CLINICAL REVIEW

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Established Name	Ciclesonide
(Proposed) Trade Name	Alvesco
Therapeutic Class	Corticosteroid
Applicant	Aventis
Priority Designation	S
Formulation	HFA Inhalation Aerosol
Dosing Regimen	Once and Twice Daily
Indication	Persistent Asthma
Intended Population	12 years of age and older

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ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
AUC	Area Under the Curve
BID	Twice Daily Dosing
C40	Ciclesonide 40 mcg once daily
C80	Ciclesonide 80 mcg twice daily
C80/160	Ciclesonide 80 mcg twice daily for 4 weeks followed by ciclesonide 160 mcg once daily
C160	Ciclesonide 160 once daily
C320	Ciclesonide 320 mcg twice daily
CI	Confidence Interval
C_{max}	Maximum concentration of a drug in the blood after dosing
CRF	Case report form
CS	Corticosteroid
DB	Double Blind
BDP	Beclomethasone
DSI	Division of Scientific Investigation
ECG	Electrocardiogram
FEV_1	Forced Expired Volume in 1 second
FVC	Forced vital capacity
GI / L	Giga cells/liter
HFA	Hydrofluroalkane
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
ICS	Inhaled corticosteroids
IOP	Intra-ocular pressure
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention to Treat
IVRS	Interactive Voice Response System
L	Liters
LABA	Long-acting beta agonist
.LOCF	Last observation carried forward
LOCS III	Lens Opacification Classification System III
LS	Least Square
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
Meq	Milliequivalent
mITT	Modified Intent-To-Treat
NAEPP	National Asthma Education and Prevention Program
NIB	Non-inferiority bound
OCS	Oral corticosteroids
PCA	Predefined Change Abnormal
PSC	Posterior Sub-Capsular
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PP	Per Protocol

QD	Once daily dosing
RM1	Primary active metabolite of R-ciclesonide.
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic Transaminase
SGPT	Serum glutamic pyruvic Transaminase
SOC	System Organ Classification
T1/2	The time it takes for the blood level of a drug to reach ½ of its peak level.

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Ciclesonide HFA MDI 80, 160, and 320 mcg BID is recommended for the maintenance treatment of asthma in adults and adolescents 12 years of age and older. The recommendation is based on the results of well designed pivotal efficacy trials of appropriate length in subjects with mild to severe persistent asthma. Direct comparisons of once vs twice daily dosing regimens showed clear superiority of twice daily dosing compared to the same nominal dose administered once daily. [redacted]. In year-long studies submitted with the original NDA, a benign adverse event profile was documented. In an additional year-long, carefully monitored study to assess the development of cataracts during treatment with ciclesonide, the overall incidence of lens opacities was not higher than seen during treatment with a comparator corticosteroid. Therefore ciclesonide is safe to administer chronically with the usual class warnings and precautions that accompany inhaled corticosteroids.

This complete response to the approvable action taken on the original submission contains no new pediatric (<12 years of age) studies. Efficacy was not supported for doses of 40, 80, or 160 mcg once daily in studies submitted with the original NDA in subjects 4 – 11 years of age, and

[redacted]

1.2 Recommendation on Post-marketing Actions

[redacted]

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ciclesonide HFA MDI is a synthetic corticosteroid formulated to be administered by oral inhalation. The proposed indication is "for the maintenance treatment of asthma as prophylactic therapy in adult and [redacted] patients [redacted] years of age and older". The proposed doses range

between 160 mcg [redacted] as the starting dose in subjects not previously treated with inhaled corticosteroids (ICS) to 320 mcg BID for patients [redacted] on maintenance corticosteroids prior to the initiation of treatment with ciclesonide.

The proposal for approval in adults and adolescents (≥ 12 years of age) is based on the results of studies submitted with the original application and new studies undertaken subsequently in response to the approvable action. Four twelve-week efficacy and safety studies (Study 321, 322, 323/324, and 325) were submitted with the original NDA. Studies 321 and 322 (N=524 and 489 enrolled, respectively) were conducted in patients with mild to moderate asthma who had been treated with either bronchodilators and/or inhaled corticosteroids (ICS) prior to enrollment. All of the study treatments (80, 160, and 320 mcg daily) were administered once daily. Study 323 (N=527 enrolled) was conducted in patients with moderate to severe asthma, all of whom were on maintenance ICS at the time of enrollment, and all of whom were treated with 160 or 320 mcg twice daily.. Study 325 (N=141 enrolled) was conducted in patients with severe asthma who were on maintenance oral corticosteroids at the time of enrollment. Doses of 320 or 640 mcg twice daily of Ciclesonide or placebo was administered for 12 weeks. The new studies include one 16-week trial (Study 3031; N=708 enrolled) in adults and adolescents who had not received ICS in the 30 days prior to enrollment. Patients were treated with placebo, ciclesonide 160 mcg QD, ciclesonide 80 mcg BID for 16 weeks, or with ciclesonide 80 mcg BID for 4 weeks followed by 12 weeks of ciclesonide 160 mcg QD. Study 3030 (N=456 enrolled) was of 12 weeks duration, and subjects were treated with placebo, ciclesonide 80 mcg BID or ciclesonide 160 mcg QD. All of these subjects had been on maintenance ICS prior to enrollment.

No new efficacy trial was submitted for subjects <12 years of age. Studies 341 and 342 were submitted with the original NDA (N=514 enrolled in each). The patients were 4 to 11 years of age, they had mild to moderate asthma, and were treated once daily with ciclesonide or placebo. The studies are referenced in the summary discussions of efficacy.

Safety is supported by the adverse event experience observed in the pivotal safety and efficacy trials, as well as year-long safety follow-up trials (Study 326 and 323/324LT) that were reviewed with the original application. Study 326 enrolled 226 subjects in an open-label 52-week, variable-dose follow-up of patients originally enrolled in Studies 321 and 322. Study 323/324LT followed 293 of the subjects who had been enrolled in Study 323/324. Of those enrolled in the long-term follow-up, 197 were randomized to ciclesonide and 97 to beclomethasone. The safety evaluation in Study 323/324LT included a slit lamp examination as well as adverse. The complete response also included a 52-week safety trial in adults (≥ 18 years of age) to determine the effect of ciclesonide on the lens (Study 3027; N=1568 enrolled). Subjects were treated with ciclesonide 320 mcg BID or beclomethasone 320 mcg BID and the outcome was based on a detailed slit lamp examination as well as visual acuity and intraocular pressure measurements. Safety in the pediatric population was further assessed with a 52-week growth study (Study 343; N=661 enrolled) performed in prepubescent children (<8.5 years of age). Linear growth was assessed during treatment with placebo, ciclesonide 40 mcg QD or ciclesonide 160 mcg QD. Finally, the complete response included a study evaluating functionality of a dose counter (Study 3028; N=125 enrolled). The study followed 125 subjects for 15 or 30 days and compared the diary account of doses taken with canister weights and the dose counter readings.

A total of 4131 subjects were treated with ciclesonide in the pivotal 12-week efficacy studies . Of these, 2923 were adults and 1208 children < 12 years of age. The most frequently administered dose was 160 mcg once daily (Table 1).

Table 1. Total Population (Safety population) Enrolled in Efficacy Trials of Ciclesonide

Age, yrs	40 QD	80 QD	80 BID	80BID/ 160QD	160 QD	160 BID	320 QD	320 BID	640 BID
≥12		257	325	173	704	127	294	994	49
<12	476	260			472				

Although not reviewed with this application, long term (52-week) safety follow-up studies were reviewed with the original NDA for both adult and adolescent and pediatric populations, so that there is now an extensive experience with inhaled ciclesonide. In the two 52-week studies submitted with this application 703 adults and 395 children < 12 years of age were treated for at least 6 months and 268 adults and 116 children were treated for at least 12 months. Including the long-term studies from the original NDA there have been 1045 adults and 756 children <12 years of age that have received ciclesonide for at least 6 months and 572 adults and 437 children < 12 years of age who have been treated for at least 12 months. This exposure is sufficient to assess the safety of ciclesonide in the adult and pediatric population.

1.3.2 Efficacy

In the original NDA, efficacy in patients with mild to moderate asthma was evaluated only with once daily regimens of ciclesonide. The results showed efficacy for a once daily dose of 320 mcg once daily, but efficacy of the 160 and 80 mcg once daily doses could not be replicated. It was also noted that patients who had been treated with ICS prior to enrollment in the trial had a larger response to ciclesonide than the patients who had not been previously treated with ICS. In studies of more severe asthma, twice daily dosing regimens were successful, and the suggestion was made that the applicant assess additional dosing regimens in patients with mild to moderate asthma. The new efficacy studies submitted with this complete response had as a primary objective the comparison of once and twice daily dosing.

Two randomized, double-blind, placebo-controlled trials were conducted that compared dosing with 80 mcg BID and 160 mcg QD in subjects with mild to moderate persistent asthma. In Study 3031 the subjects had not received maintenance ICS in the 30 days prior to enrollment and in Study 3030 all of the subjects had received ICS within 30 days of enrollment. In study 3031 an additional treatment arm was included to mimic the clinical condition of switching a patient from a twice daily to a one daily regimen. Patients were treated with 80 mcg BID for 4 weeks and then switched to 160 mcg for 12 weeks. The subjects who received 80 mcg BID or 160 mcg QD were treated for 16 weeks. There were approximately 170 subjects per treatment group in Study 3031 and 150 subjects per group in Study 3030.

In Studies 3030 and 3031 all of the active treatment groups produced statistically significant improvement in FEV_1 when compare to placebo. However, the patients treated with the twice

daily regimens improved more than those treated with once daily ciclesonide, and in the case of the patients who had not previously been treated with corticosteroids, treatment with the twice daily regimen resulted in improvement that was double that seen with the once daily regimens. In the steroid naïve subjects the FEV_1 increased by 120 mL after treatment for 16 weeks with 160 mcg QD and 240 mL after treatment with 80 mcg BID. In the subjects who were on maintenance ICS at the time of enrollment, the increase over placebo was 140 and 190 mL after treatment with 160 mcg QD and 80 mcg BID, respectively. In the steroid naïve patients, the secondary outcomes, AM peak flow, albuterol use, and asthma symptom score all showed more improvement after twice daily compared to once daily dosing. In the maintenance corticosteroid- treated patients, only the AM peak flow was substantially better maintained in the 80 mcg BID group compared to the 160 mcg QD group.

The results of all of the submitted trials can be assessed in the subgroups of patients divided on the basis of prior ICS use. In patients who had not received ICS in the 30 days prior to enrollment, there was only one study that showed efficacy of the 160 mcg once daily dosing (Study 3031). In a post-hoc sub-set analysis, none of the doses (80, 160, and 320 mcg QD) administered in studies 321 or 322 produced significant improvement when compared to placebo. In addition, while the 160 mcg once daily dose produced statistically significant improvement in FEV_1 in Study 3031, the improvement with the same nominal dose administered twice daily was so much greater that it would be inappropriate to recommend once daily dosing in the patient population. Patients who had been previously treated with maintenance ICS responded somewhat better to the once daily regimens. Patients treated with 160 mcg once daily had an improvement of 140 mL in FEV_1 compared to placebo and those treated with 80 mcg BID had a 190 mL improvement. On the other hand, the AM peak flow decreased in all of the treatment groups suggesting that asthma control was not perfectly maintained by either of the active treatment regimens. The responses to once daily dosing in the subjects previously treated with ICS in studies 321 and 322 ranged between 110 and 240 mL with statistical significance compared to placebo replicated for the 320 mcg dose.

Lastly, study 323/24 was conducted in patients with moderate to severe asthma who had been on maintenance ICS at the time of enrollment. These patients were assumed to require more intense treatment and they were all treated with BID regimens. There was a 110 mL increase in FEV_1 compared to placebo in those treated with 160 mcg BID and a 180 mL increase compared to placebo in those treated with 320 mcg BID, and both improvements were statistically significant. Similarly, the patients in Study 325, who had severe, oral corticosteroid-dependent asthma, were treated with twice daily dosing. Both 320 and 640 mcg twice daily produced significant, quantitatively similar decreases in oral corticosteroid requirement. Given the advantage of twice daily dosing in the mild end of the spectrum and the requirement for twice daily dosing at the more severe end of the disease spectrum it would not be prudent to recommend twice daily dosing for most asthmatic patients.

The complete response does not include any new studies in subjects less than 12 years of age. In studies 341 and 342, submitted with the original NDA, the response to 160 mcg QD was significant in Study 341 alone: efficacy was not replicated for any of the doses tested (40, 80, and 160 mcg QD).

A Trudell dose counter has been added to the ciclesonide drug product, and Study 3028 was designed to test it's functioning in clinical practice. Ciclesonide was administered as 4 puffs of 40 mcg once daily for 15 days in 25 patients and for 30 days in 100 patients 4 years of age or older with mild to moderate asthma. The counter did not appear to affect the delivered dose or the particle size distribution, and only 5/125 (4%) of the canisters tested were deficient as defined by the Applicant's criteria of an, undercounted of [redacted] or greater when compared to the diary recordings. In data submitted with the original NDA, a mean fill weight for the 120-actuation canisters was demonstrated to be 9.6 g with a standard deviation of 0.28 g. These data show substantial overfill and a probability that any canister would have less than [redacted] extra doses (beyond the prescribed 120) of [redacted]. This, combined with the finding that only [redacted] of the counters undercounted by more than [redacted] counts suggests that there is less than a 0.1% probability that a counter would register a positive number when it was actually empty. Functionality will be further improved by additional guidelines in the patient instructions on the correct use of the delivery device.

1.3.3 Safety

Ciclesonide HFA MDI has now been administered to more than 4000 subjects in randomized, double-blind, placebo-controlled efficacy and safety trials. Including the open label long-term follow-up trials, over 1000 adults and 700 children < 12 years of age have been treated for 6 months and more than 500 adults and 400 children <12 years of age have been treated for at least 12 months (See Section 1.3.1, above). Ciclesonide HFA MDI has also been marketed for three years in 42 countries with an estimated total exposure of [redacted] patients who have been exposed to 148,677,120 daily doses (See Section 7.1.17 Post-marketing Experience). The adverse event experience has shown the same type and distribution of adverse events as is commonly seen during exposure to inhaled corticosteroids. Most of the adverse events have been mild to moderate: upper respiratory tract infections are common in asthmatics and have been reported in patients treated with ciclesonide at rates that are only a few percentage points higher than similar patients treated with placebo. Oropharyngeal candidiasis has been reported infrequently in the ciclesonide clinical trials, although cases have been included in spontaneous post-marketing reports.

Two issues were considered unresolved at the conclusion of the review of the original NDA. Study 323/34 had shown an unusually high incidence of cataracts in subjects treated with ciclesonide when compared to placebo and to fluticasone. The patients all had moderate to severe asthma and had been on maintenance ICS at the time of enrollment. They were treated with placebo, ciclesonide 160 mcg or 320 mcg BID, or fluticasone 440 mcg BID for 12 weeks and had slit lamp examinations at baseline and at the end of treatment. The results showed an incidence of 1.0%, 3.4%, 8.6%, and 1.0% in the placebo, ciclesonide 160 mcg BID, ciclesonide

320 mcg BID, and fluticasone groups, respectively. Study 3027 was initiated to further evaluate the potential for ciclesonide to induce cataracts. Over 1500 patients with mild to moderate asthma, all of whom had been previously treated with ICS, were randomized to treatment with either ciclesonide 320 mcg BID or beclomethasone 320 mcg BID. Treatment continued for 52 weeks and the outcomes included a detailed slit lamp examination, visual acuity and intraocular pressure measurements at baseline, 4, 8 and 12 months of follow-up. The slit lamp examination was quantitated using the LOCS III grading system. Lens opacities were described for the cortical, nuclear, and posterior sub-capsular regions separately using standard photographs to grade the degree of density.

The results of Study 3027 showed a higher than expected incidence of lens opacities in both treatment groups. The mildest changes (CLASS I) were detected in >30% of the population and the most severe changes (CLASS III) were detected in approximately 8% of the population. In all of these groups, the changes were more frequent in the patients treated with beclomethasone (CLASS I = 36.8%) compared to those treated with ciclesonide (CLASS I = 34.3%). Class III changes were detected in 7.7% of the ciclesonide and 8.8% of the beclomethasone patients. The study enrolled patients 18 years of age and older, but most were less than 60 years of age. Sub-groups analysis based on an age cutoff of 40 years did not detect a difference in the distribution of LOCS III CLASS changes comparing the younger and older populations. However, the incidence in patients older than 60 years was slightly higher in the ciclesonide than the beclomethasone-treated subjects. In the 67 ciclesonide subjects who were over 60 years of age at enrollment, 53.7%, 25.4%, and 22.4% developed CLASS I, II, and III changes, respectively compared to 52.4%, 17.5%, and 17.5% of the 63 beclomethasone patients. In addition, when the three types of opacity (nuclear, cortical, posterior sub-capsular) were examined separately, the incidence of posterior sub-capsular opacities, the most characteristic location for corticosteroid induced densities, the incidence was very slightly higher in the ciclesonide patients.

Overall, the incidence of lens opacities was similar in the two corticosteroid treatment groups (ciclesonide and beclomethasone). Corticosteroid effects on the eye are well described and precautions and warnings are routinely included in the package insert for all of these products. The risks due to ciclesonide do not appear to be markedly different from at least one marketed product and the ciclesonide label will include the routine class labeling.

The second safety issue that remained after the review of the original NDA was to evaluate the effects of ciclesonide on growth in prepubertal children. Study 343 was initiated to assess the effects of ciclesonide 40 mcg and 160 mcg, both administered once daily, on 400 children age 5 to 8.5 years. Growth during the 52 weeks of randomized treatment was 5.84, 5.85, and 5.66 cm/yr in the placebo, ciclesonide 40 mcg and ciclesonide 160 mcg groups, respectively. Compared to the run-in period, the rates were 0.73, 0.84, and 0.6 cm/year less during randomized treatment in the placebo, ciclesonide 40 mg and ciclesonide 160 mcg groups, respectively. This decrease in growth compared to run-in in the actively treated patients is similar to that seen with other corticosteroids. However, the decrease in the placebo patients is difficult to explain. Compliance with study medication based on diary data was high (>85% medication taken in >92% of all the treatment groups), and concomitant use of prohibited corticosteroids was dose-related: 10% in the placebo and ciclesonide 40 mcg group, and 6.4% in the C160 group. On the

other hand, withdrawal due to lack of efficacy or an asthma attack did not show a clear dose response: Eight (3.9%) of the subjects in the ciclesonide 40 mcg group withdrew compared to 4 (2.0%) in the other two treatment groups. Pulmonary function was stable throughout the year, however, it was normal at baseline and a decrement would not necessarily have been expected even if corticosteroids had not been administered. Finally an attempt to assess the HPA-axis function was unsuccessful due to inadequate urine collections. All in all, it is difficult to accept the results of this study as a definitive quantitative assessment of the effects of ciclesonide on growth. If ciclesonide actually does have a negligible effect on the HPA-axis, some additional definitive evidence of drug usage will have to be incorporated into future protocols. Furthermore, the doses used in the growth study were shown to be not effective in pivotal efficacy studies, therefore, these HPA-axis data have little if any utility.

1.3.4 Dosing Regimen and Administration

Approval of ciclesonide HFA MDI is recommended for the maintenance treatment of asthma in patients 12 years of age and older. The recommended starting dose, in a patient who has not previously been treated with corticosteroids, is 80 mcg BID. If control is inadequate, 160 mcg BID can be administered. In subjects with more severe asthma who have previously been treated with inhaled corticosteroids, doses as high as 320 mcg BID may be required. Ciclesonide is also recommended, at 320 mcg BID, for the maintenance treatment of patients with asthma who require maintenance oral corticosteroid treatment. Once daily dosing is not recommended because of the demonstrated superiority of twice daily dosing when compared to administration of the same nominal dose once a day. Approval for patients less than 12 years of age is not recommended because an appropriate dose has not been defined.

1.3.5 Drug-Drug Interactions

In study CP-036 a significant interaction between ciclesonide and ketoconazole was demonstrated. When ciclesonide at 320 mcg was administered after ketoconazole 400 mcg daily for 7 days the AUC for ciclesonide increased 3 fold compared to administration of the ciclesonide alone. This interaction has been noted for other corticosteroids and will be noted in the label.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ciclesonide is a non-halogenated glucocorticoid, administered by inhalation as a metered dose aerosol. The formulation contains [redacted] Dehydrated Alcohol, USP and [redacted] HFA-134a (1,1,1,2-tetrafluoroethane) propellant. It is formulated in two strengths that deliver 80 mcg, and 160 mcg (ex-actuator) per actuation, respectively. Ciclesonide inhalers are available in two strengths: the 80 mcg/actuation which comes in a 6.1 g canister and assures 60 actuations, and 160 mcg/actuation which comes in canisters that assure 60 or 120 actuations (9.6 g), respectively.

2.2 Currently Available Treatment for Indications

Currently five molecular entities in 10 formulations that include a corticosteroid are approved for the treatment of asthma (Table 2). They are available as dry-powder inhalers, pressurized multiple-dose canisters, and a suspension for jet nebulization. While most of the products are approved in children as young as 4 years of age, Pulmicort Respules are approved for children as young as 12 months of age. Most of the products are recommended for twice daily dosing, but mometasone formulation can be effective with once daily dosing.

Table 2 . Currently Available Inhalation Corticosteroids Approved for the Treatment of Asthma

Drug	Trade Name	Approval Date	Formulation	Regimen	Age (yrs)
Triamcinolone	Azmacort	4/13/07	Microcrystalline suspension in 1% dehydrated alcohol and dichlorodifluoromethane propellant	BID →QID	≥6
Beclomethasone	QVAR	11/20/06	Solution in HFA propellant in a pressurized, metered-dose aerosol	BID	≥5
Fluticasone propionate	Flovent-HFA	10/23/06	Microcrystalline suspension in propellant HFA	BID	≥4
	Flovent-Diskus	9/14/05	Dry Powder Inhaler	BID	≥4
	Advair-HFA	6/8/06	Microcrystalline suspension in propellant HFA	BID	≥12
	Advair-Diskus	3/2/06	Fluticasone and salmeterol as a dry powder inhaler	BID	≥4
Mometasone	ASMANEX Twisthaler	3/30/05	Dry powder inhaler with lactose	QD PM→BID	≥12
Budesonide	Pulmocort Flexhaler	2/16/07	Inhalation-driven dry powder inhaler	BID	≥6
	Pulmocort Respule	6/18/07	Micronized suspension for jet nebulization in sodium edentate, chloride, and citrate, citric acid & polysorbate 80	QD or BID	1-8
	Symbicort	7/21/06	Budesonide and formoterol in a pressurized metered dose inhaler with HFA propellant	BID	≥12

2.3 Availability of Proposed Active Ingredient in the United States

The product is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Ciclesonide given by inhalation has low systemic bioavailability. However, it is a corticosteroid and therefore has the potential to produce the adverse events associated with corticosteroid administration if it is taken in high enough doses. These adverse effects include adrenal suppression, a poor response to infections and wound healing, delayed bone maturation and growth in children, osteoporosis in older individuals, cataracts and glaucoma.

2.5 Presubmission Regulatory Activity

The first NDA for the use of ciclesonide in the United States was submitted to the Agency on December 22, 2003. The proposed indication was for the maintenance treatment of asthma in subjects years of age and older. The proposed doses ranged from 80 to In September of 2004 an approvable action was taken due to the failure to demonstrate efficacy with the doses and dosing regimens proposed. In discussions following the action, the Agency emphasized the need to compare once daily to twice daily dosing to ascertain an appropriate recommended regimen. The preclinical data submitted with the original NDA was deemed to be adequate. Subsequently, an NDA (22-004) for the use of ciclesonide as a nasal spray for allergic rhinitis was submitted to the Agency. On October 20, 2006 ciclesonide, formulated as an aqueous suspension (Omnaris), was approved for the treatment of allergic rhinitis in subjects ≥ 12 years of age.

Protocols designed to compare once daily to twice daily dosing with Alvesco were submitted for review prior to initiation of the trials. Referring to the comparison between once daily and twice daily dosing, the Sponsor asked the following question:

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The drug product is unchanged from that described in the original NDA with the exception of the addition of a dose counter. The addition of the dose counter did not change the delivered dose or particle size distribution. The functionality of the counter, given the planned overfill is acceptable. See detailed study review (Appendix Study 5) and CMC review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submission is based on five new studies (2 clinical efficacy, 1 growth, 1 cataract, and 1 dose counter study-Table 3) in conjunction with the results of efficacy studies (321, 322, 323/324, and 325) submitted with the original NDA (Table 4). No new pediatric study was submitted.

4.2 Tables of Clinical Studies

Table 3. Phase III Efficacy and Safety Trials

Study #	Design*	Asthma	Dose (mcg)	Freq	Compar-ator	Rx Duration	N exposed Ciclesonide	Outcome
321	R, DB, PC	mild-mod (Stratified)	80 160 320	QD	Placebo	12 w	133 128 131	FEV1 QOL Cortisol
322	R, DB, PC	Mild-mod (Stratified)	80 160 320	QD	Placebo	12 w	124 123 124	FEV1 QOL Cortisol
323/ 324	R, DB, PC	Severe On ICS	160 320	BID	Placebo FP	12 w	127 130	FEV1
325	R, DB, PC	Severe on OCS	320 640	BID	Placebo	12 w	47 49	OCS reduction

3030	R, DB, PC	Mild-Mod Prev Controller	80 160	BID QD	Placebo	12 w	152 152	FEV1
3031	R, DB. PC	Mild-Mod Prev BD only	80 160 80->160	BID QD B->Q	Placebo	16 w	173 176 173	FEV1

* R – Randomized; DB – Double Blind; PC – Placebo Controlled

Table 4 . Supportive Trials

Study	Design*	Asthma	Dose (mcg)	Freq	Comparator	Rx Duration	N exposed	Outcome
102	R, DB, PC	Mild-Mod	320	QD BID	Placebo FP	12 w	80	PD
3027	R, DB, PC	Mod-Severe	320	BID	Placebo BDP	12 m	776	Cataract
343	R, DB, PC	Mild	40 160	QD	Placebo	12 w	221 219	Growth Velocity
3028	R, OL	Mil-Mod	160	QD	---	15 d 30 d	25 100	Dose Counter

* R- Randomized; DB – Double Blind; PC – Placebo Controlled

4.3 Review Strategy

Study 3030 and 3031 compared once daily to twice daily dosing of ciclesonide for the maintenance treatment of asthma. Both studies were reviewed in detail. Studies 321, 322, 323/324, and 325 were all reviewed with the original NDA and the results are summarized in the review of the Complete Response ISS and ISE. No new pediatric study was submitted.

Four additional studies were submitted to support safe and effective use of ciclesonide for the treatment of asthma. Three of these have not been previously reviewed (3027, 343, 3028). They all had important implications for the use of ciclesonide and were reviewed in detail. Study 3027 examined the development of cataracts in adult asthmatics treated with moderate doses of ciclesonide for one year. Study 343 was also a year in duration and it examined the effects of once daily ciclesonide on linear growth in children 5 to 8 years of age. Study 3028 assessed the accuracy of a dose counter to be incorporated into the canister actuators. Finally, Study 102, a PD study submitted with the original NDA was included in the integrated safety review. The results of 102 will be highlighted in the PD section of this review.

4.4 Data Quality and Integrity

The quality of the data was deemed to be complete and accurate. There was no concern regarding the results obtained at any particular center and many of these sites were site visited during the original submission. Therefore, no additional DSI auditing was performed.

4.5 Compliance with Good Clinical Practices

All of the studies were performed in compliance with Good Clinical practices. All of the studies were reviewed by independent ethics committees and all subjects signed informed consent forms.

4.6 Financial Disclosures

Six investigators were listed as having a potential financial conflict of interest. In all cases the investigators received more than $25,000 in speaking fees and other honoraria. The six investigators participated in Study 343 (5), Study 3027 (3), and Study 3031 (1). The three investigators who are noted in Study 3027 also participated in Study 343 or 3031. Given the large number of investigators participating in these studies it is unlikely that any bias could have been introduced by this degree of financial involvement with Aventis. There was also no indication in the data of bias.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetics were reviewed in detail in the original NDA. Blood levels of ciclesonide and the active metabolite (M1) were proportional to dose and the bioavailablity of M1 was 50%. A population PK analysis showed that gender age, and body weight did not have a significant effect on the PK or M1.

A newly submitted drug-drug interaction study (BY9010/CP-036) showed a 3.6-fold higher AUC for ciclesonide during co-administration of ketoconazole. The AUC, C_{max}, and $T_{1/2}$ were 2.98 mcg•hr/mL, 0.64 mcg/L, and 8.83 hours, respectively when ciclesonide was administered alone. After administration of ciclesonide 320 mcg and oral ketoconazole 400 mg daily for 7 days the respective AUC, C_{max}, and $T_{1/2}$ were and 10.80 mcg•hr/mL, 1.38 mcg/L, and 6.94 hours. In Study 3027 blood levels of ciclesonide and M1 were measured as a secondary assessment of compliance. Samples were positive for M1 in >88% of the 236 subjects tested at 4 and 12 months. In seven subjects who terminated early, 57% had detectable M1 in their blood. The levels of M1 varied widely (0.01 to 1.2 ng/mL), however, most were less than 0.6 ng/mL. These are similar to the peak levels calculated in the population PK analysis reported in the original NDA.

5.2 Pharmacodynamics

Pharmacodynamics were reviewed in detail in the original submission.. In Study 103, 35 adults with mild asthma were treated for 29 days with ciclesonide 320 or 640 mcg twice daily or placebo. At the end of 29 days the mean (SE) change from baseline in 24-hour urinary free cortisol were -8.69 (5.6), -4.01 (5.03), and -8.84 (5.02) in the placebo, C320 and C640 daily, respectively. The mean difference from placebo was +4.7 and =0.16 for the C320 and C640 groups, respectively. The study also included a corticosteroid comparator which showed a positive response indicating that the assay was sensitive enough to evaluate HPA axis effects.

In the studies submitted with the complete response, 24-hour urine for cortisol was collected in the growth study (Study 343/age 5 to 8.5 years). However,, only 13% of the samples met the prespecified criteria for an adequate specimen. Many of the urine volumes were very low and this data was not considered accurate.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is "for the maintenance treatment of asthma as prophylactic therapy in adult and [redacted] patients [redacted] years of age and older".

6.1.1 Methods

The new studies were all randomized, double-blind, placebo-controlled efficacy and safety trials.

6.1.2 General Discussion of Endpoints

The primary endpoint in Studies 3031 and 3030, as well as the pivotal trials submitted in the original NDA (321, 322, 323/324) was the AM pre-dose FEV_1 comparing the end of the treatment period to baseline. This is a standard metric for this disease and the tests were performed using standardized procedures. Study 325 was conducted in patients with severe asthma who were treated with oral corticosteroids at the time of enrollment. The primary outcome measure was the decrease in oral corticosteroids required to maintain a satisfactory symptom level. This is a clinically meaningful outcome. The secondary efficacy measures were other spirometric variables and symptoms and rescue medication use as recorded in a daily diary. These assessments are also commonly used to assess the efficacy of drugs to treat asthma.

6.1.3 Study Design

Study 3031 and 3030 were both randomized, double-blind and placebo controlled. They were both of appropriate length (at least 12 weeks of maintenance treatment) to assess the effect of the

various drug regimens, and the subjects were selected (1 study enrolled only subjects who had been previously treated with ICS [3030] and the other enrolled only subjects who had not previously been treated with ICS [3031]) so that efficacy could be assessed in each pre-treatment defined subgroup. One limitation of these studies is that they only assessed a limited number of doses. In both cases, only the 80 mcg BID and 160 mcg QD doses were compared. Both studies were adequately powered (150 to 177 subjects/treatment group) to detect a clinically meaningful improvement.

Studies 321, 322, and 323/324 were also randomized, double-blind and placebo controlled and of adequate duration. Of note, Studies 321 and 322 tested only once daily regimens in subjects with mild to moderate disease. Also, Studies 321 and 322 enrolled subjects regardless of their history of prior ICS use, while Study 3031 enrolled only subjects who had not received ICS in the month prior to enrollment and Study 3030 enrolled only subjects who had received ICS in the month prior to enrollment. Study 323/324 was conducted in subjects with moderate to severe asthma, all of whom had been treated with ICS. All of the subjects were treated with a BID regimen.

6.1.4 Efficacy Findings

In Study 3031 adult asthmatics previously treated with only bronchodilators were randomized to receive treatment with ciclesonide 80 mcg BID or 160 mcg BID for 16 weeks, or 80 mcg BID for four weeks followed by 160 mcg QD for 12 weeks, or placebo. While all of the active treatment regimens resulted in statistically significant increases in FEV_1, the increase in the 80 mcg BID group was almost double that seen in the other two ciclesonide treatment groups (Table 5). The LS mean increase in FEV_1 was 300 mL in the C80 group, significantly better than the190 mL seen in the other ciclesonide treatment groups. Compared to placebo, the increase was 120 mL in the once daily treatment group compared to 240 mL in the twice daily group.

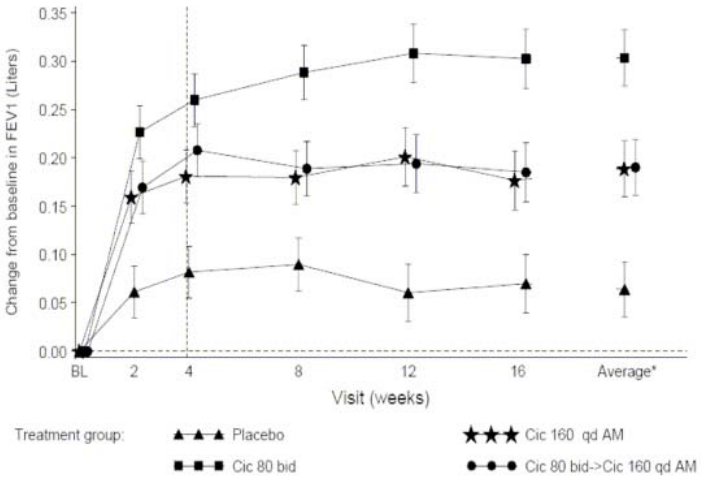
Table 5. Primary Efficacy Results from Study 3031

		Dose of Ciclesonide		
Fev_1	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline, mean L	2.45	2.54	2.39	2.49
Change from baseline LS mean, L 95% CI	 0.06 0.01, 0.12	 0.19 0.13, 0.25	 0.19 0.13, 0.25	 0.30 0.25, 0.36
Difference from placebo LS mean, L 95% CI p- value		 0.12 0.05, 0.20 0.002	 0.13 0.05, 0.20 0.002	 0.24 0.16, 0.32 <0.001
C80 Difference from C160 & C80/160 LS mean, L		 0.11	 0.11	

95% CI p-value		0.03, 0.19 0.005	0.03, 0.19 0.005	

The results (Figure 1) of treatment with 80 mcg BID followed by 12 weeks of C160 were essentially identical to the results during treatment with 160 mcg QD and both were inferior to the results of treatment with 80 mcg BID.

Figure 1. FEV1 During Treatment with Ciclesonide



The results of the secondary efficacy measures were more similar across the treatment groups. However, in all of the assessments the greatest improvement was seen in the C80 group. The diary-recorded AM PEF increased by 3.4, 26.7, 34.1, and 39.6 L/min in the placebo C160, C80/160, and C80 subjects, respectively. Albuterol use decreased by 0.97, 1.38, 1.57, and 1.69 puff/day, and the asthma symptom score decreased by 1.06, 1.33, 1.38, and 1.63 points in the placebo, C160, C80/160 and C80 groups, respectively. The rate of withdrawal followed a similar pattern: withdrawal of the C160 subjects (14.5%) followed close on the rate of withdrawal in the placebo subjects (22.6%). This is compared to withdrawal rates of 9.9% and 7.6% in the C80/160 and C80 subjects, respectively.

In Study 3030 adult and adolescent asthmatics, all of whom had been treated with ICS within a month of enrollment, were randomized to receive placebo, ciclesonide 80 mcg BID or 160 mcg QD. During a 7-14 day run-in period they continued their maintenance ICS therapy. As could have been predicted, the subjects who were switched to placebo during the randomized treatment period experienced a fall in FEV_1. The subjects treated with C160 had essentially no change in FEV_1 (increase of 10 mL) and the subjects treated with C80 had an increase of 70 mL by the end of the 12-week treatment period (Table 6).

Table 6. Change in FEV_1 During Treatment with Ciclesonide in Subjects Previously Treated with ICS.

		Dose of Ciclesonide	
Fev_1	Placebo	160 QD	80 BID
N	147	150	149
Baseline, mean L	2.63	2.64	2.67
Change from baseline LS mean, L 95% CI	 -0.12 -0.18, -0.07	 0.01 -0.04, 0.07	 0.07 0.01, 0.12
Difference from placebo LS mean, L 95% CI p- value		 0.14 0.06, 0.22 0.0006	 0.19 0.11, 0.27 <0.0001
Difference from cicles-80* LS mean, L 95% CI p-value		 0.05 -0.03, 0.13 0.195	

The AM peak expiratory flow rates fell in all of the treatment groups, and the LS mean difference (95% CI) comparing the C160 group to placebo was not significant (7.1 [-0.8, 14.9] L/min). The LS mean (95% CI) difference between C80 and placebo was 8.4 (0.60, 16.2) L/min, suggesting that function was better maintained during treatment twice daily than once daily. Albuterol use increased more in the placebo group (0.67 puffs/day) compared to either ciclesonide group (0.08 and 0.04 puffs/day in the C160 and C80 groups), and the asthma symptom score increased in the placebo group compared to a decrease of 0.05 points in both of the ciclesonide groups.

Studies 321, 322, and 323/324 were not integrated with the new studies because of differences in study design and in the patient populations. In studies 321 and 322 efficacy could not be replicated for the once daily regimens except for the highest dose tested (320 mcg BID). On the other hand, twice daily dosing in Study 323/324 was efficacious at both doses studied (160 and 320 mcg BID). As shown in Table 7, there is not much of a dose response, and efficacy appears to be driven as much by prior ICS use and regimen than by the total daily dose. In general, the subjects who had been treated previously with ICS responded more vigorously to ciclesonide that did those who had not been so treated. And, as was demonstrated in Study 3031, even when the once daily dosing was statistically significant, the quantitative response to twice daily administration of the same nominal dose was substantially greater. Even the 320 mcg QD dose was effective only in the subjects who had been previously treated with ICS in Studies 321 and 322.

Table 7. Difference from Placebo in FEV_1 (L) after 12 Weeks of Treatment with Ciclesonide

Dose	80 QD	160 QD	80 BID	320 QD	160 BID	320 BID
Study	A. All Subjects Regardless of Prior ICS Therapy					
321	0.12	0.07		0.15		
322	0.12	0.19		0.12		
3031*		0.12	0.24			

3030		0.14	0.19			
323/324					0.11	0.18
Study	B. No Prior ICS					
321	0.07	0.02		0.04		
322	-0.01	0.13		0.08		
3031*		**0.12**	**0.24**			
3030						
323/324						
Study	C. ICS During the 30 Days Prior to Enrollment					
321	0.15	0.11		0.24		
322	0.19	0.22		0.13		
3031*						
3030		0.14	0.19			
323/324					0.11	0.18

* Total treatment duration = 16 weeks

6.1.6 Efficacy Conclusions

In a trial (3031), designed to compare ciclesonide at 80 mcg BID to 160 mcg QD and finally to 160 QD following a one-month course of 80 mcg BID, the 80 mcg BID regimen was clearly superior. While all of the active treatments were statistically superior to placebo, the 80 mcg BID regimen was twice as effective as the once daily dosing regimens in subjects who had not been on maintenance ICS.

was more effective in subjects who had previously received maintenance ICS. Subjects who were stabilized on inhaled corticosteroids during the run-in period, switching to ciclesonide 80 mcg BID or 160 mcg QD did not experience a deterioration in the FEV_1. However, the AM peak flow decreased in all of the treatment groups, including the ciclesonide 80 mcg BID group. The decrease in AM peak flow was marginally greater in the 160 mcg once daily group than in the 80 mcg twice daily group, but the change in albuterol use and symptom score was essentially identical in the two active treatment groups. Only BID regimens were tested in the more severely effected subjects enrolled in Study 323/24. Because twice daily therapy was superior in mildly affected subjects who had never been treated with ICS and appeared to be required in the moderate to severe end of the spectrum, it is appropriate to recommend only twice daily dosing.

No new studies were submitted

However, once daily dosing is not recommended for adults

While the 40 mcg once daily regimen showed no evidence of efficacy in the studies submitted with the original NDA (341 & 342),

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the pivotal efficacy trials (3031, 3030), the pediatric growth trial (343) or the dose counter trial (3028). There were two deaths in study 3027, the cataract study that enrolled subjects 18 years of age and older. A 54 year-old female died with a heart attack and a 31 year-old male committed suicide. It is reasonable to conclude that these two deaths were not study drug related.

There were no deaths reported in Studies 321, 322, 323/324, 325 or 102. There was one death in long-term follow-up Study 323/324. A 75 year-old female was found dead at home. She had a history of hypertension and the death certificate listed myocardial infarction as the cause of death. No autopsy was performed. It is reasonable to conclude that the death was not related to ciclesonide.

