2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

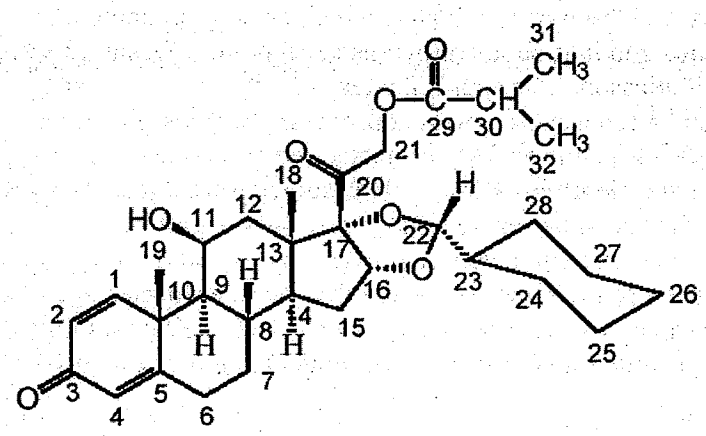
2.1. Chemistry, Manufacturing and Controls

Ciclesonide is a non-halogenated glucocorticoid, administered by inhalation as a metered dose aerosol. The formulation contains [redacted] w/w Dehydrated Alcohol, USP and [redacted] HFA-134a (1,1,1,2-tetrafluoroethane) propellant. The inhaler is formulated in three strengths: [redacted] These strengths deliver [redacted] mcg, 100 mcg, and 200 mcg ex-valve per actuation, respectively. The delivered doses ex-actuator are [redacted] mcg, 80 mcg, and 160 mcg, respectively. Ciclesonide inhalers are available in two pack sizes, delivering a minimum of 60 or [redacted] actuations respectively.

Reviewer: The ex-actuator doses are used throughout the clinical review unless noted otherwise.

The chemical name of ciclesonide is pregna-1,4-diene-3,20-dione,16,17[[R-cyclohexymethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α). The molecular weight is 540.7 and the molecular formula is $C_{32}H_{44}O_7$.

Figure 1. Chemical Structure of Ciclesonide



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The ester moiety attached to carbon position 21 of ciclesonide is enzymatically cleaved *in vitro* and *in vivo* to provide an active metabolite, des-ciclesonide (C21-desmethylpropionyl-ciclesonide or C21-desisobutyryl-ciclesonide [abbreviated as RM1]). Alvesco™ contains only the R-epimer of ciclesonide [redacted] S-epimer.

The manufacturing controls, stability, and particle size distribution of ciclesonide have all been reviewed by the Agency chemists and found to be acceptable. HFA-134a and this concentration of alcohol are approved for use in inhalation products. A dose counter is not included in the current device and this will have to be added and tested [redacted] *(see Chemistry Review for details)*

2.2. Animal Pharmacology and Toxicology

2.2.1. Animal Pharmacology

Ciclesonide and its active metabolite RM1 have anti-inflammatory and immunosuppressive activity in vitro. Ciclesonide and RM1 inhibit rat spleen cell proliferation, and human peripheral blood monocyte (PBMC) proliferation in response to concanavalin A. RM1 also inhibits the CD3-mediated proliferation of PBMC. Ciclesonide and RM1 inhibit CD3-mediated release of interleukin-2 (IL-2) from PBMC, and TNF-α, IL-4 and IL-5 from activated lymphocytes. Finally, TNF release from monocytes and dentritic cells after LPS exposure is also inhibited by ciclesonide and RM1.

While RM1 has 100 times the affinity for the corticosteroid receptor as does ciclesonide, the relative potency in physiologic assays listed above show a closer correspondence between RM1 and its parent compound. In the lymphocyte proliferation assays, RM1 was approximately as potent as budesonide and 1.5 to 8 times more potent than ciclesonide. In the same assay RM1 was approximately 5 times less potent than fluticasone. In the cytokine release studies RM1 was approximately as potent as budesonide and only 2 – 3 times more potent than ciclesonide. Fluticasone was, again, 5 times more potent than RM1.

Intratracheal installation of ciclesonide and RM1 have been compared to budesonide and fluticasone in their ability to protect animal lungs from allergic inflammation and from sephadex-induced lung edema. Ciclesonide and RM1 were essentially equipotent in protecting rats from lung edema, and in producing thymus involutions after intratracheal administration of sephadex. Fluticasone was approximately 10 times more potent at protecting from lung edema and 4 times more potent at producing thymus involution. Intratracheal administration of ciclesonide or RM1 protected sensitized Brown Norway rats against antigen exposure. When ciclesonide, RM1, or budesonide were injected 24 and 1 hour prior to exposure and bronchoalveolar lavage performed 48 hours after exposure, ciclesonide, RM1 and budesonide were equipotent in preventing exudation of neutrophils, eosinophils, and protein into the airway. However, when BAL was performed at 24 hours post exposure ciclesonide was approximately twice as potent as RM1. Prior administration of ciclesonide also protected the rats from the increase in bronchial hyperrresponsiveness that is seen after antigen challenge.

Reviewer: The above findings suggest that there may not be a simple 1:1 relationship between the corticosteroid receptor binding activity and all of the physiologic activity of ciclesonide and RM1.

2.2.2. Animal Toxicology

2.2.2.1. General Toxicity

Ethanol (—) has been used as an excipient in inhaled drug products and is considered safe b(4)
for human use. The pharmacology/toxicology of the propellant HFA 134a has been well studied and determined to be safe for use in inhaled drug products

The median lethal dose was >2000 mg/kg and >200 mg/Kg when ciclesonide was administered orally or intraperitoneally as a single dose in mice and rats respectively.

In repeat dose studies ciclesonide was evaluated for up to 6 months in rats after oral and inhalation exposure. At doses of up to 160 mcg/Kg/day changes were seen in body weight and food consumption, RBC counts increased, WBC counts decreased, bilirubin increased , and slight- to- moderately decreased in thymus and adrenal gland weights were seen. Microscopic examination confirmed the presence of thymic atrophy and lymphoid depletion in spleen and lymph nodes. In dogs exposed to 92 mcg/Kg/day via inhalation for 12 months slightly decreased body weight, cortisol suppression, and decreased adrenal gland weights were seen. In addition, there was nasal turbinate osteofibrosis and chondrosis, ovary changes, regression of mammary gland tissue, slight hepatocellular centrilobular hypertrophy, and vacuolization of the liver. These were all attributed to a corticosteroid class effect.

2.2.2.2. Genotoxicity

Ciclesonide was not mutagenic in a bacterial assay with *Salmonella typhimurium, Escherichia coli,* or in Chinese hamster V79 cells. Ciclesonide was also not clastogenic in chromosome aberration in human lymphocytes or in the micronucleus test in Chinese hamster cells. In 3 of 4 mouse micronuleus tests using doses of 0.25 – 2000 mg/kg, an increase in the incidence of micronulecated polychromatic erythrocytes was seen. The relevancd of this increase is unclear as the increases were minimal, there was no dose-response relationship, and similar effects are reported in the literature for other glucocorticoids. When tests were performed to compare ciclesonide with budesonide and dexamethasone, equivalent increases in micronuclei were seen with all three compounds.

2.2.2.3. Carcinogenicity

In two 24-month carcinogenicity studies in rats there was no indication of a carcinogenetic potential when ciclesonide was given by inhalation in doses of up to 96.5 mcg/kg/day or via gavage in PEG in doses up to 900 mcg/Kg/day. In an oral carcinogenicity study performed in mice, a significant increase in gastric adenomas were seen in the female animals only. Because the adenomas are not malignant and they occurred only at high doses it was concluded that these results did not suggest a significant risk for human exposure.

2.2.2.4. Reproductive and Developmental toxicity

In rats administered ciclesonide orally at doses of up to 900 mcg/Kg/day for 4 weeks no effects were seen on fertility or early embryofetal parameters. In two studies in rabbits administered ciclesonide subcutaneously in doses up to 400 mcg/Kg/day from day 6 to 28 after mating, there were effects on embryofetal development in rabbits receiving doses ≥5 mcg/Kg/day. In doses of 5 – 100 mcg/Kg/day, the effects were reduced fetal litter weight, dry, thin skin, cleft palates, flexure of paws, enlarged fontanelles, and incomplete ossification. The 400 mcg/Kg/day group contained no live fetuses. These results were thought to be compatible with a corticosteroid class effect. Rabbits are known to be extremely sensitive in reproductive assays, and the results were not taken to indicate a risk to the fetus that is any greater than that associated with ingestion of other corticosteroids.

Ciclesonide was administered orally to pregnant/lactating rats of doses up to 900 mcg/Kg/day from day 6 post mating until day 20 post partum. In the dams of the F0 generation there were decreased body weight and decreased food consumption at 900

mcg/Kg/day. There were no effects on the F0 reproduction parameters. Pups of mothers receiving 900 mcg/Kg/day had decreased body weight gains. There were no compound-related effects on developmental indices, behavioral tests or reproductive performance on the F1 pups.

Early in the development program for ciclesonide, a dog toxicology study was reported to have found "spermiogenic dysfunction" in animals treated with ciclesonide. The pathology was reviewed by a Pathology Working Group that was constituted by the applicant, but that was made up of pathologists outside of the company. The review concluded that the original findings were an artifact.

Reviewer: Agency pharmacotoxicologists have reviewed the toxocology data presented by the applicant and agree with the findings that the reproductive toxicity is equivalent to that seen with other corticosteroids and will be listed as a Category C teratogen in the label. They also agree that the finding of increased formation of micronuclei is not an approvability issue, but that a comment will go into the label describing the findings. The "spermiogenic dysfunction" is also accepted as an artifact.

2.3. Microbiology

No sterility problems have been identified with the drug product. For more details refer to the CMC review.

2.4. Statistics

In all of the studies the primary analysis was in the ITT population (all subjects who received study drug and who had at least one follow-up measurement for the outcome variable). A statistical comparison was made between ciclesonide treatment and placebo in the change in outcome variable (FEV_1, FEV_1 % predicted, percentage decrease in daily OCS use) over the 12-week treatment period. A step-down procedure was used to adjust for multiple comparisons. Using this method, the highest dose of ciclesonide was compared to placebo and only if the comparison was statistically significant (α=0.05) was the next lower dose of ciclesonide compared to placebo for statistical significance. All doses below a dose that was not significantly superior to placebo were determined to be not superior to placebo. No adjustment for multiple comparisons was made for the secondary outcome measures as they were considered to be supportive only.

The treatment effect was assessed using analysis of covariance with pooled clinical center, pervious therapy, baseline FEV_1, age, and gender included as covariates. Pair wise comparisons were based on least-squares estimates of treatment means and associated standard errors from the primary analysis model. Two-sided 95% confidence intervals for the difference in least–squares means were constructed for each treatment comparison. The studies were designed to have a 90% power to detect a minimal change of 200 ml in FEV_1 or a 6% change in FEV_1%.

The results of the Agency statistical analysis are referred to in the individual study review in the Appendix and in the Clinical Review.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

After inhalation of single doses of 360 mcg by normal volunteers, the C_{max} of ciclesonide and RM1 occurred at 1.1 and 0.25 hours respectively. The mean $AUC_{0-\infty}$ of RM1 (1.72 ng*hr/ml) ranged from 2.5 to 3-fold higher than that observed for the parent drug. However, the C_{max} (0.3 ng/ml) was 3.5-fold lower than the parent drug. The AUC of RM1 that was modeled from the data in the population sample was linear and dose-proportional in the range of 40 to 3520 mcg.

The mean C_{max} and $AUC_{0-\infty}$ of RM1 following multiple doses of ciclesonide 360 mcg QD increase up to 26% compared to those after single administration. The T_{max} was similar to that after single dose administration and it is estimated that the time to reach steady-state would be within 2 – 3 days. The RM1 half-life increased from 5.2 to 6.7 hours. Following multiple doses of ciclesonide (250 and 1000 mcg BID), C_{max} and AUC were both dose proportional.

Inhaled bioavailability of ciclesonide + RM1 following inhalation of ciclesonide via MDI was 41%. Both ciclesonide and RM1 are rapidly absorbed: the KA values ranged from 7.3 to 10.8/hr across sub-populations (asthmatics, healthy adults and children, male, female, etc). The volume of distribution following IV administration was 207 L and 898 L for ciclesonide and RM1, respectively. Protein binding for RM1 and ciclesonide was higher than 98.5%, however, high non-protein binding was also reported in this study.

Following IV administration, the half-lives and plasma clearance of ciclesonide and RM1 were 0.94 hr and 2.8 hr, and about 152 and 228 L/h, respectively, indicating high extraction ratio drugs. Based on population PK analysis, mean clearance ranged from 267.3 – 339.7 L/hr. Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) and IV (65.95%) administration. The biotransformation of ciclesonide is catalyzed by an esterase which has not been identified. RM1 appears to be the major metabolite after esterification, however, mass balance studies showed that only 20% of the total plasma radioactivity corresponds to RM1. RM9, another metabolite whose pharmacologic potency is unknown, was found in plasma in concentrations equal to those of RM1, so it appears that the full range of potentially active metabolites has not be characterized to date.

RM1 is esterified to form fatty acid conjugates in the lung. The reaction is catalyzed by CYP3A4 (83%), CYP2D6 (~30%), and CYP2C8 (~11%), although the exact role of each enzyme had not been completely elucidated. RM1 does not produce significant inhibition (<25%) of major cytochrome P450 enzymes and the potential for ciclesonide to produce inhibition has not been tested. At therapeutic serum concentrations, ciclesonide is not likely to induce the major CYP enzymes.

The systemic exposure of ciclesonide and RM1 in asthmatic patients receiving a single dose of ciclesonide 1600 mcg was similar to that in healthy subjects. Based on population PK analysis, there were no clinically relevant differences in RM1 pharmacokinetics due to race, gender, weight, or age. The mean AUC_{pop} normalized to 200 mcg in children and elderly

was similar to that in adults (0.82 ng*hr/ml±0.3 and 0.82 ng*hr/ml±0.2 vs. 0.6 ng*hr/ml±0.4 in adults). The mean systemic exposure (AUC_{pop}) in the Black and "Others" population was significantly lower (60% and 70% respectively) than that in the White population. However, these results may be due to uneven distribution of gender, body weight and other factors because the minority population was small. The difference may also not be clinically relevant since the dose-exposure response was flat in the range of doses tested.

The effect of renal impairment on ciclesonide and RM1 metabolism was not tested since the drug is excreted primarily via the liver. In 8 subjects with severe and 8 with moderate hepatic injury, the C_{max} and $AUC_{0-\infty}$ increased in the range of 1.4 to 2.7 fold compared to 8 healthy adults. In addition, the $T_{1/2}$ of RM1 increased in patients with moderate to severe hepatic impairment by 2.3 to 4.6 hours.

The systemic exposure to ciclesonide and RM1 after a single dose of 800 mcg ciclesonide in healthy subjects did not change during co-administration with a single dose of erythromycin 500 mg. The arithmetic mean C_{max} and $AUC_{0-\infty}$ of RM1 increased in the presence of erythromycin by < 12%. The applicant did not test inhibitors of CYP3A4 that are more portent than erythromycin. Since other corticosteroid preparations have been shown to have a greater interaction with ketokonazole or ritonavir than with erythromycin, the label will indicate that a full evaluation of drug/drug interaction with CYP inhibitors has not been carried out.

3.2. Pharmacodynamics

Based on population PK/PD analysis using data from phase I and Phase III studies, there was a trend for higher doses of ciclesonide to produce a higher cortisol suppression (13%, 8%, and 49% decrease in serum cortisol AUC for dose of 800 to 1200 mcg, 1600 mcg, and 3520 mcg respectively. A dose response relationship was not seen in part due to the high variability in the data. Nevertheless, the degree of cortisol suppression caused by ciclesonide in the range of proposed therapeutic doses was not higher than that observed for fluticasone propionate.

Cosyntropin stimulation testing was performed on selected subjects in the phase III clinical trials. In general there was little change in the post-stimulation serum cortisol after 12 weeks to 1 year of treatment with ciclesonide. These studies are reviewed in the Appendix and summarized in the Integrated Safety Summary.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

The clinical data reviewed for this application were all contained in the original NDA application and the 120-day update to the NDA. No reference was made to other development programs or to the literature. In addition a follow-up severe adverse event report was made to IND 53,391 and this was also reviewed.

4.2. Overview of Clinical Trials

The adult program (≥ 12 years of age) consisted of 2 pivotal 12-week trials (321 & 322) in mild-to-moderate asthmatics and one (323/324) in moderate-to severe asthmatics that used FEV_1 as the primary outcome variable. An additional 12-week trial (325) in OCS-dependent asthmatics was conducted with the goal of reducing the subject's OCS requirements. One-year safety follow-up trials were carried out for both the mild-to-moderate (study 326) and moderate-to-severe (study 323/324lt) subjects. The pediatric program consisted of 2 pivotal 12-week trials (341 and 342) conducted in children age 4 – 11 years of age with mild to severe asthma. The FEV_1% of predicted was the primary outcome variable. Three 1-year safety trials of identical design were carried out. Study 341lt and 342lt were continuations of 341 and 342 and study 344 was an additional safety study. Study 102 was a 12-week adult trial to assess the effect of ciclesonide treatment on the HPA-axis. It was reviewed primarily for the safety outcomes.

