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21-658

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Ciclesonide
(Proposed) Trade Name	Alvesco
Therapeutic Class	Corticosteroid
Applicant	Aventis

Priority Designation	S
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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	Hydrofluoroalkane
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

1.2 Recommendation on Post-marketing Actions

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 [] as the starting dose in subjects not previously treated with inhaled corticosteroids (ICS) to 320 mcg BID for patients [] 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 FEV₁ when compared 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 [] 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 [] extra doses (beyond the prescribed 120) of []. This, combined with the finding that only [] of the counters undercounted by more than [] 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 [] 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 [] Dehydrated Alcohol, USP and [] 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
	Pulmocort Flexhaler	2/16/07	Inhalation-driven dry powder inhaler	BID	≥6
Budesonide	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

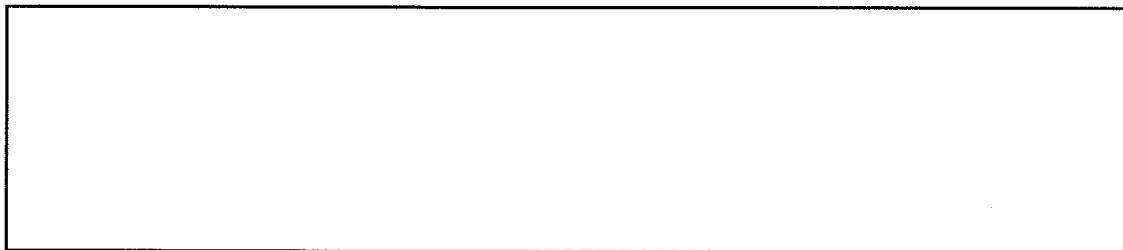
Ciclesonide given by inhalation has low systemic bioavailability. However, it is a corticosteroid and therefore has the potential to produce the adverse events associated with corticosteroid administration if it is taken in high enough doses. These adverse effects include adrenal suppression, a poor 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	Comparator	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 Controlle r	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 bioavailability 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 patients 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 FEV₁ 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 FEV₁, 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 FEV₁ was 300 mL in the C80 group, significantly better than the 190 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.

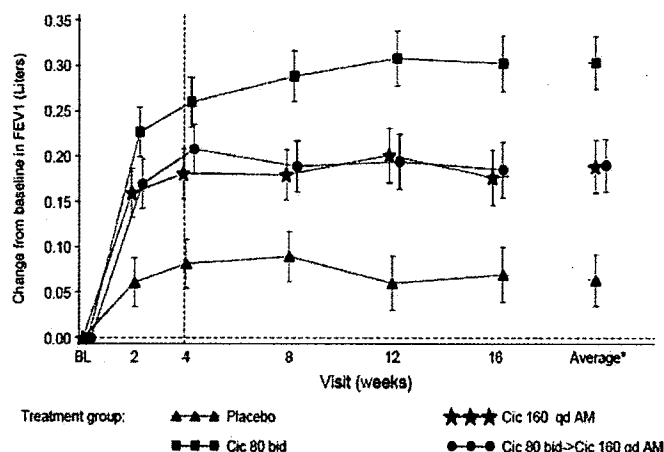
Table 5. Primary Efficacy Results from Study 3031

		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	0.06	0.19	0.19	0.30
95% CI	0.01, 0.12	0.13, 0.25	0.13, 0.25	0.25, 0.36
Difference from placebo				
LS mean, L		0.12	0.13	0.24
95% CI		0.05, 0.20	0.05, 0.20	0.16, 0.32
p- value		0.002	0.002	<0.001
C80 Difference from C160 & C80/160				
LS mean, L		0.11	0.11	

95% CI		0.03, 0.19	0.03, 0.19	
p-value		0.005	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 FEV₁. The subjects treated with C160 had essentially no change in FEV₁ (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 FEV₁ 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	-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	<0.0001
Difference from cicles-80*			
LS mean, L		0.05	
95% CI		-0.03, 0.13	
p-value		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 than 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 FEV₁ (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. [REDACTED]

