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STATISTICAL REVIEW(S)



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SECONDARY STATISTICAL REVIEW

NDA/Serial Number: 21-658/N000

Drug Name: Ciclesonide metered dose inhaler (ALVESCO™)

Indication(s): Maintenance treatment of asthma as prophylactic therapy in patients – years of age and older

Applicant: Nycomed Inc.

Date(s): Received 07/10/07

Review Priority: Standard

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Background

Ciclesonide metered dose inhaler (MDI) was originally submitted on December 23, 2003 for the indication of maintenance treatment of asthma in adult patients from 12 years of age and older. An approvable letter was issued on October 21, 2004, addressing deficiencies in efficacy, safety, dose-counting, as well as pharmacodynamic information. The efficacy deficiencies included the following:

- The clinical data did not support the efficacy in patients with mild and moderate asthma and previously maintained on bronchodilators alone.
- The clinical data did not support a once daily dosing regimen for various proposed doses.
- Efficacy for patients below 12 years of age was not demonstrated.

The safety deficiency was the concern of excessive cataracts observed in studies of 12-week duration. The sponsor was asked to conduct an ophthalmic safety study of at least 12-month duration.

In this re-submission, the sponsor provided studies to respond the deficiencies addressed in the approvable action letter. The newly submitted clinical studies included two efficacy studies -- Studies 3030 and 3031, a 12-month ophthalmologic safety study -- Study 3027, and a 12-month growth study -- Study 343. Studies 3030 and 3031 were designed to address the efficacy deficiencies in the original submission by incorporating two ciclesonide MDI treatment groups at the dose level of 160 mcg per day administered either once or twice daily and enrolling patients previously maintained on bronchodilator alone (Study 3031). Study 3027 was a 12-month ophthalmologic safety study conducted according to the agency's request. The 12-month growth study evaluated the effect of ciclesonide on children's growth rate over 1 year.

The original submission included six placebo-controlled Phase 3 clinical studies conducted by Sanofi-Aventis:

- Studies 321 and 322 in adults and adolescents with mild to moderate persistent asthma previously maintained on either inhaler corticosteroids (ICS) or bronchodilator alone
- Study 323/324 in adults and adolescents with severe persistent asthma
- Study 325 in adults and adolescents with severe persistent asthma requiring oral corticosteroids (OCS) use for asthma control
- Studies 341 and 342 in children with mild, moderate and severe asthma

The primary statistical reviewer was Dr. Ted Guo for both the original and this re-submission. The secondary statistical reviewer for the original submission was Ms. Ruthanna Davi. This reviewer conducted the primary statistical review for the growth study submitted in this re-submission. This growth study was concurrently reviewed by Ms. Ruthanna Davi. No primary statistical evaluation was conducted on two important clinical studies, Study 325 from the original submission and Study 3027 from this re-submission. As Dr. Guo's reviews did not cover sufficient information in study design and evaluation of secondary endpoints, this secondary statistical review includes relatively detailed information in study design and study results. In addition, the secondary statistical review also covers the review of the two clinical studies that had not been reviewed. This review is organized as the following based on the study objectives and study design in the evaluation of ciclesonide MDI:

- Maintenance treatment of asthma in patients ≥ 12 years of age
- Maintenance treatment of asthma in patients from 4-11 years of age
- The effect on the reduction of OCS use in OCS dependent patients with severe persistent asthma
- The effect on ophthalmologic safety
- The effect on children's growth rate.

Evaluation of the effect on maintenance treatment of asthma in patients ≥ 12 years of age

Study design

Five phase III and placebo-controlled studies were evaluated collectively for the maintenance treatment of asthma in patients aged 12 years and older. The five studies included two studies, Studies 3031 and 3030, from the re-submission to address the efficacy deficiencies and three studies, Studies 321, 322, and 323/324, from the original submission. The main differences in study design as well as the dosing regimens of ciclesonide MDI and controls are summarized in Table 1.

Table 1: Summary of studies for the efficacy evaluation of ciclesonide MDI in patients ≥ 12 years of age.

Studies	Patient population	Regimens (ex-actuator)	Controls	Randomization stratification
3031	Previously treated by bronchodilators alone	80 mcg BID 160 mcg QD 80 mcg BID (4 wks) ->160 mcg QD (12 wks)	Placebo	
3030	Previously maintained by ICS	80 mcg BID 160 mcg QD	Placebo	
321	Mild and moderate asthma	80 mcg QD 160 mcg QD 320 mcg QD	Placebo	Stratified by previous therapy in the past 30 days: controller therapy or reliever therapy with bronchodilator alone
322	Mild and moderate asthma	80 mcg QD 160 mcg QD 320 mcg QD	Placebo	Stratified by previous therapy in the past 30 days: controller therapy or reliever therapy with bronchodilator alone
323/ 324	Severe persistent asthma	160 mcg BID 320 mcg BID	Fluticasone 880 mcg/day Placebo	

All the studies were randomized double-blinded, placebo-controlled, multi-center, and parallel group clinical trials and equal number of patients was randomized to each treatment group within each study. The double-blind treatment duration was 12 weeks with clinical visits at Weeks 0 (randomization), 1, 2, 4, 8, and 12, except Study 3031, which had study duration of 16 weeks and an extra clinical visit at Week 16. Pulmonary function tests were performed at clinical visits including the baseline visit before the morning dose.

The primary endpoint was the change from baseline to Week 12 in FEV₁. The last on-treatment observation was carried forward if the assessment at Week 12 was missing. The secondary

endpoints included percent change from baseline at Week 12 in FEV₁, change from baseline at Week 12 in percent predicted FEV₁, FVC, and FEF_{25-75%}, as well as assessments based on diary recording such as AM and PM peak expiratory flow (PEF), total asthma symptom scores as the sum of the daytime and nighttime scores, and albuterol use. The diary recordings were averaged by the values of the last available 7 days on treatment for the value of Week 12 and 5-7 days before randomization for the baseline value. Proportion of symptom-free days during double-blinded treatment, proportion of nights awake during double-blind treatment period, and rate and time to withdrawal from the study due to lack of efficacy were also assessed as secondary endpoints.

ANCOVA model with covariates treatment, pooled center, previous therapy strata (if randomization was stratified), gender, baseline FEV₁, and age was used to analyze treatment difference. An intent-to-treat (ITT) population was used for all the analyses. The ITT population included all randomized patients who received at least 1 dose of double-blind study medication and had a valid baseline and at least 1 post-baseline measurement of the primary efficacy assessment.

For Study 3031, the primary endpoint was the change from baseline in the average FEV₁ measures obtained at Weeks 12 and 16. If patient's last observation was before Week 12, the last observation was used for the analysis. If the last observation was after Week 12, the average of the FEV₁ observed at Week 12 and the last observation was used. The secondary endpoints were similarly defined except that the changes were from baseline to Week 16.

Study Results

The abbreviated patient disposition and demographic information of the five studies is summarized in Table 2. Demographic and baseline characteristics were reasonably balanced among the treatment groups in all the studies. Overall, the placebo treatment arms in all studies had higher discontinuation rates compared with the ciclesonide treatment groups. The reasons for the majority of the discontinuation in the placebo groups were either due to AE or lack of efficacy, or both, except Study 3031 which had only 3% patients discontinued the study due to the lack of efficacy.

Table 2: Patient disposition and demographic information based on the study reports.

Study	Regimens (ex-actuator)	Rando mized	Discontinued N (%)			ITT	Demo Cross treatment
			Total	AE	Lack of eff.		
3031	80 mcg BID	175	18(10%)	4(2%)	2(1%)	170(97%)	Age: 36.7 years
	160 mcg QD	178	30(17%)	14(8%)	2(1%)	173(97%)	Female: 54%
	80 BID->160 QD	177	22(12%)	8(5%)	0	171(97%)	White: 75%
	Placebo	178	41(23%)	23(13%)	5(3%)	177(99%)	%predicted FEV ₁ : 72%
3030	80 mcg BID	152	17(11%)	8(5%)	3(2%)	149(98%)	Age: 39.3 years
	160 mcg QD	152	18(12%)	7(5%)	5(3%)	150(99%)	Female: 62%
	Placebo	152	49(32%)	23(15%)	14(9%)	147(97%)	White: 86% %predicted FEV ₁ : 79%
321	80 mcg QD	133	21(16%)	5(4%)	18(14%)	133(100%)	Age: 36.6 years
	160 mcg QD	128	23(18%)	9(7%)	12(9%)	127(99%)	Female: 59%
	320 mcg QD	131	19(15%)	5(4%)	8(6%)	131(100%)	White: 87%
	Placebo	134	48(35%)	22(16%)	40(30%)	133(99%)	%predicted FEV ₁ : 71%

322	80 mcg QD	124	15(12%)	6(5%)	7(6%)	124(100%)	Age: 36.5 years
	160 mcg QD	123	13(11%)	5(4%)	7(6%)	123(100%)	Female: 59%
	320 mcg QD	124	22(18%)	6(5%)	9(7%)	124(100%)	White: 87%
	Placebo	118	36(31%)	17(14%)	23(20%)	116(98%)	%predicted FEV ₁ : 71%
323/ 324	160 mcg BID	127	26(21%)	8(6%)	20(16%)	127(100%)	Age: 43 years
	320 mcg BID	130	26(20%)	10(8%)	14(11%)	130(100%)	Female: 59%
	Fluticason	138	25(18%)	6(4%)	10(7%)	136(99%)	White: 79%
	Placebo	136	66(49%)	27(20%)	55(40%)	134(99%)	%predicted FEV ₁ : 54%

*Patients might have more than one reason for discontinuation.

The results of the primary efficacy endpoint of the five studies based on the sponsor's analyses are summarized in Table 3. The primary endpoints showed statistically significantly better change in FEV₁ compared with placebo, except the ciclesonide 160 mcg QD treatment group in Study 321 which only showed numerical trend in favor of ciclesonide. No clear dose-response trend was observed based on the primary endpoint for ciclesonide MDI QD regimens. However, the ciclesonide 80 mcg BID regimen showed statistically significantly greater improvement in FEV₁ than the 160 mcg QD regimen in Study 3031 and numerically better control of FEV₁ in Study 3030.

For the severe persistent patient population, both of the ciclesonide 160 and 320 mcg BID regimens showed statistically significantly better improvement in FEV₁ in comparison to placebo in the primary endpoint in Study 323/324. Ciclesonide 320 mcg BID had numerically larger effect in comparison to ciclesonide 160 mcg BID. However, the improvement in FEV₁ in the fluticason treatment group was the highest among all the treatment groups and was statistically significantly better than ciclesonide 160 mcg BID and numerically better than ciclesonide 320 mcg BID.

Table 3: Results of the primary efficacy endpoint based on the study reports.

Treatment	LS Baseline	LS Chg from Baseline	Difference: MF DPI - placebo		
			Difference	2-side 95% CI	2-sided p-value
Study 3031					
80 mcg BID (n=170)	2.49	0.30	0.24	(0.16, 0.32)	<0.001
160 mcg QD (n=173)	2.54	0.19	0.12	(0.05, 0.20)	0.002
80 mcg BID->160 mcg QD(n=171)	2.39	0.19	0.13	(0.05, 0.20)	0.002
Placebo (n=177)	2.45	0.06			
Study 3030					
80 mcg BID (n=149)	2.67	0.07	0.19	(0.11, 0.27)	<0.001
160 mcg QD (n=150)	2.64	0.01	0.14	(0.06, 0.22)	<0.001
Placebo (n=147)	2.63	-0.12			
Study 321					
80 mcg QD (n=133)	2.44	0.32	0.12	(0.03, 0.21)	0.012
160 mcg QD (n=127)	2.46	0.26	0.07	(-0.03, 0.16)	0.165
320 mcg QD (n=131)	2.44	0.35	0.15	(0.06, 0.25)	0.001
Placebo (n=133)	2.46	0.20			
Study 322					
80 mcg QD (n=124)	2.40	0.25	0.12	(0.02, 0.22)	0.022
160 mcg QD (n=123)	2.34	0.32	0.19	(0.09, 0.29)	<0.001
320 mcg QD (n=124)	2.51	0.25	0.12	(0.02, 0.22)	0.017
Placebo (n=116)	2.43	0.13			

Study 323/324						
160 mcg BID (n=127)	1.78	0.36	0.11	(0.01, 0.21)	0.037	
320 mcg BID (n=130)	1.82	0.43	0.18	(0.07, 0.28)	0.001	
Fluticason (n=136)	1.77	0.50	0.24	(0.14, 0.35)	<0.001	
Placebo (n=134)	1.77	0.25				

Results of the secondary endpoints relating to the pulmonary functions based on the study reports are summarized in Table 4.

Table 4: Results of the secondary endpoints in pulmonary function assessments.

Treatment	%predicted FEV ₁ (%)	FVC (L)	FEF _{25%-75%} (L/second)	AM PEF (L/min)	PM PEF (L/min)
Study 3031					
80 mcg BID (n=170)	9.02, <0.001	0.20, <0.001	0.43, <0.001	39.6, <0.001	19.4, <0.001
160 mcg QD (n=173)	5.00, 0.013	0.13, 0.029	0.27, 0.042	26.7, 0.001	13.2, 0.002
80 BID->160QD(n=171)	4.94, 0.014	0.12, 0.032	0.25, 0.072	34.1, <0.001	12.2, 0.001
Placebo (n=177)	2.00	0.01	0.14	3.4	-8.09
Study 3030					
80 mcg BID (n=149)	1.56, <0.001	-0.02, 0.194	0.16, <0.001	-4.4, 0.035	-1.3, 0.035
160 mcg QD (n=150)	0.09, <0.001	0.02, 0.043	0.02, 0.083	-5.8, 0.077	-0.3, 0.019
Placebo (n=147)	-4.14	-0.09	-0.08	-12.8	-10.0
Study 321					
80 mcg QD (n=133)	8.83, 0.008	0.30, 0.063	0.33, 0.453	13.4, 0.003	12.9, 0.036
160 mcg QD (n=126)	7.66, 0.084	0.27, 0.196	0.36, 0.227	16.8, <0.001	17.6, 0.003
320 mcg QD (n=130)	9.70, 0.001	0.33, 0.015	0.33, 0.396	22.4, <0.001	17.6, 0.003
Placebo (n=131)	5.39	0.20	0.27	-2.2	2.3
Study 322					
80 mcg QD (n=124)	7.31, 0.006	0.22, 0.334	0.30, 0.022	8.2, 0.087	6.6, 0.229
160 mcg QD (n=123)	8.84, <0.001	0.28, 0.041	0.31, 0.016	25.7, <0.001	18.3, <0.001
320 mcg QD (n=124)	7.07, 0.010	0.27, 0.058	0.30, 0.019	11.8, 0.017	11.6, 0.025
Placebo (n=116)	3.45	0.16	0.10	-1.1	0.8
Study 323/324					
160 mcg BID AM(n=127)	10.90, 0.009	0.45, 0.166	0.33, 0.042	18.1, <0.001	15.5, <0.001
320 mcg QD AM (n=130)	12.57, <0.001	0.51, 0.015	0.43, 0.001	20.7, <0.001	14.6, <0.001
Fluticason (n=136)	14.74, <0.001	0.53, 0.006	0.52, <0.001	31.7, <0.001	28.2, <0.001
Placebo (n=134)	6.90	0.36	0.18	-9.7	-7.6

Additional secondary endpoints are summarized as follows:

Albuterol use:

- In Study 3031, the reduction was statistically significantly greater at Week 16 in all of the ciclesonide treatment groups compared to placebo.
- In Studies 3030, 321, and 322, the reduction was statistically significantly greater at Week 12 in all of the ciclesonide treatment groups compared to placebo.
- In Study 323/324, all of the ciclesonide treatment groups showed statistically significantly greater benefit in albuterol use compared to placebo at Week 12.

Total asthma symptom scores:

- In Study 3031, the reduction at Week 16 was greater in all of the ciclesonide treatment groups compared to placebo and the treatment differences compared with placebo were

statistically significant for the ciclesonide 80 mcg BID group and the 80 mcg BID followed by 160 mcg QD group.

- In Study 3030, the reduction at Week 12 was statistically significantly greater in all ciclesonide treatment groups compared to placebo.
- In Studies 321 and 322, the reduction at Week 12 was statistically significantly greater in all of the ciclesonide treatment groups compared to placebo, except ciclesonide 320 mcg QD in Study 322.
- In Study 323/324, the treatment differences at Week 12 were statistically significantly greater in all ciclesonide treatment groups compared to placebo.

Number of awakenings per night:

- In Study 3031, the reduction at Week 16 was greater in all of the ciclesonide treatment groups compared to placebo and the treatment difference between ciclesonide 80 mcg BID and placebo was statistically significant.
- In Studies 3030, 321 and 322, the reduction at Week 12 was significantly greater in all of the ciclesonide treatment groups compared to placebo.
- In Study 323/324, the reduction at Week 12 was greater for all of the ciclesonide treatment groups in comparison to placebo and the difference between ciclesonide 320 mcg BID and placebo was statistically significant.

Various subgroup analyses were performed by gender, race, age groups, baseline % predicted FEV₁ and randomization strata (controller therapy primarily with ICS or reliever therapy with bronchodilator alone). Overall, No consistent subgroup by treatment interaction was observed across studies.

Statistical issues and comments

Several step-down closed testing procedures were specified to control type I error rate for multiple regimens of ciclesonide MDI and for certain secondary endpoints. These procedures were not applied in this statistical evaluation. When evidence was evaluated collectively from multiple studies for decision making, such procedures protect the error rate of wrongly approving a product that is not efficacious in a rigid and illogical manner. They are not of any help in identifying the optimal dosing regimen either. Rather, a common sense is applied here to evaluate evidence collectively. That is, the chance for all the ciclesonide regimens to show significant treatment effect in all studies when a drug product does not work is very small. Based on the totality of the evidence across all of the five studies in the primary and the secondary efficacy endpoints, the error rate of wrongly approving a drug is well protected. Under this protection, no adjustment is needed for the comparisons among dosing regimens for the purpose of identifying the optimal regimen.

Patients in the age groups between 12 and 18 years and ≥ 65 years were under represented (less than 10% of the overall enrolled patients).

Conclusions

In evaluating the maintenance treatment of asthma in patients ≥ 12 years of age with mild and moderate asthma, the ciclesonide 80 mcg BID dosing regimen showed better treatment effect than ciclesonide 160 mcg QD. Statistically significant better treatment effect of the BID regimen compared with the QD regimen was observed in Study 3031 in all of the primary and secondary endpoints. Numerically better treatment effect of the BID regimen compared with the QD regimen was observed in Study 3030 in the primary endpoint and the majority of the secondary endpoints. Ciclesonide 80 mcg QD appeared to be the lowest effective dose.

In treating patients with severe persistent asthma, the ciclesonide 160 and 320 mcg BID regimens demonstrated statistically significant treatment benefit in comparison to placebo in Study 323/324. Ciclesonide 320 mcg BID was numerically better than 160 mcg BID in the primary and the majority of the secondary endpoints. In addition, the fluticasone treatment group was consistently numerically better than all ciclesonide MDI treatment groups and statistically significantly better than ciclesonide 160 mcg BID in all of the primary and secondary endpoints.

Study 3031 sufficiently addressed the deficiency in lacking clinical data to support the efficacy in patients with mild and moderate asthma and previously maintained on bronchodilators alone.

Both Studies 3031 and 3030 addressed the deficiency that clinical data did not support a once daily dosing regimen for various proposed doses.

For labeling, the statistical discipline recommended that the graphs in the labels depicting the FEV₁ change from baseline over the course of treatment should use a consistent scale in a y-axis. This is to avoid misleading visual effect which could amplify small treatment differences by using different various scales in y-axes.

Evaluation of the effect on the maintenance treatment of asthma in children 4-11 years of age

Study design

The pediatric program consisted of two Phase 3 studies, Studies 341 and 342, which were similarly designed as Studies 321 and 322 in the adult and adolescent clinical program. The patient population included mild, moderate, or severe persistent asthmatic children aged from 4-11 years. The ciclesonide MDI dosing regimens used in the two studies were 40, 80, and 160 mcg QD in the morning. The primary efficacy endpoint was change from baseline to the end of the study (Week 12) in % predicted FEV₁.

Results

Patient disposition and demographic information based on the sponsor's study report is summarized in Table 5. In both studies, the discontinuation rates in the placebo groups were not outstandingly higher than the ciclesonide MDI regimens. No large imbalance was observed in the demographic and baseline information.

Table 5: Patient disposition and demographic information for pediatric studies.

Study	Regimens (ex-actuator)	Randomized	Discontinued N (%)			ITT	Demographic info. Cross treatment
			Total	AE	Lack of eff.		
341	40 mcg QD	126	23(18%)	14(11%)	10(8%)	124(98%)	Age: 8 years Female: 40% White: 42% %predicted FEV ₁ : 68%
	80 mcg QD	135	18(13%)	11(8%)	8(6%)	134(99%)	
	160 mcg QD	122	18(15%)	9(7%)	9(7%)	119(98%)	
	Placebo	131	24(18%)	15(12%)	14(11%)	127(97%)	
342	40 mcg QD	130	21(16%)	8(6%)	11(9%)	128(99%)	Age: 8 years Female: 33% White: 82% %predicted FEV ₁ : 69%
	80 mcg QD	126	17(14%)	8(6%)	8(6%)	125(99%)	
	160 mcg QD	134	13(10%)	7(5%)	5(4%)	134(100%)	
	Placebo	127	27(21%)	19(15%)	18(14%)	127(100%)	

Patients might have more than one reason for discontinuation.

The results of the sponsor's primary efficacy analyses are summarized in Table 6. As can be seen from Table 6, none of the three dosing regimens of ciclesonide MDI demonstrated consistent statistically significant treatment effect compared with placebo. Most of the secondary endpoints did not demonstrate significant treatment differences between the three ciclesonide MDI dose regimens and placebo in both of the studies.

Table 6: The sponsor's efficacy analysis in % predicted FEV₁.

