	0.0772	-0.10	0.9199	-0.1907	0.1752
100mcg2PfsQD vs Placebo	0.1340	0.0775	1.73	0.0855	-0.0497	0.3177
200mcg2PfsQD vs Placebo	0.0782	0.0788	0.99	0.3223	-0.1085	0.2649

At endpoint (Week 12 [LOCF]), The FEV₁, as a percent of baseline, increased by 5.4%, 11.2%, 13.6%, and 10.7% in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. As was true of the absolute FEV₁, the differences between baseline and Week 12 (LOCF) were significant for all of the active treatment groups. The change in FEV₁, as a percent of predicted, followed the same pattern. There was a 3.45%, 7.31%, 8.84%, 7.07% increase in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. The difference between active treatment and placebo was significant for all of the active treatment groups.

The baseline values for the secondary outcome variables were similar in all of the treatment groups (Table 37).

Table 37. Baseline Values for Secondary Efficacy Variables in Study 322

		Placebo	Ciclesonide		
			80 mcg	160 mcg	320 mcg
Dose of ciclesonide	mcg/day (n)	0 (116)	80 mcg (124)	160 mcg (123)	320 mcg (124)
AM PEF (L/min)	Mean (SD)	371.3 (100.9)	367.1 (96.3)	344.9 (73.8)	378.1 (88.3)
	Range	162.9 – 765.0	192.0 – 634.3	200.0 – 551.4	165.0 – 655.7
Asthma Severity Score	Mean (SD)	2.8 (1.5)	2.6 (1.5)	2.5 (1.5)	2.6 (1.4)
	Range	0 – 5.7	0 – 6.1	0 – 6.7	0 – 6.1
Daily albuterol use (puffs/day)	Mean (SD)	3.2 (2.6)	3.0 (2.4)	3.1 (2.6)	3.1 (2.7)
	Range	0 – 11.1	0 – 9.2	0 – 14.1	0 – 13.7
Nighttime awakenings	Mean (SD)	0.33 (0.55)	0.28 (0.53)	0.27 (0.48)	0.24 (0.43)
	Range	0 – 2.9	0 – 3.4	0 – 2.5	0 – 3.0

The change in the secondary outcome variables with treatment mirrored the changes in FEV₁ (Table 38). The mean AM PEF fell slightly in the placebo-treated subjects and increased in all of the ciclesonide treated patients (-1.12, 8.15, 25.72, and 11.77 L/min change from baseline in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively.) The difference from placebo in the active treatment groups was 9.27 L/min for ciclesonide-80, 26.8 L/min for ciclesonide-160, and 12.89 L/min for ciclesonide-320 and was significant for all active treatment groups.

Table 38. Secondary Outcome Variables Given as Change from Baseline / Week 12 (LOCF) Difference from Placebo Study 322

	Ciclesonide*		
	80 mcg	160 mcg	320 mcg
AM PEF (L/min)	8.2 / 9.3	25.7 / 26.8	11.8 / 12.9
AM PEF variability (%)	-1.53 / -1.79	-2.52 / -2.78	-1.82 / -1.82
Daily albuterol use (puffs/day)	-0.80 / -1.03	-1.02 / -1.24	-0.79 / -1.01
Total asthma severity rating score	-0.62 / -0.46	-0.68 / -0.52	-0.41 / -0.25
Nighttime awakenings	-0.08 / -0.18	-0.12 / -0.22	-0.12 / -0.21

* 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 (-0.16, -0.62, -0.68, and -0.41 in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively). The difference between placebo and active treatment was -0.46 for ciclesonide-80, -0.52 for ciclesonide-160, and -0.25 for ciclesonide-320.

Daily albuterol use increased in the placebo-treated subjects and decreased in the ciclesonide treated subjects. The change between baseline and Week 12 (LOCF) was 0.23, -0.80, -1.02, and -0.79 puffs per day in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. The difference between placebo and active treatment was -1.03 for ciclesonide-80, -1.24 for ciclesonide-160, and -1.01 for ciclesonide-320.

Both AM and PM PEF variability decreased in the ciclesonide- treated subjects and increased in the placebo- treated subjects. Compared to placebo the AM PEF variability decreases were 1.78% for the ciclesonide-80 group, 2.78% for the ciclesonide-160 group, and 2.08% for the ciclesonide-320 group. The number of nighttime awakenings increased in the placebo subjects and decreased in the ciclesonide-treated subjects. Compared to placebo the decrease was 0.18 in the ciclesonide-80 group, 0.22 for the ciclesonide-160, and -0.21 awakenings a night for the ciclesonide-320 group. This corresponds to a difference between placebo and the ciclesonide-160 of 1 awakening / 5 nights.

Analysis of Withdrawals

In a time-to-event analysis the withdrawal rate for any cause was higher for the placebo subjects than for the ciclesonide treated subjects. The withdrawals were 29.3%, 12.1%, 10.6%, and 17.7% from the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups. Discontinuation for lack of efficacy showed the same pattern (19.0%, 5.6%, 5.7%, and 7.3%) in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively.

Time of Onset Analysis

An analysis of the changes in AM PEF, Asthma Severity Score, and albuterol use during the first week of therapy was undertaken to determine the onset of action of ciclesonide. In the

ciclesonide 160 and 320 treatment groups improvement in AM PEF was seen at day 7. The Asthma Severity Rating Score was lower than placebo by day 4 in all treatment groups. However, the difference decreased on day 6 for the ciclesonide-80 treatment group. The difference between placebo and active treatment in albuterol use was consistently favorable after day 6.

Patient Reported Outcomes

The overall AQLQ score was available for 466 subjects. Of these, 73 (29 in placebo, 15 in ciclesonide-80, 10 in ciclesonide-160, and 19 in ciclesonide-160 group) withdrew early so that the last AQLQ was performed after approximately 4 weeks of therapy. In the LOCF analysis only the ciclesonide-160 treatment group had a clinically important improvement (≥ 0.5) in the overall score (Table 39). In the individual domains, important improvements were seen only in the Symptoms and Emotional Function domains. The Activity Limitation domain did not improve in any of the treatment groups.

Table 39. Summary Score on AQLQ for Subject Enrolled in Study 322

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Overall Score				
Placebo	108	4.77	0.14 (0.09)	---
Ciclesonide-80	119	4.66	0.54 (0.09)	0.40 (0.12)
Ciclesonide-160	119	4.61	0.63 (0.09)	0.50 (0.12)
Ciclesonide=320	120	4.71	0.57 (0.08)	0.43 (0.12)
Symptoms				
Placebo	108	4.62	0.11 (0.10)	---
Ciclesonide-80	119	4.49	0.61 (0.10)	0.50 (0.14)
Ciclesonide-160	119	4.45	0.74 (0.10)	0.63 (0.14)
Ciclesonide=320	119	4.58	0.65 (0.10)	0.54 (0.14)
Activity Limitation				
Placebo	108	5.07	0.17 (0.09)	---
Ciclesonide-80	117	4.97	0.55 (0.09)	0.38 (0.12)
Ciclesonide-160	119	4.91	0.58 (0.09)	0.41 (0.12)
Ciclesonide=320	117	5.04	0.48 (0.09)	0.31 (0.12)

	N	Baseline Mean*	Change from Baseline*	Difference from Placebo*
Emotional Function				
Placebo	110	4.72	-0.01 (0.11)	
Ciclesonide-80	121	4.49	0.55 (0.10)	0.56 (0.14)
Ciclesonide-160	120	4.40	0.60 (0.10)	0.61 (0.14)
Ciclesonide=320	120	4.50	0.58 (0.10)	0.59 (0.14)
Exposure to Environmental Stimuli				
Placebo	108	4.48	0.32 (0.10)	
Ciclesonide-80	117	4.59	0.39 (0.09)	0.07 (0.13)
Ciclesonide-160	119	4.50	0.53 (0.09)	0.21 (0.13)
Ciclesonide=320	117	4.45	0.51 (0.09)	0.19 (0.13)

* LS Mean (SE)

1.2.2.3. Safety Outcomes

Extent of exposure

The safety population consisted of the 489 subjects originally enrolled in the study. The mean time on study medication was 67.5, 78.1, 78.8, and 76.1 days in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups respectively. The median exposure was 83.5, 84.0, 84.0, and 84.0 days respectively.

Adverse Events

Overall, 318/489 (65.0%) of subjects reported adverse events. As shown in Table 40, the incidence was comparable in all of the treatment groups (Placebo, 66.9%; ciclesonide-80, 62.1%; ciclesonide-160, 65.9%; and ciclesonide-320, 65.3%). The most common organ involvement was the respiratory tract with 36.4%, 29.8%, 23.6%, and 28.2% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups reporting events respectively. If the asthma exacerbations are removed from this category then the remaining respiratory AEs are 18.6%, 17.7%, 21.1%, and 25.8% of subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups reporting events respectively.

Table 40. Summary of Adverse Events Reported in Study 322

	Number (%) Subjects				
	Placebo	Ciclesonide			
Dose of ciclesonide, mcg	0	80	160	320	All
N	118	124	123	124	371
Patients with adverse events	79 (66.9)	77 (62.1)	81 (65.9)	81 (65.3)	239 (64.4)
Respiratory & Thoracic	43 (36.4)	37 (29.8)	29 (23.6)	35 (28.2)	101 (27.2)
Nasopharyngitis	12 (10.2)	12 (9.7)	13 (10.6)	16 (12.9)	41 (11.1)
Pharyngitis	7 (5.9)	9 (7.3)	4 (3.3)	8 (6.5)	21 (5.7)
Asthma aggravated	21 (17.8)	10 (8.1)	3 (2.4)	3 (2.4)	16 (4.3)
Nasal congestion	0	5 (4.0)	1 (0.8)	2 (1.6)	8 (2.2)
Rhinitis NOS	1 (0.8)	4 (3.2)	1 (0.8)	2 (1.6)	7 (1.9)
Infections	30 (25.4)	35 (28.2)	28 (22.8)	44 (35.5)	107 (28.8)
Upper respiratory	15 (12.7)	19 (15.3)	9 (7.3)	9 (7.3)	37 (10.0)
Upper respiratory, viral	2 (1.7)	3 (2.4)	0	7 (5.6)	10 (2.7)
Sinusitis	7 (5.9)	7 (5.6)	6 (4.9)	5 (4.0)	18 (4.9)
Influenza	2 (1.7)	3 (2.4)	3 (2.4)	6 (4.8)	10 (2.7)
Nervous System	20 (16.9)	15 (12.1)	23 (18.7)	22 (17.7)	60 (16.2)
Headache	14 (11.9)	10 (8.1)	16 (13.0)	16 (12.9)	42 (11.3)
Musculoskeletal	13 (11.0)	12 (9.7)	7 (5.7)	15 (12.1)	34 (9.2)
Back, neck, or limb pain	8 (6.7)	10 (8.8)	5 (4.0)	12 (9.7)	27 (7.2)
Arthralgia	4 (3.4)	4 (3.2)	2 (1.6)	2 (1.6)	8 (2.2)
Gastrointestinal	23 (19.5)	13 (10.5)	18 (14.6)	12 (9.7)	43 (11.6)
Diarrhea	5 (4.2)	2 (1.6)	1 (0.8)	0	3 (0.8)
Dyspepsia	4 (3.4)	1 (0.8)	7 (5.7)	3 (2.4)	11 (3.0)
Abdominal pain	2 (1.7)	2 (1.6)	4 (3.3)	1 (0.8)	7 (1.9)
General Disorders	11 (9.3)	6 (4.8)	5 (4.1)	10 (8.1)	21 (5.7)
Influenza-like illness	5 (4.2)	0	1 (0.8)	3 (2.4)	4 (1.1)

The second most frequently reported AE was infections. This occurred in 25.4%, 28.2%, 22.8%, and 35.5% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 group respectively. Upper respiratory tract infection was more common in the placebo and low-dose ciclesonide group than in the ciclesonide-160 and 320 treatment groups. However, influenza and other viral URI were more common in the ciclesonide-320 group (4.8% and 5.6% compared with <3% in the other treatment groups). If “influenza-like illness” is combined with influenza and viral URI, the overrepresentation in the ciclesonide-

320 group remains (placebo 9 (7.6%); ciclesonide-80, 4 (3.2%); ciclesonide-160, 4 (3.3%); and ciclesonide-320, 16 (12.9%). The incidence of oropharyngeal candidiasis was low; 1 (0.8%), 1 (0.8%), 0, and 2 (1.6%) of subjects in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups reporting events-respectively.