[REDACTED] 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 FEV₁. 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 [REDACTED]

[REDACTED] However, once daily dosing is not recommended for adults [REDACTED]

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

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 in 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					16.9 / 7.9					
3030	12 wks	32.0 / 15.1			10.3 / 2.3	12.4 / 4.5	11.8 / 4.6					
321	12 wks	35.8 / 16.4			11.2 / 5.3		18.0 / 7.0		14.5 / 3.8			
322	12 wks	30.5 / 14.4		15.8 / 3.8			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	0				
3027		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 the 12/16 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			1.0	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.

	Placebo (N=759) 456 (60.1)	160 mcg / day			320 mcg / day		640 mcg / day
		160 QD (N=579) 327 (56.5)	80 BID (N=325) 175 (53.8)	80 BID/160 QD (N=173) 100 (57.8)	320 QD (N=295) 172 (58.3)	160 BID (N=127) 78 (61.4)	
All TEAs							
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	6.2
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 Pharmacodynamics, 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 [] 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 FEV₁ in the subjects who received twice daily dosing regimens using \geq 160 mcg BID.

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

		Daily Dose of Ciclesonide						Total
		160			320			
		160 QD (N=579)	80 BID (N=325)	80/160 (N=173)	320 QD (N=295)	160 BID (N=127)	320 BID (N=172)	
Gender, N								
Male		305 454	138 187	71 102	135 160	52 75	75 97	1024 1376
Age, yrs								
12 to <18 yrs		79	49	20	23	7	5	254
18 to <65 yrs		652	263	143	264	110	157	2081
≥65 yrs		28	13	10	8	10	10	95
Mean (SD)		38.2 (14.8)	36.5 (15.4)	37.7 (16.2)	36.8 (14.1)	43.5 (15.1)	41.9 (13.8)	
Range		12 - 79	12 - 72	11 - 73	11 - 75	13 - 82	12 - 79	11 - 82
Race, N								
White		612	264	129	259	97	140	1886
Black		77	16	20	23	17	20	216
Other		70	45	24	13	13	12	228
Duration of Asthma, yrs								
Mean (SD)		18.3 (14.2)	18.6 (13.7)	14.7 (13.0)	18.6 (13.7)	25.9 (16.1)	23.1 (14.4)	
Prior ICS		426	152	0	142	127	130	
FEV1, mean (SD)								
Liters/predicted		2.38 (0.69)	2.58 (0.61)	2.39 (0.59)	2.57 (0.68)	1.79 (0.49)	2.09 (0.71)	
		70.3	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 FEV₁ % 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 FEV₁ 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

Study Type	Study Number*	Duration of Treatment with Ciclesonide				
		≤ 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		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 FEV₁ 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. The efficacy of 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 (Study 341 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. [REDACTED]

[REDACTED]. Because of the large difference in response noted between once and twice daily dosing in the adult population, [REDACTED]

Since 80 mcg BID was effective in the adult population, [REDACTED]

[REDACTED] 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

[REDACTED]

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-FEV₁ (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-FEV₁ 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 FEV₁ instead of AM PEF;** randomization criteria changed from FEV₁ 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 $\geq 60\%$ and $\leq 85\%$ predicted to $\leq 95\%$ 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, FEV₁ of $\geq 60\%$ and $\leq 85\%$ of predicted normal and AM PEF of $\leq 95\%$ 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 FEV₁ by at least 12% (relative to the pre-bronchodilator value in liters [L]) after inhalation of 180 µg albuterol (ex-actuator)
- FEV₁ at randomization within 15% of the FEV₁ 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
- (pCO₂ > 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 FEV₁ of $\geq 20\%$ 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 β_2 -agonists other than the albuterol
- Long-acting β_2 -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
- Lipxygenase 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 FEV₁. 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 FEV₁ 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 FEV₁ and post albuterol value.

