CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-441/S002

STATISTICAL REVIEW(S)

Hilfiker

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: SEP 28 1998

NDA#:	**20-441**
Applicant:	**Astra USA, Inc.**
Name of Drug:	**Pulmicort Turbuhaler Once Daily (budesonide administered via Turbuhaler)**
Indication:	**Asthma**
Documents Reviewed:	**10/9/97; electronic data 10/9/97**
Statistical Reviewer:	**Barbara Elashoff, M.S.**
Medical Input:	**Mary Purucker, M.D.**

Summary of Pulmicort Once-Daily

- The sponsor submitted one large (n=376) placebo-controlled study (Study CR-0009) to support the safety, efficacy and maintenance of efficacy of Pulmicort Turbuhaler once daily (AM) treatment with 200 μg or 400 μg of budesonide administered via Turbuhaler in patients with mild to moderate asthma. The study had 2 phases: a 6-week treatment phase, followed by a 12-week maintenance phase.

- The treatment effects of the average change from baseline ranged from [redacted] L/min for the differences between placebo and active treatments for AM PEF, one of the primary efficacy variables. The observed treatment effects of the other primary variable, FEV1, ranged from [redacted] L for the differences between placebo and active treatment groups.

- The 400/200 treatment regimen was statistically significantly better than placebo, even with a conservative *post-hoc* multiple-comparisons adjustment. The 200/200 dose was statistically significantly better than placebo for one of the 2 primary variables (FEV_1) in both phases and for the other (AM PEF) in the maintenance phase, but not the treatment phase.

- The treatment effects should be evaluated with caution because the responses were markedly different between two subgroups of patients: the patients who were not taking glucocorticoid steroids before randomization (GCS-free) and the patients who were taking glucocorticoid steroids for at least 8 weeks before randomization (GCS-dependent).

- For the GCS-free patients, the mean differences between placebo and active treatment group were small and not judged clinically relevant by the reviewing medical officer. The differences in change from baseline were particularly small during the first six weeks for one of the two primary variables (AM PEF mean difference with placebo in change from baseline, 200/200 QD: 6.0 L/min; 400/200 QD: 7.9 L/min).

- For the GCS-dependent patients, there was a large and differential dropout rate (placebo: 44%, 200/200 QD: 16%, 400/200 QD: 7.1%). Of the patients who remained in the study the full 18 weeks, the mean differences between placebo and active treatment in change from baseline AM PEF scores was approximately 12 L/min for 200/200 QD and 21 L/min for 400/200 QD. Due to

the large placebo dropout rate, the magnitude and confidence intervals of the treatment effect within this subgroup of GCS-dependent patients cannot be estimated reliably.

- The mean baseline AM PEF and FEV_1 scores of the 200/200 QD dose regimen were statistically significantly lower than those of the placebo patients. After accounting for these baseline differences, the results of the primary analyses were less compelling.

Table of Contents

Study CR-0009

1. Design

"The objective of this multicenter, randomized, double-blind placebo-controlled, parallel-group study was to determine the safety, efficacy and maintenance effect of once daily (QD) treatment in the morning with 200 µg or 400 µg of budesonide administered via Turbuhaler, versus placebo, in patients with mild-to-moderate chronic asthma. The study consisted of a 2-week baseline period, followed by a 6-week treatment phase, and a 12-week maintenance phase. On entry into the treatment phase, patients were randomized to receive 200 µg Pulmicort Turbuhaler, 400 µg Pulmicort Turbuhaler, or placebo each administered once daily in the morning. During the 12-week maintenance phase of the study, patients who had been receiving 400 µg QD Pulmicort Turbuhaler had their dose reduced to 200 µg QD without unmasking (referred to as the 400/200 µg QD group). Patients who had been receiving placebo or 200 µg QD Pulmicort Turbuhaler during the treatment phase of the study continued to do so throughout the maintenance phase (referred to as the placebo and the 200/200 µg QD Pulmicort Turbuhaler groups, respectively).