Musculoskeletal and connective tissue disorders were somewhat less frequent in the ciclesonide-160 treatment group. There were (11.0%), (9.7%), (5.7%), and (12.1%) subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups who reported these events respectively.

Headaches occurred with approximately equal frequency in all of the treatment groups

Serious and Important Adverse Events

There were no deaths reported and only one serious adverse event. This event was in a placebo-treated subject who had a moderately severe exacerbation of asthma on day 72 of treatment.

A total of 32 subjects were withdrawn due to adverse events: 17 in the placebo group and 15 in the ciclesonide treated subjects (Table 41). The most common reason for withdrawal was aggravation of asthma. Only 7 subjects withdrew for an AE not related to worsening asthma. In the placebo group there was one rib fracture and in the ciclesonide-80 group there was one case of contact dermatitis. In the ciclesonide-160 group there was one case each of sinusitis and drug hypersensitivity, and in the ciclesonide-320 group there was one case each of URI, bronchitis, and influenza. The drug hypersensitivity was a 48 year old female who had an acute reaction to an immunotherapy shot.

Table 41. Other Adverse Events Reported in Study 322

	Placebo	Ciclesonide		
Daily dose of ciclesonide	0	80 mcg	160 mcg	320 mcg
N	118	124	123	124
Subjects with other significant AEs	74 (62.7)	65 (52.4)	71 (57.7)	73 (58.9)
AE resulted in:				
Discontinued from study	17 (14.4)	6 (4.8)	4 (3.3)	5 (4.0)
Therapy temporarily interrupted	0	0	0	1 (0.8)
Other intervention	10 (8.5)	5 (4.0)	6 (4.9)	8 (6.5)
Treated with counter active measure	73 (61.9)	65 (52.4)	70 (56.9)	71 (57.3)
Important laboratory abnormality	1 (0.8)	2 (1.6)	2 (1.6)	1 (0.8)

The percentage of patients who had “other significant AEs” was slightly lower in the active treatment groups when compared to placebo; 62.7%, 52.4%, 57.7% and 58.9% in the placebo, ciclesonide-80, ciclesonide-160 and ciclesonide-320 group respectively (Table 41).

Laboratory Abnormalities

Liver function abnormalities were infrequent and occurred more frequently in the placebo than ciclesonide-treated subjects. The SGPT reached the PCA level (abnormal at the end of the study and having increased by > 28 U/L during the study) in 3.7% of the placebo and 3.4% of the ciclesonide-160 subjects. There were no elevations to this level in the ciclesonide-80 and ciclesonide-320 subjects. Abnormalities in the SGOT, SGGT, and alkaline phosphatase occurred in <3% of the subjects in all of the treatment groups. One placebo-treated subject had liver enzyme abnormalities recorded as an adverse event (Maximum SGPT = 89, and maximum SGGT = 155 U/L).

The absolute eosinophils counts reached the PCA (>0.57 x 10³ and an increase of 0.38 * 10³ cells/μL) level in 1.8%, 6.8%, 5.0%, and 1.7% of the subjects in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320 groups who reported these events respectively. Five subjects had eosinophil counts higher than 1 x 10³ cells /μL (one on placebo - 1.32 x 10³ cells /μL; 2 on ciclesonide-160 – 1.12 and 1.63 x 10³ cells/μL; and 2 on ciclesonide-320 – 1.14 and 1.28 x 10³ cells /μL).

Isolated subjects had other abnormalities. One ciclesonide-80 treated subject had a glucose level that was > 2 ULN (331 mg/dL). In addition to the placebo-subject with abnormal liver enzymes, 5 additional subjects had abnormal laboratory values reported as adverse events. Two ciclesonide-80 treated subjects had elevated cholesterol values, one ciclesonide-160 subject had an elevated uric acid and one had an elevated glucose. One ciclesonide-320 subject had hematuria. None of the events necessitated a change in the study medication.

HPA-axis Evaluation

Evaluation of the HPA-axis was performed at 7 centers on a total of 15 placebo- treated subjects and 55 -ciclesonide treated subjects (Table 42). At baseline, the peak serum cortisol after stimulation with 1 μg cosyntropin did not differ among the treatment groups. After 12 weeks of treatment the peak cortisol rose slightly in the control subjects, fell slightly in the ciclesonide- 80 and increased in the ciclesonide-160 and 320 groups. None of the changes in the ciclesonide-treated subjects differed from the response in placebo-treated subjects. Similarly, the degree of stimulation (peak – baseline cortisol), were similar in the treatment groups at the beginning of the study.

Table 42. Peak Post-cosyntropin Stimulation Serum Cortisol in Study 322

	N	Baseline Mean	Change from Baseline LS Mean (SE)	Difference from Placebo LS Mean (SE)
Peak post-stimulation cortisol, mg/dL				
Placebo	15	26.27	2.10 (1.56)	
Ciclesonide-80	17	24.12	-0.65 (1.49)	-2.75 (2.08)
Ciclesonide-160	22	25.77	2.45 (1.36)	0.35 (1.93)
Ciclesonide-320	16	23.50	1.55 (1.48)	-0.55 (2.08)

Defining normal HPA function as a baseline cortisol of at least 5 µg/dL, and a post-simulation serum cortisol of at least 18 µg/dL, all but two of the placebo subjects were normal at baseline. Two subjects who were normal at baseline (1 (4.5%) on ciclesonide-80 and 1 (8.7%) on ciclesonide-160) were abnormal at the end of the study. The subject in the ciclesonide-80 group had a flat post-simulation serum cortisol with a maximum cortisol of 7 µg/dL. This compared to a maximum of 19 µg/dL pre-treatment. One subject in the ciclesonide-160 group had a maximum post-simulation serum cortisol of 17 µg/dL.

Urine was collected for cortisol at the 8 centers where blood was collected. Urine volumes are not reported, and there is no indication why subjects were excluded from this population. The results of the urinary cortisol measurement did not contradict the conclusions drawn from the serum measurements.

Other Safety Data

There were no clinically important changes in vital signs in any of the treatment groups. No ophthalmologic examinations were performed in this study.

1.2.3. Discussion and Conclusions

This study is identical in design to study 321. After 12 weeks, subjects with mild to moderate persistent asthma who were treated with ciclesonide 80, 160, or 320 mcg QD showed significant increases in their AM pre-dose FEV₁ and the increase was greater than placebo in all of the active treatment groups. Secondary efficacy measurements supported efficacy for all of the doses administered. Looking at the results of both studies there appears to be little relationship between dose and response of the FEV₁. In study 322 the secondary efficacy measures (AM PEF, AM PEF variability, daily albuterol use, asthma severity score, and nighttime awakenings) also showed no dose ordering. As in study 321, the subjects who were being treated with ICS at the time of enrollment had a significant increase in pre-dose FEV₁ whereas, the subjects previously maintained on bronchodilators alone did not. As in study 321 the subjects in Stratum 1 had worse pulmonary function than those in Stratum 2 and many in Stratum 1 would be characterized as severe (FEV₁ % predicted < 60%) by the NAEPP guidelines. This supports the conclusion that only subjects with more severe disease would be benefited by ciclesonide given in the doses used in these studies.

The withdrawal rate for any reasons or for lack of efficacy was higher in the placebo group. In this study, only the ciclesonide-160 treatment group, reached the threshold minimum improvement for the overall AQLQ score considered to be clinically meaningful (≥ 0.5) compared to placebo.

The sponsor performed a time of onset analysis to determine the onset prior to one week. However, the AM PEF had not clearly improved before day 7, while the Asthma Severity Score improved by day 4, and albuterol use improved by day 2. These changes do not support the claim _____

b(4)

Adverse events were reported in 65% of the subjects (66.9% in the placebo and 64.4% in the ciclesonide group). The respiratory tract was the source of AEs in 29.4% (36.4% in the placebo and 27.2% in the ciclesonide group) of the subjects and Infections were responsible for 28% (25.4% placebo and 28.8% ciclesonide). The excess of respiratory AEs in the placebo subject was primarily due to the increased rate of asthma exacerbations. There were

more infections in the ciclesonide-320 subjects, but viral upper respiratory infection was the only subcategory where there were notably more events in the high-dose ciclesonide group (1.7% in the placebo, 2.4% in the ciclesonide-80, 0 in the ciclesonide-160, and 5.6% in the ciclesonide-320 group). The other infectious-AEs in the ciclesonide-320 group occurred in less than 3 subjects each. Musculoskeletal disorders were slightly less frequent in the ciclesonide-160 group (5.7% compared with 11.0% in the placebo, 9.7% in the ciclesonide-80, and 12% in the ciclesonide-320 group). There were no deaths and the only serious event was an asthma exacerbation in a placebo subject.

Laboratory abnormalities were infrequent, mild, and for the most part not related to active treatment. As in study 321, increased eosinophil counts were seen in the tabulation of PCA and clinically notable values. The incidence of abnormal results by either criteria was 1 (0.8%) for placebo, 4 (3.2%) for ciclesonide-80, 5 (4.1%) for ciclesonide-160, and 3 (2.4%) for ciclesonide-320 subjects. Despite the lack of a dose response, there is a suggestion of an association between ciclesonide treatment and eosinophilia, an unexpected reaction to a glucocorticosteroid. Assessment of the HPA-axis using the low-dose Cosyntropin test showed few abnormalities: 1 subject each in the ciclesonide-80 and -160 groups were normal at baseline and had minimally abnormal results at the end of the trial.

1.3. Study #326It

A Multicenter (36 US sites), open-label, long-term (1 year) safety study of ciclesonide metered dose inhaler 80 mcg/day to 320 mcg/day (ex-actuator) administered once daily for the treatment of mild to moderate persistent asthma in adolescents and adults.

Reviewer: This review is based on the 120-day safety update which includes the final study report.

1.3.1. Protocol

1.3.1.1. Administrative

Active Patient Follow-up: February 28, 2002 – October 6, 2003

Clinical Director: _____

b(4)

Sites: 36 clinics in the United States

1.3.1.2. Objective

To establish the long-term (1 year) safety and efficacy of ciclesonide metered-dose inhaler (MDI) at doses of 80 mcg to 320 mcg/day (ex-actuator) in adults and adolescents with mild persistent to moderate persistent asthma.

