

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-658

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS-DISCIPLINE TEAM LEADER

Date	January 7 th , 2008
Reviewer	Lydia I Gilbert-McClain, MD, FCCP
NDA	21-658
Proprietary / Established (USAN) names	ALVESCO [®] (Ciclesonide) Inhalation Aerosol
Dosage forms / strength	Metered dose inhaler/ 80 mcg, 160 mcg ex-actuator per actuation
Proposed Indication(s)	Maintenance treatment of asthma as prophylactic therapy in adults and adolescents
Recommended	Complete Response

1. Introduction to Review

A new drug application for ciclesonide inhalation aerosol was submitted to the Agency on December 22, 2003 under 505 (b) (1) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50 to obtain marketing approval for ciclesonide inhalation aerosol for the maintenance treatment of asthma in adults _____ in doses ranging from 80 mcg once daily up to 320 mcg twice daily depending on asthma severity and prior asthma therapy. Upon review of the application, it was determined that the submitted data from the clinical program did not support efficacy of ciclesonide for the proposed indication and this NDA was given an approvable action on October 21, 2004. This memo will address the Applicant's complete response to the Approvable letter to NDA 21-658. This memo will consider in greater detail the Division's evaluation of the efficacy support for the indication in _____, adequacy of the dosing frequency – once daily vs. twice daily dosing, and the adequacy of the study submitted to assess growth velocity.

b(4)

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The deficiency stated in the action letter of October 21, 2004, was that the clinical program did not support efficacy of ciclesonide for the proposed indication of maintenance treatment of asthma as prophylactic therapy in adult _____. In the action letter it was noted that the clinical data did not support the efficacy of ciclesonide for the maintenance treatment of asthma in patients with mild to moderate disease who were on bronchodilators alone and that the clinical data also did not support _____ dosing regimen for the various proposed doses. Further, efficacy for patients below 12 years of age has not been demonstrated. To address the deficiencies, the Applicant was asked to do the following:

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- Provide data from adequate and well-controlled studies to demonstrate efficacy of ciclesonide for the maintenance treatment of asthma that covers the full range of severity, particularly mild to moderate asthma. These studies should cover a range of doses and dosing frequencies so that an adequately supported recommendation can be made on the dosing regimen. _____

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In the action letter the applicant was also asked to address the apparent excess of cataracts seen with ciclesonide treatment during the 12-week treatment period in study 323/324. The Applicant was asked to perform an ophthalmic safety study of at least 12 months treatment duration to address the safety signal. In the action letter, the Applicant was also reminded that a dose counter should be developed for the product.

The Applicant submitted a complete response to the approvable letter on July 10th, 2007. Upon review, the response was determined to be complete and the PDUFA goal date for this submission is January 11th, 2008. The applicant submitted the following studies to address the comments in the action letter:

- Study 3030 – A twelve week double-blind placebo-controlled study in patients with mild to moderate asthma previously maintained on ICS
- Study 3031 – A 16 week study in patients previously on bronchodilators alone
- Study 343 – a growth study of 1 year treatment duration
- Study 3028 – a study to assess the functionality of the dose counter
- Study 3027 – Ocular safety study

3. CMC/Microbiology/Device

There were no approvable CMC issues in the original submission. The product is a non-halogenated glucocorticoid with a molecular weight of 540.7 with the molecular formula $C_{32}H_{44}O_7$. Ciclesonide inhalation aerosol is developed as pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA 134a and ethanol. Of note, in the original submission, the Applicant proposed product strengths for marketing – 80 mcg/ex-actuator (100 mcg ex-valve), and 160 mcg/ ex-actuator (200 mcg ex-valve. However, in the re-submission, the Applicant only submitted the 80 mcg and the 160 mcg strength. In a request for an explanation, the Applicant indicated that they have chosen the 80 mcg strength product. The CMC team confirmed that there were no CMC issues with the 80 mcg strength product.

The Applicant developed a dose counter for the product and included it with the resubmission. Clinical study 3028 was conducted to assess the functionality of the dose counter. Both the CMC reviewer and the primary clinical reviewer reviewed the study.

The dose counter study was a multi-center, randomized, open-label, parallel-group study to assess the accuracy, functionality, and reliability of the TrudellTM dose counter in 125 subjects with asthma. The Applicant used the 80 mcg product to assess the use of the dose counter at daily doses of 160 mcg once daily for 15 or 30 days. Patients 4 years of age and older were included in the study and the ciclesonide product used in the study had 120 actuations. Patients kept diaries to record the dose counter readings, as well as the number of puffs of medication that they took. Basically, the dose counter is labeled in decrements of 20 actuations but the indication advances after 10 actuations. A red zone appears when there are only 20 actuations remaining. The diary record and the dose counter were said to be in

agreement when they were within $\pm 1\%$ of one another. Undercounting was observed in $\pm 1\%$ of the canisters. The Applicant indicated that the counter is known to undercount if the actuator is not depressed in the center and if the actuations are repeated too close to one another. To address this, the Applicant has incorporated 3 concentric rings on the top of the dose counter with instructions for the patient to depress the actuator in the center. The problem of repeated actuations is less of an issue since the applicant the 320 mcg product. The CMC data (minimum fill weight, minimum desired overfill) indicate that the probability that undercounting will be an issue of clinical concern is very small ($\sim 1\%$) [See *summary in primary clinical review page 154 – 155*].