The primary efficacy variables for this study were mean changes from baseline in morning peak expiratory flow (PEF) and [morning] forced expiratory volume in one second (FEV1)."

Volume 1, page 75

2. Patient Population

The patient population in this study was patients with mild to moderate asthma. Inclusion criteria included:

a) FEV1 75% of predicted for patients receiving beclomethasone up to 10 puffs per day or FEV1>=60% and <=90% of predicted for inhaled GCS-free patients at Visit 1 (per Protocol Amendment Number 1); and,

b) reversible airways obstruction at Visit 1, defined by >=15% increase in FEV1 after inhaling a standard dose of albuterol. Patients receiving the glucocorticosteroid, beclomethasone dipropionate, who could not achieve a >=15% increase in FEV1 at Visit 1 were allowed to enter the study if they had a documented >=15% reversibility within 6 months prior to Visit 1, where Visit 1 was the first day of the baseline phase.

Patients were either **inhaled GCS-free** (defined as not receiving any inhaled glucocorticosteroids for 6 months prior to Visit 1) or **inhaled GCS-dependent** (defined as having received an inhaled glucocorticosteroid for a minimum of 8 weeks prior to Visit 1, of which beclomethasone - up to 10 puffs per day - was administered for the 4 weeks immediately preceding Visit 1).

At the end of the baseline phase (Visit 2), patients were randomized to one of three treatment groups. The randomization was stratified based on patients prior use of glucocorticoid steroid. Patients receiving glucocorticoid steroids discontinued this medication at Visit 2.

Reviewer Comment

The GCS-dependent patients discontinued using the glucocorticoid steroid at Visit 2. Therefore, the rate of dropout of the GCS-dependent patients who were randomized to placebo was very high compared to the other treatment groups. The FEV_1 and PEF scores of the GCS-dependent patients who were randomized to placebo (who remained in the study) decreased markedly after Visit 2. This marked decrease may have compromised the blinding of the study. The FEV_1 and PEF scores of the GCS-dependent patients who were randomized to active treatment remained stable through the treatment period. This is in contrast to the GCS-free patients randomized to placebo and active treatment. During the treatment period the scores of the placebo and active treatment patients stayed the same and increased, respectively.

3. Objectives

There were two "phases" to the study: treatment and maintenance. The sponsor summarized the objectives for each phase as follows:

1) Primary
   a) Treatment Phase: to determine the efficacy of once daily dosing of 2 doses of budesonide versus placebo in asthmatic patients; and
   b) Maintenance Phase: to compare the maintenance of efficacy for 12 weeks, of a single dose (200 µg) budesonide versus placebo in this same patient population.

2) Secondary: to evaluate the safety of budesonide in this patient population.

4. Primary Efficacy Variables

The sponsor stated in the protocol that the primary efficacy variables were mean changes from baseline in morning peak expiratory flow (AM PEF) and forced expiratory volume in one second (FEV_1), but the sponsor did not specify the primary efficacy variable comparison in the study protocol.

The protocol describes the primary comparison: "A pairwise comparison of the two doses of budesonide versus placebo will be carried out."

Reviewer Comment

Since this is a once-daily regimen, it is important to examine the endpoints at the end of the dosing interval to determine if the drug is efficacious throughout the dosing interval. Both endpoints, (AM PEF and FEV_1) were measured at the end of the dosing interval.

There were two phases to the study; therefore, the question arises: in which phase was the study designed to show a difference?[1] Did the sponsor expect to show a difference in both phases? Further, there were two "primary" variables and two doses. Therefore there were a total of six comparisons if one combines the two active treatment groups during the maintenance phase (as it appears the sponsor planned to do in the protocol), or a total of eight comparisons, if one leaves the two active treatments separate during the maintenance phase (as it appears in the study report). In summary, either way the two active treatment groups are analyzed in the maintenance phase (combined or separate) it appears that the 400/200 dose is statistically significantly better than placebo, even with the most conservative multiple-comparisons adjustment (alpha=0.05/8=0.00625) for one of the two variables (FEV_1) in both phases ($p<=0.001$), and for the other (AM PEF) in the maintenance phase ($p=0.002$), but only marginally statistically significant in the treatment phase ($p=0.007$). Similarly, the 200/200 dose is statistically significantly better than placebo for FEV_1 in both phases ($p<=0.002$), and AM PEF in the maintenance phase ($p=0.004$), but not the treatment phase ($p=0.056$), using the very conservative adjustment of alpha=0.00625.