1.3.1.3. Design

This is an open-label one-year extension of pivotal studies 321 and 322. Subjects were enrolled within 4 weeks of the end of the pivotal trials. If patients were withdrawn prematurely from studies 321 or 322 due to an adverse event or an asthma exacerbation, they could still be enrolled in study 326 if the event/exacerbation had resolved and they had received at least 2 weeks of randomized treatment in study 321 or study 322. In addition, screen failures from studies 321 and 322 were eligible to enroll in study 326 if the screen

failure was based on a lack of a fall in FEV₁ or the failure to develop 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. For the open label follow-up, all subjects were treated with 320 mcg ciclesonide QD for two weeks. Subsequently, the investigator could lower the dose of ciclesonide with the goal of finding the lowest dose between 80 and 320 mcg QD 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 of no more than 7 days each. If the subject required a third course of corticosteroid 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.

Subjects were seen in the clinic at baseline, 2 and 6 weeks, and at month 3, 6, 9, and 12. Phone contact was made at week 1, and at months 5, 8, and 11.

Outcome measures included adverse events, vital signs, physical exam, laboratory evaluation, ophthalmologic examination and HPA-axis evaluation. The ophthalmologic examination was performed by an ophthalmologist or optometrist and was to include a slit lamp examination without dilation "unless there was a finding that required it." There was no protocol for the ophthalmologic examination. Serum for cortisol at baseline and after cosyntropin stimulation, and 24-hour urine for cortisol were collected at screening, and at 6 and 12 months at 7 pre-selected centers. AM pre-dose FEV₁, performed at all visits, was a secondary outcome.

For analytic purposes, the final, end-of-study laboratory values for study 321/322 were taken as the baseline values for study 326 for subjects who were enrolled within two weeks of completing participation in 321/322. Screen failures and early drop-outs from the pivotal studies had repeat baseline studies at visit 1 of study 326. Adverse events, laboratory values, and HPA-axis evaluation were analyzed as described for study 321 above (pg 67).

1.3.2. Results

1.3.2.1. Study Population

At the end of the pivotal trials, 229 subjects were screened at 36 of the 76 sites that enrolled subjects into study 321 and 322. Of the 229 re-screened, 226 were enrolled into study 326. Of those enrolled 179 (79.2%) completed 1 year of treatment and 47 were withdrawn. The most common reason for withdrawal was withdrawal of consent 18 (8.0%), lack of efficacy 8 (3.5%), lost to follow-up 8 (3.5%), protocol violation 7 (3.1%) and adverse events 5 (2.2%). Of the 8 protocol violations, 3 were due to subcapsular cataracts on the baseline examination.

Reviewer: Exclusion of subjects from the study due to a history of cataracts was at the discretion of the investigator. However, it is unclear why three subjects were excluded while the results section describes 19 other subjects with cataracts at baseline who were not excluded

The demographic characteristics of the population are shown in table 43. The subjects had a mean age of 37.6 years, 88 (38.9%) were male, and 86.7% were White. The mean duration of asthma was 18.6 years.

Table 43. Demographic Characteristics in Study 326

Characteristic		N = 226
Gender n (%)	Male	88 (38.9)
	Female	138 (61.1)
Age (years)	Mean (SD)	37.6 (15.5)
	Range	12-85
Race, n (%)	White	196 (86.7)
	Black	15 (6.6)
	Asian	7 (3.1)
	Other	8 (3.6)
Hispanic Origin, n (%)		30 (13.3)
Duration of Asthma (years)	Mean (SD)	18.6 (14.3)
	Range	0.5 – 64.8
FEV1, (L)	Mean (SD)	2.67 (0.72)
	Range	0.94 – 4.99
FEV1, (% predicted)	Mean (SD)	79.6 (12.3)
	Range	39.5 – 109.7

After enrollment in study 326, subjects were treated for a mean of 310.5 days (median 364, range 1-390). The six-month follow-up included 194 individuals and the 12-month follow-up includes 175 subjects. Forty percent of the subjects (n=90) were treated with the maximum dose (320 mcg/day throughout the study), and sixty percent were treated with less than 320 mcg. Diary-recorded compliance was > 90% in 93.8% of the subjects.

During the study, all the subjects used short-acting β -agonists as needed. Oral corticosteroids were used by 12.8%, of subjects, long-acting β -agonists by 11.0 %, leukotriene receptor antagonists by 1.8%, other inhaled corticosteroids by 1.3%, and other agents by less than 3 subjects each.

1.3.2.2. Safety Results

By the end of follow-up 164 (72.6%) of the subjects had reported at least 1 adverse event (Table 44). There were 8 serious AEs, of which 3 were bacterial pneumonia, and there was 1 case each of appendicitis, overbite, dehydration, spontaneous abortion, and prostate cancer. The three pneumonias occurred in the ciclesonide-320 group after 3 days of treatment in an 85 year old female, after a month of treatment in a 32 year old diabetic female, and after 214 days in a 29 year old female. Two of the subjects with pneumonia were withdrawn from the study. There were no serious asthma exacerbations. Two subjects with moderately severe

asthma exacerbations, and 1 subject each with anxiety and vertebral disc herniation were withdrawn from the study.

Table 44. Adverse Events Reported by Subjects in Study 326

	Total Subjects treated with ciclesonide = 226
All adverse events, n (%)	164 (72.6)
Serious adverse events, n (%)	8 (3.5)
Deaths, n (%)	0
Other significant adverse events resulted in the following: n (%)	149 (65.9)
Discontinue study medication	5 (2.2)
Interruption of therapy	3 (1.3)
Dose reduced	1 (0.4)
Dose increased	6 (2.7)
Other intervention	33 (14.6)
Treated with counteractive medication	145 (64.2)
Medically important laboratory abnormality, n (%)	8 (3.5)

Reviewer: The applicant states that none of the serious AEs was drug-related. However, all of the serious AEs (except the overbite) occurred in subjects taking the highest dose of ciclesonide, and of these three were pneumonia. This could be an indication of an increased susceptibility to infection while taking ciclesonide.

As seen in Table 45, the distribution of adverse events was similar to that seen in the 12-week trials. The most common treatment-emergent adverse event by system was in the infections and infestations class, and the next most common was in the respiratory system. Two patients (0.9%) were reported to have oral candidiasis; one was moderate and the other mild in intensity.

Table 45. Treatment Emergent Adverse Events Occurring in >3% of the 226 Subjects Enrolled in Study 326

	N (%)
All adverse events	164 (72.6)
Infections and infestations	112 (49.6)
Upper respiratory tract	38 (16.8)
Nasopharyngitis	30 (13.3)
Sinusitis	22 (9.7)
Urinary tract	8 (3.5)
Bronchitis, acute	7 (3.1)
Gastroenteritis, viral	7 (3.1)
Respiratory manifestations	64 (28.3)
Asthma exacerbation	31 (13.7)
Pharyngolaryngeal	11 (4.9)
Bronchitis	9 (4.0)
Nervous system	29 (12.8)
Headache	18 (8.0)
Musculoskeletal	27 (11.9)
Back pain	9 (4.0)
Psychiatric Disorders	13 (5.8)
Anxiety	7 (3.1)

Eye Abnormalities

Pre and post-treatment ophthalmologic examinations were performed on 197 subjects. Three subjects had normal examinations at baseline and trace to 1+ cataracts at the 1-year exam. All three subjects had cortical cataracts and one had posterior subcapsular involvement as well. Three additional subjects had trace cataracts at baseline that were 1+ by the end of the study. One of these individuals also developed posterior subcapsular involvement in addition to the original nuclear cataracts. Five subjects had trace to 1+ cataracts that improved during therapy. In four of these subjects, the change was from 1+ to trace and in one it was 1+ to none. On balance, 6 subjects has worsening cataracts, 2 of which included posterior subcapsular involvement, and 5 subjects had improving of cataracts of approximately one step change.

Laboratory Abnormalities

There were no changes in the mean values comparing baseline to end-of-study in any of the laboratory variables, and none of the subjects had clinically noteworthy values at the end of the study. On the other hand, ten laboratory abnormalities were reported as adverse events in

8 subjects. No single variable was abnormal in more than one subject except for the SGGT which was reported as an adverse event in 4 subjects. The abnormal values for the SGGT were 677, 88, 124, and 281 U/L (normal 4-49 U/L). All of these subjects had abnormal values at baseline (84, 58, 62, 79 U/L) and had substantial increases during treatment. The shift tables also suggested that the medication might have affected liver function. There was an increase of 22 to 29 U/L for the liver enzymes SGPT, SGOT, and SGGT at the end of the study in 9 (4.4%), 5 (2.5%), and 10 (4.9%) subjects respectively. Seven subjects had abnormalities in two or more of these enzymes or alkaline phosphatase. (Sources: Table T-40, pg226: *clinstat\322\study322.pdf*).

HPA-axis Evaluation

Blood was obtained at beginning of study 326 for HPA-axis evaluation in all 34 subjects enrolled in the 7 participating sites, and a follow-up sample was available in 29 subjects. For the 29 with paired samples, the mean baseline, pre-stimulation serum cortisol was 15.6 mcg/dL. This decreased to 13.2 mcg/dL at the end of the study. The peak, post-cosyntropin serum cortisol was 27.6 mcg/dL at baseline and decreased to 26.1 mcg/dL at the end of the study. The change from baseline in the post-stimulation peak cortisol was -1.8 mcg/dL (95% CI = -4.5, 0.8). In 76.5% of the subjects the cortisol levels were normal at baseline and at the end of the study (See study 321 for definition of normal HPA-axis function, pg. 62). One subject with normal HPA axis function at baseline was reported to have an abnormal result at the end of the study. This was a 26 year old female who received 2 bursts of oral corticosteroids and was withdrawn from the study when she required an additional course of oral corticosteroids on day 241. Despite having a peak post-stimulation cortisol of 33 mcg/dL, she was characterized as having an abnormal HPA-axis response because the degree of stimulation was 6 (lower limit of normal = 7) she was on oral contraceptives.

In this study, twenty-four hour urine cortisol was reported without accompanying urine volume measurements. The free cortisol went from 19.37 mcg/day to 28.58 mcg/day and the cortisol corrected for creatinine went from a baseline of 0.0186 mcg/mg creatinine to 0.0162 mcg/mg creatinine.

Pulmonary Function Results

FEV₁ results were available in 219 subjects. The baseline mean value at the beginning of study 326 was 2.67 L and there was an increase of 80 mL (95% CI [30, 130]) over the period of the study. The FEV₁ % predicted was 79.7% at baseline and increased to 81.4% at the end of the study.

1.3.3. Discussion and Conclusions

In this open-label safety extension of the pivotal studies in mild to moderate adult asthmatics, 179 (79.2%) of the subjects completed 1 year of follow-up. Withdrawal was infrequently related to lack of efficacy (3.5%) or adverse events (2.2%). There were no deaths and most adverse events were mild to moderate. There were 8 serious AEs, most of which were clearly not related to therapy. However, three pneumonias all occurring in the subjects taking 320 mcg ciclesonide QD could possibly be related to ICS therapy. Overall, adverse events were reported by 72.6% of the subjects and most of these were classified as

infectious/infestations (49.6%) or respiratory manifestations (28.3%). Upper respiratory tract infection occurred in 16.8% of subjects. Nasopharyngitis, classified as infectious occurred in 13.3% and Pharyngeolarygeal respiratory involvement occurred in 4.9% of subjects. Asthma exacerbations occurred in 13.7% of the subjects, but in no case did the exacerbations result in withdrawal of the subject from the study. The incidence of oral candidiasis was low (2 cases). Laboratory abnormalities were infrequent and mild. However, there was a suggestion of elevation of liver enzymes in subjects who had had previous evidence of abnormal liver function tests. Some of these cases were left unresolved at follow-up. Cataracts developed in three subjects *de novo* and in three others there was worsening of cataracts that had been present at baseline. On the other hand, 5 subjects had cataracts detected at baseline that improved during follow-up. One of 34 subjects had normal HPA-axis function at baseline and abnormally low cortisol stimulation at the end of the study due to the failure to increase the post-stimulation cortisol by > 7 mcg/dl. Also, this individual had had difficult to-control asthma requiring two bursts of oral corticosteroids and was withdrawn from the study due to the requirement for a third course of corticosteroids.

