

Statistical Methodologies

Study 321

The sponsor applied ANOVA on the change in FEV₁ at Week 12 (Visit 8) from the baseline. The statistical method was described in the following quotes from the application:

“Change from baseline in FEV1 was analyzed using an ANCOVA model that included parameters for treatment, pooled center, previous therapy, and the following covariates: gender, baseline FEV1, and age. Previous therapy has two levels: stratum 1 and stratum 2 (Table 12-43, p247, study321.pdf).”

“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 320 µg/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 160 µg/day and placebo was to be performed. If that comparison was statistically significant, then the ciclesonide 80 µg/day group was to be compared with placebo at a significance level of $\alpha=0.05$ (p76, study321.pdf).”

Study 322, Study 323/324, Studies 341 and 342

The methods of the statistical analyses used in these studies were identical to that for Study 321.

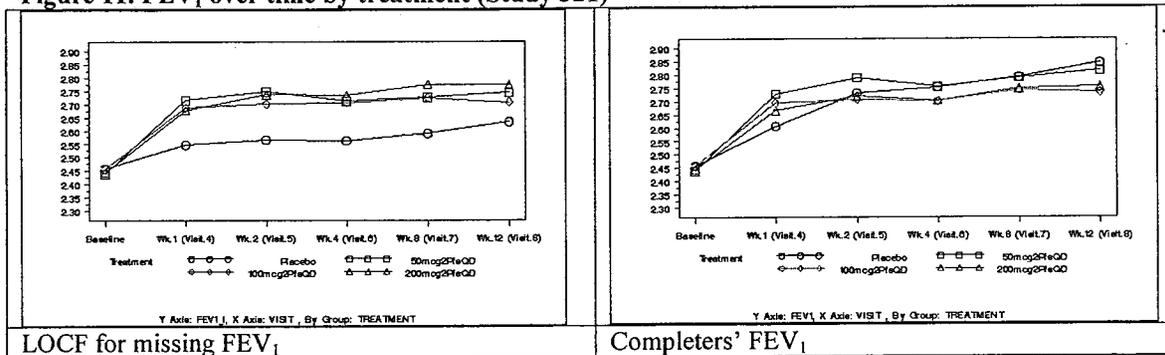
Statistical Analyses

One of the purposes of this reviewer’s statistical analysis based on the sponsor’s data is to understand and verify the sponsor’s statistical findings and conclusions. The main focus is to confirm the sponsor’s analyses specified in the protocol by reproducing the sponsor’s statistical results. Different approaches are also employed to reflect the practice commonly used in reviews for similar new drug submissions. This ensures that the efficacy conclusions are consistent and robust to minor variations of statistical models. Selected subgroup analyses are also done to explore the influence due to imbalance in patient characteristics, such as demography and baseline disease status.

Study 321

Figure 11 shows FEV₁ over time by treatment.

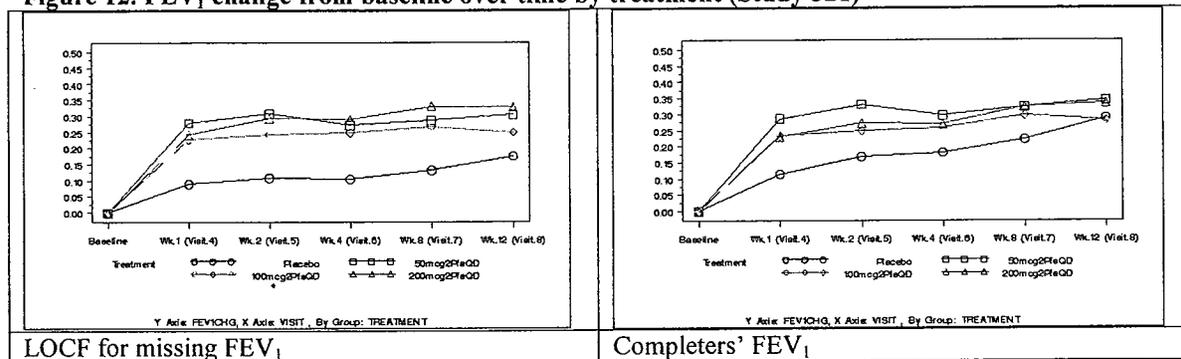
Figure 11. FEV₁ over time by treatment (Study 321)



The graph on the left panel is based on FEV₁ with missing imputed using LOCF (FEV₁_I), while the one on the right is based on completers' FEV₁ alone. The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

Figure 12 shows FEV₁ change from baseline over time by treatment.

Figure 12. FEV₁ change from baseline over time by treatment (Study 321)



The graph on the left panel for the FEV₁ changes from baseline over time is based on FEV₁ with missing imputed using LOCF (FEV₁_I), while the one on the right is based on completers' FEV₁ alone.

Figure 11 and Figure 12 show:

- Over time, the FEV₁ changes from baseline are consistently lower in the placebo group than in the other groups.
- Alvesco at 100 µg does not appear as effective as the 50 and 200 µg groups. Alvesco at 200 µg performs numerically better than at 50 µg does as compared with placebo at Week 12 (Visit 8).

- The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

This reviewer verified the sponsor's reported analysis and determined the results to be valid and accurate. Three Alvesco groups are compared with the placebo. The results are shown in Table 30, below.

Table 30. ANOVA on FEV₁ change at Visit 8 from baseline: Full model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50 µg 2PfsQD vs Placebo	0.1205	0.0348	2.52	0.0122	0.0076	0.2335
100 µg 2PfsQD vs Placebo	0.0676	0.0356	1.40	0.1635	-0.0466	0.1817
200 µg 2PfsQD vs Placebo	0.1536	0.0351	3.20	0.0015	0.0405	0.2667

As was done by the sponsor, this reviewer included the baseline FEV₁ as the covariate and the following factors in the statistical model: TREATMENT, CENTER, STRATA, AGE, and SEX. According to the sponsor's step-down procedure for multiple-comparison adjustment, Alvesco at 200 µg alone proves to be statistically superior to the placebo.

This reviewer considers a reduced model, including TREATMENT, CENTER, and STRATA, to be more appropriate to pursue. The need for inclusion of AGE or SEX as factors is minimized since randomization in general balances treatment groups with respect to baseline characteristics. Note though that baseline variables, such as age or sex, may be useful in a model as they may explain a large amount of the variability in the data. Here are the analysis results based on the reduced model.

Table 31. ANOVA on FEV₁ change at Visit 8 from baseline: Reduced model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50 µg 2PfsQD vs Placebo	0.1344	0.0351	2.77	0.0058	0.0200	0.2487
100 µg 2PfsQD vs Placebo	0.0738	0.0359	1.50	0.1331	-0.0418	0.1895
200 µg 2PfsQD vs Placebo	0.1584	0.0353	3.25	0.0012	0.0436	0.2732

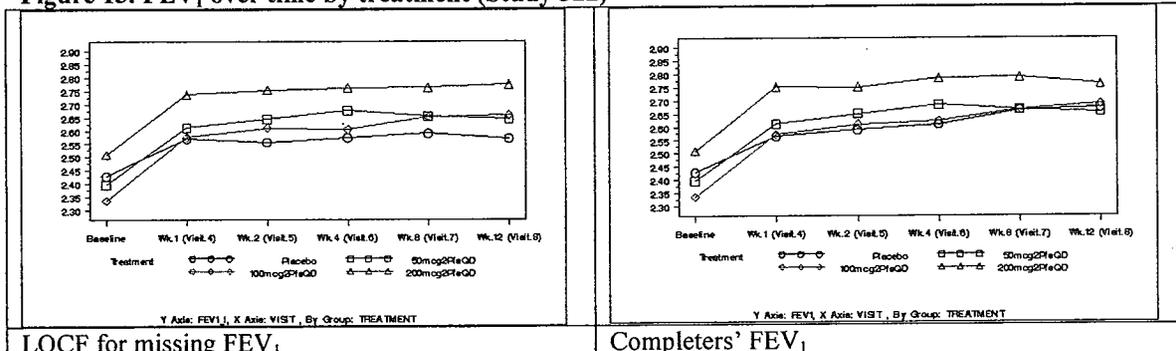
The results from Table 30 and Table 31 demonstrate that Alvesco at the 200 µg dose levels is significantly more effective than the placebo, according to the step-down procedure. Because of the step-down procedure used for multiple-comparison adjustments and the lack of statistical significance in comparing Alvesco 100 µg versus placebo, the test of Alvesco, 50 µg versus placebo is not considered to be statistically significant. These findings are not changed under either the sponsor's model or the reviewer's reduced model.

However, 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. Unlike the analysis of those on corticosteroids, a statistically significant difference between Alvesco and placebo was not demonstrated among the patients on bronchodilators. Therefore, results in the overall group could be misleading and the reader should refer to the section titled "SUBGROUP: STRATA" for discussion of efficacy within each stratum.

Study 322

Figure 13 shows FEV₁ over time by treatment.

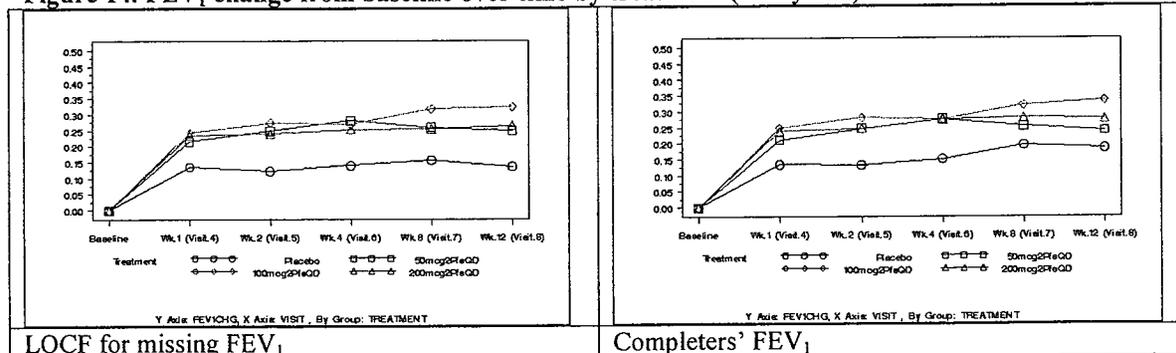
Figure 13. FEV₁ over time by treatment (Study 322)



The graph on the left panel is based on FEV₁ with missing imputed using LOCF (FEV₁_I), while the one on the right is based on completers' FEV₁ alone. The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

Figure 14 shows FEV₁ change from baseline over time by treatment.

Figure 14. FEV₁ change from baseline over time by treatment (Study 322)



The graph on the left panel for the FEV₁ changes from baseline over time is based on FEV₁ with missing data imputed using LOCF (FEV₁_I), while the one on the right is based on completers' FEV₁ alone.

Figure 13 and Figure 14 show:

- Over time, the FEV₁ changes from baseline are consistently lower in the placebo group than in the other groups.
- Alvesco groups consistently demonstrate greater values in the FEV₁ changes from baseline, over time, than the placebo group does.
- The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

This reviewer verified the sponsor's reported analysis and determined the results to be accurate. Three Alvesco groups are compared with the placebo. The results are shown in Table 32, below.

Table 32. ANOVA on FEV₁ change at Visit 8 from baseline: Full model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1165	0.0359	2.29	0.0224	-0.0032	0.2362
100mcg2PfsQD vs Placebo	0.1873	0.0362	3.67	0.0003	0.0673	0.3073
200mcg2PfsQD vs Placebo	0.1217	0.0361	2.40	0.0169	0.0022	0.2413

As was done by the sponsor, this reviewer included the baseline FEV₁ as the covariate and the following factors in the statistical model: TREATMENT, CENTER, STRATA, AGE, and SEX. According to the sponsor's step-down procedure for multiple-comparison adjustment, Alvesco at all three dose levels proved to be statistically superior to the placebo.

This reviewer considers a reduced model, including TREATMENT, CENTER, and STRATA, to be more appropriate to pursue. The need for inclusion of AGE or SEX as factors is minimized since randomization in general balances treatment groups with respect to baseline characteristics. Note though that baseline variables, such as age or sex, may be useful in a model as they may explain a large amount of the variability in the data. Here are the analysis results based on the reduced model.

Table 33. ANOVA on FEV₁ change at Visit 8 from baseline: Reduced model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1167	0.0361	2.27	0.0237	-0.0044	0.2378
100mcg2PfsQD vs Placebo	0.1930	0.0362	3.75	0.0002	0.0717	0.3142
200mcg2PfsQD vs Placebo	0.1204	0.0363	2.34	0.0196	-0.0006	0.2414

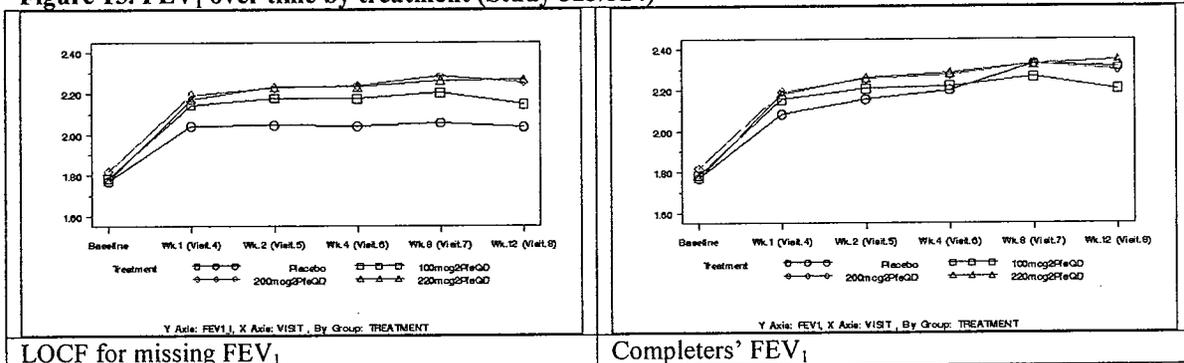
The results from Table 32 and Table 33 demonstrate that in Study 322 Alvesco at the 50, 100, and 200 µg dose levels is significantly more effective than the placebo, according to the step-down procedure used by the sponsor.

However, 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. Unlike the analysis of those on corticosteroids, a statistically significant difference between Alvesco and placebo was not demonstrated among the patients on bronchodilators. Therefore, results in the overall group could be misleading and the reader should refer to the section titled "SUBGROUP: STRATA" for discussion of efficacy within each stratum.

Study 323/324

Note that in this combined study, the highest dose, 220µg, represents the dose level for Fluticasone, while others, 100µg and 200µg, Alvesc . The following Figure 15 shows FEV₁ over time by treatment.

Figure 15. FEV₁ over time by treatment (Study 323/324)

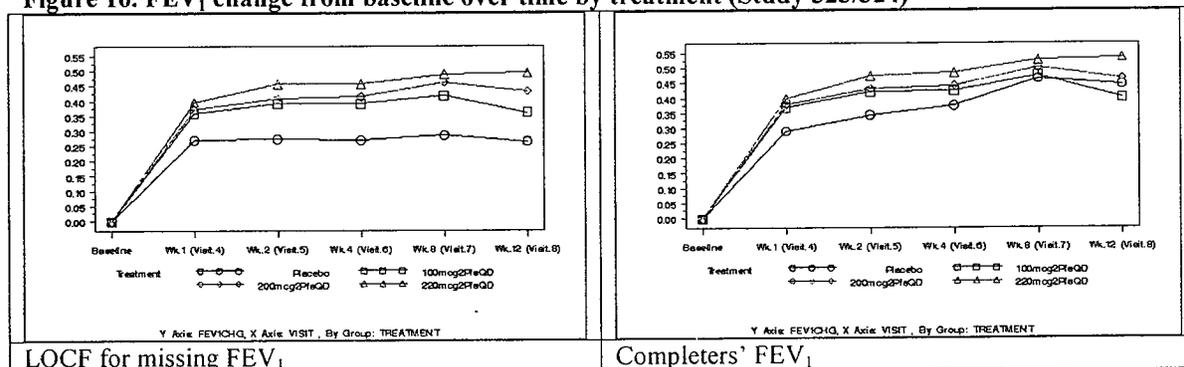


Symbol in graph: 220µg2Pfs BID represents Fluticasone dosage. Other dosages belong to Alvesco.

The graph on the left panel is based on FEV₁ with missing imputed using LOCF (FEV_{1_I}), while the one on the right is based on completers' FEV₁ alone. The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

Figure 16 shows FEV₁ change from baseline over time by treatment.

Figure 16. FEV₁ change from baseline over time by treatment (Study 323/324)



Symbol in graph: 220µg2PfsQD represents Fluticasone dosage. Other dosages belong to Alvesco.

The graph on the left panel for the FEV₁ changes from baseline over time is based on FEV₁ with missing imputed using LOCF (FEV_{1_I}), while the one on the right is based on completers' FEV₁ alone.

Figure 15 and Figure 16 show:

- Over time, the FEV₁ changes from baseline are consistently lower in the placebo group than in the other groups when missing values are imputed using LOCF.
- Alvesco and Fluticasone groups consistently demonstrate greater values in the FEV₁ changes from baseline, over time, than the placebo group does. Fluticasone at 220 µg appears to be more effective than the Alvesco doses of 100 µg and 200 µg.
- The influence of LOCF FEV₁ is obvious. The imputed FEV₁ values clearly set placebo apart from the Alvesco groups.

This reviewer verified the sponsor's reported analysis and determined the results to be accurate. The results are show in Table 34, below.

Table 34. ANOVA on FEV₁ change at Visit 8 from baseline: Full model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.1099	0.0377	2.10	0.0360	-0.0133	0.2331
200mcg2PfsQD vs Placebo	0.1757	0.0374	3.39	0.0007	0.0537	0.2976
220mcg2PfsQD vs Placebo	0.2509	0.0370	4.89	0.0000	0.1299	0.3718

Note: The 220-mcg group represents the Fluticasone arm.

As was done by the sponsor, this reviewer included the baseline FEV₁ as the covariate and the following factors in the statistical model: TREATMENT, CENTER, AGE, and SEX. According to the sponsor's step-down procedure for multiple-comparison adjustment, fluticasone at 220 µg, Alvesco at 200 µg and 100 µg prove to be statistically superior to the placebo.

This reviewer considers a reduced model, including TREATMENT, CENTER, and STRATA, to be more appropriate to pursue. The need for inclusion of AGE or SEX as factors is minimized since randomization in general balances treatment groups with respect to baseline characteristics. Note though that baseline variables, such as age or sex, may be useful in a model as they may explain a large amount of the variability in the data. Here are the analysis results based on the reduced model.

Table 35. ANOVA on FEV₁ change at Visit 8 from baseline: Reduced model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.0962	0.0380	1.82	0.0696	-0.0285	0.2208
200mcg2PfsQD vs Placebo	0.1633	0.0376	3.12	0.0019	0.0398	0.2867
220mcg2PfsQD vs Placebo	0.2340	0.0371	4.52	0.0000	0.1118	0.3561

The results from Table 34 and Table 35 show:

- Fluticasone at 220 µg is significantly more effective than placebo.
- Alvesco at 200 µg is significantly more effective than placebo.
- Alvesco at the lower dose, 100 µg does not show statistical superiority to the placebo under the reduced model, however, it does show superiority under the full model used by the sponsor.

Study 341

Note that the primary efficacy variable in this study was the change of percent-predicted FEV₁ at Week 12 (Visit 8) from baseline. This study involved patients of 4-11 years of age.

This reviewer verified the sponsor's reported analysis and determined the results to be valid and accurate. This reviewer compared the three dose groups of Alvesco with placebo. The results are shown in Table 37, below.

Table 36. ANOVA on percent-predicted FEV₁ change at Visit 8 from baseline: Full model (Study 341)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	1.1714	1.4599	0.59	0.5573	-3.5303	5.8731
100mcg1PfQD vs Placebo	3.9304	1.4052	2.00	0.0459	-0.6972	8.5579
200mcg1PfQD vs Placebo	3.3617	1.4753	1.66	0.0984	-1.4230	8.1464

As was done by the sponsor, this reviewer included the baseline percent predicted FEV₁ as the covariate and the following factors in the statistical model: TREATMENT, CENTER, STRATA, AGE, and SEX. The ANOVA indicates that **none** of the Alvesco dose groups demonstrated a statistical superiority to the placebo.

This reviewer considers a reduced model, including TREATMENT, CENTER, and STRATA, to be more appropriate to pursue. The need for inclusion of AGE or SEX as factors is minimized since randomization in general balances treatment groups with respect to baseline characteristics. Note though that baseline variables, such as age or sex, may be useful in a model as they may explain a large amount of the variability in the data. Here are the analysis results based on the reduced model.

Table 37. ANOVA on percent-predicted FEV₁ change at Visit 8 from baseline: Reduced model (Study 341)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	1.2025	1.4433	0.60	0.5462	-3.4906	5.8956
100mcg1PfQD vs Placebo	4.0178	1.3936	2.06	0.0404	-0.5904	8.6260
200mcg1PfQD vs Placebo	3.5087	1.4722	1.74	0.0824	-1.2431	8.2606

The analysis shows that, consistent with that under the full model, **none** of the Alvesco dose groups demonstrated a statistical superiority to the placebo. Although the p-value for the comparison of Alvesco 100 µg versus placebo is less than 0.05, it is not considered statistically significant, because of the step-down procedure used for multiple-comparison adjustment and the lack of statistical significance with the Alvesco 200 µg versus placebo comparison.

However, 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. Unlike the analysis of those on corticosteroids, a statistically significant difference between Alvesco and placebo was not demonstrated among the patients on bronchodilators. Therefore, results in the overall group could be

misleading and the reader should refer to the section titled “SUBGROUP: STRATA” for discussion of efficacy within each stratum.

Study 342

Note that the primary efficacy variable in this study was the change of percent-predicted FEV₁ at Week 12 (Visit 8) from baseline. This study involved patients of 4-11 years of age.

This reviewer verified the sponsor’s reported analysis and determined the results to be valid and accurate. This reviewer compared the three dose groups of Alvesco with placebo. The results are show in Table 38, below.

Table 38. ANOVA on percent-predicted FEV₁ change at Visit 8 from baseline: Full model (Study 341)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	1.3504	1.2093	0.83	0.4064	-2.4786	5.1795
100mcg1PfQD vs Placebo	1.7176	1.2309	1.05	0.2951	-2.1433	5.5786
200mcg1PfQD vs Placebo	3.5446	1.2025	2.20	0.0283	-0.2525	7.3418

As was done by the sponsor, this reviewer included the baseline percent predicted FEV₁ as the covariate and the following factors in the statistical model: TREATMENT, CENTER, STRATA, AGE, and SEX. The ANOVA indicates that only Alvesco at the 200 µg dose group demonstrated a statistical superiority to the placebo.

This reviewer considers a reduced model, including TREATMENT, CENTER, and STRATA, to be more appropriate to pursue. The need for inclusion of AGE or SEX as factors is minimized since randomization in general balances treatment groups with respect to baseline characteristics. Note though that baseline variables, such as age or sex, may be useful in a model as they may explain a large amount of the variability in the data. Here are the analysis results based on the reduced model.

Table 39. ANOVA on percent-predicted FEV₁ change at Visit 8 from baseline: Reduced model (Study 342)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	1.3548	1.1998	0.83	0.4045	-2.4704	5.1800
100mcg1PfQD vs Placebo	1.5953	1.2167	0.98	0.3296	-2.2560	5.4466
200mcg1PfQD vs Placebo	3.3699	1.1864	2.10	0.0362	-0.4097	7.1495

The analysis shows that, consistent with that under the full model, only Alvesco at the 200 µg dose group demonstrated a statistical superiority to the placebo.

However, 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. Unlike the analysis of those on corticosteroids, a statistically significant difference between Alvesco and placebo was not demonstrated among the patients on bronchodilators. Therefore, results in the overall group could be misleading and the reader should refer to the section titled “SUBGROUP: STRATA” for discussion of efficacy within each stratum.

Results and Conclusions

Study 321

The efficacy evaluation of Alvesco is summarized in the following points:

- Alvesco at 200 µg, 2 puffs, QD, was statistically superior to placebo.
- No increasing or decreasing trend of dose-response is seen in Study 321.

Study 322

The efficacy evaluation of Alvesco is summarized in the following points:

- Alvesco at all dose levels (50, 100, and 200 µg, 2 puffs), QD, was statistically superior to placebo.
- No increasing or decreasing trend of dose-response is seen in Study 322.

Study 323/324

The efficacy evaluation of Alvesco is summarized in the following points:

- Alvesco at the dose levels, 100, and 200 µg, 2 puffs, BID, was statistically superior to placebo.
- Fluticasone at the dose level, 220 µg, 2 puffs, BID, also was statistically superior to placebo.
- Alvesco at 200 µg level appears to have greater dose response than the 100 µg does numerically.
- Although not statistically significantly different, Fluticasone at 220 µg appears to outperform the Alvesco groups numerically.

Study 341

The efficacy evaluation of Alvesco indicates that **none** of the Alvesco dose groups demonstrated a statistical superiority to the placebo.

Study 342

The efficacy evaluation of Alvesco indicates that **only** Alvesco at the 200 µg dose group demonstrated a statistical superiority to the placebo.