5. Secondary Efficacy Variables

Secondary efficacy variables were mean change from baseline for the following:

1. Asthma symptom severity scores (i.e., daytime and nighttime symptoms)
2. Concomitant use of bronchodilators (i.e., number of inhalations of albuterol per day)
3. Evening PEF
4. Other PFT variables (FVC and $FEF_{25-75\%}$)
5. Quality of Life parameters (a difference in score of ≥ 0.5 units was considered clinically relevant)
6. Discontinuation rates
7. Time from randomization to response (response was defined as ≥ 10% increase from baseline in morning PEF)

[1] The sample size calculations did not answer this question.

Reviewer Comment
The sponsor's Quality of Life results are not discussed in this review.

6. Method of Analysis

6.1 Primary Efficacy Variables

Analysis of variance of change from baseline AM PEF and FEV_1 were used to compare the treatment groups. The models were as follows:

change in FEV_1 = center + treatment + center-by-treatment interaction

change in AM PEF = center + treatment + center-by-treatment interaction

If the interaction between treatment and center was not statistically significant (at the level of 0.10), the final model did not include the interaction.

An additional analysis of variance for the primary efficacy variables included an indicator variable for whether or not the patient used inhaled glucocorticosteroids at baseline.

6.2 Secondary Efficacy Variables

An analysis of variance (identical to that performed for the primary variables) was performed for the following secondary efficacy parameters: asthma symptoms severity scores, concomitant use of bronchodilators, evening PEF, FVC, $FEF_{25-75\%}$ and Quality of Life (QOL).

The numbers of patients who discontinued were compared between the Pulmicort Turbuhaler group and placebo using a Chi-square test.

To assess onset of action, the sponsor analyzed time from randomization to response using five-day running averages of the daily morning PEF measurements. The five-day running average was calculated using the first five consecutive post-baseline observations. Subsequent five-day running averages were calculated until response was achieved. The time at which response occurred was considered to be the last day of the five-day interval in which the response was achieved. The study report states that patients who discontinued without meeting the definition of "either response" were censored at the time of discontinuation. Treatment groups were compared using the log-rank test. In addition, pairwise comparisons were conducted between each Pulmicort Turbuhaler treatment group and the placebo group.

Reviewer Comment
The study report states that "response" was defined as ≥ 10% increase from baseline in morning PEF, however, the study report also refers to patients who discontinue without meeting the definition of "either response". The study report states that these patients were censored at the time of discontinuation for the analysis of time to response. It is unclear what "either response" refers to.

Perhaps the sponsor used two definitions of response. This discrepancy complicates the conclusions drawn from the analysis.

7. Interim Analysis

"A pre-planned administrative analysis of two primary efficacy variables (morning PEF and FEV) was performed when the first 150 patients randomized in the study had data available for these two variables. The purpose of this administrative analysis was to prepare for a possible meeting with regulatory authorities. This meeting never took place. It should be noted that no decisions were made with regard to the conduct of the trial following this administrative analysis, and no changes in the data collection and processing procedures were made. Because of the nature of this analysis, no formal hypothesis testing was performed and only descriptive statistics were presented."

Volume 23, page 41

The protocol stated that no decisions would be made with regard to the conduct of the trial following this interim analysis, nor would there be any changes in the data collection or processing procedures. The results were restricted to key personnel within Astra.

Reviewer Comment

The protocol stated that no decisions would be made regarding the conduct of the trial following this interim analysis. However, the interim analysis has potentially compromised the reported results of the study.