4.2.1. Study 321 & 322

Study 321 and 322 were multicenter, randomized, double-blind placebo controlled trials of identical design. Subjects with mild-to-moderate persistent asthma were enrolled using entry criteria that were dependent upon their prior medication status. Subjects who had been on ICS for the 30 days prior to screening had to have and FEV_1 of 65-100% predicted, and subjects who had been treated with bronchodilators only had to have an FEV_1 of 60-85% predicted. After a run-in period of 5 to 28 days during which subjects were treated with placebo and albuterol for rescue, subjects who had been on ICS prior to screening were eligible for randomization if their FEV_1 had fallen by 10% while subjects who had been treated with bronchodilators only were eligible for randomization if they became symptomatic during the placebo run-in. If eligible, they were randomized to receive ciclesonide 80, 160, or 320 mcg daily or placebo, taken in the morning for 12 weeks. The primary outcome variable was the change in FEV_1 (L) over the 12 week treatment period comparing ciclesonide to placebo treatment. PEF, albuterol use, Symptoms, and the Asthma Quality of Live Questionnaire (AQLQ) were secondary outcome variables. The function of the HPA-axis was assessed with a low-dose (1 mcg) cosyntropin stimulation test. 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). There were 489 subjects enrolled in study 322 (118, 124, 123, and 124 in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 groups respectively).

4.2.2. Study 323/324

Study 323/324 was a multicenter, randomized, double-blind placebo controlled trial that enrolled subjects with moderate to severe asthma, all of whom had been treated with ICS prior to enrollment. During a 5 to 28 day run-in period subjects were instructed to take one half of their regular ICS dose. To be eligible for enrollment their FEV_1 had to fall by at least 10% during the run-in and the FEV_1 also had to be between 40 and 65% of predicted. At enrollment subjects were randomized to ciclesonide 160 mcg BID (n=127), ciclesonide 320 mcg BID (n=130), placebo (n=133) or fluticasone propionate MDI 440 mcg BID (n=138). As in study 321 and 322 the outcome variables were change in FEV_1, PEF, albuterol use, symptoms, and AQLQ over the 12-week treatment period comparing active treatment to placebo. The HPA-axis function was also tested with the low dose consyntropin stimulation test.

4.2.3. Study 325

Study 325 was a multicenter, randomized, double-blind placebo controlled trial that enrolled subjects with moderate-to-severe asthma who were taking OCS at the time of screening. During a 4 week run-in period the dosage of OCS was decreased to the lowest effective dose (LEF) that maintained asthma control. If at the end of the run-in the subjects were taking at least 5 mg prednisone, they could be randomized to ciclesonide 320 mcg BID (n=47), ciclesonide 640 mcg BID (n=49), or placebo (n=45). Subjects were seen weekly and attempts were made to further reduce the maintenance dose of OCS. The primary outcome variable was the percent reduction in OCS in the ciclesonide- treated subjects compared to placebo. Pulmonary function was measured as a secondary outcome variable.

4.2.4. Study 326

Study 326 was an open-label, 1-year follow-up of subjects (n=226) who had been enrolled in studies 321 and 322. Subjects were initially treated with 320 mcg ciclesonide daily and then the dose was adjusted at the investigator's discretion to maintain the lowest dose of ciclesonide that provided control of the subjects' asthma. The primary objective of the study was safety, and pulmonary function was measured as a secondary outcome.

4.2.5. Study 323/324lt

This was a randomized, double blind, 1-yr safety follow-up of study 323/324. At the end of the pivotal trial, subjects were re-randomized to receive ciclesonide (n=198) or beclomethasone (QVAR® n=99). After enrollment subjects were treated with ciclesonide or QVAR 320 mcg BID for two weeks. Subsequently, the investigator could raise or lower the dose of the medication between 160 and 320 mcg BID with the goal of finding the lowest dose to maintain asthma control. The primary outcome measures were adverse events, and pulmonary function was measured as a secondary outcome.

4.2.6. Study 341 and 342

Study 341 and 342 were multicenter, randomized, double-blind placebo controlled trials of identical design. Subjects aged 4-11 years with mild to severe persistent asthma were enrolled using entry criteria that were dependent upon their prior medication status.

Subjects who had been on ICS for the 30 days prior to screening had to have an FEV_1 of 40-100% predicted and subjects who had been treated with bronchodilators only had to have an FEV_1 of 40-85% predicted. After a placebo run-in period of 5-21 days, during which subjects were treated with albuterol for rescue, subjects were eligible for randomization if they had been on ICS prior to screening and their FEV_1 fell by 10% or if they had been treated with bronchodilators only prior to screening and became symptomatic during the placebo run-in. If eligible, they were randomized to receive ciclesonide 40, 80, or 160 mcg daily or placebo, taken in the morning for 12 weeks. The primary outcome variable was the change in FEV_1 % predicted over the 12- week treatment period comparing ciclesonide to placebo treatment. PEF, albuterol use, and Symptoms were secondary outcome variables. A Pediatric AQLQ was administered to subjects 7 years and above. The function of the HPA-axis was assessed with a low-dose (1 mcg) cosyntropin stimulation test. There were 514 subjects enrolled in study 341 (131 in the placebo, 126 in the ciclesonide-40, 135 in the ciclesonide-80 and 122 in the ciclesonide-160 groups). There were 517 subjects enrolled in study 342 (127, 130, 126, and 134 in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively).

4.2.7. Study 341lt, 342lt, 344lt

These three studies are of identical design except that subjects enrolled in studies 341lt and 342lt were re-randomized after completing studies 341 or 342, whereas subjects were enrolled *de novo* from the community into study 344lt. Subjects were randomized to receive ciclesonide (n= 129, 128, and 186 in studies 341lt, 342lt, and 344lt respectively) or fluticasone (Flovent® n= 64, 62, and 46 in studies 341lt, 342lt, and 344lt respectively). Treatment was initiated with 160 mcg daily of ciclesonide or 100 mcg BID of fluticasone MDI, and after two weeks the dose could be altered by the investigator to optimize asthma control at the lowest possible dose of study drug. The primary outcome was adverse events.

4.2.8. Study 102

This study was conducted in adults (≥ 18 years of age) with mild-to-moderate asthma who were not taking ICS at the time of screening. Subjects were 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). They were treated for 12 weeks and low and high-dose cosyntropin tests were performed at baseline and follow-up. Twenty-four hour urine was collected for cortisol and adverse events were assessed.

4.2.9. Study 126_99 (FK1 103)

This was a physiology study conducted in 15 subjects with mild asthma. The design was a 2-week cross-over trial using ciclesonide 400 mcg (ex valve) (320 mcg ex-actuator) or budesonide 400 mcg (ex valve). There was a 3 to 8 week washout period between the two active treatments. The outcome variables were bronchial responsiveness to AMP, exhaled nitric oxide, and sputum eosinophil counts.

4.3. Postmarketing Experience

Ciclesonide had not yet been marketed in any country.

4.4. Literature Review

A literature review was not submitted. A PubMed search by this reviewer revealed few clinical articles, most of which were publications of the applicant's data that are thoroughly reviewed in the NDA submission.

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

The clinical section of the original NDA submission contains complete study reports for 36 trials. Of these, 11 were reviewed in detail for safety and efficacy, and are summarized in the Description of Clinical Data, above. In addition, one of the 36 (FK1 103) was a study that addressed the physiologic responses to ciclesonide treatment. The results are referred to in the label and the study was reviewed here. One 12-week PD trial (study 102 in the Biopharmacology section) was reviewed for safety. Twenty-four of the submitted clinical studies were conducted by Byk-Gulden, the original developer of ciclesonide. They were not included in the applicant's ISS or ISE and were not reviewed.

At the time of the original submission, the 1-year follow-up studies (326, 323/324lt, 341lt, 342lt, and 344lt) were not complete. The final study reports were submitted with the 120-day safety update. The reports in the 120-day safety update were used for the current review.

5.2. Materials Consulted and Documentation

The original NDA was submitted as an electronic NDA in a CTD format on December 22, 2003. However, the links intended to aid navigation within each study report did not work, (*\\CDSESUB1\N21678\N_000\2004-02-05*). The amendment contained all the data for the NDA with working links and this amendment to the NDA was used for this review. In the original submission, the 1-year safety follow-up studies were submitted as interim analyses. The final study reports were submitted with the 120-day safety update on April 26, 2004 (*\\CDSESUB1\N21678\N_000\2004-04-26*) and these were used for the safety reviews as well as other updated information. One of the subjects enrolled in study 341lt died while taking study medication. A detailed autopsy report was submitted to the ciclesonide IND as a follow-up of a serious and unexpected adverse event, and this was also reviewed *(IND 53,391, series 216, stamp date May 14, 2004).*

Responses to Agency queries about HPA-axis function tests were submitted by the applicant on April 26 and August 4, 2004 (*\\CDSESUB1\N21678\N_000\2004-04-26A, \\CDSESUB1\N21678\N_000\2004-08-04*). Responses to queries related to the Pediatric Research Equity Act were submitted on March 22, 2004 and May 27, 2004 (*\\CDSESUB1\N21678\N_000\2004-05-27\\CDSESUB1\N21678\N_000\2004-03-22*).

5.3. Data Quality and Integrity

The Agency's Division of Scientific Integrity (DSI) was requested to perform an audit of four US clinical sites (28, 40, 83, and 160) on the basis of the number of subjects they enrolled. In addition, the one pediatric death occurred at site 28. No discrepancies were found during these inspections. At the time the NDA was submitted, two sites (132 and 150) were already scheduled for inspections for cause. At site 132 several minor omissions were found in subjects treated on protocol 321. Three subjects (2 placebo and one ciclesonide-80) did not have minor adverse events (head cold, yeast infection, eye infection) recorded in the

case report form. An FDA Form 483 was sent and the investigator sent a response indicating that appropriated corrective measures were being taken. These minor protocol deviations were not severe enough or frequent enough to impeach the integrity of the study.

5.4. Ethical Standards

The applicant has certified that all of the trials were conducted in accordance with the Declaration of Helsinki and local legal, ethical and Good Clinical Practices requirements

(pg 14, ...\summary\2.7.3aclinicalefficacy.pdf, and pg 11, ...\summary\2.7.3bclinicalefficacy.pdf). All subjects also signed IRB-approved informed consent forms (pg 39, ...clinstat\321\study321.pdf; pg 40, ...clinstat\322\study322.pdf.; pg 35, ...clinstat\study323_324\study323_324.pdf; pg 36 , ...clinstat\325\study325.pdf; pg 49, ...clinstat\341\study341.pdf; pg 50, ...clinstat\342\study342).

5.5. Financial Disclosure

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Four investigators reported receiving $26,000 to $40,000 each from the applicant in addition to grant-related payments. [redacted] of the investigators worked in [redacted] However, they worked at different sites and on different studies. One of the investigators [redacted] screened [redacted] patients and enrolled [redacted] The other screened [redacted]

One investigator in [redacted] screened [redacted] patients [redacted] and [redacted] investigator in [redacted] screened [redacted] patients and enrolled [redacted]

On the basis of the small number of subjects that were actually enrolled by these investigators it is unlikely that any financial considerations would have affected the outcome of the studies. In addition, the children enrolled in study [redacted] by investigator [redacted] and the adults enrolled by investigator [redacted] in study [redacted] had baseline pulmonary function, change in function over the study, and drop-out rates similar to the other subjects enrolled in the study.

APPEARS THIS WAY ON ORIGINAL

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

In adults and adolescents (≥ 12 years of age) with mild-to-moderate persistent asthma, the only dose of ciclesonide that was reproducibly effective in increasing FEV_1 was 320 mcg once daily in the morning. In addition, in this patient population no dose was effective in subjects who had been treated with bronchodilators only prior to enrollment. All of the effect was seen in subjects who were taking ICS at the time of screening, and even in this group, doses lower than 320 mcg daily were not reproducibly effective. In patients ≥ 12 years of age with moderate to severe asthma, both 160 mcg BID and 320 mcg BID effectively improved pulmonary function. In adults with moderate to severe asthma who were maintained on oral corticosteroids, ciclesonide 320 mcg BID and 640 mcg BID lowered the requirement for OCS by 47 and 63% respectively. For the doses of ciclesonide that were effective in improving pulmonary function, the response was maintained throughout the 1-year of follow-up. However, the applicant's claim of [redacted] was not substantiated. b(4)

In children age 4 – 11 years, ciclesonide failed to reproducibly increase the FEV_1% predicted at any dose.

6.2. General Approach to the Efficacy Review

The conclusions about efficacy were based primarily on the demonstration of statistically significant differences between ciclesonide and placebo-treated subjects in the increase in the primary outcome variable (absolute FEV_1 [L] in adults and adolescents and FEV_1 % predicted in children 4 to 11 years) over the 12-week treatment period of the pivotal trials (321, 322, 323/324, 341, and 342.) For the OCS reducing trial the primary outcome variable was the percentage decrease in prednisone dose. The data were analyzed in a hierarchical fashion such that the highest dose of ciclesonide was compared to placebo first and lower doses were analyzed in a step-wise fashion only if the highest dose showed statistically significant improvement compared to placebo. For a description of the trials see Description of Clinical Data and Sources above.

6.3. Summary of Trials by Indication

6.3.1. Studies for the Maintenance Treatment of Asthma in Adults and Adolescents age 12 years and older

6.3.1.1. Study Design

Study Population

There were four pivotal efficacy studies (study 321, 322, 323/324, 325) in adults and adolescents 12 years of age and older. These studies were all randomized placebo controlled studies with a treatment period of 12 weeks.

Studies 321 and 322 were of identical design in which subjects were treated with ciclesonide 80 mcg (40 mcg x 2 puffs), ciclesonide 160 mcg (80 mcg x 2 puffs), ciclesonide 320 mcg (160 mcg x 2 puffs) [dose measured ex-actuator]) or placebo, once daily in the morning. All subjects were required to have a history of mild to moderate asthma for at least 6 months, to have FEV_1 reversibility of at least 12% following inhalation of albuterol, and to have not smoked tobacco in the year prior to screening. Additional entry criteria were dependent upon spirometric findings and the subject's asthma treatment for the 30 days prior to screening. Subjects were divided into 2 strata on the basis of prior use of inhaled corticosteroids (ICS). Stratum 1 consisted of subjects who had been treated with any combination of ICS, leukotriene receptor antagonists, or bronchodilators. ICS could not exceed the equivalent of 500 µg/day fluticasone DPI or 1000 µg/day budesonide. Stratum 2 was made up of subjects who had been treated only with bronchodilators. At screening, subjects in stratum 1 had to have an FEV_1% predicted of 65 – 100%; subjects in stratum 2 had to have an FEV_1 of 60 – 85% predicted. After meeting the screening criteria, the subjects were put on a placebo inhaler for 5 to 28 days. After the placebo treatment, the FEV_1 had to be between 60-85% predicted in both strata. In addition, the FEV_1 of stratum 1 subjects had to have fallen by 10% compared with the screening value. Stratum 2 subjects had to have had a minimum symptom level for 3/7 days prior to randomization as assessed by Asthma Symptom Score (≥3 [*see Procedures, pg 25*]), PEF variability (≥20%), or albuterol use (≥ 2 puffs/ day). The spirometry measured at the post-placebo randomization visit was used as the baseline value to assess efficacy. The primary outcome variable was the difference between active treatment and placebo in the change from baseline to end of study in the absolute FEV_1 (L).

Study 323/324 was conducted in subjects with moderate to severe asthma. In this study subjects were treated for 12 weeks with ciclesonide 160 mcg (80 mcg x 2 puffs) BID, ciclesonide 320 mcg (160 mcg x 2 puffs) BID [dose measured ex-actuator]), fluticasone CFC MDI 440 mcg BID, or placebo. Subjects were required to have taken ICS (equivalent of ≥500 µg/day of fluticasone or 800µg/day budesonide) for at least 1 month prior to screening and to use a β-adrenergic agonist > 2 times per week. They had to have an FEV_1 ≤ 80% predicted at screening and to have an FEV_1 40 – 65% after a 5 to 28-day run-in period. During the run-in period, subjects were instructed to take 50% of their baseline ICS dose. To be eligible for randomization, the FEV_1 had to fall by at least 10% during the 5 to 28-day run-in period. The primary outcome variable was the same as for studies 321 and 322; i.e., the difference between active treatment and placebo in the change from baseline to end of study in the absolute FEV_1 (L).