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4. Non clinical Pharmacology/Toxicology

There are no unresolved preclinical issues. All relevant non clinical studies were reviewed in the original NDA review. Animals receiving repeat doses of ciclesonide by inhalation (up to 6 months in rats and 12 months in dogs) showed decrease body weight, adrenal suppression, and lymphoid tissue (thymus, spleen, lymph nodes, bronchus-associated lymphoid tissue) in a dose-dependent and duration-dependent manner. These are typical glucocorticoid effects. For further details see Dr. Huiqing Hao's Pharmacology/Toxicology review.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted clinical pharmacology studies which were submitted and reviewed in the original NDA application. Ciclesonide is a pro-drug that is enzymatically cleaved by esterases. Esterase's are ubiquitous enzymes found in just about any tissue in the body. Orally inhaled ciclesonide would therefore be cleaved via esterases in the lungs (in contrast to nasally inhaled ciclesonide being cleaved by esterases in the nasal mucosa). One of the metabolites identified – des-ciclesonide or RM1 has anti-inflammatory activity with affinity for glucocorticoid receptors and this metabolite is purported to be the main active metabolite of ciclesonide. However, mass balance studies would indicate that des-ciclesonide represents $\sim 1\%$ of the radioactivity of intravenous ^{14}C -ciclesonide, confirming that there may be other as yet unidentified metabolites.

Metabolism of des-ciclesonide is fundamentally via CYP3A4 and to a lesser extent CYP 2D6. The oral bioavailability of ciclesonide and des-ciclesonide are both $< 1\%$, and the pharmacokinetics of ciclesonide nor des-ciclesonide do not appear to be affected by race, age, or gender.

In the resubmission, the Applicant submitted 2 clinical pharmacology studies. One study, CP-036 was an open-label, non-randomized, repeat-dose investigation of the steady state PK of ciclesonide inhalation aerosol 320 mcg once daily with and without co-administration of ketoconazole (CYP3A4 inhibitor) 400 mcg once daily. The results of the study showed that there is a 3.6 fold increase in the AUC of des-ciclesonide whereas; the levels of ciclesonide remained unchanged. A 3-fold increase in AUC is not of clinical concern and there does not need to be any special precautionary statements in the label regarding co-administration of ciclesonide and ketoconazole. The other study was an open-label, single-dose (320 mcg) study to assess the lung deposition of $^{99\text{m}}\text{Tc}$ -labeled ciclesonide inhalation aerosol in adults with mild asthma. The clinical significance of lung deposition studies is unknown and results of this study should not be included in the label.

The submission also included results of urine cortisol in children 5 to 8.5 years of age but these data are not reliable (*see discussion of growth study 343 section 7.2.5 "Special safety concerns"*). The entire adult (patients 12 years of age and older) studies included low-dose Cosyntropin assessments but these evaluations are not best suited for evaluating HPA axis effects. The Applicant conducted two dedicated PD studies study 102 and 103 in adults and adolescents. Study 102 was of 12-weeks treatment duration and in addition to low-dose Cosyntropin, evaluated 24-hour urine cortisol. However, the Applicant did not include urine volume measurements in the study report and the urine cortisol values are questionable. The mean urinary free cortisol levels at baseline were in the range of 1.3 to 1.8 mcg/mL and the individual urinary free cortisol for the placebo group ranged from 0.5 to 4 mcg/day at Week 12. Laboratory reference values show that normal levels for urinary free cortisol range from 10 to 100 mcg/day. Study 103 was a 29 day study in adults and this study is of adequate design to assess HPA axis effects. Thus, HPA axis data for adults and adolescents is limited to one study. In this study, 59 adults were randomized to ciclesonide inhalation aerosol 320 or 640 mcg twice daily, placebo twice daily, or fluticasone propionate 400 mcg or 880 mcg twice daily. The mean change from baseline in 24 hr urinary free cortisol compared to placebo following 29 days of treatment was 4.7 mcg/day [95% CI: -1058; 19.93] and -0.16 mcg/day [95% CI: -15.20; 14.89]. A dose-dependent decrease in urinary free cortisol was seen with the fluticasone propionate. There are no adequate HPA axis studies in the pediatric population under 12 years of age. For additional details on the clinical pharmacology of ciclesonide, please see Dr. Sandra Suarez-Sharp's primary reviews of the original NDA and the resubmission.

6. Clinical Microbiology

There are no sterility issues with the product. The microbiology aspects of the drug product were reviewed and found to be acceptable. For further details, please see the Microbiology consult review completed April 4, 2004 by Bryan Riley.

7. Clinical/Statistical

The complete response to this NDA includes 2 pivotal efficacy studies in adults and adolescents 12 years of age and older, 1 ophthalmologic safety study in adults, one dose counter study and one growth study in pediatric patients. The entire clinical program for ciclesonide metered dose inhaler (including the studies submitted in the original NDA is summarized in the following table of clinical trials. Studies noted with a * indicates studies submitted with the complete response.

Table 1: Clinical Program

Study / (No. of patients)	Design/objective Ciclesonide dose	Patient characteristics	Treatment Duration	Number Exposed ciclesonide/placebo/active control (ITT population)	Number of Males/Females [Age range]
Efficacy studies Adults and Adolescents 12 years of age and older					
321 (n = 524)	Efficacy/Dose ranging [Pts. stratified by prior Rx] 80, 160, 320 mcg QD	Mild/moderate asthma [mean FEV ₁ 2.44; 70% predicted]	12 weeks	391/133	213/311 [12-72]
322 (n = 487)	Efficacy/Dose-ranging [Pts. stratified by prior Rx] 80, 160, 320 mcg QD	Mild/moderate asthma [mean FEV ₁ 2.44L; 70% predicted]	12 weeks	371/116	200/287 [11-79]
323/324 (n = *527) (*includes 136 pts on FP)	Efficacy/160 BID; 320 BID; FP MDI 440 BID	Moderate/Severe asthma [mean FEV ₁ 1.79L; 53% predicted]	12 weeks	257/134	162/229 [12-82]
325 (n = 140)	Efficacy/320 BID; 640 BID	Severe persistent asthma on OCS [mean FEV ₁ 1.79L; 53% predicted]	12 weeks	95/45	44/96 [12-74]
*3030 (n = 446)	Efficacy 80 mcg BID; 160 mcg QD		12 weeks	299/147	168/278 [12 -79]
*3031 (n = 691)	80 mcg BID, 160 mcg QD; 80 mcg BID → 160 QD		16 weeks	514/177	316/375 [11 - 73]
Safety studies Adults and Adolescents 12 years of age and older					
326lt (n = 226)	OL Long term safety/80 mcg to 320 mcg QD (doses could be adjusted during study)	Previously enrolled in 321 or 322	1 year	226 enrolled	88/138 [12 -85]
323lt/324lt (n = 293)	OL Long term safety/320 - 640 mcg BID; QVAR; (doses could be adjusted during study)	Previously enrolled in 323/324	1 year	293 (197 on ciclesonide)/96 QVAR	125/168 [12-76]
*3027 (n = 1485)	Eye safety/320 BID; QVAR		1 year	743/742	592/898 [18 -80]
Efficacy studies Pediatric Patients 4 to 11 years of age					
341 (n = 504)	Efficacy/Dose-ranging 40, 80, 160 mcg QD	Mean FEV ₁ 1.28L (68%)	12 weeks	377/127	306/198 [4 -11]