8. Results

8.1 Patient Accounting and Demographics

A total of 376 patients were enrolled into the baseline phase of the study. Of these 376 patients, 67 were discontinued prior to randomization. The majority of these patients were not randomized because they did not meet either FEV1 (17 patients) or reversibility criteria (16 patients).

A total of 309 patients were randomized: 103 patients were randomized to the Pulmicort Turbuhaler 200/200 µg QD group, 102 patients to the Pulmicort Turbuhaler 400/200 µg QD group, and 104 patients were assigned placebo. There were 20 investigators, with between 6 and 21 patients each. The investigators were located across the United States.

Patient demographics and baseline characteristics are shown in Appendix Table A1. A total of 107 (35%) males and 202 (65%) females participated in the study. The mean (± SD) age of all patients was 36.7±12.1 years (range 18 to 70 years), and the reported duration of asthma was a mean of 18.1±12.4 years (range 5 months to 59.8 years). Overall, 176 (57%) patients were not receiving inhaled GCSs, and 133 (43%) patients were receiving inhaled GCSs prior to randomization. Caucasians accounted for 266 (86%) of the patients, with 19 (6%) black, 22 (7%) other, and 2 (<1%) Asian.

The three treatment groups were comparable with respect to gender, age, weight, height, race, diastolic and systolic blood pressure, pulse rate, and duration of asthma. The pulmonary function tests (PFTs) were comparable, although the 200/200 µg QD Pulmicort Turbuhaler group had statistically significantly lower mean baseline morning PEF (348 L/min) and FEV_1 (2.50 L) scores

than the placebo group (AM PEF: 381 L/min, p=0.0208; FEV1: 2.87 L, p=0.0019).[2] Patient demographics and baseline characteristics were similar for inhaled GCS-dependent and inhaled GCS-free patients except for baseline lung function. The patients using inhaled corticosteroids had slightly higher baseline lung function scores (see Table 1, below).

Table 1: Demographics

Parameter	Inhaled GCS-Free (n =176)	Inhaled GCS-Dependent (n=133)
Age, years (mean ± SD) **Range**	35.7 ± 12 18-68	38.1 ± 12.3 18-70
Mean Morning PEF (L/min, ± SD)	351 ± 95	386 ± 103
Mean FEV_1 (L, ± SD) **Mean Percent of predicted**	2.6 ± 0.72 77%	2.8 ± 0.79 89%
Duration of asthma, years (mean ± SD)	17.5 ± 11.7	18.9 ± 13.3

Reviewer Comment

The patients dependent on GCS were not "washed out" of the steroids before the study began. Therefore, the pulmonary function level of the GCS-dependent patients who were randomized to placebo fell markedly during the initial weeks of the study. A large percentage (24%) of the placebo patients dropped out within the first three weeks. (This effect will be examined more in section 8.2 below and section 8.4.3).

8.2 Study Completion Summary

The numbers of patients discontinued from the study is summarized in Table 2 and Figure 1 below. Of the 309 randomized patients, 258 (83%) completed all phases of the study and 51 patients (17%) were discontinued from the study: 35 patients (11%) during the treatment phase, and 16 (5%) during the maintenance phase.

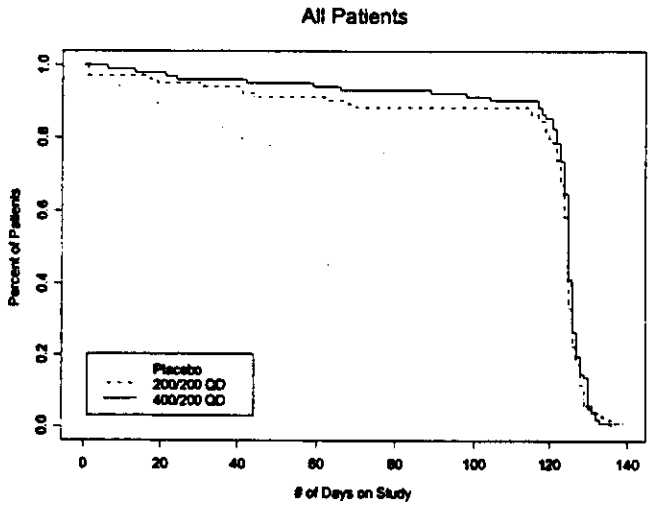
Table 2: Allocation and Discontinuation of Patients by Treatment and Study Phase