1.4. Study 323/324

A phase III randomized, double-blind, double-dummy, parallel-group, multi-center, placebo-controlled, efficacy and safety study of ciclesonide MDI 320 mcg/day, 640 mcg/day (ex-actuator) and Flovent MDI 880 mcg/day administered twice daily for 12 weeks in the treatment of severe persistent asthma in adolescents and adults.

1.4.1. Administrative

Enrollment: April 9, 2001 - September 16, 2002

Clinical Director: _____

b(4)

Sites: 87 in the United States

1.4.2. Objectives

To compare the efficacy and safety of twice-daily administration of 2 doses of ciclesonide MDI (320 & 640 mcg/day, ex-actuator) to placebo and fluticasone propionate MDI 880 mcg/day.

1.4.3. Study Design

This is a randomized, double-blind, placebo and active controlled trial in asthmatics 12 years of age or older. To be enrolled, the subjects must have taken the equivalent of at least 500 mcg/day fluticasone or mometasone or at least 800 mcg/day budesonide, beclomethasone, or flunisolide throughout the 30 days prior to enrollment. At screening the subjects had to have an FEV₁ of $\leq 80\%$ predicted. Then, after a 5-28 day run-in period during which the subjects took one half of their usual ICS dose, the FEV₁ had to be between 40 and 65% of predicted

and at least 10% less than the FEV₁ measured at screening. Subjects who met enrollment criteria were randomized to the following regimens:

Placebo

Ciclesonide HFA MDI 160 mcg (2 puffs 80mcg/dose) BID + 2 puffs placebo fluticasone

Ciclesonide HFA MDI 320 mcg (2 puffs 160mcg/dose) BID + 2puffs placebo fluticasone

Fluticasone propionate MDI 440 mcg (2 puffs 220mcg/dose) BID + 2puffs placebo ciclesonide.

Subjects with a history of life-threatening asthma, two or more in-patient hospitalizations in the past year or anyone taking systemic corticosteroids within 2 months of screening were ineligible. Subjects with a past history of lenticular opacities were also excluded. Subjects were seen in the clinic at 1, 2, 4, 8, and 12 weeks post randomization. The primary outcome variable was AM pre-dose FEV₁. Secondary outcome variables included FVC and FEF₂₅₋₇₅, diary record of asthma severity rating, nighttime awakenings, albuterol use and daily PEF measurements. Safety was assessed with physical examination including oropharyngeal exam at all visits. An ophthalmologic examination, with slit-lamp, was performed at screening and at week 12 or end-of-study. Routine laboratory examination was performed at screening and at week 12. Serum cortisol before and after cosyntropin stimulation and 24-hour urine for cortisol were collected at selected sites at baseline and end-of-study. PK samples were also collected at selected sites. The Asthma Quality of Life Questionnaire was administered at baseline, 4 and 12 weeks. The Asthma Severity Score was calculated as in study 321 (pg. 66).

The subjects were instructed to contact the investigator if they felt that their asthma was not adequately controlled, if the morning PEF measurements on any 2 consecutive days were below 80% of the PEF recorded at screening, or if albuterol use was more than 8 puffs per day on three consecutive days. Further treatment and/or withdrawal of the subject from the study was at the discretion of the investigator. Patients could also be withdrawn for lack of efficacy, or if they developed serious intervening diseases or became pregnant.

As in study 321 and 322, a step-down procedure was used for the analysis of the primary outcome variable to address multiplicity. Ciclesonide 640 mcg/day was first compared to placebo if that was found to be significant, then the comparison between ciclesonide 320 mcg/day and placebo was conducted. No correction for multiple comparisons was made for the secondary outcome variables.

1.4.4. Results

1.4.4.1. Study Population

Of 1225 subjects screened, 531 were enrolled (136 in the placebo group, 127 in the ciclesonide-160 BID group, 130 in the ciclesonide-320 BID group and 138 in the fluticasone-440 BID group). More subjects withdrew from the placebo arm (Table 46)

Table 46. Disposition of Subjects in Study 323/324

	Placebo	Ciclesonide		Fluticasone	Total
	0	160 mcg BID	320 mcg BID	440 mcg BID	N/A
Randomized Subjects	136	127	130	138	531
Completed study	70 (51.5)	101 (79.5)	104 (80.0)	113 (81.9)	388 (73.1)
Discontinued from study	66 (48.5)	26 (20.5)	26 (20.0)	25 (18.1)	143 (26.9)
Reason for Discontinuation					
Lack of efficacy	55 (40.4)	20 (15.7)	14 (10.8)	10 (7.2)	99 (18.6)
Adverse event	27 (19.9)	8 (6.3)	10 (7.7)	6 (4.3)	51 (9.6)
Consent withdrawn	6 (4.4)	2 (1.6)	5 (3.8)	5 (3.6)	18 (3.4)
Protocol violation	3 (2.2)	0	3 (2.3)	2 (1.4)	8 (1.5)
Loss to follow-up	1 (0.7)	2 (1.6)	3 (2.3)	4 (2.9)	10 (1.9)
Poor compliance	1 (0.7)	2 (1.6)	0	0	1 (0.2)
Death	0	0	0	0	0
Other	1 (0.7)	0	0	2 (1.4)	5 (0.9)

than from any of the active treatment arms due to lack of efficacy (*see Analysis of Withdrawals, pg. 109*). Two of the protocol violations were due to baseline posterior subcapsular cataracts that were not recognized prior to randomization. All of the subjects were included in the ITT population except for 4 who had no post-treatment FEV₁. This resulted in an ITT population of 527 and a safety population of 531. (*pg 88 of study report: clincstat\323_324\study323_324.pdf*). Diary-recorded compliance was high with more than 94% of the subjects in each of the study groups being recorded as compliant.

Demographics

There were 214 (40.6%) males and 313 (59.4% females) (Table 47). The mean age was 43.0 years, 416 (78.9%) were White and 70 (13.3%) were Black. The mean duration of asthma was 23.2 years and the mean FEV1 was 1.79 L (53.7% predicted). The variables were distributed evenly across the treatment groups.

Table 47. Demographic and Clinical Variables for ITT Subjects Enrolled in Study 323/324

	Placebo	Ciclesonide		Fluticasone	Total
	0 (n=133)	160 mcg BID (n=127)	320 mcg BID (n=130)	440 mcg BID (n=138)	N/A (n=527)
Gender: n (%)					
Male	55 (41.0)	52 (40.9)	55 (42.3)	52 (38.2)	214 (40.6)
Female	79 (59.0)	75 (59.1)	75 (57.7)	84 (61.8)	313 (59.4)
Age, mean years (SD)	41.5 (13.1)	43.5 (15.1)	43.1 (14.0)	44.0 (14.6)	43.0 (14.2)
Range	12-79	13-82	12-79	15-85	12 – 88

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	Placebo	Ciclesonide		Fluticasone	Total
Dose of Ciclesonide	0	160 mcg BID	320 mcg BID	440 mcg BID	0
Race: n (%)					
White	103 (76.9)	97 (76.4)	103 (79.2)	113 (83.1)	416 (78.9)
Black	21 (15.7)	17 (13.4)	16 (12.3)	16 (11.8)	70 (13.3)
Asian	3 (2.2)	6 (4.7)	2 (1.5)	5 (3.7)	16 (3.0)
Other	7 (5.2)	7 (5.5)	9 (7.0)	2 (1.5)	20 (3.8)
Duration of Asthma					
Mean (SD)	21.6 (13.3)	26.0 (16.1)	23.1 (14.4)	22.2 (15.3)	23.2 (14.8)
Range	1.3 – 58	1.8 – 65.4	1.0 – 77.0	1.2 – 63.3	1.0 – 77.0
FEV ₁ , mean (SD)	1.77 (0.48)	1.78 (0.49)	1.82 (0.47)	1.77 (0.48)	1.79 (0.48)
Range	0.78 – 3.04	0.79 – 3.11	0.95 – 3.09	0.66 – 2.93	0.66 – 3.11
FEV ₁ %, mean (SD)	52.9 (8.6)	54.1 (8.5)	54.4 (7.5)	53.5 (9.1)	53.7 (8.4)
Range	36.8 – 72.5	27.4 – 69.2	29.4 – 79.7	18.5 – 71.8	18.5 – 79.7

Prior to enrollment all of the subjects were taking a short-acting β -agonist and 98.7 % were taking an inhaled corticosteroid. Almost 80% of the entire group was taking inhaled fluticasone. In addition, 34.7 % were taking a long acting β -agonist, and 16.5% were taking a leukotriene receptor antagonist. Pulmonary function showed a severely reduced FEV₁ (54% predicted) with a range of 0.66 to 3.11 Liters.

1.4.4.2. Efficacy Outcomes

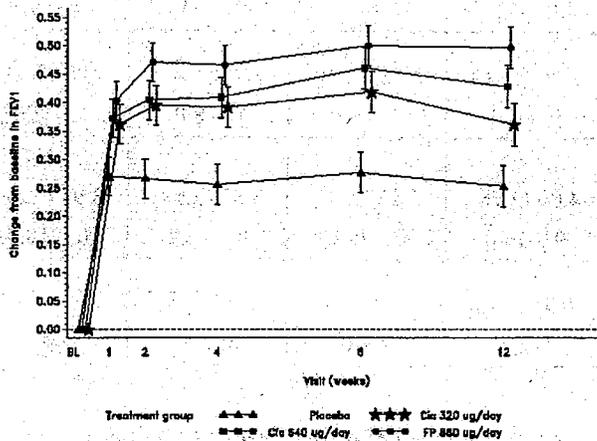
At Week 12 (LOCF) the FEV₁ had increased by 250 mL, 360 mL, 430 mL, and 500 mL in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID -treated subjects respectively. Table 48 shows the difference in the baseline to Week 12 (LOCF) value between the placebo and active treatment groups. All of the active treatment groups were significantly different from placebo. However, the active treatment groups did not differ significantly from one another.

Table 48. (Baseline-12 week) Change in FEV₁ for Subjects Enrolled in Study 323/324

	N	LS mean difference (mL)	95% Confidence Interval	p-value
Difference between baseline and Week 12 (LOCF) in pre-dose AM FEV₁				
Placebo	134	250	180, 330	
Ciclesonide-160 BID	127	360	290, 440	
Ciclesonide-320 BID	130	430	360, 500	
Fluticasone-440 BID	136	500	430, 570	
Baseline – Week 12 (LOCF) change in FEV₁ comparing active treatment to placebo				
Ciclesonide-160 BID-placebo	127	110	10, 210	0.0374
Ciclesonide-320 BID-placebo	130	180	70, 280	0.0008
Fluticasone-440 BID-placebo	136	240	140, 350	0.0001

The change in FEV₁ in the treatment groups is depicted graphically in figure 6. The change from baseline for all time points represent LOCF.

Figure 6. Response of FEV₁ in subjects enrolled in Study 323/324



When the pre-dose FEV₁ was analyzed without LOCF the increase from baseline in the FEV₁ was 445 (n=70), 401 (n=127), 464 (n=464), and 535 (n=113) in the placebo, ciclesonide 160 BID, ciclesonide-320 BID, and fluticasone groups respectively. The differences from placebo were -44, 19, -12, and 90 mL respectively.