Study / (No. of patients)	Design/objective Ciclesonide dose	Patient characteristics	Treatment Duration	Number Exposed ciclesonide/placebo/active control (ITT population)	Number of Males/Females [Age range]
342 (n = 514)	Efficacy/Dose- ranging 40, 80, 160 mcg QD	Mean FEV ₁ 1.31L (69%)	12 weeks	387/127	
Safety studies Pediatric Patients 4 to 11 years of age					
341lt (n = 193)	OL Long term safety/ 40 – 160 mcg QD (doses could be varied); FP DPI 50 -mcg BID	Previously enrolled in 341	1 year	129/64	118/75 [4 -12]
342lt (n = 189)	OL long term safety/ 40-160 mcg QD (varied doses); FP DPI 50 - 100 mcg BID	Previously enrolled in 342	1 year	128/61	118/71 [4 -12]
344lt (n = 232)	OL Long term safety/40-160 mcg QD (varied doses) FP DPI 50 -100 mcg BID	Persistent asthma. No prior enrollment in 12-week efficacy study	1 year	186/46	151/81 [4 -11]
*343	Growth velocity study/40 mcg and 160 mcg QD	Mild asthma	1 year		
Pharmacodynamic (PD) studies					
102 (n = 164)	Placebo/active controlled Ciclesonide 320 QD, 320BID, FP HFA 440 BID	Mild to moderate persistent asthma	12 weeks	82/41/41	79/85 [18 -78 yrs]
103 (n =60) [one subject not evaluated]	Placebo/active controlled: Ciclesonide 320 and 640 BID, FP 440 BID	Moderate/severe asthma	30 days	12/ treatment group	27/33 [22 -66]
Other Studies					
*3028 (n = 125)	OL/Dose Counter evaluation 160 mcg QD	Mild to moderate asthma	15 – 30 days	125	45/80 [6-76]

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The development program for ciclesonide inhalation aerosol included a range of doses in several of the efficacy studies. This approach to evaluating doses is appropriate for inhaled corticosteroids where dose response is not easily demonstrated. In the original application,

there were two 12-week treatment studies that evaluated once daily doses of 80 mcg, 160 mcg, and 320 mcg in patients 12 years of age and older, and two efficacy studies that evaluated once daily doses of 40 mcg, 80 mcg, and 160 mcg in patients 4 to 11 years of age with mild to moderate persistent asthma. In none of these studies was a clear dose-response relationship observed. In the two efficacy studies submitted with the complete response, once daily vs. twice daily dosing was compared. The results of these studies confirmed that the twice daily dosing frequency was the optimal dosing regimen.

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The applicant conducted 6 pivotal efficacy studies in adults and adolescents. Four of these studies were submitted in the original NDA submission and previously reviewed. These four studies evaluated fixed doses of ciclesonide inhalation aerosol administered once daily (studies 321, 322) or twice daily (studies 323/324, and 325). The other two studies were submitted in the complete response and evaluated fixed doses of ciclesonide inhalation aerosol administered once daily and twice daily (studies 3030 and 3031). The first four studies are briefly summarized below followed by a more in depth discussion of the two studies submitted in the complete response.

Studies 321, 322, 323/324, 325

Studies 321 and 322 were identical in design and conducted in patients 12 years of age and older with mild to moderate persistent asthma (mean baseline FEV₁ 2.44 L [70% predicted]). The subjects were stratified based on prior asthma therapy (i.e. ICS, or steroid-naïve [maintained on bronchodilators alone]). In these 2 studies, ciclesonide was studied in doses of 80, 160, or 320 mcg once daily and a step down approach was used in the statistical analysis of efficacy to address multiplicity issues. The primary endpoint was the mean change from baseline in AM pre-dose FEV₁ at Week 12 (Endpoint). In study 322, all three doses showed statistically significant improvement in AM pre-dose FEV₁ compared to placebo, whereas, in study 321, only the 320 mcg dose was significant. Furthermore, a dose-response was not seen in these studies. In addition, when the results were analyzed by prior asthma therapy, only patients who had been on prior corticosteroid therapy showed efficacy. This observation held true even when the results of both studies were pooled. In studies 323/324 and 325 patients with moderate to severe persistent asthma (mean baseline FEV₁ 1.7L[53% predicted]) were evaluated using higher doses of ciclesonide: 160 mcg and 320 mcg twice daily in study 323/324 and 320 mcg and 640 mcg twice daily in study 325. In study 325, patients were on oral corticosteroid therapy (mean prednisone dose 12 mg/day) and the primary efficacy variable was reduction in prednisone dose. A summary of the FEV₁ results for studies 321, 322, and 323/324 is shown in the table below.