	Placebo	Pulmicort Turbuhaler 200/200 µg QD	Pulmicort Turbuhaler 400/200 µg QD	Total
Randomized	104	103	102	309
Completed	78 (75%)	88 (85%)	92 (90%)	258 (83%)
Discontinued: Treatment Phase*	22 (21%)	9 (9%)	4 (4%)	35 (11%)
Discontinued: Maintenance Phase	4 (4%)	6 (6%)	6 (6%)	16 (5%)

* Discontinued during Treatment Phase or on the last day of Treatment Phase

[2] Baseline was included in the model of the primary analyses for this review. The results for the 200/200 QD comparison with placebo for both AM PEF and FEV_1 changed slightly (see Section 8.4.1).

Figure 1: Percent of Patients in Study by Day

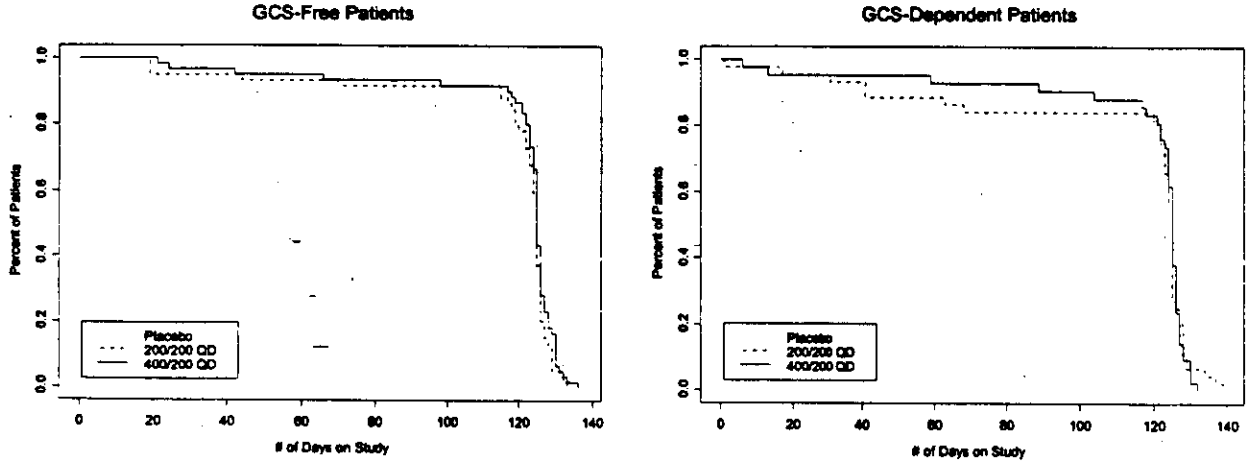


Reasons patients were discontinued from the study include adverse event (17 patients, 6%), disease deteriorated or not improved (16 patients, 5%), and other reasons (18 patients, 6%).

More patients were discontinued from the placebo group (26 patients, 25%) than from the 200/200 µg QD Pulmicort Turbuhaler group (15 patients, 15%) or the 400/200 µg QD Pulmicort Turbuhaler group (10 patients, 10%). Differences in discontinuations from the study approached significance comparing the placebo group with the 200/200 µg QD Pulmicort Turbuhaler group (p=0.062), and were statistically significant (p=0.005) comparing the placebo group with the 400/200 µg QD Pulmicort Turbuhaler group. Of the 16 patients who discontinued the study due to deterioration of their disease, 11 patients were in the placebo group, 4 patients were in the 200/200 µg QD Pulmicort Turbuhaler group (compared with placebo, p=0.074), and 1 patient was in the 400/200 µg QD Pulmicort Turbuhaler group (compared with placebo, p=0.019).