7.1.2 Other Serious Adverse Events

In the combined, newly submitted, pivotal efficacy studies there were a total of 12 serious adverse events: 2 each in the placebo, C160, and C80/160 subjects, and 6 in the C80 group. Only 2 diagnoses were reported in more than one subject: 2 placebo subjects developed a serious asthma attack and 2 ciclesonide subjects (1 each in the C80 and C80/160 groups), developed pneumonia. In study 343, conducted for 12 months in 5 to 8 year-olds, there were a total of 6, 11, and 7 serious events in the placebo, C40 and C160 subjects, respectively. Again, asthma and pneumonia were the only events that occurred in more than 1 subject. There were 4, 6, and 1 severe asthma attack in the placebo, C40, and C160 subjects. Two C40 subjects developed pneumonia

In Study 3027 more than 1500 adults, previously treated with ICS were treated with high-dose ciclesonide or budesonide. No placebo was included. It is therefore impossible to directly compare the results of this study to the other studies in this submission. However, even in this patient population the incidence of severe events was low (31 [4.0%] and 46 [5.9%] in the ciclesonide and BDP groups, respectively). The most common events were asthma (5 and 4 events), pneumonia (3 and 1 events), and nephrolithiasis (2 and 0 events) in the C320 and BDP subjects, respectively.

In the 12-week pivotal trials submitted with the original application (Study 321, 322, 323/324, 102) ten serious adverse events were reported in the 1102 subjects treated. Asthma requiring hospitalization or withdrawal occurred in one subject, each, treated with 160 and 320 mcg ciclesonide QD and in 4 placebo subject. Three subjects reported myocardial infarctions. All

other events were reported in only one subject, including 1 pneumonia in a ciclesonide 320 BID subject.

In Study 325 there were 8 serious events reported in 141 patients during 12 weeks of treatment. The relatively high rate was probably related to the severe underlying asthma and concomitant requirement for medications. Of the 8 serious events, 5 were asthma exacerbations. There was one serious pneumonia is a subject treated with ciclesonide 320 mcg BID. In the long-term follow-up studies, there were 8 serious events (3 pneumonias) in the 226 subjects treated in Study 326 and 12 (1 pneumonia) in the 197 subjects treated with ciclesonide in Study 323/324/LT.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall drop-out rate was uniformly higher in the placebo subjects compared to those who received active treatment (Table 8). In the 12-week trials, from 23 – 48% of the placebo subjects were withdrawn in all but Study 102, where only 12.2% were withdrawn. Study 102 was a PD study designed to test the effect of ciclesonide on the HPA-axis. Only 40 subjects were enrolled per treatment arm. They had mild to moderate asthma, but were treated with relatively high doses of ciclesonide (up to 320 mcg BID). No other characteristic identified this group as different from the other study subjects. Excluding Study 102, withdrawal in the active treatment groups ranged between 10 and 20% with the higher rates in the BID and 320 mcg QD treatment groups. This is probably related to the underlying disease rather than treatment as the withdrawal rate in the placebo subject who received 320 mcg BID was 48%.

In Study 343, withdrawal was the same (18.1%) in the placebo and C40 subjects and lower in the C160 subjects (14.2%). In Study 3027, 14.4% of the C320 withdrew compared to 12.9% of the BDP subjects.

Withdrawal due to adverse events was also uniformly higher in the placebo than active treatment groups in all of the studies.

In Study 325 withdrawal and withdrawal due to adverse events was also substantially higher in the placebo than actively treated subjects. Thirty-two percent of the placebo and 19% of the actively treated subjects withdrew, and 26.7% of the placebo and 15.6% of the actively treated subjects withdrew due to adverse events.

Table 8. Percentage of Subjects Withdrawn from the Trials (Total Withdrawals/Withdrawals Due to Adverse Events)

Study	Duration	Placebo	C40 QD	C80 QD	C80 BID	C80 BID/ 160 QD	C160 QD	C160 BID	C320 QD	C320 BID	FP440 BID	BDP320 BID
3031	16 wks	23.0 / 12.9			10.3 / 2.3	12.4 / 4.5	16.9 / 7.9					
3030	12 wks	32.0 / 15.1			11.2 / 5.3		11.8 / 4.6					
321	12 wks	35.8 / 16.4		15.8 / 3.8			18.0 / 7.0		14.5 / 3.8			
322	12 wks	30.5 / 14.4		12.1 / 4.8			10.6 / 4.1		17.7 / 4.8			
323/4	12 wks	48.5 / 19.9						20.5 / 6.3		20.0 / 7.7	26.9 / 9.6	
102	12 wks	12.2 / 7.3							7.5 / 2.5	7.1 / 0	12.2 / 2.4	
343	52 wks	18.1/6.3	18.1/6.3				14.2/3.2					
3027	52 wks									14.4/3.7		12.9/2.8

7.1.3.2 Adverse events associated with dropouts

Table 9 . Percentage of Subjects Withdrawn Due to Asthma and Respiratory Infections.

Study	Placebo	C40	C80 QD	C80 BID	C80/160	C160 QD	C160 BID	C320 QD	C320 BID	FP440 BD	BDP
Asthma											
3031	10.1			1.7	2.3	5.1					
3030	13.8					1.3					
321	0.7		0					0			
322	0.8										
323/4	0						0		0		
102	7.2		2.0					0	0	0	
343	4.1	5.4			0.8	2.7					
3027		0			0		0		1.4		0.1
Respiratory Tract Infections											
3031	1.7			0	0.6	0					
3030	1.3			0.7		1.3					
321	0		0			0		0			
322	0		0			0		0			
323/4	0						0		0		
102	0						0		0	0	
343	0.9	0.5				0					
3027									0.01		0.01

The most frequent cause of withdrawal was an asthma attack (Table 9). These were more frequent in the placebo group and occurred infrequently in any of the active treatment groups. Respiratory tract infections were the next most frequent event, but these occurred in no more than 3 subjects in any one treatment group.

The integrated ISS did not include the C80 QD subjects. In the remainder treated for 12/16 weeks, the overall drop-out due to adverse events was 15.2, 5.9, 3.7, 4.6, 3.7, 6.3, and 5.8% in the placebo, C160 QD, C80 BID, C80 BID→160 QD, C320 QD, C160 BID, and C320 BID, respectively. The respective rates for withdrawal due to asthma were 13.2, 3.3, 1.8, 2.3, 2.0, 6.3, and 5.2%. The higher rates in the C160 BID (6.1%) and C320 BID (5.2%) is probably related to the fact that the subjects all had moderate-severe asthma and had been on chronic ICS therapy prior to enrollment. Bronchitis was listed as the reason for withdrawal in 1.6% of the C160 BID subjects, but all other events were listed for less than 1% of the treatment group.

Reviewer: Study 102 enrolled only 40 subjects per treatment arm so the effect was not large. However, the low rate of withdrawal tended to decrease the mean withdrawal and withdrawal due to asthma in the placebo, C320 QD and C320 BID groups. If Study 102 is not integrated then the dropout rate in the C320 BID group would have been 20% with 7.7 due to adverse events.

Three subjects in the dose counter study (Study 3028) withdrew due to chest pain: once case each of increased heart rate, upper respiratory tract infection, and chest pain.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited at all follow-up visits in each of the trials. In addition, the subjects were issued diary cards in which they were instructed to record "all unusual health-related events". At the clinic visits the investigators transferred the reports of those events they classified as adverse events to the CRF. An adverse event was defined as "any unfavorable and unintended sign, symptom, syndrome, or illness that developed or worsened during the period of observation in the clinical study".

Reviewer: There is no information about the way these entries were assessed. There is no analysis of the subject entries compared to those that were entered into the CRF.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were summarized using MedDRA System Organ Classification and Preferred Terms. In addition, because of the known adverse event profile of inhaled corticosteroids, separate groupings of events related to oropharyngeal irritation and infection, and eye events were constructed.

7.1.5.3 Incidence of common adverse events

Adverse events were reported for 52 to 58% of the subjects enrolled in the12/16 week studies (Table 10). In the 52-week studies, adverse events were reported for 90 to 94% of the subjects.

Serious events were reported in 1.7 to 5.3% of the subjects treated with ciclesonide and up to 5.9% of the placebo subjects. The incidence of serious events in the subjects treated for 52 weeks was 2.3 to 4.5% in the growth study (ages 5 to 8.5 years) and 4.0% for the adults treated with ciclesonide in the cataract study

Table 10 . Percentage of Subjects Reporting Adverse Event During Randomized Treatment

Study	Exposure (Weeks)	Placebo	C40 QD	C80 QD	C80 BID	C80/160 BID/QD	C160 QD	C160 BID	C320 QD	C320 BID	FP440 BID	BDP BID
Any Event												
3031	16	57.3			55.5	57.8	52.8					
3030	12	55.3			52.0		57.9					
321	12	53.7		57.1			50.8		50.4			
322	12	66.9		62.1			65.9		65.3			
323/324	12	61.8						61.4		54.6	60.1	
102	12	85.4							62.5	66.7	78.0	
343*	52	89.6	94.6				90.0					
3027	52									83.5		85.6
Serious Events												
3031	16	3.4			4.6	1.7	4.0					
3030	12	5.9			3.3		5.3					
321	12	0		1.5					0.8			
322	12	0.8		0			0		0			
323/324	12	2.9						2.4		1.5	0	
102	12	0							0	0	0	
343*	52	3.6	4.5			1.6	2.3					
3027	52									4.0		5.9

Reviewer: Looking at the individual trials that were included in the Applicant's ISS of the 12-week trials, Study 102 stands out as anomalous. The overall adverse events rate was high (85.4% in the placebo group compared to 55 to 65% in the other studies) while the serious event rate and the rate of adverse events that resulted in withdrawal was very low (0 and 7.3%, respectively). This may be related to the relatively high doses of corticosteroids that were used in this study to treatment subjects with mild asthma.

7.1.5.4 Common adverse event tables

Table 11 . Integrated Adverse Events Reported in Studies of 12-16 weeks duration.

		160 mcg / day			320 mcg / day		640 mcg / day
	Placebo (N=759)	160 QD (N=579)	80 BID (N=325)	80 BID/160 QD (N=173)	320 QD (N=295)	160 BID (N=127)	320 BID (N=172)
All TEAs	456 (60.1)	327 (56.5)	175 (53.8)	100 (57.8)	172 (58.3)	78 (61.4)	99 (57.6)
Infections & Infestations	**27.1**	**30.9**	**30.8**	**31.2**	**33.2**	**31.5**	**22.7**
Nasopharyngitis	7.6	10.5	10.5	5.2	8.8	10.2	6.4
Upper Respiratory tract Infection	7.6	6.0	7.1	7.5	5.8	8.7	4.7
Sinusitis	3.3	4.7	3.1	3.5	4.4	5.5	5.2
Influenza	1.8	2.9	2.2	3.5	3.7	1.6	1.2
Respiratory, thoracic and mediastinal	**27.4**	**16.2**	**15.1**	**19.7**	**15.3**	**21.3**	**25.0**
Asthma	16.6	5.4	4.3	10.4	2.0	7.9	8.7
Pharyngolaryngeal pain	4.6	4.0	4.3	2.3	6.1	3.9	4.7
Nervous System	**10.1**	**12.3**	**7.4**	**11.6**	**13.9**	**17.3**	**11.6**
Headache	8.2	8.3	4.9	8.7	10.5	11.0	9.3
Gastrointestinal disorder	**9.4**	**9.2**	**7.1**	**9.8**	**10.5**	**6.3**	**9.9**
Musculoskeletal & connective tissue	**6.2**	**6.0**	**4.0**	**6.4**	**9.5**	**10.2**	**9.9**
Back pain	2.4	1.9	0.6	3.5	4.4	3.9	1.2
Arthralgia	0.7	0.9	0.9	0.6	0	2.4	3.5
Pain in extremity	1.1	0.3	0.3	0.6	0	3.1	2.3
Injury, poisoning, procedure	**6.2**	**4.7**	**5.8**	**5.2**	**7.5**	**3.1**	**6.4**
General disorders and administration site	**4.5**	**2.8**	**3.7**	**1.7**	**5.4**	**3.1**	**6.4**
Skin and subcutaneous tissue	**3.2**	**4.7**	**2.5**	**2.9**	**4.4**	**2.4**	**5.2**
Eye disorders	**1.4**	**1.0**	**0.9**	**2.3**	0.7	**7.1**	**7.0**
Cataract nuclear	0.1	0	0	0	0	3.1	5.2
Reproductive and breast disorders	**1.3**	**1.2**	**0.6**	**3.5**	**1.4**	**0**	**1.2**

Table 11 is an integrated listing of adverse events reported in studies 321, 322, 323/324, 3030, 3031, and 102. Overall, 54 to 61% of the subjects reported adverse events, with the highest rates in the placebo and C160 BID group. Infections were more common in the actively treated subjects, while respiratory events were more common in the placebo group. As noted previously, the respiratory

events usually represented an asthma attack. Overall, the events are distributed without a clear dose relationship. Note that the ISS does not include the 80 mcg daily dose. However, from Table 10, it appears that the overall AE rate was not lower in treated with 80 mcg daily.

Common adverse events in the 52-week ophthalmology study closely followed the distribution of the events in the 12-week studies, although the overall incidence was higher due to the longer duration of the study. Of the subjects treated with C320 BID, 83.5% reported AEs, of which 65.2% were infectious, 31.3% respiratory, and 21.3% musculoskeletal. This compares to the BDP 320 BID group where 85.6% reported events of which 66.6% were infectious, 27.3% were respiratory and 18.0% were musculoskeletal. There was no placebo for comparison.

The distribution of events in the 52-week growth study was also similar to the distribution in the 12-week studies. The overall rate of events was 89.6, 94.6, and 90% of the placebo, C40 and C160 subjects, respectively. Infections were reported in 75.1, 81.9, and 79.9% of the placebo, C40 and C160 subjects, respectively, and the respective percentage of respiratory events was 48.4, 54.8, and 41.6%. In no SOC were the events in the active treatment groups markedly more frequent than in the placebo group.

7.1.5.6 Additional analyses and explorations

Oropharyngeal Adverse Events

Oropharyngeal adverse events were infrequent in the 12 and 16-week studies (Table 12). Even in the highest doses tested (320 mcg) the incidence of oropharyngeal candidiasis was less than 2%.

Table 12 . Oropharyngeal Adverse Events in the Integrated 12 and 16-Week Studies

		160 mcg / day			320 mcg / day		640 mcg / day
	Placebo	160 QD	80 BID	80 BID/ 160 QD	320 QD	160 BID	320 BID
Oral Candidiasis	0.5	0	0.3	0	1.7	1.6	0.6
Pharyngitis	0.1	0.5	1.5	1.7	0	0.8	1.2
Pharyngolaryngeal pain	4.6	4.0	4.3	2.3	6.1	3.9	4.7
Dysphonia	0.5	0.2	0	0	1.4	0	1.2

Even in the 52-week adult study (Table 13) the incidence of oral candidiasis was less than 2%. This compares to the incidence of 6.3% after a year of treatment with budesonide.

Table 13. Oropharyngeal Adverse Events in Study 3027

	320 mcg / day	
	C320 BID	BPD320 BID
Oral Candidiasis	1.4	6.3
Pharyngitis	2.6	1.8
Pharyngolaryngeal pain	5.4	6.6
Dysphonia	2.2	1.5

In the 52-week growth study (subjects <8.5 years of age) there was only one case of oral candidiasis in a placebo subject. Thirteen to 16% of the subjects (12.8% of the C160) complained of pharyngitis and 3 to 4% (4.1% of the C160 subjects) of pharyngolaryngeal pain.

Ophthalmology Events

Study 3027 was designed to assess the potential for ciclesonide to induce cataracts. In addition to routine adverse events reported above, a detailed slit lamp examination was performed after 4, 8, and 12 months of follow-up of asthmatic adults (≥ 18 years) who had previously been treated with ICS. Cataracts were characterized using the LOCS III grading system. The results in 743 subjects treated with Ciclesonide 320 mcg BID and 742 subjects with beclomethasone 320 mcg BID showed a slightly lower incidence of opacities in the C320 subjects (Table 14). A Class I event is the mildest abnormality in this grading system and was seen in 36.1% of the C320 and 38.4% of the BDP subjects. Class II events were more severe: they were observed in fewer subjects, but more often in the BDP subjects (16.4%) compared to the C320 subjects (14.0%). Sustained events were those that were demonstrated on more than one examination and they, too were more frequent in the BDP subjects.

Table 14. Summary LOCS III Scores for Subjects Treated for 52 Weeks with Ciclesonide or Beclomethasone.

	N	% of Subjects with Class I event	Risk ratio	95% CI	Non-inferiority bound
C320	743	36.1 (1.82)	0.94	0.82, 1.08	1.33
BDP	742	38.4 (1.83)			
	N	% of Subjects with Class II event	Risk ratio	95% CI	Non-inferiority bound
C320	743	14.0 (1.31)	0.86	0.67, 1.10	1.62
BDP	742	16.4 (1.39)			
	N	% of Subjects with sustained Class II event	Risk ratio	95% CI	Non-inferiority bound
C320	743	9.4 (1.11)	0.821	0.60, 1.12	1.796
BDP	742	11.5 (1.20)			

The overall LOS III score is a compilation of scores in three different regions: one each for cortical, nuclear, and posterior subcapsular (PSC) location. PSC opacities were seen less frequently than nuclear or cortical opacities. However the posterior subcapsular region is thought to be area most characteristically affected by corticosteroid use. Comparing the scores for PSC opacities in the two treatment groups showed a slightly higher frequency in the C320 subjects compared to BDP (Table 15).

Table 15 . Percentage of Subjects with Posterior Subcapsular Opacities

Change in LOCS III	C320	BDP 320
Class I	2.8 (0.6)	2.4 (0.6)
Class II	1.4 (0.4)	0.8 (0.3)
Sustained Class II	0.7 (0.3)	0.1 (0.1)
Class III	0.9 (0.4)	0.5 (0.3)

Subgrouping the population by age 40 years showed a persistently higher frequency of Class I, II, and III events in the C320 group compared to BDP in both those younger and 40 years or older. However, in subjects older than 60 years all of the events were more frequent in the C320 (N=67; CLASS I=53.7%, CLASS II=25.4%, and CLASS III=22.4%) than the BDP320 (N=63; CLASS I=52.4%, CLASS II=17.5%, CLASS III=17.5%) subjects.

Study 3027 was initiated to respond to the increase in cataracts that was seen in Study 323/324. Study 323/24 was conducted in subjects with severe persistent asthma who were being treated with ICS at the time of enrollment. Treatment with 160 or 320 mcg BID continued for 12 weeks, and fluticasone 440 mcg BID was administered as a comparator drug. A slit lamp examination at baseline and at the end of the study was specified in the protocol; opacities were recorded as cortical, nuclear, posterior subcapsular and graded as trace, 1+, 2+, and "Other". Of the subjects with a normal slit lamp examination at the beginning of the study 1/112 (1.0%) placebo, 3/88 (3.4%) of the C160, 8/93 (8.6%) of the C320, and 1/98 (1.0%) of the FP440 subjects had cataracts detected at the end of 12 weeks of treatment.

Reviewer: The numbers and percentage of subjects listed in the above paragraph are slightly different from those reported in the review of the original NDA. In the original review, the number of subjects who developed cataracts was reported for the entire population and not for those at risk, i.e., those with normal examinations at the beginning of the study and a second examination at a later date.

The high incidence of LOCS III CLASS changes seen in Study 3027 is undoubtedly due, at least in part, to the very precise standards used in the measurements and grading. It is difficult to interpret the difference between ciclesonide and fluticasone treatment seen in Study 323/24 and the difference between ciclesonide and beclomethasone treatment in 3027 because 1) the comparator drug is different, and 2) no placebo was used in Study 3027. The subjects in Study 323/324 had more severe asthma, and even though the duration of asthma was only 2 years longer, it is probable that they had had more intense corticosteroid treatment prior to study enrollment. In addition, there was no restriction on smokers in Study 323, and in fact, 30% were active smokers. These factors would tend to increase the incidence in Study 323/24 compared to 3027, not decrease them, and how the difference in populations would affect the relative incidence in ciclesonide and comparator drug is unknown. In the long-term follow-up of patients who were originally enrolled in Study 323/324, the incidence of cataracts was similar in the ciclesonide and beclomethasone-treated patients. New or worsening opacities were reported in 7.1% and 8.4% of the ciclesonide and beclomethasone-treated patients, respectively. However, as in Study 3027, the incidence of PSC opacities was higher in the ciclesonide-treated subjects.

Ophthalmologic adverse events were captured in the 12 to 16-week studies as adverse events. As seen in Table 10 (Section: 7. 1.5.4 Common Adverse Events.). There was a suggestion of dose ordering with 0.1% of the placebo subjects, 0 of the subjects who received 160 mcg daily, 0 of the subjects who received 320 once daily, 3.1% of the C160 BID and 5.2% of the 320 BID subjects reported events. These adverse events were not systematically looked for, and may have been underreported in subjects who received the lower doses.

Abnormalities in the eye examination and ocular complaints were recorded in study 3027 in addition to the LOCSIII scoring. A total of 218 and 172 alert term were reported for the C320 and BDP 320 subjects, respectively. These ophthalmology alert terms were reported by the investigators as clinically significant events. The alert terms covered a wide range of specific diagnoses. The most frequently reported were conjunctivitis, eye pain, vision blurred and migraine. These occurred in 19, 16, 13, and 10 C320 subjects and 10, 3, 16, and 0 of the BDP subjects. All of the other events occurred in less than 10 individuals other than vitreous floaters which were reported in 12 BDP subjects.

In study 343 (Growth study in 5.0 to 8-year olds) more ciclesonide-treated subjects reported ophthalmologic events than the BDP subjects. Six placebo (2.7%), 12 (5.4%) C40 subjects, and 11 (5.0%) of the C160 subjects reported events. As in the other studies, there was no concentration of any specific event in any of the treatment groups.

Ophthalmology Discussion

In one 12-week study conducted in subjects with moderate to severe asthma who had been treated with ICS prior to enrollment, an increase in the incidence of cataracts was demonstrated in subjects taking ciclesonide at 160 and 320 mcg BID compared to both placebo and fluticasone at 440 mcg BID. In a much larger study (N>700 per treatment group) conducted for 1 year, the overall incidence of lens opacities was high (>30% for the mildest changes), but it was not greater in the ciclesonide-treated than the beclomethasone-treated subjects. Unfortunately, there was no placebo group in the 52-week safety study with which to calibrate the results in these two populations which had differing baseline characteristics and in whom the metric for quantitating the outcome was so different. The higher incidence of LOCS III CLASS changes and of PSC in the older subjects treated with ciclesonide suggests that the risk of developing cataracts with ciclesonide is not negligible.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine safety laboratory (hematology, chemistry, and urinalysis) tests were performed at baseline and follow-up in studies 3031, 3030, 3027, and 343.

7.1.7.2 Standard analyses and explorations of laboratory data

In all of the submitted data sets the mean values at baseline and follow-up were within normal limits. Shifts in individual values from normal to abnormal, over the course of the trials, was infrequent and did not suggest a drug effect. Individual values that were clinically meaningfully abnormal were rare and not consistent across the studies. Abnormally high eosinophil counts were the most common abnormality and were seen in all patient groups and always at less than 2% of the treatment group in the 12 – 16-week studies. Similar frequencies were seen in the other studies.

Laboratory abnormalities reported as adverse events were seen in approximately equal frequencies across the treatment groups. In the 12-16-week studies the maximum frequency in any treatment group was 3.1%, and only blood glucose (N=2) and hepatic enzyme increase (N=2) reported in more than a single subject. In the 52-week ophthalmology study 3.4% of the C320 and 3.9% of the BDP subjects had abnormal laboratory vales reported as adverse events. No abnormal test was reported in more than 0.5% of the subjects.

No safety signal was detected in the laboratory data submitted in the original review of Studies 321, 322, 323/24 or 102.

7.1.7.5 Special assessments

For HPA-axis testing, see Pharmacodymamics, Section 5.2

7.1.8 Vital Signs

Vital signs were obtained at baseline and at the end of follow-up in all of the submitted studies. The mean values were consistently within normal limits. Individual shifts from normal to abnormal, and clinically meaningful abnormal values were infrequent and not indicative of a drug effect.

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed in this program. This is appropriate for a drug in a class that has been extensively tested and used in the community and been free of cardiovascular adverse events.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There was no evidence of abuse and no suggestion of withdrawal or rebound effects.

7.1.14 Human Reproduction and Pregnancy Data

Eight pregnancies were reported in the 12 – 16 week studies, and 15 in the 52-week ophthalmology study. Of the 15 reported in Study 3027, one resulted in a spontaneous abortion

of < 30 weeks, 1 induced abortion, 1 cesarean section at 40 weeks, one delivery pending and the rest live births.

7.1.15 Assessment of Effect on Growth

Study 343 was designed to test the effects of ciclesonide on linear growth in prepubertal children. Subjects were treated for 52 weeks with ciclesonide 40 or 160 mcg once daily or placebo. The differences in growth rate were small during the treatment period. Linear growth using a 2-point method of estimation was 5.84, 5.85, and 5.66 in the placebo, C40 and C160 groups, respectively. The LS mean difference compared to placebo was -0.02 and -0.15 for the C40 and C160 subjects, respectively. The difference comparing growth during the 6-month, steroid free-run-in to the growth during randomized treatment was -0.73, -0.84, and -0.60 for the placebo, C40, and C160 groups, respectively. The changes comparing run-in to ICS treatment are expected for this class of drug, however the changes in the placebo can not be explained. Given the difficulty with the placebo results, it is difficult to accept the difference in growth rate comparing ciclesonide treatment to placebo as quantitatively rigorous. Furthermore, efficacy was not demonstrated in pivotal efficacy studies in patients 4 to 11 years of age using doses of 40 mcg or 160 mcg once daily so these data even if they were deemed reliable would have little utility.

7.1.16 Overdose Experience

There were 7 cases of overdose (defined as a dose 3 times or greater than that specified in the protocol) in the newly submitted studies. There were no adverse events associated with these events.

7.1.17 Postmarketing Experience

Ciclesonide was first approved for the prophylactic treatment of asthma on February 24, 2004 in Australia. Between February 2004 and February 2007 42 countries have granted marketing authorization for ciclesonide MDI with recommended doses of 80 to 1280 mcg/day. Ciclesonide has not been withdrawn from any market and it is estimated that [redacted] patients have been exposed to 148,677,120 daily doses. Over the three year period 6076 adverse events (398 serious) have been received from clinical trials, spontaneous reports and various Altana registries. However, only events that were considered by the investigator and the Applicant as "not unrelated" (unlikely/possible/likely/definite) were included in the PSURs. The PSUR-reported events were submitted in separate 6-monthly reports that included separate listings for events that had been reported using different mechanisms (spontaneous reports, reports from clinical trials, results of observational trials, and reports from worldwide agencies). Listings were submitted for 235 non-serious and 51 serious events. For the most part the adverse events show the same distribution as was shown in the clinical trials. Of those included in the line listings, there were 62 cases (17 severe) of difficulty breathing/increased asthma/paradoxical bronchospasm, 24 (1 serious) of oropharyngeal candidiasis, 5 serious pneumonias, and 18 cases of allergic reactions/rash. Of this last group there were 4 cases involving facial edema, one of which was called angioneurotic edema.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In the summary of safety the Applicant included the results of the studies submitted in the complete response (3030, 3031, 3027, 2028, and 343) along with the results of the pivotal trials submitted in the original NDA (321, 322, and 323/324) and the results of a small PD trial (102) also submitted with the original NDA.

7.2.1.1 Study type and design/patient enumeration

Study 321 and 322 were identical 12-week randomized, double-blind, placebo-controlled efficacy and safety studies in adult and adolescents (≥12 years of age) with mild to moderate asthma. Subjects were enrolled without regard to prior use of corticosteroids. There were 526 subjects enrolled in Study 321 (130 in the placebo, 133 in the ciclesonide-80, 128 in the ciclesonide-160 and 131 in the ciclesonide-320 groups) and 489 subjects enrolled in study 322 (118, 124, 123, and 124 in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively). The safety assessment included adverse events, routine laboratory examination, and corticotrophin stimulation tests.

Study 323/24 was a 12-week randomized, double-blind, placebo-controlled efficacy and safety study in adult and adolescents (≥12 years of age) with moderate to severe asthma, all of whom had been treated with ICS prior to enrollment. There were 528 subjects randomized (133 to placebo, 127 to ciclesonide 160 mcg BID, 130 to ciclesonide 320 mcg BID, and 138 to fluticasone propionate MDI 440 mcg BID). The safety assessment included adverse events, routine laboratory examination, and corticotrophin stimulation tests. In addition, a slit-lamp examination was performed at baseline and at the end of treatment.

Study 325 was a 12-week randomized, double-blind, placebo-controlled efficacy and safety study in adult and adolescents (≥ 12 years of age) with severe asthma who had been treated with oral corticosteroids prior to admission. There were 47 patients randomized to 320 mcg BID and 49 to 640 mcg BID ciclesonide. The safety assessment included adverse events, routine laboratory examination, and lo-dose corticotrophin stimulation tests.

Study 102 was a 12-week randomized, double-blind, placebo-controlled PD study in adults (>18 years) with mild-moderate asthma who were not being treated with ICS at the time of enrollment. There were 163 subjects randomized to receive placebo (n=40), ciclesonide 320 mcg QD (n= 40), ciclesonide 320 mcg BID (n=42), or fluticasone MDI 440 mcg BID (n=41). High and low-dose corticotrophin studies as well as 24-hour urine collections for cortisol were performed at baseline and at the end of treatment.

Study 3030 was a 12-week randomized, double-blind, placebo-controlled efficacy and safety study in adult and adolescents (≥12 years of age) with mild to moderate persistent asthma, all of whom had been treated with ICS prior to enrollment. There were 456 subjects randomized to receive placebo (N=152), ciclesonide 160 mcg QD (N=152), and ciclesonide 80 mcg BID (N=152). The safety evaluation included adverse events, with a categorization for ophthalmologic alert events. In addition, routine laboratory examinations were performed.

Study 3031 was a 16-week randomized, double-blind, placebo-controlled efficacy and safety study in adult and adolescents (≥12 years of age) with mild to moderate persistent asthma, who had not been treated with ICS in the 30 days prior to enrollment. There were 708 subjects randomized to receive placebo (N=178), ciclesonide 160 mcg QD (N=178), and ciclesonide 80 mcg BID (N=175) and ciclesonide 80 mcg BID for 4 weeks followed by ciclesonide 160 mcg QD for 12 weeks (N=177). The safety evaluation included adverse events, with a categorization for ophthalmologic alert events. In addition, routine laboratory examinations were performed.

Study 3027 was a 52-week randomized, double-blind, active-controlled safety study in adult and adolescents (≥18 years of age) with moderate to severe persistent asthma, who had been treated with ICS in the 30 days prior to enrollment. There were 1568 subjects randomized to receive ciclesonide 320 mcg BID (N=785), or beclomethasone 320 mcg BID (N=783). The safety evaluation included adverse events, and a detailed ophthalmologic examination. At baseline, 6 and 12 months the subjects had a slit lamp examination and a classification of lens opacities with the LOS III grading system. Visual acuity and intraocular pressure were also measured. A subset of subjects had blood drawn for ciclesonide and the M1 metabolite as a secondary assessment of compliance.

Study 3028 was a 30-day randomized, open-label assessment of the Trudell dose counter in subjects with mild to moderate asthma age 4 years and greater. Twenty-five were randomized to receive 160 mcg QD for 15 days and 30 were randomized to receive 160 mcg QD for 30 days. The safety assessment consisted of adverse events and specific queries about difficulty using the counter.

Study 343 was a 52-week randomized, double-blind, placebo-controlled safety study in prepubescent children (5 to 8.5 years of age) with mild persistent asthma. There were 661 subjects randomized to receive placebo (N=221), ciclesonide 40 mcg QD (N=221), or ciclesonide 160 mcg QD (N=219). In addition to adverse events, linear height was measured at monthly intervals. Radiographic bone age was estimated at baseline and at the end of treatment.

7.2.1.2 Demographics

The demographics of the adult and adolescent subjects who were enrolled in the 12-16 week studies are summarized in Table 16. Approximately 40 to 43% were male, the mean age ranged between 36.5 and 43.5 years, and 75 to 88% were White. These characteristics were generally distributed evenly across the treatment groups. The duration of asthma ranged from a mean of 14.7 to 25.9 years. The longest durations (23.1 and 25.9 years) were in the subjects treated with

the higher doses of ciclesonide (160 and 320 mcg BID) which goes along with the more severe disease that was selected for in these studies. The baseline pulmonary function also shows the more depressed FEV_1 in the subjects who received twice daily dosing regimens using ≥160 mcg BID.

Table 16. Demographics of Subjects Enrolled in 12/16 Week Studies*

		Daily Dose of Ciclesonide						Total
		160			320		640	
	Placebo (N=759)	160 QD (N=579)	80 BID (N=325)	80/160 (N=173)	320 QD (N=295)	160 BID (N=127)	320 BID (N=172)	2430
Gender, N								
Male	305	248	138	71	135	52	75	1024
Female	454	331	187	102	160	75	97	1376
Age, N								
12 to <18 yrs	79	71	49	20	23	7	5	254
18 to <65 yrs	652	492	263	143	264	110	157	2081
≥65 yrs	28	16	13	10	8	10	10	95
Mean (SD)	38.2 (14.8)	37.7 (14.9)	36.5 (15.4)	37.7 (16.2)	36.8 (14.1)	43.5 (15.1)	41.9 (13.8)	
Range	12 - 79	12 - 73	12 - 72	11 - 73	11 - 75	13 - 82	12 - 79	11 – 82
Race, N								
White	612	485	264	129	259	97	140	1986
Black	77	43	16	20	23	17	20	216
Other	70	51	45	24	13	13	12	228
Duration of Asthma, yrs								
Mean (SD)	18.3 (14.2)	18.4 (14.0)	18.6 (13.7)	14.7 (13.0)	18.6 (13.7)	25.9 (16.1)	23.1 (14.4)	
Prior ICS	426	292	152	0	142	127	130	
FEV1, mean (SD)								
Liters	2.38 (0.69)	2.50 (0.60)	2.58 (0.61)	2.39 (0.59)	2.57 (0.68)	1.79 (0.49)	2.09 (0.71)	
% predicted	70.3	73.5	75.5	71.2	72.5	54.1	61.2	

* 321, 322, 323/24, 3031, 3030, 102

In the 52-week ophthalmologic study (3027) the mean age was 43.1 years, 39.8% were male, 83.5% were White, and 84.7% were enrolled in the United States. The overall mean duration of asthma was 21.9 years and the mean FEV_1 % predicted was 77.1. The mean age at enrollment in the growth study (343) was 6.7 years and 67.2% were male. Seventy-one percent were White and 70% were enrolled in South America. The overall mean height was 119.66 cm and the mean duration of asthma was 3.9 years. At

randomization (6 months after enrollment) the mean age was 7.2 years, and the mean height was 122.95 cm. Forty-eight percent had growth retardation as assessed by the chronologic relative to radiographically determined bone age. Pulmonary function in this study was normal as indicated by the mean FEV_1 percent predicted of 95%.Extent of exposure (dose/duration)

The safety assessment included all subjects who received at least one does of study medication. The original NDA summarized the experience for 5586 subjects (4541 adults and adolescents and 1045 children) treated with ciclesonide, as well as for 1236 treated with placebo and 1901 treated with an active comparator. As shown in Table 17, exposure to an additional 1630 adults and adolescents and 440 children has occurred since the original application. A total of 703 adults and adolescents and 395 children were treated for >26 weeks and 268 adults and 116 children were treated for >52 weeks.

Table 17. Overall Summary of Exposure to Ciclesonide

		Duration of Treatment with Ciclesonide				
Study Type	Study Number*	≤ 12	>12 to ≤ 26	>26 to ≤ 52	>52	Total
12-16 weeks – S&E (Adults)	321,322,323/24, 102	1126	33	0	0	1159
	3031, 3030	303	466	0	0	769
52 week - Ophthal	**3027**	20	33	435	268	756
30-day dose counter	**3028**	125	0	0	0	125
Total Adult		**1574**	**532**	**435**	**268**	**2809**
12-wk – S & E (children)	341, 342	689	79	0	0	768
52 wk – growth (children)	**343**	36	9	279	116	440
Total Children		**725**	**88**	**279**	**116**	**1208**
Grand Total		**2299**	**620**	**714**	**384**	**4017**

* Trials in bold font were first submitted with the complete response

In the integrated 12-16-week efficacy and safety studies in adults and adolescents 1928 subjects were randomized to double-blind treatment with ciclesonide (Table 18). The majority of these subjects were exposed to study medication for > 78 days (Mean exposure was 71.3, 84.1 and 76.2 days in the placebo, ciclesonide, and active control subjects, respectively). The median exposure was 84 days in all of the treatment groups including the placebo subjects.

In the 52-week ophthalmology study mean exposure to ciclesonide was 337.7 days and the median was 358 days. Seven hundred-three were treated for 6 months and 268 for 12 months or longer. In the 52-week growth study in children the mean (SD) exposure was 329.5 (91.6) and 332.6 (89.4) days in the C40 and C160 groups, respectively. Of the ciclesonide-treated subjects 395 were treated for at least 6 months and 116 were treated for over 12 months. Median exposure was 363 days in both active treatment groups.

Table 18 . Exposure of Adults and Adolescents to Ciclesonide in 12 – 16-Week Studies.

		Daily Dose of Ciclesonide					
		160			320		640
	Placebo	160 QD	80 BID	80/160	320 QD	160 BID	320 BID
1 to 14	101	24	11	4	12	7	7
15 to 28	58	20	7	4	7	9	8
29 to 84	339	271	121	7	191	69	104
85 to 91	114	109	27	1	78	37	77
>91	147	155	159	157	7	5	9
Mean (D)	71.3 (34.0)	84.3 (25.8)	92.3 (25.4)	105.1 (23.1)	77.7 (19.2)	74.3 (23.4)	76.1 (22.5)
Median	84	84	88	112	84	84	84

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.2 Post-marketing experience

See Section 7.1.17

7.2.3 Adequacy of Overall Clinical Experience

As discussed in section 7.2.1.3, the exposure to ciclesonide is now extensive. Exposure of >4000 subjects are included in the studies reported in the complete response and of these 714 were treated for >6 months and 384 were treated for a year or more. Additional long-term safety follow-up studies were submitted with the original NDA that were accepted as showing long-term safety.

7.2.5 Adequacy of Routine Clinical Testing

Adverse events and laboratory evaluation was appropriate. Throughout the development program ciclesonide has shown an adverse event distribution that is seen with other ICS when used to treat an asthmatic population. Laboratory abnormalities have been reported rarely and extensive further testing is not required. Similarly, there was no requirement for further ECG monitoring.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Two of the studies submitted with this application were specifically directed towards adverse events that are known to be a potential problem during ICS treatment. In Study 3027 over 700 adult subjects were treated with a relatively high dose of ciclesonide (320 mcg BID) for 12 months and meticulous ophthalmology examinations were performed at baseline and 6 and 12 months. It is unfortunate that no placebo arm was included in the study design because there was a substantially higher incidence of lens opacities than expected. It is impossible to know if this is related to the method of assessment (LOCS III scoring system) which is probably more sensitive than other techniques or to a peculiarity in the population treated. Compared to Study 323/24, the overall incidence of cataracts was substantially higher, although not higher than the comparator drug, beclomethasone. Given the design questions, the study supports non-inferiority of ciclesonide compared to a marketed product for the development of cataracts.

Study 343 (growth study) was also directed to assess a known complication of ICS therapy. A total of 440 prepubertal children were treated for 52 weeks with adequate doses of ciclesonide to assess the affect on growth. Compliance with the drug regimen was assessed with diary entries.

Maintenance of FEV_1 could not be used to assess compliance because pulmonary function was basically normal at baseline. Deterioration would not have been expected even if corticosteroids had not been administered. Twenty-four hour urines were collected for cortisol determination. However, only 13% met the prespecified criteria for an adequate sample, so the results are not very helpful. Use of prohibited corticosteroids during randomized treatment was inversely related to ciclesonide dose, but withdrawal due to an asthma exacerbation was not strictly dose-related. Therefore, there is still some question as to the overall exposure to ciclesonide in this trial.

7.2.8 Assessment of Quality and Completeness of Data

The database is adequate to assess general safety of ciclesonide in the adult population. The overall safety profile shows only mild to moderate and infrequent adverse events and this has been true for all of the studies in the development program. The special safety concern that was raised about the potential for ciclesonide to induce the development of cataracts was addressed in a large (>1500 patients) long (52 weeks) study in which events that occurred during ciclesonide treatment were compared to events that occurred during beclomethasone treatment. The outcome was assessed by ophthalmologists and included carefully quantitated slit lamp examinations. There was a higher overall incidence of opacities than expected, and it would have been nice to have a placebo-treated group to see if the differences were related to the population or to the treatment. However, the patients had moderate to severe asthma and were being treated with ICS at the time of enrollment. It would have been difficult to keep a population of this description off of ICS for the duration of the study.
Theefficacyof ciclesonide in the treatment of patients less than 12 years of age has not been fully elucidated. The optimal dose and safety in terms of HPA-axis suppression has not been characterized. Carefully conducted studies collecting either 24-hour urine or population studies for 24-hour serum measurements are required to assess safety in the pediatric population.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See discussion of ophthalmologic studies and growth studies, above. A limitation of the ophthalmology study was the absence of a placebo group. However, the demonstration of non-inferiority to beclomethasone is sufficient to support approval as all corticosteroids are known to promote the development of cataracts and that warning will remain in the label as a corticosteroid class action. Corticosteroids are also known to have the potential to depress bone growth. In study 343 growth was slower during randomized treatment than during the run-in, although the changes were as severe in the placebo as in the actively treated subjects. It is possible that this is an example of the difficulty in conducting equivalence trials. However, as for the findings in the ophthalmology study, the class warning about growth will remain in the ciclesonide label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the safety assessment the adverse events reported in all of the 12 or 16 week efficacy and safety trials and a 12-week PD trial were combined. Since these studies were conducted in similar populations and for similar durations, this is appropriate. The other studies include unique populations and or assessments, and the results were not pooled.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Although the 160 once daily dose of ciclesonide was statistically superior to placebo, in the same study the same nominal dose administered twice daily (80 mcg BID) was almost twice as effective. Therefore only BID dosing is recommended. Well designed, randomized, placebo controlled studies have demonstrated effectiveness of the 80, 160 and 320 mcg BID doses in subjects with mild to severe asthma, and in adults and adolescents who have previously treated with ICS and those who had not. Therefore the starting recommend dose is 80 mcg BID with increased doses with more severe asthma.