Table 2. Mean change from Baseline in FEV₁ (liters) at week 12 (Endpoint) studies 321, 322 and 323/324

	Baseline	Change*	Difference	p-value
Study 321				
Placebo (n= 133)	2.46	0.20		
Ciclesonide 80mcg QD (n = 133)	2.44	0.32	0.12	0.0123
Ciclesonide 160 mcg QD (n = 127)	2.46	0.26	0.07	0.16
Ciclesonide 320 (n=131)	2.44	0.35	0.15	0.001

Study 322				
Placebo (n=133)	2.43	0.13		
Ciclesonide 80 (n=124)	2.40	0.25	0.12	0.022
Ciclesonide 160 (n=123)	2.34	0.32	0.19	0.0003
Ciclesonide 320 (n=124)	2.51	0.25	0.11	0.017
Study 323/324				
Placebo (n=134)	1.77	0.25		
Ciclesonide 160 BID	1.78	0.36	0.11	0.0374
Ciclesonide 320 BID	1.82	0.43	0.18	0.0008
Flovent MDI 440 BID	1.77	0.50	0.24	0.0001

¹In Study 325, both doses were efficacious in reducing oral corticosteroid use compared to placebo (4% increase in oral corticosteroids). The reduction in corticosteroid use was not statistically better with the 640 mcg BID arm compared to the 320 mcg BID treatment arm (% 66.75% and 51.59% reduction respectively)

Study 3030

This was a multi-center, randomized, double-blind placebo-controlled study in patients 12 years of age and older with mild to moderate persistent asthma that had been previously treated with inhaled corticosteroids. Patients were eligible for enrollment if they had a history of asthma for at least 6 months prior to screening, and had a mean baseline FEV₁ between 60 and 90% predicted (if previously treated with ICS monotherapy and between 70 and 95% predicted (if previously treated with ICS and a long-acting beta agonist). The 2 weeks prior to randomization was used as the run-in period in which patients maintained treatment with their inhaled corticosteroid and as-needed beta-agonist use. After the run in period, they were randomized to ciclesonide 160 mcg once daily (from the 160 mcg/actuation product) in the AM, ciclesonide 80 mcg (from the 80 mcg/actuation product) twice daily, or placebo. The design was a double dummy so that each patient received 2 inhalers to administer 1 inhalation twice daily. The primary efficacy endpoint was change from baseline in FEV₁ (L) to Week 12 (Endpoint).

Results

There were 456 patients randomized in the study. Of these, 446 patients (168 males and 278 females) made up the ITT population because 10 patients did not have post-treatment FEV₁ measurements and were excluded from the efficacy analysis. All the randomized patients who received at least one dose of study medication were included in the safety population. Of the patients in the ITT population, 150 were randomized to ciclesonide 160 mcg once daily, 149 to ciclesonide 80 mcg twice daily, and 147 to placebo. A total of 372 (81%) patients completed the study. The mean duration (years) of asthma was 21.66 years and the mean FEV₁ at baseline was 2.64L. There was a statistically significant improvement in FEV₁ (L) at Week 12 compared to placebo in both ciclesonide treatment groups although the improvement in the ciclesonide 80 mcg BID treatment group was numerically better than the ciclesonide 160 mcg QD group. The trend was similar in the supportive secondary endpoints where the twice daily

¹ The imputation method employed in this analysis was revised from the original method in the initial protocol however; re-analysis using the initial per-protocol imputation method yielded essentially the same results (a difference of ~2% between the two methods).

regimen was numerically better than the once daily regimen. These FEV₁ results and the results for some of the secondary endpoints are shown in the table below.

Table 3. Efficacy Results Study 3030

	Baseline	LS mean Change (L) 95% CI	Difference from placebo	p-value
FEV1 (L)				
Placebo (n= 147)	2.63	-0.12 (-0.18, -0.07)	----	
Ciclesonide 80mcg BID (n = 149)	2.67	0.07 (0.01, 0.12)	0.19 (0.11, 0.27)	<0.001
Ciclesonide 160 mcg QD (n = 150)	2.64	0.01 (-0.04, 0.07)	0.14 (0.06, 0.22)	0.0006
AM PEF (L/min)				
Placebo	379	-12.8 (-18.5, -7.2)	---	
Ciclesonide 80 mcg BID	386	-4.4 (-10.1, 1.3)	8.4 (0.60, 16.2)	
Ciclesonide 160 mcg QD	393	-5.8 (-11.5, -0.03)	7.1 (-0.8, 14.9)	
Albuterol Use (puffs/day)				
Placebo	1.30	0.67 (0.45, 0.90)	---	
Ciclesonide 80 mcg BID	1.18	0.04 (-0.19, 0.26)	-0.64 (-0.95, -0.33)	
Ciclesonide 160 mcg QD	1.19	0.08 (-0.15, 0.30)	-0.60 (-0.91, -0.28)	
*Asthma symptoms Score				
Placebo	1.40	0.33 (0.17, 0.49)	---	
Ciclesonide 80 mcg BID	1.32	-0.05 (-0.21, 0.12)	-0.37 (-0.60, -0.15)	
Ciclesonide 160 mcg QD	1.37	-0.05 (-0.21, 0.11)	-0.38 (-0.60, -0.15)	
Maximum score is 4. The scale is 0 - 4 where 0 = No symptoms; 1= occasional wheezing, cough, or shortness of breath but no interference with daily activities or sleep; 2 = Occasional wheezing, cough, or shortness of breath which interfere with daily activities or sleep; 3 = Frequent or continuous wheezing, cough or shortness of breath which interfere with daily activities or sleep; 4 = Symptoms which prevent the patients from engaging in daily activities or sleep				

The rate of withdrawal for any cause, and withdrawal due to efficacy was higher in the placebo group compared to the ciclesonide treatment groups. Withdrawal due to a lack of efficacy occurred in 32 (21.8%) patients in the placebo group compared to 8 (5.3%) patients in the ciclesonide 160 mcg QD treatment group and 6 (4.0%) patients in the ciclesonide 80 mcg BID treatment group.