The rate of discontinuation of the placebo GCS-dependent patients between days 0 and 45 was noticeably higher than the other groups (see Figure 2 and Table 3 below).

Figure 2: Percent of Patients in Study by Day and by Previous Glucocorticosteroid Experience



The placebo GCS-dependent patients dropped out earlier and in greater numbers than the other groups. Approximately a quarter of placebo GCS-dependent patients had dropped out by the end of

Week 3 and over a third by the end of Week 6. Almost half the patients had dropped out by the 12th week. All the other groups had dropout rates of approximately 5% at the third week and less than 20% at the twelfth week. The rate of dropout appeared to slow after the twelfth week.

Table 3: Discontinuation Rates by Previous Glucocorticosteroid Experience

	Total Randomized	# (%) who dropped out by the end of :		
GCS-Free		Week 3	Week 6	Week 12
Placebo	56	2 (3.6)	5 (8.9)	6 (10.7)
200/200 QD	57	3 (5.3)	3 (5.3)	5 (8.8)
400/200 QD	60	1 (1.7)	3 (5.0)	4 (6.7)
GCS-Dependent				
Placebo	46	[redacted]	[redacted]	20 (43.5)
200/200 QD	44	2 (4.6)	5 (11.4)	7 (16.0)
400/200 QD	42	2 (4.8)	2 (4.8)	3 (7.1)

Reviewer Comment

It is clear that the interpretation of the study results may be different in the GCS-free and GCS-dependent groups.

In the primary analysis, twenty-five percent of the GCS-dependent placebo patients' data between Weeks 4 and 18 has been carried forward from Week 3. This means that essentially a quarter of the data analyzed for the placebo GCS-dependent patients is Week 3 data. By the end of Week 12, almost half (43.5%) of the GCS-dependent placebo patients had dropped out. This large dropout rate among the placebo patients and the large differential dropout rate between the placebo and treatment groups seriously compromises the treatment vs. placebo comparisons among the GCS-dependent patients. The primary analysis carried forward the last values of the dropout patients. Carrying forward the last values of 45% of the patients potentially introduces bias into estimate of the treatment difference. Assuming the patients would have continued to decline had they remained in the study, the direction of this treatment bias probably underestimated the true treatment difference.

8.3 Compliance

Compliance was monitored by review of patient diaries. In addition, at Visit 2, patients were instructed in the proper use of the Turbuhaler. To insure that patients took the first dose appropriately, they were observed and, if necessary, given further instruction.

Reviewer Comment

No information regarding the results of patient compliance was provided in the study report or the electronic datasets.

8.4 Primary Efficacy Variable Analyses

Table 4 summarizes the results of the study.

Table 4: Study CR-0009 Results[1]
(ANOVA with center and treatment)

Variable	Phase	Weeks	Placebo n=102	Pulmicort Turbuhaler 200/200 QD n=101	Pulmicort Turbuhaler 400/200 QD n=102
Morning PEF (L/min)	**Treatment Phase**	0-6			
	Change from Baseline[2]		**0.6**	**10.4**	**14.4**
	Mean Difference[3]			9.8	13.8
	95% CI[4]			(-.2,19.9)	(3.7,23.8)
	p-value			0.056	0.007
	Maintenance Phase	6-18			
	Change from Baseline		**0.7**	**21.0**	**22.0**
	Mean Difference			20.3	21.3
	95% CI			(6.6,34)	(7.6,35)
	p-value			0.004	0.002
FEV_1 (L)	**Treatment Phase**	3-6			
	Change from Baseline		**-0.3**	**0.12**	**0.13**
	Mean Difference			0.15	0.17
	95% CI			(0.06,0.25)	(0.07,0.26)
	p-value			0.002	0.001
	Maintenance Phase	10-18			
	Change from Baseline		**-0.09**	**0.10**	**0.11**
	Mean Difference			0.19	0.21
	95% CI			(0.09,0.29)	(0.10,0.31)
	p-value			<0.001	<0.001

1. The PEF scores for the treatment and maintenance phases were analyzed as the mean of the daily values for Weeks 0-6 and for Weeks 6-18, respectively. Spirometry test variables were measured only at scheduled clinic visits (Weeks 3, 6, 10, 14 and 18), and were therefore analyzed as mean values for Weeks 3-6 and Weeks 10-18 for the treatment and maintenance phases, respectively.
2. Least squares means from an ANOVA model with center and treatment as variables.
3. Comparison with placebo.
4. Confidence interval has not been adjusted for multiple comparisons.

