CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-658

SUMMARY REVIEW

DIVISION DIRECTOR'S DECISIONAL REVIEW

Date: January 10, 2008

To: NDA 21-658

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Alvesco (ciclesonide) Inhalation Aerosol 80 mcg, 160 mcg

Applicant: Nycomed Inc.; (Aventis Pharmaceuticals Inc. was the original applicant)

Administrative and Introduction

Nycomed submitted a complete response to a previous approvable action on this new drug application (NDA 21-658) on July 10, 2007, (received on July 11, 2007, CDER stamp date). The PDUFA due date on this application is January 11, 2008. The application is for use of Alvesco (ciclesonide) Inhalation Aerosol 80 mcg and 160 mcg in patients [redacted]. The submitted data supports approval of this product for use in patients 12 years of age and older, [redacted] In subsequent sections of this document brief comments are made on findings that have direct bearing on the regulatory decision on this application and labeling of this product. For details the reader is referred to Dr. Gilbert-McClain's summary review, and various primary and secondary discipline reviews of the original application and this complete response. b(4)

Regulatory History

The drug development program for Alvesco was initially carried out by Byk Gulden with Altana as the US representative. Aventis later assumed the development program and conducted the entire phase 3 program. Aventis submitted the original NDA for Alvesco as a 505(b)(1) application on December 22, 2003. The proposed indication was maintenance treatment of asthma in adult and [redacted] years of age and older. An approvable action on that application was taken on October 21, 2004, primarily due to failure to demonstrate efficacy for all ages at the proposed doses and dosing regimen. The proposed doses ranged from 80 mcg [redacted] twice daily [redacted]. Emphasis on the clinical development program and in the application was towards [redacted] dosing frequency. The applicant did not conduct any clinical studies to compare the same nominal dose administered [redacted] to a more frequent dosing interval to show that [redacted] was the appropriate dosing frequency for this drug. Efficacy at [redacted] dosing regimen was marginal and not consistent. In the approvable action letter and in subsequent interactions with the applicant, the Agency asked for comparative efficacy evaluation of the same total dose administered at different dosing frequency to determine the optimum dosing frequency. The Agency in principle agreed that a [redacted] b(4) b(5)

[redacted] twice daily dosing regimen. The applicant conducted two studies comparing once daily to twice daily dosing of the same total dose. These two clinical studies along with some other studies are submitted with this complete response.

Alvesco NDA was the first application for use of ciclesonide in the United States. Subsequently an NDA (22-004) for use of ciclesonide nasal spray (Omnaris) in patients with allergic rhinitis was approved.

The current holder of the Alvesco NDA is a company called Nycomed. Aventis merged with Sanofi Pharmaceuticals to become Sanofi-Aventis in 2006. Sanofi-Aventis transferred the ownership of this NDA to Nycomed in 2007.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance ciclesonide is a non-halogenated glucocorticoid. Alvesco is a solution formulation of ciclesonide in [redacted] dehydrated ethanol with HFA-134a as the propellant. The device contains a standard valve and canister with a standard press-and-breathe actuator. The inhaler is formulated in two strengths, with both strengths utilizing the same valve. The ex-actuator delivered doses of the two strengths are 80 mcg, and 160 mcg, which correspond to ex-valve dose of 100 mcg, and 200 mcg, respectively. The formulations are not proportional in terms of excipients to active, since each strength contains [redacted]% ethanol but different amounts of ciclesonide ([redacted]%, and [redacted]%). There are two presentation of the finished product, 60 actuation fill for the 80 mcg product, and 60 or 120 actuation fill for the 160 mcg product. b(4)

The drug substance is manufactured in a facility in Germany. The finished dosage form is manufactured at a [redacted] Byk Gulden facilities in Germany are responsible for microbial testing, and for release and stability testing. There are no major CMC issues with the drug product. There are some minor CMC issues identified in the first cycle CMC review, which are addressed in this complete application. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. b(4)

The device submitted with the original application did not have a dose counter. The applicant has now added a canister-top mounted dose counter. The addition of the dose counter has not changed the functionality of the device, and in vitro characteristics of the delivered dose. The dose counter tended to undercount in the patient evaluation study. The functionality of the dose counter with the planned overfill is acceptable. These are discussed in detail in the CMC discipline review and in the Clinical reviews.

Nonclinical Pharmacology and Toxicology

Aventis submitted results of a complete preclinical toxicology program with the original submission, which were found to be adequate. Preclinical inhalation toxicity studies showed findings typical of corticosteroids. Early in development there was a concern regarding the potential of testicular toxicity. A dog toxicology study was reported to

have found "spermiogenic dysfunction" in animals tested with ciclesonide. On further review of the slides a panel of Pathologists convened by the company concluded that the earlier reading was an artifact. Our Pharmacology and Toxicology team accepts that conclusion. Studies addressing genotoxicity, carcinogenity, and reproductive toxicity did not show any unique finding for ciclesonide. All genotoxicity studies were negative except the in vivo mouse micronucleus test that was positive. Two-year carcinogenicity studies conducted in mice and rats with oral dosing and inhalation dosing, respectively, were negative. Reproductive toxicology studies with ciclesonide in rabbits showed some known teratogenic effects of corticosteroids. There were no unique findings with ciclesonide. The pregnancy category for ciclesonide was determined to be C, which is same category for most corticosteroids.

Clinical Pharmacology and Biopharmaceutics

The applicant submitted results from a comprehensive clinical pharmacology program with the original application. The program addressed the key clinical pharmacology and biopharmaceutics issues, such as in vitro studies to assess protein binding and metabolism, pharmacokinetic parameters after single and multiple dose, and effect of hepatic impairment. These studies were found to be adequate. There are a couple of points about ciclesonide that are worth noting. Ciclesonide is a pro-drug that is hydrolyzed by esterases to a biologically active metabolite des-ciclesonide. Des-ciclesonide has approximately a 120-fold greater affinity for the glucocorticoid receptor than the parent drug ciclesonide. Ciclesonide and des-ciclesonide have less that 1% oral bioavailability due to low gastrointestinal absorption and high first-pass metabolism. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly CYP3A4 and to a lesser extend by CYP2D6. Plasma concentrations of ciclesonide and des-ciclesonide were measured and compared following oral inhalation of Alvesco and intravenous administration of ciclesonide. The absolute bioavailability of ciclesonide was 22% and the relative systemic exposure of des-ciclesonide was 65%.

The effect of Alvesco on HPA axis was assessed in adults and adolescents and in children in several studies. Most of the studies were not acceptable for reasons stated in the clinical pharmacology review, and primary and secondary clinical reviews. Of the various studies that assessed HPA axis, study 103 was most reliable. Study 103 was randomized, double-blind, double-dummy, parallel group, and placebo-controlled in design. Study subjects were treated with Alvesco 320 mcg and 640 mcg twice daily for 29 days. HPA axis function was assessed by 24 hour urinary free cortisol. The study included a comparator corticosteroid that validates the sensitivity of the study. At the end of 29 days of treatment the mean change in 24 hour urinary free cortisol were -8.69 mcg/day, -4.01 mcg/day, and -8.84 mcg/day, for placebo, Alvesco 320 mcg twice daily, and Alvesco 640 mcg twice daily, respectively.

Clinical and Statistical

The overall characteristics of the clinical program for Alvesco were typical of a new molecular entity developed as a controller therapy for asthma. Multiple phase 3 studies

were done with a range of doses of Alvesco covering the whole spectrum of asthma severity. Characteristics of the some of the studies are shown in Table 1.

