

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-949**

**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES  
OFFICE OF BIostatISTICS

## Statistical Review

NDA: 21,949  
Drug Name : Pulmicort Turbuhaler M3  
Indication: Asthma  
Applicant: AstraZeneca  
Dates: Electronic submission dated 09/12/2005  
Biometrics Division: Division of Biometrics II (HFD-715)  
Statistical reviewers: James Gebert, Ph.D.  
Concurring Reviewer: Ruthanna C. Davi, M.S., Statistics Team Leader  
Medical Division: Division of Allergy and Pulmonary Drug Products  
(HFD-570)  
Clinical reviewer: J. Kaiser, M.D.  
Medical Team Leader: P. Starke, M.D.  
Project manager: C. Jackson  
Keywords: Clinical studies, NDA review

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The following statistical issues were identified and resolved as part of this review.

- When this reviewer was attempting to duplicate some of the sponsor results for study SD-004-0620 in an analysis of differing amounts of Pulmicort put into the reservoir, he found that the sponsor had incorrect values for the CONTENT variable. The sponsor was asked to provide a new file \_PULM02 which contained the correct values for the CONTENT variable for the M3 devices. This was supplied in the sponsor's 2005-12-19 submission. That new submission also contained some corrected tables which are used in this review.
- For study SD-004-0620, this reviewer was able to duplicate the sponsor's analyses of the primary efficacy variables and selected secondary variables from datafiles supplied with the submission. With the new CONTENT variable in datafile \_PULM02 for Study SD-004-0620 in the 2005-12-19 submission, this reviewer was able to verify the sponsor's analyses of data before and after the increase in the amount of Pulmicort added to the reservoir of the 180 mcg M3 device and that data indicated that the slight increase in the delivered dose for subjects in the US centers enrolled after July of 2003 appeared to numerically favor the higher content for all of the primary and secondary parameters.
- Of the 621 subjects enrolled in study SD-004-0620, 185 subjects discontinued treatment early. The main reason for discontinuation was for study-specific discontinuation criteria. The withdrawal rate was highest in the placebo group (48.4%) and the percentage of subjects withdrawing in the Pulmicort Turbuhaler M3 180 mcg QD group (31.7%) was higher than the other active groups ranging from (28.2% to 19.2%). Qualitative conclusions from the analyses of the primary efficacy endpoint using the observed data alone were consistent with those from the analyses of the primary efficacy group using a LOCF approach.
- Of the 516 subjects enrolled in study SD-004-0726, 106 subjects discontinued treatment early. The main reason for discontinuation was for study-specific discontinuation criteria. The withdrawal rate was highest in the placebo group (23.6%) although there was not much difference between treatment groups (16.7% to 23.6%). Qualitative conclusions from the analyses of the primary efficacy endpoint using the observed data alone were consistent with those from the analyses of the primary efficacy group using a LOCF approach.

## 2. Introduction

### 2.1 OVERVIEW

#### 2.1.1 STUDY SD-004-0620

SD-004-0620 was a double-blind, placebo-controlled, randomized, parallel group, multicenter trial with a 5 to 40 day run-in period and a 12-week randomized treatment period in adults with asthma who had a recent history that included the use of oral inhaled corticosteroids for at least 3 months before a screening visit. The treatment groups were Pulmicort Turbuhaler M3, 360 mcg BID and 180 mcg QD, Pulmicort M0-ESP, 400mcg BID and 200 mcg QD, and a combined Placebo group (i.e., a pooling of the four placebo groups each one of which was designed to match one of the four active treatments). This study used the 180 mcg M3 device to provide the M3 doses.

There were 85 centers geographically spread over the USA and Asia.

During this study, the US clinical sites used drug supplies of Pulmicort Turbuhaler M3 that had 2 slightly different budesonide reservoir contents. The difference in the contents was the budesonide lactose blend contained in the powder reservoir of the inhaler resulting in a slight increase in the delivered dose for subjects in the US centers enrolled after July of 2003. The average delivered dose was 98.8% of the target dose in the batches manufactured prior to the change and 100.5% of the target dose in the batches

## 2.1.1 STUDY SD-004-0726

Study SD-004-0726 was similar in design to Study SD-004-0620 with the following exceptions:

- It was in children and adolescents 6-17 years of age.
- The targeted sample size was 460 subjects, 92 per treatment group.
- The primary efficacy variable was change from baseline in percent predicted FEV<sub>1</sub> averaged over the treatment period.
- This study used the 90 mcg M3 device to give the M3 doses.