Treatment	Baseline	LS Chg from Baseline	Difference: MF DPI - placebo		
			Difference	2-side 95% CI	2-sided p-value
Study 341					
40 mcg QD (n=124)	68.6	13.8	1.2	(-2.8, 5.1)	0.563
80 mcg QD (n=134)	67.9	16.5	3.9	(0.1, 7.8)	0.046
160 mcg QD(n=119)	67.0	16.0	3.3	(-0.7, 7.3)	0.101
Placebo (n=127)	68.1	12.6			
Study 342					
40 mcg QD (n=128)	68.4	10.0	1.4	(-1.8, 4.5)	0.406
80 mcg QD (n=125)	68.7	10.3	1.7	(-1.5, 4.9)	0.298
160 mcg QD(n=134)	69.2	12.2	3.6	(0.4, 6.7)	0.028
Placebo (n=127)	69.0	8.6			

Important subgroup analyses included subgroups by randomization strata (controller with primarily ICS or reliever with bronchodilator). It appeared that the reliever groups had better treatment effect compared with the controller group. However, the interaction of the treatment by the strata was not consistently significant in both studies.

Conclusion

None of the three dosing regimens of ciclesonide MDI, 40, 80, and 160 mcg QD had demonstrated convincing treatment benefit in the pediatric patient population. It was clear that ciclesonide MDI 40 mcg QD was not effective in the pediatric patients.

Evaluation of the effect on OCS

Study design

Study 325 was designed to evaluate the effect of ciclesonide MDI 320 and 640 mcg BID in comparison to placebo in the reduction of OCS use in patients ≥ 12 years of age with severe persistent asthma requiring OCS (prednisone) for symptom control. This study was a multi-center, double-blind, placebo-controlled and parallel group study. Patients were randomized to ciclesonide MDI 320 or 640 mcg BID or placebo in 1:1:1 ratio. This study included a 1 to 4-week screening period and a treatment period of 12 weeks. During the screening period, patients' minimum effective OCS dose was identified. Patients were randomized at Visit 3 (Week 0). Clinic Visits 4-15 were scheduled weekly during the 12-week treatment period. At Visits 4-14, patients were evaluated for eligibility for prednisone dose reduction based on the satisfactory of the following criteria jointly:

- $FEV_1 \geq 80\%$ of baseline (pre-randomization) actual FEV_1 ; In addition, $\%$ predicted $FEV_1 \geq 40\%$;
- AM PEF $\geq 80\%$ of baseline mean AM PEF on all days since the last visit;
- Mean nocturnal awakenings $\leq 50\%$ increase over the baseline per night;
- For any 2 consecutive days since the last visit, abulterol use was not > 4 puffs per day above the baseline daily mean or > 12 puffs per day;
- No prednisone burst required since the previous visit.

If patients met all the criteria above, the investigators should reduce the prednisone dose based on the schedules provided in Table 7:

Table 7: Prednisone dose reduction schedule for Visits 4-14.

Present Dose	Dosing every day		Dosing every other day	
	Present Dose	Reduce dose by	Present Dose	Reduce dose by
12.5 -30 mg		5 mg	25 - 60 mg	10 mg
7.5 - 10 mg		2.5 mg	15 - 20 mg	5 mg
≤ 5 mg		1.25 mg	≤ 10 mg	2.5 mg

The primary endpoint for Study 325 was the percent change from baseline to the end of the study in the prednisone dose. The data imputation method used in the study report was different from the one define in the study protocol. In the study report, the imputation method was that

- If the patient completed the study, the prednisone dose at Visit 15 (Week 12) was considered the final prednisone dose.
- 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.

However, the protocol defined imputation method was as follows:

- If the patient completed the study, the prednisone dose at Visit 15 would be considered the final prednisone dose.
- 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 lack of efficacy discontinuation was defined in the protocol as follows:

- Patients had an asthma exacerbation leading to hospitalization;

- Patients required an increase in any concomitant asthma medication other than inhaled albuterol or oral prednisone to control symptoms or was administered a disallowed medication;
- Patients required a second burst of prednisone to treat worsening symptoms.

The secondary endpoints included percent of patients eliminated OCS use, time to withdrawal due to lack of efficacy, change from baseline of FEV₁, AM PEF, and albuterol use.

The ITT patient population was used for the primary efficacy analysis. The ITT patient population included all randomized patients who had at least one dose of double-blind treatment. ANCOVA model was used for the primary efficacy analysis with covariates including treatment, baseline OCS use, prior ICS use, baseline % predicted FEV₁, pooled center, age and gender. Prior to the analysis, data with higher than 100% increase in OCS use were truncated and capped at 100%.

Study results

A total of 141 patients were enrolled and randomized to ciclesonide 320 mcg BID (47 patients), 640 mcg BID (49 patients), and placebo (45 patients). Patient disposition information is summarized in Table 8. The rate of study discontinuation was higher in the placebo group (31%) in comparison to ciclesonide 320 mcg BID (17%) and ciclesonide 640 mcg BID (10%). The majority of the discontinuation was due to either adverse event or lack of efficacy, or both. No large imbalance in demographic and baseline information was observed among treatment groups. The mean age was 48 years. The majority was female (69%) and white (56%). The mean % predicted FEV₁ at baseline was 55%.

Table 8: Discontinuation frequencies by treatment and reasons during treatment.

	Number (%) of Patients		
	Placebo	Cicles. 320 mcg BID	Cicles. 640 mcg BID
Randomized	45	47	49
ITT population	45(100%)	47 (100%)	48 (98%)
discontinued 12-wk treatment	14 (31%)	8 (17%)	5 (10%)
Reason for discontinue *			
Adverse event	12 (27%)	7 (15%)	4 (8%)
Lack of efficacy	13 (29%)	6 (13%)	3 (6%)

*Patients might report more than one reason for discontinuation.

The efficacy results based on the study report were summarized in Table 9 for the primary and secondary endpoints.

Table 9: Sponsor's analyses for the primary and secondary endpoints.

Treatment	Baseline	LS % Chg from Baseline	Difference: MF DPI – placebo		
			Difference	2-side 95% CI	2-sided p-value
Primary endpoint: percent change in prednisone dose from baseline					
320 mcg BID (n=47)	13.6	-47.4	-51.6	(-78.9, -24.3)	<0.001
640 mcg BID (n=48)	11.5	-62.5	-66.8	(-94.1, -39.4)	<0.001
Placebo (n=45)	12.0	4.2			

Change from baseline to the end of study in FEV₁					
320 mcg BID (n=47)	1.58	0.04	0.17	(0.02, 0.31)	0.024
640 mcg BID (n=48)	1.71	0.04	0.17	(0.02, 0.31)	0.028
Placebo (n=45)	1.62	-0.13			
Change from baseline to the end of study in AM PEF					
320 mcg BID (n=47)	265.4	4.32	5.02	(-12.9, 23.0)	0.580
640 mcg BID (n=48)	283.0	15.97	16.7	(-1.6, 35.0)	0.074
Placebo (n=45)	254.5	-0.70			
Change from baseline to the end of study in total asthma severity rating score					
320 mcg BID (n=47)	2.58	0.10	0.33	(-0.26, 0.92)	0.267
640 mcg BID (n=48)	2.22	-0.31	-0.07	(-0.67, 0.53)	0.820
Placebo (n=45)	2.32	-0.24			
Change from baseline to the end of study in daily albuterol use					
320 mcg BID (n=46)	5.04	-0.07	-0.39	(-1.80, 1.02)	0.585
640 mcg BID (n=47)	4.68	-0.08	-0.40	(-1.83, 1.03)	0.581
Placebo (n=45)	4.86	0.32			

As the sample sizes were small in each treatment group, no conclusion is drawn based on subgroup analyses in this study.

Statistical issues

The sponsor felt that it was reasonable to impute the final prednisone dose level 10 mg higher than the level that a patient had at discontinuation. As a result, many patients had imputed prednisone level more than 100% above the baseline level. Ironically, the sponsor felt that it was unreasonable to have more than 100% dose increase. Therefore, the data with more than 100% increases were truncated to 100%. After this convoluted data manipulation, the treatment differences using the new imputation method in conjunction with data truncation were similar to the treatment difference with the old imputation method specified in the protocol. Without data truncation, the new imputation rule could exaggerate the treatment difference over 16%.

After examining the data, this reviewer found that the imputed dose levels of some patients did not follow any of the two imputation rules. After a t-con discussion, it appeared that the imputation rules were altered by the sponsor's clinicians. Since the number of patients with the irregular imputation was equally distributed among treatment groups, the impact of these patients on the treatment difference should be small.

Conclusion

Ciclesonide MDI 320 and 640 mcg BID were statistically significantly effective compared with placebo in reducing OCS dependence in patients with severe persistent asthma.

Evaluation of the effect on Cataracts

Study design

Study 3027 was designed to evaluate the effect of ciclesonide in the occurrence of Class I lens events for nuclear opalescence, cortical, or posterior subcapsular lens opacification within 12

months in comparison with beclomthasone HFA. This study was an international, multicenter, randomized, double-blinded, parallel group, and active-controlled study. Patients aged 18 years and above were randomized in 1:1 ratio to ciclesonide 640 mcg/day or beclomethasone 640 mcg/day, given as twice daily. The treatment duration was 12 months. Lens opacification was evaluated by slit-lamp examination performed after papillary dilation to at least 6.0 mm before randomization, and 4, 8, and 12 months after the start of treatment. Best-corrected visual acuity (BCVA) and intraocular pressure were also measured at each eye examination visit. In addition, pulmonary function was assessed before randomization, at Day 1, and Months 2, 4, 6, 8, 10, and 12 post-randomization.

Lens events using LOCS III classification for grading lens opacities were defined as follows:

- Class I: increase from baseline in LOCS III grade of ≥ 0.5 in nuclear opalescence, ≥ 0.8 in cortical, ≥ 0.5 in posterior subcapsular, or cataract surgery since baseline.
- Class II: increase from baseline in LOCS III grade of ≥ 0.9 in nuclear opalescence, ≥ 1.5 in cortical, ≥ 0.9 in posterior subcapsular, or cataract surgery since baseline.
- Sustained Class II: a Class II lens event observed at any timepoint with presence of a Class I event in the same eye at the next time point. If the Class II lens event was observed only at the last examination done, then it should be also a Class I lens event in the same eye at the timepoint immediately preceding the last one.
- Class III: LOCS III grade of ≥ 2.0 for any type of opacity and increase from baseline in LOCS III grade of ≥ 0.9 in nuclear opalescence, ≥ 1.5 in cortical, ≥ 0.9 in posterior subcapsular, or cataract surgery since baseline.

The primary endpoints were the Class I lens events and cataract surgery. The secondary endpoints included change from baseline to Month 12 in LOCS III grade for nuclear opalescence, cortical opacity, and posterior subcapsular opacity, cumulative incidence rates of Class II or III events at Month 12, changes from baseline to Month 12 in the BCVA and intraocular pressure. In addition, change in FEV₁ from baseline to Month 12 was evaluated.

A modified intent-to-treat (mITT) patient population was used for the analysis of the primary endpoint. The mITT population included all randomized patients who received at least one dose of study medication, and had a pre-treatment and at least one post-treatment LOCS III measurement or a post-treatment cataract surgery within 14 days after the last dose of study medication. Cumulative incidence rates between the two treatment groups were compared using a life-table method. Any event occurring after 390 days was censored for the analysis. Patients with early termination visit within the first 30 days after the first study drug intake were censored regardless of the outcome of the LOCS III examination. This censoring scheme violated the mITT principle. However, as shown later, the number of patients discontinued the study was low in both treatment group, therefore the censoring scheme would not have large impact in inferences. Non-inferiority boundaries, for the upper limit of the 2-sided 95% CI for the ratio of the cumulative incidence rates of ciclesonide vs. beclomethasone at the end of the study, were defined as $(1.63 - \sqrt{p_c})e^{\sqrt{1/(80 p_c)}}$, where p_c was the cumulative incidence rate of beclomethasone at Month 12, expected to be within a range of 2-12%. The definition of the non-inferiority

boundary was further extended to be the maximum of $((1.63 - \sqrt{p_c})e^{\sqrt{1/(80 p_c)}} , 1.33)$ due to higher than expected incidence rates obtained in the study.

Results

A total of 1,568 patients were randomized to ciclesonide (785) and beclomethasone (783). Among the randomized patients, about 14% of the patients in either treatment group did not complete the study, and 95% of the patients in either treatment group included in the mITT population. There was no large imbalance in demographic and baseline information. The mean age was 43 years. The majority was female (60%), white (84%), and recruited from US (85%).

Results of the ophthalmologic endpoints including the primary endpoints are summarized in Table 10 based on the sponsor's analyses. No analysis was performed for the endpoint of cataract surgery because only one patient in the beclomethasone treatment group had the surgery.

Table 10: Analyses results of the primary and secondary endpoints based on the study reports.

Endpoint	Ciclesonide (N=743)	Beclomethasone (N=742)	Relative risk	2-sided 95%CI Upper limit	Non-inferiority limits
Class I	36.1%	38.4%	0.940	1.08	1.33
Class II	14.0%	16.4%	0.857	1.10	1.62
Sustained Class II	9.4%	11.5%	0.821	1.12	1.80
Class III	8.1%	9.2%	0.885	1.25	1.92

Source: Page 6 of the study report for Study 3027.

No large treatment difference was observed in any of the other secondary endpoints including endpoints in pulmonary function.

Subgroup analyses were assessed by the sponsor in subgroups divided by age, gender, and country. No significant treatment by subgroup interaction was observed in the primary endpoints.

Conclusion

The study results suggested that the effect of ciclesonide MDI 640 mcg/day taking twice daily on ophthalmologic safety was no worse than belcomethasone MDI 640 mcg/day taking twice daily.

Evaluation of the effect on growth rate in children

Study design

Study 343 was designed to evaluate the effect of ciclesonide MDI 40 and 160 mcg (ex-actuator) administered once daily in the morning on growth velocity in comparison to placebo in children with mild persistent asthma over a 12-month treatment. This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in asthmatic children aged 5-7.5 years for girls and 5-8.5 years for boys. The patient population included patients who had mild persistent asthma for more than 3 months at screening. This study was divided into three periods: a 6-month run-in period with placebo, a 12-month double-blind treatment period, and a 2-month

within the margin of -0.5 cm/year. The results of the reviewer's analysis based on the 2-point method are displayed in Table 12.

Table 12: Reviewer's analysis on growth velocity during double-blind treatment period using the 2-point method.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
Placebo (n=201)	5.83		
Ciclesonide 40 mcg (n=206)	5.85	0.02 (-0.18, 0.21)	0.870
Ciclesonide 160 mcg (n=202)	5.62	-0.21 (-0.41, -0.02)	0.032

Based on the sponsor's analyses, at the treatment endpoint, which was defined as the last pulmonary function assessment during the double-blind treatment period, all the treatment groups showed no improvement in the predicted FEV₁ from the baseline. No treatment difference was observed among the three treatment groups. The sponsor's efficacy results are summarized in Table 13.

Table 13: Treatment effect in % predicted FEV₁.

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. placebo		
				LS mean ± SE	2-sided 95% CI	p-value
FEV₁ percent predicted						
Placebo	201	92.97	-3.74 ± 0.817	-	-	-
Ciclesonide 40 µg/day	206	96.26	-3.62 ± 0.801	0.11 ± 1.104	(-2.06, 2.28)	0.9193
Ciclesonide 160 µg/day	202	94.87	-2.45 ± 0.808	1.28 ± 1.103	(-0.88, 3.45)	0.2458
Percent change in FEV₁ ^a						
Placebo	201	1.407	9.56 ± 1.001	-	-	-
Ciclesonide 40 µg/day	206	1.435	8.89 ± 0.988	-0.67 ± 1.355	(-3.33, 1.99)	0.6213
Ciclesonide 160 µg/day	202	1.419	10.32 ± 0.997	0.77 ± 1.356	(-1.90, 3.43)	0.5719

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.

^a FEV₁ at baseline measured in liters.

Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: Table 39 on Page 148 in the study report for Study 343.

The sponsor performed several subgroup analyses in gender, age groups, regions, baseline growth rates (< 4cm/year, ≥4 cm/year) and some other post-hoc subgroups. No major treatment-by-subgroup interactions were observed in these analyses of growth velocities.

Statistical issues

The main issue of the study is the enrolled patient population which had very mild asthma with baseline average % predicted FEV₁ about 95%. This patient population might not need to use the study medication to control their disease, which leads to the question of patients' incentive of taking the medicine. The efficacy results further elevated this concern. There was no treatment difference in efficacy among the three treatment groups in FEV₁ assessment. The patient

population selected and the lack of efficacy response raised the concern of assay sensitivity of detecting treatment difference in growth velocities in this study due to possible non-compliance.

The sponsor's primary analysis was to estimate the growth velocity using linear regression slopes of height vs. time for each patient. The reviewer's primary analysis used the 2-point method because it is the correct method of estimating growth velocity irrespective of growth rate assumptions.

Conclusion

Although the lower bounds of the 2-sided 95% CIs for the differences between the ciclesonide regimens and placebo were larger than the margin -0.5 cm/year, specified in the study protocol for a claim of no worse than placebo in growth rate, there was no valid confirmation on whether the patients who did not need the study drug indeed took the medication. Therefore, no conclusion should be drawn from the study results.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: N21-658/N000
Drug Name: Ciclesonide metered dose inhaler (ALVESCO™)
Proposed Indication(s): Maintenance treatment of asthma as prophylactic therapy in patients \geq years of age and older
Applicant: Nycomed Inc.
Date(s): Received July 10, 2007
Review Priority: Standard

Biometrics Division: Division of Biometrics II/Office of Biostatistics
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Keywords: NDA review, Growth Study

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1. EXECUTIVE SUMMARY

1.1 Conclusions

A 52-week growth study (Study 343) was included in this re-submission, dated July 10th, 2007 under NDA21-658, for ciclesonide metered dose inhaler (MDI) to assess its growth effect in asthmatic children in comparison to placebo. The study was a randomized, double-blind, parallel-group study including two doses of ciclesonide, 40 and 160 mcg per day, and placebo, administered in the morning. The study enrolled 661 patients aged 5 to 8.5 years. These patients were equally randomized to placebo (221), ciclesonide MDI 40 mcg (221), and ciclesonide MDI 160 mcg (219). The mean baseline % predicted FEV₁ was about 95% at randomization. The estimated average growth velocities were 5.83, 5.85, and 5.62 cm/year for placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively. The differences of the growth velocities and the corresponding 2-sided 95% CIs were 0.02(-0.18, 0.21) and -0.21(-0.41, -0.02) for ciclesonide MDI 40 mcg – placebo and ciclesonide MDI 160 mcg – placebo, respectively. Although the lower bounds of the 2-sided 95% CIs for the differences were larger than the margin -0.5 cm/year, specified in the study protocol for a claim of no worse than placebo, the validity of the study results is questionable. The facts that this study was conducted in a patient population with very mild asthma and no efficacy was observed in the two doses of ciclesonide MDI raised a concern in assay sensitivity of detecting treatment differences in growth velocities.

1.2 Statistical Issues and Findings

The main issue of the study is the enrolled patient population which had very mild asthma with baseline average % predicted FEV₁ about 95%. This patient population might not need to use medication to control their disease, which leads to the question of **patients' incentive of taking the medicine. The efficacy results further elevated this concern.** In this study, only 3 out of 661 patients (2 in placebo and 1 in ciclesonide MDI 160 mcg) discontinued treatments due to lack of efficacy. There was no treatment difference in efficacy among the three treatment groups in FEV₁ assessment. The patient population selected and the lack of efficacy response raised the concern of assay sensitivity of detecting treatment difference in growth velocities in this study due to possible non-compliance.

One puzzling observation was a large difference in growth velocities between the run-in period and the double-blind treatment period in all treatment groups. To understand if this significant period effect was due to an age difference as the patients were 6 months older when entering the double-blind treatment period than the run-in period, the growth velocities were calculated by 6-month intervals in the double-blind treatment period. However, the growth rates were similar between the first 6 months and the last 6 months. It was not clear how this significant period effect should be interpreted.

2. INTRODUCTION

2.1 Overview

This re-submission intended to address efficacy and safety deficiencies identified from the original submission of ciclesonide MDI under NDA 21-658 for maintenance treatment of asthma. The statistical evaluation of the efficacy portion of ciclesonide MDI was reviewed by Dr. Ted Guo in a separate review document. This review provides detailed evaluation on the growth study, Study 343, to assess growth effect of ciclesonide MDI in children.

2.2 Data sources

Electronic document room for NDA21-658 submitted on 7-10-2007.

3. STATISTICAL EVALUATION OF STUDY 343

3.1 Study Design

The study objective was to evaluate the effect of ciclesonide MDI 40 and 160 mcg (ex-actuator) administered once daily in the morning on growth velocity in comparison to placebo in children with mild persistent asthma over a 12-month treatment.

This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in asthmatic children aged 5-7.5 years for girls and 5-8.5 years for boys. The patient population included patients who had mild persistent asthma for more than 3 months at screening. This study was divided into three periods: a 6-month run-in period with placebo, a 12-month double-blind treatment period, and a 2-month follow-up period. Qualified patients were randomized to ciclesonide 40 or 160 mcg, or placebo in 1:1:1 ratio at the end of the 6-month screening period. Randomization was stratified by center and age strata, where girls were divided by age 7 and boys by 8.

Patients' heights measured by stadiometer in cm were assessed

- During the screening period at Visits 1, 2, 3 (-6 months, -3 months and -2 weeks),
- At randomization which was at Visit 4 (time=0),
- During the treatment period at Visits 5-12 (Week 2 and Months 1,2,3,4,6,8, and 10);
- During the follow-up period at Visit 14 (Month 14).

Note that even though the treatment was discontinued early, patients were asked to return to clinic as scheduled for height assessments. Bone age measured by wrist x-ray was obtained at the baseline (Visit 3) and at the end of double-blind treatment (Visit 13). In addition, pulmonary function tests were performed at every clinic visit.

Patient compliance with study medication **was assessed based on the patient's diary records and canister weights measured at each clinic visit.**

Study endpoints

The primary growth endpoint was growth velocity during the 12-month double-blind treatment period. The secondary endpoint included the change from baseline in bone age. The efficacy endpoints included absolute and relative changes of FEV₁ from baseline to the last on-treatment observations.