The studies performed in children less than 12 years of age with once daily dosing did not demonstrate efficacy. Only one study demonstrated efficacy of 160 mcg once daily in subjects who had not previously been treated with ICS, and as mentioned above, even in this one study, twice daily dosing was superior.

8.2 Drug-Drug Interactions

Co-administration of inhaled ciclesonide and oral ketoconazole resulted in an elevation of the AUC for the active metabolite of ciclesonide by 3.6 times. A warning about this interaction is included in the proposed label.

8.3 Special Populations

The pediatric population was addressed in the 52-week growth study.

8.4 Pediatrics

Pediatric efficacy studies were submitted with the original NDA (Study341 and 342). Efficacy was not demonstrated in these studies using a once daily dosing regimen, and the only pediatric trial submitted with this application was the safety (growth) study. . Because of the large difference in response noted between once and twice daily dosing in the adult population, Since 80 mcg BID was effective in the adult population, . Studies in patients less than 4 years of age have been deferred.

8.6 Literature Review

No literature review was performed

8.7 Postmarketing Risk Management Plan

9 OVERALL ASSESSMENT

9.1 Conclusions

In a total study population of over 6000 individuals ciclesonide HFA MDI for oral inhalation has produced a statistically significant reduction in airway obstruction when administered at doses of 80 to 320 mcg BID. Once daily dosing has produced an inconsistent effect, especially in patients who have not previously been treated with ICS. Even in the one study where 160 mcg BID was effective, the same nominal dose delivered twice daily was almost twice as effective. In patients previously treated with ICS, the once daily regimens appeared to be more effective, but they were still slightly less effective than twice daily dosing.

There have been very few adequately conducted studies of the HPA-axis in patients treated with ciclesonide. However, the effects are those expected from an inhaled corticosteroid. The development of lens densities was also not higher than seen with beclomethasone as a comparator drug during a treatment period of 52 weeks. The efficacy of ciclesonide in the pediatric population has not been fully characterized. The optimal dose needs to be determined and a well controlled study of the effects of ciclesonide on the HPA-axis and on growth in the pediatric population have not been performed.

9.2 Recommendation on Regulatory Action

Approval of ciclesonide HFA MDI for the prophylactic treatment of asthma in subjects 12 years of age and older. The recommended starting dose in subjects not previously treated with ICS should be 80 mcg BID with an increase to 160 mcg BID if needed. More severe asthma can be treated with 160 or 320 mcg BID.

9.3 Recommendation on Post-marketing Actions

9.4 Labeling Review

The label was edited to conform to PRL formatting.

9.5 Comments to Applicant

The Applicant was instructed to submit a revised label for further consideration.

10 APPENDICES

1 Study # XRP1526B/3031

A multinational, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of ciclesonide metered-dose inhaler at a daily dose of 160 µg administered either in a once-daily in the morning regimen (160 µg q.d. AM) for 16 weeks or in a 160 µg q.d. AM regimen for 12 weeks preceded by a twice daily regimen (80 µg b.i.d.) for 4 weeks, or in an 80 µg b.i.d. regimen for 16 weeks, in adults and adolescents with mild to moderate persistent asthma not treated with steroids

1.1 Protocol

1.1.1 Administrative

Enrollment Dates:	September 21, 2005 – February 5, 2007
Screening Centers:	139 – USA (75), Brazil (12), Israel (12), Russian Federations (9), Poland (7), Mexico (6), Costa Rica (5), Puerto Rico (4), Chile (3), Estonia (3), Latvia (3)
Coordinating Investigator:	
Sponsor's medical expert:	

1.1.2. Objective/Rationale

The primary objective of the study was to investigate the efficacy, compared to placebo MDI, of ciclesonide MDI at a daily dose of 160 µg administered in one of 3 regimens: 160 µg q.d. AM for 16 weeks, 80 µg b.i.d. for 16 weeks, or 80 µg b.i.d. for 4 weeks followed by 160 µg q.d. AM for 12 weeks in adults and adolescents with mild to moderate persistent asthma not treated with ICS.

The secondary objective of the study was to investigate the safety, compared to placebo MDI, of the three ciclesonide regimens in adults and adolescents with mild to moderate persistent asthma not treated with ICS.

1.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group study in patients ≥12 years of age with mild to moderate persistent asthma who had not received inhaled corticosteroids (ICS) in the 30 days prior to enrollment. Eligible subjects were enrolled into a 7 to 14-day run in period at which time they were treated with a single-blind MDI

placebo BID and they recorded their symptoms. At the end of the run-in subjects were randomized (1:1:1:1) to receive placebo BID for 16 weeks, ciclesonide 160 mcg QD for 16 weeks, ciclesonide 80 mcg BID for 4 weeks followed by ciclesonide 160 mcg QD for 12 weeks, or ciclesonide 80 mcg BID for 16 weeks. Subjects who failed screening could be re-screened a maximum of 4 times (5 total attempts) before they were excluded from the study.

The subjects were seen in the clinic at screening, randomization and at 2, 4, 8, 12, and 16 weeks after randomization. The AM-FEV_1 (after 6 hours without albuterol and prior to study drug) was performed at all clinic visits. The primary efficacy outcome was the change in AM-FEV_1 comparing baseline (Week 0) to the average of the Week 12 and Week 16 value. For subjects who discontinued the study, the last available measurement was used.

1.1.3.2 Protocol Amendments

- Amendment 1 (August 3, 2005 and prior to enrollment) – Change primary endpoint to FEV_1 instead of AM PEF; randomization criteria changed from FEV_1 and AM PEF of 60 to 90% predicted to between 60 and 85% predicted; statistical analysis changed from a comparison of baseline to Week 16 to a comparison of baseline to the mean of Week 12 and Week 16, and the first analysis changed from comparison of ciclesonide 160 mcg QD to placebo to the comparison of ciclesonide 80 mcg BID to placebo.
- Amendment 2 (September 27, 2005) – Eligibility for randomization was changed from a PEF ≥ 60% and ≤ 85% predicted to ≤ 95% predicted
- Amendment 3 (January 24, 2006) – The definition of lack of asthma control during the 7 days prior to randomization was changed from an AM PEF of <80% predicted to <90% predicted on three days to avoid excessive screening failures.

1.1.4. Study Population

Inclusion Criteria

- Males or females ≥12 years of age
- History of persistent bronchial asthma for at least 6 months prior to screening
- Asthma therapy limited to bronchodilators only, such as short-acting β_2-agonists or methylxanthines, for at least 1 month prior to screening
- At screening and immediately prior to randomization, after an albuterol withhold of at least 6 hours, FEV_1 of ≥60% and ≤85% of predicted normal and AM PEF of ≤95% of predicted
- In patients using methylxanthines: discontinuation of methylxanthines from at least 24 hours prior to the screening visit onward
- During the last 7 days (with non-missing measurements) of the screening period prior to randomization all of the following signs for lack of asthma control:
    - Daytime asthma symptom score >1 on 3 or more days
    - Albuterol use on 3 or more days
    - AM PEF <90% of predicted normal on 3 or more days

- At screening or immediately prior to randomization, reversibility of FEV_1 by at least 12% (relative to the pre-bronchodilator value in liters [L]) after inhalation of 180 µg albuterol (ex-actuator)
- FEV_1 at randomization within 15% of the FEV_1 value (in L) at screening
- Non-smoker for at least 6 months prior to screening, with less than a 10 pack-year smoking history if previous smoker
- Able to demonstrate acceptable oral inhaler technique with MDI
- Written informed consent at enrollment into the study

Exclusion Criteria

- Any use of injectable or oral corticosteroids within 6 months prior to screening
- Any use of an ICS within 30 days prior to screening
- Use of β_2-adrenergic blocking agents for any reason
- Upper or lower respiratory tract infection within 30 days prior to screening
- History of chronic bronchitis, chronic obstructive pulmonary disease, or emphysema
- History of life-threatening asthma, including a history of significant hypercarbia
- (pCO_2 >45 mmHg), prior intubation, respiratory arrest, or seizures as a result of an exacerbation of asthma
- More than 2 in-patient hospitalization or emergency care visits due to asthma exacerbations in the year prior to screening
- Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change in their immunotherapy regimen within 30 days prior to screening
- Pregnancy
- Breast feeding
- Female patients of childbearing potential (ie, ovulating, pre-menopausal, not surgically sterile) unless practicing an adequate method of birth control
- Likelihood of requiring treatment during the study period with prohibited drugs
- Treatment with any investigational product within 30 days prior to screening;
- Previous randomization in this study
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease making implementation of the protocol difficult
- Any clinically relevant deviation from normal in laboratory parameters that would limit participation in the study or interfere with interpretation of study results
- History of hypersensitivity to the study drug, albuterol or any of the excipients
- History of drug or alcohol abuse
- Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study
- Patient unlikely to comply with protocol
- Patient was related to any staff associated with the study

Withdrawal Criteria

The subject was instructed to contact the investigator if they felt their asthma was not under good control. The investigator was to consider withdrawing the subject if any of the following occurred:

- Decrease in FEV_1 of ≥20% compared to baseline
- Nocturnal awakenings due to asthma requiring treatment with albuterol on 3 or more nights during any 7-consecutive-day period
- Use of 8 or more puffs per day of albuterol on 4 or more days during any 7-consecutive-day period
- Decrease in AM PEF to <80% of baseline value on 4 or more days (baseline value determined as the average value on the last 7 days with non-missing measurements prior to Visit 3)
- If a prohibited medication was prescribed the subject had to be withdrawn

Subjects could also be withdrawn at their own request, the investigator considered continued participation in the study would be detrimental to the subject or a protocol deviation was severe enough to warrant withdrawal, and if a premenarchal female at screening became menarchal and could not comply with the requirements for abstinence.

1.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Placebo MDI BID for 16 weeks (2 puffs placebo BID)
- Ciclesonide MDI 160 mcg QD for 16 weeks (2 puffs 80 mcg in AM and 2 puffs placebo in PM)
- Ciclesonide 80 mcg BID for 16 weeks (2 puffs 40 mcg BID)
- Ciclesonide 80 mcg BID for 4 weeks then ciclesonide 160 mcg QD for another 12 weeks. (2 puffs 40 mcg BID for 4 weeks then 2 puffs 80 mcg in AM and 2 puffs placebo in PM)

HFA albuterol was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Antihistamines
- H2 blockers
- Nasal anti-cholinergic agents
- Nasal corticosteroids
- Nasal or ophthalmologic preparations of nedocromil

- Maintenance immunotherapy

The following medications were prohibited from screening onward:

- Any ICS other than the study medication provided
- Systemic corticosteroids (oral or injectable)
- Short-acting β2-agonists other than the albuterol
- Long-acting β2-agonists (LABAs)
- Combination of an ICS and a LABA (Advair®)
- Ipratropium bromide or other inhaled anti-cholinergic agents (tiotropium, Combivent®)
- Methylxanthines (theophylline, aminophyllines)
- Leukotriene receptor antagonists or leukotriene synthesis inhibitors
- Lipoxygenase inhibitors
- Cromones
- Anti-immunoglobulin E therapy (Xolair®)

Compliance was assessed by the patient's notation in the diary that the medication was taken. Poor compliance was defined as <70% of the expected actuations.

Efficacy Evaluation

The primary efficacy evaluation was made on the basis of changes in FEV_1. Spirometry was performed according to ATS standards in the morning between 6 and 10 AM and was supposed to have been performed within 1 hour of the screening test. The FEV_1 was determined prior to the AM dosing with study medication and at least 6 hours after the last albuterol. Reversibility was assessed 20 minutes after inhalation of 180 mcg albuterol and was based on the difference between actual baseline FEV_1 and post albuterol value.

The subjects were provided with a PEF meter [redacted] and were instructed in its use. They were instructed to make the measurement within 15 minutes of rising, prior to the morning dose of study medication and in the afternoon before the afternoon dose of medication. Three attempts were recorded and the highest value was used in the analysis. Patients were instructed to try and withhold albuterol for 6 hours prior to the measurements

At the screening visit the subjects were issued a diary card. The cards were used twice daily to record the number of albuterol inhalations (puffs/day), the Asthma Symptom Score, the number of nocturnal awakenings, and the dose of medication taken. The Asthma Symptom Scores were graded according to the following scale:

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 that interfered with daily activities or sleep

3 = Frequent or continuous wheezing, cough, or shortness of breath that interfered with daily activities or sleep
4 = Symptoms that prevented the patient from engaging in daily activities or sleep

The number of puffs of albuterol and number of nighttime awakenings were also be recorded in the diary.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. In addition, any ophthalmologic finding which met the definition of an AE, whether severe or not, was reported as an Alert Term. These events were reviewed by the Applicant's pharmacovigilance group prior to unblinding the database. Standard hematology and urinalysis examinations were also performed at baseline and at the end of treatment. Mean values were calculated and subjects with values that were above normal were tabulated. Safety hematology and chemistry blood tests were performed at baseline and at the end of treatment. A Predefined change abnormal (PCA) value was determined for glucose and absolute eosinophil evaluations. Based on the laboratory normal values, changes from baseline and/or a change to a specific high value, clinically meaningful abnormalities were identified.

A summary of the study procedures is shown in Table 19.

Table 19. Summary of Events

			Initial Treatment Period			Maintenance Treatment		
Study Day	PreScreen	Screen	Random					
Visit number	1	2	3	4	5	6	7	8
Week	-1 (+2 days)	-1	0	2	4	8	12	16
Informed consent	X							
Randomization			X					
Medical history		X						
Physical Examination		X						X
Review medication		X	X	X	X	X	X	X
Vital Signs		X						X
Spirometry		X	X	X	X	X	X	X
Reversibility		X	X					
Laboratory tests		X						X
Pregnancy tests*		X						
Issue PEF meter & Review results		X	X	X	X	X	X	X
Issue & Review Diary		X	X	X	X	X	X	X
Adverse event review		X	X	X	X	X	X	X
Dispense appropriate medications			X	X	X	X	X	X

1.1.6. Statistical Analysis Plan

Sample Size

Sample size parameters were chosen from the results of studies 321 and 322 which compared once daily dosing of ciclesonide to placebo. In those studies, the difference from placebo at the end of the treatment period was approximately 0.13 L and the standard deviation in the steroid naïve subjects was 0.43 L. If these results can be used to predict the results of the current study, then 175 subjects per treatment group would provide 80% power to detect a difference between placebo and active treatment of 0.13 L

Study Populations

The ITT population included all randomized subjects who received medication and who had at least 1 post treatment FEV_1 measurement.

The per-protocol (PP) population consisted of all the subjects in the ITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind. The list of major protocol violation includes the following events:

- FEV_1 at baseline >90% of predicted normal
- AM PEF at baseline >95% of predicted normal
- Reversibility of FEV_1 <12% or <200 mL before randomization
- Current smoker
- Concomitant treatment with any LABA
- Concomitant use of leukotriene receptor antagonists
- Use of inhaled, injectable, or oral corticosteroids within 4 days prior to the baseline visit
- History of asthma within 3 months prior to entry to study
- Patient was discontinued less than 7 days after randomization
- Poor compliance with study medication (less than 70% of expected actuations)
- Received study medication different to which they were randomized to by IVRS

Reviewer: Ingestion of systemic corticosteroids was prohibited for 6 months prior to screening. However, this was considered a major violation only if they were taken within 4 days of the baseline visit (subjects could have taken systemic corticosteroids during the run-in.

Primary Analysis

The primary efficacy variable was the change in FEV_1 (L) from baseline (Day 1) to the average of Week 12 (Visit 7) and Week 16 (Visit 8). For subjects who discontinued between Weeks 12 and 16, the average of the Week 12 and the end-of-study measurements was used, and for subjects who discontinued before Week 12, the last measurement obtained prior to withdrawal was used. Subjects who experienced an asthma attack that required treatment with a prohibited medication were to be withdrawn from the study and all FEV_1 measurements should have been made prior to the administration of any systemic or inhalation corticosteroid. However, upon review of the data it was noted that three subjects had the FEV_1 measured after a course of

corticosteroids. For these three subjects the last measurement obtained prior to the course of corticosteroids was used.

The primary analysis (ITT population) used an analysis of covariance (ANCOVA) of the change from baseline to the average of the Week 12 and Week 16 FEV_1 measurements with factors for treatment, pooled center, and gender. Baseline FEV_1 and age were included in the models as covariates. The type I error was controlled with the following stepwise procedure:

- Step I: Ciclesonide MDI 80 µg BID was compared to placebo MDI at $\alpha = 0.05$ (2-sided). If this test was statistically significant, it was concluded that ciclesonide MDI 80 µg BID. was efficacious. Statistical testing then proceeded to Step 2

- Step II:- The average of the ciclesonide MDI 160 µg QD. AM and ciclesonide MDI 80 µg b.i.d./160 µg QD. AM groups was compared to placebo MDI at $\alpha = 0.05$ (2-sided). If this test was statistically significant, statistical testing then proceeded to Step 3. This step was included to ensure a closed testing procedure

- Step III: The ciclesonide MDI 160 µg QD AM group and the ciclesonide MDI 80 µg b.i.d./160 µg QD. AM groups were compared to placebo MDI, each at $\alpha = 0.05$ (2-sided).

Supportive analyses were performed using the PP population, and a further analysis was performed comparing baseline to the Week 16 value.

Other Efficacy Analyses

Key secondary efficacy outcomes included the following:

- AM PEF (L/min) comparing baseline to Week 16 or early termination visit
- Daily albuterol use (puffs/day) comparing baseline to Week 16 or early termination visit
- Asthma Symptom Score (sum of AM and PM scores) comparing baseline to Week 16 or early termination visit

Additional efficacy outcomes include the following:

- Rate and time to withdrawal due to worsening of asthma or lack of efficacy
- Rate and time to withdrawal due to all causes
- Change from baseline in FEV_1 (L) to each time point
- Change from baseline in FEV_1 percent predicted and percent change from FEV_1 to average of Week 12 and Week 16
- Change from baseline in FEV_1 percent predicted and percent change from FEV_1 to Week 16
- Change from baseline in forced vital capacity (FVC, in L) and forced mid-expiratory flow ($FEF_{25-75\%}$ in L/s) to Week 16 (in addition, summary by visits)
- AM PEF, weekly average change from baseline
- Daily albuterol use, weekly average change from baseline

- Total daily asthma symptom score, weekly average change from baseline
- PM PEF, change from baseline to Week 16 (Visit 8, or early termination), and weekly average change from baseline
- Nighttime awakenings due to asthma requiring treatment with albuterol, change from baseline to Week 16 (Visit 8, or early termination)

The following asthma diary variables were assessed based on the entire 12-week period:

- Percentage of symptom-free days: Both AM and PM symptom score must = 0, and at least one of the scores had to be recorded for the day to be included in the analysis.
- Percentage of nights with nighttime awakenings: Any night with at least one awakening was divided by the number of valid treatment days
- Percentage of asthma-controlled days: A day when the asthma symptom score=0, no albuterol was used, and there were no nighttime awakenings

Other Data Management Issues

The baseline values for the pulmonary function measurements was the pre-bronchodilator value recorded on Day 1 (Week 0) prior to administration of the first dose of study medication. For the diary data, the baseline was calculated as the average of the values recorded or the 7 days prior to the randomization visit. If there was missing data, values obtained up to 14 days prior to randomization could be used.

1.2. Results

1.2.1. Study Population

Disposition

A total of 2190 subjects were screened and 1482 failed, resulting in randomization of 708 subjects. Eight subjects received no study drug and so were not included in the efficacy or safety populations. An additional 9 subjects had no post treatment FEV_1 measurement and were excluded from the ITT population. This resulted in a safety population of 700 and an ITT population of 691.

Reviewer: Because of the allowance for multiple screening visits there were a total of 2917 screening visits for the 708 enrolled subjects. Eight subjects never received study medication and they were included with those who were not enrolled in the screening summary. Of the 700 subjects who were enrolled and treated with study medication, 491 (70.1%) were enrolled after 1 screening visit, 161 (23%) were enrolled after 2 screening visits, and the remainder (48 [6.9%]) were enrolled after 3 or more screening visits. This compared to 1121 (50.6%), 721 (32.5%), and 375 (16.9%) enrolled after 1, 2, or >2 screening visits, respectively, in the screen-failed population. Of those enrolled and treated there was very little difference in the distribution of number of screening visits across the treatment groups.

Of the 700 subjects who were randomized and treated, 597 (85.3) completed the course of treatment (Table 20). Withdrawal was highest in the placebo-treated subjects (23%) compared with 16.9, 12.4, and 10.3% withdrawal in the ciclesonide 160 QD (C160), Ciclesonide 80 BID/160 QD (C80/160) and the ciclesonide 80 BID (C80) groups, respectively. Adverse reactions were the most common indication for withdrawal and the distribution was similar to the distribution of overall withdrawals (12.9, 7.9, 4.5, and 2.3% in the placebo, C160, C80/160 and C80 groups, respectively). Other reasons for discontinuation were reported infrequently: 5.1% did not wish to continue, 1.3% reported lack of efficacy, 1.0% each were lost to follow-up and had a protocol violation, and 1.3% withdrew due to an "other" reason. There were no deaths.

Table 20. Disposition of Subjects in Study 3031

	Placebo	Dose of Ciclesonide			Overall
	---	160 QD	80 BID / 160 QD	80 BID	
Randomized	178	178	177	175	708
Treated	178 (100)	176 (98.9)	173 (97.7)	173 (98.9)	700 (98.9)
Discontinued	41 (23.0)	30 (16.9)	22 (12.4)	18 (10.3)	111 (15.7)
Reason for discontinuation:					
Adverse event	23 (12.9)	14 (7.9)	8 (4.5)	4 (2.3)	79 (6.9)
Lack of efficacy	5 (2.8)	2 (1.1)	0	2 (1.1)	9 (1.3)
Did not wish to continue	10 (5.6)	7 (3.9)	9 (5.2)	10 (5.8)	36 (5.1)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (1.1)	3 (1.7)	7 (1.0)
Protocol violation	0	4 (2.2)	2 (1.1)	1 (0.6)	7 (1.0)
Death	0	0	0	0	0
Other	2 (1.1)	2 (1.1)	3 (1.7)	2 (1.1)	9 (1.3)

Withdrawal because of a protocol violation was uncommon. In three of the C160 subjects, the 2 C80/160 and one C80 subjects the protocol violation was a failure to meet inclusion criteria. The cicles-160 subjects had pulmonary function that was higher than accepted or one was not treating the asthma prior to enrollment. The three other subjects in the other treatment groups had unacceptable variability in either symptom scores or FEV_1. An additional subject in the C160 group was withdrawn because he was taking prednisone, although the subject also had an asthma exacerbation.

Reviewer: Taking systemic or inhaled corticosteroids during the randomized treatment period was considered a major protocol violation. Subjects should have been removed from the protocol if they suffered an asthma attack severe enough to require treatment with prohibited medications. This practice was followed as a rule, and the withdrawal was categorized as due to an adverse event (the asthma exacerbation). There were, however, 13 subjects who continued on study medication after being treated with systemic or inhalation CS. In all but three of these subjects the last FEV_1 was determined prior to the initiation of the prohibited medication and was included in the analysis. In the three who had pulmonary function measured after initiation CS treatment, the last FEV_1 prior to the administration of CS was used in the analysis.

A total of 17 (2.4%) of the randomized subjects were excluded from the ITT population. Eight subjects received no medication and an additional 9 were lost to follow-up and did not have any post treatment functional assessment.

Reviewer: In the text of the study report (7.2.1.1 Exclusions from the ITT population, pg 68) it is noted that three subjects (1 each in the placebo, C160, and C80 groups) were excluded from the ITT population due to adverse events. Ordinarily this would not be an indication for taking the subject out of the ITT population. However, the withdrawal occurred so early in the course that no follow-up spirometry was obtained.

Twenty (2.9%) subjects were excluded from the PP population. More were excluded in the placebo (9 [5.1%]) than in the other treatment groups (3 [1.7%], 4 [2.3%], and 4 [2.4%] in the C160, C80/160, and C80 groups, respectively). The most common cause for exclusion was a normal AM PEF (8 [1.2%]) followed by poor compliance (7 [1.0%]). Both were more common in the placebo subjects, as was lack of reversibility.

Demographics

Of the 691 subjects in the ITT population 45.7% were male, the mean age (Range) was 36.7 (11 - 73) years. Ninety-six (14.0%) were less than 18 years old. The predominant racial group was white (74.5% compared with 8.8% black and 16.7% other). Most of the characteristics were distributed approximately evenly across the treatment groups (Table 21), although the percentage of males was slightly higher in the C160 group (52%).

Subjects were screened at 139 clinical centers and subjects were enrolled at 119 centers. Most of the centers (68) and most of the subjects (403 [58.3%]) were enrolled in the United States. This compares to 17.5% of the subjects who were enrolled in 22 centers in S America, 10.7 % of the subjects who were enrolled in 19 centers in Eastern Europe, and 13.5 % of the subjects who were enrolled in 12 centers in Israel.

Table 21. **Demographic Characteristics of the ITT Population**

	Placebo	Dose of Ciclesonide			Overall
		160 QD	80 BID / 160 QD	80 BID	
Total ITT Population	177	173	171	170	691
Gender, %M	(43.5)	(52.0)	(40.9)	(46.5)	316 (45.7)
Age, mean(SD)	37.1 (15.4)	36.3 (15.4)	37.9 (16.1)	35.6 (15.3)	36.7 (15.6)
Age 11 - <18, N	26	25	18	27	
Race					
White	72.9	76.9	74.3	74.1	74.5
Black	10.2	6.9	11.7	6.5	8.8
Other	16.9	16.2	14.0	18.4	16.7
Region					
USA	103 (58.2)	100 (57.8)	100 (58.5)	100 (58.8)	403 (58.3)
S. America	31 (17.5)	31 (17.9)	29 (17.0)	30 (17.6)	121 (17.5)
E. Europe	20 (11.3)	18 (10.4)	19 (11.1)	17 (10.0)	74 (10.7)
Israel	23 (13.0)	24 (13.9)	23 (13.4)	23 (13.5)	93 (13.5)

The mean (SD) duration of asthma was 14.5 (13.4) years (Table 22). The mean was slightly higher in the C80 group (16.5 years) than in the other treatment groups (13.4, 13.7, and 14.7 years in the placebo, and C160 and C80/160 groups, respectively. The mean (SD) pre-bronchodilator FEV_1 was 2.47 (0.60) L and the mean (SD) FEV_1 percent predicted was 72.0

(7.1) percent, suggesting an asthma severity of mild to moderate. Function was stable during the last half of the single-blind run-in as evidenced by a change in FEV_1 between the mid-run-in and randomization visit of -0.27 %. The mean (SD) Asthma Symptom Score was 3.1 (1.1), albuterol use was 2.74 (1.8) puffs/day, and Nighttime awakenings occurred 0.55 (0.7) awakenings per night. The Asthma Symptom Scores were identical in the treatment groups while the albuterol use 2.46 (puffs per day) and nighttime awakenings (0.46) were slightly lower in the placebo group. All but three placebo subjects had ≥ 12% reversibility and all had a ≥ 200 mL increase in FEV_1 after inhalation of albuterol.

Table 22. Characteristics of Asthma – ITT Population

	Placebo	Dose of Ciclesonide			Overall
	---	160 QD	80 BID / 160 QD	80 BID	
Total	177	173	171	170	691
Duration					
Years, mean (SD)	13.4 (13.0)	13.7 (13.3)	14.7 (13.1)	16.5 (14.1)	14.5 (13.4)
Range	0.3 – 59.3	0.4 – 60.2	0.5 – 60.7	0.7 – 59.4	0.3 – 60.7
FEV_1					
Mean Absolute, ml (SD)	2.45 (0.59)	2.54 (0.65)	2.39 (0.59)	2.49 (0.58)	2.47 (0.60)
Mean % predicted, % (SD)	72.6 (6.8)	72.3 (7.0)	71.9 (6.9)	71.9 (6.9)	72.0 (6.9)
Mean % change Visit 2 & 3	-0.20 (7.4)	-0.37 (7.1)	-0.037 (7.0)	-0.47 (6.8)	-0.27 (7.1)
AM PEF, L/min (SD)	348 (95)	350 (98)	333 (95)	350 (100)	345 (97)
Daily Total Asthma Symptom Score Mean (SD)	3.1 (1.1)	3.1 (1.3)	3.1 (1.1)	3.1 (1.2)	3.1 (1.2)
Daily albuterol Use, puffs (SD)	2.46 (1.5)	2.71 (1.9)	2.86 (1.9)	2.95 (1.7)	2.74 (1.8)
Nightly Awakenings, mean (SD)	0.46 (0.6)	0.62 (0.8)	0.56 (0.6)	0.56 (0.6)	0.55 (0.7)

Reviewer: For the most part, the asthma severity is well balanced across the treatment groups. Most of the subjects would have been assessed as candidates for inhaled corticosteroid treatment by NAEPP standards.

Concomitant medications

Within 30 days of enrollment only 2 subjects were taking any medications other than bronchodilators. One C80 subject took inhaled dexamethasone and one C160 subject took formoterol less than 30 days prior to enrollment.

Reviewer: Prior to enrollment 37 (5.4%) of the subjects were treated with inhaled steroids between 15 and 492 days prior to initiating single-blind treatment (10 [5.6%], 7 [4.0%], 9 [5.3%], and 12 [7.1%] of the placebo, C160, C80/160, and C80 groups, respectively). One C80 subject was treated 15 days prior to enrollment and 10 were treated between 1 and 2 months prior to enrollment. The others were treated more than two months prior to enrollment. One additional C80/160 subject was treated with another investigational drug for asthma 35 days prior to enrollment.

(The above numbers were calculated from post-text Table T-6, pg 2980, [for dates of prior ICS administration] and dataset "medadm.xpt" [for dates of single-blind study drug treatment].

When dates of last pre-study drug treatment with ICS containing only the month and year were listed, the first day of the month was interpolated.)

During the randomized treatment period 46 subjects took inhaled or systemic corticosteroids (25 – oral, 11 – inhaled, 10 – inhaled ICS/LABA, 6 - injectable). Combining all forms of non-topical corticosteroid treatments, 25 (14.1%) placebo, 10 (5.8%) C160, 7 (4.1%) C80/160, and 10 (5.9%) C80 subjects were treated after initiation of study treatment and during study follow-up. These were not counted as protocol violations because the onset of prohibited CS treatment usually coincided with the onset of an asthma exacerbation and the subject was withdrawn from the study. The early termination FEV_1 was therefore obtained prior to initiation of the prohibited medication was started. In three cases the last FEV_1 was obtained after a course of prohibited corticosteroids were administered. For these individuals the last FEV_1, prior to the course of corticosteroids was used in the analysis.

Reviewer: The number of subjects who were treated with non-study corticosteroids is slightly larger than the number withdrawn due to asthma. However, other subjects were withdrawn due to lack of efficacy and when these are added to the number withdrawn due to an asthma exacerbations the numbers are very close to those who received steroids: 23 (12.9%). 11 (6.3%), 4 (2.9%), and 5 (2.3%) of the placebo, C160, C80/160, and C80 were withdrawn due to either an asthma exacerbation or loss of efficacy.

1.2.2. Efficacy Results

Primary Efficacy Outcome

The primary analysis compared the pre-dose FEV_1 at endpoint (average of 12 and 16 week values) to the baseline value. Each of the treatments resulted in increases in FEV_1 that were statistically significantly better than placebo. The LS mean difference was 0.12, 0.13, and 0.24 L for treatment with C160, C80/160, and C80 (Table 23). Additionally, the change in FEV_1 after treatment with C80 BID was statistically significantly better than the change after treatment

Table 23. Change in FEV_1 after Treatment with Ciclesonide

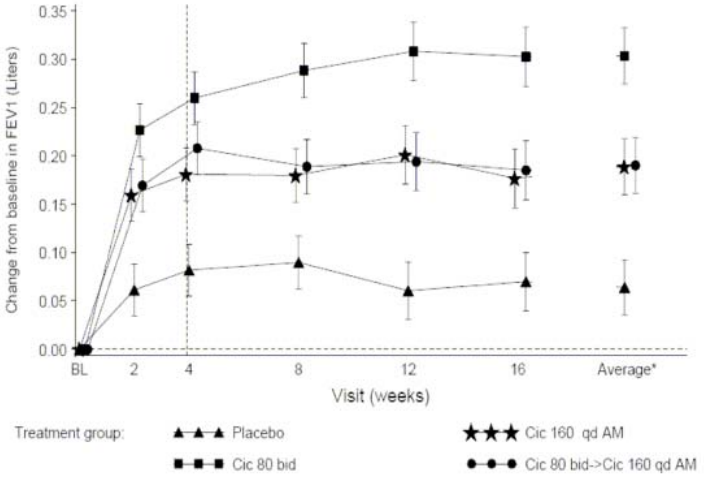
		Dose of Ciclesonide		
Fev_1	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline, mean L	2.45	2.54	2.39	2.49
Change from baseline LS mean, L 95% CI	 0.06 0.01, 0.12	 0.19 0.13, 0.25	 0.19 0.13, 0.25	 0.30 0.25, 0.36
Difference from placebo LS mean, L 95% CI p- value		 0.12 0.05, 0.20 0.002	 0.13 0.05, 0.20 0.002	 0.24 0.16, 0.32 <0.001
Difference from cicles-80* LS mean, L 95% CI p-value		 0.11 0.03, 0.19 0.005	 0.11 0.03, 0.19 0.005	

***** Taken from post-text Table – 22 in Appendix 12.3.6

with C160 and C80/160. The results are shown graphically in Figure 2. The percent change in FEV_1 was 2.6, 7.6, 7.6, and 13.0% increase during treatment with placebo C160, C80/160, and C80, respectively (Post-text Table T-32, pg 3212).

Note that the Applicant performed a sequential analysis in which C80 BID was compared to placebo first, and then step two was a comparison of the combined C160 and C80/160 arms to placebo, and finally a comparison of the C160 arm to placebo. In the FDA statistical review of the statistical analysis plan submitted prior to breaking the blind, the Applicant was informed that this was an inappropriate procedure. See FDA Stats Review of this NDA for details.

Figure 2 . Change in FEV_1 During Treatment with Ciclesonide



The various supportive analyses confirmed the results of the primary analysis. If the analysis was performed on the last observation instead of the mean of the values obtained at week 12 and week 16 the results are essentially identical. The per-protocol analysis was also almost identical to the ITT analysis. The change from baseline in FEV_1 was 0.07 in the 168 placebo subjects, 0.31 in the 166 C80 subjects, and 0.19 in both the 167 C80/160 and C160 subjects.

The Applicant noted that the only subgroup analysis that was notable was the finding that the difference between the change in FEV_1 comparing active treatment to placebo was consistently greater (all active treatments) when the baseline FEV_1 was greater than 70% predicted than when it was less. The differences were not significant in the analysis of interactions.

Reviewer: The changes with treatment were actually larger in the subjects with low baseline FEV_1 % predicted than in those with higher baseline values. However, the improvement was greatest in the placebo group with low baseline FEV_1%, so that the comparison with active treatment in this group resulted in a relatively small difference between placebo and the active treatments. The change in the placebo subjects with FEV_1 < 70 % predicted was 0.15 L

compared to the change in the subjects with FEV_1 >70% predicted at baseline of 0.00 L. Thus, while the FEV_1 increased by 0.37 L in the subjects with low baseline FEV_1% who were treated with C80, the mean (LS) difference from placebo was only 0.22L. This compares to an increase of 0.26 in the subjects with a high baseline FEV_1% which resulted in a difference from placebo of 0.26L.

Secondary efficacy outcome measures

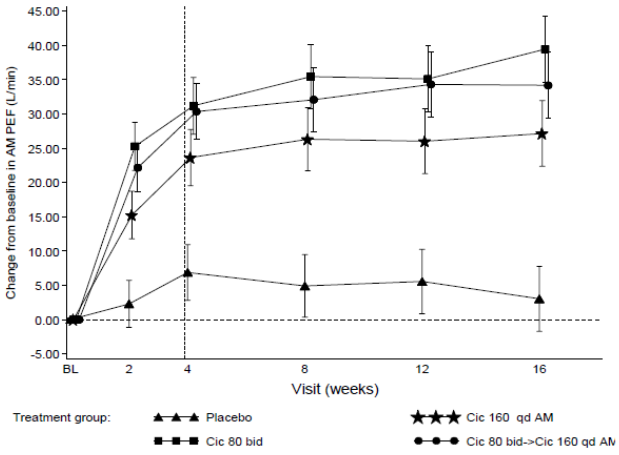
The diary-recorded AM PEF showed changes in the same direction as the changes in the FEV_1 (Table 24). The increase with treatment was 3.4, 26.7, 34.1, and 39.6 L/min in the placebo, C160, C80/160, and C80 groups, respectively.

Table 24. Change in AM peak flow

		Dose of Ciclesonide		
AM PEF	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline, mean L/min	324	318	306	320
Change from baseline LS mean, L/min 95% CI	 3.4 -5.9, 12.7	 26.7 17.3, 36.1	 34.1 24.7, 43.5	 39.6 30.1, 49.0
Difference from placebo LS mean, L/min 95% CI		 23.3 10.1, 36.5	 30.7 17.7, 43.7	 36.2 23.1, 49.2

Thus the change in AM PEF was marginally greater in the C80 than in the C80/160 group, and both of these groups showed more improvement that the subjects treated with C160 only. . The changes are shown graphically in Figure 3.

Figure 3. Change in AM PEF During Treatment of subjects who were Taking ICS at the time of Enrollment



Albuterol use decreased in all of the treatment groups (Table 25), with the greatest fall in the C80 group and least in the placebo group. The change in the C160 and C80/160 were similar to one another and intermediate in magnitude.

Table 25 . Albuterol use after Treatment with Ciclesonide

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline, puffs / day	2.46	2.71	2.86	2.95
Change from baseline LS mean, puffs / day 95% CI	 -0.97 -1.19, -0.74	 -1.38 -1.61, -1.15	 -1.57 -1.79, -1.34	 -1.69 -1.92, -1.46
Difference from placebo LS mean, puffs / day 95% CI		 -0.41 -0.73, -0.09	 -0.60 -0.92, -0.28	 -0.73 -1.04, -0.41

The Asthma Symptom Scores all decreased with treatment and as with the other variables the improvement was most dramatic in the subjects treated with ciclesonide 80 mcg BID and least in the placebo subjects (Table 26). Improvement in the C160 and C80/160 was similar in these two dosing groups and was intermediate in magnitude.

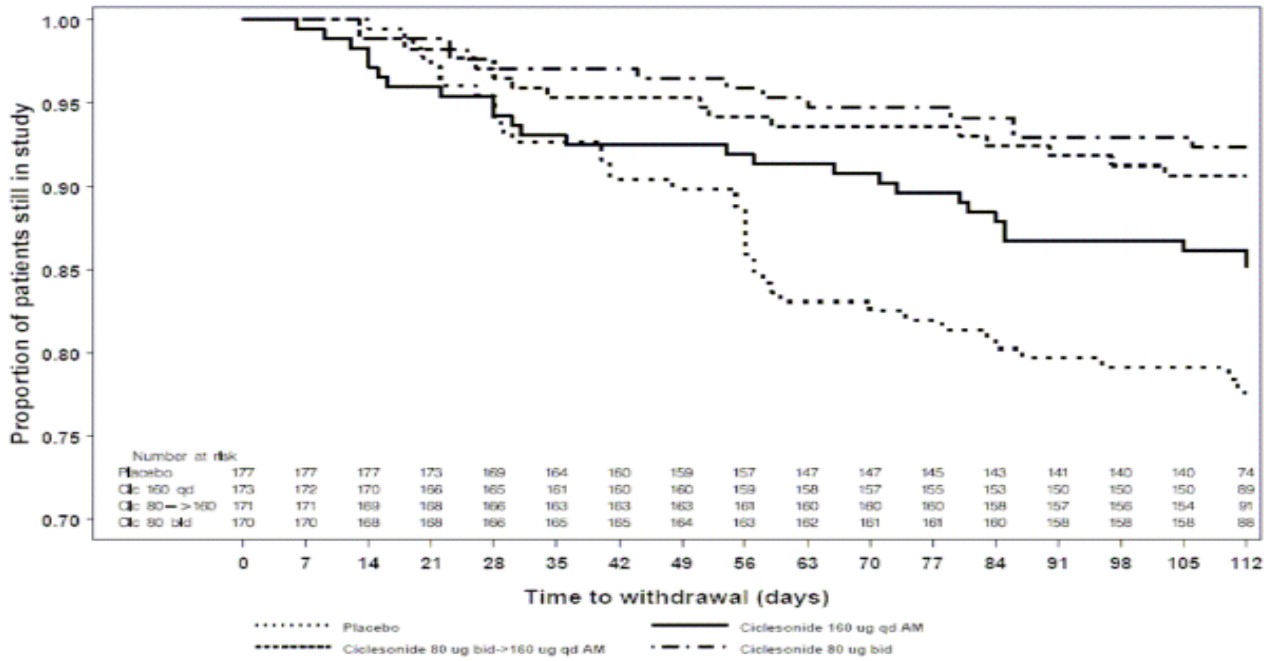
Table 26. Asthma Symptom Score

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline,	3.10	3.12	3.11	3.09
Change from baseline LS mean 95% CI	 -1.06 -1.27, -0.85	 -1.33 -1.55, -1.12	 -1.38 -1.60, -1.17	 -1.63 -1.85, -1.41
Difference from placebo LS mean 95% CI		 -0.27 -0.57, -0.03	 -0.32 -0.62, -0.03	 -0.57 -0.87, -0.27

Other Efficacy Variables

Both the rate of withdrawal for any cause and withdrawal for lack of efficacy was higher in the placebo subjects than in the active treatment groups (40 [22.6%], 25 [14.5%], 17 [9.9%], and 13 [7.6%] in the placebo, C160, C80/160, and C80 groups, respectively for overall withdrawal). However, the differences did not show up until late in the course. Over the first month of treatment, the placebo withdrawal rate was very similar to that of the subjects treated with 160 mcg daily (figure 4). The pattern was similar for withdrawal due to lack of efficacy except that the placebo withdrawal was similar to that for the C80 group and less than the withdrawal of the C160 subjects until 6 weeks had elapsed.