## 2.2 Data Sources

The data for this submission were contained in CDSESUB1\N21949\N\_000\2005-09-12 and CDSESUB1\N219489\N\_00\2005-12-19 which included a file \_PULM02 for Study SD-004-0620 with corrected CONTENT data for the M3 devices.

## 3. Statistical Evaluation

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study SD-004-0620

There were 621 subjects randomized into this study at 74 US centers (450 subjects) and 16 Asian centers (171 subjects). Of the 621 subjects randomized, subjects were assigned to treatment as follows: 130 subjects to Pulmicort Turbuhaler M3 at 360 mcg BID, 130 subjects to Pulmicort Turbuhaler M0-ESP at 400 mcg BID, 123 subjects to Pulmicort Turbuhaler M3 at 180 mcg QD, 114 subjects to Pulmicort Turbuhaler M0-ESP at 200 mcg QD, and 124 subjects to placebo. Of these 621 subjects, 185 subjects discontinued treatment. The main reason for discontinuation was for study-specific discontinuation criteria. The overall withdrawal rate was highest in the placebo group (48.4%). The percentage of subjects withdrawing in the Pulmicort Turbuhaler M3 180 mcg QD group (31.7%) was higher than the other active groups ranging from (28.2% to 19.2%).

There were 621 randomized subjects. Six hundred twelve subjects were included in the sponsor's modified ITT (MITT) analysis set. The reason that the nine (1%) subjects were excluded from the MITT analysis set was because no data were available for these subjects for at least 1 efficacy endpoint. Thirteen (2%) additional subjects were excluded leaving 599 (96%) subjects in the sponsor's primary efficacy analysis because they lacked data for that analysis. A total of 174 (28%) subjects had protocol deviations that led to exclusion from the PP analysis set leaving 447 (72%) in that analysis group. The rates of exclusion of subjects from each of the analysis groups were approximately balanced across treatment groups.

During the course of the study it was identified that e-diary data (night awakenings, rescue medication use, albuterol use) was not transmitted for 41 subjects at the 7 Indonesian sites. Information collected from paper diaries completed by the subjects was entered into a spreadsheet; however, the sponsor stated that the data generated by this process was inconsistent with the data collection standards for this study and made the data unusable. Under instruction from AstraZeneca all of these subjects enrolled or in screening were discontinued. In addition, all data collected by these sites was reviewed and assessed to ensure validity. Sites were retrained in proper diary data and collection procedures. Of the 41 Indonesian patients randomized, 39 were in the ITT population and 25 were in the PP population (those Indonesian subjects excluded from the PP analysis were excluded using the same criteria applied to the US subjects per the Statistical Analysis Plan). All subjects were included in the safety population.

In the primary efficacy analysis group, the treatment groups were generally well-balanced in demographic and baseline characteristics including pulmonary function.

To assess treatment response among the subjects who took placebo, the 4 placebo treatment groups were compared for change in FEV<sub>1</sub> from baseline to average over the treatment period (i.e., the primary efficacy variable). The FEV<sub>1</sub> mean changes from baseline for each of the placebo groups were as follows: 0.19 L and -0.02 L for the placebo Pulmicort Turbuhaler M0-ESP 200 mcg QD group and placebo Pulmicort Turbuhaler M3 180 mcg QD group, respectively; 0.11 L and 0.18 L for the placebo Pulmicort Turbuhaler M0-ESP 400 mcg BID group and placebo Pulmicort Turbuhaler M3 360 mcg BID group, respectively. The p-value comparing Placebo groups was 0.10 from a one-way ANOVA and therefore all placebo groups were pooled for the primary efficacy analysis.