Statistical methods

Several analysis populations were defined in the study protocol and its amendments, which included three modified intent-to-treat (mITT) populations, a per protocol (PP) population, and a safety population. The mITT population used for the primary analysis was defined as all randomized patients who completed at least 4 months of treatment or more during the double-blind treatment period. The PP population excluded important protocol deviations based on criteria determined prior to unblinding. The PP criteria were listed on Pages 86-7 in the study report. The safety population comprised all patients who received at least one dose of double-blind study medication.

The sponsor's primary analysis was to estimate the growth velocity using linear regression slopes of height vs. time for each patient. Other approaches of estimating the growth velocity mentioned in the protocol and the growth study report included a 2-point method and linear regression fixing baseline. The 2-point method is to estimate the growth velocity using growth change divided by the time period for the change. The treatment differences in growth velocity were analyzed using the analysis of covariance approach (ANCOVA) with covariates including treatment, pooled center, baseline growth velocity, height at randomization, age and age² at randomization, gender, gender by age interaction, race, previous corticosteroid usage during baseline period, and years of asthma since first diagnosed.

In this review, the 2-point method of estimating growth velocity was used in the majority of reviewer's analyses as this is a correct method irrespective of the shapes of growth curves. The analysis model used by the reviewer included only treatment, age stratum, baseline growth rate, and gender as covariates. The pooled center effect was removed from model because it is not clear how to interpret this artificial effect and its contribution in the analysis. The reviewer also removed several other covariates because these covariates appear to be highly correlated with covariates that were kept in the model.

The sponsor proposed a non-inferiority margin for the purpose [redacted] [redacted] The proposed non-inferiority margin was -0.5 cm/year for the lower bound of the 2-sided 95% CI for the difference of growth velocities between the ciclesonide treatment groups and placebo. The bases of the margin, according to the sponsor, were the draft guidance for industry for clinical studies in assessing the growth effect of the orally inhaled and intranasal corticosteroids issued in November 2001, as well as study results from comparing growth in pre-pubertal children treated with fluticasone propionate at a dose of 100 µg twice daily or placebo. This margin was not discussed during the review process as three review disciplines including

clinical, clinical pharmacology, and statistics concluded that the study results are unreliable.

The efficacy endpoints for the change of FEV₁ from baseline to the last on-treatment measurements were also analyzed in the mITT population using an ANCOVA model with covariates including treatment, center, baseline measurement, age at randomization, and gender.

3.2 Study results

Patient disposition

Six hundred and sixty-one patients were randomized at 63 US centers and 22 South American centers (12 in Argentina, 4 in Chile, and 6 in Venezuela). The 63 US centers enrolled only about a quarter of the total number of patients. The study was conducted between December 29, 2000 and September 15, 2004. Among the 661 randomized patients, 221, 221, 219 patients were randomized to placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively. About 92% patients were in the mITT population and 80% in the PP population. Overall, about 16% patients discontinued the double-blind treatment. Table 1 displays patient disposition information and dropout frequencies by treatment and reason.

Table 1: Discontinuation frequencies by treatment and reasons during treatment.

	Number (%) of Patients		
	Placebo	Ciclesonide 40 mcg	Ciclesonide 160 mcg
Randomized	221	221	219
mITT population	201 (91%)	206 (93%)	202 (92%)
Per Protocol population	176 (80%)	180 (81%)	179 (82%)
Completed 12-month treatment	181 (82%)	181 (82%)	188 (86%)
Reason for discontinue *			
Adverse event	14 (6.3%)	14 (6.3%)	8 (3.7%)
Lack of efficacy	2 (0.9%)	0 (0%)	1 (0.5%)
Did not wish to continue	7 (3.2%)	5 (2.3%)	6 (2.7%)
Lost to follow-up	6 (2.7%)	4 (1.8%)	5 (2.3%)
Poor compliance	3 (1.4%)	5 (2.3%)	4 (1.8%)
Protocol violation	10 (4.5%)	4 (1.8%)	5 (2.3%)
Other	5 (2.3%)	10 (4.5%)	7 (3.2%)

*Patients might report more than one reason for discontinuation.

Source: Table 3 on Page 103 and Table 8 on Page 110 of the study report for Study 343.

Demographic and baseline information

There was no large imbalance across treatment groups in demographic and baseline information. The mean age was about 7 years at randomization. The majority was male (67%), white (71%), and from South American (72%). The mean baseline % predicted FEV₁ was 95% at randomization. The average growth velocity during run-in period was 6.41 cm/year in the mITT population. One observation worth noting about the baseline growth rates was that the growth rate was lower in ciclesonide MDI 160 mcg than that in placebo. The reviewer's analysis of baseline growth rates using the 2-point approach is

summarized in Table 2. The model used for the analysis was analysis of variance which included treatment, gender, and age strata as covariates.

Table 2: Reviewer’s analysis on growth velocity during run-in period.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
Placebo (201)	6.51		
Ciclesonide 40 mcg (206)	6.57	0.06 (-0.22, 0.34)	0.675
Ciclesonide 160 mcg (202)	6.23	-0.27 (-0.56, 0.00)	0.053

Protocol violation and compliance

The sponsor reported that 27 patients had protocol violations. Among the 27 patients, 12, 8, and 7 were in placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively.

There was about 94% of patients (based on diary data) and 80% patients (based on canister weight) reported over 85% drug compliance across treatment groups. However, the reported compliance rates might not be reliable given the nature of the selected patient population who might not need the treatment for their disease.

Growth analyses

The results of the sponsor and the reviewer’s analyses were similar. The lower bounds of the 2-sided 95% CIs of the difference of growth rates between ciclesonide MDI and placebo were within the margin of -0.5 cm/year. Such results appear to indicate that the growth rates in the ciclesonide MDI regimens was not worse than that in placebo if we believe that a difference of 0.5 cm/year is not clinically important, even though the difference was statistically significant. The results of the reviewer’s analysis based on the 2-point method are displayed in Table 3.

Table 3: Reviewer’s analysis on growth velocity during double-blind treatment period using the 2-point method.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
Placebo (201)	5.83		
Ciclesonide 40 mcg (206)	5.85	0.02 (-0.18, 0.21)	0.870
Ciclesonide 160 mcg (202)	5.62	-0.21 (-0.41, -0.02)	0.032

Since estimating the slope using a linear regression for an individual patient is the **recommended approach in the guidance for the industry entitled “Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children”**, the results of this analysis are displayed in Table 4.

Table 4: Reviewer’s analysis on growth velocity during double-blind treatment period using linear regression.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
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Placebo (201)	5.79		
Ciclesonide 40 mcg (206)	5.77	-0.02 (-0.21, 0.16)	0.795
Ciclesonide 160 mcg (202)	5.63	-0.16 (-0.35, 0.03)	0.091

One puzzling observation was a large difference in growth velocities irrespective of treatment assignment between the run-in period and the double-blind treatment period in all treatment groups. This difference can be seen by cross comparing growth velocities displayed in Tables 2 and 3. To understand if this significant period effect was due to an age difference as the patients were 6 months older when entering the double-blind treatment period than the run-in period, the growth velocities were calculated by 6-month intervals in the double-blind treatment period. However, the growth rates were similar between the first 6 months and the last 6 months. It was not clear how this significant period effect should be interpreted. The reviewer further broke down the analysis to age and gender strata. Only two strata out of 12 had numerical trends of slowing down growth rates in every 6-month interval, including run-in and double-blind treatment period. The analyses are summarized in Table 5.

Table 5: Growth rates by 6-month interval and by gender and age strata

Treatment	Gender	Age(yrs)	Run-in period		Double-blind treatment period			
			N	Mean±SD	First 6 months		Last 6 month	
			N	Mean±SD	N	Mean±SD	N	Mean±SD
Placebo	Female	≤7 years	39	6.52±1.32	38	5.80±1.64	34	6.05±1.68
		>7 years	28	6.54±1.60	28	5.86±1.26	26	5.89±1.15
	Male	≤8 years	92	6.42±1.64	88	5.67±1.50	85	6.00±1.32
		>8 years	42	6.46±1.16	41	5.13±1.50	39	5.45±1.62
Ciclesonide MDI 40 mcg	Female	≤7 years	43	6.96±1.43	42	5.87±1.08	39	6.34±1.39
		>7 years	24	6.05±1.07	22	6.32±1.61	21	5.21±1.30
	Male	≤8 years	100	6.66±1.28	96	5.61±1.68	92	5.99±1.56
		>8 years	39	6.11±1.02	38	5.24±1.39	35	5.51±1.17
Ciclesonide MDI 160 mcg	Female	≤7 years	47	6.38±1.61	46	5.99±1.34	44	5.44±1.31
		>7 years	24	5.98±1.41	24	5.14±1.61	23	5.87±1.35
	Male	≤8 years	93	6.43±1.36	92	5.58±1.39	86	5.74±1.22
		>8 years	38	5.62±1.97	37	5.42±1.55	37	5.05±1.45

Efficacy evaluation

Based on the sponsor's analyses, at the treatment endpoint, which was defined as the last pulmonary function assessment during the double-blind treatment period, all the treatment groups showed no improvement in the predicted FEV₁ from the baseline. There was a small similar increase in FEV₁ calculated as percent change from the baseline. No treatment difference was observed among the three treatment groups. The sponsor's efficacy results are summarized in Table 6.

Table 6: Treatment effect in % predicted FEV₁.

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. placebo		
				LS mean ± SE	2-sided 95% CI	p-value
FEV₁ percent predicted						
Placebo	201	92.97	-3.74 ± 0.817	-	-	-
Ciclesonide 40 µg/day	206	96.26	-3.62 ± 0.801	0.11 ± 1.104	(-2.06, 2.28)	0.9193
Ciclesonide 160 µg/day	202	94.87	-2.45 ± 0.808	1.28 ± 1.103	(-0.88, 3.45)	0.2458
Percent change in FEV₁ ^a						
Placebo	201	1.407	9.56 ± 1.001	-	-	-
Ciclesonide 40 µg/day	206	1.435	8.89 ± 0.988	-0.67 ± 1.355	(-3.33, 1.99)	0.6213
Ciclesonide 160 µg/day	202	1.419	10.32 ± 0.997	0.77 ± 1.356	(-1.90, 3.43)	0.5719

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.

^a FEV₁ at baseline measured in liters.

Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: Table 39 on Page 148 in the study report for Study 343.

This efficacy response was low in the three MF DPI treatment groups. Given the mild asthmatic patient population, the treatment might not be always needed. In a patient population that does not have the absolute need to take the medicine on a regular basis, the assay sensitivity of detecting treatment differences in a safety assessment becomes a concern as compliance with the dosing regimen is questionable.

4 Findings in special/subgroup populations

The sponsor performed several subgroup analyses in gender, age groups, regions, baseline growth rates (< 4cm/year, ≥4 cm/year) and some other post-hoc subgroups. No major treatment-by-subgroup interactions were observed in these analyses of growth velocities.

5 Label Review and recommendation

If any growth study results are to be displayed in the label, as the fact that the study did not show treatment difference in efficacy should be mentioned in the label.

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this page is the manifestation of the electronic signature.**

/s/

Qian Li

1/4/2008 02:37:46 PM

BIOEQUIVALENCE STATISTICIAN

This version incorporated Ruthanna Davi's comments. An old version
of this review was mistakenly sent in DFS
on Dec. 20th, 2007.

Ruth Davi

1/4/2008 04:00:45 PM

BIOMETRICS



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation Clinical Studies

Drug Name: Alvesco (ciclesonide)

Indication(s): Alvesco is proposed to be indicated for the maintenance treatment of asthma as prophylactic therapy in adult and ~~pediatric~~ patients ¹⁸ years of age and older. **b(4)**

Applicant: Aventis Pharmaceuticals Inc.

Date(s): Applicant's letter date: July 10, 2007
Review completion date:

NDA/Serial Number: NDA 21-658/N000

Review Priority: Standard

Biometrics Division: Biometrics Division 2

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Executive Summary

Recommendations

Based on evaluation of Studies 3031 and 3030, ciclesonide at either 100 x 2 puffs q.d. or 50 x 2 puffs b.i.d. demonstrated statistically significant superiority to placebo. I recommend the approval Alvesco at these dose regimens. In addition, I recommend that the following adverse events be considered to appear in the label: headache, nasopharyngitis, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, cough, back pain, gastroenteritis viral, toothache, and dizziness.

Brief Overview of Clinical Studies

To address the deficiencies detailed in the 10/21/2004 Agency's action letter, the sponsor submitted to the Agency on 7/10/2007 a NDA Amendment – COMPLETE RESPONSE TO APPROVABLE LETTER. Submitted with this letter were two clinical studies: Studies 3030 and 3031 intended to address the issues associated with the efficacy claim for the label.

Studies 3030 and 3031 are described in the following table. Based on evidence provided in these studies, I evaluated the effectiveness of Alvesco at specified dose regimens.

Table 1 Clinical studies reviewed

Study	Objective	Design	Evaluated
3031	Efficacy and safety	Phase-3 multi-center, randomized, double-blind, placebo-controlled, parallel-group study for asthmatic patients previously on bronchodilators alone	Efficacy and safety
3030	Efficacy and safety	Same as Study 3031, except that the participating asthmatic patients were previously treated with corticosteroids	Efficacy and safety

In Table 2, below, terms written in the same row represent the same treatment, and they are used interchangeably by the sponsor in previously submitted study reports. In this report, treatments are described using the terms in the first column.

Table 2 Label of the treatments

Treatment	Ex-valve	Ex-actuator
Placebo	Placebo	Placebo
Alvesco 50 µg, 2 puffs, QD	Alvesco 100 µg/day	Alvesco 80 µg/day
Alvesco 100 µg, 2 puffs, QD	Alvesco 200 µg/day	Alvesco 160 µg/day
Alvesco 200 µg, 2 puffs, QD	Alvesco 400 µg/day	Alvesco 320 µg/day

Statistical Findings

Efficacy

Based on evaluation of Studies 3031 and 3030, ciclesonide at either 100 x 2 puffs q.d. or 50 x 2 puffs b.i.d. demonstrated statistically significant superiority to placebo as shown in Table 3. This finding satisfied the Agency's concern in 10/21/2004's action letter.

Table 3 Efficacy findings based on mean FEV₁ change from baseline to endpoint from Studies 3031 and 3030

Study	Comparator	Treatment	LS mean Diff.	P value	95% confidence interval
3031	Placebo	100 x 2 puffs q.d.	0.13	0.0022	0.05, 0.21
		50 x 2 puffs b.i.d.	0.25	<.0001	0.17, 0.33
3030		100 x 2 puffs q.d.	0.13	0.0018	0.05, 0.21
		50 x 2 puffs b.i.d.	0.20	<.0001	0.12, 0.28

Source: Sponsor's data EFPFT (ITT patients, LOCF for missing values)

The above findings were obtained from an analysis of covariance of FEV₁ change from baseline to endpoint. For Study 3031, the endpoint was defined as the average FEV₁ of Week 12 and Week 16, while for Study 3030, the FEV₁ of Week 12.

Note that in previously submitted study reports, Studies 321 and 322, the statistical superiority of ciclesonide 100 x 2 puffs q.d. to placebo was not consistently demonstrated. This issue was sufficiently addressed in Studies 3030 and 3031.

Safety

Based on the analysis of the sponsor's AE data, the most frequent AEs included headache, nasopharyngitis, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, cough, back pain, gastroenteritis viral, toothache, and dizziness (See Table 4 and Table 5, below, for AEs in 2%+ of the patients alone. Complete lists of AEs can be found in the Appendix).

Table 4 AEs in 2%+ patients (Studies 3031)

AEs in MedDRA preferred terms	Treatment								N (=700)	%
	Placebo N=178		Alvesco 100x2pf QD N=176		Alvesco 50x2pf BID N=173		Alvesco 50-to-100 N=173			
	N	%	N	%	N	%	N	%		
NO AE REPORTED	76	42.70	78	44.32	73	42.20	75	43.35	302	43.14
Asthma	26	14.61	14	7.95	10	5.78	18	10.40	68	9.71
Headache	16	8.99	18	10.23	15	8.67	18	10.40	67	9.57
Nasopharyngitis	18	10.11	19	10.80	21	12.14	9	5.20	67	9.57
Upper respiratory tract infection	11	6.18	7	3.98	10	5.78	13	7.51	41	5.86
Pharyngolaryngeal pain	8	4.49	6	3.41	8	4.62	5	2.89	27	3.86
Influenza	4	2.25	8	4.55	6	3.47	6	3.47	24	3.43
Sinusitis	3	1.69	7	3.98	5	2.89	6	3.47	21	3.00
Cough	5	2.81	4	2.27	6	3.47	3	1.73	18	2.57
Nausea	3	1.69	4	2.27	5	2.89	4	2.31	16	2.29
Back pain	3	1.69	3	1.70	3	1.73	6	3.47	15	2.14
Rhinitis allergic	3	1.69	4	2.27	5	2.89	2	1.16	14	2.00
Diarrhoea	2	1.12	3	1.70	4	2.31	3	1.73	12	1.71
Vomiting	4	2.25	2	1.14	2	1.16	4	2.31	12	1.71
Dizziness	3	1.69	1	0.57	4	2.31	3	1.73	11	1.57
Gastroenteritis viral			2	1.14	5	2.89	4	2.31	11	1.57
Nasal congestion	6	3.37	2	1.14	2	1.16	1	0.58	11	1.57
Pain in extremity	5	2.81	3	1.70	1	0.58	1	0.58	10	1.43
Pharyngitis	1	0.56	1	0.57	5	2.89	3	1.73	10	1.43
Pyrexia	2	1.12	3	1.70	3	1.73	2	1.16	10	1.43
Toothache	1	0.56	3	1.70	2	1.16	4	2.31	10	1.43
Viral infection	1	0.56	3	1.70			5	2.89	9	1.29
Bronchitis	1	0.56	3	1.70			4	2.31	8	1.14
Rhinitis	2	1.12	4	2.27	2	1.16			8	1.14
Abdominal pain	4	2.25	1	0.57			2	1.16	7	1.00
Back injury	4	2.25			3	1.73			7	1.00

Source: AE2 Somnolence

Table 5 AEs in 2%+ patients (Studies 3030)

AEs in MedDRA preferred terms	Treatment						N (=456)	%
	Placebo N=152		Alvesco 100x2pf QD N=152		Alvesco 50x2pf BID N=152			
	N	%	N	%	N	%		
NO AE REPORTED	64	42.11	62	40.79	71	46.71	197	43.20
Nasopharyngitis	10	6.58	19	12.50	16	10.53	45	9.87
Asthma	27	17.76	7	4.61	5	3.29	39	8.55
Upper respiratory tract infection	12	7.89	12	7.89	14	9.21	38	8.33

AEs in MedDRA preferred terms	Treatment						N (=456)	%
	Placebo N=152		Alvesco 100x2pf QD N=152		Alvesco 50x2pf BID N=152			
	N	%	N	%	N	%		
Pharyngolaryngeal pain	5	3.29	8	5.26	9	5.92	22	4.82
Sinusitis	7	4.61	9	5.92	5	3.29	21	4.61
Headache	6	3.95	6	3.95	7	4.61	19	4.17
Cough	4	2.63	8	5.26	3	1.97	15	3.29
Back pain	5	3.29	5	3.29	1	0.66	11	2.41
Gastroenteritis viral	2	1.32	6	3.95	1	0.66	9	1.97
Hypersensitivity	4	2.63	4	2.63	1	0.66	9	1.97
Toothache	2	1.32	5	3.29	2	1.32	9	1.97
Dizziness	1	0.66	4	2.63	2	1.32	7	1.54

Source: AE2

Introduction

Overview

In the 10/21/2004 action letter, the Division stated that the submitted clinical data did not support efficacy of Alvesco for the proposed indication in patients 4 years of age and older. Specifically, the data did not support the efficacy of the drug for patients on bronchodilators alone. In addition, the data did not support the QD regimen for various proposed doses (FDA-interactions.pdf).

Later, at a Type A meeting with the sponsor dated 12/3/2004, the division emphasized that it did not agree that the 80 and 160 mcg once daily doses were effective for lack of reproducibility of evidence, based on Studies 321 and 322, two separate, fully powered Phase-3 studies.

To address the deficiencies, the sponsor submitted to the Agency on 7/10/2007 the **NDA Amendment – COMPLETE RESPONSE TO APPROVABLE LETTER** with efficacy and safety Studies 3030, 3031, along with other studies. The Division considers the sponsor's 7/10/2007 response to be acceptable for evaluation.

Scope of Statistical Review

Studies 3030 and 3031 are evaluated for effectiveness and safety.

Data Sources

The sponsor's data were submitted to EDR as SAS transport files.

Statistical Evaluation

Evaluation of Efficacy

Study Designs and Endpoints

Studies 3031 and 3030 had similar study designs.

Studies 3031 was multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy of ciclesonide metered-dose inhaler at a daily dose of 160 µg administered either in a once-daily in the morning regimen (160 µg q.d. AM) for 16 weeks or in a 160 µg q.d. AM regimen for 12 weeks preceded by a twice-daily regimen (80 µg b.i.d.) for 4 weeks, or in an 80 µg b.i.d. regimen for 16 weeks, in adults and adolescents with mild to moderate persistent asthma not treated with steroids (treated with bronchodilators alone) (quote from study synopsis).

Studies 3030 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of ciclesonide metered-dose inhaler at a daily dose of 160 µg administered for 12 weeks either in a once-daily regimen in the morning (160 µg q.d. AM) or in a twice-daily regimen (80 µg b.i.d.) in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled corticosteroids (quote from study synopsis).

The two studies differ in the following way:

Table 6 Differences in design between Studies 3031 and 3030

Comparison of designs	Study 3031	Study 3030
International	Yes	No
Study duration	16 weeks	12 weeks
Treatment groups	(1) 100 µg q.d. (2) 50 µg b.i.d. (4 weeks) switching to 100 µg q.d. (12 weeks) (3) 50 µg b.i.d.	(1) 100 µg q.d. (2) 50 µg b.i.d.
Previous treatment	bronchodilators	corticosteroids

For these studies, the primary objective was to investigate the efficacy of ciclesonide compared to placebo. The secondary objective was to evaluate the safety of ciclesonide compared to placebo.