Table 1. Selected Alvesco clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Submitted with the original application							
321	Efficacy and safety	12 week	12 - 72	C 80 mcg QD C 160 mcg QD C 320 mcg QD Placebo	133 127 131 133	2002	USA
322	Efficacy and safety	12 week	12 - 79	C 80 mcg QD C 160 mcg QD C 320 mcg QD Placebo	124 123 124 116	2002	USA
323/324	Efficacy and safety	12 week	12 - 82	C 160 mcg BID C 320 mcg BID F 440 mcg BID Placebo	134 127 130 136	2002	USA
325	Efficacy and safety	12 week	12 - 74	C 320 mcg BID C 640 mcg BID Placebo	47 48 45	2003	USA, South Africa
341	Efficacy and safety	12 week	4 - 11	C 40 mcg QD C 80 mcg QD C 160 mcg QD Placebo	124 134 119 127	2003	USA, Mexico, Poland
342	Efficacy and safety	12 week	4 - 11	C 40 mcg QD C 80 mcg QD C 160 mcg QD Placebo	128 125 134 127	2003	USA, Mexico, Poland
Submitted with complete response							
3030	Efficacy and safety	12 week	12 - 79	C 160 mcg QD C 80 mcg BID Placebo	150 149 147	2005	USA
3031	Efficacy and safety	16 week	12 - 73	C 160 mcg QD C 80 mcg BID C 80/160 mcg Placebo	173 170 171 177	2007	USA, and world wide
343	Growth study	1 year	5 – 8.5	C 40 mcg QD C 160 mcg QD Placebo	221 219 221	2004	USA, South America
3027	Ocular safety	1 year	18 - 80	C 320 mcg BID BDP 320 mcg D	743 742	2005	USA, Poland, South Africa

* C = Alvesco, F = Flovent MDI. BDP = Beclomethasone MDI
# Year study subject enrollment ended

Pivotal efficacy and safety studies submitted with the original application supporting the adult and adolescent program (ages 12 years and above) consisted of two 12-week studies (Studies 321 and 322) in patients with mild-to-moderate persistent asthma, one 12-week study (Study 323/324) in patients with moderate-to-severe persistent asthma, and one 12-week study (Study 325) in patients with severe persistent asthma who were on oral

corticosteroids. In addition, there were two one-year safety follow up studies (Studies 326 and 323/324lt). Pivotal efficacy and safety studies supporting the pediatric program (ages 4 to 11 years) consisted of two 12-week studies (Studies 341 and 342). In addition there were three one-year safety follow up studies (Studies 341lt, 342lt, and 344). Studies 323 and 324 were originally intended to be two separate studies, but Aventis later combined the two studies into one study because of problems with enrollment and analyzed the results as one study (called Study 323/324). This was done with Agency concurrence.

Pivotal efficacy and safety studies submitted with the completed response consisted of one 12-week study (Study 3030) and one 16-week study (Study 3031) in patients with mild-to-moderate persistent asthma, one one-year pediatric longitudinal growth study (Study 343), and one-year ocular safety study (Study 3027).

Studies 321 and 322 (Adult 12-week efficacy and safety studies - once daily dosing)
These were multi-center, double-blind, placebo-controlled parallel group studies conducted in patients 12 years of age and older with mild-to-moderate persistent asthma. The studies were conducted in the United States. Patients satisfying the entry criteria were randomized into two strata, one stratum included patients previously maintained on inhaled bronchodilators alone and the other stratum included patients previously primarily maintained on inhaled corticosteroids. Study treatments were Alvesco 80 mcg, 160 mcg, 320 mcg, or placebo, all taken once daily in the morning for 12 weeks. The primary efficacy endpoint was change from baseline in the morning pre-dose FEV1 at the end of study (week 12) comparing Alvesco to placebo. A step-down procedure was utilized to address the issue of multiplicity related to multiple treatments. Secondary endpoints included peak flow, rescue albuterol use, symptom scores, nighttime awakening, and asthma quality of life questionnaire (AQLQ). Safety variables included recording of adverse events, physical examination, oropharyngeal examination, laboratory tests, and HPA axis assessment with a low dose (1 mg) cosyntropin stimulation test. Study 321 enrolled 526 patients and study 322 enrolled 489 patients. In both studies patients were divided approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that only Alvesco 320 mcg once daily was statistically significantly superior to placebo in each of the two studies (Table 2). According to the step-down procedure, the statistical difference of the lower doses cannot be considered to be significant if the higher dose was not significant. Numerical differences among the three doses did not show consistent dose ordering. Secondary efficacy endpoints tended in the direction of the primary endpoint, but the results were inconsistent and lacked dose ordering. Analyses of data pooled from the two studies based on the randomization strata showed that there was essentially no response to Alvesco therapy in patients previously maintained on bronchodilators (Table 3). Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 2. Mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
Study 321				
Placebo (n=133)	2.46	0.20		
Alvesco 80 mcg QD (n=133)	2.44	0.32	0.12	0.0123
Alvesco 160 mcg QD (n=127)	2.46	0.26	0.07	0.1645
Alvesco 320 mcg QD (n=131)	2.44	0.35	0.15	0.0014
Study 322				
Placebo (n=116)	2.43	0.13		
Alvesco 80 mcg QD (n=124)	2.40	0.25	0.12	0.0224
Alvesco 160 mcg QD (n=123)	2.34	0.32	0.19	0.0003
Alvesco 320 mcg QD (n=124)	2.51	0.25	0.11	0.0173

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Table 3. Study 321 and 322 pooled analysis of mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
All subjects				
Placebo (n=249)	2.45	0.17		
Alvesco 80 mcg QD (n=257)	2.42	0.28	0.12	0.0007
Alvesco 160 mcg QD (n=250)	2.40	0.29	0.13	0.0004
Alvesco 320 mcg QD (n=255)	2.48	0.31	0.14	<0.0001
Subjects previously on bronchodilators				
Placebo (n=114)	2.64	0.18		
Alvesco 80 mcg QD (n=115)	2.62	0.22	0.04	0.5133
Alvesco 160 mcg QD (n=111)	2.55	0.25	0.07	0.2025
Alvesco 320 mcg QD (n=113)	2.72	0.25	0.07	0.2136
Subjects previously on inhaled corticosteroids				
Placebo (n=135)	2.28	0.17		
Alvesco 80 mcg QD (n=142)	2.26	0.34	0.17	0.0002
Alvesco 160 mcg QD (n=139)	2.28	0.34	0.17	0.0004
Alvesco 320 mcg QD (n=142)	2.28	0.36	0.19	<0.0001

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Study 323/324 (Adult 12-week efficacy and safety study - twice daily dosing)

This was a multi-center, double-blind, placebo- and active-controlled parallel group study conducted in patients 12 years of age and older with moderate-to-severe persistent asthma who were all treated with inhaled corticosteroids prior to enrollment. The study was conducted in the United States. Study treatments were Alvesco 160 mcg twice daily, Alvesco 360 mcg twice daily, Flovent MDI 440 mcg twice daily, or placebo for 12 weeks. The primary efficacy endpoint, secondary endpoints, safety variables, and statistical analysis plans were the same as the previous studies 321 and 322. This study enrolled 531 patients divided approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that both doses of Alvesco were statistically significantly superior to placebo (Table 4). Secondary efficacy endpoints

also went in the direction of the primary endpoint. Unlike the once daily dosing studies described above, the efficacy results in this study tended to show dose ordering. The active comparator Flovent MDI also was statistically significantly superior to placebo. The effect size of Flovent tended to be numerically superior to both doses of Alvesco. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen, with the exception of lens opacification. Nuclear cataracts were reported in 1 (0.7%) of the placebo treated patients, 13 (5.1%) of Alvesco treated patients, and 2 (1.5%) of Flovent MDI treated patients in this 12-week study.