Study 3031

Study 3031 was designed to evaluate the efficacy of ciclesonide in patients 12 years of age and older with mild to moderate persistent asthma maintained on bronchodilators. The study was designed to also evaluate the efficacy of the same nominal dose of ciclesonide using a once daily dosing regimen in patients who are first stabilized on the twice daily dosing regimen. Patients enrolled in the study had similar characteristics to patients in the other studies expect that they needed to be off all inhaled corticosteroids for at least 30 days prior to enrollment in the study. Eligible subjects participated in a 7 to 14-day run in period during which they were treated in a single-blind fashion with placebo MDI twice daily. Following the run-in, patients were randomized in double-dummy design fashion to receive placebo BID for 16 weeks, ciclesonide 160 mcg QD for 16 weeks, ciclesonide 80 mcg twice daily for 16 weeks, or ciclesonide 80 mcg twice daily for 4 weeks, followed by ciclesonide 160 mcg QD for 12 weeks. For the 160 mcg QD treatment arm the 80-mcg/actuation product was used, and for the 80 mcg BID treatment arm, the 80 mcg/actuation product was used. The primary efficacy endpoint was the change in AM pre-dose FEV₁ from baseline to the average of the Week 12 and the Week 16 value.

Results

A total of 708 patients were randomized. Nine patients had no post-treatment FEV₁ measurements, and a total of 691 patients make up the ITT population. A total of 177 patients on placebo, 173 on ciclesonide 160 mcg QD, 170 on ciclesonide 80 mcg BID, and 171 on ciclesonide 80 mcg BID/160 QD make up the ITT population. The mean duration of asthma was 14.5 years and the mean baseline FEV₁ was 2.47L. There was a statistically significant improvement in AM pre-dose FEV₁ in the once daily and the twice daily treatment regimens however, the improvement in the twice daily regimen was statistically superior to the once daily regimen and the effect size of the twice daily regimen was twice that of the once daily regimen. Efficacy was also demonstrated in patients who were initially treated with ciclesonide 80 mcg twice daily for four weeks and then switched to ciclesonide 160 mcg once daily. The table below shows the efficacy results.

Table 4 – Efficacy Results study 3031

	Baseline	LS mean Change (L) 95% CI	Difference from placebo	p-value
FEV1 (L)				
Placebo (n= 177)	2.45	0.06 (0.01, 0.12)	---	
Ciclesonide 80mcg BID (n = 170)	2.49	0.30 (0.25, 0.36)	0.24 (0.16, 0.32)	<0.001
*Ciclesonide 160 mcg QD (n =173)	2.54	0.19 (0.13, 0.25)	0.12 (0.05, 0.20)	0.002
*Ciclesonide 80 BID/160 QD (n =171)	2.39	0.19 (0.13, 0.25)	0.13 (0.05, 0.20)	0.002
AM PEF (L/min)				
Placebo	324	3.4 (-5.9, 12.7)	---	
Ciclesonide 80 mcg BID	320	39.6 (30.1, 49.0)	36.2 (23.1, 49.2)	
Ciclesonide 160 mcg QD	318	26.7 (17.3, 36.1)	23.3 (10.1, 36.5)	
Ciclesonide 80 BID/160 QD	306	34.1 (24.7, 43.5)	30.7 (17.7,43.7)	
Albuterol Use (puffs/day)				
Placebo	2.46	-0.97 (-1.19,-0.74)	---	
Ciclesonide 80 mcg BID	2.95	-1.69 (-1.92,-1.46)	-0.73 (-1.04, -0.41)	
Ciclesonide 160 mcg QD	2.71	-1.38 (-1.61, -1.15)	-0.41 (-0.73,-0.09)	
Ciclesonide 80 BID/160 QD	2.86	-1.57(-1.79,-1.34)	-0.60 (-0.92, -0.28)	
Asthma symptoms Score				
Placebo	3.10	-1.06(-1.27,-0.85)	---	
Ciclesonide 80 mcg BID	3.09	-1.63 (-1.85,-1.41)	-0.57 (-0.87, -0.27)	
Ciclesonide 160 mcg QD	3.12	-1.33 (-1.55,-1.12)	-0.27 (-0.57,-0.03)	
Ciclesonide 80BID/160QD	3.11	-1.38 (-1.60,-1.17)	-0.32 (-0.62,-0.03)	

*The LS mean difference (L) from ciclesonide 80 mcg BID is 0.11 (0.03, 0.19) p =0.005

As was seen in the other studies, the withdrawal rate was highest in the placebo group (22.6%) compared to the active treatment groups. In the active treatment groups, the withdrawals were highest in the ciclesonide once daily treatment group (14.5%) compared to 7.6% in the ciclesonide 80 mcg BID treatment group and 9.9% in the ciclesonide 80 BID/160QD treatment group.

7.1.3. Other efficacy studies

There were no other primary efficacy studies submitted with the application. As mentioned in section 7.1.1, the applicant conducted 2 efficacy studies (341 and 342) in pediatric patients 4 to 11 years of age. These studies were submitted and review with the original submission. Briefly, they were identically designed studies to evaluate the efficacy of ciclesonide 40, 80, or 160 mcg once daily for 12 weeks. The efficacy variables were AM pre-dose FEV₁, PEF, as

well as the other usual measures of asthma control (albuterol use, asthma symptoms, nighttime awakenings, and withdrawals due to lack of efficacy). The patients were stratified by prior asthma therapy (i.e. bronchodilators alone or ICS/controller therapy) as was done in studies 321 and 322. These two studies did not support efficacy. In one study (342) ciclesonide 160 mcg once daily showed a statistically significant improvement over placebo for AM pre-dose FEV1 but this finding was not replicated. Furthermore, the results in these studies conflicted with the results in study 321 and 322. In the adult studies (321 and 322) patients previously maintained on bronchodilators alone did not demonstrate efficacy for any of the doses of ciclesonide inhalation aerosol tested. In the pediatric studies, efficacy was not demonstrated in patients previously on ICS. A summary of the efficacy results for study 342 is shown in the table below.