Efficacy Conclusions Based on Studies: 321, 322, 323/324, 341, 342

The overall conclusion regarding the efficacy evaluations of all pivotal studies is summarized in the following Table 40. This reviewer uses the following symbols to indicate the result of ANOVA on the primary efficacy variable.

- + 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

Table 40. 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

The overall statistical conclusion on the efficacy: Across the studies, Alvesco at 200 μ g, 2 puffs, QD is consistently shown to be statistically superior to the placebo.

EVALUATION OF SAFETY

This reviewer focused the safety-data evaluation on the exploration of the adverse events reported in the data file named AE. In this section, only the adverse events that at least ten (10) patients reportedly experienced are reported. For a complete report of adverse events by study, see Appendix B.

Study 321

There were 183 distinct adverse events reported in Study 321. The following table lists the adverse events that at least ten (10) patients reportedly experienced. For a complete report of adverse events for this study, see Table 97 in Appendix B.

Table 41. Reported AEs in 10 or more patients (Study 321)

N: Number of Patients	Treatment								N per AE	% per AE
	Placebo		50mcg2PfsQD		100mcg2PfsQD		200mcg2PfsQD			
	N	%	N	%	N	%	N	%		
AE: AEPTTXX NO AE	53	10.08	51	9.70	55	10.46	56	10.65	215	40.87
Headache	9	1.71	13	2.47	11	2.09	8	1.52	41	7.79
Nasopharyngitis	8	1.52	12	2.28	11	2.09	10	1.90	41	7.79
Asthma aggravated	21	3.99	6	1.14	7	1.33	3	0.57	37	7.03
Upper respiratory tract infection NOS	10	1.90	11	2.09	8	1.52	8	1.52	37	7.03
Pharyngitis	9	1.71	6	1.14	8	1.52	7	1.33	30	5.70
Sinusitis NOS	3	0.57	4	0.76	5	0.95	5	0.95	17	3.23
Back pain	2	0.38	6	1.14	3	0.57	4	0.76	15	2.85
Rhinitis NOS exacerbated	4	0.76	4	0.76	4	0.76	2	0.38	14	2.66
Arthralgia			5	0.95	4	0.76	4	0.76	13	2.47
Bronchitis NOS	2	0.38	2	0.38	3	0.57	5	0.95	12	2.28
Cough	4	0.76	3	0.57	3	0.57			10	1.90
Diarrhoea NOS	1	0.19	6	1.14	2	0.38	1	0.19	10	1.90
Dyspepsia	4	0.76	2	0.38	1	0.19	3	0.57	10	1.90
Nasal congestion	1	0.19	2	0.38	5	0.95	2	0.38	10	1.90

Note that a percentage in each treatment group represents the ratio of the number of patients over the number of all patients in the study (not the number of patients in the treatment group) for the AE indicated.

This reviewer found that headache was the most frequent adverse event reported. Forty one patients reportedly experienced headache, representing nearly 7.8% of the total 526 patients in Study 321. The percents of patients reporting each AE were fairly balanced across treatment groups.

Study 322

This reviewer focused the safety-data evaluation on the exploration of the adverse events reported in the data file named AE. There were 202 distinct adverse events reported in Study 322. The following table lists the adverse events that at least ten (10) patients reportedly experienced. For a complete report of adverse events for this study, see Table 98 in Appendix B.

Table 42. Reported AEs in 10 or more patients (Study 322)

N: Number of Patients	Treatment								N per AE	% per AE
	Placebo		50mcg2PfsQD		100mcg2PfsQD		200mcg2PfsQD			
	N	%	N	%	N	%	N	%		
AE: AEPTTXXT	33	6.75	37	7.57	34	6.95	36	7.36	140	28.63
NO AE										
Headache	17	3.48	14	2.86	23	4.70	24	4.91	78	15.95
Nasopharyngitis	15	3.07	13	2.66	15	3.07	17	3.48	60	12.27
Upper respiratory tract infection NOS	16	3.27	19	3.89	11	2.25	10	2.04	56	11.45
Asthma aggravated	22	4.50	10	2.04	3	0.61	5	1.02	40	8.18
Pharyngitis	9	1.84	11	2.25	7	1.43	11	2.25	38	7.77
Sinusitis NOS	7	1.43	7	1.43	7	1.43	5	1.02	26	5.32
Back pain	5	1.02	5	1.02	4	0.82	8	1.64	22	4.50
Dyspepsia	4	0.82	1	0.20	8	1.64	4	0.82	17	3.48
Arthralgia	6	1.23	4	0.82	2	0.41	3	0.61	15	3.07
Diarrhoea NOS	6	1.23	3	0.61	5	1.02	1	0.20	15	3.07
Upper respiratory tract infection viral NOS	2	0.41	5	1.02			7	1.43	14	2.86
Influenza	2	0.41	2	0.41	3	0.61	6	1.23	13	2.66
Influenza like illness	6	1.23			3	0.61	4	0.82	13	2.66
Cough	3	0.61	3	0.61	2	0.41	4	0.82	12	2.45
Pain NOS	5	1.02	3	0.61	2	0.41	2	0.41	12	2.45
Toothache	5	1.02	3	0.61	1	0.20	3	0.61	12	2.45
Abdominal pain upper	3	0.61	2	0.41	4	0.82	2	0.41	11	2.25
Nasal congestion			6	1.23	3	0.61	2	0.41	11	2.25
Myalgia	4	0.82	2	0.41			4	0.82	10	2.04
Rhinitis NOS exacerbated	1	0.20	4	0.82	1	0.20	4	0.82	10	2.04

Note that a percentage in each treatment group represents the ratio of the number of patients over the number of all patients in the study (not the number of patients in the treatment group) for the AE indicated.

This reviewer found that headache was the most frequent adverse event reported. Seventy eight patients reportedly experienced headache, representing nearly 15.95% of the total 489 patients in Study 322.

Study 323/324

This reviewer focused the safety-data evaluation on the exploration of the adverse events reported in the data file named AE. There were 219 distinct adverse events reported in Study 323/324. The following table lists the adverse events that at least ten (10) patients reportedly experienced. For a complete report of adverse events for this study, see Table 99 in Appendix B.

Table 43. Reported AEs in 10 or more patients (Study 323/324)

N: Number of Patients	Treatment								N per AE	% per AE
	Placebo		100mcg2PfsQD		200mcg2PfsQD		220mcg2PfsQD			
	N	%	N	%	N	%	N	%		
AE: AEPTTXX	47	8.85	44	8.29	49	9.23	48	9.04	188	35.40
NO AE										
Headache	12	2.26	14	2.64	13	2.45	16	3.01	55	10.36
Asthma aggravated	27	5.08	10	1.88	14	2.64	3	0.56	54	10.17
Nasopharyngitis	11	2.07	14	2.64	12	2.26	16	3.01	53	9.98
Upper respiratory tract infection NOS	8	1.51	14	2.64	7	1.32	8	1.51	37	6.97
Sinusitis NOS	6	1.13	8	1.51	7	1.32	10	1.88	31	5.84
Oral candidiasis	6	1.13	5	0.94	1	0.19	17	3.20	29	5.46
Pharyngitis	5	0.94	8	1.51	4	0.75	9	1.69	26	4.90
Back pain	4	0.75	7	1.32			6	1.13	17	3.20
Cataract nuclear	1	0.19	5	0.94	9	1.69	2	0.38	17	3.20
Nasal congestion	2	0.38	7	1.32	4	0.75	2	0.38	15	2.82
Arthralgia	1	0.19	5	0.94	5	0.94	3	0.56	14	2.64
Abdominal pain upper	2	0.38	5	0.94	3	0.56	2	0.38	12	2.26
Pain NOS	1	0.19	2	0.38	5	0.94	4	0.75	12	2.26
Cough	3	0.56	2	0.38	2	0.38	3	0.56	10	1.88
Influenza	3	0.56	2	0.38			5	0.94	10	1.88
Rhinitis allergic NOS	4	0.75	2	0.38	2	0.38	2	0.38	10	1.88
Sinus congestion	2	0.38	2	0.38	4	0.75	2	0.38	10	1.88

Note that a percentage in each treatment group represents the ratio of the number of patients over the number of all patients in the study (not the number of patients in the treatment group) for the AE indicated.

This reviewer found that headache was the most frequent adverse event reported. Fifty five patients reportedly experienced headache, representing nearly 10.36% of the total 531 patients in Study 323/324.

Study 341

This reviewer focused the safety-data evaluation on the exploration of the adverse events reported in the data file named AE. There were 179 distinct adverse events reported in Study 341. The following table lists the adverse events that at least ten (10) patients reportedly experienced. For a complete report of adverse events for this study, see Table 100 in Appendix B.

Table 44. Reported AEs in 10 or more patients (Study 341)

N: Number of Patients	Treatment								N per AE	% per AE
	Placebo		50mcg1PfsQD		100mcg1PfsQD		200mcg1PfsQD			
	N	%	N	%	N	%	N	%		
AE: AEPTTXXT	39	7.59	33	6.42	47	9.14	32	6.23	151	29.38
NO AE										
Asthma aggravated	31	6.03	18	3.50	23	4.47	20	3.89	92	17.90
Headache	23	4.47	18	3.50	23	4.47	16	3.11	80	15.56
Nasopharyngitis	17	3.31	15	2.92	18	3.50	14	2.72	64	12.45
Sinusitis NOS	11	2.14	14	2.72	17	3.31	9	1.75	51	9.92
Pharyngitis	12	2.33	10	1.95	13	2.53	11	2.14	46	8.95
Pyrexia	12	2.33	9	1.75	9	1.75	12	2.33	42	8.17
Upper respiratory tract infection NOS	10	1.95	6	1.17	6	1.17	6	1.17	28	5.45
Cough	4	0.78	7	1.36	8	1.56	7	1.36	26	5.06
Vomiting NOS	11	2.14	6	1.17	5	0.97	2	0.39	24	4.67
Rhinitis NOS	5	0.97	6	1.17	5	0.97	2	0.39	18	3.50
Diarrhoea NOS	3	0.58	9	1.75	3	0.58	2	0.39	17	3.31
Nasal congestion	4	0.78	4	0.78	2	0.39	4	0.78	14	2.72
Rhinitis NOS exacerbated	5	0.97	4	0.78	1	0.19	4	0.78	14	2.72
Abdominal pain upper	7	1.36	1	0.19	4	0.78	1	0.19	13	2.53
Viral infection NOS	3	0.58	3	0.58	3	0.58	3	0.58	12	2.33
Ear pain	1	0.19	4	0.78	4	0.78	2	0.39	11	2.14
Epistaxis	1	0.19	3	0.58	5	0.97	2	0.39	11	2.14
Rash NOS	1	0.19	5	0.97	2	0.39	2	0.39	10	1.95
Rhinorrhoea	2	0.39	1	0.19	5	0.97	2	0.39	10	1.95

Note that a percentage in each treatment group represents the ratio of the number of patients over the number of all patients in the study (not the number of patients in the treatment group) for the AE indicated.

This reviewer found that asthma aggravation was the most frequent adverse event reported. Ninety two 92 patients reportedly experienced asthma aggravation, representing nearly 17.9% of the total 514 patients in Study 341.

Study 342

This reviewer focused the safety-data evaluation on the exploration of the adverse events reported in the data file named AE. There were 170 distinct adverse events reported in Study 342. The following table lists the adverse events that at least ten (10) patients reportedly experienced. For a complete report of adverse events for this study, see Table 101 in Appendix B.

Table 45. Reported AEs in 10 or more patients (Study 342)

N: Number of Patients	Treatment								N per AE	% per AE
	Placebo		50mcg1PfsQD		100mcg1PfsQD		200mcg1PfsQD			
	N	%	N	%	N	%	N	%		
AE: AEP TTX	33	6.40	49	9.50	44	8.53	39	7.56	165	31.98
NO AE										
Nasopharyngitis	13	2.52	8	1.55	17	3.29	22	4.26	60	11.63
Upper respiratory tract infection NOS	18	3.49	13	2.52	14	2.71	13	2.52	58	11.24
Asthma aggravated	20	3.88	12	2.33	12	2.33	13	2.52	57	11.05
Pharyngitis	14	2.71	15	2.91	11	2.13	17	3.29	57	11.05
Headache	11	2.13	10	1.94	10	1.94	17	3.29	48	9.30
Sinusitis NOS	9	1.74	4	0.78	3	0.58	9	1.74	25	4.84
Rhinitis NOS exacerbated	3	0.58	10	1.94	6	1.16	5	0.97	24	4.65
Pyrexia	7	1.36	7	1.36	5	0.97	3	0.58	22	4.26
Abdominal pain upper	6	1.16	2	0.39	7	1.36	5	0.97	20	3.88
Vomiting NOS	4	0.78	2	0.39	7	1.36	5	0.97	18	3.49
Bronchitis NOS	4	0.78	4	0.78	4	0.78	3	0.58	15	2.91
Gastroenteritis viral NOS	4	0.78	2	0.39	5	0.97	2	0.39	13	2.52
Rhinitis NOS	3	0.58	4	0.78	4	0.78	2	0.39	13	2.52
Aphthous stomatitis	3	0.58	2	0.39	1	0.19	5	0.97	11	2.13
Otitis media NOS	3	0.58	3	0.58	1	0.19	4	0.78	11	2.13
Upper respiratory tract infection viral NOS	3	0.58	5	0.97	2	0.39	1	0.19	11	2.13
Epistaxis	3	0.58	1	0.19	3	0.58	3	0.58	10	1.94

Note that a percentage in each treatment group represents the ratio of the number of patients over the number of all patients in the study (not the number of patients in the treatment group) for the AE indicated.

This reviewer found that nasopharyngitis was the most frequent adverse event reported. Sixty 60 patients reportedly experienced nasopharyngitis, representing nearly 11.63% of the total 516 patients in Study 342.

Safety Conclusions Based on Studies: 321, 322, 323/324, 341, 342

Across studies, this reviewer found that the most frequently reported adverse events are: HEADACHE, NASOPHARYNGITIS, and ASTHMA AGGRAVATION. Among these adverse events, HEADACHE is 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.

In all studies, the percents of patients reporting each AE were fairly balanced across treatment groups.

**APPEARS THIS WAY
ON ORIGINAL**

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

SUBGROUPS: AGE RACE AND SEX

Study 321

Subgroup by Age

Table 46 describes the numbers of patients and their mean ages, along with other statistics by treatment.

Table 46. Age (Study 321)

Treatment	#Patients	Mean	Min	Max	Median
Placebo	133	37.61	12.00	68.00	37.00
50mcg2PfsQD	133	36.26	12.00	71.00	37.00
100mcg2PfsQD	127	37.39	12.00	72.00	37.00
200mcg2PfsQD	131	37.62	13.00	72.00	37.00
Overall	524	37.21	12.00	72.00	37.00

Source: DEMO1

Table 47. Number of patients by treatment and age group (Study 321)

	Age Group				Total	
	AGE<=40		AGE>40		N	%
	N	%	N	%		
Placebo	71	53.4	62	46.6	133	100.0
50mcg2PfsQD	83	62.4	50	37.6	133	100.0
100mcg2PfsQD	73	57.5	54	42.5	127	100.0
200mcg2PfsQD	77	58.8	54	41.2	131	100.0
Total	304	58.0	220	42.0	524	100.0

This reviewer decided that a subgroup analysis be done for patients over and under 40 years of age as this value was approximately the median age.

The following analysis is based on patients 40 years of age and younger. There are 304 patients in this group.

Table 48. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients 40 years of age and younger: Full Model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0925	0.0505	1.29	0.1970	-0.0761	0.2610
100mcg2PfsQD vs Placebo	0.0551	0.0530	0.74	0.4593	-0.1202	0.2303
200mcg2PfsQD vs Placebo	0.1376	0.0517	1.89	0.0593	-0.0337	0.3090

The following analysis is based on patients over 40 years of age. There are 220 patients in this group.

Table 49. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients over 40 years of age: Full Model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1792	0.0521	2.87	0.0046	0.0308	0.3275
100mcg2PfsQD vs Placebo	0.1098	0.0493	1.79	0.0749	-0.0358	0.2555
200mcg2PfsQD vs Placebo	0.1628	0.0511	2.64	0.0089	0.0166	0.3091

Subgroup by Race

The following analysis is based on race.

Table 50. Number of patients by treatment and race (Study 321)

	Race				Total	
	White		Non-white		N	%
	N	%	N	%		
Placebo	117	88.0	16	12.0	133	100.0
50mcg2PfsQD	114	85.7	19	14.3	133	100.0
100mcg2PfsQD	109	85.8	18	14.2	127	100.0
200mcg2PfsQD	116	88.5	15	11.5	131	100.0
Total	456	87.0	68	13.0	524	100.0

The ANOVA subgroup analysis was not done because there were too few non-whites.

Subgroup by Sex

The following analysis is based on sex.

Table 51. Number of patients by treatment and sex (Study 321)

	Sex				Total	
	Female		Male		N	%
	N	%	N	%		
Placebo	83	62.4	50	37.6	133	100.0
50mcg2PfsQD	78	58.6	55	41.4	133	100.0
100mcg2PfsQD	72	56.7	55	43.3	127	100.0
200mcg2PfsQD	78	59.5	53	40.5	131	100.0
Total	311	59.4	213	40.6	524	100.0

The following exploratory analysis is based on male patients. There are 213 males in this group.

Table 52. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for male patients: Full Model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1521	0.0715	1.48	0.1410	-0.0907	0.3949
100mcg2PfsQD vs Placebo	0.0579	0.0727	0.56	0.5733	-0.1843	0.3000
200mcg2PfsQD vs Placebo	0.1590	0.0716	1.54	0.1250	-0.0846	0.4027

The following exploratory analysis is based on female patients. There are 311 females in this group.

Table 53. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for female patients: Full Model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0957	0.0372	1.91	0.0575	-0.0230	0.2143
100mcg2PfsQD vs Placebo	0.0601	0.0391	1.15	0.2531	-0.0640	0.1843
200mcg2PfsQD vs Placebo	0.1253	0.0379	2.47	0.0143	0.0051	0.2455

Study 322

Subgroup by Age

Table 54 describes the numbers of patients and their mean ages, along with other statistics by treatment.

Table 54. Age (Study 322)

Treatment	#Patients	Mean	Min	Max	Median
Placebo	118	37.24	12.00	79.00	37.00
50mcg2PfsQD	124	37.36	12.00	71.00	39.00
100mcg2PfsQD	123	36.52	12.00	70.00	38.00
200mcg2PfsQD	124	37.11	12.00	76.00	38.50
	489	37.06	12.00	79.00	38.00

Table 55. Number of patients by treatment and age group (Study 322)

	Age Group				Total	
	AGE<=40		AGE>40		N	%
	N	%	N	%		
Placebo	63	53.4	55	46.6	118	100.0
50mcg2PfsQD	67	54.0	57	46.0	124	100.0
100mcg2PfsQD	68	55.3	55	44.7	123	100.0
200mcg2PfsQD	72	58.1	52	41.9	124	100.0
Total	270	55.2	219	44.8	489	100.0

This reviewer decided that a subgroup analysis be done for patients over and under 40 years of age as this value was approximately the median age.

The following analysis is based on patients 40 years of age and younger. There are 270 patients in this group.

Table 56. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients 40 years of age and younger: Full Model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0362	0.0590	0.44	0.6629	-0.1597	0.2322
100mcg2PfsQD vs Placebo	0.1171	0.0575	1.43	0.1554	-0.0768	0.3110
200mcg2PfsQD vs Placebo	0.0735	0.0556	0.91	0.3622	-0.1165	0.2636

The following analysis is based on patients over 40 years of age. There are 219 patients in this group.

Table 57. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients over 40 years of age: Full Model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.2026	0.0456	3.33	0.0010	0.0586	0.3466
100mcg2PfsQD vs Placebo	0.2175	0.0459	3.50	0.0006	0.0704	0.3646
200mcg2PfsQD vs Placebo	0.1575	0.0468	2.56	0.0114	0.0115	0.3035

Subgroup by Race

The following analysis is based on race.

Table 58. Number of patients by treatment and race (Study 322)

	Race				Total	
	White		Non-white		N	%
	N	%	N	%		
Placebo	101	85.6	17	14.4	118	100.0
50mcg2PfsQD	110	88.7	14	11.3	124	100.0
100mcg2PfsQD	105	85.4	18	14.6	123	100.0
200mcg2PfsQD	108	87.1	16	12.9	124	100.0
Total	424	86.7	65	13.3	489	100.0

The ANOVA subgroup analysis was not done because there were too few non-whites.

Subgroup by Sex

The following analysis is based on sex.

Table 59. Number of patients by treatment and sex (Study 322)

	Sex				Total	
	Female		Male		N	%
	N	%	N	%		
Placebo	68	57.6	50	42.4	118	100.0
50mcg2PfsQD	74	59.7	50	40.3	124	100.0
100mcg2PfsQD	81	65.9	42	34.1	123	100.0
200mcg2PfsQD	65	52.4	59	47.6	124	100.0
Total	288	58.9	201	41.1	489	100.0

The following analysis is based on male patients. There are 201 males in this group.

Table 60. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for male patients: Full Model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0963	0.0698	0.97	0.3344	-0.1392	0.3317
100mcg2PfsQD vs Placebo	0.2701	0.0786	2.55	0.0118	0.0191	0.5211
200mcg2PfsQD vs Placebo	0.1484	0.0657	1.55	0.1223	-0.0778	0.3745

The following analysis is based on female patients. There are 288 females in this group.

Table 61. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for female patients: Full Model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1285	0.0395	2.29	0.0231	-0.0041	0.2611
100mcg2PfsQD vs Placebo	0.1626	0.0373	2.94	0.0036	0.0321	0.2930
200mcg2PfsQD vs Placebo	0.1138	0.0422	1.97	0.0502	-0.0226	0.2503

Study 323/324**Subgroup by Age**

Table 62 describes the numbers of patients and their mean ages, along with other statistics by treatment.

Table 62. Age (Study 323/324)

Treatment	#Patients	Mean	Min	Max	Median
Placebo	134	42.02	13.00	80.00	43.00
100mcg2PfsQD	127	44.14	14.00	83.00	45.00
200mcg2PfsQD	130	43.52	13.00	80.00	44.00
220mcg2PfsQD	135	44.61	16.00	88.00	45.00
Overall	526	43.57	13.00	88.00	44.00

Table 63. Number of patients by treatment and age group (Study 323/324)

	Age Group				Total	
	AGE<=40		AGE>40		N	%
	N	%	N	%		
Placebo	58	43.3	76	56.7	134	100.0
100mcg2PfsQD	51	40.2	76	59.8	127	100.0
200mcg2PfsQD	51	39.2	79	60.8	130	100.0
220mcg2PfsQD	50	37.0	85	63.0	135	100.0
Total	210	39.9	316	60.1	526	100.0

This reviewer decided that a subgroup analysis be done for patients over and under 40 years of age as this value was approximately the median age.

The following analysis is based on patients 40 years of age and younger. There are 210 patients in this group.

Table 64. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients 40 years of age and younger: Full Model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.0910	0.0766	0.89	0.3751	-0.1525	0.3344
200mcg2PfsQD vs Placebo	0.2076	0.0754	2.03	0.0442	-0.0361	0.4513
220mcg2PfsQD vs Placebo	0.4721	0.0778	4.61	0.0000	0.2286	0.7157

The following analysis is based on patients over 40 years of age. There are 316 patients in this group.

Table 65. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for patients over 40 years of age: Full Model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.1521	0.0424	2.61	0.0096	0.0144	0.2898
200mcg2PfsQD vs Placebo	0.1727	0.0414	3.02	0.0028	0.0378	0.3077
220mcg2PfsQD vs Placebo	0.1738	0.0400	3.08	0.0023	0.0406	0.3071

Subgroup by Race

The following analysis is based on race.

Table 66. Number of patients by treatment and race (Study 323/324)

	Race				Total	
	White		Non-white		N	%
	N	%	N	%		
Placebo	103	76.9	31	23.1	134	100.0
100mcg2PfsQD	97	76.4	30	23.6	127	100.0
200mcg2PfsQD	103	79.2	27	20.8	130	100.0
220mcg2PfsQD	113	83.7	22	16.3	135	100.0
Total	416	79.1	110	20.9	526	100.0

The ANOVA subgroup analysis was not done because there were too few non-whites.

Subgroup by Sex

The following analysis is based on sex.

Table 67. Number of patients by treatment and sex (Study 323/324)

	Sex				Total	
	Female		Male		N	%
	N	%	N	%		
Placebo	79	59.0	55	41.0	134	100.0
100mcg2PfsQD	75	59.1	52	40.9	127	100.0
200mcg2PfsQD	75	57.7	55	42.3	130	100.0
220mcg2PfsQD	84	62.2	51	37.8	135	100.0
Total	313	59.5	213	40.5	526	100.0

The following analysis is based on male patients. There are 213 males in this group.

Table 68. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for male patients: Full Model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	-0.0261	0.0720	-0.26	0.7927	-0.2613	0.2091
200mcg2PfsQD vs Placebo	0.1365	0.0658	1.46	0.1462	-0.0854	0.3583
220mcg2PfsQD vs Placebo	0.0670	0.0707	0.70	0.4848	-0.1600	0.2940

The following analysis is based on female patients. There are 313 females in this group.