The primary efficacy variable was the change in FEV₁ (L) from baseline (Day 1) to endpoint. For Study 3031, endpoint was defined as the average FEV₁ of Week 12 (Visit 7) and Week 16 (Visit 8) (p. 42, 3031.pdf); for Study 3030, the FEV₁ of Week 12 (Visit 10) (p. 42, 3030.pdf). The baseline was defined as the pre-randomization FEV₁ measurement.

Analysis Patient Populations

The primary efficacy analysis was based on the ITT population for both studies. There were 691 and 456 ITT patients in Studies 3031 and 3030, respectively.

Patient Distributions of Demographic and Baseline Characteristics

The following analyses were done based on the ITT patient population.

Study 3031

Table 7 shows the numbers and percents of non-missing patients' FEV₁ data by time point. The table was produced based on data set EFPFT. This was the only data set in the submission that enables counting numbers of patients remaining in study over time. The counting of numbers of patients was done by counting number of non-missing FEV₁ over time. It is worth noting that the number of non-missing FEV₁ at a time point, say Week 16, could be different from the actual number of patients present at that time point, because it is entirely possible that some patients appeared at a time point with missing FEV₁ observation. Note, at Week 16, there were at least 78% of the patients remained in study.

Table 7 Numbers and percentages of FEV₁ present and missing by treatment and visit based on efficacy data (Study 3031)

		Total N	N	% present	% missing
Placebo	DAY1	178	178	100%	0%
	WK2	178	176	99%	1%
	WK4	178	167	94%	6%
	WK8	178	160	90%	10%
	WK12	178	145	81%	19%
	WK16	178	139	78%	22%
Alvesco 100x2pf QD	DAY1	176	176	100%	0%
	WK2	176	173	98%	2%
	WK4	176	165	94%	6%
	WK8	176	162	92%	8%
	WK12	176	155	88%	12%

		Total N	N	% present	% missing
Alvesco 50x2pf BID	WK16	176	150	85%	15%
	DAY1	173	173	100%	0%
	WK2	173	170	98%	2%
	WK4	173	166	96%	4%
	WK8	173	163	94%	6%
	WK12	173	161	93%	7%
Alvesco 50-to-100	WK16	173	158	91%	9%
	DAY1	173	173	100%	0%
	WK2	173	169	98%	2%
	WK4	173	162	94%	6%
	WK8	173	163	94%	6%
	WK12	173	158	91%	9%
	WK16	173	156	90%	10%

Source: RVISIT (analysis2.sas)

Table 8 lists the reasons for discontinuation for the ITT patients. It appeared that patients on ciclesonide q.d. regimen were more likely to drop out than those on ciclesonide b.i.d. regimen because of adverse events.

Table 8 Reason for discontinuation (Study 3031)

Reasons for withdrawal	Treatment								Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to-100			
	N	%	N	%	N	%	N	%	N	%
(Stay in study)	137	77.0	148	84.1	159	91.9	155	89.6	599	85.6
Adverse event	23	12.9	14	8.0	4	2.3	8	4.6	49	7.0
Lack of efficacy	5	2.8	2	1.1	2	1.2			9	1.3
Lost to follow up	1	0.6	1	0.6	3	1.7	2	1.2	7	1.0
Protocol violation			3	1.7	1	0.6	1	0.6	5	0.7
Did not wish to continue	10	5.6	7	4.0	3	1.7	6	3.5	26	3.7
Other	2	1.1	1	0.6	1	0.6	1	0.6	5	0.7
Total	178	100.0	176	100.0	173	100.0	173	100.0	700	100.0

Source: DEMO

Table 9 and Table 10 show the numbers and percentages of ITT patients by treatment and race or sex. About 75% of the patients were whites. Males accounted for 46% of the patients. The patients' ages ranged from 12 to 73 with an average of 37 (Table 11). Based on the demographic measures, I consider the treatment groups to be balanced.

Table 9 Number of patients by treatment and race (Study 3031)

Race	Treatment								Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to-100			
	N	%	N	%	N	%	N	%	N	%
Asian/Oriental	3	1.7	3	1.7	4	2.3	2	1.2	12	1.7
Black	18	10.1	12	6.8	11	6.4	20	11.6	61	8.7
Multiracial	11	6.2	8	4.5	9	5.2	4	2.3	32	4.6
Other	16	9.0	17	9.7	20	11.6	18	10.4	71	10.1
White	130	73.0	136	77.3	129	74.6	129	74.6	524	74.9
Total	178	100.0	176	100.0	173	100.0	173	100.0	700	100.0

Source: DEMO

Table 10 Number of patients by treatment and sex (Study 3031)

Sex	Treatment								Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to-100			
	N	%	N	%	N	%	N	%	N	%
Female	100	56.2	85	48.3	93	53.8	102	59.0	380	54.3
Male	78	43.8	91	51.7	80	46.2	71	41.0	320	45.7
Total	178	100.0	176	100.0	173	100.0	173	100.0	700	100.0

Source: DEMO

Table 11 Analysis of patient-age distribution by treatment (Study 3031)

	N	Mean	Min	Max	Lower quartile	Upper quartile
– Overall –	700	37	12	73	23	49
Placebo	178	37	12	69	24	49
Alvesco 100x2pf QD	176	36	12	72	22	49
Alvesco 50x2pf BID	173	36	12	71	23	48
Alvesco 50-to-100	173	38	12	73	24	50

Source: DEMO

Study 3030

I did the same analyses for Study 3030. They are shown in the following tables.

Table 12 shows the numbers and percents of non-missing patients' FEV₁ data by time point. The table was produced based on data set EFPFT. Note, at Week 12, there were 68% of the patients on placebo remained in study; there were 89% of the patients on ciclesonide regimen remained in study.

Table 12 Numbers and percentages of FEV₁ present and missing by treatment and visit based on efficacy data (Study 3030)

		Total N	N	% present	% missing
Placebo	DAY1	152	152	100%	0%
	WK1	152	147	97%	3%
	WK2	152	132	87%	13%
	WK3	152	120	79%	21%
	WK4	152	116	76%	24%
	WK6	152	110	72%	28%
	WK8	152	107	70%	30%
	WK12	152	104	68%	32%
Alvesco 100x2pf QD	DAY1	152	152	100%	0%
	WK1	152	150	99%	1%
	WK2	152	149	98%	2%
	WK3	152	145	95%	5%
	WK4	152	141	93%	7%
	WK6	152	139	91%	9%
	WK8	152	137	90%	10%
	WK12	152	135	89%	11%
Alvesco 50x2pf BID	DAY1	152	152	100%	0%
	WK1	152	148	97%	3%
	WK2	152	146	96%	4%
	WK3	152	145	95%	5%
	WK4	152	143	94%	6%
	WK6	152	138	91%	9%
	WK8	152	137	90%	10%
	WK12	152	136	89%	11%

Source: RVISIT (analysis2.sas)

Table 13 lists the reasons for discontinuation for the ITT patients. The reasons for dropping out appear to be expected.

Table 13 Reason for discontinuation (Study 3030)

Reasons for withdrawal	Treatment						Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%	N	%
(Stay in study)	103	67.8	134	88.2	135	88.8	372	81.6
Adverse Event	23	15.1	7	4.6	8	5.3	38	8.3
Lack of efficacy	14	9.2	5	3.3	3	2.0	22	4.8
Lost to follow up	1	0.7					1	0.2
Protocol violation	4	2.6	5	3.3	4	2.6	13	2.9
did not wish to continue	4	2.6	1	0.7	1	0.7	6	1.3
other	3	2.0			1	0.7	4	0.9
Total	152	100.0	152	100.0	152	100.0	456	100.0

Source: DEMO

Table 14 and Table 15 show the numbers and percentages of ITT patients by treatment and race or sex. About 86% of the patients were whites. Males accounted for 38% of the patients.

Table 14 Number of patients by treatment and race (Study 3030)

Race	Treatment						Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%	N	%
Asian/Oriental	2	1.3	3	2.0	1	0.7	6	1.3
Black	14	9.2	7	4.6	5	3.3	26	5.7
Multiracial	6	3.9	2	1.3	4	2.6	12	2.6
Other	7	4.6	6	3.9	7	4.6	20	4.4
White	123	80.9	134	88.2	135	88.8	392	86.0
Total	152	100.0	152	100.0	152	100.0	456	100.0

Source: DEMO

Table 15 Number of patients by treatment and sex (Study 3030)

Sex	Treatment						Total	
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%	N	%
Female	97	63.8	93	61.2	94	61.8	284	62.3
Male	55	36.2	59	38.8	58	38.2	172	37.7
Total	152	100.0	152	100.0	152	100.0	456	100.0

Source: DEMO

The patients' ages ranged from 12 to 79 with an average of 39 (Table 16). Based on the demographic measures, I consider the treatment groups to be balanced.

Table 16 Analysis of patient-age distribution by treatment (Study 3030)

	N	Mean	Min	Max	Lower quartile	Upper quartile
- Over all -	456	39	12	79	28	51
Placebo	152	39	12	79	28	50
Alvesco 100x2pf QD	152	41	12	73	32	52
Alvesco 50x2pf BID	152	38	12	72	25	49

Source: DEMO

Efficacy Analysis and Results

The sponsor applied ANCOVA of the FEV₁ change from baseline to the endpoint¹ based on the ITT population for the primary efficacy assessment. The statistical model included factors of treatment, center (pooled), sex; and covariates of age and baseline FEV₁. In the case of early termination before the endpoint, LOCF was employed to obtain the endpoint FEV₁.

I verified the sponsor's approach. I also applied a different ANCOVA model including factors of treatment, center (pooled); and baseline FEV₁ as a covariate. I analyzed the data with and without the LOCF approach to compare results. I think, in a randomized clinical study and in a fairly balanced data, age and sex are not necessarily needed in the model.

I am primarily concerned about the comparison between ciclesonide and placebo. The comparison between ciclesonide q.d. and b.i.d. are of descriptive nature. Table 19 and Table 23 show that ciclesonide in both q.d. and b.i.d. dosing regimens are statistically superior to placebo.

Study 3031

Table 17 shows mean FEV₁ change from baseline to the average FEV₁ of Week 12 and Week 16. The same statistics based on the completers can be found in Table 18. The LS-means, based on the LOCF and completer's data over time are depicted in Figure 1 and Figure 2, respectively. Note that the group of ciclesonide 50 b.i.d. to 100 q.d. switch behaved similar to the 50 b.i.d. group for the first 4 weeks, then behaved similar to the 100 q.d. group. Furthermore, at Week 16, the 50 b.i.d.-to-100 q.d. group behaved somewhat worse than the 100 q.d. group, based on completers (Figure 2). Overall, the ciclesonide b.i.d. group consistently worked better than the q.d. group.

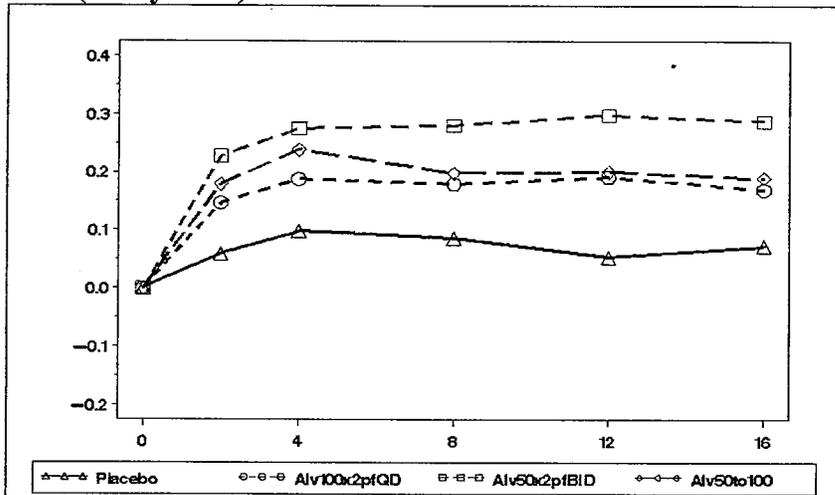
Table 17 Mean FEV₁ change from baseline to the average of Week 12 and Week 16 (Study 3031)

Treatment	#Patients	Mean	Std. Error	Lower CL	Upper CL
Placebo	177	0.06	0.03	0.00	0.11
Alv 100x2pf QD	173	0.18	0.03	0.13	0.24
Alv 50x2pf BID	170	0.30	0.03	0.25	0.36
Alv 50 to 100	171	0.19	0.03	0.13	0.24

Source: IMEAN (LOCF, analysis3.sas)

¹ For Study 3031, it is the mean FEV₁ change from baseline to the average of Weeks 12 and 16. For Study 3030, it is the mean FEV₁ change from baseline to the end of study (Week 12)

Figure 1 LS-Mean FEV₁ change from baseline over time in weeks based on LOCF data (Study 3031)



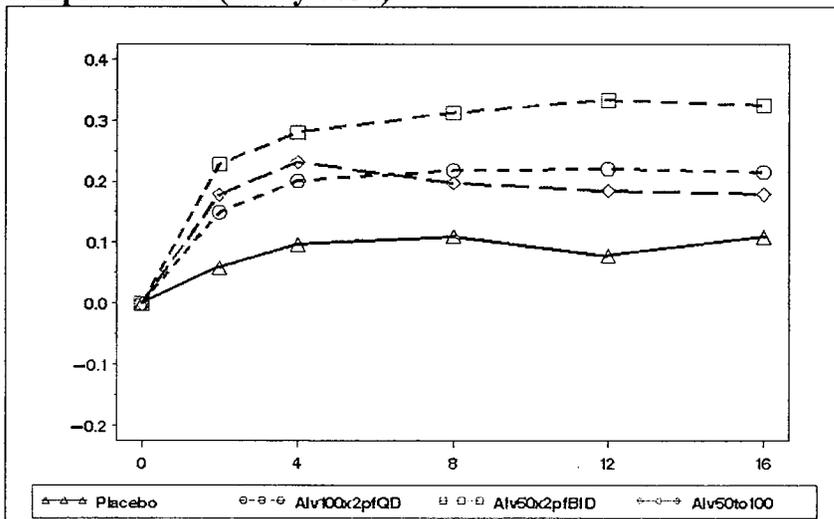
Source: IVISIT (LOCF for missing data)

Table 18 Mean FEV₁ change from baseline to the average of Week 12 and Week 16 (Completer, Study 3031)

Treatment	#Patients	Mean	Std. Error	Lower CL	Upper CL
Placebo	138	0.11	0.03	0.05	0.17
Alv 100x2pf QD	149	0.23	0.03	0.16	0.29
Alv 50x2pf BID	158	0.33	0.03	0.27	0.39
Alv 50 to 100	155	0.18	0.03	0.12	0.24

Source: RVISIT (completers)

Figure 2 LS-Mean FEV₁ change from baseline over time in weeks based on completer data (Study 3031)



Source: RVISIT (completers)

Table 19 Comparison of Alvesco with placebo based on ITT patients (Study 3031)

Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
Alv 100x2pf QD	Placebo	0.13	0.04	0.0022	0.05	0.21
Alv 50x2pf BID	Placebo	0.25	0.04	<.0001	0.17	0.33
Alv 100x2pf QD	Alv 50x2pf BID	-0.12	0.04	0.0033	-0.20	-0.04

Source: IMEAN (LOCF) (analysis3.sas)

Table 20 shows that the statistical findings based on completers (n=600) are consistent with those based on all ITT patients.

Table 20 Comparison of Alvesco with placebo based on completers (Study 3031)

Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
Alv 100x2pf QD	Placebo	0.12	0.04	0.0095	0.03	0.20
Alv 50x2pf BID	Placebo	0.22	0.04	<.0001	0.14	0.31
Alv 100x2pf QD	Alv 50x2pf BID	-0.11	0.04	0.0112	-0.19	-0.02

Source: RCOMPLETE (analysis3-ted locf_n_completer.sas)

Table 19 and Table 20, above, show that ciclesonide at 50 b.i.d. and 100 q.d. are superiority to placebo.

Study 3030

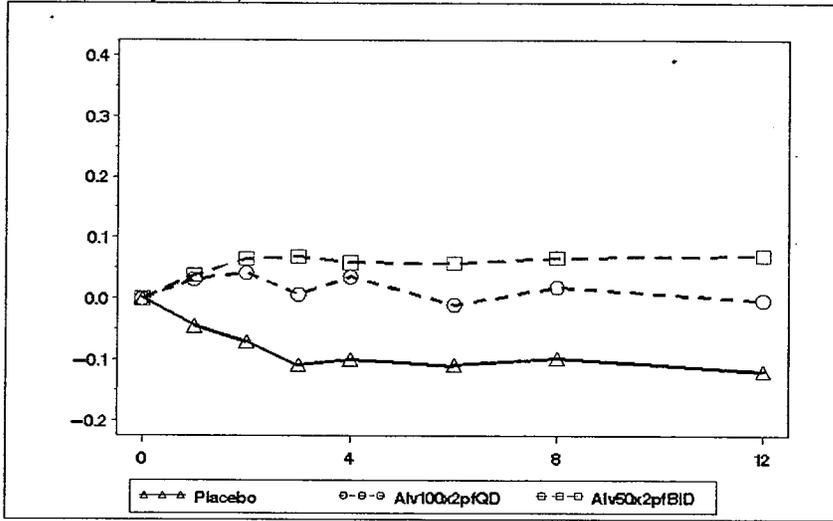
Table 21 shows mean FEV₁ change from baseline to Week 12. same statistics based on the completers can be found in Table 22. The LS-means, based on LOCF and completer's data, over time are depicted in Figure 3 and Figure 4, respectively. Note that the ciclesonide b.i.d. group consistently worked better than the q.d. group. Very much different from the statistics shown in Table 17 for Study 3031, here, the mean changes from baseline in FEV₁ at Week 12 appear to be very small numerically: 0.06 (L) for ciclesonide 50 b.i.d. and 0.01 (L) for ciclesonide 100 q.d., indicating a weak evidence for the effectiveness of ciclesonide. Table 23 does show a statistically significant difference between ciclesonide and placebo, based on the analysis of the ITT patients. This might be due to the negative change from baseline for placebo group. Moreover, the findings are not consistent between the ITT group and the completer group (See Table 24 and my comments.).

Table 21 Mean FEV₁ change from baseline to Week 12 (Study 3030)

Treatment	#Patients	Mean	Std. Error	Lower CL	Upper CL
Placebo	152	-0.13	0.03	-0.19	-0.07
Alv 100x2pf QD	152	0.00	0.03	-0.06	0.05
Alv 50x2pf BID	152	0.07	0.03	0.01	0.12

Source: IMEAN (LOCF)

Figure 3 LS-Mean FEV₁ change from baseline over time in weeks based on LOCF data (Study 3030)



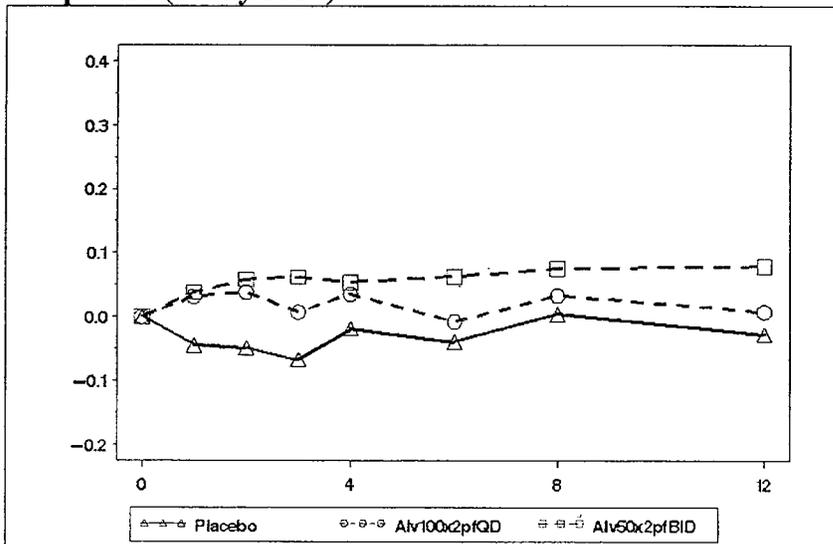
Source: IVISIT (LOCF for missing data)

Table 22 Mean FEV₁ change from baseline to Week 12 (Completer, Study 3030)

Treatment	#Patients	Mean	Std. Error	Lower CL	Upper CL
Placebo	104	-0.04	0.03	-0.10	0.02
Alv 100x2pf QD	135	0.02	0.03	-0.04	0.07
Alv 50x2pf BID	135	0.08	0.03	0.03	0.14

Source: RVISIT (completer)

Figure 4 LS-Mean FEV₁ change from baseline over time in weeks based on completers (Study 3030)



Source: RVISIT (completer)

Table 23 Comparison of Alvesco with placebo based on ITT patients (Study 3030)

Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
Alv 100x2pf QD	Placebo	0.13	0.04	0.0018	0.05	0.21
Alv 50x2pf BID	Placebo	0.20	0.04	<.0001	0.12	0.28
Alv 100x2pf QD	Alv 50x2pf BID	-0.07	0.04	0.0833	-0.15	0.01

Source: IMEAN (LOCF) (analysis3-wk12.sas)

Table 24 shows that the statistical findings based on completers (n=374) are not quite consistent with those based on all ITT patients: Note that ciclesonide 100 q.d. did not appear to perform significantly better than placebo.

Table 24 Comparison of Alvesco with placebo based on completers (Study 3030)

Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
Alv 100x2pf QD	Placebo	0.06	0.04	0.1829	-0.03	0.14
Alv 50x2pf BID	Placebo	0.12	0.04	0.0036	0.04	0.20
Alv 100x2pf QD	Alv 50x2pf BID	-0.07	0.04	0.0848	-0.14	0.01

Source: RCOMPLETE (analysis3-ted locf n completer.sas)

For Study 3030, I also analyzed the same data based on mean FEV₁ change from baseline to the average of Week 8 and Week 12, a similar approach to that for Study 3031. The results are consistent with those shown in Table 23. To keep the report concise, I omitted those exploratory analyses.

Evaluation of Safety

My safety analyses were solely based on the analyses of adverse events reported by the sponsor.