Figure 4 . Rate of Withdrawal from Study 3031



TT = intent-to-treat; Cic = ciclesonide; qd = once daily; bid = twice daily.
Source: Appendix 14.2.6, *Figure F - 2*

The PM PEF increased more in the active treatment groups than in the placebo subjects. The difference between active treatment and placebo was 20.3, 21.3, 27.4 L/min for the C160, C80/160, and C80 subjects, respectively. Nighttime awakenings decreased by 0.14 awakening per night comparing C80 to placebo. The difference was -0.07 in the C160 group and -0.8 in the C80/160 group. Asthma control improved with active treatment. The percentage of controlled days was 19.4, 25.6, 24.3, and 31.1 percent and the percentage of symptoms-free days was 23.0, 27.9, 27.9, and 34.3% in the placebo, cicles-160, cicles-80/160, and cicles-80 groups, respectively, over the course of the study.

1.2.3. Safety

1.2.3.1 Exposure

Corresponding to the higher rate of withdrawal, the exposure to study medication was lower in the placebo than the active treatment groups. The mean (SD) exposure was 97.8 (28.7), 101.5 (28.7), 105 (23.1), and 105.7 (22.3) days in the placebo, C160, C80/160, and C80 groups, respectively (Table 27). Median exposure was almost identical ranging from 111 to 112 days. The range was 1 to 141 days: 142 (79.8%), 152 (86.4%), 158 (91.3%), and 160 (92.5%) of the placebo, C160, C80/160, and C80 subjects were treated for 12 weeks.

Table 27. Exposure to Study Drug

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID / 160 QD	80 BID
N	178	176	173	173
Mean days (SD)	97.8 (28.7)	101.5 (28.7)	105 (23.1)	105.7 (22.3)
Median days Range	111.0 6 - 124	112.0 1 - 126	112.0 4 – 125	112.0 1 - 141
1 - 14 days	2 (1.1)	8 (4.5)	4 (2.4)	5 (2.9)
15 - 28	10 (5.6)	5 (2.8)	4 (2.4)	3 (1.7)
29 - 42	6 (3.3)	3 (1.7)	2 (1.2)	0
43 - 56	8 (4.4)	1 (0.6)	2 (1.2)	2 (1.2)
57 - 71	6 (3.3)	2 (1.1)	1 (0.6)	2 (1.2)
72 - 84	4 (2.2)	5 (2.8)	2 (1.2)	1 (0.6)
85 - 98	2 (1.1)	2 (1.1)	2 (1.2)	2 (1.2)
99 - 112	108 (60.7)	97 (55.1)	111 (64.2)	115 (66.5)
113 - 119	31 (17.4)	44 (25.0)	40 (25.0	37 (21.4)
>119	1(0.6)	9 (5.1)	5 (2.9)	6 (3.5)

1.2.3.2 Adverse Events

The overall incidence of AEs was similar across the treatment groups (57.3, 52.8, 57.8, and 55.5% in the placebo, C160, C80/160, and C80 groups, respectively). The incidence of serious AEs was low and the incidence of AEs leading to withdrawal was inversely related to the efficacy response (Table 28). Withdrawal was lowest in the C80 group, highest in the Placebo group, and intermediate in the C160 and C80/160 groups. Twelve, 8, 5, and 2% of the placebo, C160, C80/160 and C80 subjects withdrew from the study due to an adverse event.

Table 28 Overall Summary of Adverse Events.

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID / 160 QD	80 BID
N	178	176	173	173
All AEs	102 (57.3)	93 (52.8)	100 (57.8)	96 (55.5)
Serious AEs	1 (0.6)	2 (1.1)	2 (1.1)	3 (1.7)
AEs leading to withdrawal	22 (12.4)	14 (8.0)	8 (4.6)	4 (2.3)
Deaths	0	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system. These complaints were more common in the active treatment groups, although there was no localization of any preferred term to a specific ciclesonide regimen (Table 29). For example, nasopharyngitis was infrequent in the C80/160 group, but upper respiratory tract infection was more common in this group than in either the other active treatment groups or the placebo group. Influenza, sinusitis, and gastroenteritis were all more common in the ciclesonide treatment groups. The other events occurred in less than 3% of the subjects.

Table 29. Adverse Events Occurring in 3% or More Subjects in any Treatment Group, by System Organ Class and Selected Preferred Terms

	Placebo	Dose of Ciclesonide		
SOC and Preferred Term	---	160 QD	80 BID / 160 QD	80 BID
N	178	176	173	173
All AEs	102 (57.3)	93 (52.8)	100 (57.8)	96 (55.5)
Infections and infestations	48 (27.0)	57 (32.4)	54 (31.2)	62 (35.8)
Nasopharyngitis	17 (9.6)	19 (10.8)	9 (5.2)	20 (11.6)
Upper Respiratory Tract Infection	11 (6.2)	6 (3.4)	13 (7.5)	9 (5.2)
Influenza	3 (1.7)	8 (4.5)	6 (3.5)	6 (3.5)
Sinusitis	3 (1.7)	7 (4.0)	6 (3.5)	5 (2.9)
Gastroenteritis	0	1 (0.6)	4 (2.3)	5 (2.9)
Pharyngitis	1 (0.6)	1 (0.6)	3 (1.7)	5 (2.9)
Bronchitis	1 (0.6)	3 (1.7)	4 (2.3)	0
Viral Infection	1 (0.6)	3 (1.7)	4 (2.3)	0
Rhinitis	2 (1.1)	4 (2.3)	0	2 (1.2)
Urinary Tract Infection	0	1 (0.6)	1 (0.6)	4 (2.3)
Respiratory, thoracic, and mediastinal	46 (25.8)	30 (17.0)	34 (19.7)	29 (16.8)
Asthma	25 (14.0)	14 (8.0)	18 (10.4)	9 (5.2)
Pharyngolaryngeal pain	8 (4.5)	5 (2.8)	4 (2.3)	5 (2.9)
Cough	5 (2.8)	3 (1.7)	3 (1.7)	5 (2.9)
Rhinitis	3 (1.7)	4 (2.3)	1 (0.6)	5 (2.9)
Nasal Congestion	6 (3.4)	1 (0.6)	1 (0.6)	2 (1.2)
Nervous system disorders	18 (10.1)	20 (11.4)	20 (11.6)	16 (9.2)
Headache	14 (7.9)	16 (9.1)	15 (8.7)	10 (5.8)
Gastrointestinal disorders	10 (5.6)	18 (10.2)	17 (9.8)	14 (8.1)
N / V	3 (1.7)	6 (3.4)	7 (4.0)	5 (2.9)
Musculoskelatal disorders	14 (7.9)	13 (7.4)	11 (6.4)	8 (4.6)
Injury, poisonings and procedures	7 (3.9)	10 (5.7)	9 (5.2)	10 (5.8)
General disorders and administration site problems	6 (3.4)	6 (3.4)	3 (1.7)	9 (5.2)
Skin and Subcutaneous tissue	4 (2.2)	6 (3.4)	4 (2.3)	2 (1.2)

The next most common site of involvement was the respiratory tract. The distribution of Asthma AEs was similar to the distribution of adverse events leading to withdrawal. The next most common respiratory events were pharyngolaryngeal pain, cough, rhinitis, and nasal congestion. All were more common in the placebo subjects.

The incidence of nervous disorders, most of which were headaches, was similar across the treatment groups, but the incidence of nausea and vomiting was slightly higher in the subjects who received active treatment. Musculoskeletal problems were equally common across the treatment groups, but poisonings were slightly more common in the active treatment groups. Overall, only 3.4% of the events were considered severe with 3.4%, 4.0%, 1.7%, and 4.6% of the evens in the placebo C160, C80/160, and C80 groups, respectively reporting severe events.

Since oropharyngeal adverse events are known to be common during therapy with ICS, a grouping of pharyngolaryngeal pain, pharyngitis, and dysphonia was produced. One of these conditions was present in 10 (5.7%), 7 (4.0%), 7 (4.0%), and 10 (5.8%) of the placebo, cicles-

160, cicles-80/160, and cicles-80 subjects. Of note, no clinical evidence of oropharyngeal candidiasis was seen, although cultures were not performed routinely as part of the study.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths in this study. Serious adverse events were reported for 1 placebo, 2 each C160 and C80/160, and 3 of the C80 subjects. The placebo subject was withdrawn due to a serious asthma exacerbation and concurrent viral pneumonia (diagnosed on Chest X-ray). One C160 subject developed a staphylococcal infection in his leg and 1 developed renal colic. In neither subject was the study medication discontinued. One C80/160 subject developed cholangitis and the other pneumonia. The subject with pneumonia was withdrawn. One C80 subject was a 43 year old female with chest pain requiring prolonged hospitalization. Diagnostic work-up was negative and the subject remained in the study. The other C80 subjects with SAEs were a 71 year old female with pneumonia who was withdrawn and a 38 year old male who developed nephrolithiasis.

Withdrawal due to an adverse event occurred in 48 (6.9%) of the subjects overall. One (0.2%) had study medication temporarily interrupted, 306 (43.7%) received additional medication for an AE, and 29 (4.1%) received other interventions. Additional treatment was given in approximately the same proportions of subjects in all of the treatment groups, but other interventions were slightly more common in the C80/160 group (6.4% compared to 2.8, 4.5, and 2.9% of the placebo, C160, and C80 subjects, respectively). The adverse event leading to withdrawal was usually asthma and this occurred substantially more frequently in the placebo group than in the subjects receiving active treatment: 18 (10.1%), 9 (5.1%), 4 (2.3%), and 3 (1.7%) of the placebo, C160, C80/160, and C80 subjects, respectively. Because of the study design these rates are equivalent to the rate of asthma exacerbation that required treatment with additional corticosteroid. Thus the rate of asthma exacerbation in the placebo subjects was almost 6 times higher than the rate in the subject treated with 80 mcg ciclesonide twice daily. This rate was also 3 times higher in the subjects treated with 160 mcg once daily when compared to the twice daily (80 mcg) dosing regimen. Upper respiratory tract infection was the only other event that resulted in withdrawal of more than 1% of the subjects in any of the treatment groups (3 [1.7%], 0, 1 [.6%], and 0 of the placebo, C160, C80/160, and C80 subjects, respectively).

Other Events of Note

Eleven subjects had laboratory results reported as adverse events. All were considered mild or moderate and none resulted in withdrawal of the subject. See Laboratory results, below for details).

Ophthalmologic events were reported in 12 subjects: 4 events in 3 placebo subjects and 8 events in 7 ciclesonide subjects. The events included 1 cataract in a C160 subject as well as the following diagnoses: eye irritation, right transient visual scotomata, transient blurred vision, itchy eyes, astigmatism, left eye conjunctivitis, eye pain, bilateral ocular irritation, eye allergy, ocular itching, and allergy exacerbation. The subject with the cataract was a 59 year-old female with conjunctival irritation at baseline. By day 22 of the treatment protocol the eye symptoms

had improved. However, she had some remaining symptoms and was sent for an ophthalmologic examination. At that time (day 28) the ophthalmologist noted an anterior chamber cataract in the right eye. The subject's original eye complaints cleared up before the end of the study.

A significant overdose was defined as three or more times the morning or afternoon dose (6 puffs from either AM or PM inhaler). Two placebo and two C80 subject reported this complication. The two ciclesonide subjects had no adverse events. One placebo subject complained of rib pain 9 days before the overdose, and the other placebo patients was the 13 year-old who was withdrawn from the study due to an asthma attack. This subject was enrolled on November 21, 2005, he took 6 puffs of his PM inhaler on December 1, 2005 and reported an asthma exacerbation on January 15, 2006 (hospitalized January 17 with asthma and pneumonia).

1.2.3.3 Laboratory Results

The mean baseline and Week 16 values for all hematology and routine safety chemistry analyses were within the normal range.

For most of the hematology and chemistry examinations there were few individuals with shifts out of the normal range over the course of the study, and the distribution of these subjects was similar across the treatment groups. In the hematology set only 2 analytes showed changes in more than 5 subjects in a treatment group and more frequently with active treatment than with placebo. The leukocyte count went from normal at baseline to below the normal range in 2.9% of the ciclesonide-treated subjects compared to 1.3% of the placebo subjects. The absolute neutrophil count changed from normal at baseline to elevated at the end of the study in 2.2% of the ciclesonide-treated subjects compared to 1.9% of the placebo subjects.

In the chemistry set, glucose, cholesterol, total bilirubin, SGPT, and SGOT values showed changes from normal to abnormal in more than 5 subjects in at least one treatment group and showed more abnormalities in the actively treated subjects than the placebo subjects (Table 30) None of the differences was quantitatively large when comparing placebo to active treatment. There was, however, a surprising fall in cholesterol in 9.1% of the subjects treated with ciclesonide 160 mcg daily. This compared to a fall of 4.2%, 4.4%, and 5.7% in the placebo, C-80/160, and C-80 subjects respectively.

Table 30. Shift in Chemistry Values from Normal at Baseline to Abnormal at End-of-Study (Analytes) with >5 PCA Changes in any Treatment Group and a Larger Number Changes with Active Treatment.

	Placebo	Dose of Ciclesonide		
	---	160 QD	80 BID / 160 QD	80 BID
N	178	176	173	173
Below normal range, n(%)				
Glucose (random)	3 (1.8)	5 (3.1)	2 (1.3)	2 (1.3)
Cholesterol	7 (4.2)	15 (9.1)	7 (4.4)	9 (5.7)
Total bilirubin	6 (3.7)	7 (4.3)	6 (3.8)	3 (1.9)
Above normal range, n(%)				
Glucose (random)	7 (4.3)	9 (5.6)	10 (6.5)	7 (4.5)

Cholesterol	5 (3.0)	5 (3.0)	5 (3.1)	3 (1.9)
SGPT	6 (3.7)	6 (3.7)	3 (1.9)	9 (5.7)
SGOT	4 (2.5)	2 (1.3)	3 (2.0)	6 (4.0)

Laboratory values that reached the Predefined Change Abnormal (PCA) range were uncommon. Table 31 lists the number of subjects in each treatment group in which more abnormalities were seen in the actively treated subjects than placebo, and where at least 2 subjects showed the abnormality. In no case was there a dramatic difference between the placebo and actively treated subjects.

Table 31/. Number of Subjects with Laboratory Values with PCA Changes During Treatment

	Critera	Placebo	Dose of Ciclesonide		
	PCA Amount | direction	---	160 QD	80 BID / 160 QD	80 BID
N		178	176	173	173
Hematology					
Leukocytes	1 GI/L | ↓	2/158	1/152	3/151	2/144
Absolute eosinophils	0.37 GI/L | ↑	3/158	4/152	3/151	3/144
Erythrocytes	0.07 GI/L | ↓	0/158	1/152	2/151	1/144
Chemistry					
Glucose (random)	4.2 mmol/L | ↑	0/163	2/161	1/155	1/157
Total bilirubin	10 µmol/L | ↑	1/164	1/162	0/157	2/158

Seven subjects (5 with allergic rhinitis) had clinically significant abnormally high eosinophil counts at the end of the study (1.24, 1.05, 1.07 GI/L in a placebo, 1.35, 1.55, and 1.55 GI/L in the C160 subjects, and 1.37 GI/L in one C80 subject. Five subjects had high glucose values (16.0, 19.6, and 16.6 mmol/L in the C80/160 subjects and 13.3 and 14.2 mmol/L in the C80 subject. One C80 subject had SGOT and SGPT levels that were > 3 times the UNL.

Abnormal laboratory values were reported as adverse events for 2 placebo, 2 C160, 3 C80/160, and 4 C80 subjects. The placebo subject had an iron deficient anemia (Hgb 11.7G) and one had an eosinophil count that increased by 10 GI/L. The C160 subjects had an elevated random glucose of 183 mg/dL (normal 70-115 mg/dL) and an elevated potassium (5.6 mmol/L). In the C80/160 group, 1 subject had frank diabetes (glucose 353 mg/dL, 1 developed hypercholesterolemia(278 mg/dL) and one had in increase in blood creatinine from 1.0 to 1.3 mg/dL. In the C80 group, there was one each hematuria, hyperbilirubinemia, increased blood cholesterol and increased eosinophil count and 1 subject had hyperglycemia

1.2.3.4 Physical Examination including Vital Signs.

Overall, 6% subjects had shifts in the physical exam from normal to abnormal (7.9%, 5.7%, 6.9%, and 4.6% in the placebo, cicles-160, cicles-80/160, and cicles-80 subjects, respectively). None of the changes was assessed as clinically significant.

Mean values for baseline and Week 16 vital signs were comparable across the treatment groups. Changes during treatment were uncommon and clinically insignificant.

1.2.3.4 Pregnancy

Two placebo subjects became pregnant during the study and were withdrawn from treatment. One of the subjects had an elective abortion and the other pregnancy was ongoing as of the time of the study report.

1.3. Summary and Discussion

The primary usefulness of this study is as an aide in determining the appropriate dosing regimen for inhaled ciclesonide in the treatment of asthma. In the original NDA, the studies that used a BID dosing regimen showed efficacy, whereas the studies in which a once daily regimen was used did not show consistent effectiveness. It was, therefore, suggested that the appropriate dosing regimen for most patients with persistent asthma would employ a twice daily regimen. In Study 3031 once daily ciclesonide at 160 mcg per dose and twice daily ciclesonide at 80 mcg per dose was compared to placebo. A fourth arm (80 mcg BID for four weeks, followed by 160 mcg QD) was presumably employed to mirror the study conducted with Pulmicort Turbuhaler which demonstrated that some patients could be successfully treated with a once daily regimen of ICS once patients were stabilized on a twice-daily ICS regimen. While the original NDA tested total daily doses of 80, 160, 320, and 1280 mcg, only the 160 mcg total daily dose was included in Study 3031 for comparison of the two dosing regimens.

The efficacy results, both primary and secondary, show a consistent response in the actively treated subjects, however the response was substantially better in the C80, twice daily treated subjects, than in any of the other treatment groups. The results for treatment with C80/160 were almost identical to the results obtained with C160. For the primary outcome, the pre-dose FEV_1, improvement after treatment with C80/160 and C160 was statistically significantly better than the improvement after treatment with placebo. However, the increase in FEV_1 after treatment with C80 was almost double the increase after treatment with to the other two regimens. The changes in the secondary outcome variables were more similar across treatment groups, but in all of the analyses the subjects treated with ciclesonide twice daily fared better than those treated once daily. [redacted]
Treatment for 4 weeks with the total daily dose split into equal AM and PM doses did not render subsequent once daily dosing as effective as treatment with twice daily dosing.

Adverse events were mild, infrequent, and distributed similarly in all of the treatment groups. Past experience has indicated that ciclesonide has relatively low toxicity and no special studies were included in the study. Of note, subjects were withdrawn from the protocol if they suffered an exacerbation that required treatment with additional corticosteroids. This means that the rate of withdrawal due to "asthma" is equivalent to the rate of moderate-severe asthma exacerbation. If this outcome is thought of as an efficacy variable it also supported the effectiveness of twice daily dosing of ciclesonide. The rate of withdrawal due to asthma was only 1.7% in the subjects treated with ciclesonide 80 mcg BID while withdrawal for this adverse event was three times

higher in the subjects treated with ciclesonide 160 mcg QD and 5 times higher in the placebo group.

2 Study # XRP1526B/3030

A multinational, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of ciclesonide metered-dose inhaler at a daily dose of 160 µg administered for 12 weeks either in a once-daily in the morning (160 µg QD. AM) for 12 weeks or in a twice daily regimen (80 µg BID) for 12 weeks, in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled corticosteroids

2.1 Protocol

2.1.1 Administrative

Enrollment Dates:	July 15, 2005 – February 3, 2005
Screening Centers:	38 centers in the United States
Coordinating Investigator:	
Sponsor's medical expert:	
CRO:	

2.1.2. Objective/Rationale

The primary objective of the study was to investigate the efficacy, compared to placebo MDI, of ciclesonide MDI at a daily dose of 160 µg administered either in a 160 µg QD AM or an 80 µg BID regimen for 12 weeks, in adults and adolescents with mild to moderate persistent asthma treated previously with ICS.

The secondary objective of the study was to investigate the safety, compared to placebo MDI, of the two ciclesonide regimens administered for 12 weeks, in adults and adolescents with mild to moderate persistent asthma treated previously with ICS.

2.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group study in patients ≥12 years of age with mild to moderate persistent asthma treated previously with ICS. Eligible subjects were enrolled into a 7 to 14-day run in period at which time they were treated with their maintenance ICS and a single-blind MDI placebo BID. They also recorded their symptoms in a diary. At the end of the run-in subjects stopped their maintenance ICS and were randomized (1:1:1) to receive placebo, ciclesonide 160 mcg QD, or ciclesonide 80 mcg BID for 12 weeks. Placebo inhalers were provided so that all the subjects received BID dosing.

The subjects were seen in the clinic at screening, randomization and at 1, 2, 3, 4, 6, 8, and 12 weeks after randomization. The AM-FEV_1 (after 6 hours without albuterol and prior to study drug) was performed at all clinic visits. The primary efficacy outcome was the change in AM-FEV_1 comparing baseline (Week 0) to the Week 12 value. For subjects who discontinued the study, the last available measurement was used.

1.1.3.2 Protocol Amendments

Protocol Amendment 1 (March 2, 2005) stipulated that the number of clinical centers would be reduced from 75 to 38. It also changed the primary efficacy variable from the change in FEV_1 comparing baseline to the average of the Week 8 and Week 12 value to a comparison of baseline to the Week 12 value.

2.1.4. Study Population

Inclusion Criteria

- Males or females ≥12 years of age
- History of persistent bronchial asthma for at least 6 months prior to screening
- Asthma therapy must include ICS (monotherapy or combined with LABA) for at least 1 month prior to screening
    - Monotherapy limited to ≤ 440 mcg/day fluticasone or equivalent
    - ICS/LABA limited to ≤ 220/100 mcg/day Advair or equivalent
- At screening and immediately prior to randomization, after an albuterol withhold of at least 6 hours, FEV_1 of ≥60% and ≤90% of predicted normal if previously treated with ICS monotherapy and an FEV_1 of ≥70% and ≤95% of predicted if treated with ICS and a LABA
- At screening or immediately prior to randomization, reversibility of FEV_1 by at least 12% (relative to the pre-bronchodilator value in liters [L]) after inhalation of 180 µg albuterol (ex-actuator)
- FEV_1 at randomization within 15% of the FEV_1 value (in L) at screening
- Non-smoker for at least 6 months prior to screening, with less than a 10 pack-year smoking history if previous smoker
- Able to demonstrate acceptable oral inhaler technique with MDI
- Written informed consent at enrollment into the study

Exclusion Criteria

- Lack of stability in asthma control over the 7 days prior to randomization as evidenced by any of the following:
    - Nighttime awakenings due to asthma and treated with albuterol on ≥ 3 nights
    - Use of ≥ 8 puffs/day albuterol on 4 or more days
- Any use of injectable or oral corticosteroids within 1 month of screening or more than 3 bursts within 6 months prior to screening

- Use of β_2-adrenergic blocking agents for any reason
- Upper or lower respiratory tract infection within 30 days prior to screening
- History of chronic bronchitis, chronic obstructive pulmonary disease, or emphysema
- History of life-threatening asthma, including a history of significant hypercarbia (pCO_2 >45 mmHg), prior intubation, respiratory arrest, or seizures as a result of an exacerbation of asthma
- More than 2 in-patient hospitalization or emergency care visits due to asthma exacerbations in the year prior to screening
- Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change in their immunotherapy regimen within 30 days prior to screening
- Other exclusion criteria as enumerated in review of Study 3031 (Section 1.1.4 , pg)

Withdrawal Criteria

- The subject was instructed to contact the investigator if they felt their asthma was not under good control. The investigator was to consider withdrawing the subject if any of the following occurred:
    - Decrease in FEV_1 of ≥20% compared to baseline
    - Nocturnal awakenings due to asthma requiring treatment with albuterol on 3 or more nights during any 7-consecutive-day period
    - Use of 8 or more puffs per day of albuterol on 4 or more days during any 7-consecutive-day period
    - Decrease in AM PEF to <80% of baseline value on 4 or more days (baseline value determined as the average value on the last 7 days with non-missing measurements prior to Visit 3)
    - If a prohibited medication was prescribed the subject had to be withdrawn
- At their own request
- In the investigators opinion continued participation in the study would be detrimental to the subject
- In the event of a protocol deviation at the discretion of the Investigator or the Sponsor

2.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Placebo MDI BID (2 puffs placebo BID)
- Ciclesonide MDI 160 mcg QD (2 puffs 80 mcg in AM and 2 puffs placebo in PM)
- Ciclesonide 80 mcg BID (2 puffs 40 mcg BID)

HFA albuterol (100 µg per actuation [90 µg ex-actuator] was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Antihistamines
- H2 blockers
- Nasal anti-cholinergic agents
- Nasal corticosteroids
- Nasal or ophthalmologic preparations of nedocromil
- Maintenance immunotherapy

The following concomitant medications were prohibited from screening onward:

- Ocular steroids
- Any ICS or ICS/LABA combination other than the study medication provided after Visit 3 (randomization)
- Systemic corticosteroids (oral or injectable)
- Short-acting β_2-agonists other than the albuterol
- Long-acting β_2-agonists (LABAs)
- Ipratropium bromide or other inhaled anti-cholinergic agents (tiotropium, Combivent®)
- Methylxanthines (theophylline, aminophyllines)
- Leukotriene receptor antagonists or leukotriene synthesis inhibitors
- Lipoxygenase inhibitors
- Cromones
- Anti-immunoglobulin E therapy (Xolair®)

Compliance was assessed by the patient's notation in the diary that the medication was taken. Poor compliance was defined as <70% of the expected actuations.

Efficacy Evaluation

The primary efficacy evaluation was made on the basis of changes in FEV_1. Spirometry was performed according to ATS standards in the morning between 6 and 10 AM and was supposed to have been performed within 1 hour of the screening test. The FEV_1 was determined prior to the AM dosing with study medication and at least 6 hours after the last albuterol. Reversibility was assessed 20 minutes after inhalation of 180 mcg albuterol and was calculated as the difference between actual baseline FEV_1 and post albuterol value.

The subjects were provided with a [redacted] PEF meter and were instructed in its use. They were instructed to make the measurement within 15 minutes of rising, prior to the morning dose of study medication and in the afternoon before the afternoon dose of medication. Three attempts were recorded and the highest value was used in the analysis. Patients were instructed to try and withhold albuterol for 6 hours prior to the measurements

At the screening visit the subjects were issued a diary card. The cards were used twice daily to record the number of albuterol inhalations (puffs/day), the Asthma Symptom Score, the number

of nocturnal awakenings, and the dose of medication taken. The Asthma Symptom Scores were graded according to the following scale:

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 that interfered with daily activities or sleep
3 = Frequent or continuous wheezing, cough, or shortness of breath that interfered with daily activities or sleep
4 = Symptoms that prevented the patient from engaging in daily activities or sleep

The number of puffs of albuterol and number of nighttime awakenings were also recorded in the diary.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. In addition, any ophthalmologic finding which met the definition of an AE, whether severe or not, was reported as an Alert Term. These events were reviewed by the Applicant's pharmacovigilance group prior to unblinding the database. Standard hematology and urinalysis examinations were also performed at baseline and at the end of treatment. Mean values were calculated and subjects with values that were above normal were tabulated. Safety hematology and chemistry blood tests were performed at baseline and at the end of treatment. A Predefined Change Abnormal (PCA) value was determined for glucose and absolute eosinophil counts. Based on the laboratory normal values, changes from baseline and/or a change to a specific high value, clinically meaningful values were also identified. A summary of the study procedures is shown in Table 32.

Table 32, Summary of Events

Study Day	PreScreen	Screen	Random	Treatment Period			
Visit number	1	2	3	4, 5, 6, 7	8	9	10
Week	-1 (-2 days)	-1	0	1, 2, 3, 4	6	8	12
Informed consent	X						
Randomization			X				
Medical history		X					
Physical examination		X					X
Review medication		X	X	X	X	X	X
Vital signs		X					X
Spirometry		X	X	X	X	X	X
Reversibility		X	X				
Laboratory tests		X					X
Pregnancy tests*		X					
Issue PEF meter & Review results		X	X	X	X	X	X
Issue & Review Diary		X	X	X	X	X	X
Adverse event review		X	X	X	X	X	X

Study Day	PreScreen	Screen	Random	Treatment Period			
Visit number	1	2	3	4, 5, 6, 7	8	9	10
Week	-1 (-2 days)	-1	0	1, 2, 3, 4	6	8	12
Dispense appropriate medications			X	X	X	X	X

2.1.6. Statistical Analysis Plan

Sample Size

Sample size parameters were chosen from the results of studies 321 and 322 which compared once daily dosing of ciclesonide to placebo. In those studies the difference from placebo at the end of the treatment period in subjects previously treated with corticosteroids was approximately 0.17 L and the standard deviation was 0.45 L. If these results can be used to predict the results of the current study, then 149 subjects per treatment group would provide 90% power to detect a difference between placebo and active treatment of 0.17 L

Study Populations

The ITT population included all randomized subjects who received medication and who had at least 1 post treatment FEV_1 measurement.

The per-protocol (PP) population consisted of all the subjects in the ITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind. The list of major protocol violation includes the following events:

- FEV_1 at baseline >90% of predicted normal
- AM PEF at baseline >95% of predicted normal
- Reversibility of FEV_1 <12% or <200 mL before randomization
- Current smoker
- Concomitant treatment with any LABA
- Concomitant use of leukotriene receptor antagonists
- Use of inhaled, injectable, or oral corticosteroids within 4 days prior to the baseline visit (Visit 3)
- History of asthma within 3 months prior to entry to study
- Patient was discontinued less than 7 days after randomization
- Poor compliance with study medication (less than 70% of expected actuations)
- Received study medication different to which they were randomized to by IVRS

Reviewer: It is not clear why "History of asthma within 3 months prior to entry to study" would be seen as a protocol violation. However, this is not an important question because the criteria was not applied to any of the subjects in this study.

Primary Analysis

The primary efficacy variable was the change in FEV_1 (L) from baseline (Day 1) to the end of study (Week 12 [Visit 10]). For subjects who discontinued before Week 12 the last measurement obtained prior to withdrawal was used. The primary analysis was performed on the ITT population and used an analysis of covariance (ANCOVA) of the change from baseline to the Week 12 FEV_1 measurements with factors for treatment pooled center, and gender. Baseline FEV_1 and age were included in the models as covariates. The type I error was controlled with the following stepwise procedure:

- Step I: An ANCOVA model was used that compared all of the treatment groups. If the overall treatment effect was significant at the $\alpha = 0.05$ level there was no need to adjust the level of significance for pairwise testing

- Step II: Ciclesonide MDI 80 µg BID and ciclesonide 160 QD were compared to placebo MDI at $\alpha = 0.05$ (2-sided). If either test showed a significant improvement with active treatment, then that active treatment was declared successful

Supportive analyses were performed using the PP population, and a further analysis was performed comparing baseline to the Week 8 value.

Other Efficacy Evaluations

Key secondary efficacy outcomes included the following:

- AM PEF (L/min) comparing baseline to Week 12 or early termination visit
- Daily albuterol use (puffs/day) comparing baseline to Week 12 or early termination visit
- Asthma Symptom Score (sum of AM and PM scores) comparing baseline to Week 12 or early termination visit

Additional efficacy outcomes include the following:

- Rate and time to withdrawal due to worsening of asthma or lack of efficacy
- Rate and time to withdrawal due to all causes
- Change from baseline in FEV_1 (L) to each time point
- Change from baseline in FEV_1 percent predicted at each time point
- Percent change from baseline in FEV_1 at each time point
- Change from baseline in forced vital capacity (FVC, in L) and forced mid-expiratory flow ($FEF_{25-75\%}$ in L/s) to Week 12 (in addition, summary by visits)
- AM PEF, weekly average change from baseline
- Daily albuterol use, weekly average change from baseline
- Total daily asthma symptom score, weekly average change from baseline
- PM PEF, change from baseline to Week 12 (or early termination), and weekly average change from baseline
- Nighttime awakenings due to asthma requiring treatment with albuterol, change from baseline to Week 12 (or early termination)

The following asthma diary variables were assessed based on the entire 12-week period:

- Percentage of symptom-free days: Both AM and PM symptom score must = 0, and at least one of the scores had to be recorded for the day to be included in the analysis.
- Percentage of nights with nighttime awakenings: Any night with at least one awakening was divided by the number of valid treatment days
- Percentage of asthma-controlled days: A day when the asthma symptom score=0, no albuterol was used, and there were no nighttime awakenings

Other Data Management Issues

The baseline values for the pulmonary function measurements was the pre-bronchodilator value recorded on Day 1 (Week 0) prior to administration of the first dose of study medication. For the diary data, the baseline was calculated as the average of the values recorded or the 7 days prior to the randomization visit. If there was missing data, values obtained up to 14 days prior to randomization could be used. However, if less than 5 values were obtained prior to randomization the baseline was set to missing.

2.2. Results

2.2.1. Study Population

Disposition

A total of 850 subjects were screened and 394 failed, resulting in randomization of 456 subjects. All 456 subjects received treatment and were included in the safety population. Ten of the treated subjects had no post treatment FEV_1 measurement and were excluded from the ITT population, resulting in an ITT population of 446.

Of the 456 subjects who were randomized, 372 (81.6%) completed the course of treatment. Withdrawal was highest in the placebo-treated subjects (32.2%) compared with 11.8%, and 11.2% in the ciclesonide 160 QD (C160), and ciclesonide 80 BID (C80) subjects, respectively (Table 33). Adverse reactions were the most common indication for withdrawal and the distribution was similar to the distribution of overall withdrawals (15.1, 4.6, and 5.3% in the placebo, C160, and C80 subjects, respectively). Lack of efficacy was reported as a reason for withdrawal in 4.8% of the subjects and the incidence was highest in the placebo subjects. Other reasons for discontinuation were reported infrequently: 2.9% were withdrawn due to a protocol violation, and 1.3% did not wish to continue, and lost to follow-up and "other" in less than 1% of the subjects, each. There were no deaths.

Table 33. Disposition of Subjects in Study 3030

	Placebo	Dose of Ciclesonide		Overall
	---	160 QD	80 BID	
Randomized	152	152	152	456
Treated	152	152	173 (97.7)	372 (81.6)
Discontinued	49 (32.2)	18 (11.8)	17 (11.2)	84 (18.4)
Reason for discontinuation:				
Adverse event	25 (15.1)	7 (4.6)	8 (5.3)	38 (8.3)
Lack of efficacy	14 (9.2)	5 (3.3)	3 (2.0)	22 (4.8)
Did not wish to continue	4 (2.6)	1 (0.7)	2 (0.7)	6 (1.3)
Lost to follow-up	1 (0.7)	0	0	1 (0.2)
Protocol violation	4 (2.6)	5 (3.3)	4 (2.6)	13 (2.9)
Death	0	0	0	0
Other	3 (2.0)	0	1 (0.7)	4 (0.9)

Of the 456 subjects randomized, there were only 14 reported protocol violations, and 13 of the 14 resulted in withdrawal. Of the 4 subjects withdrawn due to protocol violations in the placebo group, 2 took disallowed medications, 1 subject took twice the number of puffs/day of study medication than stipulated in the protocol, and one subject was randomized in error. Of the 5, C160 subjects withdrawn due to violations, 2 took a higher dose of fluticasone/salmeterol prior to enrollment than allowed in the protocol, 1 had < 12% reversibility, 1 had baseline FEV_1% predicted calculated incorrectly, and 1 subject took twice the prescribed dose of study medication at the site coordinators instructions. Of the 4, C80 subjects, 2 took a higher dose of fluticasone/salmeterol prior to enrollment than allowed in the protocol, 1 had an FEV_1 of 100% at baseline, and 1 took prohibited medication.

Reviewer: Six additional subjects are listed with major protocol violations in post-text Listing in Appendix 14.2.1, pg 1599). Of these, 4 were withdrawn for other indications (2 had adverse events, and 2 showed lack of efficacy), and 2 remained in the study. The protocol violation for these last two was lack of reversibility. These extra cases result in a final sum of 8, 7, and 5 total protocol violations in the placebo, C160 and C80 subjects. If the subjects who were removed from the ITT population are also removed from this tally, then 7, 5, and 1 subject in the ITT population (analysis) had protocol violations. Note that this sum is still very low (20 protocol violations in 456 subjects followed for three months) and that only one was considered minor, suggesting that the study report does not include all of the violations. Note, also, that Text Table 6 indicated that subject 0068/0001 was discontinued from study medication due to a protocol violation. However, on the next page (Section 7.2.4) Subject 0068/0001 is said to have had only a minor violation and he was kept in the study. According to both text Table 6 and the effp.xpt data set, he was treated for 14 days and the last FEV_1 was obtained 15 days after starting double-blind medication. This may mean that the subject had two violations, one of which was minor and the other major, requiring withdrawal.

A total of 10 (2.2%) of the randomized subjects were excluded from the ITT population. In all cases the subjects were withdrawn early and had no post-treatment FEV_1. This included 6 subjects removed for protocol violations, 2 for lack of efficacy, 1 for an AE, and 1 for

administrative reasons. The subjects withdrawn for lack of efficacy and the adverse event were all treated with placebo.

Eight (1.8%) of the subjects were excluded from the PP population: 5 in the placebo group and 3 in the C160 group.

Demographics

Of the 446 subjects in the ITT population 37.7% were male, the mean age (Range) was 37.7 (12 - 79) years, and 50 (11.2%) were less than 18 years old. The predominant racial group was white (75.7% compared with 5.8% black and 8.5% other). All of the characteristics were approximately evenly distributed across the treatment groups (Table 34), although the mean age was slightly higher (41.3 years) in the C160 subjects than in the other groups (37.7 years for the overall mean).

Table 34. Demographic Characteristics of the ITT Population

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID	Overall
Total ITT Population	147	150	149	446
Gender, %M	(36.1)	(38.7)	(38.3)	(37.7)
Age, mean(SD)	38.9 (15.4)	41.3 (14.9)	37.6 (15.2)sum	39.3 (15.2)
Age 11 - <18, N	16	14	20	50
Race				
White	80.3	88.0	88.6	85.7
Black	9.5	4.7	3.4	5.8
Other	10.2	7.3	8.1	8.5

The mean (SD) duration of asthma was 21.7 (13.8) years (Table 35). The mean (SD) pre-bronchodilator was 2.65 (0.65) L and the mean (SD) FEV_1 percent predicted was 79.2 (8.3) percent. More subjects took ICS monotherapy (261) than combination ICS/LABA therapy (185) prior to enrollment and, as specified in the protocol, the function was slightly better in those who had been treated previously with combination ICS/LABA therapy (mean FEV_1 = 82.6% predicted compared to 76.9% predicted in the monotherapy group). Pulmonary function was stable during the last half of the single-blind run-in as evidenced by a change in FEV_1 between the mid-run-in and randomization visit of -0.42 %. However, there was some variability in this parameter among the treatment groups. The mean fell in the placebo subjects by 0.54% while it increased in the C160 subjects by 1.1%. Reversibility was reported as >12% in all but 1 placebo and 1 C160 subject and >200 mL in all the subjects.