The subjects were provided with a 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 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 FEV₁ 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:

- FEV₁ at baseline >90% of predicted normal
- AM PEF at baseline >95% of predicted normal
- Reversibility of FEV₁ <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 FEV₁ (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 FEV₁ 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 FEV₁ 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 FEV₁ measurements with factors for treatment, pooled center, and gender. Baseline FEV₁ 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 FEV₁ (L) to each time point
- Change from baseline in FEV₁ percent predicted and percent change from FEV₁ to average of Week 12 and Week 16
- Change from baseline in FEV₁ percent predicted and percent change from FEV₁ 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 on 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 FEV₁ 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 FEV₁. 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 FEV₁ 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 FEV₁ 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 FEV₁ was 2.47 (0.60) L and the mean (SD) FEV₁ 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 FEV₁ 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 $\geq 12\%$ reversibility and all had a ≥ 200 mL increase in FEV₁ 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.xpr” [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 FEV₁ was therefore obtained prior to initiation of the prohibited medication was started. In three cases the last FEV₁ was obtained after a course of prohibited corticosteroids were administered. For these individuals the last FEV₁, 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 FEV₁ at endpoint (average of 12 and 16 week values) to the baseline value. Each of the treatments resulted in increases in FEV₁ 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 FEV₁ after treatment with C80 BID was statistically significantly better than the change after treatment

Table 23. Change in FEV₁ after Treatment with Ciclesonide

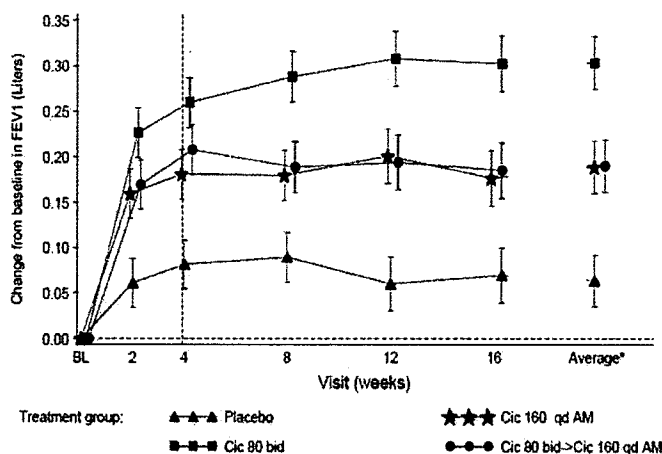
		Dose of Ciclesonide		
FeV ₁	Placebo	160 QD	80 BID / 160 QD	80 BID
N	177	173	171	170
Baseline, mean L	2.45	2.54	2.39	2.49
Change from baseline				
LS mean, L	0.06	0.19	0.19	0.30
95% CI	0.01, 0.12	0.13, 0.25	0.13, 0.25	0.25, 0.36
Difference from placebo				
LS mean, L		0.12	0.13	0.24
95% CI		0.05, 0.20	0.05, 0.20	0.16, 0.32
p- value		0.002	0.002	<0.001
Difference from cicles-80*				
LS mean, L		0.11	0.11	
95% CI		0.03, 0.19	0.03, 0.19	
p-value		0.005	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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ comparing active treatment to placebo was consistently greater (all active treatments) when the baseline FEV₁ 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 FEV₁ % predicted than in those with higher baseline values. However, the improvement was greatest in the placebo group with low baseline FEV₁%, 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 FEV₁ < 70 % predicted was 0.15 L

compared to the change in the subjects with FEV₁ >70% predicted at baseline of 0.00 L. Thus, while the FEV₁ increased by 0.37 L in the subjects with low baseline FEV₁% 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 FEV₁% which resulted in a difference from placebo of 0.26L.