Study 325 was conducted in subjects with severe asthma who were maintained on oral corticosteroids (OSC) who were also taking ICS and used β-adrenergic agonists at least twice a week for symptom control. After dependence on OCS was demonstrated in a one to four- week run-in period, subjects were randomized to ciclesonide 320 mcg (80 mcg x 4 puffs) BID, ciclesonide 640 mcg (160 mcg x 4 puffs) BID, or placebo. To be eligible for randomization, the lowest effective dose (LEF) of OCS had to be at least 5 mg/day of prednisone and the FEV_1% had to be between 40 and 80% of predicted. During the 12-week treatment period, subjects were seen in the clinic on a weekly basis for follow up and attempts to lower the dose of OCS were made. The prednisone dose was decreased by a pre-specified amount if the FEV_1 was ≥ 40% predicted and ≥ 80% of the actual FEV_1

measured at randomization, and there was no increase in asthma symptoms, nighttime awakenings, or albuterol use. The primary outcome variable was the difference between active treatment and placebo in the percent change from baseline in the prednisone dose at end-of-study.

Procedures

Subjects were seen at 1, 2, 4, 8, and 12 weeks in studies 321, 322, and 323/324. At each visit, spirometry was performed in the morning prior to the taking of study medication, and the diary entries were reviewed. Patients recorded asthma symptoms, nighttime awakenings, albuterol use, and AM and PM peak flow measurements in diaries. The AM and PM Asthma Symptom Scores were based on a 5 point scale ranging from 0 = no symptoms to 4 = symptoms which prevent the patient from engaging in daily activities or sleep. Patient reported outcomes were based on the Asthma Quality of Life Questionnaire (Juniper and Guyatt) and was self-administered by all subjects at baseline and at weeks 4, and 12 as the first procedure on testing days

In Study 325 subjects were seen at weekly intervals. If they were stable the OCS dose was decreased. At each visit spirometry was performed and the diary entries were reviewed as described for the other studies.

In all of the studies (321, 322, 323/324, and 325), subjects were advised to contact the investigator if there was any deterioration in their asthma. Criteria for asthma deterioration based on the fall in PEF and increased use of albuterol were given to the subjects, but withdrawal of the subject due to an asthma exacerbation was entirely dependent upon the discretion of the investigator. Investigators also used their discretion to withdraw subjects due to "lack of efficacy" as distinct from an asthma exacerbation adverse event.

Analysis

To address the issue of multiple comparisons, an hierarchical analysis plan was used. The first pair-wise comparison was made between the highest dose of ciclesonide and placebo. If that was significant, the next lower dose/doses of ciclesonide was/were each compared to placebo in a step-wise fashion.

For studies 321, 322, and 323/324, the primary outcome variable was the change in FEV_1 (L) between baseline and end-of-study (Week 12 [LOCF]) Secondary outcome variables included the change over the 12-week treatment period in FEV_1% predicted, AM and PM Peak Expiratory Flow (PEF), variability in PEF, Asthma Severity Score, albuterol use, and nighttime awakenings. A separate analysis of PEF, albuterol use, and Asthma Severity Score was presented to determine the onset of action in the first week. A time-to-event analysis was performed to detect differences in the drop-out rate between active treatment and placebo groups. The investigator's designation of withdrawal due to lack of efficacy was used to determine the time to withdrawal due to lack of efficacy. The AQLQ questionnaires were analyzed for mean change in scores. A change of ≥ 0.5 was taken to be clinically meaningful. No correction for multiple comparisons was applied to the secondary outcome variables because these results were considered to be supportive only.

For study 325, the primary outcome variable was the difference between active treatment and placebo in the percent change from baseline in the prednisone dose at end-of-study

(Week 12 [LOCF]). For subjects who withdrew due to lack of efficacy or for an asthma exacerbation, the dose of prednisone used as the LOCF was 10 mg plus the last recorded dose. For subjects who withdrew for any other reason, the last dose recorded was carried forward and used in the analysis. Secondary efficacy endpoints included other measures of prednisone dosage (percentage of subjects off OCS, percentage of subjects with prednisone dose reduction below 5 mg QD, and change from baseline to end-of-study in prednisone use), changes in FEV_1, AM and PM PEF, asthma symptom scores, albuterol use, and nighttime awakenings.

6.3.1.2. RESULTS

Study Population Studies 321 and 322

A total of 1015 subjects were randomized and treated in studies 321 and 322. Of these, 1011 were in the ITT population; 4 subjects were excluded from the efficacy analysis due to lack of any follow-up spirometry (2 subjects) or enrollment in study 323/324 in addition to study 321 (2 subjects). The integrated population was made up of 598 (59.1%) women and 413 (40.9%) men with a mean age of 36.6 ± 14.4 years. The majority of subjects (888 [88%]) were ≥18 years of age, and 87% of subjects were white. These variables were comparable across the treatment groups, although there were slightly fewer subjects < 18 years of age in the ciclesonide-320 group (n =23 [4.5%]) compared to the other treatment groups (range = 29 – 36 [~6.5%]).

In terms of the underlying disease, the mean duration of asthma was 18.7 years, and the mean FEV_1 at baseline was 2.44 L (70.9% predicted). The mean AM PEF was 364 L/min, and the mean Asthma Severity Score was 2.6. Mean albuterol use was 2.6 puffs/day, and the mean number of nighttime awakenings was 0.3 (approximately one awakening every three nights). These variables were evenly distributed across the treatment groups. Approximately 7% of the subjects had a baseline FEV_1% of <60% at the beginning of the study. This represents a protocol violation as the study should have been restricted to subjects with mild to moderate disease, and an FEV_1% < 60% was a specific exclusion criterion. Although the number of subjects with this violation was small, there were relatively more in the ciclesonide-320 treatment group (23 [9.0%] compared with 14-18 [~6.3%]in the other treatment groups).The majority of subjects (55.2%) were treated with ICS (Stratum 1) prior to enrollment. These ICS-treated subjects had a lower baseline mean FEV_1 (2.3 L; 68.9% predicted) compared to the subjects treated with bronchodilators alone (Stratum 2) prior to enrollment (FEV_1 2.6 L; 73.4% predicted).

Study Population Study 323/324

A total of 531 subjects were randomized and treated in study 323/324. Of these, 527 were in the ITT population; 4 subjects were excluded due to lack of any follow-up spirometry. The demographic characteristics were similar to the study population of studies 321 and 322 except for the mean age which was 43.0 ± 14.2 years and the slightly lower percentage of Caucasians (78.9%).

In terms of the underlying disease, the mean duration of asthma was 23.2 years, and the mean FEV_1 was 1.79 L (53.7% predicted). The mean AM PEF was 319 L/min, the mean Asthma Severity Score was 2.6, albuterol use averaged 3.9 puffs/day, and subjects had

approximately one nighttime awakening every 3 nights. These variables were evenly distributed across the treatment groups

Study Population Study 325

A total of 141 subjects were randomized and treated in study 325. Of these, one was excluded from the ITT population because there was no follow-up spirometry. Therefore, 140 were included in the ITT population for efficacy. There were more women (96 [68.6%]) than men (44 [31.4%]), the average age was 48.3 years and 78 (55.7%) subjects were Caucasian. The low representation of Caucasians in this study is because the study was conducted in the United States and South Africa with 43.3% of subjects enrolled in South Africa.

In terms of the underlying disease, the mean duration of asthma was 23.6 years, and the average FEV_1 was 1.64 L (55.2% predicted). The mean AM PEF was 267.9 L/min, the mean Asthma Severity Score was 2.4, albuterol use averaged 4.9 puffs/day, and the average prednisone dose was 12.4 mg/day. These variables were evenly distributed across the treatment groups.

PRIMARY EFFICACY ENDPOINTS

Studies 321 and 322

The primary efficacy endpoint was the change from baseline to end-of-study (Week 12 LOCF) in FEV_1 (L) in the ciclesonide-treated group compared to placebo. The baseline values, changes with treatment, and differences from placebo are listed in Table 1. As can be seen, only the 320 μg dose showed efficacy in both studies. In Study 321, ciclesonide-160 was not statistically superior to placebo and therefore, the effect of ciclesonide-80 cannot be assessed. However, in study 322, all three doses showed a statistically significant improvement in FEV_1 at end-of-study using the pre-specified step- wise hierarchical analysis. In study 322, the effect size (ciclesonide vs placebo) for ciclesonide reported as LS means was 120 ml for ciclesonide-320 ($p= 0.017$) and for ciclesonde-80 ($p= 0.022$), and 190 ml for ciclesonide-160 ($p=0.0003$) , whereas in study 321 the effect size was 150 ml ($p =0.0014$) for ciclesonde-320 but only 70 ml for ciclesonide-160 ($p=0.16$).

Table 1. Mean Change from Baseline in FEV_1 (L) at Week 12 (LOCF): Studies 321 and 322*

Study/ Treatment	N	Baseline mean [a] (L)	Change from baseline			Treatment comparison vs. placebo		
			LS mean	SE	95% CI	LS mean difference	95% CI	P-value
321								
Placebo	133	2.46	0.20	0.035	(0.13, 0.27)	-	-	-
Ciclesonide-80	133	2.44	0.32	0.035	(0.25, 0.39)	0.12	(0.03, 0.21)	0.0123
Ciclesonide-160	127	2.46	0.26	0.036	(0.19, 0.33)	0.07	(-0.03, 0.16)	0.1645
Ciclesonide-320	131	2.44	0.35	0.035	(0.28, 0.42)	0.15	(0.06, 0.25)	0.0014
322								
Placebo	116	2.43	0.13	0.037	(0.06, 0.21)	-	-	-
Ciclesonide-80	124	2.40	0.25	0.036	(0.18, 0.32)	0.12	(0.02, 0.22)	0.0224
Ciclesonide-160	123	2.34	0.32	0.036	(0.25, 0.39)	0.19	(0.09, 0.29)	0.0003
Ciclesonide-320	124	2.51	0.25	0.036	(0.18, 0.33)	0.12	(0.02, 0.22)	0.0173

(Source: Applicant's table 12 [2.7.3aclinicalefficacy.pdf pg 49])

Since patients were randomized based on prior asthma therapy, sub-set analyses based on strata were also performed (*See Dr. Ted Guo's biostatistical review*). Subjects who were previously maintained on bronchodilators (Stratum 2) did not have a statistically significant improvement in the primary outcome measure (FEV_1) with any dose of ciclesonide in either study. On the other hand, subjects previously treated with ICS (Stratum 1) in both studies 321 and 322, had a statistically significant improvement in the primary outcome measure with ciclesonide 320 mcg once daily. A statistically significant improvement was also seen with ciclesonide 160 and 80 mcg once daily in Stratum 1 in study 322 but these were results were not replicated in study 321.

The Applicant also did a combined analysis (pooled data from studies 321 and 322) by strata. The results of this pooled analysis (Table 2) show that there is essentially no response to ciclesonide therapy in subjects previously on bronchodilator (reliever) therapy. The maximum change in FEV_1 in this combined group compared with placebo treatment was 70 mL ($p \geq 0.2$) after treatment with either the 160 or 320 mcg dose of ciclesonide. The results from the combined analysis were reproduced by the Agency biostatistical reviewer.

Table 2. Subset analysis Controller therapy (ICS) and Reliever therapy (bronchodilators only) – ITT population (studies 321 and 322 pooled analysis)*

Treatment	N	Baseline	Change from baseline			Treatment comparison vs. placebo		
		mean[a] (L)	LS mean	SE	95% CI	LS mean difference	95% CI	P-value
All subjects								
Placebo	249	2.45	0.17	0.025	(0.12, 0.22)	-	-	-
Ciclesonide-80	257	2.42	0.28	0.025	(0.23, 0.33)	0.12	(0.05, 0.19)	0.0007
Ciclesonide-160	250	2.40	0.29	0.025	(0.24, 0.34)	0.13	(0.06, 0.19)	0.0004
Ciclesonide-320	255	2.48	0.31	0.025	(0.26, 0.36)	0.14	(0.07, 0.21)	<0.0001
Prior reliever therapy								
Placebo	114	2.64	0.18	0.039	(0.11, 0.26)	-	-	-
Ciclesonide-80	115	2.62	0.22	0.039	(0.14, 0.30)	0.04	(-0.07, 0.14)	0.5133
Ciclesonide-160	111	2.55	0.25	0.041	(0.17, 0.33)	0.07	(-0.04, 0.18)	0.2025
Ciclesonide-320	113	2.72	0.25	0.041	(0.17, 0.33)	0.07	(-0.04, 0.17)	0.2136

**(Source: Applicant's Table 17 [2.7.3aclinicalefficacy.pdf pg 51])*

There was a large difference between the LOCF analysis and the analysis performed using only subjects still being followed at the time of the measurement. This was true even for the stratum 1 subjects. In subjects treated with ICS prior to admission (n= 558 in study 321 and 322), the LOCF analysis showed a difference of 190 mL between the response to placebo and the response to ciclesonide at a dose of 320 mcg/day *(... \summary\2.7.3aclinicalefficacy, pg 55).* In the analysis performed on completers the increase in FEV_1 over the 12 weeks was only 90 ml more in the ciclesonide-320 group than in the placebo-treated subjects *(Source: ... \crt\datasets\321\effpft.xpt, ... \crt\datasets\322\effpft.xpt).* In other words, the improvement seen in the ciclesonide-320 subjects with the LOCF analysis was entirely due to the early drop-outs in the placebo group.

Study 323/324

The baseline values, changes with treatment and differences from placebo are listed in Table 3. The effect size (difference between active treatment and placebo) calculated as LS means was 110 and 180 ml for the ciclesonide 160 mcg BID and 320 mcg BID treatment groups respectively ($p \leq 0.03$). Fluticasone MDI 440 mcg BID as an active comparator also showed significant improvement (240 ml; $p = 0.0001$) compared to placebo.

Table 3. Mean Change from Baseline to Week 12 (LOCF) of FEV_1 (L) in the ITT Population in Study 323/324*

Treatment	N	Baseline	Change from baseline			Treatment comparison vs. placebo		
		mean [a] (L)	LS mean	SE	95% CI	LS mean difference	95% CI	P-value
Placebo	134	1.77	0.25	0.037	(0.18, 0.33)	-	-	-
Ciclesonide-320	127	1.78	0.36	0.038	(0.29, 0.44)	0.11	(0.01, 0.21)	0.0374
Ciclesonide-640	130	1.82	0.43	0.037	(0.36, 0.50)	0.18	(0.07, 0.28)	0.0008
Fluticasone-880	136	1.77	0.50	0.037	(0.43, 0.57)	0.24	(0.14, 0.35)	0.0001

[a] Baseline means are raw means.
LS = least-squares, SE = standard error.

(Source: Applicant's Table 28 [2.7.3aclinicalefficacy.pdf pg 63])

Study 325

The primary efficacy endpoint was the percent change from baseline in prednisone dose at Week 12 (LOCF) in ciclesonide-treated subjects compared to placebo. The baseline values, changes with treatment, and differences from placebo are shown in Table 4. The response to both doses of ciclesonide was statistically significant. There was a 51.6% and 66.8% decrease in prednisone dose in the ciclesonide 320 mcg BID and ciclesonide 640 mcg BID groups respectively compared to placebo.

Table 4. Change from Baseline to Week 12 (LOCF) in Prednisone dose ITT Population Study 325*

Treatment	N	Baseline	LS mean (SE)	Treatment comparison vs. placebo		
		mean[a] (mg)	change from baseline	LS mean difference	95% CI	P-value
Placebo	45	12.00	4.21 (10.338)	-	-	-
Ciclesonide-640	47	13.59	-47.39 (10.101)	-51.59	(-78.91, -24.28)	0.0003
Ciclesonide-1280	48	11.51	-62.54 (9.795)	-66.75	(-94.10, -39.39)	0.0001

(Source: Applicant's Table 37 [2.7.3aclinicalefficacy.pdf pg 75])

SECONDARY EFFICACY ENDPOINTS

AM and PM PEF, Albuterol use, Asthma severity score, and Nighttime Awakenings

Morning (AM) and evening (PEF), albuterol use, asthma severity score, and nighttime awakenings were assessed from diary data in the four pivotal studies. The AM PEF increased in all the ciclesonide-treated groups and decreased in the placebo group in studies 321, 322, and 323/324, however, a consistent dose response was not observed.

In studies 321 and 322, the increase in the AM PEF at the end of the study compared to placebo was 24.5 L/min and 12.9 L/min respectively in the ciclesonide 320 mcg QD group. There appeared to be a dose response in study 321 but not in study 322. AM Peak Flow variability (%), daily albuterol use (puffs/day), Asthma Severity Score, and nighttime awakenings all decreased in the ciclesonide-treated groups.

In study 323/324, the ciclesonide-treated group also showed improvement in AM PEF (L/min) , daily albuterol use (puffs/day), and Total Asthma Severity Score (0 -8) compared to placebo. Nighttime awakenings, analyzed as the percent of nights with nocturnal awakening during the double-blind period, decreased by 11% in both ciclesonide treatment groups when compared to placebo. However, there was no difference between ciclesonide and placebo-treated subjects in the percentage of symptom-free days.

In Study 325, there was essentially, no change in AM PEF, Asthma Severity Score, or albuterol use over the 12 weeks of active treatment. FEV_1 measured as a secondary outcome in this study showed an increase of 40 ml in the two ciclesonide treatment groups compared to a 130 ml decrease in the placebo group. Eleven percent of the placebo-treated subjects totally eliminated prednisone use by Week 12 compared with 29.8% and 31.3% of the ciclesonide 320 mcg BID and the ciclesonide 640 BID groups respectively.