Table 25 and Table 26 show the numbers and percentages of AEs using MedDRA terms reported in more than 2% of the patients for Study 3031 and 3030, respectively. Complete lists of AEs for both studies can be found in the Appendix. The first item in each table, NO_AE_REPORTED, represents patients from whom no AEs were reported. Of note, whether the sponsor strictly followed the MedDRA preferred term has not been examined. Some AEs might not be correctly defined. Ciclesonide is being developed to treat asthma. Reporting asthma as an adverse event, in my opinion, is not appropriate, because asthma is the disease ciclesonide is intended to treat, rather than an adverse reaction possibly induced by the drug.

Table 25 Selected AE findings (Study 3031)

AEs in MedDRA preferred terms	Treatment								N (=700)	%
	Placebo N=178		Alvesco 100x2pf QD N=176		Alvesco .50x2pf BID N=173		Alvesco 50-to-100 N=173			
	N	%	N	%	N	%	N	%		
NO AE REPORTED	76	42.70	78	44.32	73	42.20	75	43.35	302	43.14
Asthma	26	14.61	14	7.95	10	5.78	18	10.40	68	9.71
Headache	16	8.99	18	10.23	15	8.67	18	10.40	67	9.57
Nasopharyngitis	18	10.11	19	10.80	21	12.14	9	5.20	67	9.57
Upper respiratory tract infection	11	6.18	7	3.98	10	5.78	13	7.51	41	5.86
Pharyngolaryngeal pain	8	4.49	6	3.41	8	4.62	5	2.89	27	3.86
Influenza	4	2.25	8	4.55	6	3.47	6	3.47	24	3.43
Sinusitis	3	1.69	7	3.98	5	2.89	6	3.47	21	3.00
Cough	5	2.81	4	2.27	6	3.47	3	1.73	18	2.57
Nausea	3	1.69	4	2.27	5	2.89	4	2.31	16	2.29
Back pain	3	1.69	3	1.70	3	1.73	6	3.47	15	2.14
Rhinitis allergic	3	1.69	4	2.27	5	2.89	2	1.16	14	2.00
Diarrhoea	2	1.12	3	1.70	4	2.31	3	1.73	12	1.71
Vomiting	4	2.25	2	1.14	2	1.16	4	2.31	12	1.71
Dizziness	3	1.69	1	0.57	4	2.31	3	1.73	11	1.57
Gastroenteritis viral			2	1.14	5	2.89	4	2.31	11	1.57
Nasal congestion	6	3.37	2	1.14	2	1.16	1	0.58	11	1.57
Pain in extremity	5	2.81	3	1.70	1	0.58	1	0.58	10	1.43
Pharyngitis	1	0.56	1	0.57	5	2.89	3	1.73	10	1.43
Pyrexia	2	1.12	3	1.70	3	1.73	2	1.16	10	1.43
Toothache	1	0.56	3	1.70	2	1.16	4	2.31	10	1.43
Viral infection	1	0.56	3	1.70			5	2.89	9	1.29
Bronchitis	1	0.56	3	1.70			4	2.31	8	1.14
Rhinitis	2	1.12	4	2.27	2	1.16			8	1.14
Abdominal pain	4	2.25	1	0.57			2	1.16	7	1.00
Back injury	4	2.25			3	1.73			7	1.00

Source: AE2

Table 26 Selected AE findings (Study 3030)

AEs in MedDRA preferred terms	Treatment						N (=456)	%
	Placebo N=152		Alvesco 100x2pf QD N=152		Alvesco 50x2pf BID N=152			
	N	%	N	%	N	%		
NO AE REPORTED	64	42.11	62	40.79	71	46.71	197	43.20
Nasopharyngitis	10	6.58	19	12.50	16	10.53	45	9.87
Asthma	27	17.76	7	4.61	5	3.29	39	8.55
Upper respiratory tract infection	12	7.89	12	7.89	14	9.21	38	8.33

AEs in MedDRA preferred terms	Treatment						N (=456)	%
	Placebo N=152		Alvesco 100x2pf QD N=152		Alvesco 50x2pf BID N=152			
	N	%	N	%	N	%		
Pharyngolaryngeal pain	5	3.29	8	5.26	9	5.92	22	4.82
Sinusitis	7	4.61	9	5.92	5	3.29	21	4.61
Headache	6	3.95	6	3.95	7	4.61	19	4.17
Cough	4	2.63	8	5.26	3	1.97	15	3.29
Back pain	5	3.29	5	3.29	1	0.66	11	2.41
Gastroenteritis viral	2	1.32	6	3.95	1	0.66	9	1.97
Hypersensitivity	4	2.63	4	2.63	1	0.66	9	1.97
Toothache	2	1.32	5	3.29	2	1.32	9	1.97
Dizziness	1	0.66	4	2.63	2	1.32	7	1.54

Source: AE2

Findings in Special/Subgroup Populations

The purpose of the following subgroup analyses is to show consistency of the treatment effect across groups of selected demographic characteristics. Such analyses are of exploratory nature.

Table 27 Subgroup analyses by selected demographic characteristics for Study 3031

Subgroup	#Patients	Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
White	133	Alv 100x2pf QD	Placebo (N=129)	0.12	0.05	0.0132	0.03	0.22
	126	Alv 50x2pf BID		0.22	0.05	<.0001	0.12	0.31
Non-white	40	Alv 100x2pf QD	Placebo (N=48)	0.17	0.09	0.0714	-0.01	0.35
	44	Alv 50x2pf BID		0.25	0.09	0.0052	0.08	0.42
Female	83	Alv 100x2pf QD	Placebo (N=100)	0.13	0.05	0.0149	0.03	0.24
	91	Alv 50x2pf BID		0.27	0.05	<.0001	0.17	0.37
Male	90	Alv 100x2pf QD	Placebo (N=77)	0.10	0.07	0.1597	-0.04	0.25
	79	Alv 50x2pf BID		0.19	0.08	0.0135	0.04	0.33
65+	6	Alv 100x2pf QD	Placebo (N=6)	-0.31	0.49	0.5641	-1.67	1.05
	5	Alv 50x2pf BID		-0.14	0.58	0.8272	-1.75	1.48
<65	167	Alv 100x2pf QD	Placebo (N=171)	0.12	0.04	0.0066	0.03	0.20
	165	Alv 50x2pf BID		0.23	0.04	<.0001	0.15	0.31

FOREIGN	73	Alv 100x2pf QD	Placebo (N=74)	0.07	0.06	0.2466	-0.05	0.19
	70	Alv 50x2pf BID		0.20	0.06	0.0011	0.08	0.31
USA	100	Alv 100x2pf QD	Placebo (N=103)	0.16	0.06	0.0068	0.04	0.27
	100	Alv 50x2pf BID		0.25	0.06	<.0001	0.14	0.36

Source: IMEAN (analysis4-subgroup.sas)

Table 28 Subgroup analyses by selected demographic characteristics for Study 3030

Subgroup	#Patients	Treatment	Comparator	Mean	Std. Error	P-value	Lower CL	Upper CL
White	134	Alv 100x2pf QD	Placebo (N=123)	0.13	0.05	0.0032	0.05	0.22
	135	Alv 50x2pf BID		0.20	0.05	<.0001	0.11	0.29
non-white	18	Alv 100x2pf QD	Placebo (N=29)	-0.01	0.15	0.9294	-0.32	0.29
	17	Alv 50x2pf BID		0.15	0.15	0.3141	-0.15	0.45
Female	93	Alv 100x2pf QD	Placebo (N=97)	0.09	0.05	0.0602	-0.00	0.18
	94	Alv 50x2pf BID		0.14	0.05	0.0037	0.04	0.23
Male	59	Alv 100x2pf QD	Placebo (N=55)	0.20	0.08	0.0162	0.04	0.36
	58	Alv 50x2pf BID		0.28	0.09	0.0015	0.11	0.45
65+	5	Alv 100x2pf QD	Placebo (N=7)	0.22	0.15	0.1606	-0.10	0.54
	8	Alv 50x2pf BID		0.38	0.13	0.0093	0.11	0.64
<65	147	Alv 100x2pf QD	Placebo (N=145)	0.10	0.04	0.0210	0.02	0.18
	144	Alv 50x2pf BID		0.17	0.04	<.0001	0.09	0.26

Source: IWK12 (analysis4-subgroup.sas)

Note: When comparing Alv 100x2pf QD with placebo in patients 65+ years of age, the center effect was excluded from the ANCOVA model so that the LS-means and other statistics could be computed.

Summary and Conclusions

Statistical issues and Collective Evidence

Based on evaluation of Studies 3031 and 3030, ciclesonide at either 100 x 2 puffs q.d. or 50 x 2 puffs b.i.d. demonstrated statistically significant superiority to placebo. Very much

different from the statistical findings from Study 3031, in Study 3030, the mean changes from baseline in FEV₁ to the Week 12 endpoint appeared to be much smaller numerically, suggesting a weaker evidence for the effectiveness of ciclesonide in both dosage regimens. Ciclesonide at 50 b.i.d. in both studies appeared to be less effective than ciclesonide 100 q.d.

Conclusions and Recommendations

Efficacy

Based on evaluation of Studies 3031 and 3030, ciclesonide at either 100 x 2 puffs q.d. or 50 x 2 puffs b.i.d. demonstrated statistically significant superiority to placebo. In previously submitted study reports, Studies 321 and 322, significant effectiveness of ciclesonide 100 x 2 puffs q.d. over placebo was not consistently demonstrated. This issue was sufficiently addressed in Studies 3030 and 3031.

I recommend the approval Alvesco at these dose regimens.

Safety

The safety evaluation based on AE reports for Studies 3031 and 3030 showed that common AEs include: headache, nasopharyngitis, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, cough, back pain, gastroenteritis viral, toothache, and dizziness.

COMMENTS ON LABELING

I evaluated the sponsor's proposed label by verifying selected statistics presented in the areas of **Adverse Reactions** and **Clinical Studies** in the package insert.

Adverse Reactions

Table 29 that lists adverse reactions was based on the sponsor's proposed label. The sponsor produced this table based on " _____

Table 29 Sponsor's proposed label Table 1: _____

b(4)

My safety evaluation revealed more AEs than reported in this table. See Table 25 (Study 3031) and Table 26 (Study 3030) of this report for details. Based on the analysis of the sponsor's AE data, I recommend that the following adverse events be considered to appear in the label:

headache, nasopharyngitis, upper respiratory tract infection, haryngolaryngeal pain, sinusitis, cough, back pain, gastroenteritis viral, toothache, and dizziness.

Clinical Studies

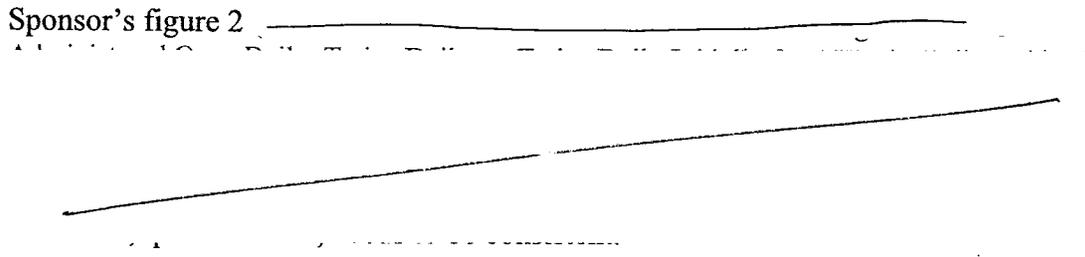
Study 3031

The sponsor in the proposed label said, " _____

b(4)

I compared these findings with the results of my own analyses (Table 17). These findings were confirmed to be correct.

Sponsor's figure 2



b(4)

Study 3030

The sponsor in the proposed label said, "At 12 weeks, significant increases in AM pre-dose FEV1 were seen for ALVESCO 160 mcg once daily (0.14 L or \sim %) and ALVESCO 80 mcg twice daily (0.19 L or \sim %) compared to a decrease of 5.2% in placebo, resulting in a difference versus placebo of 5.7% for ALVESCO 160 mcg once daily and 7.5% for ALVESCO 80 mcg twice daily."

b(4)

I compared these findings with the results of my own analyses (Table 23), which were very similar to the sponsor's findings.

I recommend that the sponsor revise the figures in the proposed label to make all the graphs with the same vertical scale. In addition, for the graphs showing the data from studies 3031 and 3030, I recommend that the sponsor use the primary efficacy variable (i.e., the mean change from baseline in FEV1 (L) other than the mean percentage values).

APPENDIX

Table 30 is the SAS program performing ANCOVA for the primary efficacy analysis.

Table 30 SAS program, analysis3.sas for ANCOVA

```
options mstored sasstore=sasuser fmtsearch=(&lib) nofmterr;
data one (label="&memlabel");
  set n2165830.IMean(rename=(center=centerind));
  rename sg_pool=center;
run;

ods trace on;
ods select None;
ods output LSmeans=lsm diffs=dif;
proc mixed data=one;
class treatment center;
model FEV1CHBL=treatment center fev1blva /e3;
lsmeans treatment/cl diff alpha=0.05;
quit;

ods select print;

proc print data=lsm noobs label;
var treatment estimate stderr lower upper;
label estimate='Mean' stderr='Std. Error'
lower='Lower CL' upper='Upper CL';
format estimate stderr lower upper 8.2;
run;

proc sort data=dif;
by _treatment;
proc print noobs label;
where treatment^=4 and _treatment^=4;
var treatment _treatment estimate stderr probt lower upper;
label trt='Treatment' _treatment='Comparator' estimate='Mean'
stderr='Std. Error' lower='Lower CL' upper='Upper CL' probt='P-value';
format estimate stderr lower upper 8.2;
run;
```

Table 31 and Table 32 list all AEs reported based on the Sponsor's data.

Table 31 AE findings (Study 3031)

AEs presented as: AEPTXT; Group totals: 178,176,173,173	Treatment								N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to- 100			
	N	%	N	%	N	%	N	%		
NO AE REPORTED	76	42.70	78	44.32	73	42.20	75	43.35	302	43.14
Asthma	26	14.61	14	7.95	10	5.78	18	10.40	68	9.71
Headache	16	8.99	18	10.23	15	8.67	18	10.40	67	9.57
Nasopharyngitis	18	10.11	19	10.80	21	12.14	9	5.20	67	9.57
Upper respiratory tract infection	11	6.18	7	3.98	10	5.78	13	7.51	41	5.86
Pharyngolaryngeal pain	8	4.49	6	3.41	8	4.62	5	2.89	27	3.86
Influenza	4	2.25	8	4.55	6	3.47	6	3.47	24	3.43

AEs presented as: AEPTXT; Group totals: 178,176,173,173	Treatment								N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to- 100			
	N	%	N	%	N	%	N	%		
Sinusitis	3	1.69	7	3.98	5	2.89	6	3.47	21	3.00
Cough	5	2.81	4	2.27	6	3.47	3	1.73	18	2.57
Nausea	3	1.69	4	2.27	5	2.89	4	2.31	16	2.29
Back pain	3	1.69	3	1.70	3	1.73	6	3.47	15	2.14
Rhinitis allergic	3	1.69	4	2.27	5	2.89	2	1.16	14	2.00
Diarrhoea	2	1.12	3	1.70	4	2.31	3	1.73	12	1.71
Vomiting	4	2.25	2	1.14	2	1.16	4	2.31	12	1.71
Dizziness	3	1.69	1	0.57	4	2.31	3	1.73	11	1.57
Gastroenteritis viral			2	1.14	5	2.89	4	2.31	11	1.57
Nasal congestion	6	3.37	2	1.14	2	1.16	1	0.58	11	1.57
Pain in extremity	5	2.81	3	1.70	1	0.58	1	0.58	10	1.43
Pharyngitis	1	0.56	1	0.57	5	2.89	3	1.73	10	1.43
Pyrexia	2	1.12	3	1.70	3	1.73	2	1.16	10	1.43
Toothache	1	0.56	3	1.70	2	1.16	4	2.31	10	1.43
Viral infection	1	0.56	3	1.70			5	2.89	9	1.29
Bronchitis	1	0.56	3	1.70			4	2.31	8	1.14
Rhinitis	2	1.12	4	2.27	2	1.16			8	1.14
Abdominal pain	4	2.25	1	0.57			2	1.16	7	1.00
Back injury	4	2.25			3	1.73			7	1.00
Hypersensitivity	2	1.12	1	0.57	3	1.73	1	0.58	7	1.00
Myalgia			3	1.70	3	1.73	1	0.58	7	1.00
Pain	3	1.69	1	0.57	2	1.16	1	0.58	7	1.00
Abdominal pain upper	2	1.12	1	0.57	1	0.58	2	1.16	6	0.86
Arthralgia	1	0.56	2	1.14	2	1.16	1	0.58	6	0.86
Lower respiratory tract infection	1	0.56	1	0.57	3	1.73	1	0.58	6	0.86
Rash	1	0.56	3	1.70	1	0.58	1	0.58	6	0.86
Respiratory tract infection	3	1.69	2	1.14			1	0.58	6	0.86
Sinus headache			1	0.57	2	1.16	3	1.73	6	0.86
Urinary tract infection			1	0.57	4	2.31	1	0.58	6	0.86
Bronchitis acute	1	0.56	1	0.57	1	0.58	2	1.16	5	0.71
Chest pain	3	1.69			2	1.16			5	0.71
Dysmenorrhoea	1	0.56					4	2.31	5	0.71
Ear pain	1	0.56	3	1.70	1	0.58			5	0.71
Neck pain	1	0.56	3	1.70	1	0.58			5	0.71
Dyspepsia	2	1.12	2	1.14					4	0.57
Dyspnoea					3	1.73	1	0.58	4	0.57
Ear infection			2	1.14	1	0.58	1	0.58	4	0.57
Epistaxis	1	0.56	1	0.57	1	0.58	1	0.58	4	0.57
Fatigue	1	0.56	2	1.14	1	0.58			4	0.57
Joint sprain	1	0.56	2	1.14	1	0.58			4	0.57
Muscle spasms	1	0.56	1	0.57	1	0.58	1	0.58	4	0.57
Musculoskeletal pain	2	1.12			1	0.58	1	0.58	4	0.57
Stomach discomfort			1	0.57	2	1.16	1	0.58	4	0.57
Viral upper respiratory tract infection					2	1.16	2	1.16	4	0.57
Acne	2	1.12					1	0.58	3	0.43
Anxiety	1	0.56	2	1.14					3	0.43
Chest discomfort	1	0.56	1	0.57			1	0.58	3	0.43
Eczema					2	1.16	1	0.58	3	0.43
Eye irritation	2	1.12					1	0.58	3	0.43
Gastritis			2	1.14	1	0.58			3	0.43
Gastroenteritis	1	0.56			1	0.58	1	0.58	3	0.43
Herpes simplex			2	1.14			1	0.58	3	0.43
Hypertension			1	0.57	1	0.58	1	0.58	3	0.43
Insomnia	1	0.56	1	0.57	1	0.58			3	0.43
Limb injury	1	0.56					2	1.16	3	0.43
Muscle strain			2	1.14			1	0.58	3	0.43
Palpitations	2	1.12	1	0.57					3	0.43
Pneumonia	2	1.12					1	0.58	3	0.43
Post-traumatic pain	1	0.56	1	0.57			1	0.58	3	0.43
Rhinorrhoea			1	0.57	1	0.58	1	0.58	3	0.43
Stomatitis	2	1.12			1	0.58			3	0.43
Tension headache					1	0.58	2	1.16	3	0.43
Breast pain							2	1.16	2	0.29
Cellulitis	1	0.56	1	0.57					2	0.29
Contusion			1	0.57			1	0.58	2	0.29
Depression	1	0.56			1	0.58			2	0.29
Dry mouth							2	1.16	2	0.29

AEs presented as: AEPTXT; Group totals: 178,176,173,173	Treatment								N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to- 100			
	N	%	N	%	N	%	N	%		
Dysphonia	1	0.56	1	0.57					2	0.29
Ecchymosis	1	0.56			1	0.58			2	0.29
Eosinophil count increased	1	0.56			1	0.58			2	0.29
Fall			1	0.57			1	0.58	2	0.29
Gastroesophageal reflux disease	2	1.12							2	0.29
Haematuria			1	0.57	1	0.58			2	0.29
Herpes virus infection			1	0.57	1	0.58			2	0.29
Hypoglycaemia					1	0.58	1	0.58	2	0.29
Influenza like illness			1	0.57	1	0.58			2	0.29
Laryngitis			1	0.57			1	0.58	2	0.29
Lymphadenopathy					1	0.58	1	0.58	2	0.29
Migraine	1	0.56			1	0.58			2	0.29
Multiple allergies	1	0.56					1	0.58	2	0.29
Nephrolithiasis					2	1.16			2	0.29
Oral pain							2	1.16	2	0.29
Otitis media	1	0.56			1	0.58			2	0.29
Pharyngeal erythema			1	0.57	1	0.58			2	0.29
Productive cough			1	0.57			1	0.58	2	0.29
Pruritus			1	0.57			1	0.58	2	0.29
Pulmonary congestion	1	0.56					1	0.58	2	0.29
Rhinitis seasonal			1	0.57			1	0.58	2	0.29
Sciatica	1	0.56			1	0.58			2	0.29
Sinus congestion					1	0.58	1	0.58	2	0.29
Skin laceration			1	0.57	1	0.58			2	0.29
Sneezing	1	0.56					1	0.58	2	0.29
Somnolence	1	0.56	1	0.57					2	0.29
Tonsillitis	1	0.56	1	0.57					2	0.29
Tooth abscess			1	0.57			1	0.58	2	0.29
Vaginal inflammation			1	0.57			1	0.58	2	0.29
Viral pharyngitis	1	0.56	1	0.57					2	0.29
Vulvovaginal mycotic infection	1	0.56					1	0.58	2	0.29
Abdominal pain lower					1	0.58			1	0.14
Acute sinusitis			1	0.57					1	0.14
Adnexa uteri pain	1	0.56							1	0.14
Allergic sinusitis							1	0.58	1	0.14
Allergy to animal					1	0.58			1	0.14
Anaemia							1	0.58	1	0.14
Animal bite			1	0.57					1	0.14
Ankle fracture							1	0.58	1	0.14
Aphthous stomatitis			1	0.57					1	0.14
Arthropod bite					1	0.58			1	0.14
Arthropod sting					1	0.58			1	0.14
Astigmatism			1	0.57					1	0.14
Atrial tachycardia							1	0.58	1	0.14
Auricular swelling	1	0.56							1	0.14
Benign neoplasm of thyroid gland			1	0.57					1	0.14
Blood alkaline phosphatase increased							1	0.58	1	0.14
Blood cholesterol increased					1	0.58			1	0.14
Blood creatinine increased							1	0.58	1	0.14
Blood glucose increased			1	0.57					1	0.14
Blood potassium increased			1	0.57					1	0.14
Bone pain							1	0.58	1	0.14
Bronchitis bacterial					1	0.58			1	0.14
Cataract					1	0.58			1	0.14
Cerebrovascular accident					1	0.58			1	0.14
Chest injury					1	0.58			1	0.14
Cholangitis acute							1	0.58	1	0.14
Cholecystitis			1	0.57					1	0.14
Concussion	1	0.56							1	0.14
Conjunctival irritation					1	0.58			1	0.14
Conjunctivitis							1	0.58	1	0.14
Conjunctivitis allergic							1	0.58	1	0.14
Conjunctivitis infective	1	0.56							1	0.14
Constipation	1	0.56							1	0.14
Costochondritis							1	0.58	1	0.14
Cyst removal			1	0.57					1	0.14
Dengue fever					1	0.58			1	0.14