Table 5 – Study 342 [Pediatric patients 4 to 11 years]

Efficacy Variable	TREATMENT DIFFERENCE AT WEEK 12 VERSUS PLACEBO		
	Ciclesonide 40 mcg QD (n=)	Ciclesonide 80 mcg QD (n=)	Ciclesonide 160 mcg QD (n=)
FEV ₁ % predicted	1.35	1.71	3.55 (p=0.0283)
FEV ₁ (L)	0.02	0.04	0.08
AM PEF (L/min)	8.66	6.24	7.90
Asthma Severity Score	-0.57	-0.47	-0.49
Daily Albuterol use (puffs/day)	-0.31	-0.45	-0.23

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

During the review cycle, the statistical secondary reviewer determined that there was a discrepancy in the statistical methods used for the analysis of the results for study 325 compared to what was described in the original protocol and requested clarification from the Applicant and a re-analysis of the data using the original analysis specified in the original protocol. Study 325 was the study conducted in patients on oral corticosteroid therapy where the primary efficacy outcome was reduction in corticosteroid therapy. The imputation method used in the statistical analysis was that if the patient completed the study, the prednisone dose at Visit 15 was considered the final prednisone dose. However, if the patient withdrew from the study due to exacerbation of asthma, or lack of efficacy, the final prednisone dose was to be imputed as 10 mg once daily (or 20 mg every other day) higher than the prednisone dose at the time of discontinuation. The statistics team leader noted that this method was different from the protocol specified method which stated that if the patient discontinued from the study for an exacerbation of asthma, the final prednisone dose would be *2.5 mg more than the prednisone dose at the time of exacerbation for patients taking daily prednisone dose and 5 mg more for patients taking prednisone on an alternate day regimen.*

The statistics team leader noted that in this study, more than 30% of patients from the placebo group discontinued as compared with 17% and 10% in the ciclesonide 320 and 640 mcg BID, respectively and almost all the patients discontinued for the reason of lack of efficacy. She noted that, the imputation method used in the analysis could potentially inflate the effect size and asked for a reanalysis and explanation of the imputation method.

The Applicant responded to the information request and explained that prior to the database lock and the unblinding of the data, it was determined that an imputed increase of 2.5 mg of prednisone for patients who discontinued the study due to lack of efficacy was not appropriate

since patients discontinuing the study for lack of efficacy would have been withdrawn for more than just mild symptoms and a 2.5 mg increase in the daily oral prednisone dose would not have been appropriate from a clinical standpoint. The Applicant explained that they submitted the finalized statistical analysis plan to the Agency on April 16th, 2003 and it was deemed acceptable. The re-analysis of the data using the initial protocol pre-specified analysis showed essentially the same results as the revised analysis.

7.1.5. Pediatric use/PREA waivers/deferrals

The adult program includes pediatric patients 12 years of age and older. This is acceptable for this disease. Appropriate dose and dosing regimen has been established for pediatric patients 12 years of age and older. The applicant conducted efficacy and safety studies in patients 4 to 11 years of age however, these studies did not demonstrate efficacy and the effective dose and dosing regimen in patients 4 to 11 years of age has not been established. In the acknowledgement letter to the original NDA submission, submission of an assessment of the safety and effectiveness of the product in pediatric patients were deferring until Oct 23, 2007. In correspondence to the Division of May 27, 2004, the Applicant submitted an outline of a

The applicant subsequently requested and was granted a waiver for studies in patients from ages birth to less than 6 months of age in a letter dated October 1, 2004. The reason for the waiver is that the disease is unlikely to exist or is difficult to diagnose in this age group. In this submission, the Applicant is requesting a deferral from the current date of October, 2007 for completion of studies in children 6 months to 4 years of age. The Applicant's reasoning is that NDA 21-658 is currently under review and the dose and dosing regimen in patients 4 years and above remains to be established. Studies in the youngest patients with asthma can commence, once the dosing of Alvesco has been determined. The Applicant's reasons are acceptable and I concur that a deferral for studies in patients 6 months to less than 4 years of age be granted.

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7.1.6. Discussion of notable efficacy issues

The original development program for ciclesonide MDI did not contain any studies comparing the once daily dosing regimen with other dosing frequencies (e.g. QD vs. BID, vs. TID, QID etc). The twice daily dosing regimen (only) was studied in asthma patients with more severe asthma (studies 323/324 and 325) and in patients with mild to moderate asthma, efficacy was evaluated using a once daily dosing regimen. In the two studies 321 and 322 (submitted in the original application, efficacy was replicated only for the 320 mcg once daily dose. In those 2 studies, patients were stratified by prior asthma therapy (maintained on bronchodilators alone, or maintained on inhaled corticosteroids). When the efficacy results were evaluated by stratum, ciclesonide did not demonstrate efficacy at any dose in patients who were previously maintained on bronchodilators alone. Even when the efficacy results of the 2 studies were pooled efficacy in patients previously on bronchodilators was still not demonstrated for any of the doses, whereas, efficacy was demonstrated for all three doses in patients previously on ICS. This observation along with the inconsistent efficacy results with the once daily dosing regimen seen for the supportive secondary outcomes support the conclusion that the most effective dosing regimen was not defined and thus the applicant assessed once daily vs. twice daily dosing in response to the deficiency in the action letter. Of note, these new studies 3030 and 3031 provide convincing evidence that the twice daily dosing regimen is superior to the once daily dosing regimen.

With respect to the lowest effective dose, the lowest effective dose appears to be 80 mcg; however, the once daily dosing regimen is not ideal.

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7.2. Safety

7.2.1. General safety considerations

The safety database for adults and adolescents is derived from 5 clinical trials [study 3030, 3031, 323/324, 325 and 102] of 12 weeks to up to 1 year in duration. One of the five studies included a safety extension follow up of one year. In the 12 to 16 week treatment studies, 720 patients (298 males and 422 females) aged 12 years and older were exposed to ciclesonide inhalation aerosol. In the long-term safety trial, 197 patients (82 males and 115 females) with severe persistent asthma from study 323/324 were re-randomized and treated for up to one year with ciclesonide inhalation aerosol 320 mcg twice daily. Of note, this safety database is considerably smaller than what is described in the original medical team leader memo for the original submission. This is because, in that review, all the once daily dosing studies were included in the safety database. Although there are once daily dosing studies of 12 weeks duration, it is not appropriate to include these studies in the safety data base for the adult and adolescent population because the once daily dosing regimen is not the most appropriate dosing regimen and the doses used in the once daily dosing studies are not higher than the twice daily dosing studies. A separate safety study of one year treatment duration - an ophthalmology safety study in adults 18 to 80 years of age, was conducted to specifically assess the ocular safety of ciclesonide inhalation aerosol. This study is discussed in more detail in section 7.2.5 – Special Safety Concerns.