Tables S1 and S2 of the sponsor provide the LS mean changes for the treatment groups and the LS means and p-values of the treatment differences for the major comparisons of this study. The primary efficacy comparisons appear in the shaded region.

**Table S1 Treatment means for treatment-period change in FEV<sub>1</sub> (LOCF, primary efficacy analysis group)**

Treatment	N	FEV <sub>1</sub> mean (SE)		(From ANCOVA)			
		Population Study SD-004-0620		LSmean			
		Baseline	Treatment period	Change	change	SE	95% CI
Pulmicort TBH M3 360 mcg BID	128	2.14 (0.05)	2.44 (0.06)	0.30 (0.02)	0.28	0.029	0.22 to 0.34
Pulmicort TBH M0-ESP 400 mcg BID	128	2.15 (0.05)	2.52 (0.06)	0.36 (0.03)	0.34	0.029	0.29 to 0.40
Pulmicort TBH M3 180 mcg QD	119	2.09 (0.05)	2.29 (0.06)	0.19 (0.02)	0.18	0.030	0.12 to 0.24
Pulmicort TBH M0-ESP 200 mcg QD	110	2.19 (0.06)	2.46 (0.07)	0.27 (0.03)	0.25	0.031	0.19 to 0.31
Placebo <sup>a</sup>	114	2.14 (0.05)	2.26 (0.06)	0.12 (0.03)	0.10	0.031	0.04 to 0.16

<sup>a</sup> All placebo groups combined.

ANCOVA Analysis of covariance; CI Confidence interval; FEV<sub>1</sub> Forced expiratory volume in 1 second; LOCF Last observation carried forward; LSmean Least squares mean; SE Standard Error of the mean; TBH Turbuhaler Pulmicort Turbuhaler M3, new device. Pulmicort Turbuhaler M0-ESP, current device.  
Data derived from Table 11.2.1.2.1, Section 11.2.

**Table S2 Treatment comparisons of treatment-period change in FEV<sub>1</sub>: ANCOVA results (LOCF), primary efficacy analysis group)**

Comparison	LSmean			
	difference	SE	95% CI	p-value
Pulmicort TBH M3 360 mcg BID – Pulmicort TBH M0-ESP 400 mcg BID	-0.06	0.04	-0.14 to 0.02	0.117
Pulmicort TBH M3 180 mcg QD – Pulmicort TBH M0-ESP 200 mcg QD	-0.07	0.042	-0.16 to 0.01	0.089
Pulmicort TBH M3 360 mcg BID – placebo <sup>a</sup>	0.18	0.041	0.1 to 0.26	<0.001
Pulmicort TBH M3 180 mcg QD – placebo <sup>a</sup>	0.07	0.042	-0.01 to 0.16	0.078
Pulmicort TBH M0-ESP 400 mcg BID – placebo <sup>a</sup>	0.24	0.041	0.16 to 0.32	<0.001
Pulmicort TBH M0-ESP 200 mcg QD – placebo <sup>a</sup>	0.15	0.043	0.06 to 0.23	<0.001

<sup>a</sup> All placebo groups combined.

ANCOVA Analysis of covariance; CI Confidence interval; FEV<sub>1</sub> Forced expiratory volume in 1 second; LOCF Last observation carried forward; LSmean Least squares mean; SE Standard Error of the mean; TBH Turbuhaler Pulmicort Turbuhaler M3, new device. Pulmicort Turbuhaler M0-ESP, current device.  
Data derived from Table 11.2.1.2.1, Section 11.2.

The Pulmicort Turbohaler M3 360 mcg BID group was significantly different from placebo whereas the Pulmicort Turbohaler M3 180 mcg QD group was not significantly different from placebo (p=0.078). The difference between the Pulmicort Turbohaler M3 180 mcg QD and placebo was only 0.07 L which was much less than the 0.23 L assumed in the sample size calculations. Similar results were seen in the analysis of change from baseline of FEV<sub>1</sub> averaged over the treatment period from the observed data with no carrying forward of data.