Table 69. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for female patients: Full Model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.1964	0.0441	3.22	0.0015	0.0520	0.3407
200mcg2PfsQD vs Placebo	0.1888	0.0434	3.17	0.0017	0.0480	0.3296
220mcg2PfsQD vs Placebo	0.3238	0.0413	5.57	0.0000	0.1864	0.4612

Study 341

Since the overall comparisons of the primary efficacy endpoint were not statistically significant, this reviewer believes that subgroup analyses, by age, race, or sex, would not add any value in evaluating this study.

Study 342

Since the overall comparisons of the primary efficacy endpoint were not statistically significant, this reviewer believes that subgroup analyses, by age, race, or sex, would not add any value in evaluating this study.

**APPEARS THIS WAY
ON ORIGINAL**

OTHER SPECIAL/SUBGROUP POPULATIONS

SUBGROUP: EVALUABLE (PER-PROTOCOL) AND COMPLETER

Study 321

Analysis on Per-Protocol (Evaluable) Patients

The following analysis was based on 451 evaluable patients.

Table 70. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on per protocol (evaluable) patients: Reduced model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0936	0.0369	1.74	0.0822	-0.0325	0.2197
100mcg2PfsQD vs Placebo	0.0496	0.0375	0.92	0.3575	-0.0769	0.1761
200mcg2PfsQD vs Placebo	0.1303	0.0374	2.43	0.0157	0.0042	0.2565

The ANOVA based on per-protocol patients' data shows that Alvesco at 200 µg/day is superior to the placebo. This analysis is consistent with that based on the ITT patients.

Analysis on Completers

The following analysis was based on 415 completers.

Table 71. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on completers: Reduced model (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0556	0.0365	1.03	0.3050	-0.0714	0.1827
100mcg2PfsQD vs Placebo	-0.0085	0.0379	-0.15	0.8774	-0.1378	0.1208
200mcg2PfsQD vs Placebo	0.0568	0.0369	1.04	0.2982	-0.0711	0.1847

ANOVA based on the completers' data does not show the superiority of Alvesco to the placebo. This is not consistent with the results of the ITT group (where LOCF was used). In the ITT analysis, the 200 µg Alvesco dose was statistically significantly better than placebo.

To help understand how the analyses, based on LOCF data and that using completers' data alone, differ significantly Table 72, below, compares means, by treatment, of FEV₁ (completers only) and FEV₁ with missing values imputed using LOCF.

Table 72. Change of FEV₁ at Week 12 from baseline: Completer and LOCF data compared (Study 321)

	FEV1CHG*	FEV1CHG_1**	Diff. in FEV1 Chg from baseline	Pct Diff. in FEV1 (Imputed) Chg from baseline
Placebo	0.2883	0.1744	-0.1139	(40%)
50 µg 2PfsQD	0.3429	0.3047	-0.0383	(11%)
100 µg 2PfsQD	0.2810	0.2491	-0.0320	(11%)
200 µg 2PfsQD	0.3354	0.3295	-0.0059	(2%)

The symbol * represents the change of FEV₁ at Week 12 from baseline using completers' data alone. The symbol ** represents the same measurement, but using LOCF. The latter appears to be smaller in number, but larger in percent decline: 40% smaller for the placebo group, compared with 2-11% in the other groups, while the LOCF estimation for missing values was employed. Consequently, the difference between the Alvesco groups and the placebo group with LOCF appears to be greater than that without LOCF. The use of LOCF appears to have played a significant role in determining the outcome of the analysis. Although neither analysis (i.e., LOCF or completers) is beyond criticism, the use of the LOCF method seems to be acceptable in this case for the following reasons.

1. LOCF was the protocol-specified method for missing-data imputation.
2. The last FEV₁ observations for most of the patients who dropped out were likely poor since the primary reasons for withdrawal were experiencing an adverse event or lack of efficacy. Carrying forward a poor value for subjects experiencing adverse events or lack of efficacy seems reasonable.

Study 322

Analysis on Per-Protocol (Evaluable) Patients

The following analysis was based on 427 evaluable patients.

Table 73. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on per protocol (evaluable) patients: Reduced model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1038	0.0362	1.96	0.0508	-0.0206	0.2282
100mcg2PfsQD vs Placebo	0.1827	0.0353	3.49	0.0005	0.0597	0.3057
200mcg2PfsQD vs Placebo	0.1338	0.0364	2.51	0.0125	0.0087	0.2589

The ANOVA based on per-protocol patients' data shows that Alvesco at 100 and 200 µg/day is superior to the placebo. Alvesco at 50 µg/day in this analysis is marginal significant while comparing with the placebo group. This analysis is consistent with that based on the ITT patients.

Analysis on Completers

The following analysis was based on 403 completers.

Table 74. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on completers: Reduced model (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0531	0.0338	1.04	0.3012	-0.0670	0.1731
100mcg2PfsQD vs Placebo	0.1466	0.0337	2.87	0.0043	0.0271	0.2661
200mcg2PfsQD vs Placebo	0.0811	0.0352	1.56	0.1205	-0.0410	0.2032

Except for the 100 µg Alvesco dose group, ANOVA based on the completers' data does not show the superiority of Alvesco to the placebo. This is not consistent with the results of the ITT group (where LOCF was used). In the ITT analysis, all the Alvesco doses were shown to be statistically significantly better than placebo.

To help understand how the analyses, based on LOCF data and that using completers' data alone, differ significantly Table 75, below, compares means, by treatment, of FEV₁ (completers only) and FEV₁ with missing values imputed using LOCF.

Table 75. Change of FEV₁ at Week 12 from baseline: Completer and LOCF data compared (Study 322)

Treatment	FEV1CHG*	FEV1CHG_I**	Diff. in FEV1 Chg from baseline	Pct Diff. in FEV1 (Imputed) Chg from baseline
Placebo	0.1848	0.1359	-0.0488	(26%)
50mcg2PfsQD	0.2405	0.2473	0.0068	3%
100mcg2PfsQD	0.3344	0.3220	-0.0124	(4%)
200mcg2PfsQD	0.2776	0.2649	-0.0127	(5%)

The symbol * represents the change of FEV₁ at Week 12 from baseline using completers' data alone. The symbol ** represents the same measurement, but using LOCF. The latter appears to be smaller in number, but larger in percent decline: 26% smaller for the placebo group, compared with 4-5% in the other groups, while the LOCF estimation for missing values was employed. Consequently, the difference between the Alvesco groups and the placebo group with LOCF appears to be greater than that without LOCF. The use of LOCF appears to have played a significant role in determining the outcome of the analysis. Although neither analysis (i.e., LOCF or completers) is beyond criticism, the use of the LOCF method seems to be acceptable in this case for the following reasons.

3. LOCF was the protocol-specified method for missing-data imputation.
4. The last FEV₁ observations for most of the patients who dropped out were likely poor since the primary reasons for withdrawal were experiencing an adverse event or lack of efficacy. Carrying forward a poor value for subjects experiencing adverse events or lack of efficacy seems reasonable.

Study 323/324

Analysis on Per-Protocol (Evaluable) Patients

The following analysis was based on 438 evaluable patients.

Table 76. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on per protocol (evaluable) patients: Reduced model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.0456	0.0404	0.77	0.4442	-0.0940	0.1852
200mcg2PfsQD vs Placebo	0.1286	0.0396	2.19	0.0293	-0.0092	0.2665
Fluticasone 220mcg vs Placebo	0.1812	0.0382	3.14	0.0018	0.0458	0.3166

The ANOVA based on per-protocol patients' data shows that Alvesco at 200 µg/day is superior to the placebo. Fluticasone at 220 µg/day in this analysis is also shown to be significant better while comparing with the placebo group. These results are consistent with the ITT analysis. However, in this analysis, Alvesco at 100 µg/day has not shown its superiority to the placebo (as it did in the ITT analysis).

Analysis on Completers

The following analysis was based on 387 completers.

Table 77. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline based on completers: Reduced model (Study 323/324)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
100mcg2PfsQD vs Placebo	0.0011	0.0413	0.02	0.9867	-0.1496	0.1517
200mcg2PfsQD vs Placebo	0.0665	0.0406	1.03	0.3019	-0.0837	0.2167
220mcg2PfsQD vs Placebo	0.1353	0.0397	2.15	0.0324	-0.0118	0.2824

In this analysis, Fluticasone alone shows its superiority to the placebo. This result is consistent with the ITT analysis. However, in this analysis, Alvesco at 100 µg and 200 µg have not been shown to be superior to placebo (as they were in the ITT analysis).

To help understand how the analyses, based on LOCF data and that using completers' data alone, differ significantly Table 78, below, compares means, by treatment, of FEV₁ and FEV₁ with missing values imputed using LOCF.

Table 78. Change of FEV₁ at Week 12 from baseline: Completer and LOCF data compared (Study 323/324)

Treatment	FEV1CHG*	FEV1CHG_I**	Diff. in FEV1 Chg from baseline	Pct Diff. in FEV1 (Imputed) Chg from baseline
Placebo	0.4454	0.2647	-0.1807	(41%)
100mcg2PfsQD	0.4007	0.3604	-0.0403	(10%)
200mcg2PfsQD	0.4642	0.4326	-0.0316	(7%)
220mcg2PfsQD	0.5345	0.4932	-0.0414	(8%)

The symbol * represents the change of FEV₁ at Week 12 from baseline using completers' data alone. The symbol ** represents the same measurement, but using LOCF. The latter appears to be smaller in number, but larger in percent decline: 41% smaller for the placebo group, compared with 7-10% in the other groups, while the LOCF estimation for missing values was employed. Consequently, the difference between the Alvesco groups and the placebo group with LOCF appears to be greater than that without LOCF. The use of LOCF appears to have played a significant role in determining the outcome of the analysis. Although neither analysis (i.e., LOCF or completers) is beyond criticism, the use of the LOCF method seems to be acceptable in this case for the following reasons.

5. LOCF was the protocol-specified method for missing-data imputation.
6. The last FEV₁ observations for most of the patients who dropped out were likely poor since the primary reasons for withdrawal were experiencing an adverse event or lack of efficacy. Carrying forward a poor value for subjects experiencing adverse events or lack of efficacy seems reasonable.

Study 341

Since the overall comparisons of the primary efficacy endpoint were not statistically significant, this reviewer believes that subgroup analyses, by age, race, or sex, would not add any value in evaluating this study.

Study 342

Since the overall comparisons of the primary efficacy endpoint were not statistically significant, this reviewer believes that subgroup analyses, by age, race, or sex, would not add any value in evaluating this study.

APPEARS THIS WAY ON ORIGINAL

SUBGROUP: STRATA

The subgroup analyses by strata – controller and reliever – are considered important, because they lead to different findings. Not only are these strata defined by pre-treatment therapy, but also are indicators of patients’ baseline conditions: The ones pretreated with corticosteroids had significantly lower average baseline FEV₁ values, while those on bronchodilators had a higher average baseline FEV₁ values. The by-stratum analyses were performed based on the statistical model used by the sponsor. The statistical model included the following factors: TREATMENT, CENTER, STRATA, AGE, and SEX. In addition, the BASELINE FEV₁ was included as the covariate. In statistical decision on the significance, the step-down procedure was used as the sponsor did.

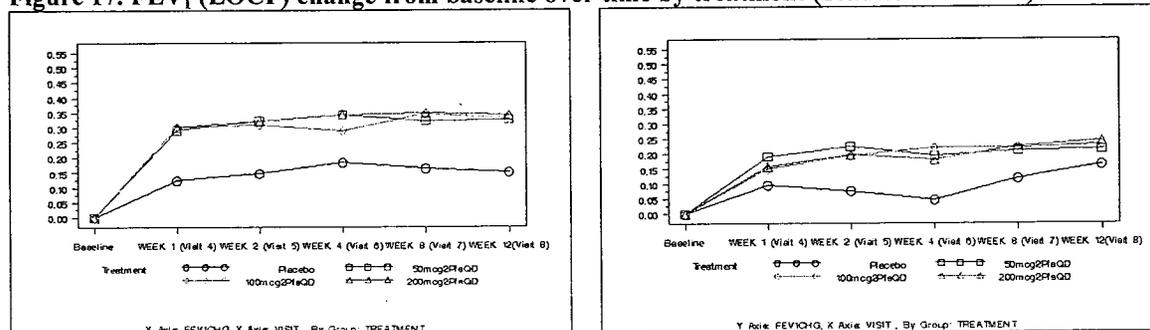
Studies 321 and 322

Comparing Stratum Difference Affecting Changes in FEV₁

Please note that the patients on Alvesco in Stratum 1 (corticosteroids) appear to gain markedly greater improvement than those in Stratum 2 (bronchodilators). To find a sufficiently reasonable explanation for this observation, we examined the difference in average baseline FEV₁ values between the strata. If it is reasonable to think that patients initially on corticosteroids prior to randomization because they were under a worse condition than those on bronchodilators, then it is not too hard to conclude that the effectiveness of Alvesco would be better demonstrated among the sicker patients than among those under relatively better initial conditions.

First, the graphs, below, depict the changes in FEV₁ from baseline over time. The graphs for each stratum are shown side-by-side for easy comparison. These graphs were drawn based on Studies 321 and 322 pooled data. The studies were combined because they had identical design and to obtain the largest possible sample size in each stratum.

Figure 17. FEV₁ (LOCF) change from baseline over time by treatment (Studies 321 & 322)

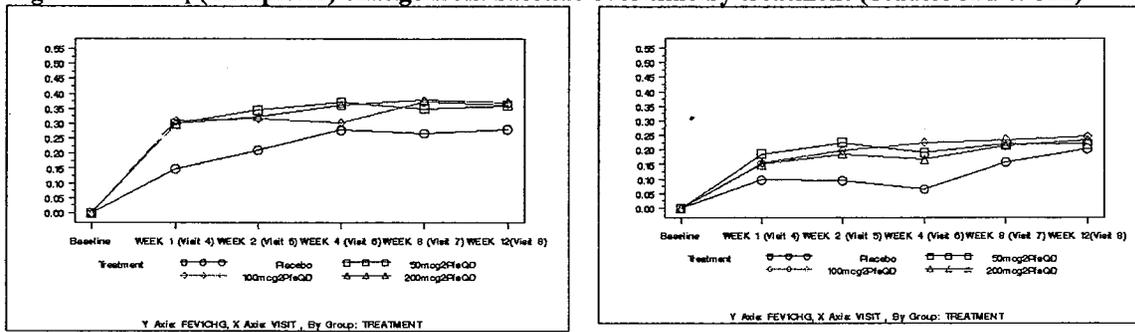


Stratum 1 (Controller)

Stratum 2 (Reliever)

Source: Studies 321 and 322 – LOCF approach is used for missing FEV₁ values.

Figure 18. FEV₁ (Completer) change from baseline over time by treatment (Studies 321 & 322)



Stratum 1 (Controller)

Stratum 2 (Reliever)

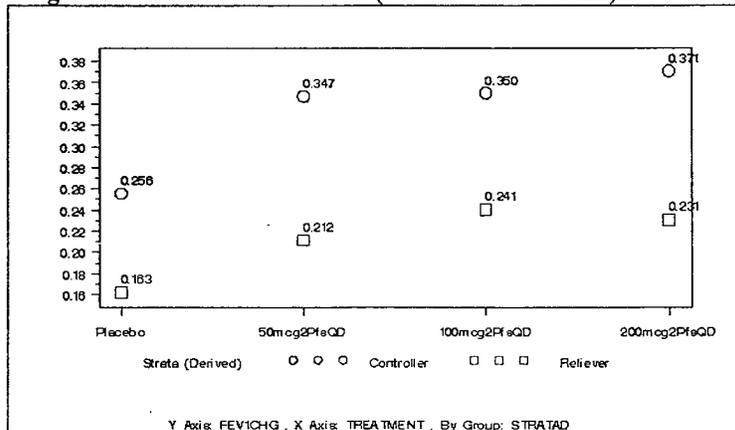
Source: Studies 321 and 322 – Based on completers.

Stratum 1 represent the patients treated with corticosteroids, while Stratum 2, bronchodilators, for the last 30 days prior to the randomization. The following observations are made.

- The Alvesco patients pre-treated with corticosteroids (Stratum 1) demonstrated a noticeably greater drug effect than those on bronchodilators (Stratum 2).
- The changes in FEV₁ from baseline had an upward trend over time among the placebo-treated patients – in both strata. The placebo effect appears to be stronger in Stratum 1
- LOCF has influence on the assessment of effectiveness of Alvesco. In particular, LOCF widens the gap between placebo and the Alvesco groups in the change of FEV₁ from baseline.

By zooming in the Week 12 data, the graph below shows changes in FEV₁ from baseline by stratum, for all treatments.

Figure 19. FEV₁ change from baseline at Week 12 (Studies 321 and 322)



Source: Studies 321 and 322 – LOCF for missing FEV₁ values.

The distance on the vertical axis between placebo and an Alvesco dose group shows the drug effect. Alvesco groups in Stratum 1 appear to out perform those in Stratum 2. A much stronger placebo effect can be seen in Stratum 1, compared with Stratum 2.

However, it is difficult to explain why such a placebo effect is shown in Stratum 1 probably just due to the fact that patients in stratum 1 were sicker. They had more room for improvement.

The following by-strata analyses were done for exploratory purposes.

Table 79. Alvesco vs. Placebo for Stratum 1 (controller) based on Studies 321 and 322 combined (No. patients: 560)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1733	0.0330	3.77	0.0002	0.0651	0.2814
100mcg2PfsQD vs Placebo	0.1705	0.0334	3.69	0.0002	0.0618	0.2792
200mcg2PfsQD vs Placebo	0.1928	0.0330	4.20	0.0000	0.0846	0.3009

Table 80. Alvesco vs. Placebo for Stratum 2 (reliever) based on Studies 321 and 322 combined (No. patients: 453)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0503	0.0385	0.94	0.3483	-0.0761	0.1767
100mcg2PfsQD vs Placebo	0.0667	0.0392	1.23	0.2186	-0.0610	0.1945
200mcg2PfsQD vs Placebo	0.0752	0.0392	1.39	0.1648	-0.0522	0.2025

To examine the stratum effect for each study separately, in the following tables, we use the step-down procedure; a test producing a p-value less than 0.05 is marked in bold face.

Table 81. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Controller (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1540	0.0627	2.46	0.0147	0.0059	0.3022
100mcg2PfsQD vs Placebo	0.1074	0.0636	1.69	0.0924	-0.0429	0.2577
200mcg2PfsQD vs Placebo	0.2442	0.0633	3.86	0.0001	0.0947	0.3937

Table 82. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Reliever (Study 321)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.0719	0.0753	0.96	0.3404	-0.1062	0.2501
100mcg2PfsQD vs Placebo	0.0223	0.0758	0.29	0.7694	-0.1572	0.2017
200mcg2PfsQD vs Placebo	0.0358	0.0750	0.48	0.6331	-0.1416	0.2133

Table 83. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Controller (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	0.1901	0.0678	2.81	0.0054	0.0303	0.3499
100mcg2PfsQD vs Placebo	0.2211	0.0671	3.29	0.0011	0.0628	0.3794
200mcg2PfsQD vs Placebo	0.1326	0.0666	1.99	0.0478	-0.0245	0.2897

Table 84. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Reliever (Study 322)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	P-Value	Lower CL	Upper CL
50mcg2PfsQD vs Placebo	-0.0078	0.0772	-0.10	0.9199	-0.1907	0.1752
100mcg2PfsQD vs Placebo	0.1340	0.0775	1.73	0.0855	-0.0497	0.3177
200mcg2PfsQD vs Placebo	0.0782	0.0788	0.99	0.3223	-0.1085	0.2649

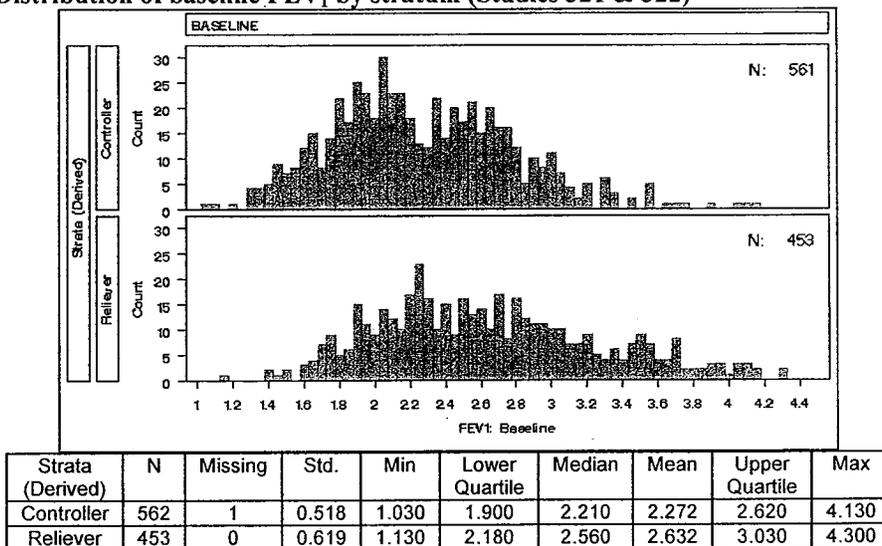
The results from individual studies are consistent with that from the pooled analyses.

Exploring Baseline Differences between Strata

The effectiveness of Alvesco differs between the strata. Such a difference might have something to do with the difference in baseline FEV₁ between the strata. A smaller mean baseline FEV₁ appears to link to a greater FEV₁ change from baseline at endpoint.

For the two studies combined, the following graph shows the distributions of patients in the two strata. Important statistics by stratum are shown in the following table.

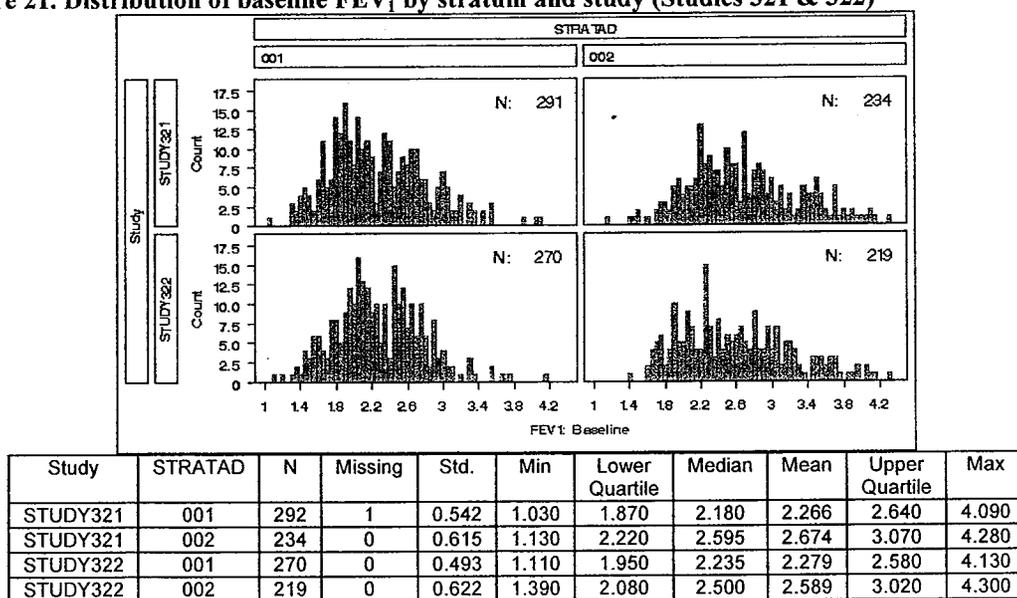
Figure 20. Distribution of baseline FEV₁ by stratum (Studies 321 & 322)



The average baseline FEV₁ is clearly smaller in Stratum 1 than in Stratum2.

Breaking down by study, the following graph shows the distributions of patients in the two strata for the two studies. Important statistics by stratum and study are shown in the following table.

Figure 21. Distribution of baseline FEV₁ by stratum and study (Studies 321 & 322)



The average baseline FEV₁ is clearly smaller in Stratum 1 than in Stratum2 across the studies. The difference between the studies in baseline FEV₁ appears to be small. The results from the individual studies are consistent with that from combined study.

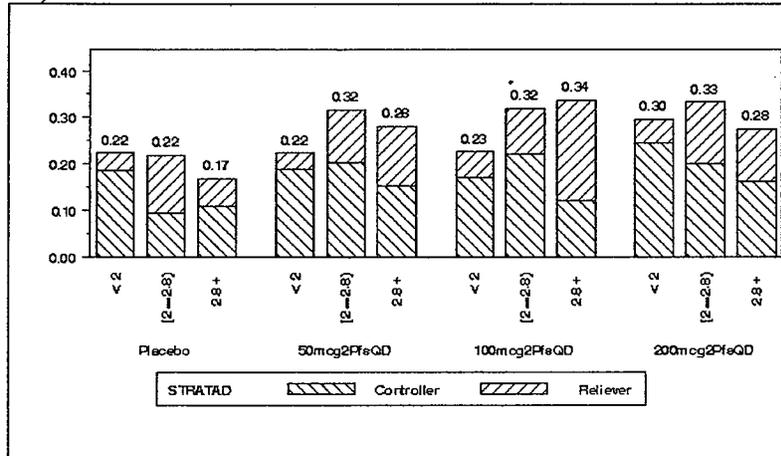
To examine whether and how Alvesco affects FEV₁ differently among patients with different level of baseline FEV₁, we break up baseline FEV₁ values into three groups based on two cutoff points: the lower quartile (the 25th percentile) and the upper quartile (the 75th percentile).