Table 4. Mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
Placebo (n=134)	1.77	0.25		
Alvesco 160 mcg BID (n=127)	1.78	0.36	0.11	0.0374
Alvesco 320 mcg BID (n=130)	1.82	0.43	0.18	0.0008
Flovent MDI 440 mcg BID (n=136)	1.77	0.50	0.24	0.0001

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Study 325 (Adult 12-week efficacy and safety study - twice daily dosing)

This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 12 years of age and older with moderate-to-severe persistent asthma who were all treated with oral corticosteroids prior to enrollment. The study was conducted in the United States and in South Africa. Study treatments were Alvesco 320 mcg twice daily, Alvesco 640 mcg twice daily, or placebo for 12 weeks. The primary efficacy endpoint was percent change from baseline in the prednisone dose at the end of study (week 12) comparing Alvesco to placebo. Secondary endpoints included changes in FEV1, peak expiratory flow, rescue albuterol use, symptom scores, and nighttime awakening. Safety parameters were the same as the previous studies. This study enrolled 141 patients divided approximately equally among the three treatment groups. Analyses of the primary efficacy endpoint showed that both doses of Alvesco were statistically superior to placebo (Table 5). Secondary efficacy endpoints also went in the direction of the primary endpoint. Unlike the once daily dosing study, the efficacy results tended to show dose ordering. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 5. Mean change from baseline in prednisone dose at week 12

	Baseline (mg)	% Change *	Difference †	p-value ‡
Placebo (n=45)	12.00	+4.21		
Alvesco 320 mcg BID (n=47)	13.59	-47.39	-51.59	0.0003
Alvesco 640 mcg BID (n=48)	11.51	-62.54	-66.75	0.0001

* LS mean change from baseline to week 12 (LOCF) in prednisone dose

† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Studies 341 and 342 (Pediatric 12-week efficacy and safety studies - once daily dosing)
The design and conduct of the studies were similar to the adult studies 321 and 322. These were also multi-center, double-blind, placebo-controlled parallel group studies. The patients enrolled were of ages 4 to 11 years and had a wide spectrum of disease severity from mild to severe persistent asthma. The study was conducted in the United States, Mexico, and Poland. As in the adult studies 321 and 322, patients in these studies were stratified based on previous medication use. One stratum included patients previously primarily maintained on inhaled bronchodilators alone and the other stratum included patients previously maintained on inhaled corticosteroids. Study treatments were Alvesco 40 mcg, 80 mcg, 160 mcg, or placebo, all taken once daily in the morning for 12 weeks. The primary efficacy endpoint, secondary endpoints, safety variables, and statistical analysis plans were the same as the adult studies 321 and 322, except that percent predicted values for the FEV1 data was used in the analysis. Study 341 enrolled 514 patients and study 342 enrolled 517 patients. In both studies patients were divided approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that only Alvesco 80 mcg once daily in study 341 and 160 mcg once daily in study 342 were statistically significantly superior to placebo (Table 6). According to the step-down procedure, the statistical difference of the lower doses cannot be considered to be significant if the higher dose was not significant. Numerical differences among the three doses did not show consistent dose ordering. Secondary efficacy endpoints tended in the direction of the primary endpoint, but the results were inconsistent and lacked dose ordering. Analyses of data pooled from the two studies based on the randomization strata showed that there was essentially no response to Alvesco therapy in patients previously maintained on inhaled corticosteroids (Table 7). This was opposite to what was seen on analyses of pooled data from the adult studies 321 and 322. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 6. Mean change from baseline in FEV1 (% predicted) at week 12

	Baseline	Change *	Difference †	p-value ‡
Study 341				
Placebo (n=127)	68.07	12.61		
Alvesco 40 mcg QD (n=124)	68.59	13.76	1.15	0.5634
Alvesco 80 mcg QD (n=134)	67.86	16.54	3.93	0.0460
Alvesco 160 mcg QD (n=119)	67.02	15.95	3.34	0.1005
Study 342				
Placebo (n=127)	69.01	8.61		
Alvesco 40 mcg QD (n=128)	68.38	9.96	1.35	0.4063
Alvesco 80 mcg QD (n=125)	68.67	10.32	1.71	0.2978
Alvesco 160 mcg QD (n=134)	69.24	12.15	3.55	0.0283

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline

	Baseline	Change *	Difference †	p-value ‡
‡ On difference between Alvesco and placebo				

Table 7. Study 341 and 342 pooled analysis of mean change from baseline in FEV1 (% predicted) at week 12

	Baseline	Change *	Difference †	p-value ‡
All subjects				
Placebo (n=254)	68.54	10.69		
Alvesco 40 mcg QD (n=252)	68.48	11.97	1.28	0.3189
Alvesco 80 mcg QD (n=259)	68.25	13.58	2.89	0.0239
Alvesco 160 mcg QD (n=253)	68.19	14.17	3.48	0.0069
Subjects previously on bronchodilators				
Placebo (n=94)	70.83	4.22		
Alvesco 40 mcg QD (n=95)	71.16	7.79	3.57	0.1007
Alvesco 80 mcg QD (n=90)	70.12	10.17	5.95	0.0070
Alvesco 160 mcg QD (n=93)	70.87	13.41	9.19	<0.0001
Subjects previously on inhaled corticosteroids				
Placebo (n=160)	67.19	15.22		
Alvesco 40 mcg QD (n=157)	66.86	15.20	-0.01	0.9932
Alvesco 80 mcg QD (n=169)	67.26	15.84	0.62	0.6930
Alvesco 160 mcg QD (n=160)	66.64	15.90	0.69	0.6677

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Study 326 and 323/324lt (Adult one-year safety studies)

Study 326 was an open-label one-year follow-up of subjects who had been enrolled in studies 321 and 322. Study 323/324lt was an open-label follow-up of subjects who were enrolled in study 323/324. Study 323/324lt used QVAR as an active comparator arm. In both studies investigators could adjust the dose of the medications with the aim of maintaining patients at the lowest dose that provided control of their asthma. The primary objective of the studies was to assess safety. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Studies 341lt, 342lt, and 344 (Pediatric one-year safety studies)

Studies 341lt and 342lt were open-label one-year follow-up of subjects who had been enrolled in studies 341 and 342. In study 344 new subjects who have not been enrolled in the shorter term studies were recruited. Flovent MDI was used as an active comparator. As in the adult studies, the dose of study medication could be titrated to maintain adequate asthma control. The primary objective of the studies was to assess safety. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Study 3030 (Adult 12-week efficacy and safety study – once daily and twice daily dosing)

This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 12 years of age and older with mild-to-moderate persistent asthma who were treated with inhaled corticosteroids prior to enrollment. The study was conducted in the United States. Study treatments were Alvesco 80 mcg twice daily, 160 mcg once daily, or placebo for 12 weeks. The primary efficacy endpoint was change from baseline in the morning pre-dose FEV1 at the end of study (week 12) comparing Alvesco to placebo. A step-down procedure was utilized to address the issue of multiplicity related to multiple treatments. Secondary endpoints included peak flow, rescue albuterol use, symptom scores, and nighttime awakening. Safety variables included recording of adverse events, physical examination, oropharyngeal examination, and laboratory tests. The study enrolled 456 patients divided approximately equally among the three treatment groups. Analyses of the primary efficacy endpoint showed that both Alvesco treatment groups were statistically significantly superior to placebo (Table 8). Alvesco 80 mcg twice daily was numerically superior to Alvesco 160 mcg once daily. Secondary efficacy endpoints tended in the direction of the primary endpoint. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 8. Mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
Placebo (n=147)	2.63	- 0.12		
Alvesco 160 mcg QD (n=150)	2.64	0.01	0.14	0.0006
Alvesco 80 mcg BID (n=149)	2.67	0.07	0.19	<0.0001

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Study 3031 (Adult 16-week efficacy and safety study – once daily and twice daily dosing)