Secondary efficacy outcome measures

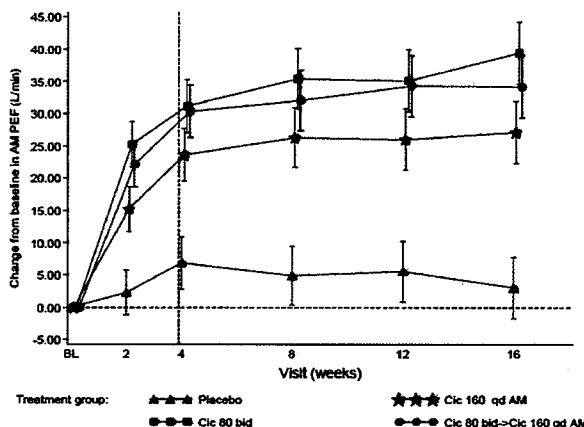
The diary-recorded AM PEF showed changes in the same direction as the changes in the FEV₁ (Table 24). The increase with treatment was 3.4, 26.7, 34.1, and 39.6 L/min in the placebo, C160, C80/160, and C80 groups, respectively.

Table 24. Change in AM peak flow

AM PEF	Placebo	Dose of Ciclesonide		
		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	3.4	26.7	34.1	39.6
95% CI	-5.9, 12.7	17.3, 36.1	24.7, 43.5	30.1, 49.0
Difference from placebo				
LS mean, L/min		23.3	30.7	36.2
95% CI		10.1, 36.5	17.7, 43.7	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 than 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	-0.97	-1.38	-1.57	-1.69
95% CI	-1.19, -0.74	-1.61, -1.15	-1.79, -1.34	-1.92, -1.46
Difference from placebo				
LS mean, puffs / day		-0.41	-0.60	-0.73
95% CI		-0.73, -0.09	-0.92, -0.28	-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.

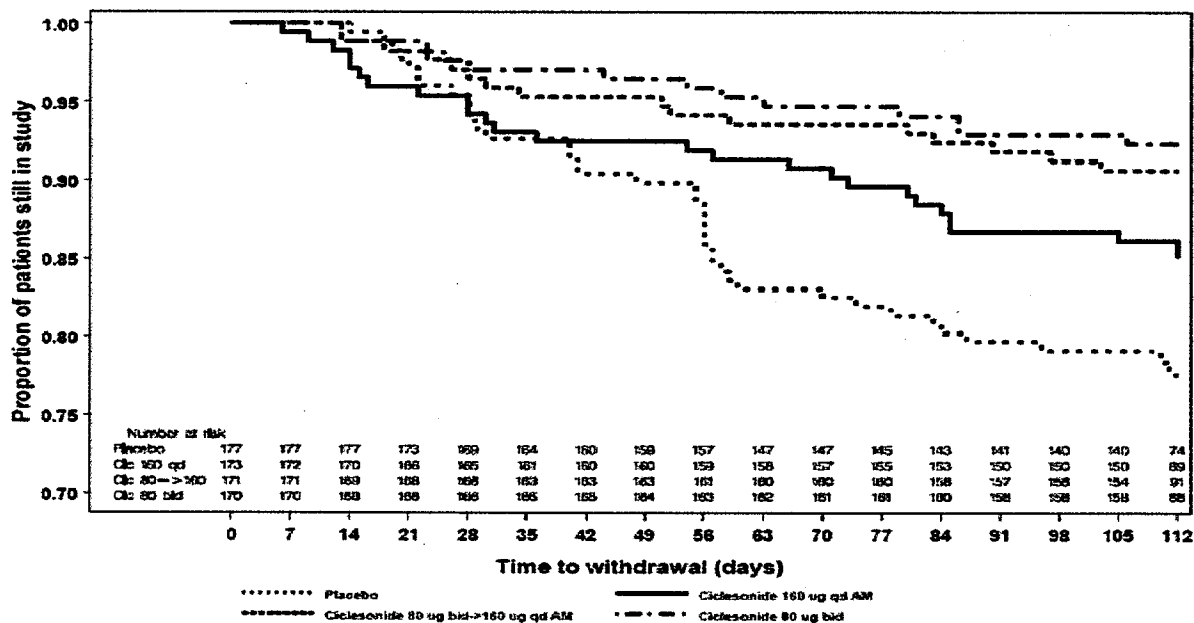
Table 26. Asthma Symptom Score

		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	-1.06	-1.33	-1.38	-1.63
95% CI	-1.27, -0.85	-1.55, -1.12	-1.60, -1.17	-1.85, -1.41
Difference from placebo				
LS mean		-0.27	-0.32	-0.57
95% CI		-0.57, -0.03	-0.62, -0.03	-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	111.0	112.0	112.0	112.0
Range	6 - 124	1 - 126	4 - 125	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