In summary, the 400/200 dose is statistically significantly better than placebo even with a stringent multiple-comparisons adjustment ($\alpha = .05 / 8 = 0.00625$) for FEV_1 in both phases and for AM PEF in the maintenance phase. The difference in AM PEF scores between the 400/200 dose and placebo almost achieves statistical significance in the treatment phase ($p=0.007$), using the conservative alpha-adjustment, $\alpha=0.00625$. The 200/200 dose is statistically significantly better than placebo for one of the 2 variables (FEV_1) in both phases and for the other (AM PEF) in the maintenance phase but not the treatment phase. These endpoints are highly correlated, thus an alpha-level of 0.00625 is very conservative. Therefore the "marginally" statistically significant 400/200 dose vs. placebo difference of the AM PEF variable is probably a conservative assessment of the results of the trial.

The analyses including an indicator variable for prior GCS use demonstrated statistical significance (at the 0.05 level) for the GCS use indicator variable. This means that the GCS-free patients had different mean responses for AM PEF and FEV_1 than the GCS-dependent patients. The treatment-by-GCS use interaction term was not statistically significant (at the 0.25 level) in any of the analyses, indicating that the treatment effects in the two GCS use groups were not statistically significantly different. The pairwise comparisons of the GCS-dependent patients demonstrated a more robust treatment effect that those of the GCS-free patients; this supported results seen in the separate analyses for each GCS use group (see Section 8.4.3).

8.4.1 Effect of Baseline Differences

Recall that the patients randomized to active treatment had lower baseline scores than placebo. The baseline scores of the 200/200 QD dose were statistically significantly lower than placebo. Analyses including baseline in the model were performed to assess the impact of the baseline difference on the results. The inclusion of baseline decreased the estimates and significance levels of the treatment effects.

Table 5: Reviewer's Analyses: Study CR-0009 Results Including Baseline in the Model[1]
(ANCOVA with center, treatment group and baseline)

Variable	Phase	Weeks	Placebo	Pulmicort Turbuhaler 200/200 QD	Pulmicort Turbuhaler 400/200 QD
			n=102	n=101	n=102
Morning PEF (L/min)	**Treatment Phase**	0-6			
	Change from Baseline[2]		**1.4**	**8.6**	**14.2**
	Mean Difference[3]			7.1	12.9
	p-value			0.1594	0.0110
	Maintenance Phase	6-18			
	Change from Baseline		**2.5**	**17.5**	**21.8**
	Mean Difference			15.1	19.3
	p-value			0.0258	0.0039
FEV_1 (L)	**Treatment Phase**	3-6			
	Change from Baseline		**-0.02**	**0.10**	**0.13**
	Mean Difference			0.13	0.15
	p-value			0.0082	0.0014
	Maintenance Phase	10-18			
	Change from Baseline		**-0.07**	**0.09**	**0.11**
	Mean Difference			0.17	0.19
	p-value			0.0020	0.0005

1. The PEF scores for the treatment and maintenance phases were analyzed as the mean of the daily values for Weeks 0-6 and for Weeks 6-18, respectively. Spirometry test variables were measured only at scheduled clinic visits (Weeks 3, 6, 10, 14 and 18), and were therefore analyzed as mean values for Weeks 3-6 and Weeks 10-18 for the treatment and maintenance phases, respectively.
2. Least squares means from an ANOVA model with center and treatment as variables.
3. Comparison with placebo.