Discontinuations due to Lack of Efficacy

Subjects were discontinued from the protocol due to lack of efficacy at the investigator's discretion. The percentage of subjects who discontinued due to lack of efficacy was consistently highest in the placebo group. In study 321 the number of withdrawals was 47 (35.3%) in the placebo group compared to 21 (15.8%), and 22 (17.3%), and 19 (14.5%) in the ciclesonide-80, ciclesonide-160, and ciclesonide-320 group respectively. In study 322 there were 34 (29.3%), 15 (12.18%), 13 (10.6%), and 22 (17.7%) withdrawals in the placebo, ciclesonide-80, ciclesonide-160, and ciclesonide-320 group respectively. In study 323/324, the number of withdrawals was 53 (39.6%) in the placebo group compared to 20 (15.7%), and 14 (10.8%) in the ciclesonide-160 BID and ciclesonide-320 BID group respectively. In study 325, the number of withdrawals in the placebo group was 13 (28.9%) compared to 6 (12.8%) and 3 (6.3%) in the ciclesonide-320 BID and ciclesonide-640 BID groups respectively.

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (AQLQ)

The ciclesonide-320 mcg QD treatment group in study 321 and the ciclesonide-160 BID and ciclesonide-320 BID treatment groups in study 323/324 had a clinically meaningful improvement (≥ 0.5) in the Overall score, as well as in the Symptoms, Activity Limitations, and Emotional Function domains however, these results were not replicated. In study 322, the ciclesonide 160 mcg QD dose had a clinically meaningful improvement (≥ 0.5) in the Overall score and in the Symptoms and Emotional Function domains but this finding was not replicated in any other studies.

Onset of Action and Duration of Action

The Applicant assessed onset of action using dairy data from the first week of double-blind treatment in studies 321, 322 and 323/324. The results of these analyses in study 321 and

322 were inconsistent. In study 321 there was improvement in Asthma Severity Score and albuterol use at 24 hours but PEF increased only in the 320 mcg group after three days. In study 322 albuterol use and PEF were not consistently improved until day 7 whereas, Asthma Severity Score improved at day 3. In study 323/324, the separation between active treatment and placebo occurred within one day for the AM PEF, and within two days for the Asthma Severity Score. Albuterol use declined by day 1 in the ciclesonide-160 BID group, but not until day 2 in the ciclesonide -320 BID group.

For the most part, the observed effects were maintained over the 12-week treatment period. The FEV_1 was stable throughout the 1-year follow-up trials (326lt and 223/324lt)

Subgroup Analysis

The applicant found no relationship to age when the data were analyzed in three age groups: 12 - < 18 years, 18 – 64 years, and ≥ 65 years. However, in combined 321/322 there were fewer than 10 subjects over the age of 65 years in any treatment group. When the subjects were divided at the age cutoff of 40 years (close to the median age of the population) in studies 321 and 322, subjects >40 years had a slightly greater response to ciclesonide 320 mcg QD than those ≤ 40 years of age (Difference from placebo in FEV_1 in Study 321 was 138 ml and 163 ml in the ≤ 40 and > 40 years age groups respectively. In study 322 the values were 74 ml and 158 ml for the ≤ 40 and > 40-year groups, respectively). The absolute differences are small and probably not clinically meaningful. In addition, in study 323/324 the response to the 320 mcg BID was larger in the younger subjects (208 ml in ≤ 40 and 173 in > 40 years age groups (*See biostats review for details).* Neither gender nor race had a substantial effect on the response to therapy. For example, in studies 321 and 322 the mean response to ciclesonide in females (n=448) was an increase of FEV_1 of 0.27 L ± 0.32 and in males (N=314) it was 0.31 L ± 0.47. The changes were consistent across the three doses. For the Caucasian subjects the increase in FEV_1 was 0.29 L ± 0.40 and for the non-Caucasian subjects it was 0.26 L ± 0.31 in these two studies.

6.3.2. Studies for the maintenance treatment of children 4 – 11 years of age with mild, moderate, and severe persistent asthma (341, 342, 341lt, 342lt, 344).

6.3.2.1. Study Design

Study Population

There were 2 pivotal trials (341, 342) of identical design in which subjects 4 – 11 years of age were treated for 12 weeks with ciclesonide (40, 80, or 160 mcg/day [dose measured ex-actuator]) or placebo, each taken as one puff in the morning. The design was similar and the testing procedures identical to those used in studies 321 and 322. Subjects were also randomized according to prior asthma therapy just as in studies 321 and 322. For stratum 1 subjects (prior ICS use) ICS could not exceed the equivalent of 200 mcg/day fluticasone DPI or 800 mcg/day budesonide. Stratum 2 was made up of subjects who had been treated only with bronchodilators.

At screening, subjects in stratum 1 had to have an FEV_1% predicted of 40 – 100%. Subjects in stratum 2 had to have an FEV_1 of 40 – 85% predicted. There was a placebo run-in period of 5 to 21 days. Following the run-in the FEV_1 had to be between 40-90% predicted in both strata. In addition, the FEV_1 of stratum 1 subjects had to have fallen by 10% compared with the screening value. Stratum 2 subjects had to have had a minimum symptom level of ≥ 3 *(see Procedures, pg. 25)* for 3/7 days prior to randomization as assessed by Asthma Symptom Score , PEF variability ≥ 20%, or albuterol use ≥ 2 puffs/ day. The FEV_1 measured at the randomization visit was the baseline value used to assess efficacy. The primary outcome variable was the difference between active treatment and placebo in the change from baseline to end of study in the percent predicted FEV_1.

The study procedures and the analysis of the data were identical to that of studies 321, 322 and 323/324. The Pediatric Asthma Quality of Life Questionnaire (Juniper and Guyatt) was administered to the subjects > 7 years of age in the absence of their parents. at baseline and at weeks 4 and 12. Withdrawal of subjects due to an asthma exacerbation was entirely dependent upon the discretion of the investigator.

6.3.2.2. Results

Study Population

A total of 1031 subjects were randomized and treated in studies 341 and 342. Of these, 12 were excluded from the efficacy analysis (6 never received double-blind study medication and 6 had no follow-up spirometry) leaving 1018 in the ITT population. As opposed to the adult populations there were more males (64.0%) than females (36.0%), 133 (13.1%) were under the age of 6, and more than 62.0% were white. The relatively low number of whites is due to the recruitment of patients in Mexico, many of whom identified themselves as "Other" in the ethnic designation. The demographic variables were comparable across the treatment groups.

Reviewer: The number of subjects removed from the ITT population is taken from the individual study reports. The applicant's ISE (pg 30 [summary\2.7.3bclinicalefficacy.pdf] states that 1025 were randomized and the reason for removal from the ITT population is not provided.

In terms of the underlying disease, the mean duration of asthma was 4.4 years. The average FEV_1 was 1.30 L (68.4% predicted). The mean AM PEF was 215.7 L/min, the mean Asthma Severity Score was 1.96, mean albuterol use was 1.6 puffs/day, and the subjects awakened at night approximately once every three nights. These variables were evenly distributed across the treatment groups. Approximately 24% of the subjects had an FEV_1% of < 60% at the beginning of the study, and were thus categorized as severe. Subjects previously treated with ICS were in the majority and comprised 63.5% of the entire group. The FEV_1 was lower in the subjects who had previously been treated with ICS (1.3L (67% predicted) than in the subjects who had been treated only with bronchodilators (1.4 L 70.8% predicted).

Primary Efficacy Endpoint Studies 341 and 342

The primary efficacy endpoint was the change in percent predicted AM pre-dose FEV_1 at end-of-study (Week 12 LOCF) compared with the change in the placebo-treated subjects.

The baseline values, changes with treatment and differences from placebo are listed in Table 5. As can be seen, the response to ciclesonide 160 mcg QD was not statistically significant in Study 341. According to the hierarchical analysis plan, the response to the lower doses can not be considered significant. In study 342 the response to ciclesonide 160 was significant, however the response to the lower doses were not. The maximum response in FEV_1 % was 3.6% when the ciclesonide 160 group was compared to placebo in study 342. This corresponded to an improvement in FEV_1 of 70 ml.

Table 5. Mean Change in FEV_1 % in ITT Population in Studies 341 and 342*

Study/ Treatment	N	Baseline mean[a] (%)	Change from baseline			Treatment comparison vs. placebo		
			LS mean	SE	95% CI	LS mean difference	95% CI	p-value
341								
Placebo	127	68.07	12.61	1.448	(9.76, 15.46)	-	-	-
Ciclesonide-40	124	68.59	13.76	1.459	(10.90, 16.63)	1.15	(-2.77, 5.07)	0.5634
Ciclesonide-80	134	67.86	16.54	1.405	(13.78, 19.30)	3.93	(0.07, 7.78)	0.0460
Ciclesonide-160	119	67.02	15.95	1.475	(13.05, 18.85)	3.34	(-0.65, 7.33)	0.1005
342								
Placebo	127	69.01	8.61	1.223	(6.21, 11.01)	-	-	-
Ciclesonide-40	128	68.38	9.96	1.210	(7.58, 12.34)	1.35	(-1.84, 4.54)	0.4063
Ciclesonide-80	125	68.67	10.32	1.231	(7.90, 12.74)	1.71	(-1.51, 4.93)	0.2978
Ciclesonide-160	134	69.24	12.15	1.203	(9.79, 14.52)	3.55	(0.38, 6.71)	0.0283

** (Source: Applicant's Table10 [2.7.3bclinicalefficacy.pdf pg 36])*

When the data were analyzed based on prior asthma therapy only subjects in stratum 2 (prior bronchodilator [reliever]) therapy showed a statistically significant effect with the 160 mcg once daily dose in both studies. Of note, these results are the opposite of the results seen in the adults where the only significant responses were seen in the subjects who had taken ICS prior to enrollment.

Most of the response in FEV_1 was seen in the subjects who were enrolled in Mexico and Poland. This was still true after the subjects were divided by pre-enrollment treatment group. In stratum 2, (prior bronchodilator therapy) of the combined group (studies 341 and 342), the response in the non-US subjects was 1.34, 6.49, and 12.8% greater than placebo with ciclesonide 40 mcg QD, ciclesonide 80 mcg QD, and ciclesonide 160 mcg QD respectively. By contrast, the response in the stratum 2 subjects enrolled in the USA was 3.56, 3.92, and 3.69 % greater than placebo in each of the ciclesonide treatment groups respectively. The etiology of these differences in response is not clear. However, the subjects from the USA had better pulmonary function than those enrolled in Mexico and Poland, even after stratifying for prior treatment. In stratum 2, the FEV_1% was 67.3% and 73.2 % in the non-US and US children respectively. The difference in response to placebo treatment (7.1% in the U.S. children compared with 19.8% in the non-US children) might be related to these differences in baseline function.

Secondary Efficacy Endpoints

In an integrated analysis (341 and 342) the changes in AM PEF, Asthma Severity Score, and albuterol use were most marked in the ciclesonide 80 mcg QD group. The AM PEF increased by 6.54, 11.42, and 8.40 L/min when compared to placebo in the ciclesonide 40 mcg QD, ciclesonide 80 mcg QD, and ciclesonide 160 mcg QD group respectively *(...summary\2.7.3bclinical efficacy, pg. 41)*. The Asthma Severity Score decreased by 0.36, 0.60, and 0.52 units and the daily albuterol use decreased by 0.27, 0.63, and 0.46 puffs/day in each of the ciclesonide groups respectively.

The subjects treated only with bronchodilators prior to enrollment had more marked changes in the secondary outcome variables than the study population as a whole, but the greatest response was still seen in the ciclesonide 80 mcg QD group. The increase in AM PEF was 10.13, 17.80, and 11.67 L/min, the decrease in Asthma Severity Score was 0.54, 1.00, 0.92 units, and the decrease in albuterol use (puffs/day) was 0.10, 0.82, and 0.57 in each ciclesonide group, respectively (*...summary\2.7.3bclinical efficacy, pg. 50)*. The subjects who had been treated previously with ICS had smaller responses in the secondary outcome variables with no consistent pattern.

Withdrawal from the study due to lack of efficacy was higher in the placebo subjects (12.6%) than in the ciclesonide-treated subjects (6.7%). However, the differential was not as great as that seen in the adult studies (321, 322) and the difference in dropout in the various doses of ciclesonide was very small (8.3, 6.2, and 5.5%) in each ciclesonide group respectively.

Onset of Action

The onset of action was determined from the diary variables AM PEF, Asthma Severity Score, and albuterol use. The separation between active treatment and placebo occurred after 2 days for the Asthma Severity Score. However, AM PEF increased more than placebo only in the ciclesonide 40 mcg QD group and this variable returned to the placebo level by day 7. Albuterol use was not consistently less in the ciclesonide-treated subjects at any of the doses. *(...summary\2.7.3bclinical efficacy, pg. 60-62).*

Duration of Action

One-year safety follow-up studies were conducted after studies 341 and 342 and study 344 was a 1-year study primarily designed to look at safety. The doses ranged between 40 and 160 mcg/day for ciclesonide and could be varied at the discretion of the investigator with the objective of maintaining asthma control at the lowest possible dose of ICS. Spirometry was available at baseline and 12 months for 432 subjects treated with ciclesonide. Over the year of follow-up the mean FEV_1 increased by approximately 150 mL in the ciclesonide group.

Subgroup Analysis

An analysis was performed on the combined population in studies 341 and 342 to determine the effect of age on the response to therapy. In the subjects < 6 years of age the responses were highly variable. Those < 6years of age subjects had a large placebo response in FEV_1% (14% compared to 10% in those >=6 years and older), but they had a dose-ordered fall in AM PEF (-0.97, -2.98, -3.47, and -9.10 L/min in the placebo, ciclesonide-40,

ciclesonide-80, and ciclesonide-160 group respectively) compared to non-dose-ordered increases of 18 to 20 L/min in the subjects 6 and older. In the subjects ≤ 6 years, albuterol use increased (0.1 puffs/day) during treatment with ciclesonide-160 whereas it decreased by 0.56 puffs/day in the subjects 6 years and older.

Neither gender nor race had a substantial effect on the response. The mean increase in FEV_1% predicted with ciclesonide in females (n=366) was 11.23, 9.36, 14.15, and 16.65% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. Similarly, in males (N=652) the increases in FEV_1% predicted were 10.26, 13.33, 13.12, and 12.46% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. In the Caucasian subjects the FEV_1% predicted increased 11.6, 13.7, 12.05, and 15.10 % and in the non-Caucasians the increase was 9.19, 9.29, 16.04, and 12.85% in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. .

Asthma Quality of Life Questionnaire

None of the doses of ciclesonide had a clinically meaningful improvement (≥0.5) in Overall score, nor were any of the individual domains in any of the studies meaningfully improved.

6.4. Efficacy Discussion and Conclusions

In two pivotal trials (321 and 322) that enrolled a total of 1015 adult and adolescent subjects 12 years of age and older with mild to moderate persistent asthma only the 320 mcg/day dose of ciclesonide showed consistent effectiveness across the two studies. Analyzing the data using prospectively identified strata based on prior asthma therapy, it was shown that ciclesonide was effective in subjects previously treated with inhaled corticosteroids but was not effective in subjects who had been treated with bronchodilators, only. This was true when the studies were analyzed separately and when the data were combined. The secondary outcome variables improved in all the ciclesonide-treated groups, however, a consistent dose response was not observed. The overall score on the AQLQ showed clinically meaningful improved with only the 320 mcg daily dose in one study but only with the 160 mcg daily dose in the other study.

In subjects with moderate to severe asthma who had been treated with ICS prior to enrollment (study 323/324), ciclesonide 160 or 320 mcg BID was effective. In these subjects, the primary outcome variable (change in AM pre-dose FEV_1), was significantly improved over placebo treatment. The secondary efficacy variables AM PEF, Asthma Severity Score, albuterol use, and the AQLQ score showed consistent improvement in the ciclesonide treated subjects. Patient reported outcomes as assessed by the AQLQ had a clinically meaningful improvement in the Overall Score in the ciclesonide 160 mcg and 320 mcg QD group.

The onset of action assessment based on dairy data showed a variable response in the diary recorded measures that were analyzed during the first week of treatment and there was no consistent improvement in these variables within 24 hours. The improvement in FEV_1 was maintained during the 12-week treatment periods and throughout the 12-month follow-up period in the long term studies.

In 141 subjects for whom the lowest effective dose of OCS had been determined in a run-in period, there was a significant decrease in OCS use during treatment with both ciclesonide

320 and 640 mcg BID. Almost 30% in the subjects who received ciclesonide 1280 mcg daily discontinued OCS altogether.

In two pivotal trials (341 and 342), 1018 children age 4 – 11 years with mild to severe persistent asthma, none of the ciclesonide doses showed consistent effectiveness across the studies. As noted in the primary review, what small effect there was, occurred primarily in the children enrolled in Poland and Mexico. Subjects who took the pediatric AQLQ questionnaire had no clinically meaningful improvement in overall score or in any individual domain.