Safety information for pediatric patients 4 to 11 years of age is obtained from once daily dosing studies as this was the only dosing regimen studied in the pediatric population. Two of these studies were designed with a 12-week double-blind treatment period followed by a long-term open label safety extension of one year, and one study was an open label safety study of one year duration. The Applicant also conducted a growth study where the effect of ciclesonide inhalation aerosol on linear growth velocity in patients 5 to 8 years of age was assessed. This study is discussed in more detail in section 7.2.5 – Special Safety Concerns.

7.2.2. Safety findings from submitted clinical trials

There were 2 deaths in the ophthalmology safety study (one case of "heart attack" and one suicide) that were unrelated to the study drug. The safety findings noted in the adult and adolescent studies did not raise any new safety concerns. The adverse event profile was in line with what is expected for this class of drug. As expected, the patients who were maintained on oral corticosteroids (study 325) reported more corticosteroid-related reactions compared to patients who were previously on bronchodilators alone or inhaled corticosteroids. The most common adverse reaction ($\geq 3\%$) in the ciclesonide-treated patients was headache. The respiratory system was second most common system in which adverse reactions occurred. Adverse reactions of nasopharyngitis, sinusitis, and pharyngolaryngeal pain were the next

most common adverse reactions. Oral candidiasis was reported in less than 1% of patients who were previously on bronchodilators or inhaled corticosteroids but in study 325 (patients on oral corticosteroids) oral candidiasis was reported with a higher frequency > 3%. The pediatric (patients 4 to 11 years of age) safety profile did not differ from that of the adult population. The safety extension studies in the pediatric patients were done comparing ciclesonide with an active comparator. The safety profile in both study arms was similar to each other and not different from what was seen in the 12-week treatment studies.

7.2.3. Safety update

The resubmission included safety data from the post-marketing experience with ciclesonide inhalation aerosol as well as safety information from the clinical development program conducted outside of the U.S. The post-marketing safety events were of the same profile of that seen in the clinical trials.

7.2.4. Immunogenicity

Not applicable

7.2.5. Special safety concerns

Like all corticosteroids, ciclesonide has certain class effects such as local toxicity effects, risks of infection, potential for growth suppression, and HPA axis suppression and the package insert carries class labeling for corticosteroid-related effects. During the original development program, an increase in lenticular opacities was noted in one of the 12-week studies (study 323/324) in patients treated with ciclesonide compared to patients who received fluticasone. A total of 13 (5.1%) cataracts were reported in the 12-week treatment period compared to 1 (0.7%) and 2 (1.4%) in the placebo and fluticasone propionate treatment groups respectively. In the 1-year follow up, 14 (3.5%) cataracts were reported in the ciclesonide-treated group compared to 7 (3.6%) in the beclomethasone dipropionate HFA (QVAR) 320 mcg BID group. As a result of these findings, the Applicant conducted a dedicated safety study to assess ocular effects with ciclesonide inhalation aerosol. The protocol was reviewed by the Agency's ophthalmology group. The study and results are briefly described below.

Study 3027 –Ocular Safety study

This was a multinational, multi-center, randomized, double-blind, active-controlled, parallel group study conducted in adult patients 18 years of age or older with a history of moderate to severe persistent asthma (FEV₁ prior to screening of ≥ 40 % and ≤ 85%) and documented use of inhaled corticosteroid therapy at any dose for at least one month prior to screening. The primary objective was to demonstrate the non-inferiority of ciclesonide inhalation aerosol compared to beclomethasone – HFA in the occurrence of a Class I lens event for nuclear opalescence, cortical, or posterior sub capsular lens opacification within 12 months.

Lens events were determined by the occurrence of a protocol-specified change in lens opacification using the Lens Opacities Classification System III (LOCS III) for grading lens opacities, or the occurrence of cataract surgery. The study medications were ciclesonide-HFA 320 mcg twice daily and beclomethasone 320 mcg twice daily. Eligible subjects were enrolled into a 1 to 14-day screening period after which they were randomized (1:1) to receive either ciclesonide or beclomethasone by inhalation. Throughout the treatment period the subjects maintained a diary indicating their daily medication intake.

Patients were seen in follow-up at 4, 8, and 12 months after initiation of treatment. At each visit a slit-lamp examination was performed to grade lens opacities. Visual acuity, intraocular pressure and pulmonary function were also assessed at each visit. The same ophthalmologist was to perform the examinations on each subject. The examination consisted of the following procedures performed in the order listed:

- Manifest refraction
- Visual acuity of each eye
- Intraocular pressure measured by tonometry.
- Slit lamp examination for Lens grading: LOC III
 - Nuclear opalescence
 - Nuclear color
 - Cortical lens opacity
 - Posterior sub capsular lens opacity

The primary efficacy evaluation was based on the ophthalmologic examination. The primary endpoint was the occurrence of a Class I lens event within 12 months. A Class I lens event was defined as any of the following events in either eye:

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

A total of 743 patients were enrolled in the ciclesonide treatment arm, and 742 patients were in the beclomethasone arm. There was no difference in the rates of cataract development between the two treatment groups. The more severe Class III effects were recorded in 8.1% of the ciclesonide-treated patients and 9.2% of the beclomethasone-treated patients. Of these Class III effects, the incidence of sub-capsular cataracts (felt by proponents in the field to be more specific for corticosteroid effects) was 0.9% in the ciclesonide-treated patients (compared to 0.5% in the beclomethasone-treated patients. The ophthalmology reviewer was consulted about the study results and he indicated that the risk of cataracts does not appear to be significantly greater in ciclesonide than with beclomethasone. The label carries class labeling language about the ocular effects of corticosteroids.