AEs presented as: AEPTXT; Group totals: 178,176,173,173	Treatment								N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to- 100			
	N	%	N	%	N	%	N	%		
Diabetes mellitus							1	0.58	1	0.14
Dislocation of sternum	1	0.56							1	0.14
Diverticulitis					1	0.58			1	0.14
Drug eruption			1	0.57					1	0.14
Drug withdrawal headache							1	0.58	1	0.14
Dry skin			1	0.57					1	0.14
Dry throat							1	0.58	1	0.14
Duodenitis							1	0.58	1	0.14
Erythema	1	0.56							1	0.14
Eustachian tube dysfunction			1	0.57					1	0.14
Eye allergy			1	0.57					1	0.14
Eye pain							1	0.58	1	0.14
Eye pruritus	1	0.56							1	0.14
Facial bones fracture							1	0.58	1	0.14
Facial palsy			1	0.57					1	0.14
Folliculitis							1	0.58	1	0.14
Food poisoning			1	0.57					1	0.14
Foreign body trauma			1	0.57					1	0.14
Gastrointestinal haemorrhage							1	0.58	1	0.14
Genital pruritus female			1	0.57					1	0.14
Gingivitis			1	0.57					1	0.14
Haemorrhoids			1	0.57					1	0.14
Hangover	1	0.56							1	0.14
Hepatic enzyme increased	1	0.56							1	0.14
Hiccups	1	0.56							1	0.14
Hordeolum	1	0.56							1	0.14
Hyperbilirubinaemia					1	0.58			1	0.14
Hypercholesterolaemia							1	0.58	1	0.14
Hyperglycaemia					1	0.58			1	0.14
Hyperventilation			1	0.57					1	0.14
Hypokalaemia					1	0.58			1	0.14
Hypotension	1	0.56							1	0.14
Hypothyroidism							1	0.58	1	0.14
Ingrowing nail					1	0.58			1	0.14
Iron deficiency anaemia	1	0.56							1	0.14
Joint stiffness							1	0.58	1	0.14
Localised infection	1	0.56							1	0.14
Menstrual disorder			1	0.57					1	0.14
Micturition urgency							1	0.58	1	0.14
Mucous membrane disorder					1	0.58			1	0.14
Musculoskeletal chest pain	1	0.56							1	0.14
Nasal discomfort							1	0.58	1	0.14
Nasal dryness	1	0.56							1	0.14
Nervousness			1	0.57					1	0.14
Ocular hyperaemia	1	0.56							1	0.14
Opisthorchiasis							1	0.58	1	0.14
Otitis externa					1	0.58			1	0.14
Palatal oedema					1	0.58			1	0.14
Paraesthesia			1	0.57					1	0.14
Parosmia					1	0.58			1	0.14
Parotitis	1	0.56							1	0.14
Pharyngitis streptococcal							1	0.58	1	0.14
Pleurisy					1	0.58			1	0.14
Pneumonia viral	1	0.56							1	0.14
Postnasal drip			1	0.57					1	0.14
Presbyopia					1	0.58			1	0.14
Procedural pain							1	0.58	1	0.14
Pseudomonas infection					1	0.58			1	0.14
Pterygium	1	0.56							1	0.14
Radiculitis	1	0.56							1	0.14
Reflux gastritis							1	0.58	1	0.14
Refraction disorder					1	0.58			1	0.14
Removal of foreign body			1	0.57					1	0.14
Renal colic			1	0.57					1	0.14
Renal pain	1	0.56							1	0.14
Respiratory disorder	1	0.56							1	0.14
Respiratory tract infection viral					1	0.58			1	0.14

AEs presented as: AEPTTXX; Group totals: 178,176,173,173	Treatment								N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID		Alvesco 50-to- 100			
	N	%	N	%	N	%	N	%		
Salpingitis					1	0.58			1	0.14
Scotoma							1	0.58	1	0.14
Scratch			1	0.57					1	0.14
Sensation of heaviness	1	0.56							1	0.14
Sensory disturbance					1	0.58			1	0.14
Skeletal injury					1	0.58			1	0.14
Sleep phase rhythm disturbance	1	0.56							1	0.14
Splinter					1	0.58			1	0.14
Sputum discoloured					1	0.58			1	0.14
Staphylococcal infection			1	0.57					1	0.14
Stress	1	0.56							1	0.14
Sunburn					1	0.58			1	0.14
Swelling face							1	0.58	1	0.14
Synovial cyst	1	0.56							1	0.14
Systemic lupus erythematosus	1	0.56							1	0.14
Temporomandibular joint syndrome			1	0.57					1	0.14
Tendonitis			1	0.57					1	0.14
Throat irritation	1	0.56							1	0.14
Throat tightness	1	0.56							1	0.14
Tinea infection					1	0.58			1	0.14
Tinea pedis					1	0.58			1	0.14
Tonsillar disorder							1	0.58	1	0.14
Tonsillar hypertrophy					1	0.58			1	0.14
Tooth extraction							1	0.58	1	0.14
Tooth impacted							1	0.58	1	0.14
Tooth infection							1	0.58	1	0.14
Tooth injury							1	0.58	1	0.14
Tremor	1	0.56							1	0.14
Upper respiratory tract infection bacterial							1	0.58	1	0.14
Urticaria			1	0.57					1	0.14
Uvulitis			1	0.57					1	0.14
Vaginal candidiasis					1	0.58			1	0.14
Vertigo							1	0.58	1	0.14
Vertigo positional							1	0.58	1	0.14
Vision blurred					1	0.58			1	0.14
Wheezing			1	0.57					1	0.14
Wisdom teeth removal			1	0.57					1	0.14
Wrist fracture							1	0.58	1	0.14

Source: AE2

Table 32 AE findings (Study 3030)

AEs presented as: AEPTXT; Group totals: 152,152,152	Treatment						N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%		
NO AE REPORTED	64	42.11	62	40.79	71	46.71	197	43.20
Nasopharyngitis	10	6.58	19	12.50	16	10.53	45	9.87
Asthma	27	17.76	7	4.61	5	3.29	39	8.55
Upper respiratory tract infection	12	7.89	12	7.89	14	9.21	38	8.33
Pharyngolaryngeal pain	5	3.29	8	5.26	9	5.92	22	4.82
Sinusitis	7	4.61	9	5.92	5	3.29	21	4.61
Headache	6	3.95	6	3.95	7	4.61	19	4.17
Cough	4	2.63	8	5.26	3	1.97	15	3.29
Back pain	5	3.29	5	3.29	1	0.66	11	2.41
Gastroenteritis viral	2	1.32	6	3.95	1	0.66	9	1.97
Hypersensitivity	4	2.63	4	2.63	1	0.66	9	1.97
Toothache	2	1.32	5	3.29	2	1.32	9	1.97
Dizziness	1	0.66	4	2.63	2	1.32	7	1.54
Herpes simplex	3	1.97	1	0.66	3	1.97	7	1.54
Bronchitis	2	1.32	2	1.32	2	1.32	6	1.32
Muscle strain	2	1.32	1	0.66	3	1.97	6	1.32
Nasal congestion			2	1.32	4	2.63	6	1.32
Sinus headache	3	1.97	2	1.32	1	0.66	6	1.32
Diarrhoea	1	0.66	2	1.32	2	1.32	5	1.10
Forced expiratory volume decreased	3	1.97	2	1.32			5	1.10
Influenza	1	0.66	3	1.97	1	0.66	5	1.10
Joint sprain	1	0.66	1	0.66	3	1.97	5	1.10
Pain	2	1.32	1	0.66	2	1.32	5	1.10
Stomach discomfort	2	1.32			3	1.97	5	1.10
Urinary tract infection	1	0.66	3	1.97	1	0.66	5	1.10
Vomiting	2	1.32	1	0.66	2	1.32	5	1.10
Anxiety			1	0.66	3	1.97	4	0.88
Arthralgia	2	1.32	1	0.66	1	0.66	4	0.88
Arthropod sting	2	1.32	2	1.32			4	0.88
Back injury	2	1.32	1	0.66	1	0.66	4	0.88
Contusion	1	0.66	2	1.32	1	0.66	4	0.88
Myalgia			4	2.63			4	0.88
Nausea			3	1.97	1	0.66	4	0.88
Neck pain	1	0.66	1	0.66	2	1.32	4	0.88
Pharyngitis streptococcal	2	1.32			2	1.32	4	0.88
Pulmonary congestion			3	1.97	1	0.66	4	0.88
Abdominal pain upper	2	1.32	1	0.66			3	0.66
Ear pain	1	0.66			2	1.32	3	0.66
Lower respiratory tract infection	1	0.66			2	1.32	3	0.66
Pharyngitis	1	0.66	2	1.32			3	0.66
Procedural pain	2	1.32			1	0.66	3	0.66
Pruritus	2	1.32	1	0.66			3	0.66
Rash			3	1.97			3	0.66
Rhinitis allergic	1	0.66	1	0.66	1	0.66	3	0.66
Rhinorrhoea	1	0.66	2	1.32			3	0.66
Sinus congestion	1	0.66	1	0.66	1	0.66	3	0.66
Viral upper respiratory tract infection	2	1.32			1	0.66	3	0.66
Vulvovaginal mycotic infection			1	0.66	2	1.32	3	0.66
Wheezing	1	0.66	2	1.32			3	0.66
Abdominal pain	1	0.66			1	0.66	2	0.44
Acute sinusitis			2	1.32			2	0.44
Arthropod bite	1	0.66	1	0.66			2	0.44
Constipation	1	0.66			1	0.66	2	0.44
Dermatitis contact			1	0.66	1	0.66	2	0.44
Dysmenorrhoea			2	1.32			2	0.44
Fall	1	0.66	1	0.66			2	0.44
Fatigue	1	0.66			1	0.66	2	0.44
Hepatic enzyme increased					2	1.32	2	0.44
Hypoesthesia			2	1.32			2	0.44
Influenza like illness	1	0.66			1	0.66	2	0.44
Insomnia	1	0.66			1	0.66	2	0.44
Limb injury	1	0.66	1	0.66			2	0.44
Menorrhagia	1	0.66			1	0.66	2	0.44
Migraine	1	0.66			1	0.66	2	0.44

AEs presented as: AEPTTXX; Group totals: 152,152,152	Treatment						N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%		
Nasal polyps			2	1.32			2	0.44
Oral candidiasis			1	0.66	1	0.66	2	0.44
Otitis media	2	1.32					2	0.44
Pyrexia	1	0.66			1	0.66	2	0.44
Rhinitis	1	0.66	1	0.66			2	0.44
Shoulder pain			1	0.66	1	0.66	2	0.44
Tonsillitis	1	0.66			1	0.66	2	0.44
Abdominal tenderness					1	0.66	1	0.22
Acne			1	0.66			1	0.22
Agitation			1	0.66			1	0.22
Alanine aminotransferase increased					1	0.66	1	0.22
Anaemia					1	0.66	1	0.22
Angina pectoris			1	0.66			1	0.22
Ankle fracture	1	0.66					1	0.22
Blood glucose decreased			1	0.66			1	0.22
Blood glucose increased					1	0.66	1	0.22
Blood urine present					1	0.66	1	0.22
Breast cancer in situ					1	0.66	1	0.22
Bronchitis acute					1	0.66	1	0.22
Candidiasis					1	0.66	1	0.22
Conjunctivitis	1	0.66					1	0.22
Conjunctivitis allergic					1	0.66	1	0.22
Cystitis					1	0.66	1	0.22
Differential white blood cell count abnormal					1	0.66	1	0.22
Drug hypersensitivity					1	0.66	1	0.22
Dysgeusia			1	0.66			1	0.22
Dyspepsia	1	0.66					1	0.22
Dysphonia	1	0.66					1	0.22
Ear infection			1	0.66			1	0.22
Epistaxis			1	0.66			1	0.22
Eustachian tube disorder					1	0.66	1	0.22
Eustachian tube dysfunction	1	0.66					1	0.22
Excoriation					1	0.66	1	0.22
Eye injury	1	0.66					1	0.22
Eye pruritus			1	0.66			1	0.22
Eye swelling			1	0.66			1	0.22
Eyelid margin crusting	1	0.66					1	0.22
Fluid retention			1	0.66			1	0.22
Folliculitis					1	0.66	1	0.22
Foot fracture	1	0.66					1	0.22
Gastrointestinal pain			1	0.66			1	0.22
Guttate psoriasis					1	0.66	1	0.22
Haematochezia	1	0.66					1	0.22
Haematoma					1	0.66	1	0.22
Hordeolum			1	0.66			1	0.22
Human bite			1	0.66			1	0.22
Hyperchlorhydria	1	0.66					1	0.22
Hypertension			1	0.66			1	0.22
Hysteroscopy	1	0.66					1	0.22
Inflammation			1	0.66			1	0.22
Inguinal hernia			1	0.66			1	0.22
Injection site cellulitis			1	0.66			1	0.22
Lacrimation increased	1	0.66					1	0.22
Laryngitis			1	0.66			1	0.22
Lethargy	1	0.66					1	0.22
Localised infection			1	0.66			1	0.22
Muscle spasms	1	0.66					1	0.22
Musculoskeletal chest pain	1	0.66					1	0.22
Neck mass					1	0.66	1	0.22
Otitis externa					1	0.66	1	0.22
Ovarian cyst			1	0.66			1	0.22
Palpitations			1	0.66			1	0.22
Paraesthesia			1	0.66			1	0.22
Paranasal sinus hypersecretion			1	0.66			1	0.22
Parotitis	1	0.66					1	0.22
Pitting oedema	1	0.66					1	0.22
Pneumonia					1	0.66	1	0.22

AEs presented as: AEPTTXX; Group totals: 152,152,152	Treatment						N	%
	Placebo		Alvesco 100x2pf QD		Alvesco 50x2pf BID			
	N	%	N	%	N	%		
Post procedural complication					1	0.66	1	0.22
Postnasal drip	1	0.66					1	0.22
Proteinuria	1	0.66					1	0.22
Rash erythematous	1	0.66					1	0.22
Rash generalised					1	0.66	1	0.22
Renal colic	1	0.66					1	0.22
Respiratory tract infection viral	1	0.66					1	0.22
Rhinitis seasonal	1	0.66					1	0.22
Rhonchi	1	0.66					1	0.22
Sinus operation					1	0.66	1	0.22
Skin laceration	1	0.66					1	0.22
Skin ulcer	1	0.66					1	0.22
Sneezing	1	0.66					1	0.22
Tendon repair					1	0.66	1	0.22
Tension headache			1	0.66			1	0.22
Throat irritation			1	0.66			1	0.22
Tinnitus			1	0.66			1	0.22
Tooth abscess			1	0.66			1	0.22
Tooth discolouration			1	0.66			1	0.22
Tooth disorder			1	0.66			1	0.22
Tooth injury					1	0.66	1	0.22
Tremor			1	0.66			1	0.22
Turbinectomy			1	0.66			1	0.22
Upper respiratory tract congestion					1	0.66	1	0.22
Uterine infection	1	0.66					1	0.22
Uterine polyp					1	0.66	1	0.22
Viral infection			1	0.66			1	0.22
Vision blurred					1	0.66	1	0.22
Whiplash injury			1	0.66			1	0.22

Source: AE2

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/s/

Ted Guo
12/19/2007 01:02:23 PM
BIOMETRICS

Qian Li
1/4/2008 02:17:41 PM
BIOEQUIVALENCE STATISTICIAN
A secondary statistical review is written.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 21-658/N000

Drug Name: Alvesco (ciclesonide): 100 µg/day, 200 µg/day, and ~~100 µg/day~~ (ex-valve), administered with metered dose inhaler (MDI) **b(4)**

Indication(s): Alvesco is proposed to be indicated for the maintenance treatment of asthma as prophylactic therapy in adult ~~patients~~ patients 4 years of age and older.

Applicant: Aventis Pharmaceuticals Inc.

Date(s): Applicant's letter date: December 22, 2003

Review Priority: Standard

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Keywords: NDA review, clinical studies

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EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Alvesco™ (ciclesonide) is proposed to be indicated for the maintenance treatment of asthma as prophylactic therapy in adult/adolescent (aged 12 and older) (). The evaluation of the effectiveness and safety is based on Studies 321, 322, 323, 324, 341, and 342. The latter two were conducted in pediatric patients. With the approval from the Agency, Studies 341 and 342, conducted as two independent studies, were combined in the sponsor's data analysis (page 15, Section 1.5.3 Phase III Studies (Aventis [US]), 2.5clinicaloverview.pdf).

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All the studies under evaluation were phase III, double-blind, placebo-controlled, parallel-group, multi-center studies. The treatment was administered via MDI, once daily, for 12 weeks. The statistical conclusions are primarily based on the analysis of the pre-specified primary efficacy variable: the change in either FEV₁ (Studies 321, 322, 323, and 324) or percent-predicted FEV₁ (Studies 341 and 342) from baseline to Week-12.

Statistical Issues and Findings

This reviewer explored, examined, and analyzed the sponsor's data from the above studies. In the statistical analysis of the data, this reviewer verified the sponsor's findings and conclusions. In addition, modified statistical approaches were also applied to reflect the practice traditionally performed in this review division in handling similar new drug applications. Both the sponsor-defined statistical model and the reviewer's variation were used in an attempt to demonstrate the robustness of the statistical results to the model selection. As a summary, Table 1 compares this reviewer's statistical results on efficacy among these studies.

Table 1. Comparisons between Alvesco and Placebo Control

Type of Study	Type of Comparison	Study No.					Findings consistently positive
		321	322	323/324	341	342	
Adult	Alvesco 50- μ g, 2 puffs, QD vs. Placebo	-	+				No
	Alvesco 100- μ g, 2 puffs, QD vs. Placebo	-	+				No
	Alvesco 200- μ g, 2 puffs, QD vs. Placebo**	+	+	+			Yes
	Alvesco 200- μ g, 2 puffs, BID vs. Placebo			+			NA
	Fluticasone 220- μ g, 2 puffs, BID vs. Placebo			+			NA
Pediatric	Alvesco 50- μ g, 1 puff, QD vs. placebo				-	-	No (Consistently Negative)
	Alvesco 100- μ g, 1 puff, QD vs. placebo				-	-	No (Consistently Negative)
	Alvesco 200- μ g, 1 puff, QD vs. placebo				-	+	No

Explanation of Symbols in Table 1:

- + Statistically significant (step-down approach with the 0.05 significance level) using either the sponsor's or the reviewer's model
- Statistical significance not demonstrated using either the sponsor's or the reviewer's model
- * The statistical significance is only shown based on the sponsor's linear model, including the terms of TREATMENT, CENTER (POOLED) STRATA, SEX, AGE, and BASELINE FEV₁, but not based on the reviewer's model, including terms of TREATMENT, CENTER (POOLED), and STRATA, and a covariate BASELINE FEV₁.
- ** In Study 323/324, the dose of Alvesco was 100- μ g, 2 puffs, BID

Conclusions and Recommendations

Efficacy Conclusions:

Consistently across the studies, Alvesco at 200 µg, 2 puffs, QD was shown to be statistically superior to the placebo. However, the dose-response trend of Alvesco was not adequately demonstrated.

Analyses by stratum suggest that patients' baseline conditions or associated pretreatment medication (corticosteroids or bronchodilators) play an important role in deciding the effectiveness of Alvesco during the evaluation. Unlike the analysis of those on corticosteroids, a statistically significant difference between Alvesco and placebo was not demonstrated among the patients on bronchodilators.

Safety Conclusions:

Across studies, this reviewer found that the three most frequently reported adverse events were: HEADACHE, NASOPHARYNGITIS, and ASTHMA AGGRAVATION. Among these adverse events, HEADACHE was the most frequently reported adverse event among the adults, based on the AE data for Studies 321, 322, and 323/324. ASTHMA AGGRAVATION and NASOPHARYNGITIS were the most commonly reported events among the children. HEADACHE, NASOPHARYNGITIS, and ASTHMA AGGRAVATION were among the most commonly reported events in each of the studies.

Recommendations:

Alvesco at 200 µg, 2 puffs, QD was demonstrated to be statistically superior to the placebo in adults/adolescents who had been receiving corticosteroids, and therefore, is recommended for approval in that group. It appears to be less effective on patients who were using bronchodilators. The leading adverse events including HEADACHE, NASOPHARYNGITIS, and ASTHMA AGGRAVATION deserve a cautionary note for labeling consideration.

INTRODUCTION

OVERVIEW

Alvesco™ (Ciclesonide), administrated via MDI, 2 puffs, (_____), at ex-valve _____ μg , 100 μg , and 200 μg (alternatively, described as at ex-actuator _____ μg , 80 μg , and 160 μg), is proposed to be indicated for the maintenance treatment of asthma as prophylactic therapy in adult/adolescent (aged 12 and older) and (_____). The purpose of this review is to evaluate the effectiveness and safety of the drug based on evidence submitted by the sponsor, Aventis Pharmaceuticals, in the NDA 21-658 dated 12/22/2003.

b(4)

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

To demonstrate the effectiveness of the drug, the sponsor submitted three studies on adult/adolescent patients: Studies 321, 322, and 323/324 (a combination of Studies 323 and 324 with identical design). In addition, the sponsor submitted Studies 341 and 342 involving pediatric patients. All these studies had similar designs. The primary efficacy variable used in the adult studies was the Week-12 FEV₁ change from baseline, while the primary efficacy variable in the pediatric studies was the percent-predicted FEV₁. Additional studies reinforcing evidence of efficacy were also included in the NDA, however, these studies were not the focus for the statistical evaluation.