This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 12 years of age and older with mild-to-moderate persistent asthma who were treated with inhaled bronchodilators only prior to enrollment. The study was an international study with centers located in the United States, Brazil, Israel, Russia, Poland, Mexico, Costa Rica, Puerto Rico, Chile, Estonia, and Latvia. Study treatments were Alvesco 80 mcg twice daily for 16 weeks, 160 mcg once daily for 16 weeks, 80 mcg twice daily for 4 weeks then 160 mcg once daily for 12 weeks, or placebo. The primary efficacy endpoint was change from baseline in the average morning pre-dose FEV1 at weeks 12 and 16 comparing Alvesco to placebo. A step-down procedure was utilized to address the issue of multiplicity related to multiple treatments. Secondary endpoints included peak flow, rescue albuterol use, symptom scores, and nighttime awakening. Safety variables included recording of adverse events, physical examination, oropharyngeal examination, and laboratory tests. The study enrolled 708 patients divided

approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that all Alvesco treatment groups were statistically significantly superior to placebo (Table 9). Alvesco 80 mcg BID was numerically and statistically superior to Alvesco 160 mcg QD. Secondary efficacy endpoints tended in the direction of the primary endpoint. Review of the safety data showed that all doses of Alvesco were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 9. Mean change from baseline in FEV1 (liters) at week 16

	Baseline	Change *	Difference †	p-value ‡
Placebo (n=177)	2.45	0.06		
Alvesco 160 mcg QD (n=173)	2.54	0.19	0.12	0.002
Alvesco 80 mcg BID (n=170)	2.49	0.30	0.24	<0.001
Alvesco 80 mcg BID > 160 mcg QD (n=171)	2.39	0.19	0.13	0.002

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between Alvesco and placebo on change from baseline
‡ On difference between Alvesco and placebo

Study 343 (Pediatric one-year growth study)

This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 5 to below 8.5 years of age with mild persistent asthma. The study was conducted in the United States, Argentina, Chile and Venezuela. Study treatments were Alvesco 40 mg once daily, 160 mcg once daily, and placebo for 52 weeks. The primary evaluation was height measured using standard stadiometry. Other assessment included spirometry, physical examination, recording of adverse events, and 24-hour urine for cortisol in a subgroup of patients. The primary endpoint was growth velocity during the double-blind treatment period. The primary analysis was non-inferiority of Alvesco on growth velocity compared to placebo with a non-inferiority delta of -0.5 cm/year. The study enrolled 661 patients divided approximately equally among the three treatment groups. Analysis of the growth data are shown in Table 10. The lower bounds of the 2-sided 95% CI of the difference of growth rates between Alvesco and placebo were within -0.5 cm/yr, but the difference for the higher dose was statistically significant. The overall validity of the study results is questionable because compliance of the study patients to medication could not be assured. The study was conducted in mild asthma patients who may or may not have required using inhaled corticosteroid for the whole year. There was no difference in efficacy measures, such as FEV1, that could assure compliance. Furthermore, ciclesonide blood levels were also not measured in the study.

Table 10. Growth velocity comparing active treatment to placebo

	Growth rate (cm/yr)	Difference from placebo Mean	95% CI	p-value
Placebo (n=201)	5.83			
Alvesco 40 mcg QD (n=206)	5.85	0.02	- 0.18, 0.21	0.870
Alvesco 160 mcg QD (n=202)	5.62	- 0.21	- 0.41, - 0.02	0.032

Study 3027 (Adult one-year ocular safety study)
This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 18 to below 80 years of age with moderate to severe. The study was conducted in the United States, Poland, and South Africa. Study treatments were Alvesco 640 mcg per day taking twice daily, and beclomethasone 640 mcg per day taking twice daily for 52 weeks. The primary evaluation was lens opacification graded using the Lens Opacification System (LOCS) III classification. Other assessments included visual acuity, intraocular pressure measurement, slit lamp examination of the eye, and spirometry. The study enrolled 1568 patients divided approximately equally to the two treatment arms. The incidence of lens opacification and other eye examination findings were similar in the two corticosteroid treatment groups suggesting that ocular safety risk of ciclesonide is not markedly different than beclemethasone.

Summary efficacy findings:
Clinical studies as reviewed above assessed the efficacy of various doses and dosing frequencies covering the full spectrum of persistent asthma severity. Based on enrollment criteria or on stratification at randomization, patients studied in the program can be grouped into three severity categories classified according to previous asthma treatment – patients on bronchodilators, patients on inhaled corticosteroids, and patients on oral corticosteroids. For an orally inhaled corticosteroid it is expected that the drug should be indicated for the full spectrum of asthma severity, with different dosing recommendations for differing disease severity. The clinical development program for Alvesco addressed this. The primary efficacy endpoint results from the pivotal studies in the three asthma severity categories are summarized in Table 11. Studies that support a specific dosing regimen based on statistically significant difference in the primary efficacy endpoint between treatment and placebo are bolded in the table.

Efficacy findings with Alvesco in general were not robust and not consistent. For adults and adolescent patients 12 years of age and older there were six pivotal efficacy studies (321, 322, 323/324, 3030, 3031, and 325). Two studies that assessed only once daily dosing frequency (321, and 322) failed to show consistent efficacy. Four studies that assessed twice daily dosing frequency (323/324, 3030, 3031, and 325) showed consistent efficacy in all three severity categories classified according to previous asthma treatment. The increase in trough FEV1 with ciclesonide over placebo ranged from 0.11 to 0.24 liter, which appears to be somewhat low for an inhaled corticosteroid. For pediatric patients 4 to 11 years of age there were two pivotal efficacy studies (341, and 342). Both studies assessed only once daily dosing frequency and failed to show consistent efficacy. The overall data support the use of Alvesco in patients 12 years of age and older at doses ranging from 80 mcg twice daily to 320 mcg twice daily based on asthma severity. b(5) b(4) Studies in patients below 12 years of age only explored once daily dosing, a dosing regimen that was not found to optimum in patients 12 year of and older.

Table 11. Efficacy support of various dosing regimens in the pivotal studies

Previous therapy	Difference between ciclesondie and placebo at study endpoint [study number]							
	40 QD	80 QD	80 BID	160 QD	320 QD	160 BID	320 BID	640 BID
Inhaled bronchodilator	3.57 * [341/342]	**5.95** * [341/342]		**9.19** * [34/342]				
		0.04 † [321/322]		0.07 † [321/322]	0.07 † [321/322]			
			0.24 † [3031]	**0.12** † [3031]				
Inhaled corticosteroid	-0.01* [341/342]	0.62 * [341/342]		0.69 * [341/342]				
		0.17 † [321/322]		**0.17** † [321/322]	**0.19** † [321/322]			
						0.11 † [323/324]	**0.18** † [323/324]	
			0.19 † [3030]	**0.14** † [3030]				
Oral corticosteroid							**-51.6** § [325]	**-66.7** § [325]

* FEV1 in % predicted – studies in patients 4 to 11 years of age
† FEV1 in liters – studies in patients 12 years of age and older
§ Percent change from baseline in prednisone dose – study in patients 12 years of age and older

Studies where the primary endpoint was statistically significantly superior to placebo are bolded

Summary safety findings:

Relevant safety data for patients 12 years of age and older come from studies where patients were dosed with Alvesco twice daily. These include four studies 12 to 16 weeks in duration (3030, 3031, 323/324, 325, and 102), and one year extension of study 323/324. Study 102 is a 12 week pharmacodynamic study compared ciclesonide to placebo and to fluticasone. In addition the dedicated one year ocular study to assess lens opacification (study 3027) also provides useful safety information. Adverse events that occurred more frequently in the Alvesco treatment arms than the placebo arm were typical events seen with orally inhaled corticostoroids. Oral candiadiasis was noted to occur, mostly in patients treated with higher doses of Alvesco. Clinically significant HPA axis suppression was not seen in the clinical studies or specific HPA axis studies. The specific ocular safety study showed that ocular safety risk of ciclesonide is not markedly different that beclemethasone. The ocular safety study was done to further clarify the finding lens opacification seen in study 323/324 as discussed above.