Study 343 – Growth study

The Applicant conducted a study to assess the effect of ciclesonide on linear growth velocity in the pediatric population. Linear growth velocity was measured by stadiometry. The study was a multinational study with study sites in the U.S. and South America. Briefly, children with a history of asthma aged 5 to 8.5 years of age were enrolled in this study. Only patients with mild asthma ($FEV_1 \geq 80\%$) who only required non-corticosteroid therapy were eligible for participation. The study was reviewed in detail by the statistical team leader and the primary medical officer. A total of 440 patients were randomized to ciclesonide 40 mcg once daily, ciclesonide 160 mcg once daily, or placebo for the one-year treatment period. The treatment period was preceded by a baseline 6-month observation period during which they had baseline stadiometry measurements. The applicant used diary data and canister weights to assess compliance. The primary growth endpoint was the growth velocity during the one-year double-blind treatment period and the primary estimate of growth was the linear regression estimate of growth velocity determined from the slope of the linear regression using all of the available measurements (at least 3). This method is described in the Agency's growth

11.1. Proprietary name

The proprietary name ALVESCO was reviewed by DMETS and found to be acceptable.

11.2. Physician labeling

Several sections of the label were extensively re-written to comply with the new PLR and to present the necessary prescribing information about this drug more accurately in the label. Of note, the ciclesonide metered dose inhaler for oral inhalation will be the first orally inhaled corticosteroid to be approved with the new labeling format under PLR. As a result, great care was taken in revising sections of the label that carry class labeling language since this label will serve as the prototype for all further orally inhaled corticosteroid labels. The WARNINGS/PRECAUTIONS section was extensively revised to (a) present the Warnings/precautions in order of importance (b) edit the class language to remove redundancy and vague terms (c) add specific data on certain warnings (i.e. incidence of oral candidiasis) from the clinical program with ciclesonide. The ADVERSE REACTIONS section was re-written to address safety findings from a safety database that reflect exposure from Alvesco with the recommended dosing regimen (twice daily). In the original label the Applicant

comprised of the twice daily dosing studies of at least 12 weeks duration. Revisions to the PEDIATRIC USE section included specific language to address the labeling requirements of PREA under the new FDAAA. Furthermore, in that section, the description of the growth study (Study 343) was extensively revised from the sponsor's primary iteration to

Given that the compliance in the study cannot be assured, it would be inappropriate to include the actual study results in the label. However, it is important to acknowledge that a growth study was conducted. Additional class labeling language about corticosteroids and growth were revised in that section. Finally, the CLINICAL TRIALS section of the label was revised with several salient changes from the applicant's original proposal. The determination that the once daily dosing regimen was not the appropriate dosing regimen was explained (with rationale), the data figures were revised to use the primary endpoint as analyzed in the studies to accurately reflect the data, and general clinical trial information consistent with PLR requirements was added. The final label is now acceptable to the Division.

11.3 Carton and immediate container labels

During the review cycle the Applicant was asked to revise the original carton and container labels since they contained graphic images that were unacceptable, and some of the fonts were too small. The Applicant made the necessary revisions to the artwork and text on the labels and they are acceptable.

11.4 Patient labeling/Medication guide

The Applicant included a Patient Instructions for Use which was also revised in keeping with the revisions to the package insert.

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12. DSI Audits

There were no DSI audits for this resubmission. In the original NDA submission, a DSI audit was conducted at 4 study sites. There were no irregularities found during the inspection that would have affected the integrity of the data.

13. Conclusions and Recommendations

The Applicant has demonstrated efficacy of ciclesonide metered dose inhalation aerosol for the maintenance treatment of asthma in patients 12 years of age and older. The results of the once daily dosing and twice daily dosing studies confirm that the twice daily dosing regimen is the most effective regimen for this drug product. The lowest effective dose for patients 12 years of age and older is 80 mcg twice daily. The highest recommended dose should be 320 mcg twice daily. This dose was shown to be just as effective as 640 mcg twice daily in patients with severe asthma who were taking oral corticosteroids. Although the efficacy (and safety) data for the adult program (patients 12 years of age and older) support approval of ciclesonide metered dose inhalation aerosol, the data do not support the efficacy and safety for patients under 12 years of age. The two 12-week efficacy studies in pediatric patients 4 to 11 years of age conducted with doses of 40 mcg, 80 mcg, and 160 mcg of ciclesonide administered once daily dosing did not demonstrate efficacy. Furthermore, the pediatric studies conducted did not include an adequate assessment of the HPA axis effects of ciclesonide metered dose inhalation aerosol in this age group.

_____ The results of the one year-growth study are unreliable because compliance with the study medication cannot be assured. However, the study should be mentioned in the label (i.e. that the study was conducted). A repeat of the growth study is not necessary as the label will contain class labeling language for growth in the appropriate sections of the label.

13.1. Recommended regulatory action

The regulatory action will be approval of ciclesonide inhalation aerosol (Alvesco) for the maintenance treatment of asthma in patients 12 years of age and older.

_____ The regulatory action for _____ will be approvable with specific deficiency comments conveyed to the Applicant (*see below*).

13.2. Safety concerns to be followed postmarketing

There are no unique safety concerns to be followed postmarketing.

13.3. Risk Minimization Action Plan

There are no Risk Minimization Action Plans other than labeling.

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)

No post marketing studies are recommended.

13.5. Comments to be conveyed to the applicant in the regulatory action letter

There are no deficiency comments to be conveyed in the action letter for NDA 21-658. The following comments should be conveyed in the action letter for the _____, that addresses the _____.

- The submitted clinical studies do not support efficacy and safety of ciclesonide metered dose Inhalation aerosol for patients 4 to 11 years of age. The two clinical studies conducted in patients 4 to 11 years of age that only explored once daily dosing regimen failed to show efficacy at the doses and dosing regimen that was studied.

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