Table 35. Characteristics of Asthma – ITT Population

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID	Overall
Total	147	150	149	446
Duration				
Years, mean (SD)	22.5 (14.8)	21.7 (13.9)	20.7 (12.7)	21.7 (13.8)
Range	1.1 – 64.1	1.1 – 65.1	1.0 – 56.1	1.0 – 65.1
FEV_1 (all subjects)				
Mean Absolute, ml (SD)	2.63 (0.69)	2.63 (0.62)	2.67 (0.63)	2.65 (0.65)

Mean % predicted, % (SD)	78.8 (8.8)	79.1 (8.1)	79.6 (8.2)	79.2 (8.3)
FEV_1 (Prior ICS monotherapy)				
N	86	84	91	261
Mean % predicted, % (SD)	75.9 (8.8)	76.8 (8.5)	77.3 (7.9)	76.7 (8.4)
Range	60 – 90	54 - 90	62 - 90	54 – 90
FEV_1 (Prior ICS/LABA therapy)				
N	61	66	58	185
Mean % predicted, % (SD)	82.8 (7.1)	81.9 (6.5)	83.2 (7.4)	82.6 (7.0)
Range	70 – 95	70 – 95	70 – 95	70 – 95
Change FEV_1 During Screening				
Mean % (SD)	-0.54 (6.8)	1.19 (6.5)	0.58 (6.4)	0.42 (6.6)
AM PEF, L/min (SD)	379 (92)	393 (94)	386 (89)	386 (91)
Total Asthma Symptom Score	1.4 (1.1)	1.4 (1.3)	1.3 (1.3)	1.4 (1.3)
Albuterol Use, puffs (SD)	1.30 (1.6)	1.19 (1.4)	1.18 (1.5)	1.22 (1.5)
Nighttime Awakenings, mean (SD)	0.06 (0.2)	0.06 (0.2)	0.05 (0.1)	0.06 (0.1)

The mean (SD) Asthma Symptom Score was 1.4, albuterol use was 1.22 (1.5) puffs/day, and the mean (SD) nighttime awakenings was 0.06 (0.1) awakenings per night. The Asthma Symptom Scores, albuterol use, and nighttime awakenings were very similar across the treatment groups. The slightly lower PEF in the placebo group is probably insignificant given the similarity in the FEV_1 and FEV_1% predicted values.

Reviewer: Compared to study 3031, the subjects are the same age, there are fewer men, and the duration of asthma is longer. The longer duration would be expected in a population being treated with maintenance ICS. They were well controlled and stable as evidenced by the low symptom scores, albuterol use, and nighttime awakenings. The mean symptom scores and albuterol use were substantially better in the ICS treated subjects than in the subjects not previously treated with ICS.

Data for reversibility was submitted in dataset 3030revtst.xpt, submitted on 10/31/07. Most of the subjects (62.5%) had reversibility determined from historical data and 37.5 had pre and post-albuterol determinations at the time of enrollment. Mean (range) reversibility was 22.1 % (12 – 99%) for the subjects with historical determinations and 18.7% (11 – 66%) in the subjects with measurements made for the study. These percentages were similar across the treatment groups.

The changes in FEV_1 between Visit 2 and 3 were very small and clinically insignificant. However, the difference in direction, while the subjects were all continuing their maintenance ICS, may suggest a differential requirement for corticosteroid therapy or a difference in compliance that was not detected in the diaries.

Prior and Concomitant medications

Prior to enrollment, short acting bronchodilators were taken by 99.6% of the subjects. ICS, alone, were taken by 61% and a combination ICS/LABA was taken by 42.1% of the subjects within 6 months of enrollment. The distribution of ICS and ICS/LABA use was similar across the treatment groups. Within 30 days of screening 58.8% of the subjects received ICS alone and

40.8% received a combination product. Oral/injectable CS were taken by only 2 placebo, 3 C160, and 2 C80 subjects within 6 months of screening.

During the 12-week randomized treatment period, ingestion of CS other than study medication was unusual. Eight (5.3%), 3 (2.0%), and 1 (0.7%) of the placebo, C160, and C80 subjects, respectively, received and ICS other than ciclesonide during treatment.

2.2.2. Efficacy Results

Primary Efficacy Outcome

Over the 12-week treatment period the FEV_1 fell in the placebo subjects by 0.12L while it remained unchanged in the C160 group (increase 0.01 L) and increased slightly in the C80 group (0.07 L). The test for overall treatment effect was highly significant ($p < 0.0001$), and both doses of ciclesonide were effective (Table 36). The LS mean difference from placebo treatment was 0.14 and 0.19 L in the C160 and C80 subjects, respectively. There was little difference between treatment with C160 and C80 in this patient population.

Table 36. Change in FEV_1 after Treatment with Ciclesonide

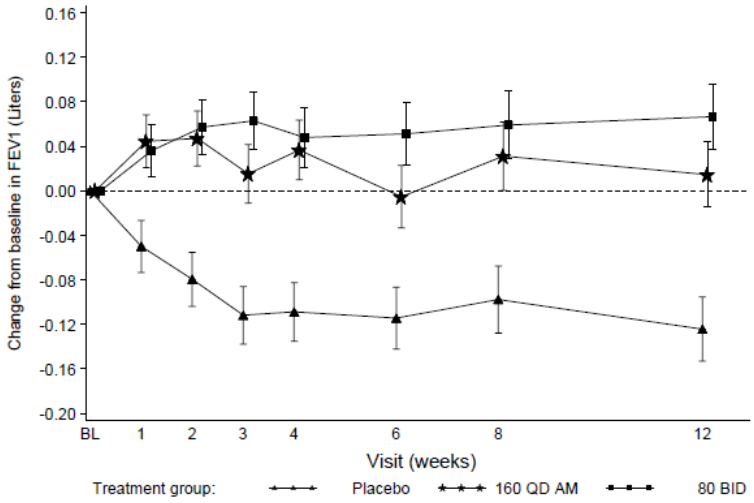
		Dose of Ciclesonide	
Fev_1	Placebo	160 QD	80 BID
N	147	150	149
Baseline, mean L	2.63	2.64	2.67
Change from baseline			
LS mean, L	-0.12	0.01	0.07
95% CI	-0.18, -0.07	-0.04, 0.07	0.01, 0.12
Difference from placebo			
LS mean, L		0.14	0.19
95% CI		0.06, 0.22	0.11, 0.27
p- value		0.0006	<0.001
Difference from cicles-80*			
LS mean, L		0.05	
95% CI		-0.03, 0.13	
p-value		0.005	

***** Taken from post-text Table – 23 in Appendix 12.3.6

The percent change in FEV_1 was -5.2, 2.6, and 2.7% with placebo C160, and C80 treatment, respectively (Post-text Table T-33, pg 1819).

The changes in absolute FEV1 are shown graphically in Figure 5.

Figure 5. Change in FEV_1 During Treatment with Ciclesonide



The various supportive analyses confirmed the results of the primary analysis. If the analysis was performed on the average of the Week 8 and Week 12 values instead of on the Week 12 values alone, the results are essentially identical. The per-protocol analysis was also almost identical to the ITT analysis. The change from baseline in FEV_1 was -0.13 in the 142 placebo subjects, 0.01 in the 147 C160 subjects, and 0.07 in the 149 C80 subjects.

There were no important subgroup interactions.

Secondary Efficacy Outcome Measures

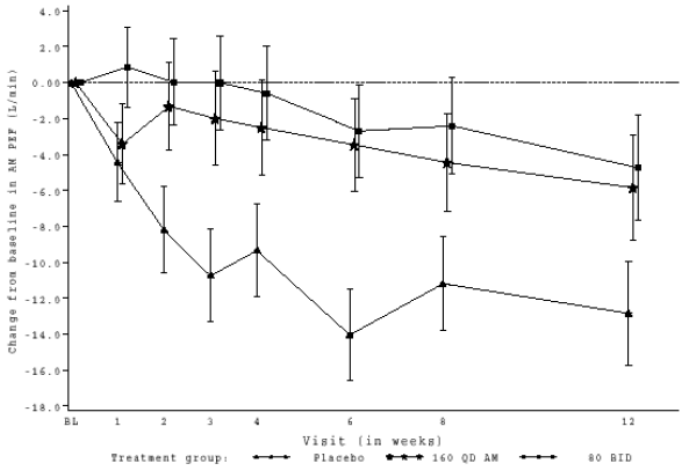
The diary-recorded AM PEF decreased in all of the treatment groups: 12.8, 5.8, and 4.4 L/min in the placebo C160 and C80 groups, respectively (Table 37). The difference between C160 and placebo was not statistically significant (p = 0.08).

Table 37. Change in AM Peak Flow

		Dose of Ciclesonide	
AM PEF	Placebo	160 QD	80 BID
N	147	150	149
Baseline, mean L/min	379	393	386
Change from baseline LS mean, L/min 95% CI	 -12.8 -18.5, -7.2	 -5.8 -11.5, -0.03	 -4.4 -10.1, 1.3
Difference from placebo LS mean, L/min 95% CI		 7.1 -0.8, 14.9	 8.4 0.60, 16.2

The changes are shown graphically in Figure 6.

Figure 6 . Change in AM PEF During Treatment with Ciclesonide



Albuterol use increased in all of the treatment groups (Table 38), although the increase was not significant during ciclesonide treatment. Both active treatment groups increased the use of albuterol less than the placebo subjects.

Table 38. Albuterol use During Treatment with Ciclesonide

		Dose of Ciclesonide	
	Placebo	160 QD	80 BID
N	147	150	149
Baseline, puffs / day	1.30	1.19	1.18
Change from baseline LS mean, puffs / day 95% CI	 0.67 0.45, 0.90	 0.08 -0.15, 0.30	 0.04 -0.19 0.26
Difference from placebo LS mean, puffs / day 95% CI		 -0.60 -0.91, -0.28	 -0.64 -0.95, -0.33

The Asthma Symptom Scores increased in the placebo subjects and decreased in the active treatment groups (Table 39). Improvement was similar in the C160 and C80 subjects.

Table 39. Asthma Symptom Score

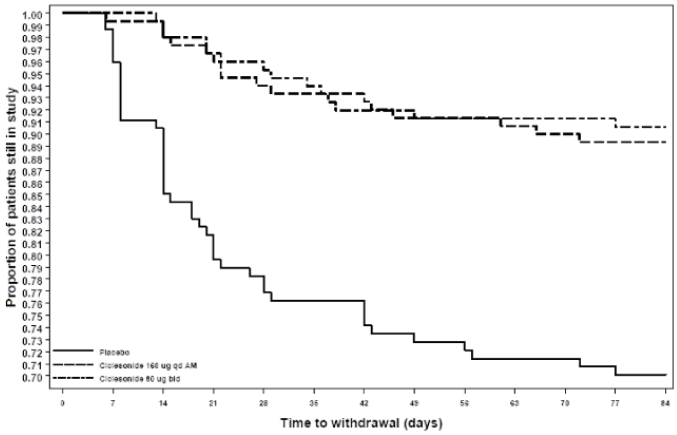
		Dose of Ciclesonide	
	Placebo	160 QD	80 BID
N	147	150	149
Baseline,	1.40	1.37	1.32
Change from baseline LS mean 95% CI	 0.33 0.17, 0.49	 -0.05 -0.21, 0.11	 -0.05 -0.21, 0.12
Difference from placebo			

LS mean 95% CI		-0.38 -0.60, -0.15	-0.37 -0.60, -0.15

Other Efficacy Variables

Both the rate of withdrawal for any cause and withdrawal for efficacy was substantially higher in the placebo subjects than in the active treatment groups (44 [29.9%], 16 [10.7%], and 14 [9.4%] in the placebo, C160, and C80 subjects, respectively for overall withdrawal). Withdrawal due to an exacerbation or lack of efficacy occurred in 32 (21.8%), 8 (5.3%), and 6 (4.0%) of the placebo, C160, and C80 subjects, respectively. Withdrawal is depicted graphically in Figure 7.

Figure 7. All-cause Withdrawal Rate



The PM PEF decreased in all of the treatment groups, but the decrease was greater in the placebo subjects than in those who received active treatment. The difference between active treatment and placebo was 9.7 and 8.7 L/min in the C160 and C80 subjects, respectively. Nighttime awakenings increased in all of the treatment groups. The difference from placebo was -0.07 and -0.8 in the C160 and C80 subjects, respectively. Asthma control improved with active treatment. The percentage of controlled days was 27.6, 32.4., and 36.9 percent and the percentage of symptoms-free days was 32.3, 37.8, and 44.4% in the placebo, C160, and C80 groups, respectively.

2.2.3. Safety

2.2.3.1 Exposure

Corresponding to the higher rate of withdrawal, the exposure to study medication was lower in the placebo than the active treatment groups. The mean (SD) number of days was 63.5 (31.1), 77.2 (19.0), and 77.1 (19.4) days in the placebo, C160, and C80 groups, respectively. Median exposure was 83 or 84 days, with a range of 2 – 101. Eighty percent of the actively treated subjects received at least 8 weeks of treatment compared to 70% of the placebo subjects.

2.2.3.5 Adverse Events

Overall Assessment of Adverse Events

The overall incidence of AEs was similar across the treatment groups (55.3, 57.9, 52.0% in the placebo, C160, and C80 groups, respectively). The incidence of serious AEs was low and the incidence of AEs leading to withdrawal was substantially higher in the placebo subjects than in those treated with ciclesonide (Table 40). There were no deaths.

Table 40 Overall Summary of Adverse Events.

		Dose of Ciclesonide		
	Placebo	160 QD	80 BID	Total
N	152	152	152	304
All AEs	84 (55.3)	88 (57.9)	79 (52.0)	167 (54.9)
Serious AEs	1 (0.7)	0	3 (2.0)	3 (1.0)
AEs leading to withdrawal	24 (15.8)	7 (4.6)	8 (5.3)	15 (4.9)
Deaths	0	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system. These complaints were more common in the C160 group than in the other treatment groups: 34.2% of the C160 subjects had an infectious AE compared to 27.6% of the placebo and 25.0% of the C80 subjects (Table 41). The incidence of nasopharyngitis was higher in both active treatment groups (12.5 and 9.2% in the C160 and C80 groups compared to 5.9% in the placebo group) and upper respiratory tract infection was slightly higher in the C80 group (9.2% compared with 7.9% in both of the other treatment groups. Gastroenteritis and sinusitis were also slightly more common in the C160 group.

Table 41. AEs Occurring in 3% or more subjects in any treatment group, by system organ class and Selected preferred terms

	Placebo	Dose of Ciclesonide		
SOC and Preferred Term	---	160 QD	80 BID /	Overall
N	152	152	152	304
All AEs	84 (55.3)	88 (57.9)	79 (52.0)	167 (54.9)
Infections and infestations	42 (27.6)	52 (34.2)	38 (25.0)	90 (29.6)
Nasopharyngitis	9 (5.9)	19 (12.5)	14 (9.2)	33 (10.9)
Upper Respiratory Tract Infection	12 (7.9)	12 (7.9)	14 (9.2)	26 (8.6)
Influenza	1(0.7)	3 (2.0)	1 (0.7)	4 (1.3)
Sinusitis	7 (4.6)	9 (5.9)	5 (3.3)	14 (4.6)
Gastroenteritis	2 (1.3)	6 (3.9)	1 (0.7)	7 (2.3)
Herpes simplex	3 (2.0)	1 (0.7)	2 (1.3)	3 (1.0)
Respiratory, thoracic, and mediastinal	40 (26.3)	26 (17.1)	20 (13.2)	46 (15.1)
Asthma	27 (17.8)	7 (4.6)	5 (3.3)	12 (3.9)
Pharyngolaryngeal pain	5 (3.3)	8 (5.3)	9 (5.9)	17 (5.6)
Cough	3 (2.0)	8 (5.3)	3 (2.0)	11 (3.6)
Nasal Congestion	0	2 (1.3)	4 (2.6)	2 (1.2)
Pulmonary congestion	0	3 (2.0)	1 (0.7)	4 (1.3)
Nervous system disorders	9 (5.9)	13 (8.6)	8 (5.3)	21 (6.9)
Headache	6 (3.9)	6 (3.9)	6 (3.9)	12 (3.9)
Gastrointestinal disorders	11 (7.2)	12 (7.9)	9 (5.9)	21 (6.9)
Toothache	2 (1.3)	5 (3.3)	0	5 (1.6)

Musculoskelatal disorders	6 (3.9)	4 (2.6)	5 (3.3)	9 (3.0)
Injury, poisonings and procedures	12 (7.9)	8 (5.3)	9 (5.9)	17 (5.6)
Skin and Subcutaneous tissue	4 (2.6)	6 (3.9)	3 (2.0)	9 (3.0)
Investigations FEV decreased	4 (2.6) 3 (2.0)	3 (2.0) 2 (1.3)	5 (3.3) 0	8 (2.6) 2 (0.7)
Psychiatric disorders	1 (0.7)	2 (1.3)	4 (2.6)	6 (2.0)
Immune system disorders	4 (2.6)	3 (2.0)	1 (0.7)	4 (1.3)

The next most common site of involvement was the respiratory tract. Asthma was the most common event reported and was actually the most common preferred term reported(Table). Asthma was substantially more common in the placebo subjects (17.8%) than in the active treatment groups (4.6 and 3.3% in the C160 and C80 groups, respectively). Since control of asthma was the objective of the treatment, counting asthma as an adverse event artificially improves the risk/benefit ratio. If all adverse events are tallied omitting asthma the result is a higher overall incidence of adverse events in the active treatment groups: 57 (37.5%), 81 (53.3%), and 7 (48.7%) in the placebo C160, and C80 subjects, respectively). If a systematic search were made for events that were probably associated with an asthma attack (e.g. decreased FEV_1) the discrepancy would have been even larger. All of the other events, including cough were most frequent in the C160 subjects.

The AEs of decrease in FEV_1 were tallied separately. Three placebo and two C160 subjects had decreases in FEV_1 of 0.21 to 0.86 L (9 – 19%). The events occurred on day 8 to 43. They were all described as moderate in intensity and none of the subjects was withdrawn from the protocol. The subjects are not described as having an asthma attack and no further explanation was provided.

The incidence of other events was relatively evenly distributed across the treatment groups. Only 4 subjects overall reported eye disorders (2 placebo and 1 each in the active treatment groups).

Since oropharyngeal adverse events are known to be common during therapy with ICS, a grouping of pharyngolaryngeal pain, pharyngitis, and dysphonia, and oral candidiasis was produced. One of these conditions was present in 6 (4.0%), 10 (6.6%), and 10 (6.6%) of the placebo, C160, and C80 subjects, respectively.

The distribution of severity scores (Mild, Moderate, Severe) was uniform across the treatment groups. Events were categorized as severe in 5.9, 5.3, and 3.3% of the placebo, C160, and C80 subjects, respectively.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths in this study. Serious adverse events were reported for 1 placebo and 3 C80 subjects. The placebo subject was withdrawn due to an asthma exacerbation and the C80 subjects had events unrelated to study drug treatment (1 post hernia repair complication, breast cancer, and life-threatening uterine bleeding and anemia). The hernia repair complication was a surgical wound infections requiring surgical debridement. The original surgery was performed 14 days after the initiation of ciclesonide therapy.

Withdrawal due to an adverse event occurred in 39 (8.5%) of the subjects overall (25[15.8%], 7 [4.6], and 8 [5.3%] in the placebo, C160, and C80 subjects, respectively). One subject (0.2%) had study medication temporarily interrupted, 202 (44.3%) received additional medication for an AE, and 20 (4.4%) received other interventions. The overwhelming number of adverse events that resulted in withdrawal were asthma attacks (27/39 [69.2%] of the AEs resulting in withdrawal were due to asthma). Of the 27 asthma attacks, 21 (77.8%) occurred in the subjects treated with placebo. Upper respiratory tract infection was the indication for withdrawal in 2, 2, and 1 individual in the placebo, C160, and C80 groups, respectively. No other event was reported in more than a single individual.

Other Events on Note

Eight subjects had laboratory results reported as adverse events. All were considered mild or moderate and none resulted in withdrawal of the subject. See Laboratory results, below for details).

Ophthalmologic events were reported in 7 subjects: 3 placebo subjects and 4 ciclesonide subjects. None of the events was related to lens opacification and none resulted in withdrawal from the protocol.

There were no cases of significant overdose, defined as three or more times the morning or afternoon dose (6 puffs from either AM or PM inhaler).

2.2.3.6 Laboratory Results

The mean baseline and Week 12 values for all hematology and routine safety chemistry analyses were within the normal range.

For most of the hematology and chemistry examinations there were few individuals with shifts out of the normal range over the course of the study, and the distribution of these subjects was similar across the treatment groups. In the hematology set, only the platelet counts showed more abnormal values in the actively treated subjects than in the placebo subjects: Elevated levels developed in 1 (0.7%), 4 (2.7%), and 7 (4.8%) of the placebo, C160, and C80 subjects, respectively.

In the chemistry set, glucose, total bilirubin, SGPT, and SGOT, uric acid, and calcium values showed changes from normal to abnormal in more than 5 subjects in at least one treatment group and showed more abnormalities in the actively treated subjects than the placebo subjects (Table 42) None of the differences was quantitatively large when comparing placebo to active treatment. There were abnormally low cholesterol values in 8.7% of the placebo subjects, but this was higher than either of the active treatment groups (4.8 and 3.3% in the C160 and C80 groups, respectively). The SGPT, SGOT, uric acid, and calcium were abnormally high in a very few more subjects in the ciclesonide-treated subjects than in the placebo subjects. This is probably a manifestation of normal outliers given the multiple anylates tested.

Table 42. Shift in chemistry values from normal at baseline to abnormal at end-of-study

	Placebo	Dose of Ciclesonide		
	---	160 QD	80 BID / 160 QD	80 BID
N	178	176	173	173
Below normal range				
Glucose (random)	4 (2.7)	4 (2.7)	9 (6.0)	13 (4.4)
Total bilirubin	2 (1.3)	5 (3.4)	6 (4.0)	11 (3.7)
Above normal range				
SGPT	6 (4.0)	8 (5.4)	4 (2.7)	12 (4.0)
SGOT	3 (2.0)	7 (4.8)	6 (4.0)	13 (4.4)
Uric Acid	2 (1.3)	2 (1.4)	6 (4.0)	8 (2.7)
Calcium	4 (2.7)	1 (0.7)	5 (3.3)	6 (2.0)

***(Limited to anaylates with >5 changes to abnormal in any treatment group and a larger number of changes in active than placebo treatment.**

Laboratory values that reached the Predefined Change Abnormal (PCA) range were uncommon. Table 43 lists the number of subjects in each treatment group in which more abnormalities were seen in the actively treated subjects than placebo, and where at least 2 subjects showed the abnormality. In no case was there a dramatic difference between the placebo and actively treated subjects.

Table 43. Laboratory Values with PCA Changes During Treatment

		Placebo	Dose of Ciclesonide		
	PCA Amount / direction	---	160 QD	80 BID / 160 QD	80 BID
N		178	176	173	173
Hematology					
Leukocytes	1 GI/L | ↓	1/149	1/149	2/148	3/297
	0.37 GI/L | ↑	2/149	3/149	0/148	3/297
Absolute eosinophils	0.37 GI/L | ↑	5/149	7/149	4/148	11/297
Platelets	107 GI/L | ↑	0/147	3/146	3/147	5/293
Chemistry					
Glucose (random)	3.2 mmol/L | ↑	0/149	3/147	2/150	5/297
BUN	3.2 µmol/L | ↑	0/150	0/147	2/150	2/297
Uric Acid	119 µmol/L | ↑	1/150	1/147	2/150	3/297
SGPT	28 U/L | ↑	2/149	2/147	5/150	7/297

Three subjects with allergic rhinitis had clinically significant abnormally high eosinophil counts at the end of the study (1.59, 4.25, 1.55 GI/L in a placebo and 2 C160 subjects, respectively. Two subjects had high glucose values (13.5 and 14 mmol/L in a placebo and C160 subject, respectively. Three had high SGPT values (116 U/L, 174 U/L, and 170 U/L in two placebo and 1 C80 subject, respectively.

Abnormal laboratory values were reported as adverse events for 1 placebo and 5 C80 subjects. The placebo subject had a random glucose of 42 mg/dL (normal 70-115 mg/dL). One C80 subject had an elevated leukocyte count (81 x 10^3 cell/mm^3) and one had blood in the urine and a blood glucose of 85 mg/dL. Three C80 subjects had abnormal hepatic enzymes.

2.2.3.7 Physical Examination including Vital Signs.

Overall, 13 % subjects had shifts in the physical exam from normal to abnormal (14.5%, 8.6%, and 13.2% in the placebo, C160, and C80 subjects, respectively). None of the changes was assessed as clinically significant.

Mean values for baseline and Week 12 vital signs were comparable across the treatment groups. Changes during treatment were uncommon and clinically insignificant.

2.2.3.8 Pregnancy

No pregnancies were reported

2.3 Summary and Discussion

This study was designed to demonstrate the efficacy of once daily dosing of ciclesonide HFA inhalation aerosol in the treatment of moderate asthmatics who were stable on inhaled corticosteroids prior to study enrollment. The investigators were successful in recruiting subjects who had been on ICS and who had FEV_1% in the high 70s and increased bronchial responsiveness. Subjects were stabilized on their maintenance ICS during a 7-14 day run-in, and then the placebo subjects received no ICS and the other subjects received either ciclesonide 80 mcg BID or 160 mcg QD. After randomization, the FEV_1 fell over the first 3 weeks in the placebo subjects. The FEV_1 in the C80 subjects increased to 70 ml greater than baseline at the end of the treatment period and the FEV_1 in the C160 subjects hovered around the baseline value. The supportive analyses and secondary efficacy variables showed changes in the same order, i.e. the C80 subjects performed best, the C160 subjects followed close behind the C80 subjects and the placebo subjects fared worse than either of the actively treated subjects. It is notable, however, that several of the secondary outcome measures deteriorated in all of the subjects. For instance, the AM PEF fell by 12.8 L/min in the placebo group, but it also fell by 5.8 and 4.4 L/min in the C160 and C80 groups. While the absolute change was small in the active treatment groups, the trajectory suggested gradual deterioration throughout the 12-week treatment period (Figure 6). Thus neither dosing regimen for ciclesonide was completely successful in maintaining function at the baseline level. This suggests that a higher dose of ciclesonide might be required in this patient population. Although the differences were small most of the efficacy measures improved more in the subjects treated with the BID regimen.

Adverse events were comparable across the treatment groups. However, many in the placebo group were classified as asthma exacerbations. If these were removed from the total there was a clear increase in the number of adverse events in the actively treated subjects compared to placebo. However, very few of the events were severe, or unexpected in this patient population.

3 Study # XRP1526B/3027

A MULTICENTER, MULTINATIONAL, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP STUDY OF THE EFFECTS OF CICLESONIDE HFA-MDI 640 µg/DAY AND BECLOMETHASONE HFA-MDI 640 µg/DAY ON LENS OPACIFICATION IN ADULT SUBJECTS WITH MODERATE TO SEVERE PERSISTENT ASTHMA

3.1 Protocol

3.1.1 Administrative

Enrollment Dates:	January 19, 2004 – June 21, 2005
Screening Centers:	102 centers in the USA, 7 in Poland and 10 in S. Africa
Sponsor's medical expert:	
CRO:	

3.1.2. Objective/Rationale

The primary objective of the study was to demonstrate the non-inferiority of ciclesonide compared to beclomethasone-HFA in the occurrence of a Class I lens event for nuclear opalescence, cortical, and posterior subcapsular lens opacification within 12 months. Lens event outcomes were determined by the occurrence of a protocol-specified change in lens opacification using the LOCS III method for grading lens opacities, or the occurrence of cataract surgery.

The secondary objective of the study was to compare ciclesonide to beclomethasone for changes in various subscores of the LOCS III.

3.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, active-controlled, parallel group study of the effects of ciclesonide-HFA 640 mcg daily and beclomethasone 640 mcg daily on lens opacification in adults with moderate to severe persistent asthma. Eligible subjects were enrolled into a 1 to 14-day screening period after which they were randomized (1:1) to receive either ciclesonide or beclomethasone by inhalation. They were treated for 12 months and seen in follow-up at 4, 8, and 12 months after initiation of treatment. At each visit a slit-lamp examination was performed to grade lens opacities. Visual acuity, intraocular pressure and pulmonary function were also assessed at each visit. Throughout the treatment period the subjects maintained a diary indicating how much study medication they took every day.

Reviewer: Although it is logical that the subjects would have continued their maintenance ICS during the run-in period, this is not specified in the protocol.

3.1.3.2 Protocol Amendments

Protocol Amendment 1 (May 19, 2004) stipulated that the number of clinical centers would be reduced from 200 to 125. It also increased the sample size from 1200 to 1500.

Protocol Amendment 2 (November 20, 2004) stated that all subjects in the modified intent-to-treat (ITT) population were to be analyzed according to the treatment randomized to unless there was a drug dispensing error. If the subject received the incorrect drug under the study staff's direction, they were to be returned to the correct arm as soon as possible. The order of the ophthalmology examinations was specified and the ophthalmologist was instructed not to review the previous LOCS III assessments.

Protocol Amendment 3 (June 28, 2005) was implemented due to an unexpectedly high incidence of Class I events. The non-inferiority bound (NIB) was originally chosen to detect infrequent events. Therefore, the sponsor adjusted the original NIB for event rates ≥30% to a constant value of 1.333. This bound allowed the conclusion of non-inferiority if the number of Class I lens events with test treatment was not more than a third larger than that of the control treatment.

Reviewer: Protocol Amendment 3 was submitted to the Agency for review. The Agency did not accept the logic for the change in NIB and reported to the Applicant that the NIB should be no higher than 1.11 (See FDA Statistics Review for details).

3.1.4. Study Population

Inclusion Criteria

- Males and females 18 years or older
- Moderate to severe persistent asthma of at least 2 months prior to Screening
- At Screening, forced expiratory volume in one second (FEV_1) ≥ 40% and ≤ 85% of predicted
- Documented use of ICS therapy at any dose for at least one month prior to Screening
- Ability to demonstrate acceptable oral inhaler technique
- Non-smoker for at least the past year and less than a 10 pack-year total smoking history
- Written informed consent agreement.

Exclusion Criteria

- History of prior cataract surgery in either eye
- Evidence of congenital cortical cataract
- LOCS III criteria
    - Inability to grade opacities in either eye with LOCS III at the baseline
    - Inability to dilate pupils to at least 6.0 mm
    - Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the baseline
    - Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the baseline
    - Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the baseline

- Elevated intraocular pressure requiring treatment
- BCVA less than 74 letters (equivalent to vision worse than 20/30) in either eye at baseline
- Females who were pregnant, lactating or had a positive pregnancy test at screening
- More than one in-patient hospitalization in the past year for asthma exacerbation
- More than 2 bursts of oral steroids per year for each of the past 2 years prior to Screening
- Chronic use of oral, injectable, or topical steroids except for ICSs for any condition. Topical corticosteroids designated as having a mild potency by the Stoughton-Cornell Scale or the European Guideline for levels of corticosteroid activity were allowed
- Any chronic condition likely to require treatment with oral or systemic corticosteroids other than asthma
- Topical ocular steroid treatment within 3 months prior to Screening
- Chronic or recurrent inflammatory disease in either eye likely to result in visual abnormalities or require treatment with ocular steroids
- History of drug or alcohol abuse
- Any clinically significant medical condition that would interfere with the subject's ability to participate in and comply with the study protocol
- Subject was the investigator or any sub-investigator, research assistant, pharmacist, study Staff or relative thereof directly involved in the conduct of the study
- Hypersensitivity to the investigational products
- Treated with any investigational drug/product within 30 days prior to Visit 1 (Screening).

Withdrawal Criteria

Subjects could be withdrawn if any of the following occurred:

- At their own request
- In the investigators opinion continued participation in the study would be detrimental to the subject
- In the event of a protocol deviation at the discretion of the Investigator or the Sponsor

Subjects had to be withdrawn if any of the following occurred:

- Poor compliance defined as failure to take medication or to come to clinic visits
- Exacerbation of asthma requiring >2 courses of systemic corticosteroids
- Pregnancy
- Cataract surgery

3.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Ciclesonide MDI-HFA 320 mcg BID (4 puffs 80 mcg BID)

- Beclomethasone-HFA MDI 320 mg BID (4 puffs 80 mcg BID)

Reviewer: The dosing regimen may have been determined by the lack of availability of a higher strength formulation of beclomethasone. However, requiring 4 puffs rather than 2 of 160, might tend to decrease compliance.

Compliance was assessed by the patient's notation in the diary that the medication was taken. The number of inhalers returned was also compared to the number dispensed. At 35 selected sites blood was collected for ciclesonide and des-ciclesonide levels as an exploratory way of measuring compliance. The intent was to collect serum samples on at least 375 randomized subjects.

Concomitant medications were supposed to have been kept to a minimum during randomized treatment. The following concomitant medications were permitted throughout the study:

- Intranasal corticosteroids: up to 1 month if absolutely necessary for severe allergic rhinosinusitis
- Systemic corticosteroids: up to 2 bursts for the treatment of acute asthma. If a third course was required the subject had to be withdrawn
    - Recommended dose of prednisone was 60 mg as a single dose for 3 days followed by a 10 mg/day taper over the next 5 days
    - The decision to initiate of continue the course for >8 days was left to the investigator, but should be discussed with sponsor
    - Sysemic corticosteroids for other conditions were allowed if absolutely necessary
- Mild-potency topical corticosteroids
- ß2-agonists, long and short-acting
- Leukotirene receptor antagonists
- Xanthine derivatives
- Cromolyn
- Anticholinergic agents

The following concomitant medications were prohibited from screening onward:

- Non-study ICS
- Chronic use of otic or ophthalmic preparations containing corticosteroids

Ophthalmologic Examination

Ophthalmologic examinations were performed at baseline, and month 4, 8, and 12. The same ophthalmologist was to perform the examinations on each subject; if this was impossible, a trained and certified examiner was to be substituted. The examination consisted of the following procedures performed in the order listed:

- Manifest refraction
- Visual acuity of each eye

- Introcular pressure measured by tonometry.
- Slit lamp examination for Lens grading: LOC III
    - Nuclear opalescence
    - Nuclear color
    - Cortical lens opacity
    - Posterior subcapsular lens opacity

To assure consistency, the examiners were trained at baseline and recertified twice during the trial. Recertification required 70% correct answers on a certification examination.

Other Safety Variables

Adverse events, routine hematology and chemistry blood tests, and urinalysis for glucose and protein were performed at baseline and at month 4 and 12. Serum for ciclesonide and des-ciclesonide was collected at selected centers at baseline and month 4 and 12. Physical examinations and vital signs completed the safety evaluation.

Efficacy Evaluation

Efficacy was not the primary objective of the study but pulmonary function was monitored with spirometry. The forced vital capacity was obtained following the 1994 ATS standards at baseline and at all follow-up visits.

Schedule of Events

The timing of the various examinations is summarized in Table 44.

Table 44. Summary of Events

	Screen	Random	Treatment Period				
Study Day	-1 to -14	0	1	60	120	180-300	365
Visit number	1		2	3	4	5,6,7	8
Informed consent	X						
Randomization		X					
Medical history	X						
Physical examination	X				X		X
Review medication	X		X	X	X	X	X
Spirometry	X		X	X	X	X	X
Ophthalmology exam*	X				X	X**	X
Laboratory tests	X				X		X
Issue & Review Diary	X		X	X	X	X	X
Adverse event review			X	X	X	X	X
Dispense appropriate medications			X	X	X	X	X

*Ophthalmologic exam consists of refraction, visual acuity, IOP, and slit lamp examination
**Only performed at visit 6 (month 8)

3.1.6 Analysis

Primary Variable

The primary efficacy evaluation was based on the ophthalmologic examination. Lens opacification was assessed by slit lamp examinations using the LOCS III classification. The primary endpoint was the occurrence of a Class I lens event within 12 months. A Class I lens event was defined as any of the following events in either eye:

- Increase from baseline in LOCS III grade of ≥0.5 (nuclear opalescence), or ≥0.8 (cortical) or ≥0.5 (posterior subcapsular)
- Cataract surgery since baseline

If a subject had any of the events listed above during the 12 months of treatment they were classified as having the event for analysis purposes. This was true even if the event was not observed at a later date.

Key secondary variables

LOCS III lens events

- Occurrence of a Class II lens event. A Class II lens event is defined as any of the following events in either eye:
  - Increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular),
  - Cataract surgery
- A sustained Class II lens event is defined as a Class II lens event observed at any time point with presence of a Class I lens event in the same eye at the next time point. If the Class II lens event was observed only at the last examination, then there should also be a Class I lens event in the same eye at the time point immediately preceding the last one.
- Occurrence within 12 months in either eye of a Class III lens event. A Class III lens event is defined as any of the following events in either eye
  - LOCS III grade of ≥ 2.0 for any type of opacity (nuclear opalescence, cortical, or posterior subcapsular) and increase from baseline in LOCS III grade of ≥ 0.9 (nuclear opalescence), ≥ 1.5 (cortical), or ≥ 0.9 (posterior subcapsular),
  - Cataract surgery.

Change in LOCS III grade from baseline

- Maximum increase in LOCS III grade during the study for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity by eye and in either eye
- Change from baseline to each timepoint in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, and (c) posterior subcapsular opacity. The change from baseline was derived by eye and for the highest value in either eye for each subject.

Other secondary variables

- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (nuclear opalescence) in either eye
- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.8 (cortical) in either eye

- Lens event defined as an increase from baseline in LOCS III grade of ≥ 0.5 (posterior subcapsular) in either eye

Best-corrected visual acuity score

The BCVA score was calculated as the sum of the number of letters read correctly at the 4-meter distance plus 30 added if 20 or more letters were read correctly. If fewer than 20 letters were read, the score was the sum of the number of letters read correctly at the 4-meter distance plus the number of letters read at the 1-meter distance.

The following endpoints were reported:

- Change from baseline to each time-point in BCVA, derived by eye and for the lowest value in either eye for each subject;
- Change from baseline to the lowest on-study visual acuity by eye and in either eye.

Intraocular pressure

Two measurements were made and a third measurement was to be done if the first 2 measures differed by more than 2 mmHg. The median of the 2 or 3 measurements became the intraocular pressure determination. The median was calculated as the mean (midpoint) of the 2 measurements or was the middle value when the 3 measurements are arranged in ascending or descending order.

The following endpoints were reported:

- Change from baseline to each time-point in median intraocular pressure (mmHg), derived by eye and for the highest value in either eye for each subject;
- Change from baseline to the highest median intraocular pressure (mmHg) on-study by eye and in either eye.

Other events

Negative lens events were recorded when the LOS III readings decreased

A non-reversing event was one that was present at two visits

Pulmonary Function Variables

The following endpoints were reported:

- Change in post-bronchodilator FEV_1 (L) from baseline to Month 4, Month 8, Month 12 and end of study, where the end of study time point was the last available time point under treatment derived using the last observation carried forward (LOCF) principle
- Percent change in post-bronchodilator FEV_1 from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FEV_1 percent predicted from baseline to Month 4, Month 8, Month 12 and end of study
- Change in post-bronchodilator FVC (L) from baseline to Month 4, Month 8, Month 12 and end of study.

3.1.6.1 Statistical Analysis Plan

Sample Size

This study was an assessment of non-inferiority of ciclesonide-HFA compared with beclomethasone-HFA for the primary endpoint of Class I lens event. Non-inferiority was demonstrated if the upper bound of the one-sided 97.5% confidence interval of the risk ratio was less than the NIB. Sample size was computed using the following expression based on the Taylor series expansion of the variance of the logarithm of the risk ratio (1).

$$\text{var}\left(\log_e (p_T / p_C) \right) E\left(1/n\square_C \left(1/R + 1 \right) - 2/n \right)$$

A LOCS III-based Class I lens event rate of approximately 8% was anticipated in the control group. No data were available in the intended study population. The event rate was extrapolated from the finding of a 3% lens event rate (defined using a larger change in lens opacity) in subjects of 40 to 49 years of age in the Age-Related Eye Disease Study (AREDS)(2). Using the criteria described above in subjects whose mean age was approximately 65 years was anticipated to increase the rate to approximately 8% within 12 months. As specified in the protocol, approximately 503 subjects were required per treatment group to achieve 90% power for non-inferiority based on a one-sided 97.5% confidence interval of the risk ratio. The anticipated drop out rate was increased based on observations from an earlier long-term study [XRP1526B-323/324LT] completed after the original protocol for the cataract study had been written. Therefore Protocol Amendment 1 was required to increase the sample size. It was therefore planned to randomize 1500 subjects into 2 treatment groups (750 subjects per group), assuming a discontinuation rate of 30%.

Study Populations

The modified intention to treat (mITT) population included all randomized subjects who received medication and who had at least 1 valid post treatment LOC III measurement.

A LOCS III measurement was deemed valid (each eye evaluated separately) if:

- The diameter of the pupil was at least equal to 6 mm (with or without eye dilatation)
- The LOCS III grade was within the valid range for nuclear opalescence (0.1 to 6.9) and for cortical or posterior subcapsular opacities (0.1 to 5.9)
- The examination was done by a certified ophthalmologist according to the list of valid certification numbers for that site
- The post-baseline LOCS III measurements were done at least after one month following exposure to the study drug and within 14 days from the end of study treatment period

The per-protocol (PP) population consisted of all the subjects in the mITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind.

The list of major protocol violations includes the following events prior to treatment:

Prior to Screening

- No documented use of ICS therapy for asthma at any dose for at least 21 days during the month prior to Screening;
- History of prior cataract surgery in either eye
- Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the screening slit-lamp examination
- Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the screening slit-lamp examination
- Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the screening slit-lamp examination
- Elevated intraocular pressure (> 25 mmHg) requiring treatment for glaucoma (ATC S01E) at Screening
- BCVA score of less than 72 letters in either eye at Screening
- Treatment with more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable (one shot of injectable equivalent to one burst of oral) steroids per year for each of the past 2 years prior to Screening
- Topical ocular steroid treatment within 3 months prior to Screening unless agreed with the sponsor
- Chronic use of oral steroids except ICSs for any condition.