Safety database for pediatric patients 4 to 11 years of age include two studies 12 weeks in duration (341, and 342), two open-label one year extension of the two studies. Findings from these studies are limited because Alvesco was dosed once daily, which was not efficacious. In addition the applicant conducted a one-year linear growth study in pediatric patients 5 to 8.5 years of age, but the finding from the study is limited because compliance to study medication was not assured.

Data Quality, Integrity, and Financial Disclosure

DSI audited six study sites that participated in the phase 3 studies that were submitted with the original application. Four of these sites were suggested for audit by the Division. Three sites were suggested because of high enrollment, and one site was suggested because of the death of a 12 year old patient enrolled in that site. Two additional sites were selected by the DSI in response to previous complaints that DSI received. The DSI audit concluded that all of these sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Minor deviations were noted in two sites, but these were not of a magnitude that would impact the conclusions of the studies. No DSI audit was done for the studies that were submitted with the complete response. During review of the submission no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. Four investigators involved in studies that were submitted with the original application and six investigator involved in studies that were submitted with the complete response had significant financial conflict of interest with Aventis. This was not considered to be of concern because these investigators in total contributed only a small number of patients to the phase 3 program.

Pediatric Considerations

The current development program for Alvesco studied patients 4 years of age and older. The applicant requested deferral of studies in patients below 4 years of age and waiver of studies below 6 months of age. Deferral of studies for ages 6 months to 4 years are appropriate because the effective dose and dosing regiment for Alvesco in patients 4 to 11 years of age has not yet been established. The applicant's choice of the lower age bound of 4 years for initial pediatric studies is reasonable for a press-and-breathe corticosteroid MDI. Patients 4 years of age and older generally can use such a device without a spacer. Unfortunately the applicant studied only once daily dosing frequency, which was not found to optimum in patients 12 year of and older. b(5)

b(4)

Waiver of studies below 6 months of age is appropriate because asthma does not exist or is difficult to diagnose in children below 6 moths of age.

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including orally inhaled corticosteroids. The applicant conducted a one-year linear growth study with Alvesco in pediatric patients 5 to 8.5 years of age, but the finding from the study is limited because compliance to study medication was not assured. The applicant will not be asked to conduct another grow study because a study has already been done. The labeling of Alvesco will contain description of the growth

study noting its limitation, and the labeling will contain statements similar to other inhaled corticosteroids stating that Alvesco may cause a reduction in growth velocity in pediatric patients.

Product Name
The proposed product name Alvesco was reviewed by DMETS of OSE and found to be acceptable. The review team of this Division and DDMAC also finds the trade name acceptable.

Labeling
The applicant submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label are recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have agreed to the final version of the label

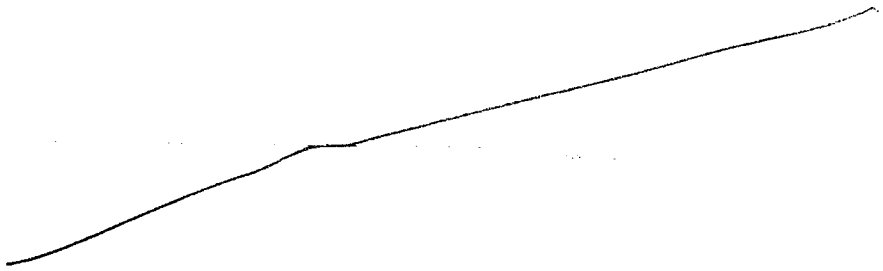
Action and Risk Benefit Assessment
The applicant has submitted adequate data to support approval of Alvesco (ciclesonide) Inhalation Aerosol for maintenance treatment of asthma in adults and adolescent patients 12 years of age and older. [redacted] b(4)
[redacted] The action on this application would be APPROVAL specific to the ages 12 years and above.

The overall risk benefit assessment supports approval of Alvesco (ciclesonide) Inhalation Aerosol for maintenance treatment of asthma in patients 12 years of age and older. Efficacy was consistently demonstrated at doses ranging from 80 mcg to 320 mcg twice daily in patients with varying asthma severity. At the recommended doses the safety findings were consistent with other orally inhaled corticosteroids for asthma. There are no post-marketing risk management activities. The pediatric efficacy and safety studies [redacted]

For administrative reasons : [redacted] b(4)
[redacted], which is consistent with the previous approvable action for this application.

b(5)

[redacted]



b(5)

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/s/

Badrul Chowdhury
1/10/2008 10:18:41 AM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: October 20, 2004

To: NDA 21-658

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Alvesco (ciclesonide) Inhalation Aerosol — mcg, 80 mcg, 160 mcg

Applicant: Aventis Pharmaceuticals Inc.

Administrative and Introduction

Aventis submitted a 505(b)(1) new drug application (NDA 21-658) on December 22, 2003, for Alvesco (ciclesonide) Inhalation Aerosol — mcg, 80 mcg, and 160 mcg for use in patients ——— and older with asthma. The PDUFA due date on this application is October 23, 2004. The proposed indication is maintenance treatment of asthma as prophylactic therapy in adult ———————————
The proposed indication covers the whole range of asthma severity as defined by prior asthma therapy. b(4)

b(4)

The drug development program for Alvesco was initially carried out by Byk Gulden with Altana as the US representative. Aventis later assumed the development program and conducted the entire phase 3 program. The submitted data from the clinical program did not demonstrate convincing evidence of efficacy to fully support the proposed indication and the dosing regimen. There are also some minor CMC deficiencies that Aventis will need to address before the application can be approved.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance ciclesonide is a non-halogenated glucocorticoid that is not marketed in the United States in any dosage form. Alvesco is a solution formulation of ciclesonide in —dehydrated ethanol with HFA-134a as the propellant (similar to ——— Inhalation Aerosol). The device contains a standard valve and canister with a standard press-and-breathe actuator. A dose counter ——————————. The inhaler is formulated in — strengths, with all —→ strengths utilizing the same valve. The ex-actuator delivered dose of the — strengths are — mcg, 80 mcg, and 160 mcg, which correspond to ex-valve dose of — mcg, 100 mcg, and 200 mcg, respectively. The b(4)

formulations are [redacted] in terms of excipients to active, since each strength contains [redacted] ethanol [redacted] b(4)
There are two presentation of the finished product for each strength, one with [redacted] actuation fill and the other with 120 actuation fill. The various DMFs associated with the manufacture of the product are adequate. The drug substance is manufactured in a facility in Germany. The finished dosage form is manufactured at a [redacted] Byk Gulden facilities in Germany are responsible for [redacted] There are no major CMC issues with the b(4)
drug product. There are some minor CMC issues that are summarized in Dr. Shaw's review. The minor CMC issues alone would not have held up an approval action, but could have been dealt with via agreements. The [redacted], was not inspected by the Agency within the review period. Since the application is not heading towards an approval because of major clinical deficiencies that will take many months to perhaps years to address, completion of the inspection is not critical.

Clinical and Statistical
The overall characteristics of the clinical program for Alvesco were typical of a new molecular entity developed as a controller therapy for asthma. Multiple phase 3 studies were done with a range of doses of Alvesco covering the whole spectrum of asthma severity. Detailed review of the clinical program can be found in Dr. Bosken's medical review and in Dr. Gilbert-McClain's team leader memorandum. Pivotal phase 3 studies that have direct bearing on the approvability of this application are briefly commented on in the following sections.