One difficulty in assessing these studies is that compliance was measured in all of the trials through history only. The unreliability of patient recall has been well documented, and the application contains its own documentation of this phenomenon. In study 102, the adult PD study, compliance was assessed by patient report (diary entry) and by canister weight. Using the diary data the compliance was >90% in >90% of the subjects in all of the treatment groups. When they assessed compliance with canister weights, however, compliance was much lower: 45% – 73% of the subjects took >90% of the medication depending on the treatment group. Since canister weights can be manipulated by the subject these latter numbers are still represent a minimum estimate of non-compliance. Variability in compliance could explain some of the variability in dose response, but this can not be assessed in retrospect.

In summary, significant responses to ciclesonide were only seen in adult and adolescent subjects 12 years of age or older who had previously been treated with ICS. In subjects previously treated with ICS and who were defined as mild to moderate, 320 mcg once daily was effective, and in subjects previously treated with ICS and defined as moderate to severe 160 and 320 mcg twice daily was effective. However, there was no direct comparison of a once daily and twice daily regimen in the same subject population. It is, therefore not known if a twice daily regimen would have benefited subjects with asthma who had not previously been treated with ICS. Similarly, the response to once daily dose of 320 mcg in subjects with mild to moderate disease was modest, and it is not know if twice daily dosing would have improved function further.

Doses of ciclesonide of 320 and 640 mcg BID were efficacious in reducing oral corticosteroid use in severe oral corticosteroid dependent asthmatics. On the other hand, multiple studies showed that ciclesonide was ineffective in the doses given in the 4 – 11 year age group.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Finding

There have been 1407 subjects ≥12 years of age exposed to ciclesonide (313 for at least 1 year) in this development program. Adverse events were generally mild and similar to those expected from treatment with inhaled corticosteroids. Oral candidiasis was uncommon, but did occur in subjects treated with the higher doses of ciclesonide. Similarly, HPA-axis suppression, as demonstrated in the low-dose consyntropin stimulation test, was uncommon, but did occur at higher doses. Lenticular opacities were seen in an unexpected number of subjects treated with 160 mcg BID and 320 mcg BID for 12 weeks. The 1-year follow-up study showed a lower rate of cataract development, but did not definitively resolve the issue. None of the studies was designed prospectively to evaluate the development of cataracts. The definitive answer will have to await completion of the on-going trial to evaluate the development of cataracts in subjects on ciclesonide treatment.

There have been 1093 children, age 4-11 years exposed to ciclesonide (326 for at least 1 year). Adverse events were generally mild, and there was a very low incidence of oral candidiasis. HPA-axis suppression was uncommon, but was evaluated in less than 100 subjects. One 12 year old girl died unexpectedly during treatment. The autopsy failed to reveal changes compatible with acute asthma and the cause of death was thought to be an arrhythmia.

7.2. Methods and Content (Materials Utilized in Review)

The safety data for the 12-week pivotal trials and the clinical safety summaries were extracted from the amended NDA submission (...N21658\N_000\2004-02-05).

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In the original submission, the 1-year safety follow-up studies were submitted as interim analyses. The final study reports were submitted with the 120-day safety update on April 26, 2004. These final study reports and the safety summary from the 120 safety update were reviewed for the ISS (...N21658\N_000\2004-04-26A).

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In the NDA ISS the applicant has summarized the data in several ways. Adverse events are presented for the combined 12-week adult studies in subjects with mild to severe asthma, including the 12-week PD study (321, 322, 323/324, and 102). Separate summaries are presented for the 12-week oral prednisone reducing study (325). The 1-year safety studies are presented in three combinations: 1 summary present the data for study 323/324, one summary presents the data for study 326, and one study presents the data for the combination of 323/324 and 326. For the current review, only the combined data will be presented in tabular form.

One of the subjects enrolled in study 341lt died while taking study medication. A detailed autopsy report was submitted to the ciclesonide IND as a follow-up of a serious and unexpected adverse event, and this was also reviewed *(IND 53391, series216, stamp date May 14, 2004).*

7.3. Description of Patient Exposure

7.3.1. Adult and Adolescent Subjects

An overall summary of the experience with ciclesonide treatment in the adolescent/adult population is shown in Table 6. There were 352 subjects treated for ≥ 6 months and 313 who were treated for ≥ 12 months.

Table 6. Total Exposure of Adults to Ciclesonide

Type of study	Study, or studies integrated	Number of subjects treated with ciclesonide				
		≤12 weeks[a]	>12 weeks[a] to <6 months[b]	≥6 months[b]	≥12 months[c]	Total
Controlled 12-week efficacy and safety studies	321, 322, 323/324, 102	1069	33	0	0	1102
Controlled 12-week study on effectiveness of reducing oral corticosteroid use	325	92	4	0	0	96
Controlled 4-week PD safety study on HPA-axis function	103	24	0	0	0	24
Controlled 1-year safety study	323/324LT	31	18	148	129	197
Uncontrolled 1-year safety study	326	27	5	194	175	226
All studies (total exposure)		967[d]	88[d]	352[d]	313[d]	1407

[a] 90 days; [b] 176 days; [c] 351 days

**(Source: applicant's table 7 [update\summary\2.7.4aclinicalefficacy. pg 36.])*

The safety population of the 12-week adult trials (321, 322, 323/324, and 102) was composed of 1102 subjects who were treated with ciclesonide 80, 160, 320 mcg QD or 160 or 320 mcg BID for a mean of 76.5 (median of 84) days. For comparison, 429 subjects were treated with placebo for a mean of 63.0 (median of 83) days and 179 subjects were treated with fluticasone 880 mcg a day for a mean of 76.2 (median of 84) days. The majority were treated for more than 78 days (63.6, 84.4, 84.9, 83.4, 84.1, and 82.1% in the placebo,

NOTE: pg 39 & 40 DID NOT DOWCRT CORRECTLY IN INTO DFS. WE ARE IN THE PROCESS OF MAKING THE CORRECTION.

ciclesonide-80, ciclesonide-160, ciclesonide-320, ciclesonide-640, and fluticasone-880 groups respectively.

In the OCS reducing study (325) the mean exposure of the 96 subjects treated with ciclesonide (640 or 1280 mcg/day) was 79.8 days (median of 84). In the 1-year safety follow-up studies (326, 323/324lt) subjects were treated with varying doses of ciclesonide (80 – 320 mcg / day) for a mean of 296.1 (median of 364) days.

7.3.2. Pediatric Population

An overall summary of the experience with ciclesonide treatment in the pediatric population is shown in Table 7. There were 370 subjects treated for ≥ 6 months and 328 who were treated for ≥ 12 months.

Table 7. Total Exposure to Ciclesonide for Subjects 4 – 11 Years of Age*

		Number of subjects treated with ciclesonide				
Type of study	Study, or studies integrated	≤12 weeks[a]	>12 weeks[a] to <6 months[b]	≥6 months[b]	≥12 months[c]	Total
Aventis controlled 12-week efficacy and safety studies	341, 342	689	79	0	0	768
Aventis controlled 1-year safety studies	341LT, 342LT, 344	45	37	361	321	443
Altana controlled PD safety studies on lower-leg growth velocity	FK1 201, M1-203	48	0	0	0	48
Total		573[d]	150[d]	370	328	1093

[a] 91 days; [b] 176 days; [c] 351 days
[d] All studies = number of subjects by exposure duration category counting total ciclesonide exposure in one or more studies (i.e., from participation in a 12-week study followed by participation in the corresponding 1-year study). The rows above refer to exposure in type of study. Hence the numbers in the columns do not add up to the numbers in the

**(Source: applicant's table 4 [update\summary\2.7.4bclinicalsafety. pg 27])*

The safety population of the 12-week pediatric trials (341 and 342) was composed of 768 subjects who were treated with ciclesonide 40, 80, or 160 mcg QD for a mean of 78.6 (median of 84). For comparison, 257 subjects were treated with placebo for a mean of 75.7 (median of 84) days. The majority were treated for more than 78 days (80.5, 83.2, 85.4, and 88.2% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. In the 1-year safety follow-up studies (341, 342, and 344) subjects were treated with varying doses of ciclesonide (80 – 160 mcg/day) for a mean of 301.8 (median of 364).

7.4. Safety Findings from Clinical Studies

7.4.1. Adult and Adolescent Populations

7.4.1.1. Adverse Events

12-Week Pivotal Trials (321, 322, 323/324, 102) in mild to severe asthma

This summary combines data from studies 321 and 322 (ciclesonide 80, 160, or 320 mcg once daily dose), 323/324 (160 mcg BID or 320 mcg BID), 102 (320 mcg QD or 320 mcg BID). Subjects in studies 321, 322, and 102 had mild to moderate asthma and subjects in study 323/324 had moderate to severe asthma. All of the subjects enrolled in 323/324 had been on ICS prior to enrollment, none of the subjects in 102 had be treated with ICS prior to enrollment, and the approximately 60% of the subjects enrolled in 321 and 322 had been treated with ICS prior to enrollment.

Of the 1102 subjects in the safety population in the 12-week pivotal trials, 42.2% were female and 57.8% male. The mean age was 38.1 ± 14.5 years and 84.8% were White. The mean duration of asthma prior to enrollment was 20.5 ± 14.2 years and 61.8% had been treated with ICS prior to enrollment. Most of the demographic variables were evenly distributed across the treatment groups. However, only 5 (2.9%) of the subjects treated with the 640 mcg daily dose of ciclesonide (320 mcg BID) were 12-18 years of age compared to 36 (14.0%), 32 (12.7%), and 30 (7.1%) subjects who were treated with daily doses of ciclesonide of 80, 160, and 320 mcg. respectively. Also, only 55.2% and 55.8% of the ciclesonide-80 and ciclesonide-160 subjects, respectively, were treated with ICS prior to enrollment. This compares to 75.6% of the subjects treated with ciclesonide-640 mcg QD, and 63.7% of the subjects treated with ciclesonide-320 mcg QD.

The AEs that occurred in ≥ 3% subjects are shown in Table 8. In the placebo group, 270 (62.9%) reported AEs compared to 153 (59.5%), 146 (58.2%), 250 (59.2%), and 99 (57.6%) in the ciclesonide-80, ciclesonide-160, ciclesonide-320, and ciclesonide-640 groups. There were 115 (64.2%) reports of AEs in the fluticasone-treated subjects.

Table 8. Adverse Events Reported in ≥ 3% of Subjects in 321, 322, 323/324, and 102 by Organ Distribution*

	Number (%) of subjects						
		Ciclesonide (µg/day)					Fluticasone
Preferred term	Placebo (N=429)	80 (N=257)	160 (N=251)	320 (N=422)	640 (N=172)	Total (N=1102)	880 µg/day (N=179)
Subjects with TEAEs	270 (62.9)	153 (59.5)	146 (58.2)	250 (59.2)	99 (57.6)	648 (58.8)	115 (64.2)
Headache	42 (9.8)	18 (7.0)	26 (10.4)	45 (10.7)	16 (9.3)	105 (9.5)	22 (12.3)
Nasopharyngitis	32 (7.5)	23 (8.9)	23 (9.2)	39 (9.2)	12 (7.0)	97 (8.8)	19 (10.6)
Upper respiratory tract infection NOS	35 (8.2)	30 (11.7)	17 (6.8)	28 (6.6)	8 (4.7)	83 (7.5)	13 (7.3)
Asthma NOS	74 (17.2)	16 (6.2)	10 (4.0)	16 (3.8)	15 (8.7)	57 (5.2)	4 (2.2)
Pharyngolaryngeal pain	22 (5.1)	13 (5.1)	10 (4.0)	23 (5.5)	8 (4.7)	54 (4.9)	7 (3.9)
Sinusitis NOS	15 (3.5)	11 (4.3)	11 (4.4)	20 (4.7)	9 (5.2)	51 (4.6)	10 (5.6)
Back pain	11 (2.6)	10 (3.9)	6 (2.4)	20 (4.7)	2 (1.2)	38 (3.4)	9 (5.0)
Arthralgia	7 (1.6)	7 (2.7)	5 (2.0)	8 (1.9)	8 (4.7)	28 (2.5)	4 (2.2)
Dyspepsia	11 (2.6)	2 (0.8)	8 (3.2)	8 (1.9)	3 (1.7)	21 (1.9)	1 (0.6)
Rhinitis NOS	5 (1.2)	8 (3.1)	4 (1.6)	7 (1.7)	0 (0.0)	19 (1.7)	2 (1.1)
Influenza	5 (1.2)	1 (0.4)	3 (1.2)	13 (3.1)	0 (0.0)	17 (1.5)	5 (2.8)
Cataract nuclear	1 (0.2)	0 (0.0)	0 (0.0)	4 (0.9)	9 (5.2)	13 (1.2)	2 (1.1)
Oral candidiasis	4 (0.9)	3 (1.2)	0 (0.0)	7 (1.7)	1 (0.6)	11 (1.0)	25 (14.0)
Hoarseness	2 (0.5)	1 (0.4)	0 (0.0)	4 (0.9)	2 (1.2)	7 (0.6)	8 (4.5)

(Source: Applicant's table 34 [summary\2.7.3aclinicalsafety.pdf, pg . 70])

The distribution of events was similar across all of the treatment groups with several notable exceptions. Asthma was reported as an adverse event in 74 (17.2%) of the placebo subjects, compared to 57 (5.2%) of the ciclesonide-treated subjects and 4 (2.2%) of the fluticasone-treated subjects. Cataracts were reported in 0.2, 0, 0, 0.9, 5.2, and 1.1% of the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320, ciclesonide-640, and fluticasone-880 subjects respectively. However, these percentages are low estimates because they are based on the number of subjects enrolled in all of the studies, and cataracts were not specifically looked for in studies 321, 322, or 102. *(For a more detailed analysis see Eye Abnormalities, pg. 46)*. Oral candidiasis was reported in 0.9, 1.2, 0, 1.7, 0.6, and 14.0% of the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320, ciclesonide-640, and fluticasone-880 subjects respectively

Most of the adverse events were mild to moderate in intensity. In the ciclesonide-treated subjects 33.4% were mild, 38.1% were moderate, and 7.1% were severe.

One-year follow-up trials after pivotal studies (326, 323/324lt) in mild to severe asthma

The 1-year safety follow-up studies enrolled 423 subjects who had been treated in the pivotal 12-week trials. In both studies 323/324lt and 326lt the dose of ciclesonide was varied by the investigator to maintain asthma control at the lowest possible dose of ciclesonide.

Table 9. Adverse Events in ≥ 3% of the Subjects in Studies 323/324lt and 326 *

Preferred term	Number (%) of subjects		
	Controlled study [a] (N=197)	Uncontrolled study [b] (N=226)	Total [c] (N=423)
Subjects with TEAEs	**146 (74.1)**	**164 (72.6)**	**310 (73.3)**
Asthma NOS	37 (18.8)	31 (13.7)	68 (16.1)
Upper respiratory tract infection NOS	22 (11.2)	38 (16.8)	60 (14.2)
Nasopharyngitis	28 (14.2)	30 (13.3)	58 (13.7)
Sinusitis NOS	27 (13.7)	22 (9.7)	49 (11.6)
Headache	19 (9.6)	18 (8.0)	37 (8.7)
Back pain	10 (5.1)	9 (4.0)	19 (4.5)
Bronchitis NOS	8 (4.1)	9 (4.0)	17 (4.0)
Pharyngolaryngeal pain	6 (3.0)	11 (4.9)	17 (4.0)
Arthralgia	8 (4.1)	4 (1.8)	12 (2.8)
Influenza	7 (3.6)	5 (2.2)	12 (2.8)
Urinary tract infection NOS	4 (2.0)	8 (3.5)	12 (2.8)
Cataract cortical	6 (3.0)	5 (2.2)	11 (2.6)
Cataract nuclear	8 (4.1)	3 (1.3)	11 (2.6)
Gastroenteritis viral NOS	4 (2.0)	7 (3.1)	11 (2.6)
Anxiety	2 (1.0)	7 (3.1)	9 (2.1)
Hypertension NOS	7 (3.6)	2 (0.9)	9 (2.1)
Pharyngitis streptococcal	6 (3.0)	3 (1.3)	9 (2.1)
Rash NOS	7 (3.6)	2 (0.9)	9 (2.1)
Upper respiratory tract infection viral NOS	7 (3.6)	2 (0.9)	9 (2.1)
Bronchitis acute NOS	1 (0.5)	7 (3.1)	8 (1.9)
Cough	6 (3.0)	2 (0.9)	8 (1.9)
Influenza-like illness	6 (3.0)	2 (0.9)	8 (1.9)
Joint sprain	6 (3.0)	2 (0.9)	8 (1.9)
Oral candidiasis	6 (3.0) [d]	2 (0.9)	8 (1.9)
Rhinitis allergic NOS	7 (3.6)	0 (0.0)	7 (1.7)
Rhinitis NOS	0 (0.0)	6 (2.7)	6 (1.4)

Table includes data from Studies 323/324LT and 326
Presented in decreasing order of frequency in the total ciclesonide column

[a] Ciclesonide subjects in controlled Study 323/324LT. Initial dose was 640 µg/day (ex-actuator), which could be titrated down to a lower dose of 320 µg/day at the investigator's discretion.