During Treatment

- Use of non-study medication ICSs for more than 14 days prior to an eye examination (i.e., between 2 consecutive visits);
- Use of any ocular steroid at any time during the treatment period for more than 14 days;
- Use of intranasal corticosteroids continuously for more than one month;
- Subject received more than 2 bursts of oral (prednisolone 60 mg/day for 3 days) or injectable
- (one shot of injectable equivalent to one burst of oral) steroids during the 12-month treatment period;
- Overall compliance to study medication was less than 70%;
- Less than 4 months on study medication.

Statistical Analysis

Analysis of the primary endpoint was determined by the life-table estimate of the event at Month 12 using the mITT population. Since the number of subjects who completed the study with no event was expected to be high, the cumulative probability of failure in the standard life-table estimate would have been an overestimate. Therefore an alternative method, which managed withdrawals with their actual fractions of completion for the interval of withdrawal was used. Three time intervals were defined as 0 to 120, 121 to 240, and 241 to 360 days. Non-inferiority of ciclesonide-HFA versus the control (beclomethasone-HFA) was demonstrated if the upper bound of the one-sided 97.5% confidence interval was less than the NIB (see section below). If non-inferiority was demonstrated, then superiority of ciclesonide-HFA over control was to be subsequently tested by comparing the upper bound of the one-sided 97.5% confidence interval to one.

If non-inferiority of ciclesonide-HFA versus the control was demonstrated for the primary endpoint of Class I lens events, then non-inferiority of ciclesonide-HFA based on Class II, sustained Class II, and Class III lens events was also assessed using a one-sided 97.5% confidence interval for each type of event.

Subjects who withdrew prior to study completion without a Class I lens event were considered censored for this analysis. Since the withdrawal of subjects before the occurrence of a Class I lens event was expected to be unrelated to lens opacification, it was assumed that the censoring for the primary endpoint of Class I lens events was non-informative. Any event occurring after 390 days was censored for the analysis. Subjects with an early termination visit within the first 30 days after first intake of study medication were censored regardless of the outcome of the LOCS III examination.

Non-inferiority bound
The NIB was defined as a function of the control event rate for p_C ranging from 2% to 12%:

$$NIB = (1.63 - \sqrt{p_C}) * \exp(\sqrt{(1/(80\ p_C))})$$

This function insured that the risk ratio would not be greater than 1.5 with 503 subjects per group, which the Applicant accepted as clinically relevant. Blinded review of the data indicated a higher rate of events than expected. Therefore the NIB function defined in the study protocol was extended to a higher range, maintaining a decreasing functional form, with a minimum of 1.333. The NIB was then the maximum of 1.333 and the value obtained by the function. The NIB could not be less than 1.333, which occurred when the estimated control event rate was 30% or higher. This insured a maximum sample risk ratio for non-inferiority higher than 1, and sufficient power for high rates of events.

Reviewer: The above analysis was not agreed upon by the Agency (See FDA Statistical Review for details). The ophthalmology consult felt that the NIB should be no higher than 1.11.

Pooling of Centers

For statistical analysis, centers with less than 3 subjects per treatment group were pooled. Centers were ordered within country (USA, Poland, and S Africa) by number of subjects. Starting with the smallest enrollers, centers were added sequentially until the pooled group contained at least 3 subjects per treatment group. For statistical purposes the pooled groups were considered single centers.

3.2. Results

3.2.1. Study Population

Disposition

A total of 2032 subjects were screened and 464 failed, resulting in randomization of 1568 subjects (785 to ciclesonide 320 mcg BID (C320) and 783 to budesonide (BDP). Of those enrolled, 1552 subjects received treatment and were included in the safety population (Table 45). Of those who were randomized and treated, 743 C320 and 742 BDP subjects had valid ophthalmologic examinations and were included in the mITT population. This represented 94.7% of the randomized population. The per-protocol (PP) population (those without major protocol violations) consisted of 673 C320 and 676 BDP subjects (86% of those randomized).

Of the 1552 subjects who were randomized and treated, 1354 (86.4% of those randomized) completed the course of treatment. Withdrawal was equivalent in the two treatment groups (14.4% in the C320 group and 12.9% in the BDP subjects). Differing from the short term efficacy trials, but similar to other long-term follow-up studies, the most common cause of withdrawal was patient request (4.2 and 4.1% of the C320 and BDP subjects, respectively). Adverse reactions were the second most common indication for withdrawal (3.7, and 2.8% in the C320 and BDP subjects, respectively). Loss to follow-up accounted for 1.7% of those randomized and lack of efficacy was reported as a reason for withdrawal in only 0.5% if those randomized,

Table 45. Disposition of Subjects in Study 3027

	C320	BPD	Overall
Randomized	785	783	1568
Treated	776 (98.9)	776 (99.1)	1552 (99.0)
Discontinued	113 (14.4)	101 (12.9)	214 (13.64)
Reason for discontinuation:			
Did not wish to continue	33 (4.2)	32 (4.1)	65 (4.1)
Adverse event	29 (3.7)	22 (2.8)	51 (3.3)
Lost to follow-up	16 (2.0)	10 (1.3)	26 (1.7)
Protocol violation	15 (1.9)	21 (2.7)	36 (2.3)
Lack of efficacy	5 (0.6)	3 (0.4)	8 (0.5)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Other	14 (1.8)	12 (1.5)	26 (1.7)

Reviewer: The drop-out was approximately ½ of the 30% expected and used to calculate the sample size.

Of the 1568 subjects randomized, 36 (2.3%) subjects were withdrawn for major protocol violations. The number withdrawn for protocol violations was greater in the BDP group (2.7% compared with 1.9% of the C320 subjects). However, the number of subjects in the mITT population who took some form of prohibited corticosteroid was greater in the C320 group (49) than in the BDP group (33) and fewer of the C320 subjects (17) than the BDP subjects (23)

failed to take study medication as prescribed. Overall, the subjects in the mITT who were treated with ciclesonide had a higher exposure to corticosteroids than did the BDP subjects. All of the subjects with concomitant steroid exposure or with failure to take study medication as prescribed were excluded from the PP population.

Reviewer: Text Table 11 (pg 113 of the study report) lists the protocol violations that were present in the mITT population, not protocol violations that led to exclusion. This is concluded from an analysis of datasheet ASV.xpt. Most of the subjects excluded from the mITT were excluded because of lack of a valid post-treatment ophthalmology examination.

Demographics

Of the 1485 subjects in the mITT population 39.9% were male and the mean age (Range) was 43.1 (18 - 80) years (Table 46). More than 60% were over 40 years of age, and 130 (63 in the C320 group and 67 in the BDP group) were over 60 years of age. The predominant racial group was White (83.5% compared with 8.8% Black and 7.7% Other). Most of the subjects (76.8%) were never smokers and the US was the site of enrollment of 84.6% of the subjects.

Table 46. Demographic Characteristics of the ITT Population

	C320	BDP	Overall
Total ITT Population	743	742	1485
Gender, % M	(40.0)	(39.8)	(39.9)
Age, mean (SD)	42.9 (12.9)	43.3 (12.6)	43.1 (12.8)
≥40 years, N (%)	460 (61.9)	466 (62.8)	926 (62.4)
Race, %			
White	83.0	84.0	83.5
Black	9.2	8.5	8.8
Other	7.8	7.5	7.7
Smoking History			
Never	76.6	77.0	76.8
Region, %			
USA	84.7	84.6	84.6
Poland	6.5	6.2	6.3
South Africa	8.9	9.2	9.0

The baseline ophthalmologic values (Table 47) were almost identical in the two treatment groups. The range of values for intraocular pressure were somewhat smaller for the BDP subjects (8.0 – 24.0) than for the C320 subjects (6.0 – 30.0), but the means were very close (14.8 and 14.6 for the right and left eyes in the C320 subjects and 4.8 and 14.7 in the right and left eyes of the BDP subjects.

Table 47. Baseline values for ophthalmologic examinations

Treatment	C320 (N=743)		BDP (N=742)	
Eye	R	L	R	L
Nuclear opalescence*	1.4 (0.9) 0.1 - 3.8	1.4 (0.9) 0.1 – 3.8	1.4 (0.9) 0.1 – 3.7	1.4 (0.9) 0.1 – 3.7

Cortical opacity*	0.4 (0.6) 0.1 - 3.2	0.4 (0.5) 0.1 – 3.1	0.4 (0.6) 0.1 – 2.9	0.4 (0.5) 0.1 – 2.9
Posterior subcapsular opacity*	0.2 (0.2) 0.1 – 1.8	0.2 (0.2) 0.1 – 2.0	0.2 (0.2) 0.1 – 1.9	0.2 (0.2) \0.1 – 2.0
Visual Acuity	87.0 (4.7) 58 – 100	86.9 (4.9) 65 – 99	87.0 (4.8) 66 - 99	87.0 (4.9) 64 – 99
Introcular pressure	14.8 (3.0) 6.0 – 30.0	14.6 (3.0) 6.5 – 28.0	14.8 (2.8) 8.0 – 22.5	14.7 (2.8) 8.0 – 24.0

* Part of LOC III examination

The mean (SD) duration of asthma was 21.7 (13.8) years (Table 48), and all of the subjects had used an inhaled corticosteroid within 90 days of enrollment. Short acting selective ß-adrenergic agonists were the second most frequently used medication (88.4 and 90.2% of the C320 and BDP subjects, respectively). The mean (SD) FEV_1 was 2.4 (0.6) L and the mean (SD) FEV_1 percent predicted was 71.7 (10.6) percent.

Table 48. Characteristics of Asthma – ITT Population

	C320	BDP	Overall
Total	743	742	1485
Duration Years, mean (SD) Range	 21.9 (15.5) 0.3 – 63.8	 22.3 (14.7) 0.2 – 64.0	 22.1 (15.1) 0.2 – 64.0
FEV_1 Mean Absolute, ml (SD) Range	 2.4 (0.6) 0.5 -4.3	 2.4 (0.6) 0.8 – 4.3	 2.4 (0.6) 0.5 – 4.3
FEV_1 Mean % predicted, % (SD) Range	 71.7 (10.7) 41.0 – 90.2	 71.6 (10.6) 40.3 – 87.1	 71.7 (10.6) 40.3 – 90.2

Compliance with Treatment

As assessed by diary recordings, more than 88% of the subjects had a compliance of at least 90%. In a subset of 255 subjects treated with ciclesonide, blood levels of ciclesonide and des-ciclesonide were measured to further assess compliance. As can be seen in Table 49, none of the subjects had the parent compound (ciclesonide) or the metabolite (des-ciclesonide) in their blood at screening. At month 4 and 12, 88 to 89% of the subjects had measurable levels of des-ciclesonide and 26 to 29% had measurable levels of ciclesonide. Subjects who terminated early had a lower incidence of positive blood levels for both ciclesonide (0%) and the metabolite (57.1%).

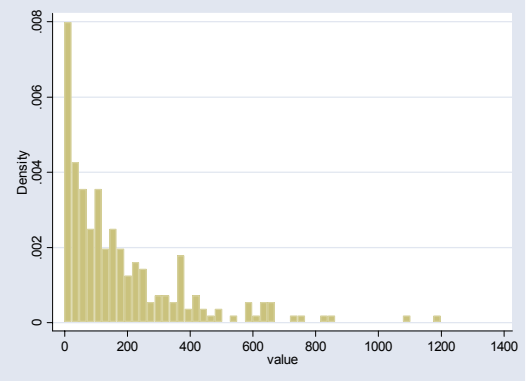
Table 49. Blood Levels of Ciclesonide and its ActiveMetabolite

	n/N (%) of subjects	
Visit / Status	Ciclesonide (pg/mL) (N = 255)	des-ciclesonide (pg/mL) (N = 255)
Screening		
Absence	242/242 (100%)	242/242 (100%)
Presence	0/242 (0%)	0/242 (0%)
Month 4		
Absence	168/236 (71.2%)	25/236 (10.6%)
Presence	68/236 (28.8%)	211/236 (89.4%)
Month 12		
Absence	173/235 (73.6%)	28/235 (11.9%)
Presence	62/235 (26.4%)	207/235 (88.1%)
Early termination		
Absence	7/7 (100%)	3/7 (42.9%)
Presence	0/7 (0%)	4/7 (57.1%)
Overall		
Absence	348/478 (72.8%)	56/478 (11.7%)
Presence	130/478 (27.2%)	422/478 (88.3%)

Note: 11 subjects among the 255 subjects to be sampled had no serum concentration measurement at any visit.

The actual values of the blood levels varied widely (Figure 8). For instance, the endpoint value for the metabolite ranged from 10.4 to 1200 pcg/mL (0.01 to 1.2 ng/mL) and the value for ciclesonide ranged from 25.4 to 1180 pcg/mL. For the RM1 metabolite at Month 12, 75% of the measurable levels were >57.9 pcg/mL and 50% were higher than 130 pg/mL (104/235 = 44.3% of the total population sampled).

Figure 8. Blood Levels of RM1 After 12 Months of Treatment



Reviewer: In the study report there is no mention of the time the samples were taken or the relationship of the blood draw to the daily study medication. The values, therefore, are random samples taken during chronic treatment and are not directly comparable to the Cmax values reported in previous studies. However, in study 41/2003 the geometric mean Cmax, obtained after treatment with a single dose of 400 mcg (320 mcg ex-actuator) was 0.313 ng/mL

3.2.2. Efficacy Results

Primary Efficacy Outcome

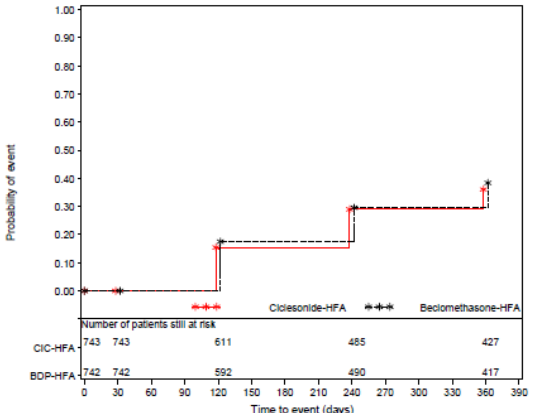
By the life-table analysis, the incidence of Class I ophthalmology events was slightly lower (36.1%) in the ciclesonide-treated subjects than in the BDP-treated subjects (38.4%). The risk ratio (95% CI) comparing ciclesonide to BDP was 0.94 (0.82, 1.08) and the p-value for non-inferiority was <0.0001 (Table 50). The results of the per-protocol analysis were supportive. If subjects with major protocol violations were excluded, the risk ratio (95% CI) was 0.926 (0.803, 1.068). As part of a further sensitivity analysis, the risk was also calculated assuming that all drop-outs as had the event. In this instance the risk ratio (95% CI) was 0.971 (0.864, 1.091).

Table 50 . Analysis of Class I Lens Events in the mITT Population by Life-table Estimate

	N	% of Subjects with Class I event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	36.1 (1.82)	0.94	0.82, 1.08	1.33	<0.0001
BDP	742	38.4 (1.83)				

The development of Class I changes in the mITT population are shown graphically in Figure 9.

Figure 9. Development of Class I events



No important subgroup interactions were noted.

Secondary efficacy outcome measures

Class II events are more severe and they were less common than Class I events. Of the subjects treated with ciclesonide, 14.0% showed Class II changes compared with 16.4% of the subjects treated with BPD. Similarly, sustained Class II (See Section 3.1.6 Key Secondary Events for definition) events were reported in 9.4% of the ciclesonide and 11.5% of the BDP-treated subjects (Table 51).

Table 51. Change in Class II Lens Events

	N	% of Subjects with Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	14.0 (1.31)	0.86	0.67, 1.10	1.62	<0.0001
BDP	742	16.4 (1.39)				
	N	% of Subjects with sustained Class II event	Risk ratio	95% CI	Non-inferiority bound	p-value
C320	743	9.4 (1.11)	0.821	0.60, 1.12	1.796	<0.0001
BDP	742	11.5 (1.20)				

Class III events were reported for 57 (7.7%) of the C320 subjects and 65 (8.8%) of the BDP-treated subjects. The only subject who had cataract surgery during the course of the trial was in the BDP group.

The LOCS III classification is made up of a combination of three evaluations: nuclear opalescence, cortical opacity, and posterior subcapsular opacity (PSC). While all may affect vision, the PSC changes are most characteristic of the changes induced with corticosteroid treatment. As shown in Table 52 the percentage of subjects with Class I, II, and III events was consistently lower in the C320-treated subjects compared to the BDP subjects, but the percentage with the Class I, II, and III changes in the sub-score for PSC opacity was consistently higher for the C320 subjects. If this represents a corticosteroid treatment-related event the small differences could become clinically meaningful over years of treatment.

Table 52. Number (%) of Subjects by LOCS III Classification and Treatment group

	Observed proportions: Number (%) of subjects		Life table estimates: Percent of subjects ± SE	
Type of lens event	CIC-HFA (N = 743)	BDP-HFA (N = 742)	CIC-HFA (N = 743)	BDP-HFA (N = 742)
Class I	**255 (34.3%)**	**273 (36.8%)**	**36.1 ± 1.8**	**38.4 ± 1.8**
Nuclear opalescence	210 (28.3%)	227 (30.6%)	29.7 ± 1.7	32.0 ± 1.8
Cortical opacity	60 (8.1%)	66 (8.9%)	8.5 ± 1.1	9.3 ± 1.1
Posterior subcapsular opacity	20 (2.7%)	17 (2.3%)	2.8 ± 0.6	2.4 ± 0.6
Class II	**99 (13.3%)**	**117 (15.8%)**	**14.0 ± 1.3**	**16.4 ± 1.4**
Nuclear opalescence	82 (11.0%)	103 (13.9%)	11.7 ± 1.2	14.5 ± 1.3
Cortical opacity	14 (1.9%)	13 (1.8%)	2.0 ± 0.5	1.8 ± 0.5
Posterior subcapsular opacity	10 (1.3%)	6 (0.8%)	1.4 ± 0.4	0.8 ± 0.3
Sustained Class II	**66 (8.9%)**	**81 (10.9%)**	**9.4 ± 1.1**	**11.5 ± 1.2**
Nuclear opalescence	55 (7.4%)	71 (9.6%)	7.9 ± 1.0	10.1 ± 1.1
Cortical opacity [a]	6 (0.8%)	9 (1.2%)	0.8 ± 0.3	1.2 ± 0.4
Posterior subcapsular opacity [a]	5 (0.7%)	1 (0.1%)	0.7 ± 0.3	0.1 ± 0.1
Class III	**57 (7.7%)**	**65 (8.8%)**	**8.1 ± 1.0**	**9.2 ± 1.1**
Nuclear opalescence	44 (5.9%)	54 (7.3%)	6.3 ± 0.9	7.6 ± 1.0
Cortical opacity	12 (1.6%)	11 (1.5%)	1.7 ± 0.5	1.6 ± 0.5
Posterior subcapsular opacity [a]	7 (0.9%)	4 (0.5%)	0.9 ± 0.4	0.5 ± 0.3

BDP = beclomethasone; CIC = ciclesonide.
NC = estimates not calculated because at least one treatment group had less than 10 events.
[a] Life table estimates were obtained using the standard life table method if there were fewer than 10 events in each treatment group because the modified method requires 10 or more events in at least one treatment group to provide robust estimates.

In addition to the categorical analysis, the mean cataract grade was compared among the treatment groups. The differences between the two treatment groups are small, but the pattern shown in the categorical analysis is repeated: Cataract size was smaller for the C320 subjects for nuclear and cortical opacities, but the PSC opacities were slightly larger compared to BPD treatment (Table 53).

Table 53 Mean changes in LOCS III Scores

Treatment	N	Baseline mean	Change from baseline: LS mean ± SE (LOCS III grade)	Ciclesonide-HFA vs. beclomethasone-HFA: LS mean ± SE	Ciclesonide-HFA vs. beclomethasone-HFA: 2-sided 95% CI
Nuclear opalescence					
Ciclesonide-HFA	743	1.33	0.22 ± 0.019	-0.016 ± 0.020	-0.056, 0.024
Beclomethasone-HFA	742	1.36	0.23 ± 0.018		
Cortical					
Ciclesonide-HFA	743	0.36	0.14 ± 0.018	-0.018 ± 0.020	-0.057, 0.021
Beclomethasone-HFA	742	0.35	0.16 ± 0.017		
Posterior subcapsular					
Ciclesonide-HFA	743	0.14	0.06 ± 0.009	0.018 ± 0.010	-0.001, 0.037
Beclomethasone-HFA	742	0.15	0.05 ± 0.009		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error.
Ciclesonide-HFA vs. beclomethasone-HFA is calculated as ciclesonide-HFA minus beclomethasone-HFA.

In the application, the argument is put forward that the distribution of size change was similar in the two treatment groups. In Table 54, the changes are grouped into decrease, no change, and three degrees of increase, and the point is made that most of the subjects had no change or a decrease.

Table 54. Distribution of Change in LOCS III Grade

Variable	Number (%) of subjects: Ciclesonide-HFA (N = 743)	Number (%) of subjects: Beclomethasone-HFA (N=742)
Nuclear opalescence		
Decrease	121 (16.3%)	145 (19.5%)
No change	151 (20.3%)	123 (16.6%)
Increase by 0.1 to 0.4	261 (35.1%)	247 (33.3%)
Increase by 0.5 to 0.8	128 (17.2%)	124 (16.7%)
Increase by ≥ 0.9	82 (11.0%)	103 (13.9%)
Cortical		
Decrease	48 (6.5%)	49 (6.6%)
No change	343 (46.2%)	320 (43.1%)
Increase by 0.1 to 0.7	292 (39.3%)	307 (41.4%)
Increase by 0.8 to 1.4	46 (6.2%)	53 (7.1%)
Increase by ≥ 1.5	14 (1.9%)	13 (1.8%)
Posterior subcapsular		
Decrease	16 (2.2%)	26 (3.5%)
No change	542 (72.9%)	550 (74.1%)
Increase by 0.1 to 0.4	165 (22.2%)	149 (20.1%)
Increase by 0.5 to 0.8	10 (1.3%)	11 (1.5%)
Increase by ≥ 0.9	10 (1.3%)	6 (0.8%)

The 2 highest categories of increase for each type of opacity together correspond to the Class I lens event criteria, and the highest categories correspond to the Class II lens event criteria.

Reviewer: The distributions in Table actually show that there were a higher proportion of subjects with large increases in PSC in the C320 group (10 [1.3%]) compared to the subjects treated with BDP (6 [0.8%]). The absolute numbers are small, but the proportion suggests that almost twice as many subjects treated with C320 developed these changes compared to the BDP group. Confirming the trend is the increased number of subjects in the BDP group whose opacities decreased (26 [3.5%]) compared to the subjects treated with ciclesonide (16 [2.2%]). Finally, an LOCS III score of 2 or greater is often taken as the cutoff for clinically significant cataracts [ ]. This criterion was satisfied by 11 ciclesonide and 4 beclomethasone subjects at the end of the study. All of these subjects had baseline values of less than 1.4 and all had an increase of at least 1.4 over the course of the study. The results of the primary and supportive secondary analysis are quite consistent. While the overall LOCS III grade was lower in the subjects treated with C320, the scores for the change in PSC were slightly higher in the C320-treated subjects.

In a sub-set analysis, it is stated that the changes in LOCS III were equivalent in all of the age groups. Table 29 in the study report, reproduced here as table 55, shows the proportion of subjects, divided into age groups of 40 and less and over 40 years of age, with Class I, II, III, and sustained Class II events The proportion with events is slightly higher in the older age groups for all of the categories other than Class III events, but the incidence in the BDP group was higher than that in the subjects treated with C320 in both age groups.

Table 55. Summary of LOCS III by Age (2 groups)

	Percent of subjects ± SE			
	< 40 years		≥ 40 years	
Type of lens event	CIC-HFA (N= 283)	BDP-HFA (N= 276)	CIC-HFA (N= 460)	BDP-HFA (N=466)
Class I lens event	31.1 ± 2.9	31.7 ± 2.9	39.1 ± 2.3	42.3 ± 2.3
Class II lens event	12.2 ± 2.0	14.8 ± 2.2	15.2 ± 1.7	17.3 ± 1.8
Sustained Class II lens event	8.7 ± 1.7	11.5 ± 2.0	9.9 ± 1.4	11.5 ± 1.5
Class III lens event	3.1 ± 1.1	4.2 ± 1.2	1.1 ± 1.5	1.2 ± 1.5

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Reviewer: Of note, all of the subjects who had an LOS III grade for PSC of 2 or greater were 40 years of age or older. On the other hand, a cutoff of 40 years of age may underestimate the ability of ICS to potentiate the development of cataracts in older subjects. If the age groups are <40, 40 to 60, and >60 years, it appears that subjects over 60 years of age developed all classes of cataracts at a higher rate when treated with ciclesonide than during treatment with beclomethasone (Table 56). The difference in treatment was most marked for Class II and III events where 25 and 22% of the ciclesonide-treated subjects, respectively, reported events compared with 17.5% of the BDP-treated subjects for both classes of events. If the incidence of PSC is examined separately, the differences are event more dramatic. The mean change in PSC grade in the over 60 age group was 0.184 compared to 0.111 (a 65% increase) in the BDP group (Table 57). Unfortunately, the over 60 age-group was not well represented in the sample. There were only 130 subjects (67 and 63 in the C320 and BDP groups, respectively) over 60 years of

age compared with over 300 in each treatment group who were 40 to 60 years of age and almost 300 in each treatment group less than 40 years of age. Despite the small number of subjects over 60 this finding is of concern since this is the age group most predisposed to develop cataracts.

Table 56. ***Number of Subjects by LOCS III Scores and Age-group (3 groups)***

	Ciclesonide		*BDP*	
	N	*N (%) Positive*	*N*	*N (%)Positive*
Class I				
Overall	*743*	*255 (34.3)*	*742*	*273 (36.8)*
<40 years	*308*	*89 (28.9)*	*298*	*93 (31.2)*
40 – 60 years	*368*	*130 (35.3)*	*381*	*147 (38.6)*
> 60 years	*67*	*36 (53.7)*	*63*	*33 (52.4)*
Class II				
Overall	*743*	*99 (13.3)*	*742*	*117 (15.7)*
<40 years	*308*	*36 (11.7)*	*298*	*43 (14.4)*
40 – 60 years	*368*	*46 (12.5)*	*381*	*63 (16.5)*
> 60 years	*67*	*17 (25.4)*	*63*	*11 (17.5)*
Class III				
Overall	*743*	*57 (7.7)*	*742*	*65 (8.8)*
<40 years	*308*	*8 (2.6)*	*298*	*13 (4.4)*
40 – 60 years	*368*	*34 (9.2)*	*381*	*41 (10.8)*
> 60 years	*67*	*15 (22.4)*	*63*	*11 (17.5)*

Table 57 . ***Mean Change in PSC Grade by Age****

Age in years	*N*	*Ciclesonide*	*BDP*
< 40	*606*	*0.040*	*0.024*
40 – 60	*749*	*0.049*	*0.043*
> 60	*130*	*0.184*	*0.111*

** Taken from datasets AEF01.xpt through AEF010.xpt*

The differences between men and women were small and not clinically meaningful. There was some variability when comparing geographic region (Table 58) but for the most part, the incidence in the C320 group was lower than in the BDP treated subjects. There was a relatively low incidence of Class I events in South Africa for both treatment groups and of Class III events in Poland. In South Africa, sustained Class II and Class III events were more common in the Ciclesonide-treated subjects.

Table 58. LOCS III Scores by Geographic Region

	Percent of subjects ± SE					
	United States		Poland		South Africa	
Type of lens event	CIC-HFA (N= 629)	BDP-HFA (N= 628)	CIC-HFA (N= 48)	BDP-HFA (N= 46)	CIC-HFA (N= 66)	BDP-HFA (N= 68)
Class I lens event	37.4 ± 2.0	39.5 ± 2.0	32.6 ± 7.0	41.8 ± 7.6	26.5 ± 5.6	25.8 ± 5.5
Class II lens event	15.0 ± 1.5	17.2 ± 1.5	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	13.9 ± 4.3
Sustained Class II lens event	9.5 ± 1.2	11.7 ± 1.3	6.3 ± 3.6	9.3 ± 4.5	10.8 ± 3.9	10.7 ± 3.9
Class III lens event	8.4 ± 1.1	9.6 ± 1.2	2.1 ± 2.1	4.7 ± 3.3	9.4 ± 3.7	7.6 ± 3.3

CIC = ciclesonide; BDP = beclomethasone. SE = standard error.

Source: *Table T - 62, pg. 484, Table T - 72, pg. 496, Table T - 82, pg. 507, Table T - 92, pg. 518*

An analysis performed on subgroups defined by baseline category of opacities showed similar changes in the two treatment groups when the absolute increase in mean area of opacities was compared. However, this analysis also showed a larger increase in PSC for most categories compared to BDP.

Other Ophthalmologic Variables

The LS mean (SE) decrease in visual acuity was 2.65 (0.15) for ciclesonide-treated subjects and 2.96 (0.15) for subjects treated with beclomethasone. The mean (SD) increase in intraocular pressure was 1.48 (2.25) and 1.64 (2.18) mm Hg in the ciclesonide and BDP-treated subjects, respectively. The median change was 1.5 mm Hg in both groups with a range of – 6.0 to 16.0 mm Hg in the ciclesonide group and -5.5 to 9.0 mm Hg in the BDP group.

Asthma Control

Post-bronchodilator pulmonary function was obtained at baseline and at each follow-up visit. The analyses were performed on the subjects who were in the study at the time of measurement. Improvement in function was seen in both treatment groups, but it was very small and the difference between C320 and BDP was inconsequential (Table 59).

Table 59. Pulmonary Function After 12 months of Treatment with C320 and BDP

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. beclomethasone-HFA LS mean ± SE	Difference vs. beclomethasone-HFA 2-sided 95% CI
FEV_1 (L)					
Ciclesonide-HFA	739	2.68	0.06 ± 0.014	-0.013 ± 0.015	-0.043, 0.017
Beclomethasone-HFA	740	2.71	0.08 ± 0.013		
FEV_1 percent predicted					
Ciclesonide-HFA	739	79.4	1.14 ± 0.401	-0.624 ± 0.445	-1.497, 0.249
Beclomethasone-HFA	740	80.5	1.76 ± 0.396		
Percent change in FEV_1 [a]					
Ciclesonide-HFA	739	2.68	3.14 ± 0.572	-0.862 ± 0.642	-2.121, 0.396
Beclomethasone-HFA	740	2.71	4.00 ± 0.569		

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; N = mITT population; SE = standard error.
[a] FEV_1 at baseline measured in liters.
Differences vs. beclomethasone-HFA are calculated as ciclesonide-HFA minus beclomethasone-HFA.
Source: *Table T - 142, pg. 595; Table T - 148, pg. 607; Table T - 145, pg. 600*

3.2.3. Safety

3.2.3.1 Exposure

The total safety population included 1552 individuals, 776 in each treatment group. Exposure to study medication was comparable in the two treatment groups. The mean (SD) exposure was 337.7 (68.7) and 339.4 (68.1) days in the C320 and BDP-treated subjects, respectively. The respective ranges were 10 to 380 and 18 to 386 days.

3.2.3.2 Adverse Events

Overall Assessment of Adverse Events

The overall incidence of AEs was slightly lower in the C320 group than in those treated with BDP (Table 60). The incidence of serious AEs and AEs leading to withdrawal was low, however serious AEs were more common in the BPD group (5.9% compared to 4.0% in the C320 group) whereas AEs leading to withdrawal were more common in the C320 group (3.6% compared to 2.6% in the BDP group). There was one death in each treatment group. Neither was considered by the investigator to be treatment related (See below for details).

Table 60. **Overall Summary of Adverse Events**.

	C320	BDP	Total
N	776	776	1552
All AEs	648 (83.5)	664 (85.6)	1312 (84.5)
Serious AEs	31 (4.0)	46 (5.9)	77 (5.0)
AEs leading to withdrawal	23 (3.6)	20 (2.6)	43 (2.8)
Deaths	1 (0.1)	1 (0.1)	2 (0.1)

Grouped by MedDRA SOC, the most common adverse events were in the Infections and infestations category (65.2 and 66.6% in the C320 and BDP groups, respectively) followed by Respiratory, Thoracic and Mediastinal disorders (31.3 and 27.3%, respectively) and Musculoskeletal and Connective Tissue Disorders (21.3 and 18.0%, respectively). Gastrointestinal Disorders, Nervous System Disorders, Injury, Poisoning, and Procedural Complications affected 15 to 17% of the subjects in both treatment groups. Eye Disorders were reported in 11% of both treatment groups and Skin, General, Psychiatric, Investigations were reported in 4 to 8%.

Listed by MedDRA preferred term, the most common events were Nasopharyngitis, Upper respiratory tract infection, Sinusitis, Asthma, and Headache (Table 61). Nasopharyngitis was reported in 3.4% more subjects treated with C320 than in subjects treated with BDP while Lower Respiratory Tract Infection and Candidiasis were reported more frequently in the BDP group (2.5 and 4.9% difference, respectively). Most of the other events occurred with similar frequency in the two groups (difference <2%), although Pain in extremity and Arthralgia were almost twice as frequent in the C320 group as in the BDP subjects. This corresponds to the elevated level of Connective Tissue Disorders seen in the listing of AEs by SOC.

Table 61. AEs Occurring in 3% or more subjects in any treatment group, by system organ class and Selected preferred terms

SOC and Preferred Term	C320	BDP
N	776	776
All AEs	648 (83.5)	664 (85.6)
Nasopharyngitis	162 (20.9)	136 (17.5)
Upper Respiratory Tract Infection	151 (19.5)	148 (19.1)
Sinusitis	114 (14.7)	108 (13.9)
Asthma	96 (12.4)	100 (12.9)
Headache	81 (10.4)	81 (10.4)
Influenza	60 (7.7)	63 (8.1)
Bronchitis	51 (6.6)	62 (8.0)
Pharyngolaryngeal pain	42 (5.4)	51 (6.6)
Cough	44 (5.7)	43 (5.5)
Back pain	41 (5.3)	53 (6.8)
Diarrhea	35 (4.5)	24 (3.1)
Arthralgia	32 (4.1)	17 (2.2)
Urinary Tract Infection	30 (3.9)	16 (2.1)
Viral upper respiratory tract infection	30 (3.9)	24 (3.1)
Pain in extremity	27 (3.5)	15 (1.9)
Gastroenteritis viral	25 (3.2)	19 (2.4)
Sinus headache	18 (2.3)	25 (3.2)

Nausea	16 (2.1)	25 (3.2)
Lower Respiratory Tract infection	12 (1.5)	31 (4.0)
Oral candidiasis	11 (1.4)	49 (6.3)

Tabulating oropharyngeal adverse events separately, resulted in a balance of events in the two treatment groups (Table 62). Oral candidiasis, oropharyngeal candidiasis and Pharyngolarygeal pain were more common during BDP treatment while Pharyngitis and Dysphonia were more common during C320 treatment.

Table 62. Oropharyngeal Adverse Events

SOC and Preferred Term	C320	BDP
N	776	776
Oral candidiasis	1.4	6.3
Oropharyngeal candidiasis	0.1	0.4
Pharyngitis	2.6	1.8
Pharyngolaryngeal pain	5.4	6.6
Dysphonia	2.2	1.5

The incidence of AEs classified as Mild and Moderate was approximately equal with > 10% classified as severe. There were 105 (13.5%) events classified as severe in the C320 group and 116 (14.9%) were classified as severe in the BDP group.

Alert Terms

The following description occurs on page 151 of the study report:

> "Ophthalmologic findings considered by the ophthalmologist to be clinically relevant were defined in the clinical study protocol as alert terms. These alert term events were subject to expedited reporting to the sponsor's Pharmacovigilance department for blinded review while the study was still being conducted. The alert term events recorded in the Pharmacovigilance database consisted of diagnoses and symptoms, and therefore do not correspond directly with the TEAE reporting in the clinical database. The alert term events were not recorded in the CRF and were therefore not entered into the clinical database."

The section further states that while there were more of these events in the C320 treatment group, some of the events were increased in the BPD group. Conjunctivitis, eye pain, migraine, conjunctivitis allergic, and eye infection more common in the C320 group and vitreous floaters, chalazion, blepharitis, and pinguecula more common in the BPD group. Referring to the reference tables *(Listing C.3.2 – 19 and C.3.2 – 20)* the total tally of events appears to be 216 for ciclesonide and 172 for BDP.

Serious Adverse Events and Events Leading to Withdrawal

One subject died in each of the treatment groups. A 54 year old obese female who was randomized to ciclesonide and who had a strong family history of myocardial infarction but no personal history of chest pain, hypertension or diabetes was admitted to the hospital

unresponsive and cyanotic. She died later in the day and the autopsy attributed death to "acute coronary insufficiency due to marked atherosclerotic cardiovascular disease, resulting in fatal myocardial infarction." One 31 year old male completed treatment with BDP and 19 days later committed suicide.

Serious adverse events were reported for 31 (4.0%) of the C320 subjects and for 46 (5.9%) of the BPD subjects. The most common events were asthma (5 [0.6%] and 4 [0.5%] in the C320 and BPD subjects, respectively), lobar pneumonia (3 [0.4%] and 1 [.1%], respectively) and nephrolithiasis (2 [0.2%] and 0, respectively). All of the other events occurred in 1 or fewer individuals. If all forms of pneumonia are combined (lobar pneumonia, bronchopneumonia, pneumonia, and pneumonia primary atypical) then there were 6 (0.8%) cases of pneumonia in the C320 group compared to 2 (0.3%) in the BPD group.

Four subjects (1 C320 and 3 BPD) were assessed by the treating physician as sustaining a severe AE that was possibly related to treatment. The C320 subjects was a 47 year-old male who had a retinal hemorrhage diagnosed on day 263 of treatment during a routine follow-up ophthalmologic examination. On day 271 the study medication was discontinued due to the onset of the third asthma exacerbation. Of the subjects treated with BDP, one developed significant hypertension and extrasystoles during treatment, one had an elevation in transaminases and one developed a cataract that was treated with surgery. The subject with the elevated transaminases was also taking arthrotec (combination of diclofenac and misoprostol), simvastatin, and zafirlukast. The tranaminases remained elevated a week after stopping BPD, but decreased after stopping the other medication.

Withdrawal from treatment due to an adverse event occurred infrequently (28 [3.6%] and 20 [2.6%] of the C320 and BPD subjects, respectively). The excess withdrawals in the C320 group were classified as asthma (11 [1.4%] and 1 [0.1%] in the C320 and BPD groups respectively), dysphonia (2 [0.3%] and 0, respectively) and hypertension (2 [0.3%] and 0 respectively). One subject in each treatment group was withdrawn due to pneumonia/bronchopneumonia but 5 subjects were withdrawn from the BDP group due to an eye complaint compared to 2 in the C320 group. A total of 47 subjects (26 [3.4%] and 21 [2.7%] of the C320 and BPD groups, respectively) had study treatment withheld temporarily due to an adverse event.

Overdosage

A 58 year-old female took 16 puffs bid of C320 on one day and 12 puffs bid on another day. No adverse effects were reported.

3.2.3.6 Laboratory Results

The mean baseline, 4-month and 12-month values for all hematology and routine safety chemistry analyses were within the normal range.

Individual shifts in laboratory values and highly abnormal values were unusual. The eosinophil counts tended to increase over the year of treatment and this trend was more prominent in the

C320 group. Of the subjects who were normal at baseline, none was low at the end of the study and 15 (1.9%) of the C320 and 5 (0.6%) of the BPD subjects had values at the end of the study that were over the laboratory normal value. Similarly, 13/750 (1.7%) of the C320 and 7/748 (0.9%) of the BPD subjects had absolute eosinophil counts that increased more than the predefined abnormal amount (PCA) of 0.37 GG/L. The clinically important level for an increase in absolute eosinophil count was > 1.0 x 10^3 mm^3 and this occurred in three C320 subject and no BPD subjects. A clinically important increase in glucose was taken as >12.8 mmol/L and this occurred in one C320 subject and 3 BPD subjects. An increase of > 5.5 mmol/L was taken as the PCA for serum potassium and this occurred in 4 BPD subjects. The greatest increase was 5.7 mmol/L.

Abnormal laboratory values were reported as adverse events for 26 (3.4%) of the C320 and 30 (3.9%) of the BPD subjects (Table 63). Other than the subject with elevated transaminase (described above) the events were all considered mild to moderate and none resulted in termination of therapy.

Table 63. Abnormal Laboratory Results

SOC and Preferred Term	C320	BDP
N	776	776
All Laboratory results reported as AEs	26 (3.4)	30 (3.9)
Blood uric acid increased	4 (0.5)	1 (0.1)
Blood glucose increased	3 (0.4)	1 (0.1)
Alanine amiontransferase increased	2 (0.3)	3 (0.4)
Aspartate aminotransferase increased	2 (0.3)	3 (0.4)
Blood alkaline phosphatase increased	2 (0.3)	0
Hypokalemia	2 (0.3)	1 (0.1)
Blood cholesterol increased	1 (0.1)	2 (0.3)
Hypercholesterolemia	1 (0.1)	2 (0.3)
Oral candidiasis	0	3 (0.4)
Diabetes mellitus	0	1 (0.1)
Hematuria	0	2 (0.3)
White blood cell increased	0	3 (0.4)

Visual Acuity

During the conduct of the study, the DSMB requested heightened follow-up of subjects with changes in visual acuity (VA). Reports were submitted to the board for any subject with a 10-letter change in visual acuity along with the investigators assessment of cause. Of the 7 subjects with a fall in VA, three in the C320 and 2 in the BPD group had associated lens opacities.