Table 85. Characteristics of Baseline FEV₁ (Studies 321 & 322)

N	Missing	Std.	Min	Lower Quartile	Median	Mean	Upper Quartile	Max
1015	1	0.593	1.030	2.000	2.370	2.433	2.790	4.300

This graph shows changes in FEV₁ from baseline, by baseline value and treatments.

Figure 22. Mean Change in FEV₁ at Week 12 from baseline by baseline value group and treatment (Studies 321 & 322)



The comparison between the strata is done by sub grouping (stratum): The subgroup segments are proportional to the subgroup's contribution to the height of the bar. It is clearly seen that for patients with smaller baseline FEV₁ values (average FEV₁ < 2.8), Alvesco appears to be more effective, indicated by a taller bar segment. This may explain why Alvesco works better among patients with lower baseline FEV₁.

The following table supplements the graph, above, to show figures of FEV₁ change from baseline among specified groups.

Table 86. Change in FEV₁ at Week 12 from baseline by baseline value group and treatment (Studies 321 & 322)

Baseline, grouped	Strata (Derived)	Treatment							
		Placebo		50mcg2PfsQD		100mcg2PfsQD		200mcg2PfsQD	
			N		N		N		N
		0.307	47	0.253	51	0.290	36	0.307	49
<2	Controller								
	Reliever	0.095	19	0.137	15	0.136	24	0.251	12
	Total	0.223	66	0.223	66	0.227	60	0.296	61
[2-2.8)	Strata (Derived)	0.193	69	0.391	66	0.365	91	0.363	69
	Controller								
	Reliever	0.245	55	0.238	57	0.251	54	0.295	48
	Total	0.220	124	0.317	123	0.320	145	0.332	117
2.8+	Strata (Derived)	0.343	22	0.413	25	0.421	13	0.532	24
	Controller								
	Reliever	0.087	40	0.205	43	0.303	33	0.163	53
	Total	0.169	62	0.281	68	0.337	46	0.275	77
Total		0.206	252	0.284	257	0.300	251	0.306	255

Handling Strata in Linear Model

It is important to test the significance of treatment-by-stratum interaction.

Table 87. Test for treatment-by-stratum interaction (Studies 321 & 322)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	376.3840758	47.0480095	289.98	<.0001
Error	1002	162.5701206	0.1622456		
Corrected Total	1010	538.9541964			

R-Square	Coeff Var	Root MSE	FEV ₁ Mean
0.698360	14.97421	0.402797	2.689941

Source	DF	Type I SS	Mean Square	F Value	Pr > F
BASELINE	1	370.5821159	370.5821159	2284.08	<.0001
TREATMENT	3	3.2492454	1.0830818	6.68	0.0002
STRATAD	1	1.9085598	1.9085598	11.76	0.0006
TREATMENT*STRATAD	3	0.6441547	0.2147182	1.32	0.2653

The test shows treatment-by-stratum interaction is not statistically significant ($p=0.2653$) under common standard. The effect of strata is statistically significant. This suggests that the term of strata be included in the ANCOVA model.

The subgroup exploratory analyses by stratum suggests that patients' pre-treatment conditions and associated medication use play an important role in driving the results of efficacy assessment. By combining the two similar studies – Studies 321 and 322 – the (*post-hoc*) ANCOVA on the two strata, separately, lead to different results: statistically significant benefit of Alvesco over placebo in Stratum 1 (controller) and no statistically significant difference between Alvesco and placebo in Stratum 2 (reliever). The combining of the two studies provides a sufficiently large sample size in the by-stratum analyses. Under such condition, the effectiveness of Alvesco is not demonstrated among the patients under bronchodilators.

Study 323 and Study 324 Combined

Strata were not defined for this study. Therefore, subgroup analysis by stratum does not apply.

Study 341

Table 88. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Controller (Study 341)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	0.4359	1.8243	0.17	0.8619	-5.4724	6.3442
100mcg1PfQD vs Placebo	0.0157	1.6952	0.01	0.9949	-5.7776	5.8091
200mcg1PfQD vs Placebo	-2.1802	1.9208	-0.84	0.4045	-8.3439	3.9835

Table 89. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Reliever (Study 341)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	2.0554	2.4867	0.63	0.5320	-5.7357	9.8464
100mcg1PfQD vs Placebo	8.5785	2.5975	2.64	0.0091	0.8587	16.2982
200mcg1PfQD vs Placebo	11.1577	2.4925	3.47	0.0007	3.5270	18.7885

Study 342**Table 90. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Controller (Study 342)**

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	-0.2461	1.6033	-0.12	0.9040	-5.0582	4.5661
100mcg1PfQD vs Placebo	1.3385	1.5891	0.66	0.5085	-3.4358	6.1127
200mcg1PfQD vs Placebo	2.6891	1.4852	1.36	0.1754	-1.9864	7.3647

Table 91. ANOVA on FEV₁ change at Week 12 (Visit 8) from baseline for stratum: Reliever (Study 342)

Parameter	LS Mean Diff.	Std. Diff.	T-Static	Pr > t	Lower CL	Upper CL
50mcg1PfQD vs Placebo	4.9553	1.9920	1.84	0.0684	-1.4456	11.3562
100mcg1PfQD vs Placebo	2.1269	2.0481	0.76	0.4458	-4.4724	8.7262
200mcg1PfQD vs Placebo	6.1197	2.1340	2.16	0.0323	-0.5930	12.8325

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SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

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, slightly different 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, the following Table 1 compares this reviewer's statistical results for all these studies.

Table 92. 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:

- + 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 comparison was: Alvesco 100-μg, 2 puffs, BID vs. Placebo

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Conclusions and Recommendations

Efficacy Conclusions:

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

Analyses by stratum suggests 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 those on corticosteroids, the efficacy of Alvesco is not demonstrated among the patients on bronchodilators.

Safety Conclusions:

Alvesco studies found that the top-three adverse events reported are: 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 most commonly reported among the children. HEADACHE, NASOPHARYNGITIS, and ASTHMA AGGRAVATION were among most commonly reported events in each of the studies.

Recommendations:

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

DISTRIBUTION LIST

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APPENDIX

Appendix A: Records of patients excluded from the ITT group

Study 321

Table 93. Patients excluded from the ITT group (Study 321)

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	FEV1: Baseline	FEV1	FEV1: Spon or-Imputed	Date of withdrawal from study	Drop out reason code
0145/321 21	Placebo	Baseline	02/27/02	02/27/02	02/27/02	02/27/02	1.03	1.03	1.03	02/27/02	Protocol violation
0145/321 21	Placebo	Wk.1 (Visit.4)	02/27/02		02/27/02	02/27/02	1.03			02/27/02	Protocol violation
0145/321 21	Placebo	Wk.2 (Visit.5)	02/27/02		02/27/02	02/27/02	1.03			02/27/02	Protocol violation
0145/321 21	Placebo	Wk.4 (Visit.6)	02/27/02		02/27/02	02/27/02	1.03			02/27/02	Protocol violation
0145/321 21	Placebo	Wk.8 (Visit.7)	02/27/02		02/27/02	02/27/02	1.03			02/27/02	Protocol violation
0145/321 21	Placebo	Wk.12 (Visit.8)	02/27/02		02/27/02	02/27/02	1.03			02/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Baseline	06/17/02		06/20/02					06/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Wk.1 (Visit.4)	06/17/02		06/20/02				3.30	06/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Wk.2 (Visit.5)	06/17/02		06/20/02				3.30	06/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Wk.4 (Visit.6)	06/17/02		06/20/02				3.30	06/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Wk.8 (Visit.7)	06/17/02		06/20/02				3.30	06/27/02	Protocol violation
0307/321 01	100mcg2Pfs QD	Wk.12 (Visit.8)	06/17/02		06/20/02				3.30	06/27/02	Protocol violation

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Study 322

No patients were excluded from the ITT group in Study 322.

Study 323 and Study 324 Combined**Table 94. Patients excluded from the ITT group (Study 323/324)**

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	FEV1: Baseline	FEV1	FEV1: Sponsor-Imputed	Date of withdrawal from study	Dropout reason code
0028/32406	Placebo	Baseline	05/21/02	05/14/02	05/23/02	05/14/02	1.66	1.66	1.66	05/28/02	Adverse event, Lack of efficacy
0028/32406	Placebo	Wk.1 (Visit.4)	05/21/02		05/23/02	05/14/02	1.66			05/28/02	Adverse event, Lack of efficacy
0028/32406	Placebo	Wk.2 (Visit.5)	05/21/02		05/23/02	05/14/02	1.66			05/28/02	Adverse event, Lack of efficacy
0028/32406	Placebo	Wk.4 (Visit.6)	05/21/02		05/23/02	05/14/02	1.66			05/28/02	Adverse event, Lack of efficacy
0028/32406	Placebo	Wk.8 (Visit.7)	05/21/02		05/23/02	05/14/02	1.66			05/28/02	Adverse event, Lack of efficacy
0028/32406	Placebo	Wk.12 (Visit.8)	05/21/02		05/23/02	05/14/02	1.66			05/28/02	Adverse event, Lack of efficacy
0087/32409	Placebo	Baseline	06/14/01	06/14/01	06/16/01	06/14/01	1.45	1.45	1.45	07/18/01	Adverse event, Lack of efficacy, Did not wish to continue
0087/32409	Placebo	Wk.1 (Visit.4)	06/14/01		06/16/01	06/14/01	1.45			07/18/01	Adverse event, Lack of efficacy, Did not wish to continue
0087/32409	Placebo	Wk.2 (Visit.5)	06/14/01		06/16/01	06/14/01	1.45			07/18/01	Adverse event, Lack of efficacy, Did not wish to continue
0087/32409	Placebo	Wk.4 (Visit.6)	06/14/01		06/16/01	06/14/01	1.45			07/18/01	Adverse event, Lack of efficacy, Did not wish to continue
0087/32409	Placebo	Wk.8 (Visit.7)	06/14/01		06/16/01	06/14/01	1.45			07/18/01	Adverse event, Lack of efficacy, Did not wish to continue
0087/32409	Placebo	Wk.12 (Visit.8)	06/14/01		06/16/01	06/14/01	1.45			07/18/01	Adverse event, Lack of efficacy

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	FEV1: Baseline	FEV1	FEV1: Sponsor-Imputed	Date of withdrawal from study	Dropout reason code
											Did not wish to continue
0011/32409	220mcg2PfsQD	Baseline	11/01/01	11/01/01	11/01/01	11/01/01	0.98	0.98	0.98	11/06/01	Protocol violation
0011/32409	220mcg2PfsQD	Wk.1 (Visit.4)	11/01/01	.	11/01/01	11/01/01	0.98	.	.	11/06/01	Protocol violation
0011/32409	220mcg2PfsQD	Wk.2 (Visit.5)	11/01/01	.	11/01/01	11/01/01	0.98	.	.	11/06/01	Protocol violation
0011/32409	220mcg2PfsQD	Wk.4 (Visit.6)	11/01/01	.	11/01/01	11/01/01	0.98	.	.	11/06/01	Protocol violation
0011/32409	220mcg2PfsQD	Wk.8 (Visit.7)	11/01/01	.	11/01/01	11/01/01	0.98	.	.	11/06/01	Protocol violation
0011/32409	220mcg2PfsQD	Wk.12 (Visit.8)	11/01/01	.	11/01/01	11/01/01	0.98	.	.	11/06/01	Protocol violation
0096/32403	220mcg2PfsQD	Baseline	08/14/01	08/14/01	11/08/01	11/09/01	1.60	1.60	1.60	.	
0096/32403	220mcg2PfsQD	Wk.1 (Visit.4)	08/14/01	.	11/08/01	11/09/01	1.60	.	.	.	
0096/32403	220mcg2PfsQD	Wk.2 (Visit.5)	08/14/01	08/27/01	11/08/01	11/09/01	1.60	1.88	1.88	.	
0096/32403	220mcg2PfsQD	Wk.4 (Visit.6)	08/14/01	09/11/01	11/08/01	11/09/01	1.60	2.07	2.07	.	
0096/32403	220mcg2PfsQD	Wk.8 (Visit.7)	08/14/01	10/09/01	11/08/01	11/09/01	1.60	1.76	1.76	.	
0096/32403	220mcg2PfsQD	Wk.12 (Visit.8)	08/14/01	11/09/01	11/08/01	11/09/01	1.60	1.27	1.27	.	
0182/32407	220mcg2PfsQD	Baseline	11/27/01	11/27/01	12/04/01	11/27/01	1.57	1.57	1.57	12/04/01	Other reason
0182/32407	220mcg2PfsQD	Wk.1 (Visit.4)	11/27/01	.	12/04/01	11/27/01	1.57	.	.	12/04/01	Other reason
0182/32407	220mcg2PfsQD	Wk.2 (Visit.5)	11/27/01	.	12/04/01	11/27/01	1.57	.	.	12/04/01	Other reason
0182/32407	220mcg2PfsQD	Wk.4 (Visit.6)	11/27/01	.	12/04/01	11/27/01	1.57	.	.	12/04/01	Other reason
0182/32407	220mcg2PfsQD	Wk.8 (Visit.7)	11/27/01	.	12/04/01	11/27/01	1.57	.	.	12/04/01	Other reason
0182/32407	220mcg2PfsQD	Wk.12 (Visit.8)	11/27/01	.	12/04/01	11/27/01	1.57	.	.	12/04/01	Other reason

Study 341**Table 95. Patients excluded from the ITT group (Study 341)**

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Drop out reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-Imputed
0031/34 102	Placebo	Baseline	06/28 /01		06/28 /01		07/05/ 01	Protocol violation			0.00	0.00
0031/34 102	Placebo	Wk.1 (Visit. 4)	06/28 /01		06/28 /01		07/05/ 01	Protocol violation				
0031/34 102	Placebo	Wk.2 (Visit. 5)	06/28 /01		06/28 /01		07/05/ 01	Protocol violation				
0031/34 102	Placebo	Wk.4 (Visit. 6)	06/28 /01		06/28 /01		07/05/ 01	Protocol violation				
0031/34 102	Placebo	Wk.8 (Visit. 7)	06/28 /01		06/28 /01		07/05/ 01	Protocol violation				
0031/34 102	Placebo	Wk.1 2 (Visit. 8)	06/28 /01		06/28 /01		07/05/ 01	Protocol violation				
0263/34 113	Placebo	Baseline	08/26 /02	08/26 /02	09/08 /02	08/26 /02	10/05/ 02	Did not wish to continue	64.84	65.00	0.00	0.00
0263/34 113	Placebo	Wk.1 (Visit. 4)	08/26 /02		09/08 /02	08/26 /02	10/05/ 02	Did not wish to continue	64.84			
0263/34 113	Placebo	Wk.2 (Visit. 5)	08/26 /02		09/08 /02	08/26 /02	10/05/ 02	Did not wish to continue	64.84			
0263/34 113	Placebo	Wk.4 (Visit. 6)	08/26 /02		09/08 /02	08/26 /02	10/05/ 02	Did not wish to continue	64.84			
0263/34 113	Placebo	Wk.8 (Visit. 7)	08/26 /02		09/08 /02	08/26 /02	10/05/ 02	Did not wish to continue	64.84			
0263/34	Placebo	Wk.1	08/26		09/08	08/26	10/05/	Did	64.84			

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Drop out reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Spon or-Imputed
113		2 (Visit. 8)	/02		/02	/02	02	not wish to continue				
0263/34 114	Placebo	Baseline	08/22/02	08/22/02	08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21	67.20	0.00	0.00
0263/34 114	Placebo	Wk.1 (Visit. 4)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21			
0263/34 114	Placebo	Wk.2 (Visit. 5)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21			
0263/34 114	Placebo	Wk.4 (Visit. 6)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21			
0263/34 114	Placebo	Wk.8 (Visit. 7)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21			
0263/34 114	Placebo	Wk.12 (Visit. 8)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	67.21			
0960/34 104	Placebo	Baseline	10/03/02				10/03/02	Protocol violation			0.00	0.00
0960/34 104	Placebo	Wk.1 (Visit. 4)	10/03/02				10/03/02	Protocol violation				
0960/34 104	Placebo	Wk.2 (Visit. 5)	10/03/02				10/03/02	Protocol violation				
0960/34 104	Placebo	Wk.4 (Visit. 6)	10/03/02				10/03/02	Protocol violation				
0960/34 104	Placebo	Wk.8 (Visit. 7)	10/03/02				10/03/02	Protocol violation				
0960/34 104	Placebo	Wk.12 (Visit. 8)	10/03/02				10/03/02	Protocol violation				
0263/34 115	50mcg1PfsQD	Baseline	08/22/02	08/22/02	08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45	66.60	0.00	0.00
0263/34 115	50mcg1PfsQD	Wk.1 (Visit. 4)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45			

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Drop out reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-Imputed
0263/34 115	50mcg1PfsQD	Wk.2 (Visit. 5)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45			
0263/34 115	50mcg1PfsQD	Wk.4 (Visit. 6)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45			
0263/34 115	50mcg1PfsQD	Wk.8 (Visit. 7)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45			
0263/34 115	50mcg1PfsQD	Wk.12 (Visit. 8)	08/22/02		08/22/02	08/22/02	09/28/02	Lost to follow-up	66.45			
0571/34 101	50mcg1PfsQD	Baseline	07/25/02	07/25/02	07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04	77.00	0.00	0.00
0571/34 101	50mcg1PfsQD	Wk.1 (Visit. 4)	07/25/02		07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04			
0571/34 101	50mcg1PfsQD	Wk.2 (Visit. 5)	07/25/02		07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04			
0571/34 101	50mcg1PfsQD	Wk.4 (Visit. 6)	07/25/02		07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04			
0571/34 101	50mcg1PfsQD	Wk.8 (Visit. 7)	07/25/02		07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04			
0571/34 101	50mcg1PfsQD	Wk.12 (Visit. 8)	07/25/02		07/25/02	07/25/02	08/08/02	Did not wish to continue	77.04			
0954/34 144	100mcg1PfsQD	Baseline	10/17/02	10/17/02	10/17/02	10/17/02	10/17/02	Lost to follow-up	71.47	83.00	0.00	0.00
0954/34 144	100mcg1PfsQD	Wk.1 (Visit. 4)	10/17/02		10/17/02	10/17/02	10/17/02	Lost to follow-up	71.47			
0954/34	100mcg1P	Wk.2	10/17		10/17	10/17	10/17/	Lost	71.47			

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Drop out reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-imputed
144	fsQD	(Visit. 5)	/02		/02	/02	02	to follow-up				
0954/34 144	100mcg1P fsQD	Wk.4 (Visit. 6)	10/17 /02		10/17 /02	10/17 /02	10/17/ 02	Lost to follow-up	71.47			
0954/34 144	100mcg1P fsQD	Wk.8 (Visit. 7)	10/17 /02		10/17 /02	10/17 /02	10/17/ 02	Lost to follow-up	71.47			
0954/34 144	100mcg1P fsQD	Wk.1 2 (Visit. 8)	10/17 /02		10/17 /02	10/17 /02	10/17/ 02	Lost to follow-up	71.47			
0267/34 107	200mcg1P fsQD	Baseline	06/04 /02	06/04 /02		06/04 /02	06/17/ 02	Protocol violation	99.65	100.00	0.00	0.00
0267/34 107	200mcg1P fsQD	Wk.1 (Visit. 4)	06/04 /02			06/04 /02	06/17/ 02	Protocol violation	99.65			
0267/34 107	200mcg1P fsQD	Wk.2 (Visit. 5)	06/04 /02			06/04 /02	06/17/ 02	Protocol violation	99.65			
0267/34 107	200mcg1P fsQD	Wk.4 (Visit. 6)	06/04 /02			06/04 /02	06/17/ 02	Protocol violation	99.65			
0267/34 107	200mcg1P fsQD	Wk.8 (Visit. 7)	06/04 /02			06/04 /02	06/17/ 02	Protocol violation	99.65			
0267/34 107	200mcg1P fsQD	Wk.1 2 (Visit. 8)	06/04 /02			06/04 /02	06/17/ 02	Protocol violation	99.65			
0963/34 108	200mcg1P fsQD	Baseline	10/18 /02				10/18/ 02	Did not wish to continue			0.00	0.00
0963/34 108	200mcg1P fsQD	Wk.1 (Visit. 4)	10/18 /02				10/18/ 02	Did not wish to continue				
0963/34 108	200mcg1P fsQD	Wk.2 (Visit. 5)	10/18 /02				10/18/ 02	Did not wish to continue				
0963/34 108	200mcg1P fsQD	Wk.4 (Visit. 6)	10/18 /02				10/18/ 02	Did not wish to				

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Drop out reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-Imputed
								continue				
0963/34108	200mcg1PfsQD	Wk.8 (Visit. 7)	10/18/02				10/18/02	Did not wish to continue				
0963/34108	200mcg1PfsQD	Wk.12 (Visit. 8)	10/18/02				10/18/02	Did not wish to continue				
0966/34109	200mcg1PfsQD	Baseline	10/23/02				10/23/02	Did not wish to continue			0.00	0.00
0966/34109	200mcg1PfsQD	Wk.1 (Visit. 4)	10/23/02				10/23/02	Did not wish to continue				
0966/34109	200mcg1PfsQD	Wk.2 (Visit. 5)	10/23/02				10/23/02	Did not wish to continue				
0966/34109	200mcg1PfsQD	Wk.4 (Visit. 6)	10/23/02				10/23/02	Did not wish to continue				
0966/34109	200mcg1PfsQD	Wk.8 (Visit. 7)	10/23/02				10/23/02	Did not wish to continue				
0966/34109	200mcg1PfsQD	Wk.12 (Visit. 8)	10/23/02				10/23/02	Did not wish to continue				

Study 342

Table 96. Patients excluded from the ITT group (Study 342)

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Dropout reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-Imputed
0123/34 206	50mcg1PfsQD	Baseline	11/22/01	11/22/01	11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90		0.00	0.00
0123/34 206	50mcg1PfsQD	Wk.1 (Visit. 4)	11/22/01		11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90			
0123/34 206	50mcg1PfsQD	Wk.2 (Visit. 5)	11/22/01		11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90			
0123/34 206	50mcg1PfsQD	Wk.4 (Visit. 6)	11/22/01		11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90			
0123/34 206	50mcg1PfsQD	Wk.8 (Visit. 7)	11/22/01		11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90			
0123/34 206	50mcg1PfsQD	Wk.12 (Visit. 8)	11/22/01		11/22/01	11/22/01	12/17/01	Did not wish to continue	56.90			
0579/34 204	100mcg1PfsQD	Baseline	09/10/02		10/03/02		10/03/02	Did not wish to continue, Protocol violation			0.00	0.00
0579/34 204	100mcg1PfsQD	Wk.1 (Visit. 4)	09/10/02		10/03/02		10/03/02	Did not wish to continue, Protocol violation				

Patient	Treatment	Visit	First date of active dose	Date of visit	Last date of active dose	Date of last visit	Date of withdrawal from study	Dropout reason code	FEV1: Pct Predicted at Baseline	FEV1: Pct Predicted	FEV1: Pct Predicted Chg from Baseline	FEV1: Pct Predicted Chg from baseline, Sponsor-Imputed
0579/34 204	100mcg1P fsQD	Wk.2 (Visit. 5)	09/10 /02		10/03 /02		10/03/ 02	on Did not wish to continue, Protocol violation				
0579/34 204	100mcg1P fsQD	Wk.4 (Visit. 6)	09/10 /02		10/03 /02		10/03/ 02	Did not wish to continue, Protocol violation				
0579/34 204	100mcg1P fsQD	Wk.8 (Visit. 7)	09/10 /02		10/03 /02		10/03/ 02	Did not wish to continue, Protocol violation				
0579/34 204	100mcg1P fsQD	Wk.1 2 (Visit. 8)	09/10 /02		10/03 /02		10/03/ 02	Did not wish to continue, Protocol violation				