[b] Ciclesonide subjects in uncontrolled Study 326. Initial dose was 320 µg/day (ex-actuator), which could be titrated down to a lower dose of 80 µg/day at the investigator's discretion.

[c] Ciclesonide subjects in integrated database for controlled Study 323/324LT + uncontrolled Study 326.

**(Source: Applicant's Table 33 [update\summary\2.7.4clinicalsafety.pdf. pg 71])*

Adverse events reported by ≥ 3% of the Subjects are listed in Table 9. Overall, 310/423 (73.3%) subjects reported adverse events and 20 (4.7%) were classified as serious. Asthma exacerbations occurred in 68 (16.1%), upper respiratory tract infection in 60 (14.2%), nasopharyngitis in 58 (13.7%), and sinusitis in 49 (11.6%) of the population as a whole. All other events occurred in less than 10% of the subjects. Oral candidiasis occurred in 8 (1.9%) of the subjects, and cataracts were reported in 5.2% *(Detailed discussion of cataracts see Eye Abnormalities, pg. 46).* Most of the events were mild to moderate (42.5% mild and 45.6% moderate) in intensity.

12-week OCS sparing study (325)

Over all, 79/96 (82.3%) subjects reported adverse events. Six (6.3%) were serious and 11 (11.5%) resulted in withdrawal from the study. Adverse events occurring in ≥ 3% of the population are listed in Table 10. Of the ciclesonide treated subjects, 33/96 (34.4%) had an asthma exacerbation. This event was dose related with 19 (40%) events reported in the ciclesonide-640 group and 14 (28.6%) reported in the ciclesonide-1280 group. In the placebo group 62.2% reported exacerbations. There were 18 (18.8%) reports of upper respiratory tract infections, 14 (14.6%) reports of headaches, and 11(11.5%) reports of sinusitis in the ciclesonide- treated subjects. There were 9 (9.4%) cases of oral candidiasis and this event was dose related: 3 (6.4%) in the ciclesonide-640 group and 6 (12.2%) in the ciclesonide-1280 group. Most of the events were mild to moderate in intensity with 13.5% of events being severe in intensity.

Table 10. Adverse Events Reported in ≥ 3% of the Subjects in Study 325 by Organ Distribution*

	Number (%) of subjects			
		Ciclesonide (µg/day)		
Preferred term	Placebo (N=45)	640 (N=47)	1280 (N=49)	Total (N=96)
Subjects with TEAEs	40 (88.9)	40 (85.1)	39 (79.6)	79 (82.3)
Asthma NOS	28 (62.2)	19 (40.4)	14 (28.6)	33 (34.4)
Upper respiratory tract infection NOS	9 (20.0)	9 (19.1)	9 (18.4)	18 (18.8)
Headache	6 (13.3)	8 (17.0)	6 (12.2)	14 (14.6)
Sinusitis NOS	2 (4.4)	5 (10.6)	6 (12.2)	11 (11.5)
Nasopharyngitis	4 (8.9)	3 (6.4)	6 (12.2)	9 (9.4)
Oral candidiasis	0 (0.0)	3 (6.4)	6 (12.2)	9 (9.4)
Arthralgia	2 (4.4)	1 (2.1)	7 (14.3)	8 (8.3)
Back pain	2 (4.4)	4 (8.5)	3 (6.1)	7 (7.3)
Fatigue	2 (4.4)	3 (6.4)	4 (8.2)	7 (7.3)
Dizziness	2 (4.4)	3 (6.4)	2 (4.1)	5 (5.2)
Gastroenteritis NOS	1 (2.2)	2 (4.3)	2 (4.1)	4 (4.2)
Bronchitis NOS	2 (4.4)	1 (2.1)	2 (4.1)	3 (3.1)
Conjunctivitis	0 (0.0)	1 (2.1)	2 (4.1)	3 (3.1)
Dyspepsia	2 (4.4)	3 (6.4)	0 (0.0)	3 (3.1)
Hoarseness	1 (2.2)	3 (6.4)	0 (0.0)	3 (3.1)
Influenza	0 (0.0)	1 (2.1)	2 (4.1)	3 (3.1)
Musculoskeletal chest pain	1 (2.2)	2 (4.3)	1 (2.0)	3 (3.1)
Pain NOS	1 (2.2)	2 (4.3)	1 (2.0)	3 (3.1)
Pneumonia NOS	0 (0.0)	3 (6.4)	0 (0.0)	3 (3.1)
Pharyngolaryngeal pain	4 (8.9)	1 (2.1)	2 (4.1)	3 (3.1)
Rhinitis NOS	3 (6.7)	1 (2.1)	1 (2.0)	2 (2.1)
Vomiting NOS	6 (13.3)	0 (0.0)	2 (4.1)	2 (2.1)

Table includes data from Study 325

(Source: Applicant's Table 39 [summary\2.7.4acinicalsafety.pdf, pg 79])

Eye Abnormalities

In the applicant's integrated safety summary, nuclear cataracts were reported in 1 (0.2%) of the placebo subjects, 13 (1.2%) of the ciclesonide-treated subjects, and 2 (1.1%) of the fluticasone-treated subjects in the 12-week pivotal trials. The incidence in the ciclesonide-640 group was reported as 9 (5.2%).

Reviewer: In studies 321, 322, and 102 ophthalmologic examinations were not performed. In addition, the percentage of subjects with cataracts reported by the applicant is calculated using the number of subjects enrolled as the denominator. Not all of the subjects who were originally enrolled completed the study and had follow-up examinations. The Comment Table was constructed using only the subjects who had both baseline and follow-up examinations (Listing 38, page 4120, clinstat\323_324\study323_324b.pdf). The eye exam was only considered normal if both eyes were normal. The last column summarizes all of the subjects who deteriorated or improved no matter what their baseline status. In all, there was deterioration in 1.7, 3.5, 9.5, and 1.8% of the placebo, ciclesonide- 320, ciclesonide-640 and fluticasone -880 subjects respectively. Improvement was reported in 0.3, 0.9, and 2.7% of the placebo, ciclesonide- 320, ciclesonide-640 and fluticasone- 880 subjects respectively. In one subject in each of the ciclesonide-320, ciclesonide-640, and fluticasone-880 groups one eye worsened and 1 improved.. These three subjects were considered unchanged in the table.

Comment Table: Cataracts in Study 323/324

	Baseline		*Follow-up*		*Total worse or improved*
	State	*N*	*Outcome*	*N (%)*	*N (%)*
Placebo (N=118)	*Normal*	*96*	***Worse***	*1 (1.0)*	***1/118 (0.8)***
	Opacity	*22*	***Worse***	*0*	
			Improved	*0*	*0*
Ciclesonide 320 mcg (N = 115)	*Normal*	*88*	***Worse***	*3 (3.4)*	***4/115 (3.5)***
	Opacity	*27*	***Worse***	*1 (3.7)*	
			Improved	*2 (7.4)*	*2/115 (0.03)*
Ciclesonide 640 mcg (N=116)	*Normal*	*92*	***Worse***	*8 (8.7)*	***11/116 (9.5)***
	Opacity	*24*	***Worse***	*3 (12.5)*	
			Improve	*1 (4.2)*	*1/116 (0.9)*
Fluticasone 880 mcg (N = 112)	*Normal*	*90*	***Worse***	*0*	***2/112 (1.8)***
	Opacity	*22*	***Worse***	*2*	
			Improve	*3*	*3/112 (2.7)*

Of the long-term follow-up studies 158 of the mild-to-moderate asthmatic subjects (study 326lt) had normal lenses at baseline and 29 had opacities. Of the normals 3 (1.9%) developed new opacities. Of those with baseline opacities, 3 (10.3%) progressed and 5 (17.2%) improved. In total 6/187 (3.2%) progressed and 5/187 (2.7%) improved.

In the 1-year follow-up of the moderate-to-severe asthmatics (study 323/323lt) 165 of ciclesonide-treated subjects had ophthalmologic exams at baseline and follow-up. In the QVAR group 85 subjects received both exams. Of those who were normal at baseline, 6/113 (5.3%) of the ciclesonide subjects and 2/60 (3.3%) of the QVAR subjects developed cataracts during treatment. Of those who had baseline opacities, 8/52 (15.4%) of the ciclesonide and 6/25 (24.0%) of the QVAR subjects deteriorated.

Glaucoma was reported in two subjects in the 1-year follow-up study of subjects with moderate-to-severe asthma (323/324lt). One of these cases was mild and repeat examination 5 days after study termination failed to replicate the findings. One subject had severe progression of the glaucoma and was withdrawn from the study due to the eye changes.

7.4.1.2. Deaths

One adult subject died during the 1-year follow-up in study 323/324lt. This subject was a 75 year old female who died suddenly at home. No autopsy was performed and the death certificate recorded myocardial infarction as the cause of death. The subject had a past medical history of hypertension. The patient had been treated with fluticasone-440 BID in study 323/324, and she was transferred to ciclesonide 320 mcg BID at the beginning of 323/324lt. Twenty-nine days before her demise the dose of ciclesonide was decreased to 160 mcg BID.

7.4.1.3. Serious Adverse Events

12-week Pivotal Trials

Of the 1102 subjects treated with ciclesonide in the 12-week adult trials, 10 reported serious AEs. There was 1 case of asthma exacerbation in the ciclesonide 160 and 1 in the ciclesonide 320 mcg/day groups. The only other asthma or possibly treatment-related AE was a case of pneumococal pneumonia in a subject in the ciclesonide 640 mcg/day group. Other serious AEs were unlikely to be treatment-related: there was one case each of appendicitis and anaphylactic reaction to walnuts in the ciclesonide-80 group, a gunshot wound in a ciclesonide -160 subject, 1 case of peripheral edema and 3 cases of coronary artery disease in a ciclesonide -320 group, and 1 case of fever, dysuria, and rectal pain in a ciclesonide- 640 subject. This compares to the placebo group where there were 4 cases of asthma exacerbation requiring hospitalization and 1 case of cellulitis. There were no serious AEs in the 179 subjects treated with fluticasone.

Adverse events requiring withdrawal of the subject occurred in 69 (16.1%), 11 (4.3%), 14 (5.6%), 20 (4.7%), 10 (5.8%), and 7 (3.9%) of the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320, ciclesonide-640, and fluticasone-880 subjects respectively. The vast majority of these withdrawals were due to an asthma exacerbation. Withdrawal due to an adverse event not related to worsening asthma occurred in only 8 (1.9%), 1 (0.4%), 6 (2.4%), 7 (1.7%), 1 (0.6%), 4 (2.2%) of the placebo, ciclesonide-80, ciclesonide-160,

ciclesonide-320, ciclesonide-640, and fluticasone-880 subjects respectively. One case of adrenal insufficiency was reported in a fluticasone-treated subject. The episode was described as moderate in intensity and "recovered" at follow-up. No details were provided relating to prior or concurrent corticosteroid ingestion.

12-week OCS-Reducing Trial

In the 12-week OCS-reducing trial there were 8 serious adverse events reported. There were 5 cases of asthma exacerbation (1 in the placebo group, 3 in the ciclesonide- 640 group and 1 in the ciclesonide -1280 group. In addition, there was one case of cellulitis in the placebo group, 1 case of pneumonia in the ciclesonide- 640 group, and 1 case of bruising after trauma in the ciclesonide- 1280 group.

1- year follow-up studies

Twenty of the subjects treated with ciclesonide in the safety follow-up studies reported serious AEs: there were 2 myocardial infarctions and 1 case each of spinal stenosis, menometrorrhagia, depression, melanoma, vaginal prolapse, endometriosis, cellulitis, and pneumonia. In the budesonide-treated subjects there was 1 case each of asthma and abdominal pain. One subject was treated with both ciclesonide and budesonide and reported 2 episodes of asthma exacerbation prior to being withdrawn from the study.

7.4.1.4. Laboratory abnormalities

When all of the laboratory values were combined, abnormalities were infrequent, mild, and distributed evenly across the treatment groups. Extreme values were defined in 2 ways in all of the studies. The PCA value was one that was above the laboratory normal range and that had increased by a pre-specified amount during the course of the study. The other measure was a "clinically noteworthy value" which was defined prospectively. It was used most frequently in reference to the absolute eosinophil counts where $> 1.0 \times 10^3$ cells/mm^3 was taken to be clinically noteworthy or for glucose where the value was 2 times the upper limit of normal (approximately 230 mg/dL). There was a suggestion of more extreme values (>230 mg/dL) for glucose in the subjects treated with ciclesonide BID, however the numbers were small (Table 11).

Table 11. End-of-Study Values for Glucose (mg/ dL) in Studies 321, 322, and 323/324

Treatment Regimen	End of Study Value	Increase during the study
Placebo	238	49
Ciclesonide 80 QD	331	68
Ciclesonide 160 QD	244	19
Ciclesonide 160 BID	466* 233	356 18
Ciclesonide 320 BID	297 262	70 131

*** the applicant reported the value of 448, which was a repeat after the end of study value of 466.**

In the 12-week OCS reducing study the glucose reached the PCA level (abnormal and increased by 75 mg/dL in 2/42 (4.8%) 0, 1/45 (2.2%) of the placebo, ciclesonide- 640 and ciclesonide -1280 groups. In the 1-year follow-up studies glucose levels in the PCA range were reported for 1/161 (1.9%) of the ciclesonide subjects but for none of the 85 QVAR subjects. There were no clinically notable values for glucose.

In the combined group of 12-week pivotal trials, absolute eosinophil counts at the end of the study were > 1.0 x 10^3 cells/ mm^3 in 4 (1%), 0, 2 (0.9%), 4 (1.0%), and 2 (1.3%) of the placebo, ciclesonide- 80, ciclesonide-160, ciclesonide-320, and ciclesonide-640 subjects respectively. In the 12-week OCS reducing trial, the eosinophil count reached the PCA level (abnormal and increased by 0.37 x 10^3 cells/mm^3 in 3/43 (7.0%), 4/42 (9.5%), 3/43 (7.0%) of the placebo, ciclesonide- 640, and ciclesonide- 1280 subjects respectively. In the 1-year safety studies, the eosinophil counts reached the PCA level in 2/154 (1.3%) of the ciclesonide- treated subjects and in 4/79 (5.1%) of the budesonide- treated subjects.

7.4.1.5. HPA-Axis evaluation

The primary objective of the 12-week PD study (102) was to assess the HPA-axis after 12 weeks of treatment with ciclesonide or fluticasone in subjects with mild to moderate asthma who had not been previously treated with ICS or OCS. The low-dose (1 mcg) consytropin test showed no significant changes from baseline in the peak post-stimulation serum cortisol for any of the treatment groups (ciclesonide-320, ciclesonide-640 and fluticasone -880 mcg daily), although the peak decreased more in the fluticasone group (-2.28 mcg/dL compared to -0.37, 0.60, -0.50 mcg/dL in the placebo, ciclesonide-320 and ciclesonide-640 groups). Changes in the degree of stimulation (Peak – basal level) also did not differ between the treatment groups (-0.23, -0.25, -0.48, and -0.62 in the placebo, ciclesonide -320, ciclesonide -640, and fluticasone groups). The mean decrease in post-stimulation cortisol with the high-dose (250 mcg) cosyntropin stimulation was greater after treatment with fluticasone than with the other treatment groups (0.79, 1.01, -1.08, and -2.60 mg/dL mean decrease over the 12-week treatment period for the placebo, ciclesonide-320, ciclesonide-640, and fluticasone-880 groups respectively).

Defining abnormal function as a basal serum cortisol of < 5 mcg/dL or a peak post-stimulation cortisol of < 18 mcg/ dL or an increase of < 7 mcg/dL in females on oral contraceptive pills, all of the subjects in study 102 had normal HPA-axis function at the beginning of the study. After 12 weeks of treatment 2/39 (5.1%), 2/39 (5.1%), 7/41 (17.1%), and 10/40 (25%) of the placebo, ciclesonide-320, and ciclesonide-640, and fluticasone-880 subjects were abnormal. These results suggest that HPA-axis suppression after treatment with ciclesonide is not more severe than is seen after treatment with fluticasone. However, the results can not be taken as evidence that ciclesonide is safer because the two drugs were not administered in equipotent doses. At the doses use in this study fluticasone-440 mcg BID produced more than twice the increase in FEV_1 than was seen with either dose of ciclesonide.

Serum was obtained for basal and post low-dose cosyntropin stimulation cortisol in all of the efficacy trials. In general, changes in function were infrequent and mild. Table 12 summarizes the mean change from baseline in post-stimulation peak serum cortisol in the

pivotal 12-week trials. The 95% confidence intervals cross zero for all of the regimens studied.