There was a significant region effect with the Asia mean change 0.19 L and the U.S. mean change of 0.27 L (p=0.009). The Region-by-treatment interaction was not significant, p=0.37 indicating that although the magnitude of the treatment effect differed across regions, the direction of the effect was consistent. The US least squares mean change was higher for all groups than the Asian least squares mean change except for the 180 mcg QD groups.

In terms of secondary endpoints, statistically significant improvements for both M3 dose groups relative to placebo were seen in changes from baseline averaged over the treatment period for diary variables morning and evening PEF, day and night asthma symptom scores and total albuterol use.

Tables 45 and 46 of the sponsor (correction tables in December 16, 2005 submission U.S. sites only) provide mean changes from baseline and differences in mean changes for the two different reservoir fill groups for the 180 mcg QD and 360 mcg BID treatment groups. Adding more budesonide in the reservoir numerically favored the high content dose for all of these parameters.

**Table 45**

**Comparison of PULMICORT TURBUHALER M3 180 mcg QD groups**

Variable	Change from baseline	Change from baseline	Difference in change from baseline
FEV <sub>1</sub> (L)	0.14	0.28	0.13
Night asthma symptoms	-0.34	-0.45	-0.11
Day asthma symptoms	-0.39	-0.45	-0.06
Morning PEF	3.8	16.4	12.6
Evening PEF	1.3	12.2	10.9
Albuterol use	-0.81	-1.32	-0.51

FEV<sub>1</sub> Forced expiratory volume in 1 second; PEF Peak expiratory flow.

b(4)

**Table 46**

**Comparison of PULMICORT TURBUHALER M3 360 mcg BID groups**

Variable	Change from baseline	Change from baseline	Difference in change From baseline
FEV <sub>1</sub> (L)	0.30	0.38	0.09
Night asthma symptoms	-0.29	-0.51	-0.22
Day asthma symptoms	-0.36	-0.69	-0.36
Morning PEF	9.0	34.5	25.5
Evening PEF	7.5	22.0	14.5
Albuterol use	-1.46	-1.67	-0.21

FEV<sub>1</sub> Forced expiratory volume in 1 second; PEF Peak expiratory flow.

b(4)

Table 47 provides the mean changes in the primary efficacy variable within each of the treatment groups for subject enrolled before versus after the amount of Pulmicort added to the reservoir was increased. Numeric increases in the primary efficacy endpoint were seen in all M3 groups including the placebo group.

**Table 47**

**Treatment means for treatment period change in FEV<sub>1</sub> (L) (LOCF), ITT**

Treatment	N	FEV <sub>1</sub> , mean (SE)		
		Baseline	Period	Change
PULMICORT TBH M3 360 mcg BID	54	2.26(0.07)	2.56 (0.09)	0.30 (0.03)
PULMICORT TBH M3 360 mcg BID	39	2.25 (0.09)	2.63 (0.11)	0.38 (0.05)
PULMICORT TBH M3 180 mcg BID	51	2.18 (0.07)	2.32 (0.09)	0.14 (0.04)
PULMICORT TBH M3 180 mcg BID	34	2.26 (0.08)	2.54 (0.09)	0.28 (0.04)
Placebo	42	2.30 (0.08)	2.40 (0.10)	0.10 (0.05)
Placebo	39	2.12 (0.07)	2.31 (0.10)	0.19 (0.07)

**b(4)**

SE Standard error of the mean; TBH TURBUHALER.  
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.  
Placebo  Placebo used during the period of the study in which the  mg budesonide per gram of product of PULMICORT TURBUHALER M3 was used.  
Placebo  Placebo used during the period of the study in which the  mg budesonide per gram of product of PULMICORT TURBUHALER M3 was used.

**3.1.2 Study SD-004-0726**

There were 516 subjects randomized into this study at 54 US centers (347 subjects) and 14 Asian centers (169 subjects). Of the 516 subjects randomized, subjects were assigned to treatment as follows: 96 subjects to Pulmicort Turbuhaler M3 at 360 mcg BID, 102 subjects to Pulmicort Turbuhaler M0-ESP at 400 mcg BID, 108 subjects to Pulmicort Turbuhaler M3 at 180 mcg QD, 104 subjects to Pulmicort Turbuhaler M0-ESP at 200 mcg QD, and 106 subjects to placebo. Of these 516 subjects, 106 subjects discontinued treatment. The main reason for discontinuation was for study-specific discontinuation criteria. The overall withdrawal rate was highest in the placebo group (23.6%) although there was not much difference between treatment groups (16.7% to 23.6%).