Appendix B: Reported AEs**Table 97. AEs Reported (Study 321)**

No.	AE: AEP TTX	# Patients	% Patients
1	No AE	215	40.87
2	Headache	41	7.79
3	Nasopharyngitis	41	7.79
4	Asthma aggravated	37	7.03
5	Upper respiratory tract infection NOS	37	7.03
6	Pharyngitis	30	5.70
7	Sinusitis NOS	17	3.23
8	Back pain	15	2.85
9	Rhinitis NOS exacerbated	14	2.66
10	Arthralgia	13	2.47
11	Bronchitis NOS	12	2.28
12	Cough	10	1.90
13	Diarrhoea NOS	10	1.90
14	Dyspepsia	10	1.90
15	Nasal congestion	10	1.90
16	Influenza like illness	9	1.71
17	Joint sprain	8	1.52
18	Abdominal pain upper	7	1.33
19	Headache NOS aggravated	7	1.33
20	Nausea	7	1.33
21	Rash NOS	7	1.33
22	Upper respiratory tract infection viral NOS	7	1.33
23	Urinary tract infection NOS	7	1.33
24	Sinus headache	6	1.14
25	Influenza	5	0.95
26	Pain in limb	5	0.95
27	Toothache	5	0.95
28	Dizziness	4	0.76
29	Dysmenorrhoea	4	0.76
30	Fatigue	4	0.76
31	Hoarseness	4	0.76
32	Lower respiratory tract infection NOS	4	0.76
33	Muscle spasms	4	0.76
34	Myalgia	4	0.76
35	Oral candidiasis	4	0.76
36	Pharyngitis streptococcal	4	0.76
37	Pyrexia	4	0.76
38	Sinusitis acute NOS	4	0.76
39	Vomiting NOS	4	0.76
40	Bladder infection NOS	3	0.57
41	Gastrooesophageal reflux disease	3	0.57
42	Migraine NOS	3	0.57
43	Oedema peripheral	3	0.57
44	Sinus congestion	3	0.57
45	Skin laceration	3	0.57
46	Thermal burn	3	0.57
47	Urticaria NOS	3	0.57
48	Vaginitis fungal NOS	3	0.57
49	Animal bite	2	0.38
50	Aphthous stomatitis	2	0.38
51	Arthropod bite	2	0.38
52	Back injury NOS	2	0.38
53	Body temperature increased	2	0.38
54	Chest pain	2	0.38
55	Chest tightness	2	0.38
56	Contusion	2	0.38
57	Depression	2	0.38

No.	AE: AEP TTX	# Patients	% Patients
58	Dermatitis contact	2	0.38
59	Ear infection NOS	2	0.38
60	Epistaxis	2	0.38
61	Eye irritation	2	0.38
62	Food poisoning NOS	2	0.38
63	Gastroenteritis viral NOS	2	0.38
64	Gastrointestinal upset	2	0.38
65	Hand fracture	2	0.38
66	Hypertension aggravated	2	0.38
67	Hypoaesthesia	2	0.38
68	Insomnia	2	0.38
69	Liver function tests NOS abnormal	2	0.38
70	Muscle cramp	2	0.38
71	Muscle strain	2	0.38
72	Musculoskeletal stiffness	2	0.38
73	Oral pain	2	0.38
74	Otitis media NOS	2	0.38
75	Pruritus	2	0.38
76	Rhinitis NOS	2	0.38
77	Sinobronchitis	2	0.38
78	Tension headaches	2	0.38
79	Tooth abscess	2	0.38
80	Viral infection NOS	2	0.38
81	Weight increased	2	0.38
82	Abdominal pain lower	1	0.19
83	Abrasion NOS	1	0.19
84	Acne NOS	1	0.19
85	Allergy aggravated	1	0.19
86	Allergy to animal	1	0.19
87	Anaphylactic reaction	1	0.19
88	Appendicitis perforated	1	0.19
89	Appetite increased NOS	1	0.19
90	Asthenia	1	0.19
91	Azotaemia	1	0.19
92	Back pain aggravated	1	0.19
93	Blister	1	0.19
94	Blood uric acid increased	1	0.19
95	Body tinea	1	0.19
96	Bone injury	1	0.19
97	Breast pain	1	0.19
98	Bronchospasm NOS	1	0.19
99	Burn infection	1	0.19
100	Bursitis	1	0.19
101	Cardiac murmur NOS	1	0.19
102	Carpal tunnel syndrome	1	0.19
103	Cellulitis	1	0.19
104	Choking sensation	1	0.19
105	Clavicle fracture	1	0.19
106	Compartment syndrome	1	0.19
107	Constipation	1	0.19
108	Cyst NOS	1	0.19
109	Diabetes mellitus NOS	1	0.19
110	Disorientation	1	0.19
111	Disturbance in attention	1	0.19
112	Dry mouth	1	0.19
113	Dyspnoea NOS	1	0.19
114	Ear pain	1	0.19
115	Ecchymosis	1	0.19
116	Eczema	1	0.19
117	Eczema exacerbated	1	0.19
118	Emotional distress	1	0.19
119	Eye infection NOS	1	0.19
120	Eye pruritus	1	0.19
121	Fibromyalgia	1	0.19

No.	AE: AEP TTX T	# Patients	% Patients
122	Flank pain	1	0.19
123	Gamma-glutamyltransferase increased	1	0.19
124	Gastritis NOS	1	0.19
125	Gingival ulceration	1	0.19
126	Gun shot wound	1	0.19
127	Haematocrit decreased	1	0.19
128	Hangover	1	0.19
129	Heart rate increased	1	0.19
130	Hiatus hernia	1	0.19
131	Hordeolum	1	0.19
132	Hypotension NOS	1	0.19
133	Infected insect bite	1	0.19
134	Inflammation localised	1	0.19
135	Ingrowing nail	1	0.19
136	Injection site pain	1	0.19
137	Joint dislocation	1	0.19
138	Joint ligament rupture	1	0.19
139	Joint stiffness	1	0.19
140	Lethargy	1	0.19
141	Malaise	1	0.19
142	Migraine aggravated	1	0.19
143	Mouth ulceration	1	0.19
144	Muscle injury NOS	1	0.19
145	Muscle stiffness	1	0.19
146	Musculoskeletal pain	1	0.19
147	Myopia	1	0.19
148	Nasal mucosal disorder NOS	1	0.19
149	Nasal oedema	1	0.19
150	Nasal turbinate hypertrophy	1	0.19
151	Neck pain	1	0.19
152	Otitis externa NOS	1	0.19
153	Pain NOS	1	0.19
154	Pain in foot	1	0.19
155	Panic attack	1	0.19
156	Paraesthesia	1	0.19
157	Paranasal sinus hypersecretion	1	0.19
158	Post procedural pain	1	0.19
159	Productive cough	1	0.19
160	Purpura NOS	1	0.19
161	Rash erythematous	1	0.19
162	Rash maculo-papular	1	0.19
163	Rash papular	1	0.19
164	Renal failure acute	1	0.19
165	Rhabdomyolysis	1	0.19
166	Rhinitis allergic NOS	1	0.19
167	Rhinorrhoea	1	0.19
168	Seasonal allergy	1	0.19
169	Seborrhoeic keratosis	1	0.19
170	Sinus pain	1	0.19
171	Soft tissue injury NOS	1	0.19
172	Status asthmaticus	1	0.19
173	Stress symptoms	1	0.19
174	Sweating increased	1	0.19
175	Swelling face	1	0.19
176	Tension	1	0.19
177	Throat irritation	1	0.19
178	Tinea pedis	1	0.19
179	Tonsillar hypertrophy	1	0.19
180	Tooth caries NOS	1	0.19
181	Tracheitis NOS	1	0.19
182	Transaminases increased	1	0.19
183	Tremor	1	0.19
184	Ulna fracture	1	0.19
185	Wrist fracture	1	0.19

Table 98. AEs Reported (Study 322)

No.	AE: AEP TTX T	# Patients	% Patients
1	No AE	140	28.63
2	Headache	78	15.95
3	Nasopharyngitis	60	12.27
4	Upper respiratory tract infection NOS	56	11.45
5	Asthma aggravated	40	8.18
6	Pharyngitis	38	7.77
7	Sinusitis NOS	26	5.32
8	Back pain	22	4.50
9	Dyspepsia	17	3.48
10	Arthralgia	15	3.07
11	Diarrhoea NOS	15	3.07
12	Upper respiratory tract infection viral NOS	14	2.86
13	Influenza	13	2.66
14	Influenza like illness	13	2.66
15	Cough	12	2.45
16	Pain NOS	12	2.45
17	Toothache	12	2.45
18	Abdominal pain upper	11	2.25
19	Nasal congestion	11	2.25
20	Myalgia	10	2.04
21	Rhinitis NOS exacerbated	10	2.04
22	Gastroenteritis viral NOS	8	1.64
23	Nausea	8	1.64
24	Neck pain	8	1.64
25	Pain in limb	8	1.64
26	Ear pain	7	1.43
27	Fatigue	7	1.43
28	Urinary tract infection NOS	7	1.43
29	Bronchitis NOS	6	1.23
30	Contusion	6	1.23
31	Dysmenorrhoea	6	1.23
32	Epistaxis	6	1.23
33	Headache NOS aggravated	6	1.23
34	Migraine NOS	6	1.23
35	Pyrexia	6	1.23
36	Sinus headache	6	1.23
37	Vomiting NOS	6	1.23
38	Dermatitis contact	5	1.02
39	Ear infection NOS	5	1.02
40	Insomnia	5	1.02
41	Joint sprain	5	1.02
42	Skin laceration	5	1.02
43	Urticaria NOS	5	1.02
44	Vaginosis fungal NOS	5	1.02
45	Viral infection NOS	5	1.02
46	Muscle spasms	4	0.82
47	Oral candidiasis	4	0.82
48	Rash NOS	4	0.82
49	Anxiety	3	0.61
50	Aphthous stomatitis	3	0.61
51	Constipation	3	0.61
52	Dizziness	3	0.61
53	Dry mouth	3	0.61
54	Gastrooesophageal reflux disease	3	0.61
55	Herpes simplex	3	0.61
56	Hypoaesthesia	3	0.61
57	Limb injury NOS	3	0.61
58	Migraine aggravated	3	0.61
59	Muscle cramp	3	0.61
60	Muscle strain	3	0.61
61	Rhinitis allergic NOS	3	0.61

No.	AE: AEPTTXX	# Patients	% Patients
62	Rhinorrhoea	3	0.61
63	Rigors	3	0.61
64	Sinus pain	3	0.61
65	Abdominal pain NOS	2	0.41
66	Bereavement reaction	2	0.41
67	Blood glucose increased	2	0.41
68	Blood pressure increased	2	0.41
69	Chest pain	2	0.41
70	Conjunctivitis bacterial NOS	2	0.41
71	Dermatitis NOS	2	0.41
72	Drug hypersensitivity	2	0.41
73	Fluid in middle ear	2	0.41
74	Food poisoning NOS	2	0.41
75	Gastroenteritis NOS	2	0.41
76	Hoarseness	2	0.41
77	Lower respiratory tract infection NOS	2	0.41
78	Motion sickness	2	0.41
79	Nasal oedema	2	0.41
80	Nasal polyps	2	0.41
81	Oral mucosal eruption	2	0.41
82	Peripheral swelling	2	0.41
83	Productive cough	2	0.41
84	Pruritus	2	0.41
85	Pulmonary congestion	2	0.41
86	Rash papular	2	0.41
87	Rosacea	2	0.41
88	Sinus congestion	2	0.41
89	Skin papilloma	2	0.41
90	Stomatitis	2	0.41
91	Sunburn	2	0.41
92	Tooth abscess	2	0.41
93	Varicella	2	0.41
94	Vertigo	2	0.41
95	Acne cystic	1	0.20
96	Acquired hypothyroidism	1	0.20
97	Allergy to animal	1	0.20
98	Anaemia NOS	1	0.20
99	Animal bite	1	0.20
100	Animal scratch	1	0.20
101	Anorexia	1	0.20
102	Appetite decreased NOS	1	0.20
103	Arthropod bite	1	0.20
104	Arthropod sting	1	0.20
105	Aspartate aminotransferase increased	1	0.20
106	Back pain aggravated	1	0.20
107	Bartholin's cyst	1	0.20
108	Bipolar affective disorder aggravated	1	0.20
109	Blood cholesterol increased	1	0.20
110	Blood in stool	1	0.20
111	Blood uric acid increased	1	0.20
112	Bronchial infection	1	0.20
113	Bronchitis acute NOS	1	0.20
114	Bronchopneumonia NOS	1	0.20
115	Burning sensation NOS	1	0.20
116	Carpal tunnel syndrome	1	0.20
117	Chest tightness	1	0.20
118	Clavicle fracture	1	0.20
119	Concussion	1	0.20
120	Conjunctivitis	1	0.20
121	Cough aggravated	1	0.20
122	Depression	1	0.20
123	Diabetes mellitus non-insulin-dependent	1	0.20
124	Dry throat	1	0.20
125	Eczema exacerbated	1	0.20

No.	AE: AEPTXT	# Patients	% Patients
126	Epidermal naevus	1	0.20
127	Epigastric discomfort	1	0.20
128	Erythema	1	0.20
129	Eye penetration	1	0.20
130	Eye swelling	1	0.20
131	Face injury	1	0.20
132	Faecaloma	1	0.20
133	Feeling jittery	1	0.20
134	Food allergy	1	0.20
135	Foot fracture	1	0.20
136	Furuncle	1	0.20
137	Gingival bleeding	1	0.20
138	Glossodynia	1	0.20
139	Goitre	1	0.20
140	Gout aggravated	1	0.20
141	Haematuria	1	0.20
142	Haemophilus infection NOS	1	0.20
143	Hand fracture	1	0.20
144	Hangover	1	0.20
145	Heart rate increased	1	0.20
146	Heat exhaustion	1	0.20
147	Herpes zoster	1	0.20
148	Hot flushes NOS	1	0.20
149	Hyperacidity	1	0.20
150	Hyperlipidaemia NOS	1	0.20
151	Hyperreflexia	1	0.20
152	Hyperventilation	1	0.20
153	Hypoglycaemia NOS	1	0.20
154	Kidney infection NOS	1	0.20
155	Laceration	1	0.20
156	Laryngitis NOS	1	0.20
157	Lip pain	1	0.20
158	Lymphadenopathy	1	0.20
159	Malaise	1	0.20
160	Meniscus lesion	1	0.20
161	Menorrhagia	1	0.20
162	Mood swings	1	0.20
163	Mouth injury	1	0.20
164	Nail disorder NOS	1	0.20
165	Nail infection NOS	1	0.20
166	Nail tinea	1	0.20
167	Nasal mucosal disorder NOS	1	0.20
168	Nasal turbinate hypertrophy	1	0.20
169	Obstructive airways disorder NOS	1	0.20
170	Oedema peripheral	1	0.20
171	Oral discomfort	1	0.20
172	Oral infection	1	0.20
173	Oral mucosal blistering	1	0.20
174	Oral pain	1	0.20
175	Otitis media serous NOS	1	0.20
176	Papillary thyroid cancer	1	0.20
177	Pharyngitis streptococcal	1	0.20
178	Post procedural pain	1	0.20
179	Postnasal drip	1	0.20
180	Restless legs syndrome	1	0.20
181	Retching	1	0.20
182	Rhinitis seasonal	1	0.20
183	Rib fracture	1	0.20
184	Seborrhoeic dermatitis	1	0.20
185	Skin disorder NOS	1	0.20
186	Sneezing	1	0.20
187	Swelling face	1	0.20
188	Temporomandibular joint disorder NOS	1	0.20
189	Tension headaches	1	0.20

No.	AE: AEPTTXX	# Patients	% Patients
190	<u>Thermal burn</u>	1	0.20
191	<u>Throat irritation</u>	1	0.20
192	<u>Tinea pedis</u>	1	0.20
193	<u>Tinnitus</u>	1	0.20
194	<u>Tonsillitis</u>	1	0.20
195	<u>Tooth infection</u>	1	0.20
196	<u>Tooth injury</u>	1	0.20
197	<u>Tracheo-laryngeal bronchitis NOS</u>	1	0.20
198	<u>Transaminases increased</u>	1	0.20
199	<u>Traumatic haematoma</u>	1	0.20
200	<u>Trismus</u>	1	0.20
201	<u>Vaccination complication</u>	1	0.20
202	<u>Vaginal candidiasis</u>	1	0.20
203	<u>Vaginitis bacterial NOS</u>	1	0.20

Table 99. AEs Reported (Study 323/324)

No.	AE: AEPTXT	# Patients	% Patients
1	No AE	188	35.40
2	Headache	55	10.36
3	Asthma aggravated	54	10.17
4	Nasopharyngitis	53	9.98
5	Upper respiratory tract infection NOS	37	6.97
6	Sinusitis NOS	31	5.84
7	Oral candidiasis	29	5.46
8	Pharyngitis	26	4.90
9	Back pain	17	3.20
10	Cataract nuclear	17	3.20
11	Nasal congestion	15	2.82
12	Arthralgia	14	2.64
13	Abdominal pain upper	12	2.26
14	Pain NOS	12	2.26
15	Cough	10	1.88
16	Influenza	10	1.88
17	Rhinitis allergic NOS	10	1.88
18	Sinus congestion	10	1.88
19	Diarrhoea NOS	9	1.69
20	Pain in limb	9	1.69
21	Dyspepsia	8	1.51
22	Hoarseness	8	1.51
23	Influenza like illness	8	1.51
24	Nausea	8	1.51
25	Bronchitis NOS	7	1.32
26	Ear pain	7	1.32
27	Myalgia	7	1.32
28	Rash NOS	7	1.32
29	Urinary tract infection NOS	7	1.32
30	Epistaxis	6	1.13
31	Headache NOS aggravated	6	1.13
32	Joint sprain	6	1.13
33	Musculoskeletal stiffness	6	1.13
34	Nasal turbinate hypertrophy	6	1.13
35	Pulmonary congestion	6	1.13
36	Rhinitis seasonal	6	1.13
37	Vomiting NOS	6	1.13
38	Chest pain	5	0.94
39	Dysmenorrhoea	5	0.94
40	Sinus headache	5	0.94
41	Sinus pain	5	0.94
42	Upper respiratory tract infection viral NOS	5	0.94
43	Conjunctivitis	4	0.75
44	Dizziness	4	0.75
45	Dry mouth	4	0.75
46	Hypertension NOS	4	0.75
47	Lymphadenopathy	4	0.75
48	Migraine NOS	4	0.75
49	Muscle strain	4	0.75
50	Neck pain	4	0.75
51	Otitis media NOS	4	0.75
52	Pyrexia	4	0.75
53	Rhinitis perennial	4	0.75
54	Rhinorrhoea	4	0.75
55	Toothache	4	0.75
56	Urticaria NOS	4	0.75
57	Vaginitis fungal NOS	4	0.75
58	Abrasion NOS	3	0.56
59	Acne NOS	3	0.56
60	Anxiety	3	0.56
61	Arthropod sting	3	0.56

No.	AE: AEPTTX	# Patients	% Patients
62	Bronchitis acute NOS	3	0.56
63	Conjunctivitis allergic	3	0.56
64	Contusion	3	0.56
65	Dermatitis contact	3	0.56
66	Dysgeusia	3	0.56
67	Gastroenteritis viral NOS	3	0.56
68	Insomnia	3	0.56
69	Limb injury NOS	3	0.56
70	Lower respiratory tract infection NOS	3	0.56
71	Oedema peripheral	3	0.56
72	Pain in foot	3	0.56
73	Pharyngitis streptococcal	3	0.56
74	Post procedural pain	3	0.56
75	Sinusitis acute NOS	3	0.56
76	Skin laceration	3	0.56
77	Abdominal pain NOS	2	0.38
78	Angioneurotic oedema	2	0.38
79	Back injury NOS	2	0.38
80	Cataract cortical	2	0.38
81	Chest wall pain	2	0.38
82	Conjunctivitis bacterial NOS	2	0.38
83	Constipation	2	0.38
84	Corneal abrasion	2	0.38
85	Depression	2	0.38
86	Dermatitis allergic	2	0.38
87	Fatigue	2	0.38
88	Herpes simplex	2	0.38
89	Irritability	2	0.38
90	Myocardial infarction	2	0.38
91	Nasal oedema	2	0.38
92	Oral pain	2	0.38
93	Pneumonia NOS	2	0.38
94	Postnasal drip	2	0.38
95	Respiratory tract infection NOS	2	0.38
96	Rhinitis NOS	2	0.38
97	Rhinitis NOS exacerbated	2	0.38
98	Sneezing	2	0.38
99	Soft tissue inflammation	2	0.38
100	Thirst	2	0.38
101	Throat irritation	2	0.38
102	Tinea pedis	2	0.38
103	Tooth abscess	2	0.38
104	Viral infection NOS	2	0.38
105	Adrenal insufficiency NOS	1	0.19
106	Ageusia	1	0.19
107	Allergy to arthropod bite	1	0.19
108	Angina pectoris	1	0.19
109	Aphthous stomatitis	1	0.19
110	Appetite decreased NOS	1	0.19
111	Appetite increased NOS	1	0.19
112	Arthritis NOS	1	0.19
113	Arthropod bite	1	0.19
114	Aspiration	1	0.19
115	Bladder infection NOS	1	0.19
116	Blepharospasm	1	0.19
117	Blister	1	0.19
118	Blood glucose increased	1	0.19
119	Blood potassium decreased	1	0.19
120	Body tinea	1	0.19
121	Bulimia nervosa	1	0.19
122	Bursitis	1	0.19
123	Cataract subcapsular	1	0.19
124	Cellulitis	1	0.19
125	Cerumen impaction	1	0.19

No.	AE: AEPTXT	# Patients	% Patients
126	Chemical burns of eye	1	0.19
127	Chorioretinitis	1	0.19
128	Conjunctival oedema	1	0.19
129	Conjunctivitis infective	1	0.19
130	Coronary artery disease NOS	1	0.19
131	Cough aggravated	1	0.19
132	Dermatitis exfoliative NOS	1	0.19
133	Drug hypersensitivity	1	0.19
134	Dry eye NOS	1	0.19
135	Dyspepsia aggravated	1	0.19
136	Dysphagia	1	0.19
137	Dysuria	1	0.19
138	Ear infection NOS	1	0.19
139	Endodontic procedure	1	0.19
140	Epidermal cyst	1	0.19
141	Extrasystoles NOS	1	0.19
142	Eye disorder NOS	1	0.19
143	Eye haemorrhage NOS	1	0.19
144	Eye injury NOS	1	0.19
145	Eye irritation	1	0.19
146	Eye pain	1	0.19
147	Eye pruritus	1	0.19
148	Eye redness	1	0.19
149	Eye swelling	1	0.19
150	Faecal abnormality NOS	1	0.19
151	Feeling hot	1	0.19
152	Fluid retention	1	0.19
153	Foot fracture	1	0.19
154	Gastroenteritis NOS	1	0.19
155	Gastrointestinal upset	1	0.19
156	Gastrooesophageal reflux disease	1	0.19
157	Glossodynia	1	0.19
158	Haemorrhoids	1	0.19
159	Halitosis	1	0.19
160	Hand fracture	1	0.19
161	Heat exhaustion	1	0.19
162	Hordeolum	1	0.19
163	Hunger	1	0.19
164	Hypertension aggravated	1	0.19
165	Hypokalaemia	1	0.19
166	Intraocular pressure increased	1	0.19
167	Joint dislocation	1	0.19
168	Kidney infection NOS	1	0.19
169	Laryngeal oedema	1	0.19
170	Laryngitis NOS	1	0.19
171	Laryngotracheitis NOS	1	0.19
172	Ligament injury NOS	1	0.19
173	Localised infection	1	0.19
174	Motion sickness	1	0.19
175	Mouth ulceration	1	0.19
176	Muscle cramp	1	0.19
177	Muscle injury NOS	1	0.19
178	Muscle stiffness	1	0.19
179	Musculoskeletal chest pain	1	0.19
180	Nasal polyps	1	0.19
181	Nephrolithiasis	1	0.19
182	Oropharyngeal swelling	1	0.19
183	Paraesthesia	1	0.19
184	Paraesthesia oral	1	0.19
185	Paranasal sinus hypersecretion	1	0.19
186	Periorbital haematoma	1	0.19
187	Pitting oedema	1	0.19
188	Pleuritic pain	1	0.19
189	Pneumonia streptococcal	1	0.19

No.	AE: AEPTXT	# Patients	% Patients
190	Polycystic ovaries	1	0.19
191	Proctalgia	1	0.19
192	Rales	1	0.19
193	Rash papular	1	0.19
194	Rash scaly	1	0.19
195	Rectal haemorrhage	1	0.19
196	Reflux oesophagitis	1	0.19
197	Rigors	1	0.19
198	Scabies infestation	1	0.19
199	Scratch	1	0.19
200	Sinusitis chronic NOS	1	0.19
201	Snoring	1	0.19
202	Soft tissue injury NOS	1	0.19
203	Somnolence	1	0.19
204	Swelling face	1	0.19
205	Syncope	1	0.19
206	Tachycardia NOS	1	0.19
207	Tendon injury	1	0.19
208	Tendonitis	1	0.19
209	Tension headaches	1	0.19
210	Tongue coated	1	0.19
211	Tonsillitis	1	0.19
212	Tooth infection	1	0.19
213	Tremor	1	0.19
214	Tympanic membrane disorder NOS	1	0.19
215	Upper respiratory tract congestion	1	0.19
216	Urinary incontinence	1	0.19
217	Vaginitis	1	0.19
218	Vision blurred	1	0.19
219	Weight increased	1	0.19
220	Wisdom teeth removal	1	0.19

Table 100. AEs Reported (Study 341)