SOC and Preferred Term	Placebo	Dose of Ciclesonide		
	---	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)
Musculoskeletal 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 events 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

	Criteria	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 an 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 FEV₁, improvement after treatment with C80/160 and C160 was statistically significantly better than the improvement after treatment with placebo. However, the increase in FEV₁ 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-FEV₁ (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-FEV₁ 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 FEV₁ 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 $\leq 220/100$ mcg/day Advair or equivalent
- At screening and immediately prior to randomization, after an albuterol withhold of at least 6 hours, FEV₁ of $\geq 60\%$ and $\leq 90\%$ of predicted normal if previously treated with ICS monotherapy and an FEV₁ of $\geq 70\%$ and $\leq 95\%$ of predicted if treated with ICS and a LABA
- At screening or immediately prior to randomization, reversibility of FEV₁ by at least 12% (relative to the pre-bronchodilator value in liters [L]) after inhalation of 180 μ g albuterol (ex-actuator)
- FEV₁ at randomization within 15% of the FEV₁ 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 FEV₁ of $\geq 20\%$ 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 μ g per actuation [90 μ g 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 FEV₁. 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 FEV₁ 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 FEV₁ and post albuterol value.

The subjects were provided with a 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 FEV₁ 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:

- FEV₁ at baseline >90% of predicted normal
- AM PEF at baseline >95% of predicted normal
- Reversibility of FEV₁ <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 FEV₁ (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 FEV₁ measurements with factors for treatment pooled center, and gender. Baseline FEV₁ 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 FEV₁ (L) to each time point
- Change from baseline in FEV₁ percent predicted at each time point
- Percent change from baseline in FEV₁ 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 on 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 FEV₁ 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 FEV₁% 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 FEV₁ 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 FEV₁ 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 FEV₁. 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) FEV₁ 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 FEV₁ = 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 FEV₁ 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 FEV₁ and FEV₁% 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 FEV₁ 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 FEV₁ 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 FEV₁ after Treatment with Ciclesonide

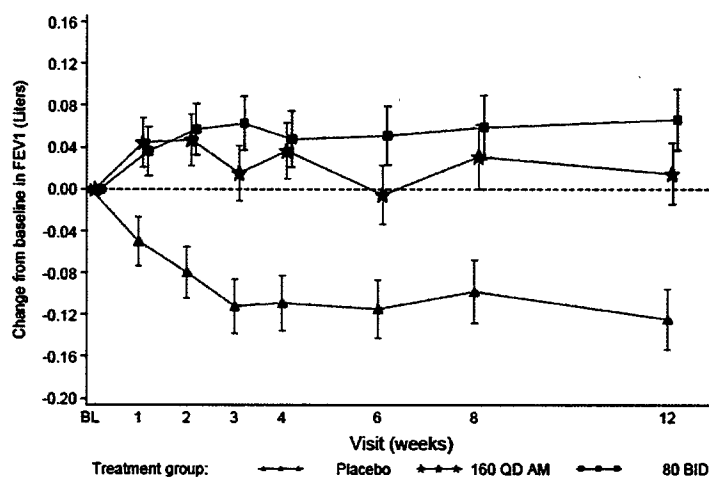
		Dose of Ciclesonide	
Fev ₁	Placebo	160 QD	80 BID
N	147	150	149
Baseline, mean L	2.63	2.64	2.67
Change from baseline			
LS mean, L	-0.12	0.01	0.07
95% CI	-0.18, -0.07	-0.04, 0.07	0.01, 0.12
Difference from placebo			
LS mean, L		0.14	0.19
95% CI		0.06, 0.22	0.11, 0.27
p- value		0.0006	<0.001
Difference 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 FEV₁ 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 FEV₁ 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 FEV₁ 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