There were 516 randomized subjects. Five hundred four subjects were included in the sponsor's modified ITT (MITT) analysis set. The reason that the twelve (2%) subjects were excluded from the MITT analysis set was because no data were available for these subjects for at least 1 efficacy endpoint. Eleven (2%) additional subjects were excluded leaving 493 (96%) subjects in the primary efficacy analysis because they lacked data for this analysis. A total of 70 (14%) subjects had protocol deviations that led to exclusion from the per-protocol (PP) analysis set. An additional nine (2%) subjects were excluded leaving 437 (85%) in that PP analysis. The rates of exclusion of subjects from each of the analysis groups were approximately balanced across treatment groups.

In the primary efficacy analysis group, the treatment groups were generally well-balanced in demographic and baseline characteristics including pulmonary function.

To assess treatment response among the subjects who took placebo, the 4 placebo treatment groups were compared for change in % Predicted FEV<sub>1</sub> from baseline to average over the treatment period (i.e., the primary efficacy variable). The FEV<sub>1</sub> mean % changes from baseline for each of the placebo groups are as follows: 0.11 % and 1.81% for the placebo Pulmicort Turbuhaler M0-ESP 200 mcg QD group and placebo

Pulmicort Turbuhaler M3 180 mcg QD group, respectively; -0.54% and 0.24% for the placebo Pulmicort Turbuhaler M0-ESP 400 mcg BID group and placebo Pulmicort Turbuhaler M3 360 mcg BID group, respectively. The p-value comparing Placebo groups was 0.78 from a one-way ANOVA and therefore all placebo groups were pooled for the primary efficacy analysis.

Tables S1 and S2 of the sponsor provide the LS mean changes for the treatment groups and the p-values of the treatment differences for the major comparisons of this study. The primary efficacy comparisons appear in the shaded region.

**Table S1 Treatment means for treatment-period change in % Predicted FEV<sub>1</sub> (LOCF, primary efficacy analysis group) Study SD-004-0726**

Treatment	N	FEV <sub>1</sub> mean (SE)		(From ANCOVA)			
		Baseline	Treatment period	Change	LSmean change	SE	95%CI
Pulmicort Turbuhaler M3 360 mcg BID	90	84.16 (0.95)	89.98 (1.10)	5.82 (0.98)	5.57	0.83	3.94 to 7.20
Pulmicort Turbuhaler M0-ESP 400 mcg BID	98	86.60 (0.76)	90.69 (0.84)	4.09 (0.74)	4.44	0.80	2.88 to 6.01
Pulmicort Turbuhaler M3 180 mcg QD	103	84.65 (1.02)	87.34 (1.20)	2.68 (0.81)	2.55	0.78	1.03 to 4.08
Pulmicort Turbuhaler M0-ESP 200 mcg QD	101	84.43 (0.91)	87.31 (1.03)	2.89 (0.79)	2.69	0.79	1.1 to 4.24
Placebo <sup>a</sup>	101	84.45 (0.93)	84.82 (0.99)	0.37 (0.75)	0.19	0.79	-1.36 to 1.73

<sup>a</sup> All placebo groups combined.  
 LSmean Least squares mean. SE Standard error of the mean.  
 Pulmicort Turbuhaler M3, new device. Pulmicort Turbuhaler M0-ESP, current device.