No.	AE: AEPTXT	# Patients	% Patients
1	No AE	151	29.38
2	Asthma aggravated	92	17.90
3	Headache	80	15.56
4	Nasopharyngitis	64	12.45
5	Sinusitis NOS	51	9.92
6	Pharyngitis	46	8.95
7	Pyrexia	42	8.17
8	Upper respiratory tract infection NOS	28	5.45
9	Cough	26	5.06
10	Vomiting NOS	24	4.67
11	Rhinitis NOS	18	3.50
12	Diarrhoea NOS	17	3.31
13	Nasal congestion	14	2.72
14	Rhinitis NOS exacerbated	14	2.72
15	Abdominal pain upper	13	2.53
16	Viral infection NOS	12	2.33
17	Ear pain	11	2.14
18	Epistaxis	11	2.14
19	Rash NOS	10	1.95
20	Rhinorrhoea	10	1.95
21	Skin laceration	9	1.75
22	Gastroenteritis viral NOS	8	1.56
23	Influenza like illness	8	1.56
24	Limb injury NOS	8	1.56
25	Pharyngitis streptococcal	8	1.56
26	Influenza	7	1.36
27	Rhinitis allergic NOS	7	1.36
28	Abrasion NOS	6	1.17
29	Tonsillitis	6	1.17
30	Toothache	6	1.17
31	Upper respiratory tract infection viral NOS	6	1.17
32	Abdominal pain NOS	5	0.97
33	Arthralgia	5	0.97
34	Bronchitis NOS	5	0.97
35	Head injury	5	0.97
36	Musculoskeletal chest pain	5	0.97
37	Otitis media NOS	5	0.97
38	Conjunctivitis	4	0.78
39	Conjunctivitis allergic	4	0.78
40	Ear infection NOS	4	0.78
41	Gastroenteritis NOS	4	0.78
42	Myalgia	4	0.78
43	Nausea	4	0.78
44	Pain NOS	4	0.78
45	Pain in limb	4	0.78
46	Pharyngitis viral NOS	4	0.78
47	Pulmonary congestion	4	0.78
48	Anorexia	3	0.58
49	Arthropod bite	3	0.58
50	Dyspepsia	3	0.58
51	Joint sprain	3	0.58
52	Lymphadenopathy	3	0.58
53	Nasal oedema	3	0.58
54	Odynophagia	3	0.58
55	Otitis externa NOS	3	0.58
56	Sinusitis acute NOS	3	0.58
57	Sneezing	3	0.58
58	Throat irritation	3	0.58
59	Urinary tract infection NOS	3	0.58
60	Varicella	3	0.58
61	Allergy aggravated	2	0.39

No.	AE: AEPTXT	# Patients	% Patients
62	Contusion	2	0.39
63	Dermatitis contact	2	0.39
64	Dizziness	2	0.39
65	Eczema	2	0.39
66	Eye pain	2	0.39
67	Gastrointestinal upset	2	0.39
68	Herpes simplex	2	0.39
69	Hordeolum	2	0.39
70	Laceration	2	0.39
71	Mood swings	2	0.39
72	Muscle cramp	2	0.39
73	Otitis media serous NOS	2	0.39
74	Pneumonia NOS	2	0.39
75	Scratch	2	0.39
76	Urticaria NOS	2	0.39
77	Abdominal pain lower	1	0.19
78	Abdominal tenderness	1	0.19
79	Abnormal behaviour NOS	1	0.19
80	Acne NOS	1	0.19
81	Aggression	1	0.19
82	Allergy to arthropod sting	1	0.19
83	Ankle fracture	1	0.19
84	Anxiety	1	0.19
85	Aphthous stomatitis	1	0.19
86	Appetite decreased NOS	1	0.19
87	Arthropod sting	1	0.19
88	Attention deficit/hyperactivity disorder	1	0.19
89	Back pain	1	0.19
90	Blood cortisol increased	1	0.19
91	Body temperature increased	1	0.19
92	Bronchitis acute NOS	1	0.19
93	Bronchitis viral	1	0.19
94	Cataract	1	0.19
95	Cataract bilateral NOS	1	0.19
96	Cataract subcapsular	1	0.19
97	Cerumen impaction	1	0.19
98	Chalazion	1	0.19
99	Chest pain	1	0.19
100	Chest wall pain	1	0.19
101	Chondritis	1	0.19
102	Constipation	1	0.19
103	Corneal abrasion	1	0.19
104	Cortisol free urine decreased	1	0.19
105	Croup infectious	1	0.19
106	Dermatitis NOS	1	0.19
107	Dermatophytosis NOS	1	0.19
108	Dry mouth	1	0.19
109	Dry skin	1	0.19
110	Dysphonia	1	0.19
111	Dysuria	1	0.19
112	Eczema exacerbated	1	0.19
113	Erythema	1	0.19
114	Exanthem	1	0.19
115	Eye allergy	1	0.19
116	Eye pruritus	1	0.19
117	Eye redness	1	0.19
118	Eye swelling	1	0.19
119	Face injury	1	0.19
120	Faecaloma	1	0.19
121	Fall	1	0.19
122	Fatigue	1	0.19
123	Flank pain	1	0.19
124	Gastrointestinal infection NOS	1	0.19
125	Gingival pain	1	0.19

No.	AE: AEP TTX	# Patients	% Patients
126	Gingival ulceration	1	0.19
127	Gingivitis	1	0.19
128	Hand fracture	1	0.19
129	Heat rash	1	0.19
130	Impetigo NOS	1	0.19
131	Injury NOS	1	0.19
132	Insomnia	1	0.19
133	Intermittent pyrexia	1	0.19
134	Irritability	1	0.19
135	Laryngitis NOS	1	0.19
136	Lip ulceration	1	0.19
137	Localised infection	1	0.19
138	Maxillary sinusitis	1	0.19
139	Menarche	1	0.19
140	Muscle strain	1	0.19
141	Musculoskeletal stiffness	1	0.19
142	Nasal passage irritation	1	0.19
143	Nasal turbinate hypertrophy	1	0.19
144	Neck pain	1	0.19
145	Open wound	1	0.19
146	Pain in foot	1	0.19
147	Periorbital haematoma	1	0.19
148	Peripheral swelling	1	0.19
149	Pharyngeal erythema	1	0.19
150	Pharyngolaryngeal pain	1	0.19
151	Pharyngotonsillitis	1	0.19
152	Pharynx discomfort	1	0.19
153	Post procedural site wound infection	1	0.19
154	Post streptococcal glomerulonephritis	1	0.19
155	Post-traumatic headache	1	0.19
156	Rash maculo-papular	1	0.19
157	Rhinalgia	1	0.19
158	Rigors	1	0.19
159	Scabies infestation	1	0.19
160	Sinus headache	1	0.19
161	Sinus pain	1	0.19
162	Skin candida	1	0.19
163	Skin lesion NOS	1	0.19
164	Skin nodule	1	0.19
165	Skin ulcer	1	0.19
166	Somnolence	1	0.19
167	Status asthmaticus	1	0.19
168	Sunburn	1	0.19
169	Sweating increased	1	0.19
170	Swelling face	1	0.19
171	Tooth caries NOS	1	0.19
172	Tooth injury	1	0.19
173	Tracheitis NOS	1	0.19
174	Tympanic membrane perforation	1	0.19
175	Unevaluable reaction	1	0.19
176	Urogenital disorder NOS	1	0.19
177	Vaginal irritation	1	0.19
178	Vasovagal attack	1	0.19
179	Vision blurred	1	0.19
180	Wound NOS	1	0.19

Table 101. AEs Reported (Study 342)

No.	AE: AEP TTX	# Patients	% Patients
1	No AE	165	31.98
2	Nasopharyngitis	60	11.63
3	Upper respiratory tract infection NOS	58	11.24
4	Asthma aggravated	57	11.05
5	Pharyngitis	57	11.05
6	Headache	48	9.30
7	Sinusitis NOS	25	4.84
8	Rhinitis NOS exacerbated	24	4.65
9	Pyrexia	22	4.26
10	Abdominal pain upper	20	3.88
11	Vomiting NOS	18	3.49
12	Bronchitis NOS	15	2.91
13	Gastroenteritis viral NOS	13	2.52
14	Rhinitis NOS	13	2.52
15	Aphthous stomatitis	11	2.13
16	Otitis media NOS	11	2.13
17	Upper respiratory tract infection viral NOS	11	2.13
18	Epistaxis	10	1.94
19	Diarrhoea NOS	9	1.74
20	Dyspepsia	9	1.74
21	Nausea	9	1.74
22	Viral infection NOS	9	1.74
23	Bronchitis acute NOS	8	1.55
24	Ear pain	8	1.55
25	Nasal congestion	8	1.55
26	Conjunctivitis	7	1.36
27	Cough	7	1.36
28	Influenza	6	1.16
29	Pharyngitis streptococcal	6	1.16
30	Toothache	6	1.16
31	Abdominal pain NOS	5	0.97
32	Arthralgia	5	0.97
33	Productive cough	5	0.97
34	Rash NOS	5	0.97
35	Sinusitis acute NOS	5	0.97
36	Ear infection NOS	4	0.78
37	Gastroenteritis NOS	4	0.78
38	Joint sprain	4	0.78
39	Rhinitis allergic NOS	4	0.78
40	Skin laceration	4	0.78
41	Urticaria NOS	4	0.78
42	Acne NOS	3	0.58
43	Contusion	3	0.58
44	Eye irritation	3	0.58
45	Head injury	3	0.58
46	Headache NOS aggravated	3	0.58
47	Influenza-like illness	3	0.58
48	Lymphoid tissue hyperplasia	3	0.58
49	Nasal oedema	3	0.58
50	Oral candidiasis	3	0.58
51	Pain NOS	3	0.58
52	Pneumonia NOS	3	0.58
53	Rales	3	0.58
54	Status asthmaticus	3	0.58
55	Varicella	3	0.58
56	Abrasion NOS	2	0.39
57	Allergy aggravated	2	0.39
58	Arthropod sting	2	0.39
59	Cataract subcapsular	2	0.39
60	Cerumen impaction	2	0.39
61	Conjunctivitis allergic	2	0.39

No.	AE: AEP TTX	# Patients	% Patients
62	Eczema	2	0.39
63	Fluid in middle ear	2	0.39
64	Gastritis NOS	2	0.39
65	Hoarseness	2	0.39
66	Lower respiratory tract infection NOS	2	0.39
67	Myalgia	2	0.39
68	Otitis externa NOS	2	0.39
69	Pain in foot	2	0.39
70	Pharyngeal erythema	2	0.39
71	Post procedural pain	2	0.39
72	Postnasal drip	2	0.39
73	Pulmonary congestion	2	0.39
74	Rhinorrhoea	2	0.39
75	Sinus congestion	2	0.39
76	Tracheitis NOS	2	0.39
77	Upper limb fracture NOS	2	0.39
78	Affect lability	1	0.19
79	Alanine aminotransferase increased	1	0.19
80	Allergic conjunctivitis aggravated	1	0.19
81	Anaphylactic reaction	1	0.19
82	Animal bite	1	0.19
83	Appetite increased NOS	1	0.19
84	Arthropod bite	1	0.19
85	Aspartate aminotransferase increased	1	0.19
86	Bacterial infection NOS	1	0.19
87	Blood triglycerides increased	1	0.19
88	Bronchiolitis	1	0.19
89	Bronchopneumonia NOS	1	0.19
90	Burns first degree	1	0.19
91	Burns second degree	1	0.19
92	Chest wall pain	1	0.19
93	Cough aggravated	1	0.19
94	Croup infectious	1	0.19
95	Cyst NOS	1	0.19
96	Cystitis NOS	1	0.19
97	Dehydration	1	0.19
98	Dermatitis atopic	1	0.19
99	Dermatitis contact	1	0.19
100	Dermatophytosis NOS	1	0.19
101	Dizziness	1	0.19
102	Dry mouth	1	0.19
103	Dysuria	1	0.19
104	Ear discomfort	1	0.19
105	Eczema exacerbated	1	0.19
106	Euphoric mood	1	0.19
107	Eye pain	1	0.19
108	Eye redness	1	0.19
109	Eye swelling	1	0.19
110	Face oedema	1	0.19
111	Fatigue aggravated	1	0.19
112	Food allergy	1	0.19
113	Gamma-glutamyltransferase increased	1	0.19
114	Gas poisoning	1	0.19
115	Gastrooesophageal reflux disease	1	0.19
116	Growing pains	1	0.19
117	Hallucination, visual	1	0.19
118	Heat rash	1	0.19
119	Herpes simplex	1	0.19
120	Herpes zoster	1	0.19
121	Hypertriglyceridaemia	1	0.19
122	Impetigo NOS	1	0.19
123	Injection site infection	1	0.19
124	Interstitial pneumonia	1	0.19
125	Laceration	1	0.19

No.	AE: AEPTT	# Patients	% Patients
126	Laryngitis NOS	1	0.19
127	Laryngitis acute NOS	1	0.19
128	Laryngotracheitis NOS	1	0.19
129	Malaise	1	0.19
130	Measles	1	0.19
131	Menarche	1	0.19
132	Milk allergy	1	0.19
133	Molluscum contagiosum	1	0.19
134	Multiple allergies	1	0.19
135	Muscle cramp	1	0.19
136	Muscle injury NOS	1	0.19
137	Muscle strain	1	0.19
138	Musculoskeletal stiffness	1	0.19
139	Nervousness	1	0.19
140	Oral pain	1	0.19
141	Osteochondrosis	1	0.19
142	Pain in limb	1	0.19
143	Palpitations	1	0.19
144	Pericarditis acute infective	1	0.19
145	Pharyngitis viral NOS	1	0.19
146	Pneumonitis NOS	1	0.19
147	Pruritus	1	0.19
148	Pulpitis dental	1	0.19
149	Respiratory disorder NOS	1	0.19
150	Respiratory tract infection NOS	1	0.19
151	Respiratory tract infection viral NOS	1	0.19
152	Sensation of pressure in ear	1	0.19
153	Sinus pain	1	0.19
154	Skin fungal infection NOS	1	0.19
155	Skin lesion NOS	1	0.19
156	Skin papilloma	1	0.19
157	Staphylococcal impetigo	1	0.19
158	Sunburn	1	0.19
159	Teething	1	0.19
160	Tendon rupture	1	0.19
161	Throat tightness	1	0.19
162	Tinea capitis	1	0.19
163	Tinnitus	1	0.19
164	Tonsillitis acute NOS	1	0.19
165	Tooth caries NOS	1	0.19
166	Tooth infection	1	0.19
167	Tooth injury	1	0.19
168	Urticaria papular	1	0.19
169	Venomous sting	1	0.19
170	Viral labyrinthitis	1	0.19
171	Viral rash NOS	1	0.19

--TedGuo-- Wednesday, September 22, 2004 -- EOF --

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ted Guo
9/28/04 10:32:18 AM
BIOMETRICS

Ruth Davi
9/28/04 11:06:44 AM
BIOMETRICS

Steve Wilson
9/29/04 12:26:45 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION OF RAT AND MOUSE
CARCINOGENICITY STUDIES

ADDENDUM

NDA: 21-658

Name of drug: Alvesco (Ciclesonide)

Sponsor: Aventis Inc.

Indication: Bronchial Asthma

Documents reviewed: B9207-015

1. **Rat Study:** Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats

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2. **Mouse Study:** Carcinogenicity Study by Oral Gavage Administration to B6C3F1 Mice for 104 Weeks

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Project manager: Colette Jackson

Pharmacology reviewer: Huiqing Hao, Ph.D.

Dates: Electronic Submission, Dated December 22, 2003

Statistical reviewer: Joan Buenconsejo, MS

Secondary reviewer: Karl Lin, Ph.D.

Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, carcinogenicity studies, survival

As per the request of the pharmacology/toxicology reviewer, two additional sets of analyses were performed in the mouse and rat studies, and they are:

- (1) Negative Control versus treatment
- (2) Vehicle Control versus treatment

The tumor incidence rates and the tumor types with asymptotic p -values less than 0.05 for dose-response relationships are presented. Additional pairwise analyses between different control groups and treatment groups were performed when there is at least one positive significant trend observed. In addition, tumor trend analyses were performed again for combination tumors identified to be relevant by the pharmacology reviewer.

The results from these two additional sets of analyses support the conclusion formulated from the previous analyses using pooled control group. **Tests on tumor data showed a statistically significant positive trend in Adenoma (antrum) of the stomach organ indicating a positive carcinogenic potential in female mice.** Pairwise comparison between the pooled control group and the high dose group did show significant difference at 0.05 level of significance in the number of adenoma (stomach organ) in female mice ($p=0.0427$). Meanwhile, no significant positive tumor trend was found in male mice, male rats, or female rats.

As for the mortality analyses, test results showed no statistically significant differences in survival across treatment groups, as well as no statistically significant dose-mortality trend in male or female mice and rats.

All the results are presented in the Appendix.

APPENDIX:

I. FEMALE MICE

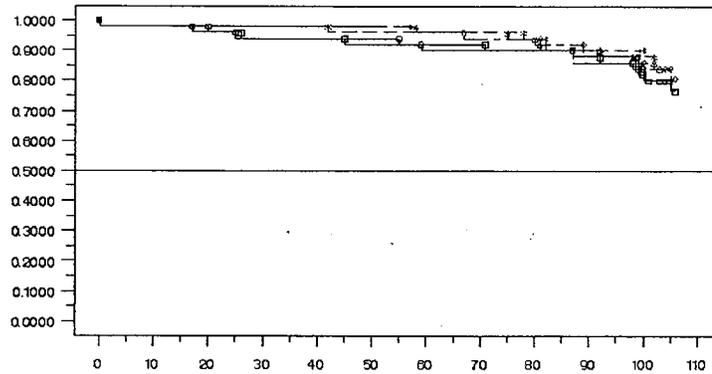
1. Original Data

A. Pooled Control vs. Treatment:

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
BO	BONE	166	OSTEOSARCOMA	0	0	0	0	1	Go	0.2068	0.0427
DU0	DUODENUM	738	EARLY ADENOCARCINOMA	0	0	0	0	1	Go	0.2115	0.0446
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	0	3	Go	0.0088	0.0015
UT0	UTERUS	689	FIBROMA	0	0	0	0	1	Go	0.2105	0.0441

! implies statistical significance

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	0.2237	0.9737	0.2476	0.9696
Dose-Mortality Trend	1.4681	0.2256	1.5340	0.2155
Homogeneity	1.6918	0.7922	1.7816	0.7758



□-□-□ CTR1 ○-○-○ CTR2 ◇-◇-◇ LOW △-△-△ MED *-*-* HIGH

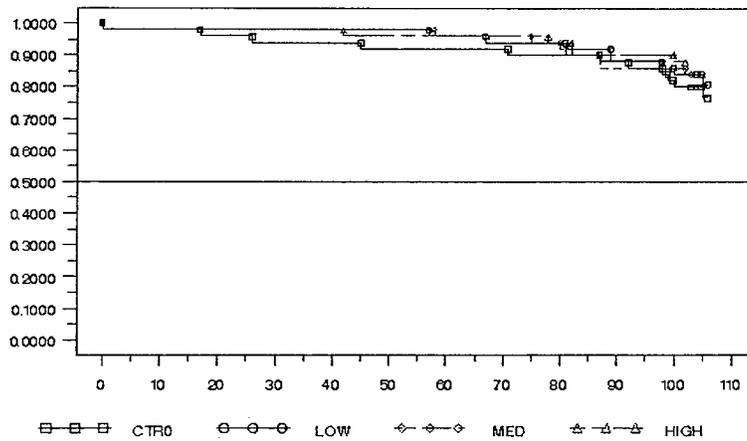
Pairwise Comparison: Pooled versus High

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	3	Go	0.0427	0.0093

B. Negative Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	GG	0.0168	0.0046
UT0	UTERUS	742	ENDOMETRIAL ADENOCARCINOMA	0	0	0	2	GG	0.0666	0.0171

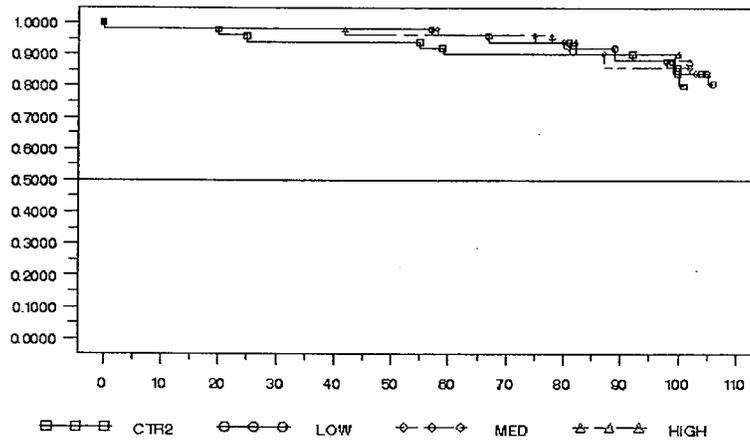
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.5519	0.7589	0.5483	0.7602
Depart from Trend				
Dose-Mortality Trend	0.8584	0.3542	0.9106	0.3399
Homogeneity	1.4103	0.7031	1.4589	0.6918



C. Vehicle Control vs. Placebo

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MED	HIGH	2x2 Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	Go	0.0168 !	0.0046

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	0.5272	0.7683	0.5090	0.7753
Dose-Mortality Trend	0.8501	0.3565	0.8935	0.3445
Homogeneity	1.3773	0.7109	1.4025	0.7050



2. Combination tumors within organ

A. Pooled Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	GTR1	GTR2	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
BO	BONE	166	OSTEOSARCOMA	0	0	0	0	1	Go	0.2068	0.0427
DU0	DUODENUM	738	EARLY ADENOCARCINOMA	0	0	0	0	1	Go	0.2115	0.0446
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	0	3	Go	0.0088 !	0.0015
UT0	UTERUS	689	FIBROMA	0	0	0	0	1	Go	0.2105	0.0441

B. Negative Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	Go	0.0168 !	0.0046
UT0	UTERUS	742	ENDOMETRIAL ADENOCARCINOMA	0	0	0	2	Go	0.0666	0.0171

C. Vehicle Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	Go	0.0168 !	0.0046

3. Combination organs within tumor

A. Pooled Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
DU0	DUODENUM	738	EARLY ADENOCARCINOMA	0	0	0	0	1	Go	0.2115	0.0446
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	0	3	Go	0.0088 !	0.0015
UT0	UTERUS	689	FIBROMA	0	0	0	0	1	Go	0.2105	0.0441

B. Negative Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	LOW	MED	HIGH	2XC Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	Go	0.0168 !	0.0046
UT0	UTERUS	742	ENDOMETRIAL ADENOCARCINOMA	0	0	0	2	Go	0.0666	0.0171

C. Vehicle Control vs. Treatment

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MED	HIGH	2x2 Table	P-Value (Exact Method)	P-Value (Asymptotic Method)
ST0	STOMACH	308	ADENOMA (ANTRUM)	0	0	0	3	Go	0.0168	0.0046

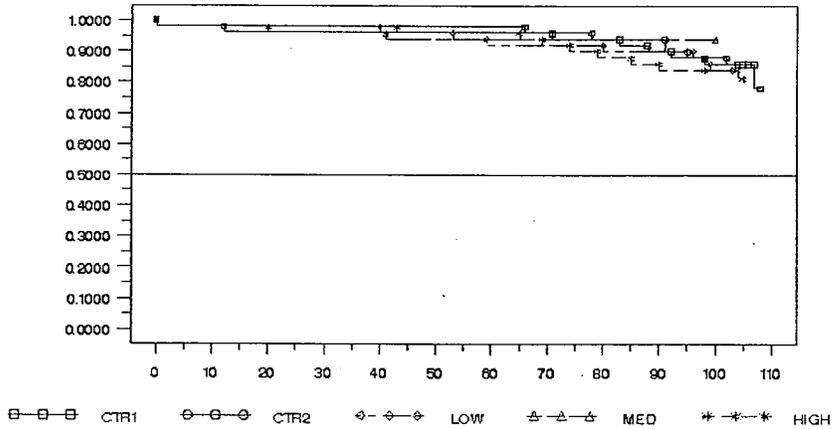
II. MALE MICE:

1. Original Data

A. Pooled Control vs. Treatment:

No tumors found to be significant.

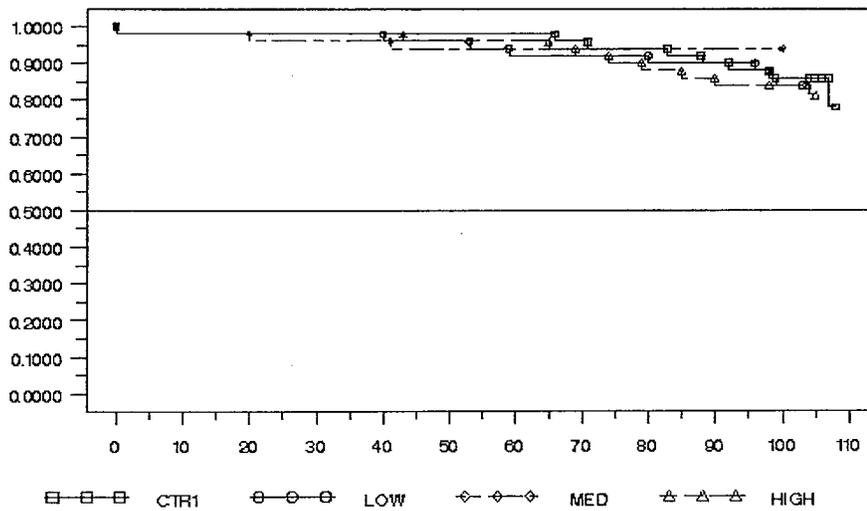
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.9307	0.4024	2.8595	0.4138
Depart from Trend				
Dose-Mortality Trend	0.0891	0.7654	0.1157	0.7337
Homogeneity	3.0198	0.5545	2.9752	0.5620



B. Negative Control vs. Treatment

No tumors found to be significant.