At end-of-study, the percent increase in FEV₁ was 12.7, 21.2, 24.5, and 30.1% in the placebo, ciclesonide 160 BID, ciclesonide-320 BID, and fluticasone-440 BID treated subjects respectively. The change from baseline to Week 12 (LOCF) was significantly larger than placebo in all of the active treatment groups, although the differences between ciclesonide and fluticasone were not significant. Similarly, the increase in the FEV₁ percent predicted was significantly more than placebo in all of the treatment groups (4.0%, 5.7%, and 7.8% for the ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID respectively) and the active treatment groups did not differ from one another.

The mean baseline values for the secondary outcomes are listed in Table 49. Consistent with the degree of asthma severity of the population enrolled, the baseline peak flow Severity Score, albuterol use, and nighttime awakenings were all more abnormal than the values for the subjects enrolled in studies 321 and 322.

Table 49. Secondary Efficacy Variables for Subjects in Study 323/324

	Placebo	Ciclesonide		Fluticasone	Total
Dose, mcg/day	0	160 BID	320 BID	440 BID	NA
N	133	127	130	138	133
AM PEF, L/min Mean (SD)	328.6 (97.5)	311.3 (83.1)	324.1 (92.8)	310.8 (80.2)	318.7 (88.8)
Range	157.1-578.6	143.6-520.0	144.3-615.7	132.7-615.7	132.7-615.7
Asthma severity score, Mean (SD)	2.49 (1.53)	2.76 (1.46)	2.73 (1.48)	2.49 (1.45)	2.61 (1.48)
Range	0 - 6.3	0 - 6.9	0 - 6.6	0 - 8.0	0 - 8.0
Albuterol use, puffs, Mean (SD)	3.67 (2.80)	4.04 (2.76)	4.13 (2.67)	3.87 (2.98)	3.93 (2.80)
Range	0 - 18.0	0 - 14.0	0 - 12.0	0 - 14.9	0 - 18.0
Nighttime awakenings Mean (SD)	0.33 (0.5)	0.38 (0.6)	0.30 (0.6)	0.33 (0.5)	0.34 (0.5)
Range	0-2.3	0-2.7	0-4.0	0-2.3	0-4.0

The changes in the secondary efficacy variables and the differences from placebo are listed in table 50. The mean AM PEF fell slightly in the placebo-treated subjects and increased in all of the subjects who received active treatment (-9.69, 18.11, 20.71, and 31.73 L/min change from baseline in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, fluticasone-440 BID groups respectively.) The difference from placebo was greater in the active treatment groups and the increase with fluticasone-440 BID was almost twice that seen after treatment with ciclesonide-320 BID.

Table 50. Secondary Efficacy Outcome Variables Given as Change from Baseline / 12-Week Difference from Placebo in Study 323/324

	Ciclesonide		Fluticasone
Drug dose, mcg	160 BID	320 BID	440 BID
AM PEF (L/min)	18.11 / 27.8	20.71 / 30.39	31.73 / 41.42
AM PEF variability (%)	-1.30 / -1.80	-0.84 / -1.34	-1.99 / -2.50
Daily albuterol use (puffs/day)	-0.62 / -1.69	-0.49 / -1.57	-1.12 / -2.19
Total Asthma Severity Score	-0.39 / -0.71	-0.49 / -0.80	-0.59 / -0.91
Nighttime awakenings	0.06 / -0.10	-0.08 / -0.24	-0.12 / -0.28

* 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 active treatment groups (-0.39, -0.49, and -0.59 ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone

440 BID groups respectively) and increased (0.32) in the placebo group. The difference between placebo and active treatment was -0.71 for ciclesonide-160 BID, -0.80 for ciclesonide-320 BID and -0.91 for fluticasone-440 BID.

Daily albuterol use increased in the placebo-treated subjects and decreased in the ciclesonide-treated subjects. The change between baseline and Week12 was 1.07, -0.62, -0.49, and -1.12 puffs per day in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID groups respectively. The difference between placebo and active treatment was -1.69 for ciclesonide-160 BID, -1.57 for ciclesonide-320 BID, and -2.19 for fluticasone-440 BID.

Both AM and PM PEF variability decreased more in the ciclesonide-160 BID and fluticasone-440 BID- treated subjects than in those treated with ciclesonide-320 BID. The decreases in AM PEF variability relative to placebo were -1.80 for the ciclesonide-160 BID group, -1.34 for the ciclesonide-320 BID group, and -2.50% for the fluticasone-440 BID group. The number of nighttime awakenings increased in the placebo subjects and decreased in the ciclesonide-treated subjects. The decrease relative to placebo was -0.10 in the ciclesonide-160 BID group, -0.24 for the ciclesonide-320 BID and -0.28 for the fluticasone-440 BID group.

Analysis of Withdrawals

In a time-to-event analysis, the withdrawal rate for any cause was higher for the placebo subjects than for the active treatment groups (47.8%, 20.5%, 20.0%, and 16.9% withdrew from the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID groups respectively). Discontinuation for lack of efficacy showed the same pattern, but there appeared to be more of a dose-response. The withdrawal rate for lack of efficacy was 39.6%, 15.7, 10.8%, and 7.4% in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID groups respectively.

Time of Onset Analysis

An analysis of the changes in AM PEF, Asthma Severity Rating Score, and albuterol use during the first week of therapy was undertaken to determine the onset of action of ciclesonide. There were improvements in AM PEF at day 1 in all treatment groups. Improvement was apparent in the Asthma Severity Score at day 2, and albuterol use at day 3.

Patient Reported Outcomes

The overall AQLQ score was available for 509 subjects. However, of the 509 only 388 completed the trial (67 in placebo, 98 in ciclesonide-160 BID, 102 in ciclesonide-320 BID and 113 in fluticasone-440 BID groups). Since the AQLQ was administered only at baseline, 4 weeks, and at the end of the study, this means that 26.9% of the reported values are based on 4 weeks of observation only. In this LOCF analysis both doses of ciclesonide had an improvement in the overall score and in 3 of the 4 domains that was clinically significant (> 0.5). Fluticasone-440 BID had a clinically significant improvement in the overall score and in all 4 domains (Table 51). When the data were reanalyzed using only the subjects who were

Table 51. AQLQ for Subjects in Study 323/324

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Overall Score				
Placebo	129	4.42	-0.11 (0.09)	---
Ciclesonide-160 BID	122	4.46	0.50 (0.09)	0.61 (0.13)
Ciclesonide- 320 BID	125	4.35	0.54 (0.09)	0.65 (0.13)
Fluticasone 440 BID	133	4.54	0.80 (0.09)	0.91 (0.13)
Symptoms				
Placebo	131	4.42	-0.19 (0.10)	---
Ciclesonide 160 BID	122	4.35	0.54 (0.11)	0.74 (0.15)
Ciclesonide 320 BID	126	4.32	0.55 (0.10)	0.75 (0.14)
Fluticasone 440 BID	132	4.48	0.86 (0.10)	1.06 (0.14)
Activity Limitation				
Placebo	122	4.70	-0.03 (0.09)	---
Ciclesonide 160 BID	121	4.70	0.47 (0.09)	0.50 (0.13)
Ciclesonide 320 BID	120	4.55	0.57 (0.09)	0.60 (0.13)
Fluticasone 440 BID	129	4.84	0.75 (0.09)	0.79 (0.13)
Emotional Function				
Placebo	132	4.10	-0.11 (0.11)	---
Ciclesonide 160 BID	123	4.35	0.51 (0.12)	0.63 (0.16)
Ciclesonide 320 BID	127	4.06	0.51 (0.12)	0.62 (0.16)
Fluticasone 440 BID	133	4.17	0.82 (0.11)	0.93 (0.16)
Exposure to Environmental Stimuli				
Placebo	132	4.25	0.08 (0.10)	---
Ciclesonide 160 BID	123	4.32	0.47 (0.10)	0.38 (0.13)
Ciclesonide320 BID	127	4.15	0.50 (0.10)	0.41 (0.13)
Fluticasone 440 BID	133	4.38	0.78 (0.09)	0.70 (0.13)

* *LS mean (SE)*

still in the study at 12 weeks the improvement in score was 0.07, 0.14, and 0.32 when ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID, respectively, are compared to placebo.

1.4.4.1. Safety Outcomes

Extent of exposure

The safety population consisted of the 531 subjects originally enrolled in the study. The mean time on study medication was 56.1, 74.3, 74.6, and 75.5 days in the placebo, ciclesonide 160 BID, ciclesonide 320 BID, and fluticasone 440 BID groups respectively. The median exposure was 81.5, 84.0, 84.0, and 84.0 days respectively.

Adverse Events

Overall, 316/531 (59.5%) subjects reported adverse events. As shown in Table 52, the overall incidence was comparable in all of the treatment groups. The most common organ involvement was the respiratory tract with 36.0%, 31.5%, 29.2%, and 27.5% of the subjects in the placebo, ciclesonide-60 BID, ciclesonide-320 BID, and the fluticasone-440 BID groups reporting events respectively. In the high-dose ciclesonide group 10.9% of the subjects suffered an asthma exacerbation compared with 19.9% of the placebo-treated subjects and 2.3% of the fluticasone-treated subjects.

The second most frequently reported AE was infections. This occurred in 19.9%, 23.6%, 13.8%, and 34.8% of the subjects in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, fluticasone-440 BID groups reporting events respectively. Most of the AEs in this category in the fluticasone-treated subjects were due in large part to the increase in oral candidiasis (11.6%) compared with 0.8% in the ciclesonide-treated subjects and 2.2% in the placebo treated subjects. Sinusitis was also more common with fluticasone treatment (7.2%) compared with 5.4% of the ciclesonide-treated subjects.

Table 52. Adverse Events Reported in Subjects Enrolled in Study 323/324

	Number (%) Subjects				
	Placebo	Ciclesonide			Fluticasone
Drug dose, mcg	0	160 BID	320 BID	Total	440 BID
N	136	127	130	257	138
Patients with treatment-emergent adverse events	84 (61.8)	78 (61.4)	71 (54.6)	149 (58.0)	83 (60.1)
Respiratory & Thoracic	49 (36.0)	40 (31.5)	38 (29.2)	78 (30.4)	38 (27.5)
Nasopharyngitis	10 (7.4)	13 (10.2)	9 (6.9)	22 (8.6)	15 (10.9)
Pharyngitis	4 (2.9)	6 (4.7)	4 (3.1)	10 (3.9)	7 (5.1)
Asthma aggravated	27 (19.9)	10 (7.9)	14 (10.9)	24 (9.3)	3 (2.3)
Nasal congestion	1 (0.7)	7 (5.5)	3 (2.3)	10 (3.9)	0
Rhinitis, seasonal	1 (0.7)	1 (0.8)	4 (3.1)	5 (1.9)	0
Hoarseness	1 (0.7)	0	3 (2.3)	2 (0.8)	5 (3.6)

	Number (%) Subjects				
	Placebo	Ciclesonide			Fluticasone
Drug dose, mcg	0	160 BID	320 BID	Total	440 BID
Infections	27 (19.9)	30 (23.6)	18 (13.8)	48 (18.7)	48 (34.8)
Upper Respiratory	8 (5.9)	11 (8.7)	7 (5.4)	18 (7.0)	8 (5.8)
Sinusitis	5 (3.7)	7 (5.5)	7 (5.4)	14 (5.4)	10 (7.2)
Oral candidiasis	3 (2.2)	2 (1.6)	0	2 (0.8)	16 (11.6)
Nervous System	11 (8.1)	23 (18.1)	12 (9.2)	35 (13.6)	15 (10.9)
Headache	8 (5.9)	11 (8.7)	10 (7.7)	21 (8.2)	13 (9.4)
Eye Disorder	3 (2.2)	9 (7.1)	11 (8.5)	20 (7.8)	5 (5.8)
Cataract, nuclear	1 (0.7)	4 (3.1)	9 (6.9)	13 (5.1)	2 (1.4)
Musculoskeletal	5 (3.7)	13 (10.5)	8 (6.2)	21 (8.2)	7 (5.3)
Back or limb pain	2 (1.4)	9 (7.0)	1 (0.8)	10 (3.8)	7 (5.0)
Arthralgia	1 (0.7)	5 (3.9)	5 (3.8)	10 (3.9)	3 (2.2)
General Disorders	8 (5.9)	4 (3.1)	9 (6.9)	13 (5.1)	9 (6.5)
Pain	1 (0.7)	1 (0.8)	4 (3.1)	5 (1.9)	4 (2.9)

Cataracts

Cataracts were more common in the ciclesonide- treated subjects. More than 5 times as many cataracts developed in the subjects treated with ciclesonide-320 BID (8/130 [6.1%]) as in the subjects treated with fluticasone-440 BID (1/138 [0.7%]). Subjects treated with ciclesonide-160 BID had an intermediate incidence (3.1%). Clinical details of the subjects who developed cataracts during the observation period are provided in Table 53. Two cases were identified in subjects at 7 and 71 days of treatment, during their early-withdrawal examination, and the other examinations were performed at the planned completion of the study. The incidence is clearly higher in the higher doses of ciclesonide.