**Table S2 Treatment comparisons of treatment-period % predicted FEV<sub>1</sub>: ANCOVA results (LOCF), primary efficacy analysis group**

Comparison	difference	LSmean	SE	95% CI	p-value
Pulmicort Turbuhaler M3 360 mcg BID – Pulmicort Turbuhaler M0-ESP 400 mcg BID		1.13	1.14	-1.11 to 3.36	0.323
Pulmicort Turbuhaler M3 180 mcg QD – Pulmicort Turbuhaler M0-ESP 200 mcg QD		-0.14	1.09	-2.28 to 2.00	0.897
Pulmicort Turbuhaler M3 360 mcg BID – placebo <sup>a</sup>		5.38	1.13	3.17 to 7.60	<0.001
Pulmicort Turbuhaler M3 180 mcg QD – placebo <sup>a</sup>		2.37	1.09	0.23 to 4.50	0.030
Pulmicort Turbuhaler M0-ESP 400 mcg BID – placebo <sup>a</sup>		4.26	1.10	2.09 to 6.43	<0.001
Pulmicort Turbuhaler M0-ESP 200 mcg QD – placebo <sup>a</sup>		2.51	1.09	0.36 to 4.66	0.022

<sup>a</sup> All placebo groups combined.  
 LSmean Least squares mean. SE Standard error of the mean.  
 Pulmicort Turbuhaler M3, new device. Pulmicort Turbuhaler M0-ESP, current device.

Both the Pulmicort M3 180 mcg QD and Pulmicort M3 360 mcg BID groups were significantly different from the combined placebo group in mean changes from baseline in % predicted FEV<sub>1</sub> averaged over the treatment period (p<0.001 and p=0.030, respectively). Similar results were seen in the analysis of the % predicted FEV<sub>1</sub> averaged over the treatment period from the observed data with no carrying forward of the data.

Unlike Study SD-004-0620, the region effect was not significant with the Asia mean change of -1.56% and the U.S. mean change of 1.35%. ( $p=0.089$ ) indicating that the magnitude of the treatment effect was not significantly different across regions. Like Study SD-004-0620, the direction of the treatment effect was consistent across regions.

In terms of secondary endpoints, statistically significant improvements for the 360 mcg BID group relative to placebo were seen in changes from baseline in morning and evening PEF<sub>R</sub> averaged over the treatment period.

### 3.2 Evaluation of Safety

No specific safety endpoints or hypotheses were identified by the medical division for formal statistical exploration. The reader is referred to the clinical review of this application for a discussion of the safety of the product.

## 4. Findings in special /subgroup Populations

### 4.1 Gender/Age/Race

This program has not been designed to allow for extensive subpopulation analyses. Efficacy was demonstrated in adults in Study SD-004-0620 and in children and adolescents in Study SD-004-0726. However, the ability to identify differences in other subgroups was limited. The sponsor provided summary statistics of the primary efficacy variable for males and females, race groups for both studies and for age groups (6-11 and 12 to 17) in Study SD-004-0726. The treatment mean changes for the subgroups were fairly consistent with the overall treatment means of the primary efficacy variables when the sample size was large enough.

Table 19 of the sponsor provides the treatment differences for the pediatric children and adolescents. No major differences are apparent.

**Table 19 Treatment comparisons by age group for treatment-period % predicted FEV<sub>1</sub> (LOCF): primary efficacy analysis group**

Comparison	Age group	Treatment Group Difference
PULMICORT TURBUHALER M3 360 mcg bid – PULMICORT TURBUHALER M0-ESP 400 mcg bid	6 to 11	0.1
	12 to 17	3.1
PULMICORT TURBUHALER M3 180 mcg qd – PULMICORT TURBUHALER M0-ESP 200 mcg qd	6 to 11	0.6
	12 to 17	-1.0
PULMICORT TURBUHALER M3 360 mcg bid – placebo <sup>a</sup>	6 to 11	4.1
	12 to 17	6.6
PULMICORT TURBUHALER M3 180 mcg qd – placebo <sup>a</sup>	6 to 11	1.9
	12 to 17	2.5
PULMICORT TURBUHALER M0-ESP 400 mcg bid – placebo <sup>a</sup>	6 to 11	4.1
	12 to 17	3.5

PULMICORT TURBUHALER M0-ESP 200 mcg qd – placebo <sup>a</sup>	6 to 11	1.4
	12 to 17	3.5

<sup>a</sup> All placebo groups combined.

LOCF Last observation carried forward. PULMICORT TURBUHALER M3, new PULMICORT device. TURBUHALER M0-ESP, current device.