3.2.3.7 Physical Examination including Vital Signs.

The mean values for vital signs were within the normal range in both treatment groups. Physical examinations included abnormalities in 30% of the subjects at 4 and 12 months in both treatment groups. However, in only 8% of the subjects had a normal exam at baseline and an abnormal exam at the end of the study.

Mean values for baseline and Week 12 vital signs were comparable across the treatment groups. Changes during treatment were uncommon and clinically insignificant.

3.2.3.3 Pregnancy

Fifteen pregnancies were reported during the course of the study. Of these 5 were females taking C320 and 5 were females taking BPD. In addition 3 female partners of male subjects in the C320 group and 2 female partners of males in the BPD group became pregnant. None of the subjects in the C320 group had a negative outcome. One BPD subject had a cesarean section at 40 weeks of gestation and at an unknown time after that reported that the baby's left kidney was larger than the right kidney. The baby was jaundiced at birth. No medical confirmation of this event was reported. There was, in addition, one spontaneous abortion at 20 weeks in the BPD group.

3.3 Summary and Discussion

This study was designed to compare the development of cataracts in adults treated with ciclesonide 320 mcg BID to adults treated with beclomethasone 320 mcg BID. Treatment lasted for 12 months and the outcomes were careful measurements of lens opacities using the LOCS III scoring system. The primary outcome, the difference in the proportions of subjects developing Class I (the smallest) changes, was consistently slightly smaller in the ciclesonide-treated subjects when compared to subjects treated with BDP. On the other hand the LOCS III scoring system is made up of three components. It assesses opacities in the nucleus, the cortical, and the posterior subcapsular region. Opacification of the PSC region is more typical of the reaction to corticosteroid treatment than in opacification of the other two regions. While the differences in treatment were quantitatively small, the mean increase in PSC score was larger in the C320-treated subjects compared to the BDP subjects. Also, in subjects over 60 years of age, the increase in Class of lens opacities was greater in the C320 subjects Therefore, while the overall evaluation of lens opacities using the LOS III grading system showed fewer increases for the ciclesonide-treated subjects compared with subjects treated with BPD, some of the sub-group analysis suggest that the risk for lens opacification during treatment with inhaled ciclesonide is not inconsequential,

4 Study # XRP1526B/343

A PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO CONTROLLED, NONINFERIORITY STUDY ASSESSING THE EFFECTS OF CICLESONIDE METERED DOSE INHALER 50 µG/DAY AND 200 µG/DAY (EX-VALVE) ADMINISTERED ONCE DAILY ON GROWTH IN CHILDREN WITH MILD PERSISTENT ASTHMA

4.1 Protocol

4.1.1 Administrative

Enrollment Dates:	December 29, 2000 – September 15, 2004
Screening Centers:	63 centers in the United States, 12 in Argentina, 4 in Chile, and 6 in Venezuela
Sponsor's medical expert:	
CRO:	.

4.1.2. Objective/Rationale

The primary objective of this study was to determine if ciclesonide MDI 50 µg/day or 200 µg/day (ex-valve) (40 µg/day or 160 µg/day [ex-actuator]) administered once daily in the morning is non-inferior to placebo with respect to growth velocity in children with mild persistent asthma following a 12-month treatment period.

Secondary objectives were to investigate changes in growth in terms of bone age (wrist X-ray), and to investigate maintenance of asthma control and safety, after administration of ciclesonide MDI 40 µg/day or 160 µg/day, compared to placebo.

4.1.3. Study Design

This was a multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group study in prepurbertal patients with mild persistent asthma treated previously with ICS. Eligible subjects were enrolled into a 6-month run in period at which time they were observed and baseline stadiometer measurements were collected. All corticosteroid medications were discontinued at the screening visit. During the last 2 weeks of the run-in the subjects received a placebo inhaler to use at home and baseline laboratory, X-ray, and PFT data were obtained. At the end of the run-in subjects were randomized (1:1:1) to receive placebo, ciclesonide 40 mcg QD (C40) or ciclesonide 160 mcg QD (C160) for 12 months.

The subjects were seen in the clinic at screening, 3 months and at randomization (6 months after screening visit). After randomization they were seen at 2 weeks and 1, 2, 3, 4, 6, 8, and 12 months after randomization. A final follow-up visit occurred 2 months after stopping study medication. Stadiometry was performed at all visits. The AM-FEV_1 (after 6 hours without albuterol and prior to study drug) was performed 6, 3, and 0.5 months prior to randomization; at randomization and at 2 weeks, and 2, 4, 6, 8, 10, 12, and 14 months. Diaries were maintained throughout the treatment period to record adverse events, study medication doses and concomitant medications.

Protocol Amendments

Amendment 1 (March 28, 2001) stipulated that the dose of study medications was to be given between 8:00 and 8:30 AM instead of in the early evening. This was to facilitate obtaining PFTs prior to the dose.

Amendment 2 (January 29, 2002) changed the dosing time from 8:00 to 8:30 to 6:00 to 11:00 AM. In addition the normal ranges for urinary cortisol were amended by the central laboratory.

4.1.4. Study Population

Inclusion Criteria

- Females aged 5 to 7.5 years and males aged 5 to 8.5 years at screening
- History of mild persistent asthma for ≥3 months prior to screening
- Forced expiratory volume in one second (FEV_1) ≥80% of predicted at screening, following at least a 4-hour albuterol withhold
- FEV_1 ≥80% of predicted at Visit 3 and at Visit 4, following at least a 4-hour albuterol withhold
- Current asthma therapy with non-corticosteroid asthma medications on an as-needed (i.e., albuterol) or daily (i.e., cromones, leukotriene receptor antagonists, long-acting β_2-agonists, theophylline, etc.) basis, or low doses of ICS
- Tanner Classification of Sexual Maturity no greater than Stage 1
- Height within normal limits (5th to 95th percentile inclusive) at screening
- Growth velocity ≥3rd percentile during the 6-month run-in period
- Ability to demonstrate the effective use of the MDI devices and perform reproducible PFTs
- Willingness and ability to comply with the study procedures, and appropriate written informed consent for the subject obtained from parent or guardian.

Exclusion Criteria

- Asthma severity:
    - History of life-threatening asthma, including any history of significant hypercarbia (pCO_2 >45 mm Hg), prior intubation, respiratory arrest, or seizures as a result of an exacerbation of asthma

  - Severe respiratory impairment (≥2 inpatient hospitalizations within 1 year prior to Visit 1, or any emergency room visit for asthma within 6 months prior to Visit 1)
- Other medical conditions:
  - History or evidence of abnormal growth
  - Any disease or condition that might substantially affect growth
  - Any clinically relevant deviation from normal in either the general physical examination or laboratory parameters, as evaluated by the principal investigator, that might interfere with the study, that might require treatment, or might interfere with the ability to obtain height measurements
  - History of substance abuse, mental illness or retardation
  - History or presence of glaucoma or posterior subcapsular cataracts
  - Known hypersensitivity to any ingredients in the study medications
  - Abnormal oropharyngeal examination at Visit 3. Any physical findings suggestive of oral candidiasis were to be verified with a culture analyzed by the central laboratory. A positive culture for oral candidiasis disqualified the subject from the study
- Preceding and concomitant medication:
  - Previous daily or alternate-day OCS treatment for a total of ≥60 days within the 2 years prior to Visit 3 and/or any use of OCS within 30 days prior to Visit 1 or during the run-in period. Subjects requiring OCS during the run-in period were not to be included in the study;
  - Treatment with ICS for more than one 14-day course during the run-in period or during the 30 days prior to Visit 1 with more than the following doses of ICS:
    - Beclomethasone: 168 μg/day
    - Triamcinolone: 400 μg/day
    - Flunisolide: 500 μg/day
    - Fluticasone: 100 μg/day
    - Budesonide Turbuhaler: 200 μg/day
  - Treatment with intranasal corticosteroids during the baseline period for more than two 14-day courses at least 3 months apart. Subjects were not allowed to use any intranasal corticosteroids during the double-blind treatment period
- Inability or unwillingness to use all study medication devices as instructed.

Withdrawal Criteria

- Any subject who progressed to Tanner Stage 2
- Any female who developed menses
- If a subject required a prohibited medication
- If the urine cortisol corrected for creatinine was abnormal at the randomization visit
- The following conditions could be an indication for withdrawal:
  - Use of a non-study ICS
  - A respiratory illness
  - Less than 75% compliance with the study medication

4.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Placebo MDI BID (1 puff QD)
- Ciclesonide MDI 160 mcg QD (1 puff QD)
- Ciclesonide 40 mcg BID (1 puff QD)

HFA albuterol (100 μg per actuation [90 μg ex-actuator] was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Topical corticosteroids: Low-potency topical corticosteroid creams or ointments equivalent to ≤1% hydrocortisone were permitted for occasional dermatologic use
- Non-steroidal asthma medications:
  - Inhaled short-acting β_2 agonists (albuterol),
  - Leukotriene receptor antagonists (montelukast sodium, zafirlukast),
  - Cromones (cromolyn sodium, nebulized cromolyn, nedocromil),
  - Xanthine derivatives (theophylline, aminophylline);

The following medications were to be withheld prior to PFTs conducted at Visits 3 to 14:

- Inhaled or nebulized albuterol or other short-acting β_2-agonists for at least 4 hours
- Oral β_2-agonists (albuterol tablets) for at least 12 hours
- Atrovent® (ipratropium bromide) or immediate-release theophylline for at least 12 hours
- Serevent®(salmeterol xinofoate) for at least 24 hours
- Sustained-release theophylline for at least 48 hours

The following concomitant medications were prohibited from screening onward:

- Any ICS or ICS/LABA combination other than the study medication
- Any intranasal corticosteroid
- Any investigational drug other than randomized study medication

Compliance was assessed by the patient's notation in the diary that the medication was taken and by weighing the returned canisters. Non-compliance was a possible indication for exclusion if there was more than 2 periods with 5 consecutive days of non-compliance.

Efficacy Evaluation

Height was measured using standard stadiometry techniques. The stadiometer was calibrated within 4 hours prior to each measurement. Four acceptable measurements were taken at each visit and the median value was used in the analysis. Measurements were made with the subject in bare feet and care was taken that they stood tall.

Wrist X-rays were obtained to assess bone age. The films were graded according to the Greulich and Pyle radiographic atlas [4].

Spirometry was performed according to the 1995 ATS standards, and the FEV_1 in liters and as a percent of predicted was recorded. Measurements were obtained in triplicate within 1 hour of the previous day's dose of study medication, and 4 hours after the last albuterol dose. Peak flow meters were distributed at the discretion of the investigator. The readings were not included in the case report forms.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. In addition, 24-hour urines for cortisol were collected at 39 sites and 10-hour urine cortisol measurement were obtained at 36 sites (5 sites collected both) at randomization and at the end of the study. Oropharyngeal examination was performed 2 weeks prior to randomization, and at 2, 4, 6, 8, 10, 12 and 14 months of follow-up.

A summary of the study procedures is shown in Table 64.

Table 64. Schedule of Study Events

Activity	Run-in period (Screening/Baseline/ Qualifying Phases)			Double-blind period										Follow-up period
				Randomization									Final/ Early D/C[b]	
Visit	1[a]	2[a]	3[a]	4	5	6	7	8	9	10	11	12	13	14
Month or week	-6 mon	-3 mon	-2 wk	0	2 wk	1 mon	2 mon	3 mon	4 mon	6 mon	8 mon	10	12 mon	14 mon
Study day	-180±7	-90±7	-14±5	1	14±3	30±5	60±5	90±5	120±5	182±5	240±5	300±5	365±5	
Informed consent/assent	X													
Medical history	X													
Physical exam (w/Tanner evaluation)	X		X						X		X		X	
Oropharyngeal examination[c]			X				X		X	X	X	X	X	X
Pulmonary function test	X	X	X	X	X		X		X	X	X	X	X	X
Vital signs	X		X	X	X		X		X	X	X	X	X	X
Clinical laboratory sample			X							X			X	
Urine cortisol test			X[d]										X	X
Dispense urine collection container			X									X	X	
Hand-wrist X-ray			X										X	
Inclusion/exclusion criteria review	X		X	X										
Height measurement by stadiometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X			X		X	X	X	X	X	X
Issue diary	X	X	X	X	X		X		X	X	X	X	X	
Dispense peak flow meter	X													
Collect and review diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense single-blind study drug			X											

Activity	Run-in period (Screening/Baseline/ Qualifying Phases)			Double-blind period										Follow-up period
				Randomization									Final/ Early D/C[b]	
Visit	1[a]	2[a]	3[a]	4	5	6	7	8	9	10	11	12	13	14
Month or week	-6 mon	-3 mon	-2 wk	0	2 wk	1 mon	2 mon	3 mon	4 mon	6 mon	8 mon	10	12 mon	14 mon
Study day	-180±7	-90±7	-14±5	1	14±3	30±5	60±5	90±5	120±5	182±5	240±5	300±5	365±5	
Collect single-blind study drug				X										
Dispense double-blind study drug				X	X	X	X		X	X	X	X		
Collect double-blind study drug					X	X	X	X	X	X	X	X	X	
Weigh study drug canister			X	X	X	X	X	X	X	X	X	X	X	
Dispense rescue medication and update study medication log	X	X	X	X	X	X	X	X	X	X	X	X		
Instruct subject on emergency treatment	X	X		X	X		X		X	X	X	X		
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X	X	X	X	X	X	

Note: For double-blind treatment months not listed for a scheduled visit (months 5, 7, 9, and 11), phone calls for compliance were to be made.

[a] *Subject (and parent or guardian) was to be contacted twice between Visit 1 and Visit 2 and twice between Visit 2 and Visit 3.*

[b] *For subjects who discontinue (D/C) double-blind study treatment early (before 50 weeks).*

[c] *If a fungal infection of the mouth or throat was suspected, a culture was to be obtained to confirm the diagnosis.*

[d] *The results from the urine sample had to be reviewed prior to randomization.*

4.1.6. Statistical Analysis Plan

Analysis Variables

The primary growth endpoint was the growth velocity during the double-blind treatment period. The primary estimate of growth velocity was the linear regression estimate of growth velocity which was determined from the slope of the linear regression using all of the available measurements (at least 3). A supportive estimate was base on the difference in height measurement at the last available visit compared to the baseline value. An additional supportive analysis was performed using only subjects who completed at least 50 weeks of treatment.

Secondary growth endpoints were a shift analysis of change in growth velocity, change from baseline in height, growth velocity during the follow-up period, and shift analysis of bone age vs chronologic age, and a completer analysis. Analyses were further performed on a subgroup of subjects who had not reached sexual maturity during the study, and a subgroup including subjects who were never treated with non-study corticosteroids during the trial.

Pulmonary function was analyzed as the change from baseline at each visit.

Withdrawal was analyzed as the time to and rate of withdrawal from double-blind treatment due to lack of efficacy, time to and rate of withdrawal from double-blind treatment due to lack of efficacy or asthma adverse event, and time to and rate of withdrawal for any reason.

Adverse events and laboratory values were analyzed in the standard manner. For the laboratory values a Predefined change abnormal (PCA) is a change from baseline to an abnormal level and is an increase from baseline of at least a predefined amount. Values for the PCA were defined for each analate. The Clinically noteworthy abnormal laboratory value (CNALV) was a value that was considered medically important by the sponsor. They were predetermined for glucose levels (> 2 times ULN) and absolute eosinophil counts (> $1.0 * 10^3$cells/mm^3).

A total of 39 study sites were assigned to collect 24-hour urine samples for cortisol and 36 sites were assigned to collect 10-hour urine samples. Samples were obtained at baseline, end of active treatment and at the end of 2 months off of treatment. The free cortisol and cortisol corrected for creatinine were reported. An additional analysis of the "valid" samples, based on the quality of the urine sample, were planned. However, only 13% of the samples qualified so the sub-set analysis was not performed. The number of invalid samples was assumed to be related to the fact that the quality criteria were based on adult values.

Sample Size

Sample size was calculated assuming a common SE of 1.4 cm/year, a non-inferiority delta of 0.5 cm/year, and 90% power to conclude non-inferiority. Non-inferiority of each ciclesonide dose vs placebo was assessed using a 95% one-sided confidence interval. Using these specifications a sampled size of 135 subjects per treatment arm was required. Assuming a 10% drop-out rate 150 subjects per arm (total 450) were planned for recruitment. To be absolutely sure of enough subjects, 661 were randomized.

Study Populations

The safety population included all subjects who received at least one dose of double-blind study medication.

The modified intent to treat mITT population included all randomized subjects who received at least 4 months of study medication and who had at least one stadiometer reading at baseline and 4 months.

The per-protocol (PP) population consisted of all the subjects in the ITT population who did not have an important protocol deviation. The determination about the presence of an important protocol deviation was made for each subject prior to breaking the blind. The list of major protocol violation includes the following events:

- The subjects was > Tanner stage 1 at baseline
- Study medication for < 4 months
- Diary recorded compliance <70% during double-blind treatment
- Use of prohibited medications as described in exclusion criteria
- Height at screening M 5th percentile
- Growth velocity during the run-in < 3rd percentile
- Beyond age specification

In addition, individual measurements were not included if they had been made directly after a short course of corticosteroids.

Primary Analysis

The primary objective of the study was to demonstrate the non-inferiority of ciclesonide on growth compared to placebo. The analysis used an ANCOVA of the linear regression estimate of growth velocity with baseline growth velocity, height, age and age^2, gender, gender-by-age interaction, race, previous corticosteroid use and age of asthma diagnosis as co-variates. The non-inferiority of ciclesonide treatment was assessed by comparing the 2 ciclesonide dose regimens against placebo using a 2-sided 95% confidence interval. A stepwise procedure was used to control the Type I error rate. The initial 2-sided 95% confidence interval was for the difference between ciclesonide 40 µg/day and placebo. If non-inferiority of ciclesonide 40 µg/day compared to placebo could be concluded (lower limit of ciclesonide 40 µg to placebo difference was greater than –0.5 cm/yr), then the non-inferiority of ciclesonide 160 µg/day as defined by the 2-sided 95% confidence interval for ciclesonide 160 µg/day minus placebo was formally assessed. The non-inferiority bound of -0.5 cm/year was derived from the results of previous studies comparing growth in pre-pubertal children treated with fluticasone and placebo.

4.2. Results

4.2.1. Study Population

Disposition

A total of 1127 subjects were screened and 661 were randomized and treated; 221 to placebo, 221 to C40, and 219 to C160. Of the screening failures, 35 were not enrolled due to abnormal growth at baseline. The mean height of the screen failures at baseline was 118.78 cm compared to 119.59 cm for the subject enrolled.

Of the randomized subjects, 369 (83.9%) completed the course of treatment. Withdrawal was the same in the placebo and C40 groups (18.1%) and slightly less (14.2%) in the C160 group (Table 65). Adverse reactions were the most common indication for withdrawal and the distribution was similar to the distribution of overall withdrawals (6.3, 6.3, and 3.7% in the placebo, C40, and C160 subjects, respectively). Lack of efficacy was reported as a reason for withdrawal in only 2 (0.9%) of the placebo subjects and 1 C160 subject, although protocol violations were reported in 4.5% of the placebo subjects compared with 1.8 and 2.3% of the C40 and C160 subjects. There were no deaths. A total of 169 (76.5%), 164 (74.2%), and 164 (74.9%) of the placebo, C40, and C160 subjects, respectively, completed the treatment and follow-up phase of the study. The completer population consisted of 183 placebo, 184 C40, and 187 C160 subjects. The discrepancy between these numbers and the number discontinued early is due to a few subjects who were treated for more than 350 days, but who stopped study medication prior to the last visit, which was scheduled for up to a few days later than 350 days after starting the medication.

Table 65. Disposition of Subjects in Study 343

	Placebo	Dose of Ciclesonide		
	---	40 QD	160 QD	Overall
Randomized & treated	221	221	219	440
Discontinued	40 (18.1)	40 (18.1)	31 (14.2)	71 (16.1)
Reason for discontinuation:				
Adverse event	14 (6.3)	14 (6.3)	8 (3.7)	22 (5.0)
Did not wish to continue	7 (3.2)	5 (2.3)	6 (2.7)	11 (2.5)
Lost to follow-up	6 (2.7)	4 (1.8)	5 (2.3)	9 (2.0)
Poor compliance	3 (1.4)	5 (2.3)	4 (1.8)	9 (2.0)
Protocol violation	10 (4.5)	4 (1.8)	5 (2.3)	9 (2.0)
Lack of efficacy	2 (0.9)	0	1 (0.5)	1 (0.2)
Death	0	0	0	0
Other	5 (2.3)	10 (4.5)	7 (3.2)	17 (3.9)
Entered follow-up period	179 (81.0)	177 (80.1)	184 (84.0)	361 (82.0)
Completed 55 days of follow-up	169 (76.5)	164 (74.2)	164 (74.9)	328 (74.5)

There were only 19 reported protocol violations that resulted in withdrawal. Of the 10 placebo subjects withdrawn due to protocol violations, 6 were due to use of prohibited asthma medications. These 6 subjects remained in the mITT population. Four subjects were excluded

from the mITT due to procedural errors: incorrectly measured growth, accidentally breaking the blind, incorrect timing of visit and low growth at baseline. Four subjects in the C40 group were withdrawn due to protocol violation: three due to use of prohibited medication and 1 due to an abnormal urinary cortisol at baseline. The latter subject was excluded from the mITT. In the C160 group there were 5 subjects withdrawn due to protocol violations: 2 for prohibited medications, 1 low FEV_1, 1 was excluded at the investigator's discretion and one for poor compliance.

Compliance with study medication was high: >90% compliance in >85% of the subjects in each treatment group by diary record. Compliance assessed by canister weight was slightly lower: 79.6, 81.9, and 80.4% in the placebo, C40, and C160 groups, respectively. This was attributed to errors in canister weighing procedures.

A total of 52 (7.9%) of the randomized subjects were excluded from the ITT population. The exclusion was based on a failure to receive medication and/or to have a stadiometer height after 115 days of treatment. The mITT population included 609 subjects: 210, 206, and 202 placebo, C40 and C160 subjects, respectively.

There were 126 (19.1%) subjects excluded from the PP population: 45 in the placebo group, 41 in the C40 group, and 40 in the C160 group. Most of the exclusions were due to the same exclusions that resulted in exclusion from the mITT or due to ingestion of prohibited medication.

Demographics

Of the 661 subjects randomized 67.2% were male, and the mean age (Range) was 6.7 (5.0 – 8.6) years. The girls were < 7.5 and all but one of the boys was <8.5 years of age. The one boy who was 8.6 years of age did not progress beyond Tanner Stage I during the trial. The predominant racial group was white (71.0% compared with 4.2% black and 24.8% other). All of the characteristics were approximately equal across the treatment groups (Table 66). Approximately 60% of the subjects in each group was Hispanic which is due in part to the large enrollment in South America. Seventy-three percent of the subjects were enrolled in Argentina, Chile, or Venezuela, compared with 27% in the US despite the larger number of centers located in the USA. On average 7 plus subjects were enrolled at each US site compared to 30 plus at each site in South America.

Table 66. **Demographic Characteristics of the Enrolled Population**

		Dose of Ciclesonide		
	Placebo	40 QD	160 QD	Overall
Total ITT Population	221	221	219	440
Gender, % M	(66.5)	(67.9)	(67.1)	(67.5)
Age, mean (SD)	6.7 (0.95)	6.6 (0.97)	6.7 (0.93)	6.7 (0.95)
Race, %				
White	69.7	68.8	74.4	71.6
Black	4.5	4.1	4.1	4.1
Other	25.8	27.1	21.5	24.3

Hispanic, %	57.5	60.2	62.6	61.4
Geographic region, %				
USA	30.3	29.0	25.1	27.0
South America	69.7	71.0	74.9	73.0
Stadiometer height, mean cm (SD)	120.1 (7.5)	119.3 (7.2)	119.7 (6.9)	119.5 (7.0)
Weight, mean kg (SD)	24.9 (5.7)	24.6 (5.2)	24.8 (5.6)	24.7 (5.4)

The mean height (SD) of the entire group was 119.7 (7.2) cm and the mean weight (SD) was 24.8 (5.5) kg. The means were similar across the treatment groups.

Because the run-in lasted for 6 months, the mean age, height, and weight of the children had increased by the time of randomization as shown in Table 67. Approximately 48% of the children had a chronologic age that was older than the radiographic bone age, suggesting bone mineralization delay in a substantial number of the children. The percentage of children with delayed bone mineralization did not differ across the treatment groups or geographic regions.

Reviewer: The delayed bone mineralization was attributed to the underlying disease despite the fact that the asthma was mild by PFT criteria (mean FEV1 = 94% predicted, see below) and only 20% of the children had taken corticosteroids prior to enrollment. Findings by region…

Table 67. Demographic Variables at Randomization

		Dose of Ciclesonide		
	Placebo	40 QD	160 QD	Overall
Total ITT Population	221	221	219	440
Age, mean (SD)	7.2 (0.95)	7.1 (0.97)	7.2 (0.93)	7.2 (0.95)
Stadiometer height, mean cm (SD)	123.4 (7.6)	122.6 (7.1)	122.9 (6.9)	122.7 (7.0)
Weight, mean kg (SD)	26.4 (6.3)	26.1 (5.5)	26.3 (6.1)	26.2 (5.8)
Bone age relative to chronologic age, n (%)	219	221	219	440
High	36 (16.3)	44 (19.9)	41 (18.7)	85 (19.3)
Normal	75 (33.9)	70 (31.7)	75 (34.2)	145 (33.0)
Low	108 (48.9)	107 (48.4)	103 (47.0)	210 (47.7)

Reviewer: Fifteen to 20 subjects were not included in the mITT population. The demographic characteristics of mITT were similar to the characteristics of the randomized subjects .

Height was measured during the 6-month baseline period to obtain a baseline value for linear growth (Table 68). The baseline mean values (SD) for the subjects in the C160 treatment group were lower (6.20 [1.6]) than in the placebo (6.45 [1.5]) and C40 groups (6.59 [1.3]). This difference was seen in all of the subgroups, but was particularly prominent in the older children. In the girls older than 7, the mean baseline growth (SD) was 6.57 (1.7) and 5.90 (1.4) cm/yr in the children treated with placebo and C160, respectively. In the boys older than 8 the respective rates were 650 (1.1) and 5.58 (1.8). The relatively low growth rates in the C160 group were

reported in subjects enrolled in the USA and in South America. It is noted that relatively few US subjects (47) were treated with C160.

Table 68. Baseline growth of mITT population calculated using linear regression of all measured points

		Dose of Ciclesonide		
	Placebo	40 QD	160 QD	Overall
mITT population	201	206	202	408
Overall, mean (SD)	6.49 (1.5)	6.59 (1.3)	6.20 (1.6)	6.39 (1.5)
Females, n	67	67	71	138
All, cm/yr	6.54 (1.5)	6.64 (1.4)	6.18 (1.6)	6.40 (1.5)
≤ 7 years, cm/yr	6.52 (1.3)	6.95 (1.5)	6.32 (1.6)	6.62 (1.6)
> 7 years, cm/yr	6.57 (1.7)	6.09 (1.0)	5.90 (1.4)	5.99 (1.2)
Males, n	134	139	131	270
All, cm/yr	6.47 (1.5)	6.56 (1.3)	6.21 (1.6)	6.39 (1.4)
≤ 8 years, cm/yr	6.45 (1.6)	6.73 (1.3)	6.46 (1.4)	6.60 (1.3)
> 8 years, cm/yr	6.50 (1.1)	5.85 (1.5)	5.58 (1.8)	5.85 (1.5)
Region				
USA, n	56	60	47	107
Cm/yr	6.65 (1.9)	6.66 (1.3)	6.37 (1.5)	6.53 (1.4)
South America, n	145	146	155	301
Cm/yr	6.43 (1.3)	6.56 (1.3)	6.15 (1.5)	6.35 (1.5)

Reviewer: The difference in growth rates in the treatment groups could not be explained by differences in steroid use prior to enrollment because steroid use prior to enrollment was similar in all of the treatment groups (see below). In addition, when the baseline rate of growth was analyzed by prior steroid use, baseline growth was not slower in those who had previously taken steroids.

Asthma

Asthma was diagnosed 3.8, 3.8, and 4.0 years prior to enrollment in the placebo, C40, and C160 subjects respectively. The mean absolute FEV_1 was 1.4 L in each treatment group and this corresponded to a FEV_1 % predicted of 93.0 to 96.2% (Table 69).

Table 69. Characteristics of Asthma in the Randomized Population

		Dose of Ciclesonide		
	Placebo	40 QD	160 BID	Overall
Total	221	221	219	440
Duration				
Years, mean (SD)	3.8 (2.0)	3.8 (2.0)	4.0 (2.0)	3.9 (2.0)
Range	0 - 7.9	0 - 8.2	0.1 – 8.2	0.1 – 8.2
FEV_1				
Mean Absolute, ml (SD)	1.4 (0.29)	1.4 (0.28)	1.4 (0.26)	2.65 (0.65)
Mean % predicted, % (SD)	93.0 (9.7)	96.2 (12.0)	94.4 (11.0)	79.2 (8.3)

At least 93% of the subjects in each treatment group took a ß-adrenergic agonist in the 30 days prior to enrollment. The next most common medication was a leukotriene receptor antagonist

which was taken by 52.0, 52.0, and 47.9% of the placebo, C40, and C160 subjects, respectively. Some form of inhaled corticosteroid was taken by 19.0, 19.5, and 21.0% of the placebo, C40, and C160 subjects, respectively. The mean values and distributions for these variables were not different in the mITT population. During the run-in period, medication usage was similar to that seen prior to enrollment except that inhaled corticosteroid use decreased to 10.0, 10.9, and 12.8% of the placebo, C40, and C160 subjects.

4.2.2. Efficacy Results

Primary Efficacy Outcome

The primary analysis was performed on the growth rates during the run-in and randomized treatment period using a linear regression method of all the measurements. However the growth rate during follow-up (after study medication was discontinued) was obtained at only two time points and the analysis was based on the difference between the two points. As a supportive analysis and to aid in the comparison between the randomized treatment period and the follow-up period, growth was also analyzed by the two-point method during randomized treatment.

Using the linear regression method of analysis, the mean growth rate was less during randomized treatment than during the run-in in all of the treatment groups. The baseline growth rates (6.49 and 6.59 cm/yr in the placebo and C40 groups, respectively) and changes that occurred during randomized treatment (decrease of 0.73 and 0.84 cm/yr in the placebo and C40 group respectively) were similar in the placebo and C40 groups. The children in the C160 group had a slightly lower baseline growth rate (6.2 cm/yr), and the unadjusted change during treatment was a decrease of 0.60 cm/yr (Table 70).

Comparing growth during the follow-up period to that observed during the randomized treatment period (using the 2-point analysis for both time periods) there was a less than 0.1 cm/year difference in the placebo and C160 group, while growth in the C40 group was 0.21 cm/year higher during the follow-up than during randomized treatment. If the 2-point analysis of the follow-up period is compared to the linear regression results for the randomized treatment period for the placebo and C160 subjects, there again appears to very little effect of treatment. In the C40 group growth during the follow-up period was 0.31 cm/yr greater than during randomized treatment. There was no apparent explanation for the lower baseline growth rate in the C160 group as the baseline age, height, and pre-enrollment steroid use were similar across the treatment groups. Concomitant ICS use was less in the C160 group (6.4%) than in the other treatment groups (10.0 and 10.4% in the placebo and C40 groups, respectively).

Table 70 . Growth Velocity (cm/year) During Baseline Period, Randomized Treatment, and Follow-up

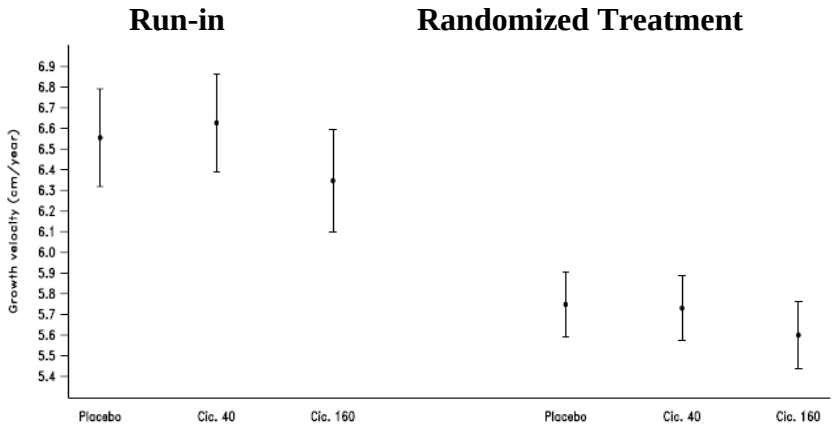
		Dose of Ciclesonide		
	Placebo	40 QD	160 BID	Overall
Total	201	206	202	408
Run-in, mean (SD) (Linear Regression)	6.49 (1.5)	6.59 (1.3)	6.20 (1.6)	6.36 (1.5)

Median (Range)	6.32 (3.5-15.5)	6.46 (3.2-10.6)	6.15 (1.5-12.6)	6.36 (1.5-12.6)
Randomized Treatment (Linear Regression)				
Mean (SD)	5.76 (1.0)	5.75 (1.0)	5.60 (0.9)	5.67 (1.0)
Median (Range)	5.74 (2.3-10.1)	5.66 (3.3-8.8)	5.58 (2.2-9.5)	5.64 (2.2-9.5)
Randomized Treatment (2-point assessment) Mean (SD)	5.84 (0.08)	5.85 (0.09)	5.66 (0.09)	
Follow-up (2-point assessment) Mean (SD)	5.75 (3.2)	6.06 (4.1)	5.64 (3.4)	5.85 (3.8)

Reviewer: The Applicant used the linear regression method for the randomized treatment period because there were multiple measurements and the estimate of growth was thought to be more precise. However, if growth was not linear throughout the period, and it probably was not, then the two point estimate may actually be more accurate. The FDA statistical reviewer performed an analysis of growth in 6-month periods using the 2-point comparisons. The growth during follow-up covered only a 2 month period. The baseline mean (SD) growth was 6.47 (1.47), 6.55 (1.28), and 6.22 (1.57) in the placebo, C40, and C160 groups respectively. The baseline growth was significantly less in the C160 subjects than in the other two groups. The growth rate in the first 6 months of randomized treatment was lower than the growth rate during the run-in period in all of the treatment groups (5.61 [1.51], 5.67 [1.53], and 5.59 [1.45] in the placebo C40, and C160 groups, respectively). In the second six months of randomized treatment growth increased slightly in the placebo and C40 groups (5.87 [1.44] and 5.88 [1.47], respectively) and fell further in the C160 group (5.55 [1.32]). During the follow-up period, after randomized treatment had been discontinued, the growth rate in the placebo group decreased slightly and it increased in the C40 and C160 groups (5.75 [3.17], 6.06 [4.11], and 5.64 [3.37] in the placebo C40, and C160 groups, respectively). The most dramatic change in growth rate occurred between the run-in period and the first 6 months of randomized treatment, and the growth rate decreased in all of the treatment groups. It is unlikely that this was due to the increased age of the subjects as the rates increased subsequently despite the increased age of the subjects and no change in randomized treatment. .

The mean growth results are shown graphically in Figure 10.

Figure 10. **Growth Velocity During Run-in and Randomized Treatment**



The statistical analysis of the difference between treatment groups showed no difference (Table 71) comparing ciclesonide to placebo treatment. The values in the table were obtained using the linear regression method. The results of the statistical analysis using the two point method were essentially identical.

Table 71. **Growth Velocity Comparing Active Treatment to Placebo**.

Treatment	N	LS mean (SE) Cm/yr	Difference from placebo		
			LS mean (SE)	95% CI	Inferiority p-value
Placebo	201	5.75 (0.08)			
C40	206	5.73 (0.08)	-0.02 (0.09)	-0.19, 0.16	0.0001
C160	202	5.60 (0.08)	-0.15 (0.09)	-0.33, 0.03	0.0001

The results of the per-protocol analysis were also supportive of the conclusion of non-inferiority. The results of other supportive analyses were also almost identical. This included an analysis restricted to subjects who completed the study, and an analysis performed on all subjects who had measurements at 12 months of follow-up even if they had discontinued the study medication at some time in the past. For this analysis the mean (SE) growth was 5.78 (0.09) cm/yr in the placebo (n=191), 5.78 (0.08) cm/yr in the C40 (n=193) and 5.65 (0.09) cm/yr in the C160 (n=194) subjects.

Secondary Efficacy Outcomes

Few subjects had extremely high or low growth rates during the double-blind treatment period. Most of the values lay between 25 to 75%: 64.2, 55.8, and 64.9% of the subjects in the placebo, C40, and C160 groups, respectively. Less than 2% of the subjects in any of the treatment groups had growth curves that were <3% or >97% of the predicted normal values.

Reviewer: It is not stated explicitly, but I believe the percentiles refer to the Baumgartner Growth Velocities percentiles (3)

Compared to placebo, there were no systematic differences in the shift in growth category (high, normal, low growth rates) in the subjects treated with ciclesonide (Table 72).

Table 72. Percentage of Subjects Within each Treatment Group with Shifts in Growth Category During Double-Blind Treatment

	Height Compared to Normal Standards*			
Study / EndBaseline	Low	Normal	High	Total
Placebo				
Low	5.0	8.5	3.4	19.4
Normal	9.0	30.8	7.5	41.8
High	5.0	24.9	6.0	38.9
Ciclesonide, 40 mcg				
Low	3.9	10.7	2.9	20.4
Normal	12.6	23.8	6.8	38.0
High	7.8	21.3	10.3	41.7
Ciclesonide, 160 mcg				
Low	5.9	16.4	5.5	23.9
Normal	9.4	28.2	2.0	39.1
Hihg	7.5	20.3	5.0	37.2

* Low, normal, and high is defined in terms of normal growth curves. For this table, Low = lower 25th percentile, Normal = 25 to 75th percentile, and High = higher than the 75th percentile.

The distribution of bone age as related to chronological age was also examined at the beginning and end of the trial. A high chronological age compared to bone age suggests a slowing of bone maturation. The percentage of subjects who went from a normal ratio to a high ratio (delayed bone maturation) was 9.0, 8.6, and 9.1% in the placebo, C40, and C160 groups, respectively (Table 73).

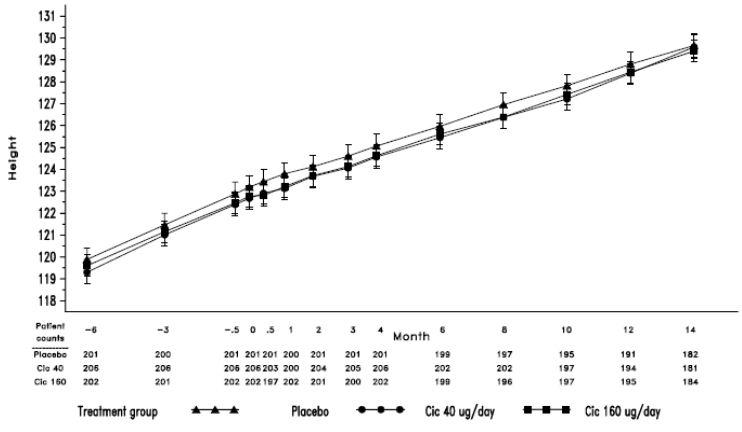
Table 73. Changes in Chronological/Bone Age during Treatment

Treatment Baseline status	Number (%) of subjects at end of double-blind treatment period			
	Low	Normal	High	Total
Placebo				
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	11 (6.2%)	122 (68.9%)	7 (4.0%)	140 (79.1%)
High	0 (0.0%)	16 (9.0%)	21 (11.9%)	37 (20.9%)
Ciclesonide 40 µg/day				
Low	6 (3.2%)	3 (1.6%)	0 (0.0%)	9 (4.9%)
Normal	15 (8.1%)	115 (62.2%)	8 (4.3%)	138 (74.6%)
High	0 (0.0%)	16 (8.6%)	22 (11.9%)	38 (20.5%)
Ciclesonide 160 µg/day				
Low	3 (1.7%)	1 (0.6%)	0 (0.0%)	4 (2.3%)
Normal	11 (6.3%)	119 (68.0%)	2 (1.1%)	132 (75.4%)
High	0 (0.0%)	16 (9.1%)	23 (13.1%)	39 (22.3%)

mITT = modified intention-to-treat.

The measured stadiomter heights are plotted by visit in Figure 11 .

Figure 11. Stadiometer Height



Sub-group Analysis

In the placebo group, the mean growth rate was slightly higher for girls (mean [SE] 5.85 [0.12 cm/yr]) compared to the boys (mean [SE] 5.67 [0.084] cm/yr). However the differences between placebo and ciclesonide treatment were similar. When divided into age-gender strata, the older girls (>7 years) who were treated with C160 may have had a greater slowing of growth (mean [SE] -0.59 [0.27] cm/yr) that either the girls < 7 years of age (mean [SE] -0.03 [0.21] cm/yr) or either of the male groups (mean [SE] -0.11 [0.14] and -0.19 [0.21] cm/yr in those ≤8 and >8 years, respectively).

Only one third of the subject population was enrolled in the US. However, in this sample (N=163) there was no apparent effect of ciclesonide on growth (Table 74). The mean [SE] difference between growth during ciclesonide treatment compared to placebo was 0.03 (0.17) and 0.01(0.18) cm/yr in the C40 and C160 groups, respectively. This is in comparison to the growth rates (mean [SE]) observed in South America of (mean [SE] -0.05 [0.11] cm/yr and [SE] -0.17 [0.11] cm/yr comparing C40 and C160 to placebo, respectively).