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Table 53. Subjects Who Developed Cataracts in Study 323/4

	Age	Sex	Duration of Therapy	Prior Therapy	Baseline		Follow-up*	
					OS	QD	OS**	QD
Placebo	47	M	84	Advair	0	0	Tr/NC	Tr/NC
Ciclesonide-160 BID	71	M	7†	Flovent	0	0	Tr/NC	Tr/NC
	41	M	84	Flovent	0	0	Tr/NC	Tr/NC
	30	F	82	Flovent	0	0	Tr/NC	Tr/NC
Ciclesonide-320 BID	64	M	84	Azmacort	0	0	Tr/NC	Tr/NC
	35	F	83	Flovent	0	0	Tr/NC	Tr/NC
	56	F	71†	Advair	0	0	Tr/NC	Tr/NC
	74	M	84	Flovent	0	0	1+/NC	1+/NC
	59	M	85	Flovent	0	0	Tr/NC	Tr/NC
	59	F	87	Flovent	0	0	Tr/NC	Tr/NC
	31	F	84	Advair	0	0	Tr/NC	Tr/NC
42	F	84	Flovent	0	0	Tr/CC	Tr/CC	
Fluticasone-440 BID	50	F	84	Flovent	0	0	Tr/PSC	0

* Tr = trace, NC = nuclear cataract, CC = cortical cataract, PSC = posterior subcapsular cataract; ** OS = Left eye, OD = right eye; † = subject withdrawn prematurely due to lack of efficacy

Additional subjects experienced worsening of pre-existent cataracts. This occurred in 2 subjects in each of the active treatment groups as shown in table 54. All follow-up examinations were performed at the end of the study except for one 62 year old man in the fluticasone group who withdrew early due to lack of efficacy. The largest increase in grade (0 to 2+) occurred in this subject. All other increases were one step or less and there was a decrease in grade in one cataract in a 71 year old man in the ciclesonide 160 BID group.

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Table 54. Subjects with Worsening Cataracts in Study 323/324

	Age	Sex	Day of Rx	Prior Therapy	Baseline		Follow-up*	
					OS	OD	OS**	OD
Ciclesonide-320	71	M	86	Flovent	1+ NC,CC	2+ NC, CC	2+ NC, CC	1+ NC
	44	F	84	Flovent	Tr/NC	Tr/NC	1+/NC	1+/NC
Ciclesonide-604	63	M	84	Flovent	Tr/NC	Tr/NC	1+/NC	1+/NC
	76	F	81	Flovent	1+/NC	1+/NC	1+/NC	2+/NC
Fluticasone-880	56	M	84	Advair	Tr/NC	Tr/NC	1+/NC	1+/NC

* Tr = trace, NC = nuclear cataract, CC = cortical cataract, PSC = posterior subcapsular cataract; ** OS = Left eye, OD = right eye; † = subject withdrawn prematurely due to lack of efficacy

There was a decrease in the density of the cataract in five subjects (2 on ciclesonide 160 BID one on ciclesonide 320 BID and one on fluticasone 440 BID) (Table 55).

Table 55. Subjects with Evidence of Decreasing Cataracts in Study 32/324

Study Drug	Age	Sex	Day of Rx	Prior Therapy	Baseline		Follow-up*	
					OS	OD	OS**	OD
Ciclesonide-160 BID	60	F	84	Flovent	1+/NC	1+/NC	Tr/NC	TR/ NC
	61	M	84	Flovent	1+/NC	1+/NC	0	0
Ciclesonide-320 BID	6	M	81	Flovent	Tr/NC	Tr/NC	0	0
Fluticasone-440 BID	39	M	85	Flovent	Tr/NC	Tr/NC	0	0

* Tr = trace, NC = nuclear cataract, CC = cortical cataract, PSC = posterior subcapsular cataract; ** OS = Left eye, OD = right eye; † = subject withdrawn prematurely due to lack of efficacy

If the step changes in tables 53-55 are combined (i.e. 0 -> Tr = 1+, 1+ -> Tr = -1, etc) then cataracts appeared or worsened in 2 Placebo, 2 Ciclesonide 160 BID, 20 Ciclesonide 320 BID, and 5 Fluticasone 440 BID subjects.

Serious and Important Adverse Events

There were no deaths reported and there were 9 serious adverse events. There were 4 asthma exacerbations, 3 in the placebo-treated subjects and one in the ciclesonide-160 BID group. There was one case of cellulitis in a placebo subject, two myocardial infarctions in the ciclesonide-160 BID-treated subjects, and 1 case each of fever/dysuria, and pneumonia in the ciclesonide-320 BID subjects.

A total of 51 subjects were withdrawn due to adverse events: 27 in the placebo group and 18 in the ciclesonide treated subjects (Table 56). The most common reason for withdrawal was aggravation of asthma. Only 11 subjects withdrew for an AE not related to worsening asthma. In the placebo group there was 1 case each of upper respiratory tract infection (URI), herpes simplex, nasopharyngitis, and 2 cases of sinusitis. In the ciclesonide-160 BID group there were 2 cases of bronchitis, and in the ciclesonide-320 BID group there was one withdrawal due to seasonal rhinitis. One fluticasone-440 BID subject withdrew due to adrenal insufficiency, one due to scabies, and one due to laryngitis. Subjects categorized as having "other significant AEs" were distributed evenly across the treatment groups. The medically important laboratory abnormalities included 2 placebo subjects with hypokalemia and 1 fluticasone subject with an elevated glucose.

Table 56. Other Clinically Important Adverse Events in Study 323/324

	Placebo	Ciclesonide		Fluticasone
		160 BID	320 BID	
Drug dosage, mcg	0			
N		127	130	138
Subjects with other significant AEs, n(%)	73 (53.7)	64 (50.4)	61 (46.9)	75 (54.3)
AE resulted in:				
Discontinued from study, n(%)	27 (19.9)	8 (6.3)	10 (7.7)	6 (4.3)
Therapy temporarily interrupted, n(%)	1 (0.7)	1 (0.8)	1 (0.8)	0
Other intervention, n (%)	2 (1.5)	4 (3.1)	7 (5.4)	6 (4.3)
Treated with counteractive measure, n(%)	68 (50.0)	62 (48.8)	59 (45.4)	74 (53.6)
Important laboratory abnormality, n(%)	2 (1.5)	0	0	1 (0.7)

Laboratory Abnormalities

Liver function tests performed at the end of the study were unremarkable in all of the treatment groups.

The eosinophil counts reached the PCA level in less than 3% of all the subjects tested. (2.5%, 2.6%, 0.9%, and 1.6% in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and fluticasone-440 BID groups). However, 4 subjects were categorized as having “clinically noteworthy” values ($>1 \times 10^3$ cells/ μ L). Two of these subjects were in the placebo group and two in the ciclesonide 160 BID group. The shift tables showed a preponderance of increases over decreases. However this trend was the same in the placebo-treated subjects and the other groups.

Random glucose values were in the clinically noteworthy range ($> 2x$ ULN) in 5 subjects; 1 in the placebo group (238 mg/dL) and 2 each in the ciclesonide-160 BID (448 and 233 mg/dL) and ciclesonide-320 BID groups (297 and 262 mg/dL). In no case was the PCA value reached, however 1 fluticasone-treated subject had a glucose of 151 mg/dL reported as an adverse event.

Two placebo-treated subjects had mild hypokalemia (3.3 Meq/L) reported as an adverse event.

HPA-axis evaluation

Blood was collected on all but 4 of the 140 subjects enrolled in the 16 pre-selected sites chosen to evaluate the HPA-axis. Of these, 120 also had follow-up measurements (Table 57). At baseline, the peak serum cortisol after stimulation with 1 μ g cosyntropin did not differ among the treatment groups. After 12 weeks of treatment the peak cortisol fell in all but the ciclesonide-320 treatment group. None of the changes in the active treatment groups differed from the response in placebo-treated subjects. Similarly, the degree of stimulation (peak – baseline cortisol), were similar in the treatment groups at the beginning of the study.

Table 57. Cosyntropin Stimulation Test : Study 323/324

	N	Baseline Mean	Change from Baseline*	Difference from Placebo*
Peak Serum Cortisol after cosyntropin stimulation, mcg/dL				
Placebo	30	21.87	-0.44 (0.93)	
Ciclesonide-160 BID	29	25.07	-2.06 (0.95)	-1.63 (1.26)
Ciclesonide-320 BID	31	23.45	0.75 (0.87)	1.19 (1.21)
Fluticasone-440 BID	30	24.53	-1.05 (0.91)	-0.61 (1.23)

* LS Mean (SE)

Defining normal HPA function as a basal cortisol of at least 5 μ g/dL and a post-simulation serum cortisol of at least 18 μ g/dL, 64.9%, 63.6%, 80.6%, and 71.4% of the subjects were normal at baseline and follow-up in the placebo, ciclesonide-160 BID, ciclesonide-320 BID, and FP-440 BID groups respectively. Shifts from normal at baseline to abnormal at follow-up occurred in 18 subjects: 5 in the (13.5%) placebo group, 7 (21.2%) in the ciclesonide-160 BID group, 1 (2.8%) in the ciclesonide-320 BID group, and 4 (14.3%) in the FP-group. Although there were more subjects in the ciclesonide-160 BID group with abnormal post stimulation peak cortisol, most of the values were close to normal. By contrast, both the

placebo and fluticasone groups had fewer abnormal values, however, some were very low. (Table 58)

Table 58. End-of-Study Values for Serum-Cortisol for Subjects with Normal Values at Baseline and Abnormal at End-of-Study 323/324

	Placebo	Ciclesonide	Ciclesonide	Fluticasone
Dose, µg/day	0	160 BID	320 BID	440 BID
Peak Post-stimulation	3	12	17	2
Cortisol, µg/dL	13	16		7
(Normal ≥ 18)	14	16		15
	15	17		17
	17	17		
		17		

Urine was collected for cortisol at the same 16 centers, and the results were supportive of the findings in the blood samples. There was no difference among the treatment groups for the baseline to Week 12 change in 24- hour excretion of free cortisol corrected for creatinine.