Table 12. Changes from Baseline in Peak Post-cosyntropin Stimulation Serum Cortisol *

Treatment	N	Baseline mean (µg/dL)	Mean change (95% CI) from baseline
Placebo	72	24.4	0.2 (-1.3, 1.6)
Ciclesonide-80	47	25.9	0.1 (-1.2, 1.4)
Ciclesonide-160	49	28.0	1.2 (-0.5, 2.9)
Ciclesonide-320	70	25.0	-0.4 (-1.7, 0.9)
Ciclesonide-640	31	23.3	0.5 (-0.7, 1.7)
Fluticasone-880	31	24.2	-1.5 (-3.5, 0.5)

Table includes pooled data from Studies 321, 322, 323/324.

**(Source: Applicant's Table 103 [summary\2.7.4aclinicalsafety.pdf, pg 190])*

The number and percentage of subjects who started normal and shifted to abnormal in the 12 week trials are shown in Table 13. Subjects treated with ciclesonide once a day or 320 mcg BID had fewer shifts to abnormal than the placebo population. Subjects in the ciclesonide 160 BID and FP 440 BID groups had approximately 2 times as many shifts to abnormal as the placebo subjects. Of note, more than 10% of the placebo-treated subjects went from normal at baseline to abnormal at the end of the study.

Table 13. Shift to Abnormal HPA -Axis Function in Studies 321, 322, 323/324, and 102*

	Abnormal at End of Study	Normal At Beginning of Study	Percent Shift to Abnormal
Placebo	14	108	12.96
Ciclesonide 80 mcg QD	1	37	2.70
Ciclesonide 160 mcg QD	3	49	6.12
Ciclesonide 320 mcg QD	1	78	1.28
Ciclesonide 160 mcg BID	7	28	25.0
Ciclesonide 320 mcg BID	6	71	8.45
Fluticasone 440 mcg BID	15	70	21.4

**(Source: Applicant's In-Text Table 104 [summary\2.7.4aclinicalsafety.pdf, pg 191] and Table 23 [hpbio\hupharm\102\study102.pdf, pg 89])*

In the OCS reducing study, many of the baseline cosyntropin stimulation tests were abnormal as expected. Of these, 19/74 (25.6%), 3/23 (13.0%), 9/28 (32.1%), and 7/23 (30.4%) in the placebo, ciclesonide- 640 and ciclesonide -1280 groups respectively shifted to normal during the course of the study. On the other hand, of the 26 subjects who had normal cosyntropin stimulation tests at baseline, 3/9 (33%), 1/8 (12.5%), and 3/9 (33.3%) of the placebo, ciclesonide-640, and ciclesonide-1280 shifted to abnormal during the course of the study.

In the 1-year safety follow-up studies, 6/57 (10.5%) of ciclesonide-treated subjects and 3/12 (25%) of budesonide treated subjects shifted from having a normal cosyntropin response at baseline to abnormal at the end of the study.

7.4.2. Pediatric Population (4-11 years of age)

7.4.2.1. Adverse Events

12-week pivotal trials

This section combines data from studies 341 and 342 where subjects were treated with ciclesonide 40, 80, or 160 mcg QD. The subjects had mild to severe persistent asthma, and approximately 60% had been treated with ICS prior to enrollment.

Of the 768 subjects treated with ciclesonide in the safety population in the 12-week pivotal trials, 63.4% were male and 36.6% male. The mean age was 8.2 ± 2.1 years and 98 were less than 6 years of age. There was a relatively large representation of minorities because one of the recruiting centers was in Mexico. There were 469 (61.1%) White, 98 (12.8%) Black, 8 (1.0%) Asian, 27 (3.5%) Multiracial, and 166 subjects of "Other" race. Two hundred nine (27.2%) of the subjects identified themselves as Hispanic and most of these were classified as "Other" or "Multiracial" in the primary classification. Subjects were also enrolled in Poland and the United States. All together, approximately 60% of the subjects were enrolled in the United States and 40% were enrolled abroad. The mean duration of asthma prior to enrollment was 4.3 ± 2.8 years and 63.5% of subjects had been treated with ICS prior to enrollment. Most of the demographic variables were evenly distributed across the treatment groups. However, only 23 (9.1%) of the subjects treated with the 160 mcg QD dose of ciclesonide were < 6 years of age compared to 42 (16.5%) and 33 (12.7%) in the ciclesonide-40 and ciclesonide-80 groups respectively.

Overall, 179 (69.6%) AEs were reported in the placebo group compared to 158 (62.0%), 160 (61.5%), and 175 (69.2%) in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively. Serious AEs occurred in 5 (1.9%) of the placebo subjects and 6 (0.8%) of the ciclesonide-treated subjects. Adverse Events that occurred in ≥ 3% subjects are shown in Table 14. The distribution of events was similar across all of the treatment groups with several notable exceptions. Asthma was reported as an adverse event in 48 (18.7%) of the placebo subjects, compared to 94 (12.2%) of the ciclesonide-treated subjects. While nasopharyngitis showed dose ordering in the ciclesonide- treated subjects (7.1, 12.7, 13.0% in the ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups) the incidence was not much different from the incidence in the placebo-treated subjects (10.1%). Pharyngolaryngeal pain was reported less frequently in the ciclesonide groups (3.6%) than placebo (5.1%). Two cases of oral candidiasis were reported: 1 each in the ciclesonide-80

and ciclesonide-160 groups. Subcapsular cataracts occurred in 1 subject each in the placebo, ciclesonide-80, and ciclesonide-160 groups.

Table 14. Adverse Events Reported in ≥3% of the Subjects Enrolled in Studies 341 and 342*

	Number (%) of subjects				
		Ciclesonide (µg/day)			
Preferred term	Placebo (N=257)	40 (N=255)	80 (N=260)	160 (N=253)	Total (N=768)
Subjects with TEAEs	**179 (69.6)**	**158 (62.0)**	**160 (61.5)**	**175 (69.2)**	**493 (64.2)**
Asthma NOS	48 (18.7)	30 (11.8)	32 (12.3)	32 (12.6)	94 (12.2)
Nasopharyngitis	26 (10.1)	18 (7.1)	33 (12.7)	33 (13.0)	84 (10.9)
Headache	26 (10.1)	20 (7.8)	26 (10.0)	29 (11.5)	75 (9.8)
Upper respiratory tract infection NOS	27 (10.5)	19 (7.5)	19 (7.3)	18 (7.1)	56 (7.3)
Sinusitis NOS	17 (6.6)	18 (7.1)	19 (7.3)	17 (6.7)	54 (7.0)
Rhinitis NOS	15 (5.8)	21 (8.2)	13 (5.0)	8 (3.2)	42 (5.5)
Pharyngitis	10 (3.9)	9 (3.5)	13 (5.0)	14 (5.5)	36 (4.7)
Pyrexia	16 (6.2)	12 (4.7)	11 (4.2)	9 (3.6)	32 (4.2)
Pharyngolaryngeal pain	13 (5.1)	12 (4.7)	7 (2.7)	9 (3.6)	28 (3.6)
Vomiting NOS	11 (4.3)	8 (3.1)	10 (3.8)	6 (2.4)	24 (3.1)
Abdominal pain upper	9 (3.5)	2 (0.8)	10 (3.8)	6 (2.4)	18 (2.3)

Table includes pooled data from Studies 341, 342.

**(Source:Applicant's Table 19 [summary\2.7.4bclinicalsafety.pdf, pg 53])*

Most of the adverse events were mild in intensity. In the placebo group 10 (3.9%) were characterized as severe and in the ciclesonide group 20 (2.6%) were severe in intensity.

One-year follow-up trials (341lt, 342lt, 344) in mild to severe asthma

Over all, 380/443 (85.8%) subjects reported adverse events during ciclesonide treatment and 139 (81.3%) reported events during fluticasone treatment. The incidence of AEs was slightly higher in the group of subjects who were followed for the entire year (91.3 and 90.6% in the ciclesonide- and fluticasone-treated subjects respectively). Serious events occurred at equivalent rates in the two treatment groups (4.5% and 4.7% for ciclesonide and fluticasone respectively). Events reported in ≥ 3% of the subjects are listed in Table 15. Most were infrequent and reported with similar frequencies in both treatment groups. Asthma exacerbations were reported in 152 (34.3%) of the ciclesonide-treated subjects and in 40 (23.4%) of the fluticasone-treated subjects. Oral candidiasis was reported in 4 (0.9%) of the ciclesonide-treated and 5 (2.9%) of the fluticasone- treated subjects. Pneumonia was reported in 4 (0.9%) of the ciclesonide- and 6 (3.5%) of the fluticasone-treated subjects. One cataract was reported in the ciclesonide group. Overall 36 (8.1%) of the ciclesonide-

treated subjects and 16 (9.4%) of the fluticasone-treated subjects reported events that were classified as severe in intensity.

Table 15. Adverse Events Occurring in ≥ 3% of Subjects in 1-year Follow-up Studies*

	Number (%) of subjects					
	Total population		6-month population		12-month population	
Preferred term	Cic[a] (N=443)	FP-DPI[b] (N=171)	Cic[a] (N=361)	FP-DPI[b] (N=140)	Cic[a] (N=321)	FP-DPI[b] (N=127)
Subjects with TEAEs	**380 (85.8)**	**139 (81.3)**	**325 (90.0)**	**124 (88.6)**	**293 (91.3)**	**115 (90.6)**
Asthma NOS	152 (34.3)	40 (23.4)	123 (34.1)	35 (25.0)	109 (34.0)	30 (23.6)
Nasopharyngitis	104 (23.5)	31 (18.1)	102 (28.3)	30 (21.4)	91 (28.3)	29 (22.8)
Upper respiratory tract infection NOS	102 (23.0)	35 (20.5)	92 (25.5)	32 (22.9)	81 (25.2)	28 (22.0)
Headache	89 (20.1)	31 (18.1)	76 (21.1)	28 (20.0)	69 (21.5)	26 (20.5)
Sinusitis NOS	71 (16.0)	27 (15.8)	65 (18.0)	22 (15.7)	56 (17.4)	20 (15.7)
Pyrexia	69 (15.6)	22 (12.9)	64 (17.7)	21 (15.0)	58 (18.1)	19 (15.0)
Pharyngolaryngeal pain	51 (11.5)	20 (11.7)	48 (13.3)	19 (13.6)	42 (13.1)	19 (15.0)
Otitis media NOS	42 (9.5)	6 (3.5)	38 (10.5)	6 (4.3)	36 (11.2)	6 (4.7)
Abdominal pain upper	36 (8.1)	12 (7.0)	34 (9.4)	11 (7.9)	29 (9.0)	10 (7.9)
Vomiting NOS	32 (7.2)	17 (9.9)	26 (7.2)	16 (11.4)	22 (6.9)	14 (11.0)
Cough	30 (6.8)	16 (9.4)	29 (8.0)	16 (11.4)	27 (8.4)	15 (11.8)
Pharyngitis streptococcal	30 (6.8)	10 (5.8)	30 (8.3)	10 (7.1)	28 (8.7)	10 (7.9)
Nasal congestion	28 (6.3)	7 (4.1)	25 (6.9)	6 (4.3)	21 (6.5)	6 (4.7)
Ear infection NOS	27 (6.1)	6 (3.5)	27 (7.5)	6 (4.3)	25 (7.8)	6 (4.7)
Upper respiratory tract infection viral NOS	24 (5.4)	8 (4.7)	22 (6.1)	7 (5.0)	21 (6.5)	7 (5.5)
Rash NOS	21 (4.7)	11 (6.4)	21 (5.8)	10 (7.1)	18 (5.6)	10 (7.9)
Viral infection NOS	21 (4.7)	13 (7.6)	19 (5.3)	13 (9.3)	17 (5.3)	12 (9.4)
Gastroenteritis viral NOS	20 (4.5)	8 (4.7)	20 (5.5)	8 (5.7)	20 (6.2)	8 (6.3)
Ear pain	18 (4.1)	7 (4.1)	17 (4.7)	7 (5.0)	17 (5.3)	7 (5.5)
Epistaxis	17 (3.8)	6 (3.5)	15 (4.2)	6 (4.3)	13 (4.0)	5 (3.9)
Rhinitis allergic NOS	17 (3.8)	7 (4.1)	12 (3.3)	7 (5.0)	11 (3.4)	7 (5.5)
Influenza	16 (3.6)	10 (5.8)	14 (3.9)	10 (7.1)	13 (4.0)	8 (6.3)
Diarrhoea NOS	14 (3.2)	5 (2.9)	13 (3.6)	5 (3.6)	10 (3.1)	5 (3.9)
Nausea	14 (3.2)	5 (2.9)	11 (3.0)	4 (2.9)	10 (3.1)	4 (3.1)
Pharyngitis	14 (3.2)	3 (1.8)	14 (3.9)	3 (2.1)	12 (3.7)	3 (2.4)
Bronchitis NOS	13 (2.9)	6 (3.5)	11 (3.0)	6 (4.3)	8 (2.5)	4 (3.1)
Hypersensitivity NOS	13 (2.9)	5 (2.9)	12 (3.3)	5 (3.6)	12 (3.7)	4 (3.1)
Influenza like illness	13 (2.9)	6 (3.5)	12 (3.3)	4 (2.9)	11 (3.4)	4 (3.1)

Continued on next page

Table 15 (continued)

Preferred term	Number (%) of subjects					
	Total population		6-month population		12-month population	
	Cic[a] (N=443)	FP-DPI[b] (N=171)	Cic[a] (N=361)	FP-DPI[b] (N=140)	Cic[a] (N=321)	FP-DPI[b] (N=127)
Limb injury NOS	12 (2.7)	4 (2.3)	11 (3.0)	4 (2.9)	9 (2.8)	4 (3.1)
Skin laceration	12 (2.7)	1 (0.6)	11 (3.0)	1 (0.7)	9 (2.8)	1 (0.8)
Toothache	12 (2.7)	6 (3.5)	12 (3.3)	6 (4.3)	12 (3.7)	6 (4.7)
Dyspepsia	9 (2.0)	5 (2.9)	9 (2.5)	5 (3.6)	9 (2.8)	5 (3.9)
Excoriation	7 (1.6)	4 (2.3)	7 (1.9)	4 (2.9)	6 (1.9)	4 (3.1)
Pain NOS	7 (1.6)	4 (2.3)	7 (1.9)	4 (2.9)	7 (2.2)	4 (3.1)
Eczema	5 (1.1)	5 (2.9)	4 (1.1)	5 (3.6)	3 (0.9)	5 (3.9)
Oral candidiasis	4 (0.9)	5 (2.9)	4 (1.1)	5 (3.6)	3 (0.9)	5 (3.9)
Pneumonia NOS	4 (0.9)	6 (3.5)	3 (0.8)	6 (4.3)	3 (0.9)	5 (3.9)

Table includes pooled data from Studies 341LT, 342LT, 344.
Presented in decreasing order of frequency in the total population for ciclesonide.
[a] Initial dose of ciclesonide was 160 µg/day (ex-actuator), which could be titrated down to lower doses of 80 or 40 µg/day at the investigator's discretion.
[b] Initial dose of fluticasone DPI was 200 µg/day (delivered dose), which could be titrated down to a lower dose of 100 µg/day at the investigator's discretion.
Cic = ciclesonide; FP-DPI = fluticasone propionate DPI; N = safety population (randomized and treated subjects); NOS = not otherwise specified; TEAE = treatment-emergent adverse event.

**(Source: Applicant's Table 14 [update\summary\2.7.4bclinicalsafety.pdf, pg 43])*

Eye Abnormalities

A total of 4 cataracts – (one in each treatment group) was reported in the 12-week studies 341 and 342. In the placebo patient, there was progression of an opacity that was present at enrollment and in each of the ciclesonide treatment groups, a new cataract developed in a previously normal cornea. In the 1-year follow-up studies (341lt, 342lt, and 344lt) 11 cataracts developed in previously normal eyes. There were 9/385 (2.3%) in the ciclesonide group and 2/151 (1.3%) in the fluticasone-treated subjects. The denominators represent the number of subjects who were normal at enrollment and who had a follow-up examination.

(Listing C.3.2 from the original submission - pg 5633 - clinstat\341\study341a.pdf; pg 4128, clinstat\342\study 342b.pdf; and from the 120-day update Listing C.3.2 pg 3573, clinstat\341lt\study341lt.pdf; pg 3630, clinstat\342lt\study342lt.pdf; pg 4519, clinstat\344lt\study342lt.pdf.)

Of the subjects with cataracts on the baseline examination, four showed improvement. Two of these were in the placebo group in studies 341and 342 and two were in the ciclesonide treatment groups in the 1-year follow-up studies. One ciclesonide-treated subject in study 344lt developed low-tension glaucoma.

7.4.2.2. Deaths

One 12 year old girl died during follow-up in study 341lt. She had been treated in the pivotal trial with ciclesonide-160 mcg QD and was transferred to the follow-up study 64 days prior to death. She was reportedly doing well on ciclesonide-160 mcg once daily when she developed an URI and stayed home from school for two days. On the day of her return to school, during warm-up exercises in the gym, she was observed to use an inhaler. She

started a sprint and within minutes fell to the floor, had difficulty breathing, vomited, suffered seizure-like activity, and became unresponsive. A police officer witnessed the arrest and began CPR immediately. She was transported to the hospital, but she could not be revived. An autopsy was performed, but no abnormalities were found. Specifically, histologic examination of the lungs, heart, and central nervous system failed to determine the cause of death. The lungs were congested, but there was no inflammation. The final cause of death was sudden cardiac arrhythmia of undetermined etiology.