Pivotal efficacy and safety studies supporting the adult and adolescent program (ages 12 years and above) consisted of two 12-week studies (Studies 321 and 322) in patients with mild-to-moderate persistent asthma, one 12-week study (Study 323/324) in patients with moderate-to-severe persistent asthma, and one 12-week study (Study 325) in patients with severe persistent asthma who were on oral corticosteroids. In addition, there were two one-year safety follow up studies (Studies 326 and 323/324lt). Pivotal efficacy and safety studies supporting the pediatric program (ages 4 to 11 years) consisted of two 12-week studies (Studies 341 and 342). In addition there were three one-year safety follow up studies (Studies 341lt, 342lt, and 344). Studies 323 and 324 were originally intended to be two separate studies, but Aventis later combined the two studies into one study because of problems with enrollment and analyzed the results as one study (called Study 323/324). This was done with Agency concurrence. Ciclesonide dosing regimen in the adult studies 321, 322, and in the pediatric studies 341 and 342 was once daily. Dosing regimen in the adult studies 324/324 and 325 was twice daily. There was no study that compared once daily dosing to a higher dosing frequency giving the same total daily dose.

<u>Studies 321 and 322 (Adult 12-week efficacy and safety studies - once daily dosing)</u>
These were multi-center, double-blind, placebo-controlled parallel group studies conducted in patients 12 years of age and older with mild-to-moderate persistent asthma. The studies were conducted in the United States. Patients satisfying the entry criteria

were randomized into two strata, one stratum included patients previously maintained on inhaled bronchodilators alone and the other stratum included patients previously maintained on inhaled corticosteroids. Study treatments were ciclesonide 80 mcg, 160 mcg, 320 mcg, or placebo, all taken in the morning for 12 weeks. The primary efficacy endpoint was change from baseline in the morning pre-dose FEV1 at the end of study (week 12) comparing ciclesonide to placebo. A step-down procedure was utilized to address the issue of multiplicity related to multiple treatments. Secondary endpoints included peak flow, rescue albuterol use, symptom scores, nighttime awakening, and asthma quality of life questionnaire (AQLQ). Safety variables included recording of adverse events, physical examination, oropharyngeal examination, laboratory tests, and HPA axis assessment with a low dose (1 mg) cosyntropin stimulation test. Study 321 enrolled 526 patients and study 322 enrolled 489 patients. In both studies patients were divided approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that only ciclesonide 320 mcg once daily was statistically significantly superior to placebo in each of the two studies (Table 1). According to the step-down procedure, the statistical difference of the lower doses cannot be considered to be significant if the higher dose was not significant. Numerical differences among the three doses did not show consistent dose ordering. Secondary efficacy endpoints tended in the direction of the primary endpoint, but the results were inconsistent and lacked dose ordering. Analyses of data pooled from the two studies based on the randomization strata showed that there was essentially no response to ciclesonide therapy in patients previously maintained on bronchodilators (Table 2). Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 1. Mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
Study 321				
Placebo (n=133)	2.46	0.20		
Ciclesonide 80 mcg QD (n=133)	2.44	0.32	0.12	0.0123
Ciclesonide 160 mcg QD (n=127)	2.46	0.26	0.07	0.1645
Ciclesonide 320 mcg QD (n=131)	2.44	0.35	0.15	0.0014
Study 322				
Placebo (n=133)	2.43	0.13		
Ciclesonide 80 mcg QD (n=124)	2.40	0.25	0.12	0.0224
Ciclesonide 160 mcg QD (n=123)	2.34	0.32	0.19	0.0003
Ciclesonide 320 mcg QD (n=124)	2.51	0.25	0.11	0.0173

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between ciclesonide and placebo on change from baseline
‡ On difference between ciclesonide and placebo

Table 2. Study 321 and 322 pooled analysis of mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
All subjects				
Placebo (n=249)	2.45	0.17		
Ciclesonide 80 mcg QD (n=257)	2.42	0.28	0.12	0.0007

	Baseline	Change *	Difference †	p-value ‡
Ciclesonide 160 mcg QD (n=250)	2.40	0.29	0.13	0.0004
Ciclesonide 320 mcg QD (n=255)	2.48	0.31	0.14	<0.0001
Subjects previously on bronchodilators				
Placebo (n=114)	2.64	0.18		
Ciclesonide 80 mcg QD (n=115)	2.62	0.22	0.04	0.5133
Ciclesonide 160 mcg QD (n=111)	2.55	0.25	0.07	0.2025
Ciclesonide 320 mcg QD (n=113)	2.72	0.25	0.07	0.2136
Subjects previously on inhaled corticosteroids				
Placebo (n=135)	2.28	0.17		
Ciclesonide 80 mcg QD (n=142)	2.26	0.34	0.17	0.0002
Ciclesonide 160 mcg QD (n=139)	2.28	0.34	0.17	0.0004
Ciclesonide 320 mcg QD (n=142)	2.28	0.36	0.19	<0.0001

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between ciclesonide and placebo on change from baseline
‡ On difference between ciclesonide and placebo

Study 323/324 (Adult 12-week efficacy and safety study - twice daily dosing)
This was a multi-center, double-blind, placebo- and active-controlled parallel group study conducted in patients 12 years of age and older with moderate-to-severe persistent asthma who were all treated with inhaled corticosteroids prior to enrollment. The study was conducted in the United States. Study treatments were ciclesonide 160 mcg twice daily, ciclesonide 360 mcg twice daily, Flovent MDI 440 mcg twice daily, or placebo for 12 weeks. The primary efficacy endpoint, secondary endpoints, safety variables, and statistical analysis plans were the same as the previous studies 321 and 322. This study enrolled 531 patients divided approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that both doses of ciclesonide were statistically significantly superior to placebo (Table 3). Secondary efficacy endpoints also went in the direction of the primary endpoint. Unlike the once daily dosing studies described above, the efficacy results in this study tended to show dose ordering. The active comparator Flovent MDI also was statistically significantly superior to placebo. The effect size of Flovent tended to be numerically superior to both doses of ciclesonide. Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen, with the exception of lens opacification. Nuclear cataracts were reported in 1 (0.7%) of the placebo treated patients, 13 (5.1%) of ciclesonide treated patients, and 2 (1.5%) of Flovent MDI treated patients in this 12-week study.

Table 3. Mean change from baseline in FEV1 (liters) at week 12

	Baseline	Change *	Difference †	p-value ‡
Placebo (n=134)	1.77	0.25		
Ciclesonide 160 mcg BID (n=127)	1.78	0.36	0.11	0.0374
Ciclesonide 320 mcg BID (n=130)	1.82	0.43	0.18	0.0008
Flovent MDI 440 mcg BID (n=136)	1.77	0.50	0.24	0.0001

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between ciclesonide and placebo on change from baseline

	Baseline	Change *	Difference †	p-value ‡
‡ On difference between ciclesonide and placebo				

Study 325 (Adult 12-week efficacy and safety study - twice daily dosing)
This was a multi-center, double-blind, placebo-controlled parallel group study conducted in patients 12 years of age and older with moderate-to-severe persistent asthma who were all treated with oral corticosteroids prior to enrollment. The study was conducted in the United States and in South Africa. Study treatments were ciclesonide 320 mcg twice daily, ciclesonide 640 mcg twice daily, or placebo for 12 weeks. The primary efficacy endpoint was percent change from baseline in the prednisone dose at the end of study (week 12) comparing ciclesonide to placebo. Secondary endpoints included changes in FEV1, peak expiratory flow, rescue albuterol use, symptom scores, and nighttime awakening. Safety parameters were the same as the previous studies. This study enrolled 141 patients divided approximately equally among the three treatment groups. Analyses of the primary efficacy endpoint showed that both doses of ciclesonide were statistically superior to placebo (Table 4). Secondary efficacy endpoints also went in the direction of the primary endpoint. Unlike the once daily dosing study, the efficacy results tended to show dose ordering. Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 4. Mean change from baseline in prednisone dose at week 12