Reviewer: As in the pivotal trials, there is no comment about the quality of the urine collections. The protocol instructs the investigators to note the urine volume and to ask the subject if there was any time during the 24-hour collection period that a voiding was not collected. This information is not included with the tabulated results or in listing 48.

1.4.5. Discussion and Conclusions

In this 12-week pivotal trial, subjects with moderate to severe persistent asthma, all of whom had been treated with ICS prior to enrollment, were treated with placebo, ciclesonide 320 mcg (160 mcg BID) ciclesonide 640 mcg (320 mcg BID) or Fluticasone 880 (440 mcg BID). The subjects in all of the treatment groups had a significant increase in pre-dose FEV₁ at endpoint compared to placebo. The secondary outcome measures supported the finding of efficacy at both doses of ciclesonide. Compared to placebo, the active comparator, fluticasone 440 BID had a greater improvement in mean pre-dose FEV₁ (240ml) than ciclesonide 320 mcg BID (180ml).

The withdrawal rate was substantially higher in the placebo than the active treatment groups, however there was no difference among the actively treated subjects. The applicant submitted an analysis of pulmonary function to define an onset of action In 24 hours. However, as in studies 321 and 322, the statistical analysis did not correct for multiple outcomes and can therefore not be used to support the claim _____

In addition, the Asthma Severity Score did not improve until day 2, and albuterol use in the ciclesonide 320 BID group did not differ from placebo on any day except day 3. There is, therefore, no support for a blanket statement of _____

b(4)

The overall score for the AQLQ improved with both doses of ciclesonide The mean increase in the scores above the change that was seen with placebo treatment, was consistent with a clinically meaningful improvement (>0.5) for all of the scores except for the category of

Exposure to Environmental Stimuli. However, these results are based on an LOCF analysis and 48% of the placebo subjects withdrew from the study before they had received 12 weeks of treatment. Because the final analysis is based on change from placebo, the high drop-out rate in placebo subjects affects the outcome for all the treatment groups. When the analysis was performed on the subjects who stayed in the study the results were less impressive.

Adverse events occurred in approximately 60% of the subjects and the distribution of events was similar to that seen in the other studies. There was a very lower incidence of oral candidiasis in the ciclesonide-treated subjects (2 (0.8%) compared with 5 (3.6%) of the fluticasone-treated subjects). On the other hand, the incidence of cataracts was higher in the ciclesonide-treated subjects. Even after taking into account subjects whose cataracts improved during the trial, there was clearly an increased incidence of worsening corneal involvement in the ciclesonide group and it appeared to be dose-related. The net increase in cataracts (subtracting the number of improved cases from those that worsened) was 2 in the placebo group, 2 in the ciclesonide 160 BID group, 20 in the ciclesonide 320 BID group and 5 in the fluticasone 440 BID group.

Abnormalities of liver function were not noted in this study. However, there were again noted several cases of high eosinophil counts with most of the cases occurring in the ciclesonide-treated subjects. Evidence of HPA-axis function were infrequent, and occurred as frequently in the placebo-treated subjects as in any of the actively treated subjects. However, more shifts from normal at baseline to abnormal at end-of-study were seen in study 323/324 than in studies 321 or 322. This is probably a function of prior steroid treatment in this more severe asthmatic population. As in the previously described studies, the 24-hour urine cortisol measurements can not be used to assess HPA-axis function because of the lack of quality control.

In general, the improvement seen after treatment with ciclesonide was greater in study 323/324 than in study 321 or 322. This could be a function of the subject characteristics or of the dosing regimen. Subjects in 323/324 had more severe disease than those in study 321/322 as judged by the FEV₁. They were all taking ICS prior to enrollment whereas, subjects in studies 321 and 322 could have been taking bronchodilators alone or ICS prior to enrollment. The results are consistent with the findings in studies 321 and 322 to the extent that only subjects previously treated with ICS were found to have a significant response to ciclesonide in those studies. Finally, subjects in 323/324 were treated twice daily while subjects in study 321/322 and were treated with a once daily regimen. Since there was no direct comparison between twice daily and once daily dosing in any of the studies, it is impossible to assess the importance of the treatment regimen using the data provided.

1.5. Study 323/324LT

A multicenter, randomized, double-blind 1-year long-term safety study of ciclesonide 400 mcg/day to 800 mcg/day (ex-valve) (320 and 640 mg/day ex-actuator) or QVAR 320 mcg/day to 640 mcg/day (ex-actuator) metered dose inhaler administered twice daily for the treatment of severe persistent asthma in adolescents and adults.

Reviewer: This review is based on the 120-day safety update which includes the final study report for 323/324lt.

1.5.1. Protocol**1.5.1.1. Administrative****b(4)**

Enrollment: June 20, 2001 – March 31, 2003

Clinical Director: _____

Sites: 63 clinics in the United States

1.5.1.2. Objective

To establish the long-term (1 year) safety and efficacy of ciclesonide metered-dose inhaler (MDI) at doses of 320 mcg to 640 mcg/day BID (ex-actuator) as compared to beclomethasone HFA (QVAR®) 320 mcg and 640 mcg/day BID (ex-actuator) in adults and adolescents with severe persistent asthma.

1.5.1.3. Overall Design

This is a randomized, double-blind one year extension of pivotal study 323/324. Subjects were enrolled within 2 weeks of the end of the pivotal trial. If patients were withdrawn prematurely from studies 323/324 due to an adverse event or an asthma exacerbation, they could still be enrolled in study 323/324LT if the event/exacerbation had resolved. In addition, screen failures from studies 323/324 were eligible to enroll in the follow-up study if the screen failure was based on a lack of a fall in FEV₁ or failure to develop 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 systemic steroids in the interim between exiting study 323/324 and enrollment into the long-term follow-up.

All subjects were randomized to high-dose ciclesonide or QVAR for two weeks as follows:

Ciclesonide 320 mcg (80 mcg/puff x 4 puffs) BID

QVAR 320 mcg (80 mcg/puffs 4 puffs) BID.

Subsequently the investigator could lower or raise the dose of ciclesonide between 160 and 320 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 of no more than 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 variables were for safety (adverse events, laboratory abnormalities, and HPA-axis function). Spirometry was recorded, but was not considered an outcome variable. For the details of the procedures and analytic techniques see review of Study 321, pg 64.

1.5.2. Results

1.5.2.1. Subjects

All of the 297 screened subjects were randomized (198 to Ciclesonide and 99 to QVAR). Of the randomized subjects, 132 (66.7%) and 69 (69.7%) of the ciclesonide and QVAR subjects completed the 1 year follow-up, respectively (Table 59). More subjects in the ciclesonide group withdrew due to withdrawal of consent and lost to follow-up (39 [19.7%] ciclesonide vs 11 [11.1%] QVAR), while more subjects in the QVAR group withdrew due to adverse events and lack of efficacy. If the adverse events due to asthma exacerbation are added to the lack of efficacy withdrawals, slightly more subjects in the QVAR group (11 [11.1%]) withdrew due to lack of efficacy than in the ciclesonide group (14 [7.1%]).

Table 59. Disposition of Subjects in Study 323/324LT

	Number (%) Subjects		
	Ciclesonide n=198	QVAR n=99	Total n = 298
Completed Study, n(%)	132 (66.7)	69 (69.7)	201 (67.7)
Reason for Discontinuation, n(%)			
Consent withdrawn	24 (12.1)	6 (6.1)	30 (10.1)
Adverse Event	14 (7.1)	10 (10.1)	24 (8.1)
Lost to follow-up	15 (7.6)	5 (5.1)	20 (6.7)
Lack of Efficacy	10 (5.1)	8 (8.1)	18 (6.1)
Other	5 (2.5)	5 (5.1)	10 (3.4)
Protocol violation	6 (3.0)	2 (2.0)	8 (2.7)
Compliance	4 (2.0)	0	4 (1.3)
Death	1 (0.5)	0	1 (0.3)

Reviewer: On page 72 of the study report [clinostat\study323_324\323lt.pdf] the applicant states that "Patients were classified as discontinued due to lack of efficacy at the discretion of the investigator and included patients who withdrew due to a treatment-emergent adverse event of asthma aggravated." Review of Table 28 (pg 117 [clinostat\study323_324\323lt.pdf]) in the body of the study report and listing C. 1.2-2 (pg 2311 or 3867 [clinostat\study323_324\323lt.pdf]) suggests that some of the asthma exacerbation AEs were listed as lack of efficacy, but not all. In the ciclesonide group there are 9 subjects listed in Table 28 as having withdrawn due to an asthma exacerbation. In Listing C. 1.2-2 five of the asthma exacerbation AEs are listed as lack of efficacy. On the other hand, 5 other subjects (009-10, 073-04, 074-06, 231-01, 274-04) are listed as a lack of efficacy in Listing C. 1.2-2 and are not listed as a withdrawal due to an adverse event. Counting each subject only once and categorizing their withdrawal as due to lack of efficacy if Listing C.1.2-2 designates them lack of efficacy or if they had an adverse event withdrawal due to asthma exacerbation results in the number in the last sentence of the above paragraph: "14 ciclesonide-treated and 11 QVAR treated subjects withdrew due to lack of efficacy". There

was, in addition, one subject treated with both ciclesonide and QVAR that was withdrawn due to status asthmaticus.

It is somewhat disconcerting to see the large number of subjects in the ciclesonide group who withdrew consent or were lost to follow-up because it is impossible to know how many of these declined to participate because they were dissatisfied with the medication. The lost-to-follow-up does not include subjects who moved out of town because these are included in the OTHER category.

After randomization, it was noted that 4 subjects received both QVAR and ciclesonide. These 4 were described separately and excluded from further analysis resulting in a safety population of 197 subjects on ciclesonide and 96 on QVAR. As can be seen in Table 60 the demographic and clinical variables were evenly distributed between the two treatment groups. Slightly more than half of the subjects were female and the mean age was 45 years. African-Americans made up 14.2% of the ciclesonide group and 7.3% of those treated with QVAR. The pulmonary function variables were closely matched with a mean FEV₁ of 2.1 L which was approximately 65% of predicted.

Table 60. Demographic and Clinical Characteristics of Subjects Enrolled in Study 323/324LT

		Ciclesonide n=197	QVAR n=96	Total n=293
Gender, n(%)	Male	82 (41.6)	43 (44.8)	125 (42.7)
	Female	115 (58.4)	53 (55.2)	168 (57.3)
Age, years	Mean (SD)	44.7 (14.4)	45.2 (14.2)	44.9 (14.3)
	Range	13-76	12-74	12 – 76
Race, n(%)	White	155 (78.7)	79 (82.3)	234 (79.9)
	Black	28 (14.2)	7 (7.3)	35 (11.9)
	Asian	4 (2.0)	5 (5.2)	9 (3.1)
	Other	10 (5.1)	5 (5.2)	15 (5.1)
Duration of Asthma (years)	Mean (SD)	24.5 (15.9)	23.3 (13.7)	24.11 (15.24)
	Range	1.2 – 62.3	1.5 – 63.8	1.2 – 63.8
FEV1, Liters	Mean (SD)	2.12 (0.66)	2.11 (0.73)	2.12 (0.69)
	Range	0.75 – 3.79	0.76 – 4.92	0.75 – 0.92
FEV1 % predicted	Mean (SD)	64.7 (14.9)	64.9 (16.0)	64.8 (15.22)
	Range	31.5 – 108.4	31.1 – 101.7	31.1 – 108.4

After enrollment in study 323/324LT, The ciclesonide subjects were treated for a mean of 279.6 days (median 363, range 1-378) and the QVAR subjects were treated for a mean for 296.3 days (median 363, range 1-372). The average daily dose of ciclesonide was 576.7 ± 113.2 mcg (range 320-640 mcg) and the average daily dose of QVAR was 573.6 ± 119.0

mcg/day (range 320-640). Seventy percent of the subjects (138 on ciclesonide and 68 on QVAR) were treated with 320 mcg BID of study drug throughout the study. Twenty-five subjects were inadvertently exposed to expired QVAR for 1 to 111 days during the study. They are included in the safety analysis. Eleven adverse events were recorded in 6 of these subjects at the time they were taking the expired drug. There were 3 asthma exacerbations, 2 headaches, and 1 case each of oral candidiasis, sinusitis and urticaria. The other AEs were related to trauma.