Studies 321 and 322 for Adult Patients

Studies 321 and 322 were phase III double-blind, placebo-controlled, parallel-group, multi-center studies. The treatment was administrated via MDI 2 puffs once daily for 12 weeks. The time line of the studies is shown in Table 2.

Table 2. Study Time Line (Studies 321 and 322)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Pre- screening: 3 to 5 days prior to Visit 2	Screening/ baseline: 5 to 28 days prior to randomization	Randomize	Week 1 post dosing	Week 2 post dosing	Week 4 post dosing	Week 8 post dosing	Week 12 post dosing

At Visit 3, the patient was randomly assigned (stratified by previous treatment: corticosteroids or bronchodilators) to one of the following treatments included in Table 3.

Table 3. Treatments (Studies 321 and 322)

Treatment*	Ex-valve	Ex-actuator
Placebo	Placebo	Placebo
Alvesco 50 µg, 2 puffs, QD	Alvesco 100 µg/day	Alvesco 80 µg/day
Alvesco 100 µg, 2 puffs, QD	Alvesco 200 µg/day	Alvesco 160 µg/day
Alvesco 200 µg, 2 puffs, QD	Alvesco 400 µg/day	Alvesco 320 µg/day

* Note that the terms written in the same row represent the same treatment, and they are used interchangeably by the sponsor.

The primary efficacy measurement was FEV₁ observed at baseline (Visit 3) and at subsequent visits prior to the morning double-blind medication. The primary efficacy variable was the change in FEV₁ from baseline at Visit 8 (Week 12) (with missing values imputed using LOCF).

Study 323/324 for Adult Patients

Study 323/324 is separate studies with similar designs as that of Studies 321 and 322. The differences in the designs of Study 323/324 and Studies 321 and 322 were:

- In Study 323/324, Alvesco was administrated BID, while in Studies 321 and 322, it was administered QD.
- The lowest dose of Alvesco in Study 323/324 is 400 µg/day (ex-valve), which is equivalent to the highest dose of Alvesco in Studies 321 and 322.
- In Study 323/324, fluticasone group was included.

The two studies were analyzed jointly, according to the study plan endorsed by the Agency (Aventis [US]), 2.5clinicaloverview.pdf). The time line of the studies is shown in Table 4.

Table 4. Study Time Line (Study 323/324)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Pre- screening: 3 to 5 days prior to Visit 2	Screening/ baseline: 5 to 28 days prior to randomization	Randomization	Week 1 post dosing	Week 2 post dosing	Week 4 post dosing	Week 8 post dosing	Week 12 post dosing

At Visit 3, the patient was randomly assigned (stratified by previous treatment: corticosteroids or bronchodilators) to one of the following treatments included in Table 5:

Table 5. Treatments (Study 323/324)

Treatment*	Ex-valve	Ex-actuator
Placebo	Placebo	Placebo
Alvesco 100 µg, 2 puffs, BID	Alvesco 400 µg/day	Alvesco 320 µg/day
Alvesco 200 µg, 2 puffs, BID	Alvesco 800 µg/day	Alvesco 640 µg/day
Fluticasone 220 µg, 2 puffs, BID	Fluticasone 1000 µg/day	Fluticasone 880 µg/day

* Note that the terms written in the same row represent the same treatment, and they are used interchangeably by the sponsor.

The primary efficacy measurement was FEV₁ observed at baseline (Visit 3) and at subsequent visits prior to the morning double-blind medication. The primary efficacy variable was the change in FEV₁ from baseline at Visit 8 (Week 12) (with missing values imputed using LOCF).

Studies 341 and 342 for Pediatric Patients

Studies 341 and 342 were phase III double-blind, placebo-controlled, parallel-group, multi-center studies. The treatment was administered via MDI once daily for 12 weeks. The time line of the studies is shown in Table 6.

Table 6. Study Time Line (Studies 341 and 342)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
2 to 6 days prior to Visit 2	5 to 21 days prior to randomization	Randomization	Week 1 post dosing	Week 2 post dosing	Week 4 post dosing	Week 8 post dosing	Week 12 post dosing

At Visit 3, patient was randomly assigned (stratified by previous treatment: corticosteroids or bronchodilators) to one of the following treatments included in Table 7.

Table 7. Treatments (Studies 341 and 342)

Treatment*	Ex-valve	Ex-actuator
Placebo	Placebo	Placebo
Alvesco 50 µg, 1 puffs, QD	Alvesco 50 µg/day	Alvesco 40 µg/day
Alvesco 100 µg, 1 puffs, QD	Alvesco 100 µg/day	Alvesco 80 µg/day
Alvesco 200 µg, 1 puffs, QD	Alvesco 200 µg/day	Alvesco 160 µg/day

* Note that the terms written in the same row represent the same treatment, and they are used interchangeably by the sponsor.

The primary efficacy measurement was FEV₁ observed at baseline (Visit 3) and at subsequent visits prior to the morning double-blind medication. The primary efficacy variable was the change in FEV₁ from baseline at Visit 8 (Week 12) (with missing values imputed using LOCF).

In all the studies, above, the primary efficacy analyses were based on the intent-to-treat (ITT) patient population. The ITT patients included all randomized patients who received at least 1 dose of double-blind study medication and had both a valid baseline and at least 1 post baseline measurement of FEV₁. If the percent-predicted FEV₁ was used as the primary efficacy variable, a valid height of the patient was required to calculate the percent-predicted FEV₁.

Missing observations were estimated using the last available observation carried forward (LOCF), which is applied to all the efficacy studies.

As an important aspect of the NDA, the sponsor tabulated adverse events in all the pivotal studies. A close examination of the adverse events reported is part of the statistical evaluation and will be reported in this review.

**APPEARS THIS WAY
ON ORIGINAL**

DATA SOURCES

The sponsor submitted this NDA including the data to the FDA Electronic Document Room. The submission is recorded in the EDR as indicated in Table 8, below. All the data submitted are in SAS v.5 transport format. The number of data files for the pivotal studies and the number of data files used in the statistical review are shown in Table 9.

Table 8. Data Source

Document 2442477		
Application: N021658	Letter Date: 22-Dec-2003	Stamp Date: 23-Dec-2003
Incoming Doc Type: N	Sup Modification Type:	In Doc Type Seq No: 000
Company: AVENTIS PHARMS		
Drug: ALVESCO (CICLESONIDE)		

Table 9. Sponsor's Data Submitted

Path/location	No. data files submitted	No. data files used in statistical review
\\Cdsub1\n21658\N_000\2003-12-22\crt\datasets\321	58	6
\\Cdsub1\n21658\N_000\2003-12-22\crt\datasets\322	57	5
\\Cdsub1\n21658\N_000\2003-12-22\crt\datasets\323324	58	5
\\Cdsub1\n21658\N_000\2003-12-22\crt\datasets\341	58	5
\\Cdsub1\n21658\N_000\2003-12-22\crt\datasets\342	58	5

The numbers of data files used in the statistical evaluation are shown in the third column. Given the large amount of data, this reviewer selected the files containing the most relevant evidence for the efficacy and safety of the drug.

STATISTICAL EVALUATION

EVALUATION OF EFFICACY

Study Design and Endpoints

All five pivotal efficacy studies under review are phase III, double-blind, placebo-controlled, parallel-group, multi-center studies. The statistical methods employed to evaluate the effectiveness of the drug are essentially identical.

Adult Studies: The following summary of the statistical method for Study 321 applies to that of Studies 322, 323/324. The sponsor summarized the statistical analysis for the primary efficacy variable in Study 321 as follows:

“The primary efficacy endpoint was the change from baseline (Day 1) to end of study (Week 12 or early termination) in FEV1, in liters, in the intent- to- treat (ITT) population. If the Week 12 (Visit 8) assessment was not available, the last available post- randomization measurement of FEV1 was carried forward (LOCF). The baseline value was the FEV1 measured at randomization (Visit 3) prior to reversibility testing (if performed) and prior to administration of double-blind study medication (p67, §4.1.1.1, study321.pdf).”

Pediatric Studies: The primary efficacy variable in Studies 341 and 342 was different from that in the other studies. The sponsor’s summary for the statistical analysis for the primary efficacy variable in Study 341 reads as follows:

“The primary efficacy endpoint was the change from baseline (Day 1) to end of study (Week 12 or early termination) in FEV1 percent predicted, i.e., [FEV1 percent predicted value at end of study – FEV1 percent predicted value at baseline]. The primary analysis was based on the intent-to-treat (ITT) population ... In general, the end-of-study FEV1 percent predicted value was the value calculated at Week 12 (Visit 8); however, if the patient discontinued prior to Week 12, the last available post-randomization value prior to discontinuation from the study was carried forward (LOCF). If the FEV1 or height measurement was missing at any particular time point, the patient’s previous available post baseline FEV1 or height value was carried forward to calculate the FEV1 percent predicted value at that time point (p80, §4.1.1.1, study341.pdf).”

In defining the ITT patient population, the sponsor stated:

“The primary analysis population for all efficacy endpoints was the intent-to-treat (ITT) population. The ITT population included all randomized patients who received at least 1 dose of double-blind study medication and had a valid baseline and at least 1 post baseline measurement of the primary efficacy analysis variable, FEV₁ (p72, §4.2.3, study321.pdf).”

In describing the statistical model, the sponsor stated:

“The primary analysis (ITT population) was conducted using an analysis of covariance (ANCOVA) model of change from baseline in FEV₁ at end of study (LOCF to Week 12). The ANCOVA model included factors for treatment, pooled center, previous therapy (based on Stratum 1 and Stratum 2), and baseline FEV₁, age, and gender as covariates (p76, §4.3.2, study321.pdf).”

To control the Type-1 error caused by multiple comparisons of each Alvesco dose to placebo, the sponsor adopted a step-down approach. For example in Studies 321 and 322:

“The efficacy of ciclesonide was assessed by pairwise comparisons of each ciclesonide dose regimen against placebo. A step-down procedure was utilized to address the issue of multiplicity. First, the primary comparison between ciclesonide 320µg/day and placebo was tested at the $\alpha=0.05$ level of significance. If the first comparison was statistically significant, then the comparison between ciclesonide 160µg/day and placebo was to be performed. If that comparison was statistically significant, then the ciclesonide 80µg/day group was to be compared with placebo at a significance level of $\alpha=0.05$ (p76, §4.3.2, study321.pdf).”

In addition to the analysis on the ITT patient population, a per-protocol analysis was also performed. To confirm and compare the sponsor's findings, this reviewer re-analyzed the sponsor's data submitted to the Agency's Electronic Document Room using the same approach as the sponsor and slightly different approaches for confirmatory purposes.

Please note the following differences among the pivotal studies:

- In addition to Alvesco, the active treatment arms in Study 323/324 included Fluticasone at 880 µg/day (ex-actuator); while the other studies had only Alvesco doses.
- The primary efficacy variable in Studies 321, 322, 323/324 was the change from baseline of FEV₁ at Week 12 (Visit 8), while the primary efficacy variable in Studies 341 and 342 was the change from baseline of percent-predicted FEV₁ at Week 12 (Visit 8) from baseline.

Patient Disposition, Demographic and Baseline Characteristics

This section focuses on descriptions of patients' dispositions based on status of completion, status of compliance, and reasons for early withdrawal.

Study 321

The ITT population “consisted of patients who were randomized, treated with double-blind study medication and had a valid baseline and post baseline measurement of the primary efficacy variable, FEV₁ (§6.4, Study321.pdf).” There were 526 patients enrolled in this study. The sponsor further excluded two patients from the ITT group.

Table 10. Number of patients excluded from the ITT group (Study 321)

Treatment	#Patients
Placebo	1
100 µg 2PfsQD	1
Overall	2

The identification numbers of these patients were 0145/32121 and 0307/32101. Table 93 in Appendix to this review contains the FEV₁ observed or imputed at each visit for these subjects. This reviewer selected a few variables (Table 11) to show the reasons for which the sponsor further excluded these patients from the ITT group.

Table 11. Patients excluded from the ITT group-See complete list in the Appendix (Study 321)

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	FEV ₁ : Baseline	FEV ₁	FEV ₁ : Sponsor-Imputed	Date of withdrawal from study	Dropout reason code
0145/32121	Placebo	Wk.12 (Visit.8)	02/27/02	.	02/27/02	02/27/02	1.03	.	.	02/27/02	Protocol violation
0307/32101	100 µg 2PfsQD	Wk.8 (Visit.7)	06/17/02	.	06/20/02	.	.	.	3.30	06/27/02	Protocol violation

Table 12, below, shows the number of ITT patients by treatment and status of completion.

Table 12. Number of ITT patients by treatment and status of completion (Study 321)

	Completer				Total	
	No		Yes		N	%
	N	%	N	%		
Placebo	47	35.3	86	64.7	133	100.0
50 µg 2PfsQD	21	15.8	112	84.2	133	100.0
100 µg 2PfsQD	22	17.3	105	82.7	127	100.0
200 µg 2PfsQD	19	14.5	112	85.5	131	100.0
Total	109	20.8	415	79.2	524	100.0

The dropouts among the placebo patients accounted for 35.3% of the patients in that group, representing a markedly higher figure than those among the active-treatment groups: 14.5-17.3%. The effect of the missing observations and their estimation will be discussed in the later sections of this report.

Having observed the high percentage of early withdrawal, particularly in the placebo group, this reviewer presents in Table 13, below, a complete list of the reasons for early withdrawal. The list was generated based on data file named COMPWI.

Table 13. Reasons for early withdrawal (Study 321)

Completer	Dropout reason	Placebo		50mcg2PfsQD		100mcg2PfsQD		200mcg2PfsQD		Total N
		N	%	N	%	N	%	N	%	
		No								
	Other reason	1	2.1	2	9.5	1	4.5	3	15.8	7
	Protocol violation	1	2.1			1	4.5	3	15.8	5
	Lost to follow-up	1	2.1			2	9.1			3
	Did not wish to continue	1	2.1	1	4.8	3	13.6	3	15.8	8
	Did not wish to continue and Lost to follow-up							1	5.3	1
	Lack of efficacy	19	40.4	11	52.4	6	27.3	4	21.1	40
	Lack of efficacy and Did not wish to continue	2	4.3	2	9.5					4
	Adverse event	2	4.3			3	13.6	1	5.3	6
	Adverse event and Other reason	1	2.1							1
	Adverse event and Lack of efficacy	18	38.3	5	23.8	6	27.3	4	21.1	33
	Adverse event and Lack of efficacy and Did not wish to continue	1	2.1							1
Total		47	100.0	21	100.0	22	100.0	19	100.0	109

Source: \CDSESUB\N21658\N_000\2004-02-05\CRT\DATASETS\321\COMPWI.XPT

The most common reasons for early dropout were “lack of efficacy” and “adverse event.” According to the sponsor’s data (COMPWI.XPT), some dropout reasons were under “lack of efficacy” alone, while others fell into both categories: “lack of efficacy” and “adverse event.” There were 2.1-15.8% of the patients in the treatment groups reported to withdraw early due to the reason, “did not wish to continue,” which does not clearly characterize the reason.

The following graphs depict the numbers and percentages of the patients remaining in study over time.

Figure 1. Numbers of patients remaining in study (Study 321)

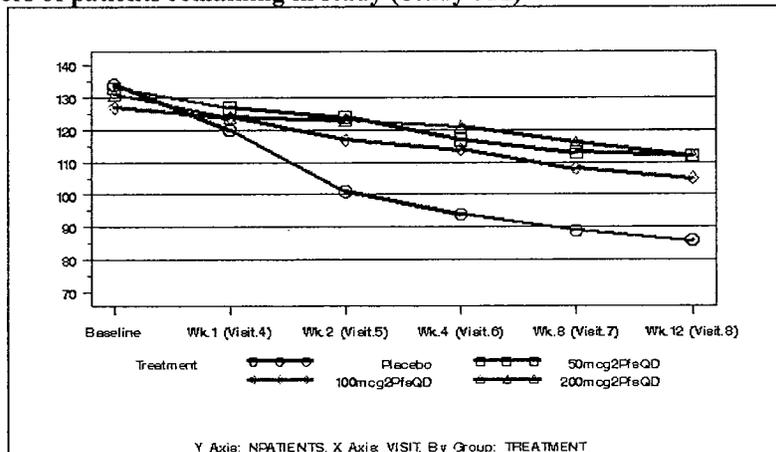


Figure 2. Percentages of patients remaining in study (Study 321)

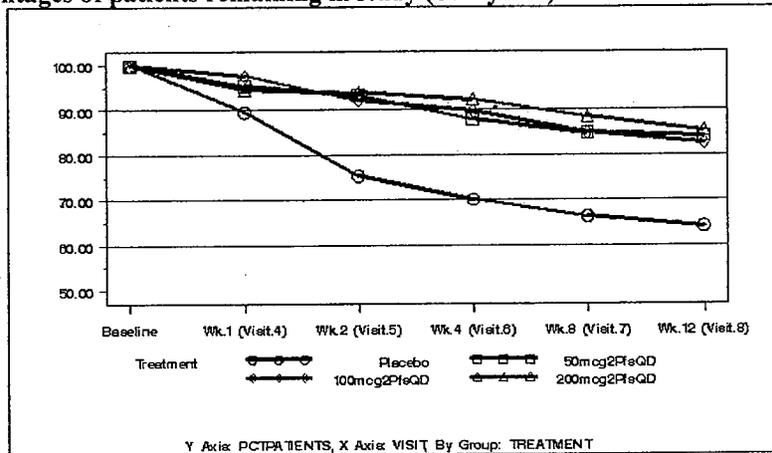


Figure 1 and Figure 2, above, show that, from Visit 5 onward, the numbers and percentages of patients remaining in study in the placebo group are much smaller than those in the other treatment groups.

The status of protocol compliance was dichotomized into one (1) and zero (0) - one represents “comply” and zero, otherwise. Table 14 shows the number of patients by treatment and compliance (evaluable)”

Table 14. Number of patients by treatment and status of compliance (Study 321)

	Evaluable				Total	
	0		1		N	%
	N	%	N	%		
Treatment	35	26.32	98	73.68	133	100.00
Placebo						
50 µg 2PfsQD	14	10.53	119	89.47	133	100.00
100 µg 2PfsQD	11	8.66	116	91.34	127	100.00
200 µg 2PfsQD	13	9.92	118	90.08	131	100.00
Total	73	13.93	451	86.07	524	100.00

Thirty-five (35) out of 133 patients in the placebo group reportedly had major protocol violations, representing 26.32% of the placebo patients, a higher rate than the patients in the other groups, ranging from 8.66%-10.53%.

Because of the disproportionately higher percentages of missing observations and the higher percentages of protocol violations among the placebo patients, a sensitivity analysis was performed to assess the impact of these facts on statistical findings and is provided in the section, OTHER SPECIAL/SUBGROUP POPULATIONS of this report.

Study 322

Table 15, below, shows the number of ITT patients by treatment and status of completion.

Table 15. Number of ITT patients by treatment and status of completion (Study 322)

	Completer				Total	
	No		Yes		N	%
	N	%	N	%		
Placebo	36	30.5	82	69.5	118	100.0
50mcg2PfsQD	15	12.1	109	87.9	124	100.0
100mcg2PfsQD	13	10.6	110	89.4	123	100.0
200mcg2PfsQD	22	17.7	102	82.3	124	100.0
Total	86	17.6	403	82.4	489	100.0

The dropouts among the placebo patients accounted for 30.5% of the patients in that group, representing a markedly higher figure than those among the active-treatment groups: 10.6-17.7%. The effect of the missing observations and their estimation will be discussed in later sections.

Table 16. Reasons for early withdrawal (Study 322)

Completer	Dropout reason									Total N
		Placebo		50mcg2PfsQD		100mcg2PfsQD		200mcg2PfsQD		
		N	%	N	%	N	%	N	%	
No	Other reason	1	2.8					3	13.6	4
	Protocol violation	3	8.3	1	6.7	1	7.7	6	27.3	11
	Lost to follow-up	1	2.8	1	6.7					2
	Lost to follow-up and Other reason							1	4.5	1
	Did not wish to continue	6	16.7	2	13.3	2	15.4	2	9.1	12
	Did not wish to continue and Other reason	1	2.8							1
	Poor compliance with treatment			2	13.3					2
	Lack of efficacy	7	19.4	3	20.0	5	38.5	4	18.2	19
	Adverse event	1	2.8	1	6.7	3	23.1	1	4.5	6
	Adverse event and Protocol violation			1	6.7					1
	Adverse event and Lack of efficacy	13	36.1	1	6.7	2	15.4	4	18.2	20
	Adverse event and Lack of efficacy and Did not wish to continue	3	8.3	3	20.0			1	4.5	7
Total		36	100.0	15	100.0	13	100.0	22	100.0	86

Source: \CDSESUB\N21658\N_000\2004-02-05\CRT\DATASETS\322\COMPWI.XPT

The most common reasons for early dropout were “lack of efficacy” and “adverse event.” According to the sponsor’s data (COMPWI.XPT), some dropout reasons were under “lack of efficacy” alone, while others fell into both categories: “lack of efficacy” and “adverse event.” There were 9.1-16.7% of the patients in the treatment groups reported to withdraw early due to the reason, “did not wish to continue,” which does not clearly characterize the reason.

The following graphs depict the numbers and percentages of the patients remaining in study over time.