Table 74. Differences in Growth Rates by Region

Region Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo LS mean ± SE	 2-sided 95% CI
USA				
Placebo	56	5.91 ± 0.127	-	-
Ciclesonide 40 µg/day	60	5.94 ± 0.124	0.03 ± 0.172	(-0.31, 0.37)
Ciclesonide 160 µg/day	47	5.92 ± 0.140	0.01 ± 0.182	(-0.35, 0.36)
South America				
Placebo	145	5.73 ± 0.087	-	-
Ciclesonide 40 µg/day	146	5.68 ± 0.087	-0.05 ± 0.108	(-0.26, 0.16)
Ciclesonide 160 µg/day	155	5.56 ± 0.086	-0.17 ± 0.106	(-0.38, 0.04)

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
Differences vs. placebo are calculated as ciclesonide minus placebo.
Source: *Table T - 53, pg. 382.*

A small difference was also seen in growth rates in subjects treated with C160 who were concomitantly taking leukotriene receptor antagonists (Table 75). However, this

Table 75 . Growth in Subjects Treated Concomitantly with Leukotriene Inhibitors.

Leukotriene receptor antagonist use Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo LS mean ± SE	 2-sided 95% CI
Without leukotriene receptor antagonist use				
Placebo	88	5.60 ± 0.110	-	-
Ciclesonide 40 µg/day	90	5.68 ± 0.112	0.08 ± 0.135	(-0.19, 0.34)
Ciclesonide 160 µg/day	92	5.65 ± 0.111	0.04 ± 0.135	(-0.22, 0.31)
With leukotriene receptor antagonist use				
Placebo	113	5.87 ± 0.104	-	-
Ciclesonide 40 µg/day	116	5.77 ± 0.102	-0.10 ± 0.121	(-0.33, 0.14)
Ciclesonide 160 µg/day	110	5.57 ± 0.108	-0.30 ± 0.122	(-0.54, -0.06)

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
Differences vs. placebo are calculated as ciclesonide minus placebo.
Source: *Table T - 59, pg. 392.*

may be affected by the relative high rate of growth in the placebo subjects who were also taking leukotriene receptor antagonists.

Excluding subjects who did not receive rescue treatment with corticosteroids during the randomized treatment period resulted in a smaller difference between treatment groups (Table 76). The mean (SE) maximum difference comparing placebo to ciclesonide treatment was -0.09 (0.090) cm/yr for the subjects treated with 160 mcg.

Table 76. Change in Growth in Subjects not Treated with Prohibited ICS

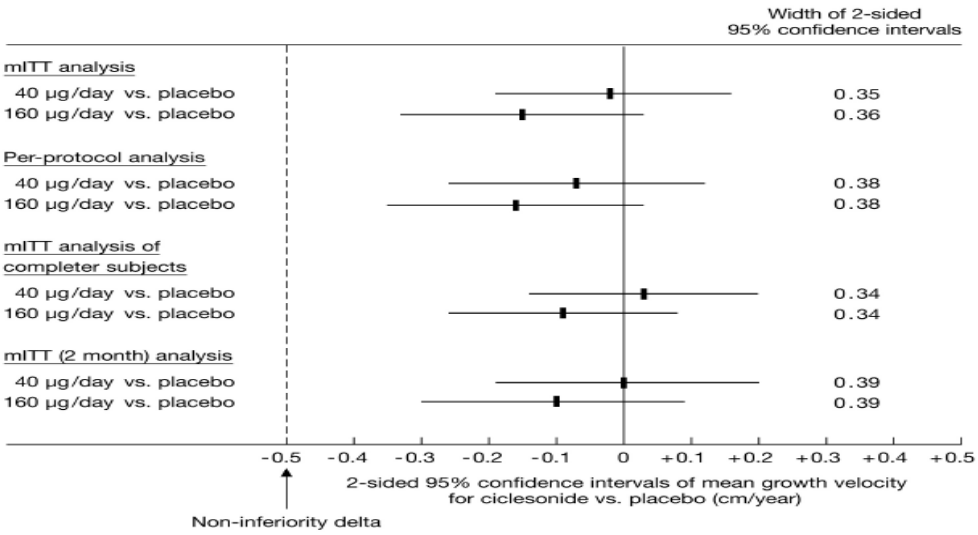
Treatment	N	LS mean ± SE (cm/year)	Difference vs. placebo	
			LS mean ± SE	2-sided 95% CI
Placebo	190	5.70 ± 0.081	–	–
Ciclesonide 40 µg/day	190	5.71 ± 0.080	0.02 ± 0.090	(-0.16 , 0.19)
Ciclesonide 160 µg/day	193	5.60 ± 0.083	-0.09 ± 0.090	(-0.27, 0.08)

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
Differences vs. placebo are calculated as ciclesonide minus placebo.
Source: *Table T - 60, pg. 394*.

Growth Summary

As can be seen in Figure 12, the changes in linear growth during ciclesonide treatment were very small. At 40 mcg per day there was no change in growth rate, and at 160 mcg daily, the mean effect size was -0.15 cm/year with the 95% confidence limits overlapping zero. In only two small subgroups did the difference in rate of growth approach statistical significance: in girls older than 7 years and in subjects treated with leukotriene receptor antagonists

Figure 12. Summary Effects of Ciclesonide on Growth



In both cases the differences were small (0.29 and 0.30 cm/yr for the gender and leukotriene analysis respectively), and of questionable clinical significance. In all of the treatment groups, including placebo, the rate of growth decreased during the randomized treatment period. This change was attributed to the subjects being older during the randomized treatment period. However, growth was slightly higher during the second six months of randomized treatment which can not be explained on the basis of a change in subject age, or a change in therapy.

One problem with the study is the failure to document drug use. Blood levels of ciclesonide (or the active metabolite) were not determined and the pulmonary function results of the (see below) are not helpful because the subjects had mild asthma and many would not have needed corticosteroids. A dramatic deterioration in pulmonary function would not have been expected even if the subjects had not received an inhaled corticosteroid.

Maintenance of Asthma Control

The safety population was used for the assessment of changes in pulmonary function. The FEV1% fell by a small amount over the course of the study in all of the treatment groups (Table 77). The absolute FEV_1 increased by 9.6, 8.9, and 10.3% in the placebo, C40, and C160 groups, respectively. However, the growth in lung size did not keep up with the growth in height because the FEV_1 % predicted decreased by 3.7, 3.6, and 2.5% in the placebo, C40 and C160 groups.

Table 77 . Change in FEV_1 and FEV_1% During 12 Months of Treatment with Ciclesonide

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. placebo LS mean ± SE	2-sided 95% CI	p-value
FEV_1 percent predicted						
Placebo	201	92.97	-3.74 ± 0.817	–	–	–
Ciclesonide 40 µg/day	206	96.26	-3.62 ± 0.801	0.11 ± 1.104	(-2.06, 2.28)	0.9193
Ciclesonide 160 µg/day	202	94.87	-2.45 ± 0.808	1.28 ± 1.103	(-0.88, 3.45)	0.2458
Percent change in FEV_1 [a]						
Placebo	201	1.407	9.56 ± 1.001	–	–	–
Ciclesonide 40 µg/day	206	1.435	8.89 ± 0.988	-0.67 ± 1.355	(-3.33, 1.99)	0.6213
Ciclesonide 160 µg/day	202	1.419	10.32 ± 0.997	0.77 ± 1.356	(-1.90, 3.43)	0.5719

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.
[a] FEV_1 at baseline measured in liters.
Differences vs. placebo are calculated as ciclesonide minus placebo.

In the mITT population 16 subjects (4 [2%]), 8 [3.9], and 4 [2.0] in the placebo, C40 and C160 groups, respectively) discontinued study medication due to lack of efficacy or an asthma attack.

Reviewer: In the safety population 27 patients were withdrawn from study medication because of an asthma attack (9, 12, and 6 in the placebo, C40, and C160 groups, respectively). See safety discussion, below.

4.2.3. Safety

4.2.3.1 Exposure

The safety population consisted of 661 subjects who were treated with double-blind medication (221, 221, and 119 were treated with placebo, C40, and C160, respectively). The mean exposure to study drug (325.3, 329.5, and 332.6 days in the placebo, C40, and C160 groups) was 7 days longer in the C160 subjects than in those treated with placebo.

4.2.3.2 Adverse Events

Overall Assessment of Adverse Events

Almost all subject reported at least on AE during the year of treatment (89.6, 94.6, 90.0% in the placebo, C40, and C160 groups, respectively). The incidence of serious AEs was low, and the highest rate was seen in the C40 group (5.0%) compared to 2.7 and 3.2% in the placebo and C160 subjects, respectively (Table 78). AEs leading to withdrawal were equally common in the placebo and C40 group (6.3%) and less common in the C160 subjects (3.2%). There were no deaths.

Table 78. Overall Summary of Adverse Events.

		Dose of Ciclesonide		
	Placebo	40 QD	160 QD	Total
N	221	221	219	440
All AEs	198 (89.6)	209 (94.6)	197 (90.0)	406 (92.3)
Serious AEs	6 (2.7)	11 (5.0)	7 (3.2)	18 (4.1)
AEs leading to withdrawal	14 (6.3)	14 (6.3)	7 (3.2)	21 (4.8)
Deaths	0	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system. Infectious disorders and most of the other SOCs and preferred terms were more common in the C40 group (Table 79). Infections were reported in 81.9% of the C40 subjects compared to 75.1 and 79.9% in the placebo and C160 subjects, respectively. Nasopharyngitis was the most common infectious manifestation, followed by pharyngitis, upper respiratory tract infection, influenza, bronchitis, and rhinitis, ear infection, and sinusitis. All of these were more common in the C40 group than either the placebo or C160 subjects.

Respiratory complaints were recorded for 48.4, 54.8, and 41.6% of the placebo, C40, and C160 subjects, respectively. The most common of these preferred terms was asthma, which was reported in 33.9, 33.5, and 29.7% of the subjects, respectively.

Table 79. AEs Occurring in 3% or More Subjects in Any Treatment Group, by System Organ Class and Selected Preferred Terms

	Placebo	Dose of Ciclesonide		
SOC and Preferred Term	---	40 QD	160 QD	Overall

N	221	221	219	440
All AEs	84 (55.3)	88 (57.9)	79 (52.0)	167 (54.9)
Infections and infestations	75.1	81.9	79.9	80.9
Nasopharyngitis	26.2	31.7	31.1	31.4
Pharyngitis	15.4	16.3	12.8	14.5
Upper Respiratory Tract Infection	11.8	14.0	12.8	13.4
Influenza	9.0	13.1	10.0	11.6
Bronchitis	10.0	10.4	10.0	10.2
Rhinitis	9.5	10.0	5.9	8.0
Ear infection	6.3	8.6	5.9	7.3
Sinusitis	4.5	7.2	5.5	6.4
Tonsillitis	3.6	5.9	6.8	6.4
Respiratory tract infection	3.2	4.1	7.3	5.7
Gastroenteritis	3.6	5.9	4.6	5.2
Varicella	3.2	4.5	5.9	5.2
Bronchitis, acute	5.4	5.0	5.0	5.0
Otitis media	3.6	5.4	4.1	4.8
Enterobiasis	1.8	1.8	4.1	3.0
Viral infection	1.8	1.8	4.1	3.0
Respiratory tract infection, viral	3.6	2.3	3.2	2.7
Viral upper respiratory tract infection	2.7	3.2	1.8	2.5
Viral pharyngitis	3.2	3.2	1.4	2.3
laryngitis	3.6	0.5	1.4	0.9
Respiratory, thoracic, and mediastinal	48.4	54.8	41.6	48.2
Asthma	33.9	33.5	29.7	31.6
Cough	5.4	9.5	7.8	8.6
Rhinitis allergic	5.9	8.1	4.1	6.1
Pharyngolaryngeal pain	3.6	3.6	4.1	3.9
Bronchial obstruction	2.3	4.5	2.7	3.6
Nasal congestion	1.8	3.2	2.7	3.0
Epistaxis	2.7	4.1	1.4	2.7
Rhinorrhea	1.8	1.4	3.2	2.3
General disorders	22.2	29.0	21.0	25.0
Pyrexia	19.9	28.1	20.1	24.1
Nervous system disorders	19.5	19.5	21.0	20.2
Headache	18.1	18.6	19.6	19.1
Gastrointestinal disorders	16.7	19.0	13.2	16.1
Vomiting	5.9	5.9	4.6	5.2
Toothache	1.4	4.1	2.3	3.2
Diarrhea	2.7	2.3	3.2	2.7
Abdominal pain	4.1	2.7	2.3	2.5
Injury, poisonings and procedures	9.5	14.0	10.5	12.3
Arthropod bite	3.2	0.5	1.4	0.9
Skin and Subcutaneous tissue	9.5	10.4	7.8	9.1
Impetigo	1.8	3.6	1.4	2.5
Eye disorders	2.7	5.4	2.0	5.2
Musculoskeletal disorders	5.4	4.5	5.5	5.0
Immune system	1.4	4.1	4.6	4.3
Hypersensitivity	0.9	4.1	1.8	3.0
Ear and labyrinth disorders	5.0	3.6	3.7	3.6
Ear pain	3.6	3.6	3.7	3.6
Blood and Lymphatic system	2.3	3.2	1.8	2.5

Most of the events were regarded as mild (81.0, 87.8, and 83.6% in the placebo, C40, and C160 groups, respectively), and less than 5% were severe (3.6, 4.5, and 2.3% in the placebo, C40, C160 groups, respectively).

Since oropharyngeal adverse events are known to be common during therapy with ICS, a grouping of pharyngolaryngeal pain, pharyngitis, and oral candidiasis was produced. There was only 1 case of oral candidiasis in a placebo subject, 25 of pharyngolaryngeal pain and 94 of pharyngitis. Pharyngitis was least frequent in the C160 subjects (12.8%) compared to 15.4 and 16.3% of the placebo and C40 subjects, respectively.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths in this study. Serious adverse events were reported for 6 placebo, 11 C40, and 7 C160 subjects. The most common serious event was asthma, which was reported in 4, 6, and 1 subject in the placebo, C40, and C160 groups, respectively. All other events were reported in 1 subject or less. There were 2 pneumonia events (lobar pneumonia and pneumonia), both reported in C40 subjects.

Withdrawal due to an adverse event occurred in 35 (5.3%) of the subjects overall. The most common event requiring withdrawal was asthma which occurred in 9 (4.1%), 12 (5.4%), and 6 (2.7%) of the placebo, C40, and C160 subjects, respectively. Two placebo subjects were withdrawn due to upper respiratory tract infections, and all other events occurred in one or less subjects. One subject was withdrawn from the placebo group due to precocious puberty.

Other Events on Note

There were 2 cases of significant overdose, defined as three or more times the morning or afternoon dose (6 puffs from either AM or PM inhaler). Neither case was associated with an adverse event. One 5 year-old male took 4 puffs daily of C160 for 24 days. A 7 year-old girl received three puffs of C40 without event.

During the follow-up period 158 subjects experienced adverse events (56 [25.3%], 61 [27.6%], and 41 [18.7%] in the placebo, C40, and C160 subjects, respectively). Asthma, Nasopharyngitis, and headache were reported by ≥ 3% of the subjects. As in the active treatment period, all of the events were slightly more frequent in the C40 group (Table 80).

Table 80. Adverse Events Reported in the Follow-up Period

		Dose of Ciclesonide		
	Placebo	40 QD	160 QD	Total
N	221	221	219	440
All AEs	56 (25.3)	61 (27.6)	41 (18.7)	102 (23.2)
Asthma	7.2	9.0	6.8	8.0
Nasopharyngitis	1.8	4.5	2.7	3.6
Headache	2.3	3.2	0.5	1.8

Ophthalmologic examinations were performed at 2 sites in response to concerns of the local IRB. In 35 subjects examined, 2 cataracts were identified more than 14 days after termination of

treatment. One of the subjects was a 5 year-old both who had been treated with placebo, and the other was a girl who had been treated with C40. Neither had been treated with corticosteroids prior to enrollment in the study. No baseline examinations were performed and follow-up is pending.

4.2.3.6 Laboratory Results

The mean baseline and Week 12 values for all hematology and routine safety chemistry analyses were within the normal range.

For both the hematology and chemistry examinations there were few individuals with shifts out of the normal range over the course of the study, and the distribution of these subjects was similar across the treatment groups.

Laboratory values that reached the Predefined Change Abnormal (PCA) range were uncommon. Table 81 lists the number of subjects in each treatment group in which more abnormalities were seen in the actively treated subjects than placebo, and where at least 3% of the subjects showed the abnormality. In no case was there a dramatic difference between the placebo and actively treated subjects. An increase in the eosinophil count was the most common abnormality, and it was seen most often in the placebo subjects (11.4% compared to 7.7 and 7.8% in the C40 and C160 subjects).

Table 81. Laboratory Values with PCA Changes During Treatment

	PCA Amount / direction	Placebo	C40	C160
N				
Alkaline phosphatase	28 U/L | ↑	15/201	17/209	14/206
Albumin	6 GI/L | ↑	5/201	7/209	8/206
Leukocytes	1 GG/L | ↓	4/202	7/208	7/206
Neutrophils	3.18 GG/L | ↑	9/202	10/208	11/206

Clinically noteworthy abnormalities were defied for glucose (> 2 time ULN) and the absolute eosinophil counts (> 1 $*10^3/mm^3$). At the end of the treatment period abnormalities were only seen in the eosinophil counts. Eleven placebo, 9 C40, and 5 C160 subjects had high eosinophil counts at the end of treatment.

Abnormal laboratory values were reported as adverse events for 1 placebo and 3 C40, and 3 C160 subjects. No single event was reported in more than one subject, and none resulted in discontinuing study medication. One C40 subject developed idiopathic thrombocytopenic purpura. The Applicant has been unable to obtain the relevant laboratory data from the local medical facility.

HPA-axis Evaluation

Urine was collected for 24-hour cortisol measurement at 39 study sites. Originally a second analysis of "valid" samples defined by the quality of the urine collection was planned. However

only 13% of the samples met the criteria, so only the overall summaries were calculated. It was hypothesized that the number of samples that did not meet the criteria was high because the criteria were derived from adults. The changes in the mean values were small over the course of treatment and the difference from the change during placebo treatment was very small (Table 82).

Table 82. Urinary Cortisol

	N	Baseline Mean	Change from Baseline LS mean (SE)	Difference from placebo	95% CI
Placebo	102	11.37	-0.24 (0.94)		
C40	109	10.56	0.31 (0.96)	0.54 (1.07)	-1.57, 2.66
C160	97	10.08	-0.70 (0.97)	-0.46 (1.12)	-2.65, 1.72

Reviewer: Without quality control it is very difficult to accept the above data as definitive.

4.2.3.7 Physical Examination including Vital Signs.

No clinically significant changes were seen during the treatment period. All subjects were Tanner Stage 1 during the run-in. One subject in each treatment groups progressed to > Stage 1 during the trial. The placebo and C160 subject did so at month 12 and the C40 subject progressed at Month 4.

4.3 Summary and Discussion

This study was designed to assess the effect of ciclesonide on growth in prepubertal children. Approximately 200 subjects in each treatment group were treated with placebo, 40 mcg or 160 mcg ciclesonide once daily for 12 months. Various assessments of growth were made and none showed a significant effect of either dose of ciclesonide compared to placebo On the other hand, a decrease in growth of 0.6 to 0.7 cm/year is in keeping with the changes seen after treatment with other inhaled corticosteroids, and it is only because there was a similar decrease in the placebo group that there is no drug effect. This unexplained decrease in growth in the placebo group makes it difficult to accept the results of this study as a definitive growth assessment. The failure to collect adequate urine samples for the cortisol measurements also does not increase confidence in the results.

5 Study # XRP1526B/3028

A multicenter, randomized, open-label, parallel-group study to assess the accuracy, functionality, and reliability of the Trudell™ dose counter in subjects with mild-to-moderate persistent asthma treated for 15 or 30 days with ciclesonide metered-dose inhaler administered at a daily dose of 160 µg once daily

5.1 Protocol

5.1.1 Administrative

Enrollment Dates:	November 18, 2005 – March 3, 2006
Screening Centers:	15 centers in the United States
Sponsor's medical expert:	
CRO:	

5.1.2. Objective/Rationale

The primary objective of the study was to evaluate the accuracy, functionality, and reliability of the Trudell dose indicator in patients with mild-to-moderate asthma treated with ciclesonide 160 µg/day (ex-actuator) for 15 or 30 days, taken as 4 puffs in the morning using the MDI fitted with an integrated Trudell dose indicator.

The Secondary objective was to assess the safety of ciclesonide administered using the MDI fitted with the Trudell dose indicator

5.1.3. Study Design

This was a multi-center, randomized, open-label, parallel group study in mild-moderate asthmatics 4 years of age or older. Subjects were randomly assigned to either a 15-day or 30 day treatment group (1:4). The subjects in both groups were issue a 120-shot canister that delivered 40 mcg ciclesonide per puff. The center staff primed the canisters with 3 actuations and then instructed the subjects to take four puffs each morning. In the 30-day group the dose indicator should have registered zero and the dose indicator should have ceased making a clicking sound if actuated further. The subjects were seen at randomization, day 8 and 15 for the 15-day group and additionally at day 22 and 30 in the 30-day group. The functionality of the dose counter was assessed by comparing the reading on the counter to daily diary entries made by the subjects at home.

Protocol Amendments

Two protocol amendments were introduced prior to subject enrollment. The amendments wre primarily administrative and for clarifying purposes.

5.1.4. Study Population

Inclusion Criteria

- Males or females 4 years of age and older
- History of mild-to-moderate persistent asthma, as defined by NAEPP Guidelines
- Forced expiratory volume in 1 second (FEV_1) ≥60% of predicted at Visit 1
- Reversibility of FEV_1 of at least 12% (relative to the pre-bronchodilator value in L) and ≥0.2 L after inhalation of 180 μg albuterol (ex-actuator), or documented history of reversibility of FEV_1 by at least 12% (relative to the pre-bronchodilator value in L) and ≥0.2 L within 1 year before screening
- Able to demonstrate acceptable oral inhaler technique
- Written informed consent at enrollment into the study

Exclusion Criteria

- Inability of the patient (or the guardian for younger patients) to read the dose indicator scale or to hear the clicking sound when the dose indicator was actuated
- Pregnancy
- Breast-feeding
- Female patients of childbearing potential unless practicing an adequate method of birth control, or unless sexual abstinence was confirmed at informed consent, or unless premenarchal and prepared to accept counseling on reproductive issues in case of becoming menarchal
- History of hypersensitivity to the investigational product or to similar dugs
- Previous randomization in this study
- Treatment with any investigational product in the last 30 days before study entry
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult
- History of drug or alcohol abuse
- Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study
- Patient unlikely to comply with protocol, eg, uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study
- Patient was the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

Withdrawal Criteria

- At their own request or at the request of their legally authorized representative
- If, in the Investigator's opinion, continuation in the study would have been detrimental to the patient's well-being
- At the specific request of the Sponsor
- Pregnancy: If a patient became pregnant during the trial, she had to be followed up until the outcome of the pregnancy was known. If pregnancy occurred, the Investigator had to contact the Sponsor immediately for further instruction
- Loss of study medication.

5.1.5. Study Procedures

Treatment

Subjects were randomized to one of the following study treatments:

- Ciclesonide MDI 160 mcg QD (4 puffs QD of a 40 mcg/puff solution) for 30 days
- Ciclesonide MDI 160 mcg QD (4 puffs QD of a 40 mcg/puff solution) for 15 days

HFA albuterol (100 μg per actuation [90 μg ex-actuator] was supplied for acute symptoms.

The following concomitant medications were permitted throughout the study as long as they were started prior to screening and the dose was kept constant:

- Topical corticosteroids: Low-potency topical corticosteroid creams or ointments equivalent to ≤1% hydrocortisone were permitted for occasional dermatologic use
- Non-steroidal asthma medications:
    - Inhaled short-acting β2 agonists (albuterol),
    - Leukotriene receptor antagonists (montelukast sodium, zafirlukast),
    - Cromones (cromolyn sodium, nebulized cromolyn, nedocromil),
    - Xanthine derivatives (theophylline, aminophylline);

The following concomitant medications were prohibited from screening onward:

- Any ICS or ICS/LABA combination other than the study medication
- Oral or injectable corticosteroid

Compliance was assessed by the patient's notation in the diary that the medication was taken and by weighing the returned canisters. Poor compliance was defined as <70% of the expected actuations.

Efficacy Evaluation

The dose counter is labeled in increments of 20 actuations, but the indicator advances after 10 actuations. A red zone appears when there are only 20 actuations remaining. The subjects

brought the MDI with them to all center visits and the counter display was recorded by the center staff. The subjects kept a diary of medication use. They entered the dose counter reading before and after dosing, and separately indicated the number of puffs they had inhaled. Finally the subjects entered the reading when the counter ceased to click.

The canisters without the actuator were weighed after priming and before distribution to the subjects. The canisters were weighed at each visit. A patient satisfaction survey was also performed.

Safety Evaluation

The primary safety analysis was based on collection and recording of adverse events in the standard manner. No laboratory data was collected.

5.1.6. Statistical Analysis Plan

Analysis Variables

The primary efficacy outcome was the comparison of the Trudell dose counter and the diary count. The two counts were considered to be in agreement when they were within 20% of one another. Primary variables included the following:

- Ratio (in percent) of correct advances of the dose indicator out of expected advances, where a correct advance was defined as one when the number of puffs between the 2 advances was within the range of 8 to 12 puffs (ie, ±20% of 10 puffs)
- Number and percentage of devices with actuation consistency at the end of the study, where actuation consistency was defined as a Trudell count within ±20% of the diary count
- Number and percentage of devices with major discrepancies, where a major discrepancy was defined as a discrepancy of more than 20 puffs between the Trudell count and the diary count at the end of the study

Secondary variables included the following:

- Number and percentage of devices with actuation consistency between the Trudell count and the canister weight count (ie, the number of puffs calculated from change in canister weight between baseline and end of study), where actuation consistency was defined as a Trudell count within ±20% of the canister weight count
- Functionality of the dose indicators that reached zero, as assessed by the percentage of dose indicators that ceased to make a clicking sound upon further actuation after reaching zero (30-day group only);
- Number and percentage of patients with a particular response for each question in the patient satisfaction survey.

Sample Size

Sample size was chosen to assure an adequate number of subjects less than 12 and greater than 65 years of age. Approximately 125 were planned to be randomized with 100 in the 30-day group and 25 in the 15-day group. Ten percent of the patients were planned to be <12 and 10% > 65 years of age.

Study Populations

The safety population included all subjects who received at least one dose of double-blind study medication.

The intent to treat ITT population included all randomized subjects who used at least 10 actuations of study medication as recorded in the diary.

Primary Analysis

Ratio of correct advances: The number of actuations between any 2 advances of the dose indicator was summarized. If the number was between 8 and 12 the two counts were determined to be in agreement. Because each canister contained 120 actuations and the counter advanced with each 10 actuations, the expected number of advances was 12 for subjects who continued in the study for 30 days. Including the acceptable 20% error rate, the acceptable number was 11.8 to 12.2.

Ratio of correct advances (%) = 100 x (correct advances/expected advances).

Actuation consistency: The actuation consistency between the Trudell dose indicator count and the diary count as compared to the daily dosing diary record was also assessed for each MDI for the entire study period. The 2 counts were considered to be in agreement when the Trudell count was within ± 20% of the diary count. The number and percentage of devices with agreement between the 2 counts was calculated for each treatment group and overall.

Percentage of devices with major discrepancies: A major discrepancy was defined as a Trudell count that differed from the diary count by >20 counts.

Analysis of Secondary Efficacy Variables

The Trudell count was compared to the canister weight for the entire treatment period. In a preliminary set of in vitro experiments, the Applicant verified that weighing the canister at the beginning of use (after priming) and at the end of use and knowing the average weight of an actuation, to assess the number of actuations actually performed. The average per-puff weight was 59.3 mg (±10%), so the number of actuations was calculated as follows:

$$W_{begin} - W_{end}/59.3$$

The dose indicator functionality was assessed as the number and percentage of dose indicators that ceased to make a clicking sound upon actuation after the canister was empty.

5.2. Results

5.2.1. Study Population

Disposition

A total of 179 subjects were screened and 125 were randomized; 100 in the 30-day group and 25 in the 15-day group. None was discontinued from the 15-day group and 7 discontinued from the 30-day group. Three of the subjects in the 30-day group withdrew due to adverse events and the others were lost to follow-up. All of the subjects received at least 10 actuations of study medication and were included in the ITT population.

Demographics

Of the 125 subjects randomized 36% were male, the mean (Range) of age was 39.6 (6 – 76) years (Table). The predominant racial group was white (80.0% compared with 7.2% black and 12.8% other). The age distribution showed 13 subjects less than 12 and 11 subjects > 65 years of age.

Table 83. Demographic Characteristics of the Enrolled Population

		Dose of Ciclesonide		
	Statistic	15-day	30-day	Overall
Total ITT Population	n	25	100	125
Gender, % M	%	(52.0)	(32.0)	(36.0)
Age (yrs)	mean (range)	32.8 (8-72)	41.3 (6-76)	39.6 (6-76)
<12	n	2	11	13
12- < 65	n	22	79	101
≥ 65	n	1	10	11
Race				
White	%	80.0	80.0	80.0
Black	%	8.0	7.0	7.2
Other	%	12.0	13.0	12.8
Height (cm)				
Overall	Mean (range)	161 (123-183)	163 (117-191)	163 (117-191)
< 12 years of age		126 (123-128)	137 (117-147)	135 (117-147)
≥ 12 years of age		165 (150-183)	166 (145-191)	166 (145-191)
Duration of Asthma (yrs)				
Overall	Mean (range)	18.8 (0.2-58.4)	23.4 (0.2-72.1)	22.5 (0.2-72.1)
< 12 years of age		6.4 (5.3-7.4)	5.3 (0.3-11.2)	5.4 (0.3-11.2)
≥ 12 years of age		19.9 (0.2-58.4)	25.6 (0.2-72.1)	24.6 (0.2-72.1)
Previous participation in a ciclesonide study	n(%)	7 (28)	29 (29)	36 (29)

The subjects in the 30-day group were older (41.3 years as compared to 32.8 years in the 15-day group). The children less than 12 years of age were on average 11 cm taller than the children in the 15-day group and the adolescents and adults in the 30-day group had had asthma approximately 6 years longer than the adults in the 15-day group.

Pulmonary Function

While the absolute spirometric volumes were smaller in the children, the FEV_1% was 77% predicted across the treatment groups and age groups (Table 84).

Table 84. Baseline Pulmonary Function

	Mean (range)		
	15-day	30-day	Overall
Total ITT Population	25	100	125
FEV1 (L)			
Overall	2.5 (1.1-4.8)	2.3 (0.7-4.9)	2.4 (0.7-4.9)
<12 years	1.2 (1.1-1.4)	1.5 (0.7 – 1.9)	1.4 (0.7-1.9)
≥ 12 years	2.6 (1.6-4.8)	2.4 (1.3 – 4.9)	2.4 (1.3-4.9)
FEV1 (%)			
Overall	77.4 (61-100)	77.0 (60-109)	77.1 (60-109)
<12 years	77.0 (75-79)	73.3 (60-86)	74.0 (60-86)
≥ 12 years	77.5 (61-100)	77.4 (60-109)	77.4 (60-109)
FVC (L)			
Overall	3.4 (1.4-5.9)	3.2 (0.8-6.2)	3.2 (0.8-6.2)
<12 years	1.6 (1.4-1.8)	1.8 (0.8-2.4)	1.8 (0.8-2.4)
≥ 12 years	3.5 (2.3-5.9)	3.3 (1.6-6.2)	3.4 (1.6-6.2)

Compliance was 100% in 96% of the 15-day subjects and in 87% of the 30-day subjects. All the remainder had 90 to 100% compliance.

5.2.2. Efficacy Results

Primary Efficacy Outcome

For the primary outcome, the Trudell advances were compared to the diary recordings. If the counter advanced after 8 – 12 puffs (± 20%) the advance was classified as correct. According to this criterion 83.5% of the advances were correct (Table 85). However, because some advances were premature and some late, at the end of the canister the overall count showed major discrepancy in only 4% (120/125 [96%] of the counters were accurate).

Table 85 . Comparison of Trudell Dose Counter and Diary Measurements

	Mean (range)		
	15-day	30-day	Overall
Total ITT Population	25	100	125
Ratio of correct advances			
Mean (SD)	79.9 (26.3)	84.4 (20.1)	83.5 (21.5)
range	16.7 - 100	8.3 – 109.1	8.3 – 109.1
Agreement between counter and diary, n (%)	24 (96.0)	96 (96.0)	120 (96.0)
Major discrepancies, n (%)	1 (4.0)	4 (4.0)	5 (4.0)

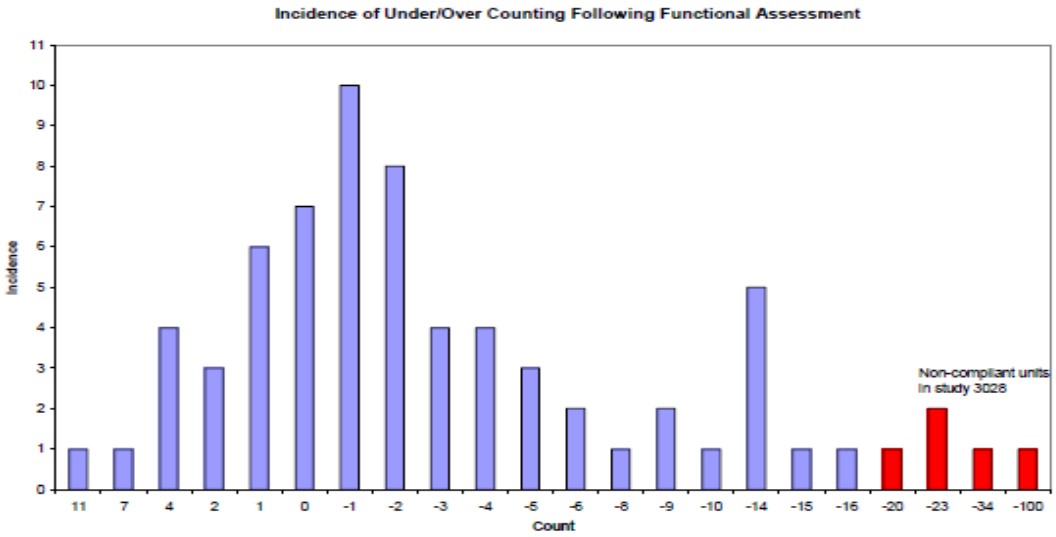
Four of the 5 devices were those identified as having major discrepancies, above. The fifth canister was only slightly out of range at +20.7%. In 4 of the 5 devices with major discrepancies

the problem was thought to be in the manufacturing process. The counters were substantially lower than either the diary entries or the canister weights, and the clinic-monitored Trudell counts agreed with the patient's diary entries. The devices were returned to the manufacturer for further examination. In one patient the counter did not agree with the diary recordings, but it did agree with the canister weights and it was thought that the subject (8 years old) may have made inaccurate entries into the diary.

Secondary Efficacy Outcomes

Fifty-two of the canisters performed as predicted, but 73 had some type of error and were subjected to further investigator. Of the total 125 canisters, 5 (4.0%) undercounted by 20 or more (Figure 13).

Figure 13. Trudell dose counter reading compared to canister weights



The sponsor attributed the undercounting to a manufacturing error, though the manufacturer examined the returned canisters and determined that there was no defect. In the CMC section of the application it is noted that the counter is known to undercount if the actuator is not depressed in the center and if the actuations are repeated too close to one another. [redacted]

Reviewer: According to the CMC submission in the original NDA the minimum fill weight was [redacted] *for the 60 or 120 actuation canisters. The minimum fill weight included the desired actuations* [redacted] *respectively) for priming for the 60 and 120 actuation canisters, respectively,* [redacted] *for leakage over a 2 year half-life, and* [redacted] *) for overfill. If the minimum desired overfill is* [redacted] *actuations then the minimum acceptable fill weight would be* [redacted] *, respectively. (These calculations are based on an average actuation weight of* [redacted] *) Actual measured fill weights were also presented in the original NDA (CMC Table P.2.3.4-1 and P.2.3.4-2). The means were 6.1 and 9.6 g for the 60 and 120-actuation canisters, respectively. Both*

distributions had a standard deviation of 0.28 g. Given the distribution of actual weights, the probability of a canister with a fill weight of [redacted] *of the normal distribution.) Assuming fill weight and counter function are independent, the probability of a drug product with a fill weight* [redacted] *and a counter that undercounted by* [redacted] *is the product of the two probabilities* [redacted]

Sixty-eight patients (68.0%) in the 30-day group recorded a total of ≥120 puffs in their diary at the end of the study, and 42 of these 68 (61.8%) also recorded that their devices reached zero (Table 86). Eleven of the 42 devices recorded as having reached zero (26.2%) were also recorded as continuing to make a clicking sound upon further actuation. Thirty-two patients (32.0%) in the 30-day group recorded a total of <120 puffs in their diary at the end of the study, and 9 of these 32 patients (28.1%) also recorded that their devices reached zero. Three of the 9 devices recorded as having reached zero (33.3%) were also recorded as continuing to make a clicking sound upon further actuation

Table 86. Counter Functionality

Total ITT Population	100
Number with >120 puffs actuations	68/100 (68%)
Number of dose counters that reached zero	42/68 (61%)
Number of dose counters that clicked after reaching zero	11/42 (26.2%)

At the end of the study 122/125 (97.6%) of the diary counts were within 20% of the canister weights. One of the three was one of the canisters with a major discrepancy discussed above.

According to the patient satisfaction questionnaire, the subjects generally thought that the counter was accurate and helped them assess the amount of medication left.

Sub-group Analysis

The results did not differ by age**.**

5.2.3. Safety

5.2.3.1 Exposure

The safety population consisted of 125 subjects. Of the 25 subjects in the 15-day group, 24 were treated for at least 9 days. Of the 100 in the 30-day group, 87 were treated for the full 30 days.

5.2.3.2 Adverse Events

Overall Assessment of Adverse Events

Four subjects in the 15-Day group and 25 in the 30-Day group reported an adverse event. None was classified as serious and none resulted in death. 3 subjects in the 30-Day group were withdrawn due to an adverse event (Table 87).

Table 87. **Overall Summary of Adverse Events**.

	Dose of Ciclesonide		
	15 Day	30 Day	Total
N	25	100	125
All AEs	4 (16.0)	25 (25.0)	29 (22.5)
Serious AEs	0	0	0
AEs leading to withdrawal	0	3 (3.0)	3 (2.4)
Deaths	0	0	0

The most common adverse events were in the Infections and infestations SOC of the MedDRA classification system: 2 (8%) of the 15-Day and 13 (13%) of the 30-Day subjects. As in the other studies in this submission, nasopharyngitis was the most common infectious manifestation, followed by, upper respiratory tract infections and influenza (Table 88). Asthma was the most common respiratory complaint and occurred in 2 subjects in each group. Oropharyngeal candidiasis was not reported in any subject.

Table 88 . AEs Occurring in 3% or More Subjects in Any Treatment Group, by System Organ Class and Selected Preferred Terms

	Dose of Ciclesonide		
SOC and Preferred Term	40 QD	160 QD	Overall
N	25	125	129
All AEs	4 (16.0)	25 (25.0)	29 (22.5)
Infections and infestations	2 (8.0)	13 (13.0)	15 (11.6)
Nasopharyngitis	2 (8.0)	3 (3.0)	5 (3.9)
Upper Respiratory Tract Infection	0	6 (6.0)	6 (4.7)
Influenza	0	2 (2.0)	2 (1.6)
Respiratory, thoracic, and mediastinal	3 (12.0)	7 (7.0)	10 (7.7)
Asthma	2 (8.0)	2 (2.0)	4 (3.1)
Pharyngolarygeal pain	0	2 (2.0)	2 (1.5)

Only one event (pain in an extremity) in a 30-Day subject was considered severe and this was unlikely to be related to drug treatment.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths or serious adverse events.

Withdrawal due to an adverse event occurred in 3 (3.0%) of the 30-Day subjects. There was one case, each, of increased heart rate in an 11 year old girl, respiratory infection, and chest pain.

Other Events

There were no overdoses. One subject reported blurred vision accompanying a headache. No cataract was seen on examination. No laboratory analysis was performed and there were no clinically important changes in vital signs.

5.3 Summary and Discussion

In this study, made up of 15- and 30-Day cohorts, the pre-specified level of accuracy was demonstrated. The counter did not appear to affect the delivered dose or the particle size distribution, and only 5/125 (4%) of the canisters tested were deficient as defined by the Applicant's criteria of an, undercounted of [redacted] or greater when compared to the diary recordings. In data submitted with the original NDA, a mean fill weight for the 120-actuation canisters was demonstrated to be 9.6 g with a standard deviation of 0.28 g. These data show substantial overfill and a probability that any canister would have less than [redacted] extra doses (beyond the prescribed 120) of [redacted] This, combined with the finding that only [redacted] of the counters undercounted by more than [redacted] counts suggests that there is less than a 0.1% probability that a counter would register a positive number when it was actually empty. Functionality will be further improved by additional warnings in the patient instructions on the correct use of the delivery device.

10.2 LINE-BY-LINE LABELING REVIEW

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/s/

Carol Bosken
12/18/2007 01:34:49 PM
MEDICAL OFFICER

Lydia McClain
12/19/2007 05:43:58 PM
MEDICAL OFFICER
I concur with the recommendation for approval