The adverse event experience of the population is summarized in table 61. Of the 12 serious AEs (10 in ciclesonide- and 2 in QVAR-treated subjects), there was 1 case of pneumonia in the ciclesonide group and 1 case of mental depression. There was 1 case each of asthma and abdominal pain in the QVAR group. The other serious AEs were not related to the respiratory tract nor generally thought to be related to drug therapy (1 case of spinal stenosis, 3 gynecologic complaints, 1 case of malignant melanoma, 2 myocardial infarctions, and 1 case of cellulitis all in the ciclesonide-treated subjects).

Table 61. Summary of Adverse Events in Study 323/324LT

	Ciclesonide n=197	QVAR n=96	Total n=293
All adverse events, n(%)	146 (74.1)	76 (79.2)	222 (75.8)
Serious Adverse Events, n(%)	12 (6.1)	2 (2.1)	14 (4.8)
Deaths, n(%)	1 (0.5)	0	1 (0.3)
Other Significant adverse events, n(%)	127 (64.5)	64 (68.8)	191 (65.2)
Discontinue medication	14 (7.1)	9 (9.4)	23 (7.8)
Interrupt therapy	2 (1.0)	1 (1.0)	3 (1.0)
Reduce dose	3 (1.5)	2 (2.1)	5 (1.7)
Increase dose	1 (0.5)	0	1 (0.3)
Other intervention	29 (14.7)	10 (10.4)	39 (13.3)
Treated with medication	124 (62.9)	64 (66.7)	188 (64.2)
Medically important laboratory abnormalities	12 (6.1)	4 (4.2)	16 (5.5)

There was one death in the ciclesonide group in a 75 year-old female who was found dead at home. The patient was not hospitalized and no autopsy was performed. The death certificate recorded acute myocardial infarction as the cause of death. She had a history of hypertension.

1.5.2.2. Adverse Events

At the end of the year follow-up 222 (75.8%) of the subjects reported at least 1 adverse event (146 [74.1%] in ciclesonide- and 73 [79.2%] QVAR-treated patients). The most common treatment-emergent adverse events by system were infections/infestations, and the next most common were respiratory events (Table 62). More subjects on QVAR complained of nasopharyngitis and URI, while a higher percentage of subjects treated with ciclesonide

complained of sinusitis. Six (3.0%) subjects treated with ciclesonide and 10 (10.4%) treated with QVAR were reported to have oral candidiasis. Asthma exacerbations occurred in equal frequency in both treatment groups. Overall, more subjects taking QVAR complained of headache (15.6% compared with 9.6% for ciclesonide-treated subjects). Cataracts occurred with approximately equal frequency in the two treatment groups. Details of the subjects who developed cataracts are presented in the section on Eye Involvement below.

Table 62. Adverse Events Reported in Study 323/324LT

	Number (%) Subjects	
	Ciclesonide n=197	QVAR n= 96
All adverse events	146 (74.1)	73 (79.2)
Infections and infestations	90 (45.7)	55 (57.3)
nasopharyngitis	28 (14.2)	19 (19.8)
Sinusitis	27 (13.7)	6 (6.3)
Upper respiratory tract	22 (11.2)	17 (17.7)
Influenza	7 (3.6)	2 (2.1)
Upper respiratory tract, viral	7 (3.6)	4 (4.2)
Oral candidiasis	6 (3.0)	10 (10.4)
Pharyngitis, streptococcal	6 (3.0)	2 (2.1)
Urinary tract	4 (2.0)	4 (4.2)
Gastroenteritis	2 (1.0)	3 (3.1)
Respiratory manifestations	69 (35.0)	29 (30.2)
Asthma exacerbation	37 (18.8)	18 (18.8)
Bronchitis	8 (4.1)	3 (3.1)
Rhinitis	7 (3.6)	2 (2.1)
Cough	6 (3.0)	3 (3.1)
Pharyngolaryngeal pain	6 (3.0)	5 (5.2)
Nasal congestion	1 (0.5)	3 (3.1)
Nervous system	28 (14.2)	19 (19.8)
Headache	19 (9.6)	15 (15.6)
Musculoskeletal	28 (14.2)	13 (13.5)
Back pain	10 (5.1)	3 (3.1)
Arthralgia	8 (4.1)	2 (2.1)
Gastrointestinal	23 (11.7)	16 (16.7)
Gastroenteritis	2 (1.0)	3 (3.1)
Tooth Ache	0	3 (3.1)
Eye Disorders	20 (10.2)	9 (9.4)
Nuclear Cataracts	8 (4.1)	4 (4.2)
Cortical Cataracts	6 (3.0)	3 (3.1)

	Number (%) Subjects	
	Ciclesonide	QVAR
Skin	21 (10.7)	12 (12.5)
Rash	7 (3.6)	0
Post procedural pain	5(2.5)	3 (3.1)
Influenza-like illness	6 (3.0)	5 (5.2)
Hypertension	7 (3.6)	0

Eye Involvement

Cataracts developed and regressed in all of the treatment groups (Table 63). Combining subjects with the *de novo* development of cataracts with those who had cataracts at baseline that progressed results in 14 (7.1%) of the ciclesonide subjects and 8 (8.4%) of the QVAR subjects with worsening eye manifestations. If the percentage is calculated using the number of subjects who had a follow-up examination 8.4% of the ciclesonide and 9.4% of the QVAR subjects had progressive eye involvement. A higher percentage of ciclesonide-treated subjects had improvement in cataracts that had been present at baseline. However, all of the posterior subcapsular cataracts occurred in subjects who had been exposed to ciclesonide. The subject who developed the cataract after receiving both medications received ciclesonide for 176 days and QVAR for 189 days.

Table 63. Subjects who Developed Cataracts in Study 323/324LT

Baseline	Follow-up	Ciclesonide n=197	QVAR n=96	Both n=4
Absent	Present Subcapsular	6 (3.0%) 3	2 (2.1%) 0	1 1
Present	Worse than Baseline	8 (4.1%)	6 (6.3%)	0
Present	Improved from Baseline Normal	8 (4.1%) 3	2 (2.1%) 2	1 1

The subjects with cataracts at baseline that deteriorated during the study had a variety of changes in grade and character. Two of the ciclesonide and four of the QVAR subjects had no change in the grade of the cataract despite being included in the list of subjects with worsening cataracts. They are described in table 64. One 58 year-old woman in the QVAR group had a decrease from 1+ to trace cataract and lamellar separation in one eye. The other eye showed a stable grade, but new lamellar separation was present at the end of the study. A 71 year-old man treated with QVAR had one eye with 2+ cortical and nuclear cataracts that decreased to 1+ at the end of the study. The other eye had a 1+ nuclear cataract at baseline that was unchanged at end- of -study, but cortical involvement had developed. Of note, this subject was only treated for 12 days due to lack of clinical efficacy of the QVAR.

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Table 64. Subjects Characterized as Worsening Cataracts but with a Constant or Decreasing Grade in Study 323/324It

	Age	Sex	Duration	Baseline		Follow-up	
				OS	OD	OS	OD
Ciclesonide	53	F	375	Tr N	Tr N	Tr N	Tr N/PS
	70	M	349	2+ N	2+ N	2+ C/N	2+ C/N
QVAR	58	F	362	1+ N/O	Tr N	Tr N/O	Tr N/O
	61	M	369	Tr N	Tr N	Tr C/N	Tr C/N
	56	M	361	Tr C	Tr C	Tr C/N	Tr C/N
	71	M	12	2+ C/N	1+ N	1+ C/N	1+ C/N

* Tr = trace, NC = nuclear cataract, CC = cortical cataract, PSC = posterior subcapsular cataract; ** OS = Left eye, OD = right eye; † = subject withdrawn prematurely due to lack of efficacy

Three cases of glaucoma were reported in the ciclesonide-treated subjects. One case was severe enough to require withdrawal of the subject from the study. There were no cases of glaucoma in the QVAR- treated subjects.

Adverse Events Leading to Withdrawal

The majority of the AEs that were severe enough to result in the subject's withdrawal from the study were due to an exacerbation of asthma. There was in addition, the case of glaucoma mentioned above and 1 case of abnormal liver function tests in a ciclesonide subject. There was also one withdrawal due to abnormal liver function in a QVAR subject. (See Laboratory Abnormalities below).

Laboratory Abnormalities

There were no abnormalities in liver function that were considered by the applicant to be "clinically meaningful". However, 8 subjects in the ciclesonide group had at least 1 liver enzyme (SGPT, SGOT, SGGT, Alkaline Phosphatase) result in the PCA range at the end of the study. Two additional subjects had lesser abnormalities in liver function reported as adverse events. Thus 10/(144-152), or approximately 6.7%, of the ciclesonide subjects had liver function changes worthy of reporting. One subject in the QVAR group had liver enzymes in the PCA range and 2 subjects had liver functions reported as adverse events. This resulted in 3/(75-79), or approximately 3.8%, of the QVAR patients having liver function results worthy of comment. The bilirubin levels were all in the normal range. The end-of-study values and increase from baseline for the individual tests is listed in Table 65 .

Table 65. Abnormal Liver Function in Subjects Treated in Study 323/324LT

	ID†	Age	Sex	Peak (ES)	Increase from Baseline
Ciclesonide (n=144 – 152)					
SGPT (U/L)	1*	44	F	156	112
	2*	25	F	186	166
	3	65	F	43	15
	4	49	F	47	21
SGOT (U/L)	1*			91	59
	2*			196	175
	3			38	12
	5*	55	M	68	36
SGGT (U/L)	1*			109	71
	4			64	27
	6*	54	F	120	62
	7*	45	M	69	31
	8*	45	F	58	32
	9*	33	M	128	40
Alk P'tase	6*		F	140	29
	10*	35		142	35
QVAR (n = 75-79)					
SGPT (U/L)	11	39	F	52	27
	12	23	M	105	19
SGOT (U/L)	12			39	-6
SGGT (U/L)	11*			117	52
Alk P'tase	13*	52	F	139	33

† - A number used only in this table to identify subjects with multiple abnormal liver function tests. Age and sex are listed only for the first entry for any given subject.

* = Value in PC range = Value above normal and increase by the following: SGPT 28 U/L, SGOT 22 U/L, SGGT 29 U/L, Alk P'tase (alkaline phosphatase) 28 U/L.

On average, the neutrophil counts increased over the course of the study to a greater extent in the QVAR-treated subjects ($0.6 \times 10^3/\mu\text{L}$) than in the ciclesonide subjects ($2 \times 10^3/\mu\text{L}$). In addition, the neutrophil count reached the PCA level in 4.9% of the QVAR subjects and only 1.9% of the ciclesonide subjects. The neutrophil count in the QVAR subjects was the only value that was at the PCA level in more than 4% of the subjects. The eosinophil counts were at the clinically noteworthy level ($>1 \times 10^3/\mu\text{L}$) in two ciclesonide subjects and 1 QVAR subject.