Figure 3. Numbers of patients remaining in study (Study 322)

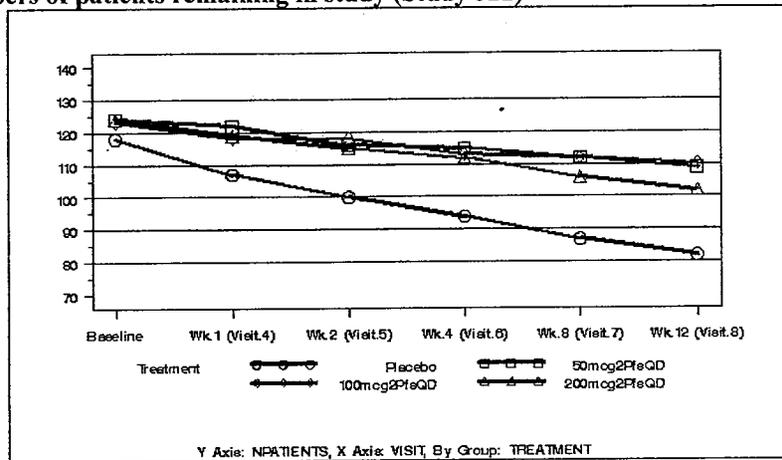


Figure 4. Percentages of patients remaining in study (Study 322)

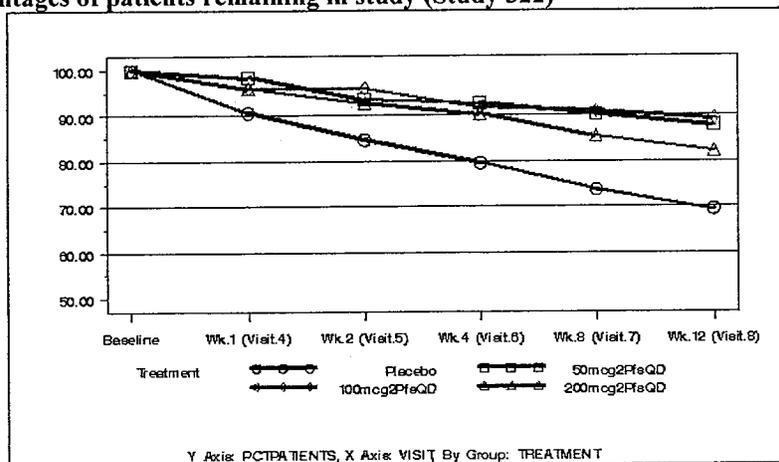


Figure 3 and Figure 4, above, show that the numbers and percentages of patients remaining in study in the placebo group decreased steadily and in a faster pace, compared to the other treatment groups.

The status of protocol compliance was dichotomized into one (1) and zero (0) - one represents “comply” and zero, otherwise. Table 17 shows the number of patients by treatment and compliance (evaluable)”

Table 17. Number of patients by treatment and status of compliance (Study 322)

Treatment	Evaluable				Total	
	0		1		N	%
	N	%	N	%		
Placebo	26	22.03	92	77.97	118	100.00
50mcg2PfsQD	14	11.29	110	88.71	124	100.00
100mcg2PfsQD	7	5.69	116	94.31	123	100.00
200mcg2PfsQD	15	12.10	109	87.90	124	100.00
Total	62	12.68	427	87.32	489	100.00

Twenty-six (26) out of 118 patients in the placebo group reportedly had major protocol violations, representing 22.03% of the placebo patients, a higher rate than the patients in the other groups, ranging from 5.69%-12.10%.

Because of the disproportionately higher percentages of missing observations and the higher percentages of protocol violations among the placebo patients, a sensitivity analysis was performed to assess the impact of these facts on statistical findings and is provided in the section, OTHER SPECIAL/SUBGROUP POPULATIONS of this report.

Study 323/324

The ITT population “consisted of patients who were randomized, treated with double-blind study medication and had a valid baseline and post baseline measurement of the primary efficacy variable, FEV₁” There were 531 patients enrolled in this study. The sponsor excluded five patients from the ITT group.

Table 18. Number of patients excluded from the ITT group (Study 323/324)

Treatment	#Patients
Placebo	2
220mcg2PfsQD	3
Overall	5

Table 94 in Appendix A of this review contains the FEV₁ observed or imputed at each visit for these subjects.

Table 19, below, shows the number of ITT patients by treatment and status of completion.

Table 19. Number of ITT patients by treatment and status of completion (Study 323/324)

	Completer				Total	
	No		Yes		N	%
	N	%	N	%		
Placebo	64	47.8	70	52.2	134	100.0
100mcg2PfsQD	26	20.5	101	79.5	127	100.0
200mcg2PfsQD	26	20.0	104	80.0	130	100.0
220mcg2PfsQD	23	17.0	112	83.0	135	100.0
Total	139	26.4	387	73.6	526	100.0

The dropouts among the placebo patients accounted for 47.8% of the patients in that group, representing a markedly higher figure than those among the active-treatment groups: 17.0-20.5%. The effect of the missing observations and their estimation will be discussed in the later sections of this report.

Having observed the high percentage of early withdrawal, particularly in the placebo group, this reviewer presents in Table 20, below, a complete list of the reasons for early withdrawal. The list was generated based on data file named COMPWI.

Table 20. Reasons for early withdrawal (Study 323/324)

										Total N
		Placebo		100mcg2PfsQD		200mcg2PfsQD		220mcg2PfsQD		
		N	%	N	%	N	%	N	%	
Completer	Dropout reason			2	7.7			1	4.3	3
No	Other reason									
	Protocol violation	3	4.7			3	11.5	1	4.3	7
	Lost to follow-up	1	1.6	2	7.7	3	11.5	4	17.4	10
	Did not wish to continue	3	4.7	2	7.7	5	19.2	4	17.4	14
	Poor compliance with treatment	1	1.6							1
	Lack of efficacy	29	45.3	12	46.2	5	19.2	6	26.1	52
	Lack of efficacy and Other reason	1	1.6							1
	Lack of efficacy and Did not wish to continue	1	1.6					1	4.3	2
	Adverse event	3	4.7			1	3.8	3	13.0	7
	Adverse event and Lack of efficacy	21	32.8	8	30.8	9	34.6	3	13.0	41
	Adverse event and Lack of efficacy and Did not wish to continue	1	1.6							1
Total		64	100.0	26	100.0	26	100.0	23	100.0	139

Source: \\CDSESUB1\N21658\N_000\2004-02-05\CRT\DATASETS\323324\COMPWLXPT

The most common reasons for early dropout were “lack of efficacy” and “adverse event.” According to the sponsor’s data (COMPWLXPT), some dropout reasons were under “lack of efficacy” alone, while others fell into both categories: “lack of efficacy” and “adverse event.” In addition, there were 4.7-17.4% of the patients in the treatment groups reported to withdraw early due to the reason, “did not wish to continue,” which does not clearly characterize the reason.

The following graphs depict the numbers and percentages of the patients remaining in study over time.

Figure 5. Numbers of patients remaining in study (Study 323/324)

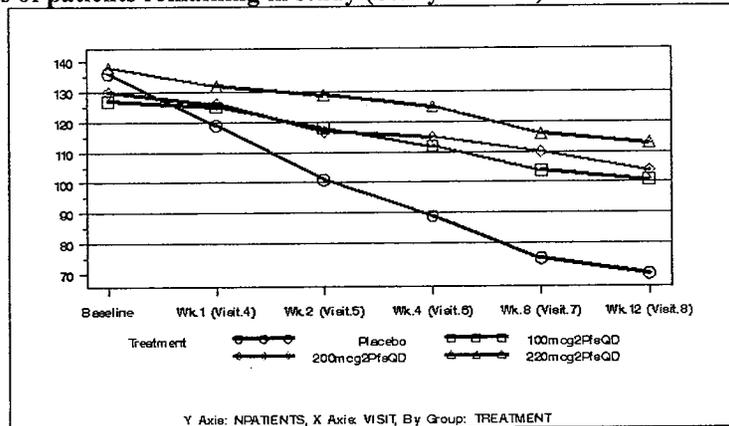


Figure 6. Percentages of patients remaining in study (Study 323/324)

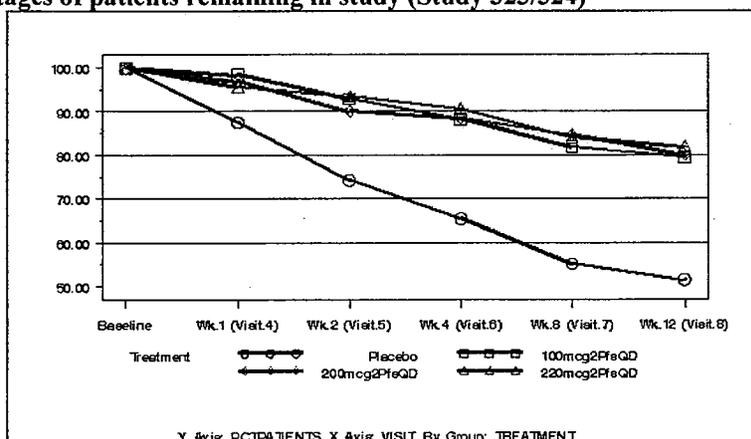


Figure 5 and Figure 6, above, show that the numbers and percentages of patients remaining in study in the placebo group decreased rapidly, compared with the other treatment groups.

The status of protocol compliance was dichotomized into one (1) and zero (0) - one represents “comply” and zero, otherwise. Table 21 shows the number of patients by treatment and compliance (evaluable).”

Table 21. Number of patients by treatment and status of compliance (Study 323/324)

	Evaluable				Total	
	0		1		N	%
	N	%	N	%		
Treatment	42	31.34	92	68.66	134	100.00
Placebo						
100mcg2PfsQD	18	14.17	109	85.83	127	100.00
200mcg2PfsQD	16	12.31	114	87.69	130	100.00
220mcg2PfsQD	12	8.89	123	91.11	135	100.00
Total	88	16.73	438	83.27	526	100.00

Forty-two out of 134 patients in the placebo group reportedly had major protocol violations, representing 31.34% of the placebo patients, a higher rate than the patients in the other groups, ranging from 8.89%-14.17%.

Because of the disproportionately higher percentages of missing observations and the higher percentages of protocol violations among the placebo patients, a sensitivity analysis was performed to assess the impact of these facts on statistical findings and is provided in the section, OTHER SPECIAL/SUBGROUP POPULATIONS of this report.

Study 341

There were 514 patients enrolled in this study. The sponsor excluded 10 patients from the ITT group.

Table 22. Number of patients excluded from the ITT group (Study 341)

Treatment	#Patients
Placebo	4
50mcg1PfsQD	2
100mcg1PfsQD	1
200mcg1PfsQD	3
Overall	10

Table 95 in Appendix A of this review contains the FEV₁ observed or imputed at each visit for these subjects.

Table 23, below, shows the number of ITT patients by treatment and status of completion.

Table 23. Number of ITT patients by treatment and status of completion (Study 341)

	Completer				Total	
	No		Yes		N	%
	N	%	N	%		
Placebo	20	15.7	107	84.3	127	100.0
50mcg1PfsQD	21	16.9	103	83.1	124	100.0
100mcg1PfsQD	17	12.7	117	87.3	134	100.0
200mcg1PfsQD	15	12.6	104	87.4	119	100.0
Total	73	14.5	431	85.5	504	100.0

In contrast to the adult studies, the numbers and percentages of early withdrawals across the treatment groups do not appear to differ very much.

Presented in Table 24, below, is a complete list of the reasons for early withdrawal. The list was generated based on data file named COMPWI.

Table 24. Reasons for early withdrawal (Study 341)

										Total
		Placebo		50mcg1PfsQD		100mcg1PfsQD		200mcg1PfsQD		N
Completer	Dropout reason	N	%	N	%	N	%	N	%	N
No	Other reason							1	6.7	1
	Protocol violation	2	10.0	2	9.5	4	23.5	1	6.7	9
	Lost to follow-up					1	5.9	1	6.7	2
	Did not wish to continue	2	10.0	2	9.5	1	5.9	1	6.7	6
	Did not wish to continue and Protocol violation			1	4.8					1
	Poor compliance with treatment			1	4.8			1	6.7	2
	Lack of efficacy	1	5.0	1	4.8			1	6.7	3
	Adverse event	1	5.0	3	14.3	2	11.8	1	6.7	7
	Adverse event and Protocol violation	1	5.0	1	4.8					2
	Adverse event and Did not wish to continue			1	4.8	1	5.9			2
	Adverse event and Lack of efficacy	13	65.0	8	38.1	8	47.1	8	53.3	37
	Adverse event and Lack of efficacy and Did not wish to continue			1	4.8					1
Total		20	100.0	21	100.0	17	100.0	15	100.0	73

Source: \\CDSESUB1\N21658\N_000\2004-02-05\CRT\DATASETS\341\COMPWI.XPT

The most common reasons for early dropout were “lack of efficacy” and “adverse event,” according to the sponsor’s data (COMPWI.XPT).

The following graphs depict the numbers and percentages of the patients remaining in study over time.

Figure 7. Numbers of patients remaining in study (Study 341)

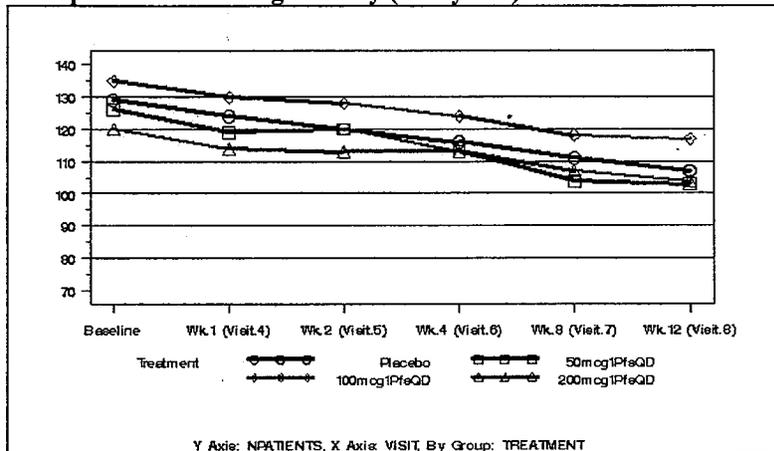


Figure 8. Percentages of patients remaining in study (Study 341)

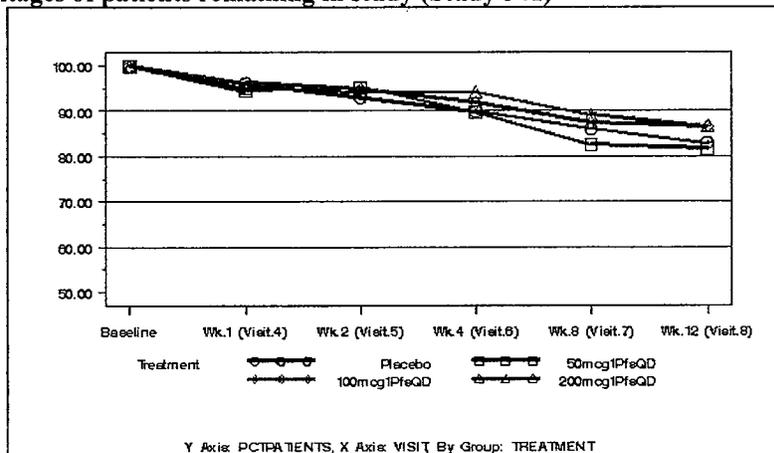


Figure 7 and Figure 8, above, show that the numbers and percentages of patients remaining in study across the treatment groups do not differ much.

The status of protocol compliance was dichotomized into one (1) and zero (0) - one represents “comply” and zero, otherwise. Table 25 shows the number of patients by treatment and compliance (evaluable).”

Table 25. Number of patients by treatment and status of compliance (Study 341)

Treatment	Evaluable				Total	
	0		1		N	%
	N	%	N	%		
Placebo	21	16.54	106	83.46	127	100.00
50mcg1PfsQD	21	16.94	103	83.06	124	100.00
100mcg1PfsQD	17	12.69	117	87.31	134	100.00
200mcg1PfsQD	11	9.24	108	90.76	119	100.00
Total	70	13.89	434	86.11	504	100.00

The numbers and percentages of the patients with major protocol violations across the treatment groups do not appear to differ much.

A sensitivity analysis was performed to assess the impact caused by protocol violations or early withdrawal on statistical findings and is provided in the section, OTHER SPECIAL/SUBGROUP POPULATIONS of this report.

Study 342

There were 516 patients enrolled in this study. The sponsor excluded 2 patients from the ITT group.

Table 26. Number of patients excluded from the ITT group (Study 342)

Treatment	#Patients
50mcg1PfsQD	1
100mcg1PfsQD	1
Overall	2

Table 96 in Appendix A of this review contains the FEV₁ observed or imputed at each visit for these subjects.

Table 27, below, shows the number of ITT patients by treatment and status of completion.

Table 27. Number of ITT patients by treatment and status of completion (Study 342)

	Completer				Total	
	No		Yes		N	%
	N	%	N	%		
Placebo	27	21.3	100	78.7	127	100.0
50mcg1PfsQD	19	14.8	109	85.2	128	100.0
100mcg1PfsQD	16	12.8	109	87.2	125	100.0
200mcg1PfsQD	13	9.7	121	90.3	134	100.0
Total	75	14.6	439	85.4	514	100.0

The numbers and percentages of early withdrawal across the treatment groups do not appear to differ much.

Having observed the high percentage of early withdrawal, particularly in the placebo group, this reviewer presents in Table 28, below, a complete list of the reasons for early withdrawal. The list was generated based on data file named COMPWL.

Table 28. Reasons for early withdrawal (Study 342)

		Treatment								Total N
		Placebo		50mcg1PfsQD		100mcg1PfsQD		200mcg1PfsQD		
Completer	Dropout reason	N	%	N	%	N	%	N	%	N
No	Other reason			1	5.3	1	6.3			2
	Protocol violation	3	11.1	2	10.5	2	12.5	4	30.8	11
	Lost to follow-up			1	5.3	1	6.3	1	7.7	3
	Did not wish to continue	2	7.4	4	21.1	2	12.5	1	7.7	9
	Poor compliance with treatment and Protocol violation					1	6.3			1
	Lack of efficacy	2	7.4	3	15.8	1	6.3			6
	Lack of efficacy and Did not wish to continue	1	3.7							1
	Adverse event	3	11.1			1	6.3	2	15.4	6
	Adverse event and Did not wish to continue	1	3.7							1
	Adverse event and Lack of efficacy	14	51.9	8	42.1	7	43.8	5	38.5	34
Adverse event and Lack of efficacy and Did not wish to continue	1	3.7							1	
Total		27	100.0	19	100.0	16	100.0	13	100.0	75

Source: \CDSE\SUB\N21658\N_000\2004-02-05\CRT\DATASETS\342\COMPWL.XPT

The most common reasons for early dropout were “adverse event, lack of efficacy” and “protocol violation,” according to the sponsor’s data (COMPWI.XPT).

The following graphs depict the numbers and percentages of the patients remaining in study over time.

Figure 9. Numbers of patients remaining in study (Study 342)

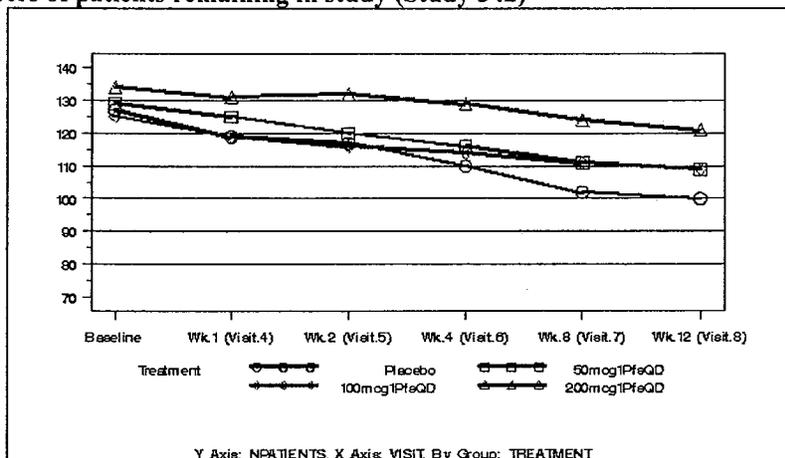


Figure 10. Percentages of patients remaining in study (Study 342)

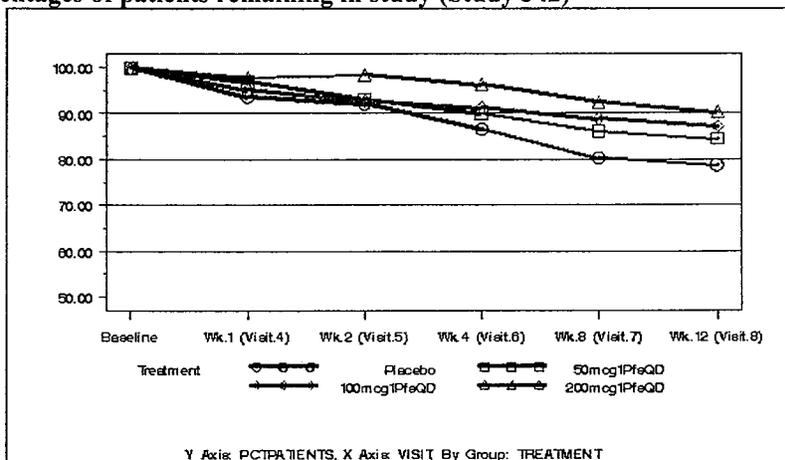


Figure 9 and Figure 10, above, show that the numbers and percentages of patients remaining in study across the treatment groups do not differ much.

The status of protocol compliance was dichotomized into one (1) and zero (0) - one represents “comply” and zero, otherwise. Table 29 shows the number of patients by treatment and compliance (evaluable).”

Table 29. Number of patients by treatment and status of compliance (Study 342)

	Evaluable				Total	
	0		1		N	%
	N	%	N	%		
Treatment	29	22.83	98	77.17	127	100.00
Placebo						
50mcg1PfsQD	11	8.59	117	91.41	128	100.00
100mcg1PfsQD	17	13.60	108	86.40	125	100.00
200mcg1PfsQD	17	12.69	117	87.31	134	100.00
Total	74	14.40	440	85.60	514	100.00

Twenty-nine (29) out of 127 patients in the placebo group reportedly had major protocol violations, representing 22.83% of the placebo patients, a higher rate than the patients in the other groups, ranging from 8.59%-12.69%.

A sensitivity analysis was performed to assess the impact caused by protocol violations or early withdrawal on statistical findings and is provided in the section, OTHER SPECIAL/SUBGROUP POPULATIONS of this report.

APPEARS THIS WAY ON ORIGINAL