7.4.2.3. Serious Adverse Events

There were 17 (3.8%) subjects with serious AEs in the integrated ciclesonide-treatment groups. Of these SAEs, there were thirteen episodes of asthma exacerbations and/or status asthmaticus in 11 subjects (Two subjects had two episodes each.). The other SAEs include the one death described above, and 1 case each of periorbital edema, suicidal ideation, and appendicitis, and trauma and fractures that required hospitalization in 2 subjects. Four (2.3%) subjects in the fluticasone treatment groups reported serious AEs. There was one case each of status asthmaticus, atelectasis, pneumonia, and fecal impaction.

More subjects were withdrawn from the ciclesonide group for adverse events (6.3%) than from the fluticasone group (2.3%) and most of these were due to asthma exacerbations (5.2% in ciclesonide and 1.2% in the fluticasone group).

7.4.2.4. Laboratory Abnormalities

There were no differences between treatment groups in the mean changes in the routine laboratory measurements during any of the studies. Compared with the adult studies there was a large number of abnormal values for alkaline phosphatase. The PCA value (abnormal and a 28 U/L increase over the course of the study) occurred in 7.4, 2.6, 5.8, and 3.4% of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects in the 12-week trials. In the 1-year follow-up studies, 8.1% of the ciclesonide and 8.6% of the fluticasone-treated subjects reached the PCA values.

The absolute eosinophil count was in the clinically noteworthy range in a few subjects in all of the studies. In the 12-week trials, 5.6, 4.4, 1.7, and 4.5% of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively had values greater than 1.0×10^3 cells/mm^3 at the end of the study. The range of elevated values was approximately the same in all of the treatment groups. The maximum values were 1.84, 2.55, 2.49, and 1.49×10^3 cells/mm^3 in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively. In the 1-year follow-up studies, 2.4% of the ciclesonide (maximum value of 2.4×10^3 cells/mm^3) and 4.1% of the fluticasone-treated subjects (maximum value of 1.51×10^3 cells/mm^3) had clinically noteworthy values. The PCA value for absolute eosinophil count (abnormal and an increase of 0.37×10^3 cells/mm^3) was reached in 6.9, 5.8, 6.4, and 7.2% of the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects enrolled in the 12-week trials. In the 1-year follow-up studies, 3.5% of the ciclesonide and 4.8% of the fluticasone-treated subjects had eosinophil counts in the PCA range.

7.4.2.5. HPA-axis function

Baseline and end-of study cosyntropin stimulation tests were available for only a few subjects in the pediatric population. Combining study 341 and 342 resulted in 60 subjects with cosyntropin stimulation performed at the beginning and end of the study. Defining normal as a basal cortisol of ≥ 5 mcg/dL and a peak post low-dose cosnytropin stimulation cortisol as ≥ 18 mcg/dl, approximately the same proportion of subjects went from normal to abnormal in all of the treatment groups: 1/15 (6.7%), 1/12 (8.3%), 1/13 (7.7%) and 1/16 (6.3%) in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 subjects respectively. In the 1-year follow-up studies, 1/25 (4%) ciclesonide-treated and 5/17 (29.4%) fluticasone-treated subjects had abnormal cosyntropin stimulation tests. Of these, the ciclesonide subject and three of the fluticasone subjects were abnormal due to peak post-stimulation cortisol values of 17 mcg/dL. Of the two other abnormal values in the fluticasone subjects, one was due to a peak level of 16 mcg/dL and the other was due to a basal value of 3 mcg/dL however the peak value was 19 mcg/dL (At the beginning of the study the basal level was 8 mcg/dL and the peak was 20 mcg.dL).

7.5. Miscellaneous Studies

The applicant submitted 26 phase I and 20 supportive phase II/III clinical studies conducted during the early development of ciclesonide. In these studies 4 adults were described who died while taking ciclesonide in studies FK105 and FK102lt. None of the events appeared to be drug-related. There was one death due to lung cancer and one to an accidental gunshot. Two subjects, each with a positive past history, died suddenly of myocardial infarctions.

7.6. Literature Review of Safety

No literature review was submitted by the applicant.

7.7. Postmarketing Surveillance

The drug has not been marketed.

7.8. Safety Update

The final study reports for the 1-year safety follow-up studies (326lt, 323/324lt, 341lt, 342lt, and 344lt) were submitted in the safety update and they were reviewed in section 7.5 and in the Appendix. The safety update also contained a study report for a [redacted]

This study was deemed inadequate in design to adequately assess the effect of ciclesonide on [redacted] and was not reviewed. Two studies were submitted [redacted] Neither of these studies employed a placebo. They are, therefore, not relevant to approvability and were not reviewed. The safety update also included a final report for a study that determined the distribution of ciclesonide using ^{99m}Tc scintigraphy and the protocol for a 1 year study to assess the development of cataracts in subjects treated with ciclesonide.

b(4)

7.9. Drug Withdrawal, Abuse, and Overdose Experience

Ciclesonide is not marketed and has, therefore never been withdrawn from any market. In the clinical trials there was only one case of overdose reported. A 9 year old boy took 8 puffs of ciclesonide (80 mcg) on one day. Three days later he was noted to have an asthma exacerbation, but no other adverse event was reported.

7.10. Adequacy of Safety Testing

A sufficient number of subjects have been exposed to ciclesonide to assess the general safety of the recommended doses. HPA-axis suppression, assessed with low-dose cosyntropin stimulation test has been reported in all of the clinical trials, and the results consistently show only modest reductions in post-stimulation serum cortisol with higher doses. However, the attempt of the applicant to show superiority to fluticasone in respect to safety is inadequate because equipotent doses of the two drugs were not directly compared. There is some HPA-axis suppression after treatment with ciclesonide and if very high doses are required to maintain adequate control of asthma, then the HPA-axis suppression may become a significant factor. In addition, it is difficult to assess the results because of the wide rang of values in all of the treatment groups and the relatively high number of subjects who appear to have HPA-suppression in the placebo groups. At this time it appears that ciclesonide does not suppress the HPA-axis more than fluticasone.

The potential for ciclesonide to promote the development of lenticular cataracts has not been adequately studied. There was a definite excess demonstrated in the adult and adolescent 12-week study of doses of 160 mcg ad 320 mcg BID, but the incidence was not as high in the 1-year follow-up of this study. Of note, none of the submitted studies was designed prospectively to detect this adverse event, and the potential for multiple outcomes (improvements and deterioration, 2 eyes, 3 types of cataracts) makes the results difficult to interpret without a prospectively designed framework. It is also important to note that very few subjects age 12 – 18 years were treated with the higher doses of ciclesonide. Since cataracts were detected in the pediatric population (4 – 11 years of age) and because ICS therapy may be required for years, it will be especially important to evaluate the potential for the development of cataracts in adolescents.

Additional studies will be needed to assess the effects of ciclesonide on growth in children and evaluation of HPA-axis may need to be further addressed in the pediatric population given that cortisol stimulation was conducted in very few patients in the pediatric studies.

7.11. Labeling Safety Issues and Postmarketing Commitments

The label must contain information about the finding of cataracts in the clinical studies with ciclesonide There is currently ongoing a clinical trial to assess this adverse event more fully.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

In adults and adolescents with mild to moderate asthma ($FEV_1 \geq 60\%$ predicted) who are [redacted] may begin with [redacted] in a [redacted] daily dose. For patients with FEV_1 of less than 60% predicted, previously on inhaled corticosteroids, a starting dose of [redacted] mcg BID is recommended. This dose can be increased to 320 mcg BID. For adults and adolescents who require oral corticosteroid therapy, a starting dose of 320 mcg BID is recommended. This can be increased to a maximum of [redacted] mcg BID. Ciclesonide is not recommended for subjects who have not previously been treated with maintenance ICS. b(4)

APPEARS THIS WAY ON ORIGINAL

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

There were no apparent differences in the safety or efficacy of ciclesonide based on the race of the subjects. However, very few subjects in the study populations of the pivotal trials were of non-white ethnicity. There were significant numbers of Black and subjects of "Other" race in the oral corticosteroid reducing trial because almost half of the subjects were enrolled in South Africa. Similarly, one of the pediatric trials enrolled subjects in Mexico which increased the Hispanic and subjects of "Other" race participation. Additional studies would have to be performed in minority populations to be able to make definitive comments.

Very few of the subjects were > 65 years of age. The age distribution of the studies was appropriate for the disease being studied, however, it is not possible to make definitive statements about the safety of ciclesonide in the elderly. The gender distribution was approximately equal and there were enough subjects to determine that there were no differences in the safety and efficacy of ciclesonide based on gender.

9.2. Pediatric Program

Two pivotal and three 1-year safety follow-up studies in subject age 4 – 11 were submitted with this NDA; they are reviewed in the Appendix and summarized in Section 6, Integrated Review of Efficacy, and Section 7, Integrated Review of Safety. On March 22, 2004 the applicant submitted a request for a waiver for subjects less than 6 months of age on the basis that the diagnosis of asthma cannot be firmly established in infants. In addition, the immune system is not fully developed in infants, and many episodes of wheezing in infancy are attributable to infections and do not represent the first symptoms of a chronic disease. It is acceptable to grant the Applicant's request for a waiver for studies in subjects less than 6 months of age.

9.3. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

No other data is required at this time.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

Ciclesonide is efficacious in adult and adolescent asthmatics who have previously been treated with ICS in doses of 320 to 640 mcg daily. Once daily dosing of the 320 mcg dose was the only dose effective in patients with mild to moderate asthma, and only in the subset of patients who had previously been maintained on ICS. Twice daily dosing and higher doses were used in patients with moderate to severe disease (160 mcg BID and 320 mcg BID) and in patients who required oral corticosteroids (320 mcg BID and 640 mcg BID). These higher doses were effective in subjects with moderate to severe asthma.

Ciclesonide is generally safe and well tolerated. The spectrum and frequency of adverse events is similar to that of other inhaled corticosteroids. However, the issue of an increased incidence of cataracts remains unsettled. The incidence of oral candidasis and HPA-axis suppression was not higher than with the comparator fluticasone propionate MDI.

10.2. Recommendations on Approvability

Ciclesonide is recommended for approval of the — mcg daily dose for the maintenance treatment of asthma in patients with mild to moderate asthma previously maintained on inhaled corticosteroids and in doses of — mcg BID up to — mcg BID in patients with moderate to severe asthma on ICS or who are taking OCS. Ciclesonide is not recommended for patients who have previously been on bronchodilators alone. b(4)

10.3. Labeling

Because of the recommendation is for approval of a limited dose range and a restricted population, the label submitted with the original application will have to be extensively edited prior to marketing. The indications will have to indicate the restrictions to patients who have previously been treated with ICS and the recommendation for a dose for adults who have had previous therapy with bronchodilators alone will have to be removed. b(4)
Similarly the indication for patients — years of age will have to be removed along with the dose recommendation. —

Finally, the claim of —

There will, also, have to be changes in the formatting and visual displays. In the draft label, — Graphs that appear in the label must display data for each trial individually. In addition, the results of the completer analysis as well as the analysis conducted with the last observation carried forward (LOCF) have to be shown. b(4)

Appendix

APPENDIX

1. DETAILED STUDY REVIEWS

1.1. Study # 321.

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

1.1.1. Protocol

1.1.1.1. Administrative

Enrollment: July 12, 2001 – October 18, 2002
Clinical Director: [redacted]
Sites: 42 clinics in the United States

1.1.1.2. Objective/Rationale

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

1.1.1.3. Overall Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study conducted in asthmatics 12 years of age and older. Subjects with mild to moderate asthma who met screening criteria were treated with a single blind placebo for 5 to 28 days prior to randomization. Randomization was carried out within each of two strata based on asthma therapy for the last 30 days prior to screening. Stratum I subjects had been treated with any combination of inhaled corticosteroids (ICS), leukotriene inhibitors, and/or cromones. Stratum II subjects had been treated with any combination of short and long acting β-adrenergic agonists and/or theophylline, but not with inhaled corticosteroids or leukotriene inhibitors.

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

Placebo once daily, taken as 2 puffs in the morning,
Ciclesonide 80 mcg once-daily, taken as 2 puffs (40 mcg/puff) in the morning,
Ciclesonide 160 mcg once-daily, taken as 2 puffs (80 mcg/puff) in the morning,
Ciclesonide 320 mcg once-daily, taken as 2 puffs (160 mcg/puff) in the morning.

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

1.1.1.4. Study Population

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

- Stratum 1- any combination of the following:
  - Inhaled corticosteroids (dose not to exceed 500 mcg/day for fluticasone DPI, 440 mcg/day for fluticasone MDI, 250/50 bid for fluticasone/salmeterol combination DPI, or 1000 mcg/day for budesonide, beclomethasone, flunisolide, and triamcinolone).
  - Leukotriene receptor antagonists
  - Cromones
- Stratum 2 – any combination of the following:
  - Short acting β- angonists
  - Long acting β- angonists
  - Methylxanthines

Inclusion criteria

- 12 years of age or older
- Diagnosis of mild or moderate persistent asthma for at least 6 months
- FEV_1 at screening:
  - Stratum 1: 65-100% predicted
  - Stratum 2: 60-85% predicted
- FEV_1 at randomization (after 5-28 days of placebo treatment) of 60 – 85% predicted AND:
  - Stratum 1: FEV_1 must be at least 10% less than FEV_1 recorded at screening
  - Stratum 2:
    - Asthma severity score ≥3 for 3/7 days prior to randomization *(see 1.1.1.9 Statistical Plan, pg. 65)* OR
    - PEF variability ≥ 20% for 3/7 days prior to randomization OR
    - Albuterol use ≥ 2 puffs/day for 3/7 days prior to randomization.
- Reversibility of FEV_1 of at least 12% (≥200 cc) following 2 inhalations of albuterol demonstrated within 1 year of screening
- No smoking for the past 1 year and < 10 pack-year smoking history
- Normal HPA-axis function for those participating in cortisol evaluation
  - AM cortisol ≥5 mcg/dL preceding low-dose (1 mcg) cosyntropin stimulation
  - Serum cortisol ≥18 mcg/dL at one or more of the following time points following low-dose cosyntropin stimulation: 20, 30, or 60 minute

Appendix

- For females on oral contraceptives or hormone replacement therapy: an increase of serum cortisol of at least 7 mcg/dL after cosyntropin stimulation

Exclusion criteria

- Females who are pregnant or lactating
- Severe asthma
  - FEV_1 <60% predicted
  - Continual asthma symptoms
  - Frequent nighttime symptoms
  - Limited physical activity due to asthma
  - History of life-threatening asthma as evidenced by intubation, respiratory arrest or PCO_2 > 45 mm Hg
  - Two or more hospitalizations for asthma in the year prior to screening
- Asthma therapy and concomitant medications:
  - Parenteral corticosteroids within 3 months of screening
  - Use of inhaled corticosteroids in doses greater than those described in the inclusion criteria
  - Began immunotherapy within 30 days of screening
- Other serious medical conditions

1.1.1.5. Study Procedures

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

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

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

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

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

1.1.1.6. Efficacy Parameters

The primary efficacy endpoint was the change from baseline to end of study in the AM FEV_1 (L) in the intent-to-treat (ITT) population. Spirometry was performed between 7 AM and 9 AM, at least 6 hours after the last dose of albuterol, and before the daily dose of study medication. If the subject withdrew prematurely, the last available post-randomization measurement was carried forward. The secondary efficacy variables included change from baseline in FEV_1 (in liters and as percent predicted) at weeks 1, 2, 4, 8, and 12 weeks; change from baseline in FVC and $FEF_{25-75\%}$ at weeks 1, 2, 4, 8, & 12; and percent change from baseline in FEV_1 at weeks 1, 2, 4, 8, and 12 weeks. Diary variables included AM and PM PEF (L/min); peak flow variability of AM and PM PEF; total Asthma Severity Scores (AM + PM) (*see 1.1.1.9 Statistical Plan, pg. 65*); albuterol use as puffs/day; and number of nighttime awakenings.

The Asthma Quality of Life Questionnaire (AQLQ) of Juniper and Guyatt was self-administered by all subjects at baseline and at Week 4 and 12. The questionnaire was filled out at the beginning of the visit before any other testing or any contact with medical personnel. Study coordinators were instructed to review the completed questionnaire and ask the patient to correct any ambiguous or double entries. The staff was not to influence the patient's response to the questions, but could help the patient understand the question.

1.1.1.7. PK data

At selected centers blood was collected for PK measurements at baseline and Week 4 of treatment. The results were combined with results from other studies and are presented as population PK data in Part 2 of the application. *(See Biopharm Review)*

1.1.1.8. Safety Evaluations

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