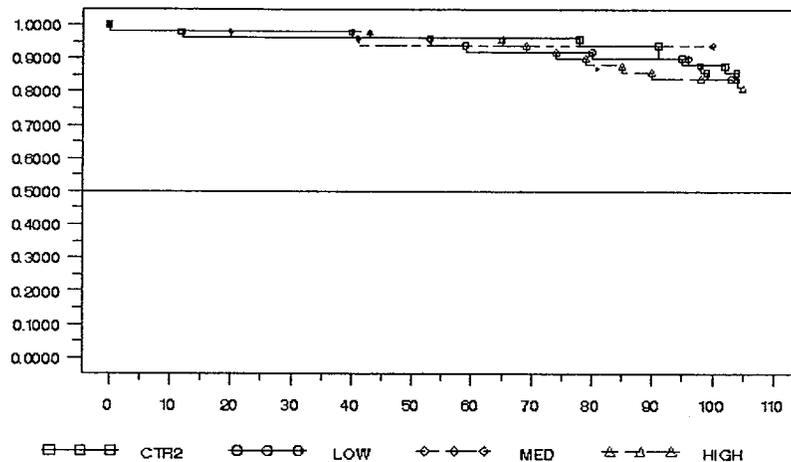
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.8728	0.2378	2.7899	0.2478
Depart from Trend				
Dose-Mortality Trend	0.0024	0.9612	0.0090	0.9243
Homogeneity	2.8752	0.4113	2.7989	0.4237



C. Vehicle Control vs. Treatment

No tumors found to be significant.

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.8900	0.2357	2.8053	0.2459
Depart from Trend				
Dose-Mortality Trend	0.0752	0.7839	0.0958	0.7569
Homogeneity	2.9652	0.3970	2.9011	0.4071



2. Combination tumors within organ

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

3. Combination organs within tumor

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

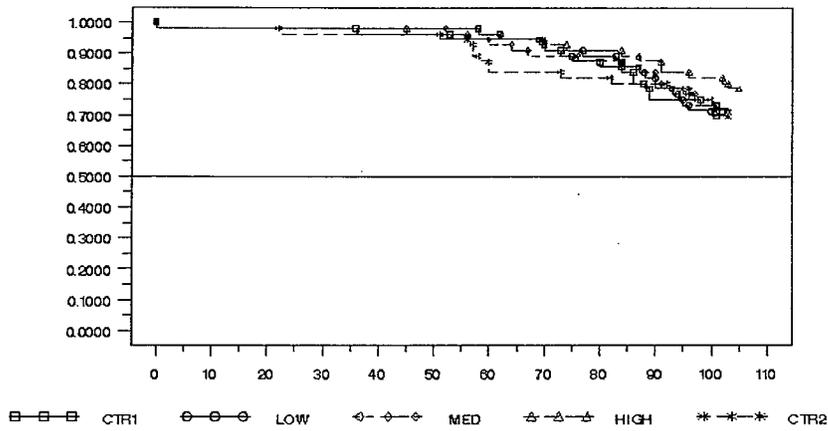
III. FEMALE RATS

1. Original Data

A. Pooled Control vs. Treatment:

No tumors found to be significant.

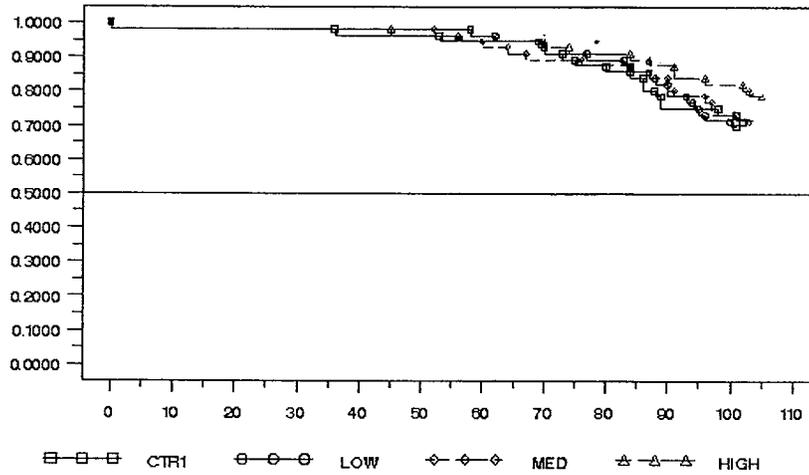
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.2337	0.9720	0.2066	0.9765
Depart from Trend				
Dose-Mortality Trend	2.0274	0.1545	2.1187	0.1455
Homogeneity	2.2611	0.6879	2.3253	0.6762



B. Negative Control vs. Treatment

No tumors found to be significant.

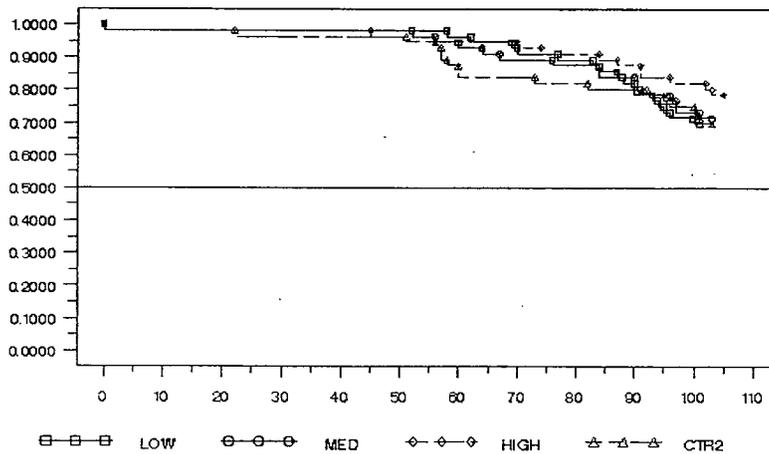
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.2400	0.8869	0.1997	0.9050
Depart from Trend				
Dose-Mortality Trend	1.7267	0.1888	1.7399	0.1872
Homogeneity	1.9667	0.5793	1.9396	0.5850



C. Vehicle Control vs. Treatment

No tumors found to be significant.

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.0690	0.9661	0.0421	0.9792
Depart from Trend				
Dose-Mortality Trend	2.1716	0.1406	2.2529	0.1334
Homogeneity	2.2406	0.5240	2.2950	0.5135



2. Combination tumors within organ

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

3. Combination organs within tumor

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

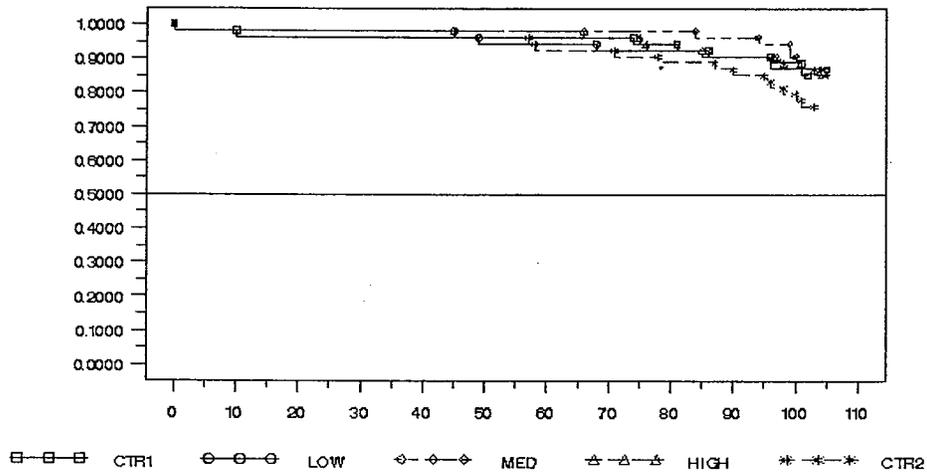
IV. MALE RATS

1. Original Data

A. Pooled Control vs. Treatment:

No tumors found to be significant.

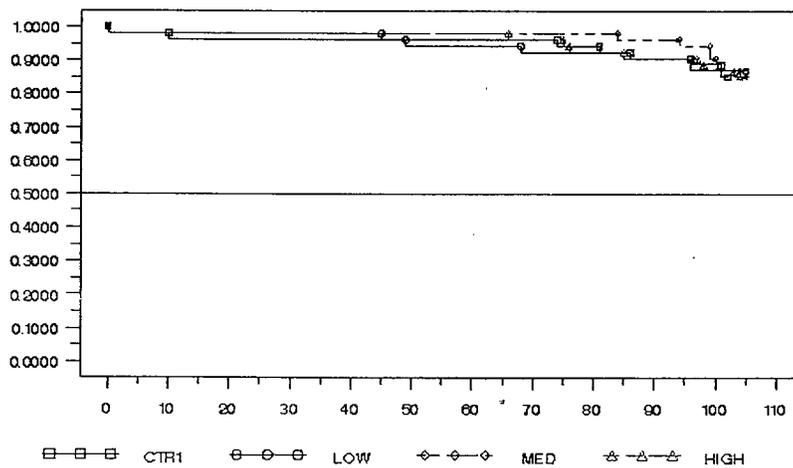
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	4.8804	0.1808	4.8498	0.1831
Depart from Trend				
Dose-Mortality Trend	0.3384	0.5607	0.3870	0.5339
Homogeneity	5.2188	0.2656	5.2368	0.2639



B. Negative Control vs. Treatment

No tumors found to be significant.

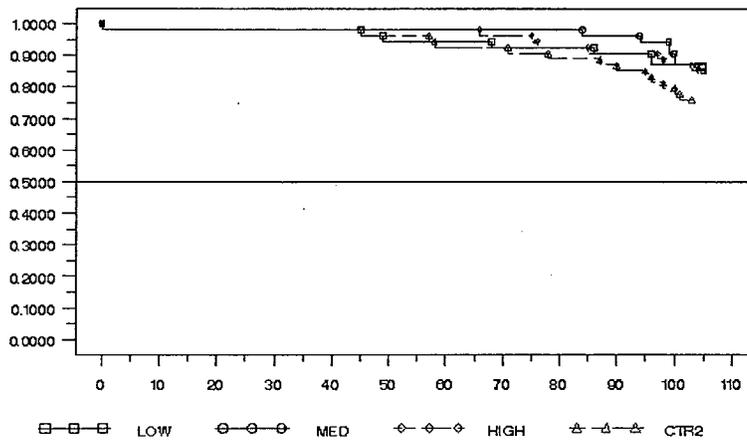
	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.7785	0.6776	0.7158	0.6992
Depart from Trend				
Dose-Mortality Trend	0.1153	0.7342	0.0977	0.7546
Homogeneity	0.8939	0.8269	0.8135	0.8462



C. Vehicle Control vs. Treatment

No tumors found to be significant.

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	4.6962	0.0955	4.6423	0.0982
Depart from Trend				
Dose-Mortality Trend	0.4647	0.4954	0.5268	0.4680
Homogeneity	5.1610	0.1604	5.1691	0.1598



2. Combination tumors within organ

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

3. Combination organs within tumor

A. Pooled Control vs. Treatment:

No tumors found to be significant.

B. Negative Control vs. Treatment:

No tumors found to be significant.

C. Vehicle Control vs. Treatment:

No tumors found to be significant.

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/s/

Joan Buenconsejo
4/28/04 12:55:51 PM
BIOMETRICS

Karl Lin
4/28/04 02:21:23 PM
BIOMETRICS
Concur with review



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION OF RAT AND MOUSE CARCINOGENICITY STUDIES

NDA: 21-658

Name of drug: Alvesco (Ciclesonide)

Sponsor: Aventis Inc.

Indication: Bronchial Asthma

Documents reviewed: B9207-015

1. **Rat Study:** Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats
\\Cdsub1\n21658\N 000\2003-12-22\pharmtox\tox\176e 99\study176e 99.pdf

2. **Mouse Study:** Carcinogenicity Study by Oral Gavage Administration to B6C3F1 Mice for 104 Weeks
\\Cdsub1\n21658\N 000\2003-12-22\pharmtox\tox\study281 2000.pdf

Project manager: Colette Jackson

Pharmacology reviewer: Huiqing Hao, Ph.D.

Dates: Electronic Submission, Dated December 22, 2003

Statistical reviewer: Joan Buenconsejo, MS

Secondary reviewer: Karl Lin, Ph.D.

Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, carcinogenicity studies, survival

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SUMMARY

In this submission report, animal carcinogenicity studies in rats and in mice were included. These studies were intended to assess the carcinogenic potential of B9207-015 (Ciclesonide) in rats and mice with appropriate drug levels for about 104 weeks for rats and mice.

Mouse Study: This study had one negative control group, one vehicle control group (PEG 400) and three treatment groups (dose levels: 150, 450, and 900 $\mu\text{g}/\text{kg}/\text{day}$) in male and female mice. Test results showed no statistically significant differences in survival across treatment groups, as well as no statistically significant dose-mortality trend in male or female mice. **Tests on tumor data showed a statistically significant positive trend in Adenoma (antrum) of the stomach organ indicating a positive carcinogenic potential in female mice ($p = 0.0088$).** Because no significant positive tumor trend was found in male mice, evaluation of the validity of the study design in male mice was conducted by the reviewer. The result suggested that enough male mice (i.e. more than 50% survival between weeks 80 to 90) were exposed to the drug for a sufficient amount of time. In addition, the result also suggested that the high dose group was over the MTD (maximum tolerated dose) level.

Rat Study: This study had two control groups (clean-air control and vehicle control) and three treatment groups receiving B9207-015 at dose levels of 1, 2.5, and 6.25 mg/m^3 . Test results showed no statistically significant differences in survival across treatment groups, as well as no statistically significant dose-mortality trend in the male or female rats. Tests on tumor data showed no significant positive trend in male or female rats. Because no significant positive tumor trend was found in either male or female rats, evaluation of the validity of the study design was conducted by the reviewer. The results indicated that enough rats in both sexes were exposed to the drug for a sufficient amount of time. Meanwhile, the results from the body weight data suggested that the high dose group was over the maximum tolerated dose level (MTD) in male and female rats. However, the evaluation based on mortality data yielded opposite results. Therefore, other clinical signs and histopathological toxic effects should be considered in the evaluation of the adequacy of the doses used.

Background

In this NDA submission, a 24-month carcinogenicity study on B6C3F1 mice and a 24-month carcinogenicity study on Wistar rats were conducted. These studies were intended to assess the carcinogenic potential of ciclesonide (B9207-015), known as a new glucocorticoid for the treatment of asthma when administered orally by gavage to male and female mice, and when administered by inhalation to male and female Wistar rats.

Study Design

The designs of the carcinogenicity studies were similar with primary differences arising in the rodent species and the routes of administration. The current review evaluates and presents results separately for each species.

1. Study in Mice (Reference No.281/2000)

Two separate experiments, one in male and one in female were conducted. In each of these two experiments, there were five treatment groups comprising of a negative control group, a vehicle control group (PEG 400) and three treatment groups receiving B9207-015 (Ciclesonide) at the following dose levels: 150, 450, and 900 µg/kg/day. There were 250 males and 250 females assigned to control and treated groups of equal size in each experiment.

During the study, clinical signs, bodyweight and food consumption data were collected. Blood samples for the analysis of red, total white and differential blood cell counts were obtained, where possible, from animals dying during the study or in Week 104 at the end of the treatment period for the study. Each animal was subjected to a necropsy. On completion of 104 weeks of treatment, all surviving animals were killed by carbon dioxide asphyxiation and subjected to a full necropsy, including histopathological evaluation.

2. Study in Rats (Reference No. 176_e99)

Two separate experiments, one in male and one in female were conducted. In each of these two experiments, there were two control groups (clean-air control and vehicle control) and three treatment groups receiving B9207-015 at dose levels of 1, 2.5, and 6.25 mg/m³. The vehicle control was a B9207-015 (Placebo) contained in identical cans as the test substance. There were 270 males and 280 females assigned to control and treated groups of equal size. Groups of 54 males and 56 females were exposed to B9207-015 in Metered Dose Inhalers (MDI) containing ethanolic HFA-134a for one hour duration per day on 7 days/week over at least 24 months up to final sacrifice.

During the study, clinical signs, bodyweight and food consumption data were collected. Blood samples for the analysis of red, total white and differential blood cell counts were obtained, where possible, from animals dying during the study or in Week 104 at the end of the treatment period for the study. Ethanol was determined on Day 100 in plasma each of five male and female animals of the clean air and vehicle control groups using the alcohol dehydrogenase method. Each animal was subjected to a necropsy. On completion of 104 weeks of treatment, all

surviving animals were killed by carbon dioxide asphyxiation and subjected to a full necropsy, including histopathological evaluation.

Sponsor's Analysis and Results

Mortality Analysis

Mortality data were analyzed using log-rank test and have been presented as life-tables and graphically using Kaplan-Meier survival curves. Two-tailed test for trend with a dose level (excluding negative control group) and a two-tailed pairwise comparison test of each treatment group against the vehicle control group were carried out in the mouse study. In the mouse study, analysis of mortality data showed no statistically significant results in male or female mice. In the rat study, mortality was comparable in all male and female groups with the exception of a slightly higher mortality in the male vehicle control group. The percent of deaths at the end of the study are also presented in Table 1 for male and female mice and rats. Lifetime analysis over all groups in the rat study according to Kaplan-Meier showed no significant difference for males and females with the exception of a slightly higher mortality in the male vehicle control group.

Table 1: Mortality Data in percent of deaths by dose level

Dose Level	No treatment	150 µg/kg/day	450 µg/kg/day	900 µg/kg/day	Vehicle Control
Mice					
Males	14%	16%	6%	16%	14%
Females	20%	16%	16%	12%	20%
Dose Level	Clean Air Control	1.0 mg/m ³	2.5 mg/m ³	6.25 mg/m ³	Vehicle Control
Rats					
Males	15%	13%	15%	15%	24%
Females	29%	30%	29%	21%	30%

Body Weight, food and water consumption

In the rat study, statistical tests on the comparison of treatment groups were performed at the level of 0.05. Body weight, food and water consumption data were analyzed using analysis of variance (ANOVA) as a global test. Pairwise comparisons of the treatment groups with the means of the clean air control group were performed using Dunnett's modification of the t-test. The sponsor observed a reduction of body weight development compared to clean air controls. The reduction resulted in a dose-dependent lower mean body weight of 6.1% - 19.8% in all treated male groups and 6.3% - 16.8% in the female 2.5 and 6.25 mg/m³ groups at study ends. These effects, the sponsor observed, were concomitant with a dose-dependent slight decrease of food consumption (between 3-8%) in the respective groups. In the females, this effect on food consumption was no longer evident after 11 weeks of treatment.

In the mouse study, sequence of statistical tests was conducted by the Sponsor for food, bodyweight and clinical pathology data. The reader is referred to the Sponsor's report on the statistical tests used. Based on Sponsor's report, body weight gain was reduced over the 104 weeks treatment in animals receiving 450 µg/kg/day (by 8% compared with vehicle controls) and in both sexes receiving 900 µg/kg/day (-14% and -12% for male and female respectively). Food

consumption was not affected by treatment among all treated groups when compared with that of the concurrent vehicle controls during the treatment period.

Tumor Trend Analysis

In the rat study, Peto's analysis was used to compare the tumor incidence in the compound-treated groups with that in the clean air control groups. For the Peto test, scores are determined according to Peto et al. 1980, where tumors which either directly or indirectly kill its host are said to be observed in a fatal context, while other tumors observed at necropsy in animals which died of some unrelated cause are said to be observed in an incidental context. All tumors found in terminal sacrificed animals are classified as incidental for analytical purposes.

Similar tumor definition is used in the mouse study. Log-rank methods were used to analyze the number of animals with tumors across treatment groups in the mouse study. Observed and expected number of tumors and the relative tumor rate across all time intervals were calculated and compared across treatment groups. The following χ^2 statistical tests were carried out: a one-tailed test for a trend using nominal dose levels (not including the negative control group); a one-tailed pairwise comparison test of each treatment group against the vehicle control group; and a one-tailed pairwise comparison test of the vehicle control group against the negative control group. Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated, using a one-tailed test until the test was no longer statistically significant. The significance level was adjusted using a continuity correction where there was one degree of freedom. Test for non-linearity was also carried out.

The sponsor presented the results for tumor incidence analyses for mouse and rat study, and the following is the summary of their results:

1. Rat study

- a. In general, the sponsor observed no marked differences with respect to the number of tumor-bearing animals between the clean air control group, the B9207-015 treated groups or the vehicle control group, either in males or in females.
- b. The sponsor found no trends in males over clean-air control and treated groups using Peto test. However, **the sponsor found a significant trend for females on pituitary, adenoma, pars distalis ($p = 0.00469$) using Peto test.** After correcting for multiple testing, the sponsor still found this to be significant ($p = 0.02567$). The incidence of pars distalis adenoma(ta) was significantly decreased in the females of the 6.25 mg/m³ B9207-015 group as compared to the clean air control group (14/56 vs. 27/56, respectively). However, the sponsor indicated that this difference is probably incidental because of an unusually high incidence of pituitary in the clean air control group, and that this incidence is within the range of historical control values for this tumor type in Wistar rats. In addition, they noted that based on another long-term inhalation carcinogenicity study that was run with the same rat strain showed no difference between the control and the treatment group.

- c. Other organ sites that were presented in the sponsor's report include:
 - i. Testes – the incidence of single or multiple Leydig cell adenoma(ta) showed a pronounced variation in males between the clean air control and the vehicle control group, as well as the 1 mg/m³ treated group and the vehicle control group
 - ii. Uterus – high number of endometrial stromal polyps was observed in females of all groups. However no statistically significant differences between the clean air control and the other groups were observed with respect to the total number of polyps.
 - iii. Mammary gland – Fibroadenomas were common in females. The frequencies were slightly higher, but not statistically significantly higher in the B9207-015 treatment groups as compared to both control groups.

2. Mouse study:

- a. **Male mice showed no evidence for a trend across the groups in different organ sites.** However pairwise comparisons showed a significant increase in the number of tumors (Benign adenoma) from the vehicle control (PEG 400) to the 150 µg/kg/day dose group ($p= 0.032$) in the Harderian glands. In addition, when benign adenoma and malignant adenocarcinoma were combined in the Harderian glands, pairwise comparison showed a significance increase in the number of tumors from the vehicle control (PEG 400) to the 150 µg/kg/day dose group ($p= 0.018$) and to the 450 µg/kg/day dose group ($p= 0.04$). Since the test for non-linearity was significant, the sponsor conclude that the pairwise comparison tests are to be preferred over the trend test
- b. **Trend test for female mice showed statistical significant ($p=0.017$) when all dose groups were included in the analysis of benign adenoma (antrum) in the stomach.** No further trend tests were performed by the sponsor because no tumors were observed in the vehicle control group or in the low or intermediate dose group. The pairwise comparison between the vehicle control (PEG 400) and the 900 µg/kg/day dose group were not significant.

Reviewer's Statistical Analysis Methods

The reviewers conducted independent analyses on the carcinogenicity data submitted by the Sponsor. The analyses conformed to the Food and Drug Administration's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May, 2001). In addition, the reviewers' analyses were primarily conducted using *eReview of Animal Carcinogenicity*, a review tool developed for and utilized by CDER reviewers.

Mortality Analysis

Tests for homogeneity and dose mortality trends were conducted using survival analysis methods described by Cox (1972) and the Kruskal-Wallis Test (Gehan, 1965; Breslow, 1970; Thomas, Breslow, and Gart, 1977) where the latter test weights early failures more heavily.

Tumor Data Analysis (Trend Test)

This reviewer conducted the trend tests on tumor incidence rates using the method described by Peto et. al. (1980) and the method of exact permutation trend test was run under Cytel's StatXact for SAS Users and incorporated in *eReview* developed by the Division of Biometrics II. The sponsor classified tumors as fatal, possibly fatal, incidental, or possibly incidental, in which case, this reviewer combined fatal and possibly fatal as one group called fatal, and combined incidental and possibly incidental in another group called incidental. Data of incidental and fatal tumors were analyzed via the prevalence and death-rates methods, respectively. A combined test was used to analyze tumors classified as both fatal and incidental. The method of exact permutation trend test was used to counter underestimation of p-values when tumor incidence across the treatment groups was small. Otherwise, the approximation method based on normal distribution was used. All tests were performed separately for males and females for both species.

Multiple Testing Adjustment

A rule proposed by Haseman (1983) could be used to adjust the effect of multiple testing. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at 0.025 level, otherwise the level should be set at 0.005. (Lin, 1995, 1997; Lin and Rahman, 1998a, 1998b) The 10% overall false positive rate is seen by CDER statisticians as appropriate in a new drug regulatory setting.

Evaluation of Validity of the Design of the Study

An evaluation of validity of the study design was conducted in mouse and rat studies, because no significant positive trend was observed in male mice, as well as male and female rats. Readers are referred to papers by Haseman (1984) and Chu, Cueto and Ward (1981) for further information about evaluating the validity of the study design for negative studies.

Results and Discussion

1. Study in Mice (Reference No. 281/2000)

Survival Analysis:

The intercurrent mortality data is shown in Table 2 for male and female mice. The result showed slight improvement in survival among the 450 µg/kg/day male mice compared to other dose groups. However, no significant difference in survival rate across different dosing levels was evident. On average, less than 20% of the animals died across different treatment groups.