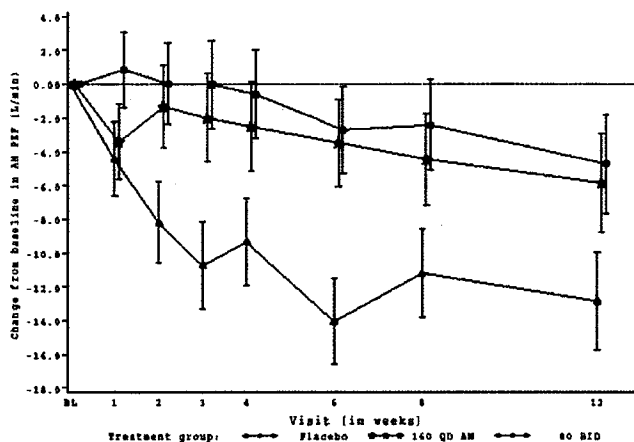
The diary-recorded AM PEF decreased in all of the treatment groups: 12.8, 5.8, and 4.4 L/min in the placebo C160 and C80 groups, respectively (Table 37). The difference between C160 and placebo was not statistically significant ($p = 0.08$).

Table 37. Change in AM Peak Flow

AM PEF	Dose of Ciclesonide		
	Placebo	160 QD	80 BID
N	147	150	149
Baseline, mean L/min	379	393	386
Change from baseline			
LS mean, L/min	-12.8	-5.8	-4.4
95% CI	-18.5, -7.2	-11.5, -0.03	-10.1, 1.3
Difference from placebo			
LS mean, L/min		7.1	8.4
95% CI		-0.8, 14.9	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	0.67	0.08	0.04
95% CI	0.45, 0.90	-0.15, 0.30	-0.19, 0.26
Difference from placebo			
LS mean, puffs / day		-0.60	-0.64
95% CI		-0.91, -0.28	-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

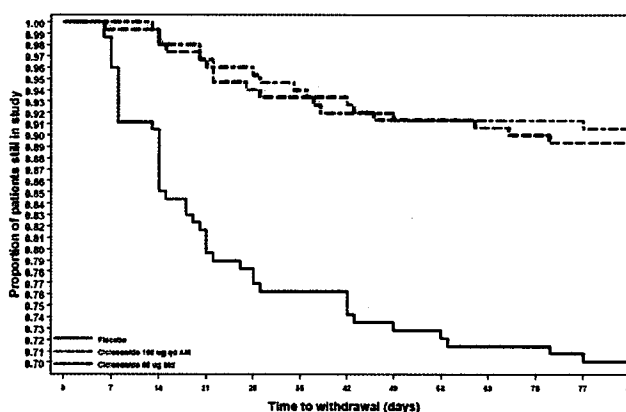
	Dose of Ciclesonide		
	Placebo	160 QD	80 BID
N	147	150	149
Baseline,	1.40	1.37	1.32
Change from baseline			
LS mean	0.33	-0.05	-0.05
95% CI	0.17, 0.49	-0.21, 0.11	-0.21, 0.12
Difference from placebo			

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

Musculoskeletal 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	4 (2.6)	3 (2.0)	5 (3.3)	8 (2.6)
FEV decreased	3 (2.0)	2 (1.3)	0	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 FEV₁) 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 FEV₁ were tallied separately. Three placebo and two C160 subjects had decreases in FEV₁ 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 analytes 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 (81×10^3 cell/mm³) 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 FEV₁% 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 FEV₁ fell over the first 3 weeks in the placebo subjects. The FEV₁ in the C80 subjects increased to 70 ml greater than baseline at the end of the treatment period and the FEV₁ 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.