	Baseline (mg)	% Change *	Difference †	p-value ‡
Placebo (n=45)	12.00	+4.21		
Ciclesonide 320 mcg BID (n=47)	13.59	-47.39	-51.59	0.0003
Ciclesonide 640 mcg BID (n=48)	11.51	-62.54	-66.75	0.0001
* LS mean change from baseline to week 12 (LOCF) in prednisone dose † LS mean difference between ciclesonide and placebo on change from baseline ‡ On difference between ciclesonide and placebo				

Studies 341 and 342 (Pediatric 12-week efficacy and safety studies - once daily dosing)
The design and conduct of the studies were similar to the adult studies 321 and 322. These were also multi-center, double-blind, placebo-controlled parallel group studies. The patients enrolled were of ages 4 to 11 years and had a wide spectrum of disease severity from mild to severe persistent asthma. The study was conducted in the United States, Mexico, and Poland. As in the adult studies 321 and 322, patients in these studies were stratified based on previous medication use. One stratum included patients previously maintained on inhaled bronchodilators alone and the other stratum included patients previously maintained on inhaled corticosteroids. Study treatments were ciclesonide 40 mcg, 80 mcg, 160 mcg, or placebo, all taken in the morning for 12 weeks. The primary efficacy endpoint, secondary endpoints, safety variables, and statistical analysis plans were the same as the adult studies 321 and 322, except that percent predicted values for the FEV1 data was used in the analysis. Study 341 enrolled 526 patients and study 342 enrolled 517 patients. In both studies patients were divided

approximately equally among the four treatment groups. Analyses of the primary efficacy endpoint showed that only ciclesonide 160 mg once daily was statistically significantly superior to placebo in one of the two studies (Table 5). According to the step-down procedure, the statistical difference of the lower doses cannot be considered to be significant if the higher dose was not significant. Numerical differences among the three doses did not show consistent dose ordering. Secondary efficacy endpoints tended in the direction of the primary endpoint, but the results were inconsistent and lacked dose ordering. Analyses of data pooled from the two studies based on the randomization strata showed that there was essentially no response to ciclesonide therapy in patients previously maintained on inhaled corticosteroids (Table 5). This was opposite to what was seen on analyses of pooled data from the adult studies 321 and 322. Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Table 5. Mean change from baseline in FEV1 (% predicted) at week 12

	Baseline	Change *	Difference †	p-value ‡
Study 341				
Placebo (n=127)	68.07	12.61		
Ciclesonide 40 mcg QD (n=124)	68.59	13.76	1.15	0.5634
Ciclesonide 80 mcg QD (n=134)	67.86	16.54	3.93	0.0460
Ciclesonide 160 mcg QD (n=119)	67.02	15.95	3.34	0.1005
Study 342				
Placebo (n=127)	69.01	8.61		
Ciclesonide 40 mcg QD (n=128)	68.38	9.96	1.35	0.4063
Ciclesonide 80 mcg QD (n=125)	68.67	10.32	1.71	0.2978
Ciclesonide 160 mcg QD (n=134)	69.24	12.15	3.55	0.0283

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between ciclesonide and placebo on change from baseline
‡ On difference between ciclesonide and placebo

Table 6. Study 341 and 342 pooled analysis of mean change from baseline in FEV1 (% predicted) at week 12

	Baseline	Change *	Difference †	p-value ‡
All subjects				
Placebo (n=254)	68.54	10.69		
Ciclesonide 40 mcg QD (n=252)	68.48	11.97	1.28	0.3189
Ciclesonide 80 mcg QD (n=259)	68.25	13.58	2.89	0.0239
Ciclesonide 160 mcg QD (n=253)	68.19	14.17	3.48	0.0069
Subjects previously on bronchodilators				
Placebo (n=94)	70.83	4.22		
Ciclesonide 40 mcg QD (n=95)	71.16	7.79	3.57	0.1007
Ciclesonide 80 mcg QD (n=90)	70.12	10.17	5.95	0.0070
Ciclesonide 160 mcg QD (n=93)	70.87	13.41	9.19	<0.0001
Subjects previously on inhaled corticosteroids				
Placebo (n=160)	67.19	15.22		
Ciclesonide 40 mcg QD (n=157)	66.86	15.20	-0.01	0.9932
Ciclesonide 80 mcg QD (n=169)	67.26	15.84	0.62	0.6930

	Baseline	Change *	Difference †	p-value ‡
Ciclesonide 160 mcg QD (n=160)	66.64	15.90	0.69	0.6677

* LS mean change from baseline to week 12 (LOCF) in pre-dose AM FEV1
† LS mean difference between ciclesonide and placebo on change from baseline
‡ On difference between ciclesonide and placebo

Study 326 and 323/324lt (Adult one-year safety studies)
Study 326 was an open-label one-year follow-up of subjects who had been enrolled in studies 321 and 322. Study 323/324lt was an open-label follow-up of subjects who were enrolled in study 323/324. Study 323/324lt used QVAR as an active comparator arm. In both studies investigators could adjust the dose of the medications with the aim of maintaining patients at the lowest dose that provided control of their asthma. The primary objective of the studies was to assess safety. Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Studies 341lt, 342lt, and 344 (Pediatric one-year safety studies)
Studies 341lt and 342lt were open-label one-year follow-up of subjects who had been enrolled in studies 341 and 342. In study 344 new subjects who have not been enrolled in the shorter term studies were recruited. Flovent MDI was used as an active comparator. As in the adult studies, the dose of study medication could be titrated to maintain adequate asthma control. The primary objective of the studies was to assess safety. Review of the safety data showed that all doses of ciclesonide were well tolerated in the studies. Adverse events were consistent with the inhaled corticosteroid class of drugs. There were no unique safety signals seen.

Summary efficacy conclusion and safety findings:
Clinical studies as reviewed above assessed the efficacy of various dosage regimens of ciclesonide covering the full spectrum of persistent asthma severity. Based on enrollment criteria or on stratification at randomization, patients studied in the program can be grouped into three severity categories classified according to previous asthma treatment – patients on bronchodilators alone, patients on inhaled corticosteroids, and patients on oral corticosteroids. The proposed dosage and administration section of the label follows this scheme of classifying asthma severity based on prior treatment. For an orally inhaled corticosteroid it is expected that the drug should be indicated for the full spectrum of asthma severity, with different dosing recommendations for differing disease severity. The clinical development program for ciclesonide attempted to address this. The dosing regimen studied in the three asthma severity categories are summarized in Table 7. Studies that support a specific dosing regimen based on statistically significant difference in the primary efficacy endpoint between treatment and placebo are highlighted in the table. It is quite clear that ciclesonide was not shown to be effective for the full range of asthma severity at the doses and dosing frequency studied. Convincing efficacy was not demonstrated for any doses in the pediatric age group. The dosing frequency studied in

the pediatric age group was once daily only. Of the two dosing frequencies studied in the adult and adolescent patients, the twice daily regimen appeared to show consistent efficacy at the doses and in the population studied, but the once daily regimen dose did not. The dosing regimens that showed replicated efficacy in adults and adolescent patients were the 320 mcg twice daily and the 320 mcg once daily in patients with moderate to severe asthma. Although the 320 mcg once daily dose was statistically significantly superior to placebo, it is difficult to conclude that once daily dosing frequency is the correct way to administer this drug when no study has compared the same total daily dose given once daily to a more frequent dosing, such as twice daily. From the clinical program, it appears that for ciclesonide twice daily would be more appropriate than once daily dosing, a finding that has been seen for other inhaled corticosteroids, such as fluticasone and budesonide.