## 4.2 Other Special/Subgroup Populations

No special populations were studied.

## 5. Summary and Conclusions

### 5.1 Statistical Issues and Collective Evidence

Upon review, the following statistical issue was identified and remains unresolved.

- Although the sponsor states the primary purpose of the studies was to compare the M3 and M0-ESP devices, the studies were not sufficiently designed to assess whether the M3 and M0-ESP devices are statistically similar within a pre-specified minimum clinically important difference in a formal statistical way. Interpretation of the confidence intervals for the differences in the M3 and M0-ESP treatment groups relies on post-hoc clinical judgment as the studies were not designed to meet a formal noninferiority objective and no noninferiority margin was pre-specified.

The following statistical issues were identified and resolved as part of this review.

- When this reviewer was attempting to duplicate some of the sponsor results for study SD-004-0620 in an analysis of differing amounts of Pulmicort put into the reservoir, he found that the sponsor had incorrect values for the CONTENT variable. The sponsor was asked to provide a new file \_PULM02 which contained the correct values for the CONTENT variable for the M3 devices. This was supplied in the sponsor's 2005-12-19 submission. That new submission also contained some corrected tables which are used in this review.
- For study SD-004-0620, this reviewer was able to duplicate the sponsor's analyses of the primary efficacy variables and selected secondary variables from datafiles supplied with the submission. With the new CONTENT variable in datafile \_PULM02 for Study SD-004-0620 in the 2005-12-19 submission, this reviewer was able to verify the sponsor's analyses of data before and after the increase in the amount of Pulmicort added to the reservoir of the 180 mcg M3 device and that data indicated that the slight increase in the delivered dose for subjects in the US centers enrolled after July of 2003 appeared to numerically favor the higher content dose for the primary and all secondary parameters.
- Of the 621 subjects enrolled in study SD-004-0620, 185 subjects discontinued treatment early. The main reason for discontinuation was for study-specific discontinuation criteria. The withdrawal rate was highest in the placebo group (48.4%) and the percentage of subjects withdrawing in the Pulmicort Turbohaler M3 180 mcg QD group (31.7%) was higher than the other active groups ranging from (28.2% to 19.2%). Qualitative conclusions from the analyses of the primary efficacy endpoint using the observed data alone were consistent with those from the analyses of the primary efficacy group using a LOCF approach.

Of the 516 subjects enrolled in study SD-004-0726, 106 subjects discontinued treatment early. The main reason for discontinuation was for study-specific discontinuation criteria. The withdrawal rate was highest in the placebo group (23.6%) although there was not much difference between treatment groups (16.7% to

23.6%). Qualitative conclusions from the analyses of the primary efficacy endpoint using the observed data alone were consistent with those from the analyses of the primary efficacy group using a LOCF approach.

## **5.2 Conclusions and Recommendations**

In Study SD-004-0762 both Pulmicort Turbuhaler M3 360 mcg BID and Pulmicort Turbuhaler M3 180 mcg QD were significantly better than placebo in changes from baseline in percent predicted FEV<sub>1</sub> averaged over the treatment period in children and adolescents. In Study SD-004-0620 Pulmicort Turbuhaler M3 360 mcg BID was significantly better than placebo in changes from baseline in treatment period average FEV<sub>1</sub> in adults. These studies found the Pulmicort Turbuhaler M3 devices to be numerically similar in effect to the Pulmicort Turbuhaler M0-ESP devices at the BID dosing; however, the studies were not sufficiently designed to assess whether the M3 and M0-ESP devices are statistically similar within a pre-specified minimum clinically important difference in a formal statistical way. Interpretation of the confidence intervals for the differences in the M3 and M0-ESP treatment groups relies on post-hoc clinical judgment as the studies were not designed to meet a formal noninferiority objective and no noninferiority margin was pre-specified.

This reviewer must leave to clinical judgment whether the recommended doses in the sponsor's label are appropriate given the present and past submissions. (e.g. a 180 mcg BID dose using the 90 mcg M3 device was not studied in this submission but a 200 mcg BID dose using the 100 mcg M0 was found to be effective when studied in the original M0 submission).

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