Table 2: Intercurrent mortality data for male and female mice

Week	Control 0		Vehicle Control		150 µg/kg/day		450 µg/kg/day		900 µg/kg/day	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
MALE MICE										
0 - 50	0	0.0	1	2.0	1	2.0	2	4.0	1	2.0
51 - 78	2	4.0	1	4.0	2	6.0	0	4.0	3	8.0
79 - 91	2	8.0	1	6.0	1	8.0	0	4.0	3	14.0
92 - 103	2	12.0	3	12.0	4	16.0	1	6.0	1	16.0
Terminal Sacrifice	44	88.0	44	88.0	42	84.0	47	94.0	42	84.0
FEMALE MICE										
0 - 52	3	6.0	2	4.0	0	0	0	0.0	1	2.0
53 - 80	1	8.0	2	8.0	2	4.0	2	4.0	1	4.0
81 - 91	1	10.0	0	8.0	2	8.0	3	10.0	1	6.0
92 - 103	5	20.0	6	20.0	3	14.0	3	16.0	3	12.0
Terminal Sacrifice	40	80.0	40	80.0	43	86.0	42	84.0	44	88.0

The Kaplan-Meier curves for death rate are given in Figures 1 and 2 for male and female mice, respectively. The survival curves were not different among the treatment groups in both male and female mice.

Figure 1: Kaplan-Meier survival curve for Male mice

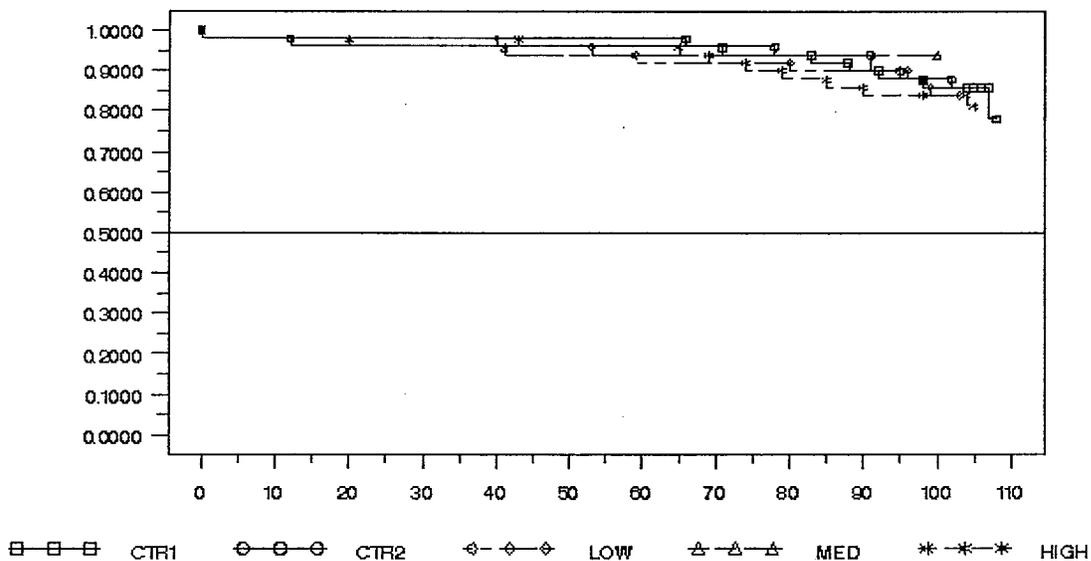
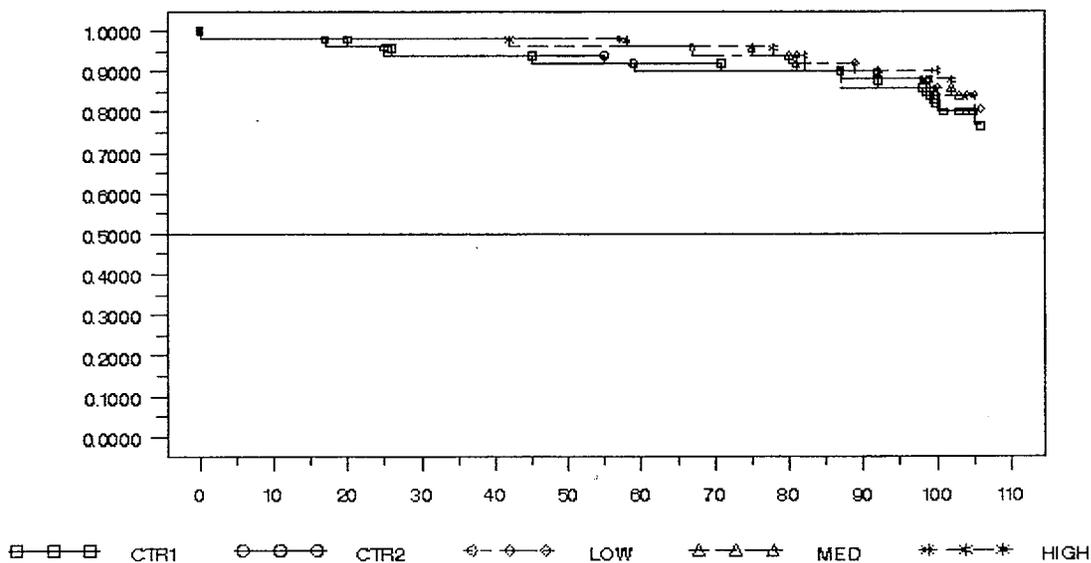


Figure 2: Kaplan-Meier survival curve for Female mice



The homogeneity of survival and dose mortality trends were tested separately for males and females and the results are presented in Tables 3 and 4, respectively. Note that for these tests, the two control groups were pooled together. The results showed no significant difference in survivals across treatment groups in male or female mice. In addition, the dose-mortality trends in both male and female mice were not statistically significant.

Table 3: Analysis of Dose-Mortality Trend for Male Mice (Pooled Control vs. Treatment)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.9307	0.4024	2.8595	0.4138
Depart from Trend				
Dose-Mortality Trend	0.0891	0.7654	0.1157	0.7337
Homogeneity	3.0198	0.5545	2.9752	0.5620

Table 4: Analysis of Dose-Mortality Trend for Female Mice (Pooled Control vs. Treatment)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.2237	0.9737	0.2476	0.9696
Depart from Trend				
Dose-Mortality Trend	1.4681	0.2256	1.5340	0.2155
Homogeneity	1.6918	0.7922	1.7816	0.7758

Tumor data analysis:

Upon consultation with the pharmacology reviewer, the placebo control and the vehicle control were pooled together for tumor incidence analysis. The tumor incidence rates and the tumor types with asymptotic p -values less than 0.05 for dose-response relationships are listed in Table 5 for female mice. Any tumor incidence rates with asymptotic p -values greater than 0.05 were not reported. Scores used were 0, 0, 150, 450, and 900 (equivalent to the dose levels) for the placebo control, vehicle control, low, medium, and high dose groups, respectively in male and female mice. The time intervals used were 0 – 52, 53 – 78, 79-91, 92-103 weeks and terminal sacrifice. Based on the result from the original data (shown in Table 5), on the basis of the Division's p -value adjustment rule, a significant positive dose-related adenoma (antrum) tumor trend was found in the stomach in female mice ($p = 0.0088$). Additional pair-wise analyses between pooled control and treatment groups were conducted on female mice. The results from pair-wise analyses showed significant difference between the pooled control and the high dose group with regards to tumor incidence in the stomach ($p = 0.0427$).

Table 5: Tumor Incidence Rates (Female Mice) with *P*-values (Asymptotic Method) Less Than 0.05, Based on Original Data

Organ Name	Tumor Name	Overall tumor type	Tumor rate as PCT in control group	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)
STOMACH	ADENOMA (ANTRUM)	Incidental	0.00	0	0	0	0	3	0.0088 < 0.025

As per request by the pharmacology reviewer, re-analyses of tumor trends were carried out based on the following:

1. combination of tumors within some organ
2. combination of organs within some tumors

In Female Mice, organs chosen to be combined within tumor were duodenum, muscle, and bone with osteosarcoma tumor; uterus and mediastinum with haemangiosarcoma tumor; colon and uterus with leiomyoma tumor; and stomach and skin with squamous cell papilloma.

On the other hand, tumors chosen to be combined within organ were Adenoma-pars intermedia, adenoma-pars distalis and carcinoma- pars distalis in the Pituitary Organ; hepatocellular carcinoma and hepatocellular adenoma in the Liver organ; and bronchioloalveolar adenoma and bronchioloalveolar adenocarcinoma in the Lung/Bronchi organ.

In Male mice, organs chosen to be combined within tumor were: L N Mesenteric, liver and spleen with haemangioma; and liver and spleen with haemangiosarcoma.

Tumors chosen to be combined within organ were: Haemangioma and haemangiosarcoma in the spleen; hepatocellular adenoma and hepatocellular carcinoma in the liver; bronchioloalveolar adenoma and bronchioloalveolar carcinoma in the lungs/bronchi; and cortical adenoma, cortical adenoma-polygonal and cortical adenoma-fusiform in the adrenals.

The result after combining tumors or combining organs did not change the conclusion. It showed positive dose-related trend on adenoma (antrum) of the stomach organ ($p = 0.0088$), and none of those combined organs or combined tumors were found to be significant.

Meanwhile, no significant positive tumor trend was observed in the male mice with or without combination.

Reviewer's Conclusion

Adenoma (antrum) of the stomach organ is found to have statistically significant positive trend indicating a positive carcinogenic potential in female mice.

Evaluation of the validity of the study design

In light of the criteria presented in the Statistical Analysis section of this review, we will now investigate the validity of the experimental design of the mouse carcinogenicity study. Male mice will be the focus in this section because of its negative findings (i.e. no significant tumor found). Table 6 presents the summary of survival data of mice in the high dose group. Based on the survival criterion Haseman proposed, it could be concluded that enough male mice (i.e. more than 50% survival between weeks 80 to 90) were exposed to the drug for a sufficient amount of time.

In Tables 7A and 7B, we present the summary of body weight gains data in the Male mice study. The result shows that relative to the controls, the high dose group had 22% decrement in body weight gain. This is 12% more than the criteria set by Chu, Cueto and Ward, thus it appears that the high dose group is over MTD level. In addition, Table 2 shows that the mortality rate in the high dose group (900 µg/kg/day) was slightly higher than the two control groups in Male Mice. The results of mortality data alone suggest that the high dose group has achieved the MTD (maximum tolerated dose) level.

Table 6: Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

Sex	Percentage of survival			
	End of 52 weeks	End of 78 weeks	End of 91 weeks	End of 103 weeks
Male	98.0	92.0	86.0	84.0

Table 7A: Mean Body Weight (gms) for Male Mice

Group	Male Mice		
	Day 0 of Study	End of Study	Weight Gain
Control 1	21.9	42.0	20.1
Control 2	21.9	38.8	16.8
Control (Average)	21.9	40.4	18.5
Low	21.4	38.6	17.2
Medium	21.8	37.2	15.5
High	21.6	35.9	14.4

Table 7B: Percent Difference in Mean Body Weight Gain from Concurrent Controls

Group	% of control Male
Low	7
Medium	16
High	22

2. Study in Rats (Reference No. 176_e99)

Survival Analysis

The intercurrent mortality data is shown in Table 8 for male and female rats. From Table 8, it shows that in male rats, survival rates decrease as doses increase, such that the highest dose group (6.25 mg/m³) had the lowest rate of survival among all the treatment groups. Meanwhile, there is no clear pattern between the survival rate and dosing level in female rats, but rather, there is curiously lower mortality rate in the high dose group compared to the other dose groups.

Table 8: The intercurrent mortality data for male and female rats

Week	Clean Air Control		Vehicle Control		1.0 mg/m ³		2.5 mg/m ³		6.25 mg/m ³	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
MALE RATS										
0 – 52	1	1.9	1	1.9	2	3.7	0	0.0	0	0.0
53 – 78	1	3.7	4	9.3	1	5.6	0	0.0	3	5.6
79 – 91	2	7.4	2	13.0	1	7.4	1	1.9	1	7.4
92 – 103	4	14.8	6	24.1	1	9.3	6	13.0	4	14.8
Terminal Sacrifice	46	85.2	41	75.9	49	90.7	47	87.0	46	85.2
FEMALE RATS										
0 – 52	1	1.8	2	3.6	0	0.0	1	1.8	1	1.8
53 – 78	5	10.7	7	16.1	5	8.9	5	10.7	3	7.1
79 – 91	6	21.4	1	17.9	5	17.9	5	19.6	3	12.5
92 – 103	4	28.6	7	30.4	7	30.4	5	28.6	4	19.6
Terminal Sacrifice	40	71.4	39	69.6	39	69.6	40	71.4	45	80.4

The Kaplan-Meier curves for death rate are presented in Figures 3 and 4 for male and female rats, respectively. The survival curves were not different among the treatment groups in both male and female rats.

Figure 3: Kaplan-Meier survival curve for Male Rats

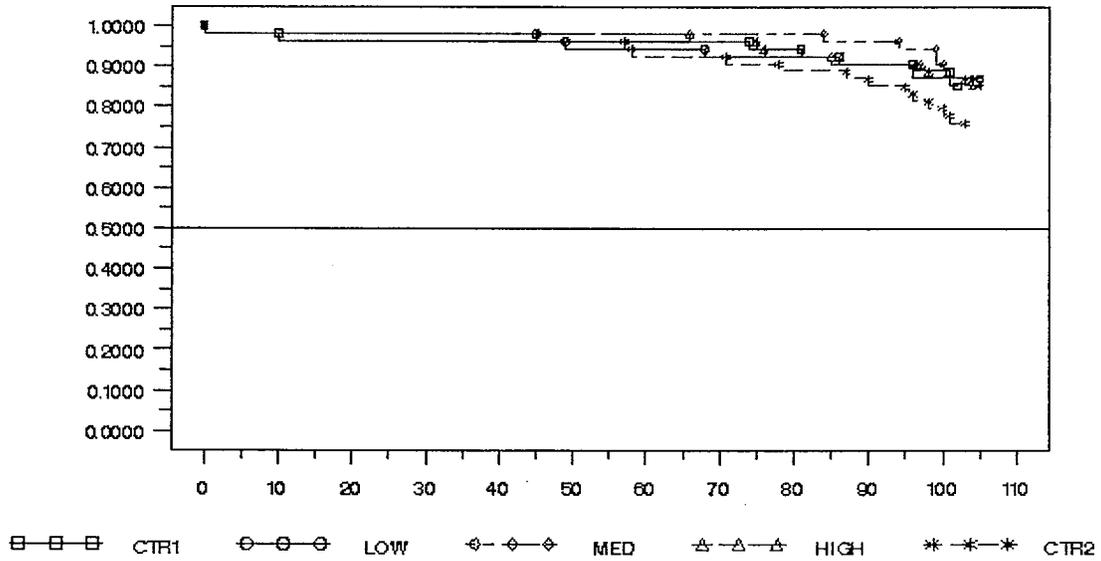
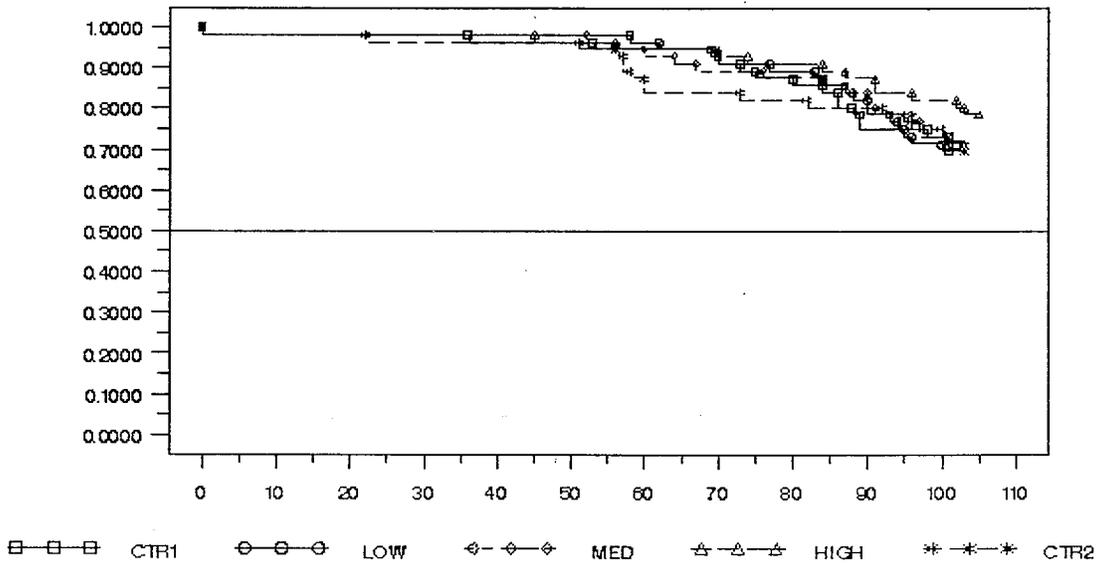


Figure 4: Kaplan-Meier survival curve for Female Rats



The homogeneity of survival and dose mortality trends were tested separately for male and female rats and the results are presented in Tables 9 and 10, respectively. Note that for these tests, the two control groups were pooled together. The results showed that no significant differences in survivals across treatment groups were evident in male or female mice. In addition, the dose-mortality trends in both male and female mice were not statistically significant.

Table 9: Analysis of Dose-Mortality Trend for Male RATS (Pooled Control vs. Treatment)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	4.8928	0.1798	4.8640	0.1820
Dose-Mortality Trend	0.3260	0.5680	0.3728	0.5415
Homogeneity	5.2188	0.2656	5.2368	0.2639

Table 10: Analysis of Dose-Mortality Trend for Female RATS (Pooled Control vs. Treatment)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	0.2225	0.9739	0.1968	0.9781
Dose-Mortality Trend	2.0385	0.1534	2.1285	0.1446
Homogeneity	2.2611	0.6879	2.3253	0.6762

Tumor data analysis

Similar to the mouse study, the untreated (clean-air) control and the vehicle control are pooled together for tumor incidence analysis. The tumor incidence rates and the tumor types with asymptotic *p*-values less than 0.05 for dose-response relationships are listed in Table 11 for male rats and Table 12 for female rats. Any tumor incidence rates with asymptotic *p*-values greater than 0.05 are not reported. Scores used were 0, 0, 1.0, 2.5, and 6.25 (equivalent to the dose levels) for the clean-air control, vehicle control, low, medium, and high dose groups, respectively in male and female rats. The time intervals used were 0 – 52, 53 – 78, 79 – 91, 92 – 104 weeks and terminal sacrifice. As shown in both Tables 11 and 12, on the basis of the Division's *p*-value adjustment rule, no significant positive trend was observed in male or female rats.

Table 11: Tumor Incidence Rates (Male RATS) with *P*-values (Asymptotic Method) Less Than 0.05, Based on the Original Data

Organ Name	Tumor Name	Overall tumor type	Tumor rate as PCT. in control group	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)
ADRENALS	GANGLIONEUROMA	Incidental	0.00	0	0	0	0	1	0.1790 > 0.025
HEART	Metastasizing endocardial SCHW	Incidental	0.00	0	0	0	0	1	0.1790 > 0.025
MESENTERY	LIPOMA	Incidental	0.00	0	0	0	0	1	0.1790 > 0.025
PITUITARY	Pars distalis ADENOMACARCINOMA	Incidental	0.00	0	0	0	0	1	0.1790 > 0.025
SKIN	MALIGNANT FIBROUS HISTIOCYTOMA	Fatal	0.00	0	0	0	0	1	0.1855 > 0.025

Table 12: Tumor Incidence Rates (Female RATS) with *P*-values (Asymptotic Method) Less Than 0.05, Based on the Original Data

Organ Name	Tumor Name	Overall tumor type	Tumor rate as PCT. in control group	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)
ADRENALS	CORTICAL ADENOCARCINOMA [M]	Incidental	0.00	0	0	0	0	1	0.1935 > 0.025
ADRENALS	PHAEOCHROMOCYTOMA [B]	Incidental	0.00	0	0	0	0	1	0.1874 > 0.025
LIVER	CHOLANGIOMA [B]	Incidental	0.00	0	0	0	0	1	0.1896 > 0.025
OVARIES	Uni-lateral GRANULOSA CELL TUM	Fatal	0.00	0	0	0	0	1	0.2036 > 0.025
OVARIES	GRANULOSA CELL TUMOUR [B]	Incidental	0.00	0	0	0	0	1	0.1981 > 0.025
RECTUM	GRANULAR CELL TUMOUR [B]	Incidental	0.00	0	0	0	0	1	0.1975 > 0.025
SKIN	SEBACEOUS CARCINOMA [M]	Fatal	0.00	0	0	0	0	1	0.1993 > 0.025

As per request by the pharmacology reviewer, re-analyses of tumor trends were carried out based on the following:

1. combination of tumors within some organ
2. combination of organs within some tumors

In Female rats, organs chosen to be combined within tumor were mesenterial lymph nodes, skin and uterus with haemangiosarcoma; and skin and uterus with schwannoma.

On the other hand, tumors chosen to be combined within organ were: Granulosa cell tumor, uni-lateral granulosa cell tumor and thecoma of the ovaries; multiple endometrial stromal polyps and endometrial stromal polyps of the uterus; papillary adenoma(ta) and endometrial adenocarcinoma of the uterus; uni-lateral medullary tumor and phaeochromocytoma of the adrenals; cortical adenocarcinoma and uni-lateral cortical adenocarcinoma of the adrenals; par distalis adenocarcinoma, multiple par distalis adeno ma(ta) and par distalis adenoma(ta) of the pituitary; c-cell carcinoma and c-cell adenoma of the thyroid; and lastly multiple adenoma(ta) and uni-lateral adenoma(ta) of the parathyroids.

In Male rats, organs chosen to be combined within tumor were: cerebrum and cerebellum with mixed glioma; mesentery, mesenterial lymph nodes and skin with haemangioma, cerebrum and cerebellum with granular cell tumor; mammary glands and glandular stomach with adenomacarcinoma tumor; and mesentery and skin with lipoma tumor.

Tumors chosen to be combined within organ were: c-cell adenoma and multiple c-cell adenoma(ta) of the thyroid; par distalis adenocarcinoma, multiple par distalis adenocarcinoma and par distalis adenoma(ta) of the pituitary; haemangioma and multiple haemangioma of the mesenterial lymph nodes; uni-lateral medullary tumor, multiple phaeochromocytoma and phaeochromocytoma of the adrenals; cortical adenocarcinoma and uni-lateral cortical adenoma of the adrenals; multiple leydig cell adenoma(ta) and uni-lateral leydig cell adenoma of the testes; islet cell adenoma and acinar islet-cell adenoma of the pancreas; and lastly, hepatocellular adenoma and hepatocellular carcinoma of the liver.

The result after combining tumors or combining organs did not change the conclusion. It showed no significant positive dose-related trend in male or female rats.

Reviewer's Conclusion

Based on the Reviewer's analysis, no significant trend for female rats on pituitary, adenoma, pars distalis was found contrary to the Sponsor's report. In addition, no significant tumor trend was found in male rats.

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Evaluation of the validity of the study design

In light of the criteria presented in the Statistical Analysis section method of this review, we will now investigate the validity of the experimental design of the rat carcinogenicity study. Table 13 presents the summary of survival data of rats in the high dose group. Based on the survival criterion Haseman proposed, it could be concluded that enough rats in both sexes were exposed to the drug for a sufficient amount of time.

Tables 14A and 14B present the summary of body weigh gains data in the rats study. The result shows that relative to the controls, the female rats in the high dose group had 34% decrement in body weight gain, while the male rats in the high dose group had 38% reduction in body weight gain. The bodyweight decrements in both male and female high dose groups showed that the high dose is over the maximum tolerated dose level (MTD). However, lower mortality rates at the highest dose groups were observed relative to the controls in male and female rats.

In conclusion, as observed from the body weight data, the high dose level used by both sexes exceeded the MTD level. However, the evaluation based on mortality data yielded opposite results. Therefore, other clinical signs and histopathological toxic effects should be considered in the evaluation of the adequacy of the doses used.

Table 13: Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

Percentage of survival				
Sex	End of 52 weeks	End of 78 weeks	End of 91 weeks	End of 103 weeks
Male	100.0	94.4	92.6	85.2
Female	98.2	92.9	87.5	80.4

Table 14A: Mean Body Weight (gms) for Male and Female Rats

Group	Male Rats			Female Rats		
	Day 0 of Study	End of Study	Weight Gain	Day 0 of Study	End of Study	Weight Gain
Control 1	230.6	506.3	275.7	160.0	287.6	127.6
Control 2	232.6	476.7	244.1	161.2	291.6	130.4
Control (Average)	231.6	491.5	259.9	160.6	289.6	129.0
Low	231.6	475.3	243.7	159.3	274.6	115.3
Medium	232.5	446.7	214.2	159.1	269.4	110.3
High	235.4	405.8	170.4	158.9	239.0	80.1

Table 14B: Percent Difference in Mean Body Weight Gain from Concurrent Controls

Group	% of control Male	% of control Female
Low	6	11
Medium	18	14
High	34	38

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