Aventis will need to conduct clinical studies to further explore and establish the benefit of various dosing frequencies and perhaps even different doses of ciclesonide. If once daily dosing is shown to be most appropriate for ciclesonide, then doses higher than 320 mcg will need to be explored because 320 mcg once daily appeared to be the lowest effective dose. However, prior regulatory experience would predict that the same nominal daily dose given in divided doses will be more effective than when given once a day with no safety disadvantage. Therefore, the expectation is that a twice daily regimen would be more likely to show benefit at lower doses and therefore be the favored dose regimen. The clinical program generally showed that ciclesonide is an effective drug for the treatment of asthma, which is not surprising for a pharmacologically active corticosteroid, but Aventis needs to conduct further clinical studies to identify the correct doses and dosing frequencies for the full spectrum of asthma in adults and in pediatric patients.

Table 7. Efficacy support of various dose regimens from the pivotal studies

Previous therapy	Active treatment arms, doses in mcg						
	40 QD	80 QD	160 QD	320 QD	160 BID	320 BID	640 BID
Inhaled bronchodilator	341 †	341 †	341 †				
	342 †	342 †	**342** †				
		321	321	321			
		322	322	322			
Inhaled corticosteroid	341 †	341 †	341 †				
	342 †	342 †	342 †				
		321	321	**321**			
		322	322	**322**			
					323/324	**323/324**	
Oral corticosteroid						**325**	**325**

* Studies where the primary endpoint was statistically significantly superior to placebo are bolded and underlined
† Pediatric studies

All doses of ciclesonide studied in the pivotal efficacy and safety studies were generally well tolerated. Adverse events that occurred more frequently in the ciclesonide treatment

arms than the placebo arm were typical events seen with orally inhaled corticostoroids. Oral candiadiasis was uncommon, but did occur in patients treated with higher doses.

Aventis studied the effect of ciclesonide on the HPA axis fairly extensively, including assessing HPA axis in phase 1, 2 and 3 studies. Based on population PK/PD analysis using data from phase 1 and phase 2 studies, there was a trend for higher doses of ciclesonide to suppress the HPA axis. At doses of 800 mcg, 1200 mcg, and 1600 mcg, serum cortisol AUC suppression was 13%, 8%, and 49%, respectively. In the phase 3 clinical studies HPA axis was assessed in a subset of patients using a low dose (1 mg) cosyntropin stimulation test. There was no remarkable change in post-stimulation serum cortisol after 12-week or 1-year of treatment with ciclesonide. Aventis also conducted multiple pharmacodynamic studies to specifically assess the HPA axis of ciclesonide. In some of these studies high dose fluticasone administered by the orally inhaled route was included as active comparator. The studies generally showed lack of HPA axis effect with ciclesonide at the proposed clinical doses. In some of the studies the numerical trend was in favor of ciclesonide compared to fluticasone. No comparative HPA axis safety conclusion can be made from these studies, because Aventis did not study equally effective doses of ciclesonide and fluticasone. The doses of fluticasone chosen were relatively high doses and would be expected to be more efficacious than the ciclesonide doses studied.

There were no unique safety signals seen with ciclesonide with the exception of lens opacification seen in study 323/324 as discussed above. Study 323/324 was not specifically designed to evaluate cataracts and there were some question as how the data were gathered, but the finding was nevertheless of concern because corticosteroids are known as a class to affect the ocular lens. Of note, one year long data from studies also not designed to study ophthalmic safety were reassuring. In any case, based on prior communication with the Division, Aventis has already initiated a one-year clinical study specifically designed to assess the effect of Alvesco on the eyes.

Clinical Pharmacology and Biopharmaceutics

Aventis submitted results from a fairly comprehensive clinical pharmacology program in support of the application. The program addressed the key clinical pharmacology and biopharmaceutics issues, such as in vitro studies to assess protein binding and metabolism, pharmacokinetic parameters after single and multiple dose, and effect of hepatic impairment. These studies were reviewed in detail in Dr. Suarez's review and were found to be adequate. There are a couple of points about ciclesonide that are worth noting. Ciclesonide is a pro-drug that is hydrolyzed by esterases to its active metabolite RM1, which is also a glucocorticoid. RM1 has approximately a 100-fold greater affinity for the glucocorticoid receptor than the parent drug. The esterases involved in the hydrolysis of ciclesonide to RM1 are not identified. RM1 appears to be predominately metabolized by CYP3A4 (about 83%), and to a lesser extend by CYP2D6 and CYP2C8. Both ciclesonide and RM1 are rapidly absorbed from the lung. Bioavailability of ciclesonide+RM1 following inhalation of ciclesonide was about 41%.

Pharmacology and Toxicology

Aventis submitted results of a complete preclinical toxicology program with this submission. These were reviewed in detail by Dr. Hao and were found to be adequate. Preclinical inhalation toxicity studies showed findings typical of corticosteroids. Early in development there was a concern regarding the potential of testicular toxicity. A dog toxicology study was reported to have found "spermiogenic dysfunction" in animals tested with ciclesonide. On further review of the slides a panel of Pathologists convened by the company concluded that the earlier reading was an artifact. Our Pharmacology and Toxicology team accepts that conclusion. Studies addressing genotoxicity, carcinogenity, and reproductive toxicity did not show any unique finding for ciclesonide. All genotoxicity studies were negative except the in vivo mouse micronucleus test that was positive. Two-year carcinogenicity studies conducted in mice and rats with oral dosing and inhalation dosing, respectively, were negative. Reproductive toxicology studies with ciclesonide in rabbits showed some known teratogenic effects of corticosteroids. There were no unique findings with ciclesonide. The pregnancy category for Alvesco was determined to be C, which is same category for many other corticosteroids.

Data Quality, Integrity, and Financial Disclosure

DSI audited six study sites that participated in the phase 3 studies. Four of these sites were suggested for audit by the Division. Three sites were suggested because of high enrollment, and one site was suggested because of the death of a 12 year old patient enrolled in that site. Two additional sites were selected by the DSI in response to previous complaints that DSI received. The DSI audit concluded that all of these sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Minor deviations were noted in two sites, but these were not of a magnitude that would impact the conclusions of the studies. During review of the submission no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. Four investigators had significant financial conflict of interest with Aventis. This was not considered to be of concern because these investigators in total contributed [redacted] patients to the phase 3 program.

b(4)

Pediatric Considerations

The current development program for ciclesonide studied patients 4 years of age and older. Aventis requested deferral of studies in patients below 4 years of age and waiver of studies below 6 months of age. A deferral was granted in the acknowledgement letter to the NDA. A partial waiver was granted for patients 6 months of age and younger on October 1, 2004. Aventis's choice of the lower age bound of 4 years for initial pediatric studies is reasonable for a press-and-breathe corticosteroid MDI. Patients below 4 years of age generally cannot use such a device without a spacer. Patients below 4 years of age can be studied later once an appropriate dose and dosing regimen is identified for patients 4 years of age and older.

b(5)

b(4)

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including orally inhaled corticosteroids. Altana has an ongoing one-year growth study in pediatric patients 5 to 8.5 years of age with doses of 40 mcg and 160 mcg once daily (study 343). This study

Product Name
The proposed product name Alvesco was reviewed by the Office of Drug Safety and found to be acceptable. The review team of this Division and DDMAC also finds the name acceptable.

Labeling
The label has been extensively reviewed by various disciplines of this Division and by DDMAC. Detailed label negotiation was not done with Aventis because the application is not heading towards an approval action. Furthermore, it is not realistic to write a comprehensible label that will instruct the health care providers on safe and effective use of the drug based on the limited clinical data that support only part of the proposed indication and dosing regimen. The detailed label review that was generated by the review team is filed in the Agency electronic records for future use.

Action
The submitted clinical data do not support the approval of Alvesco (ciclesonide) Inhalation Aerosol for the proposed indication of maintenance treatment of asthma as prophylactic therapy in adult Specifically, the clinical data do not support

b(4)

Therefore, I recommend an APPROVABLE action on this application.

To support approval of the application, Aventis will need to provide data to demonstrate efficacy of ciclesonide for maintenance treatment of asthma that covers the full range of asthma severity, particularly mild to moderate asthma.

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