Reviewer Comment

Using the conservative alpha-level of 0.00625 to determine significance, the inclusion of baseline did not change the conclusions of five of the eight comparisons:

1. *200/200 QD dose*
   a. *the AM PEF comparison during the treatment phase (not significant), and*
   b. *and FEV_1 comparison during the maintenance phase (significant); and*

2. *400/200 QD dose*
   a. *the AM PEF comparison during the maintenance phase (significant), and*
   b. *the FEV_1 comparison during the maintenance phase (significant), and*
   c. *the FEV_1 comparison during the maintenance phase (significant).*

The inclusion of baseline did change the conclusion of significant to not significant for the following comparisons:

1. *200/200 QD dose*
   a. *the AM PEF comparison during the maintenance phase, and*
   b. *the FEV_1 comparison during the treatment phase, and*

2. *400/200 QD dose*
   a. *the AM PEF comparison during the treatment phase.*

Overall, the results of this post-hoc analysis support the conclusions from the primary analysis, that is: the 200/200 QD dose regimen does not appear to have as strong of an effect for the AM PEF variable as the 400/200 QD dose regimen.

8.4.2 Effect of Last Value Carried Forward (LVCF)

The sponsor provided analyses of the maintenance phase using only those patients who completed the treatment phase. These analyses were performed to investigate the effect of carrying forward the last observations for the discontinued patients. The sponsor found that the effect, in general, was to magnify the treatment differences between placebo and the Pulmicort groups. The results of the analyses for the two primary variables are presented in the shaded cells in Table 6 below.

Table 6: Primary Analysis Using Patients Who Completed Weeks 1-6 (Phase I)

		200/200 QD		400/200 QD	
Variable	Maintenance Phase	All Patients n=101	Phase I Completers n=94	All Patients n=102	Phase I Completers n=97
Morning PEF (L/min)	Mean Difference[2]	20.3	20.2	21.3	18.3
	p-value	0.004	0.004	0.002	0.012
FEV_1 (L)	Mean Difference	0.19	0.15	0.21	0.15
	p-value	<0.001	0.007	<0.001	0.004

1. Completers in this table are defined as patients who completed the treatment phase (Weeks 1-6), not the entire 18 weeks of the study.
2. The difference is the mean difference between placebo and the active treatment groups.

Reviewer Comment

This is not a standard comparison of completers and ITT patients using last value carried forward (LVCF). The analysis on the patients who completed the treatment phase in the above table did not exclude the LVCF imputation method entirely. The analysis above used LVCF on the 13 patients who dropped out during the maintenance phase. Therefore, the effect of carrying forward the last observations in the main primary analysis for all the discontinued patients (not just those who discontinued during the treatment phase) is actually greater than that demonstrated in the above table.

8.4.3 Prior GCS-Free and GCS-Dependent Patients

The patients dependent on GCS were not "washed out" of the steroids before the study began. The GCS-dependent patients discontinued the glucocorticoid steroid at Visit 2 (after the baseline period). Therefore, the pulmonary function level of the GCS-dependent patients who were randomized to placebo fell markedly during the initial 6 weeks of the study. The marked contrast between the results of the GCS-free and GCS-dependent patients is demonstrated in Tables 7-8 and Figures 3-6 below.

Table 7: Primary Analysis Results for AM PEF by Previous GCS Experience

AM PEF (L/min)		GCS-Free			GCS-Dependent		
		Placebo	200/200	400/200	Placebo	200/200	400/200
	N	56	57	60	46	44	42
Weeks	Baseline AM PEF (L/min)	373	316	361	390	386	379
0-6	Change from baseline	**12.2**	**18.2**	**20.1**	**-13.6**	**-0.4**	**5.9**
	Mean difference		6.0	7.9		13.2	19.5
	p-value		0.369	0.230		0.077	0.010
6-18	Change from baseline	**15.8**	**33.7**	**27.5**	**-17.7**	**3.6**	**13.8**
	Mean difference		17.9	11.5		21.3	31.5
	p-value		0.050	0.191		0.038	0.002

Figure 3: Mean Change in Morning PEF (L/min)
Inhaled GCS-Free Patients
(Last Observation Carried Forward)

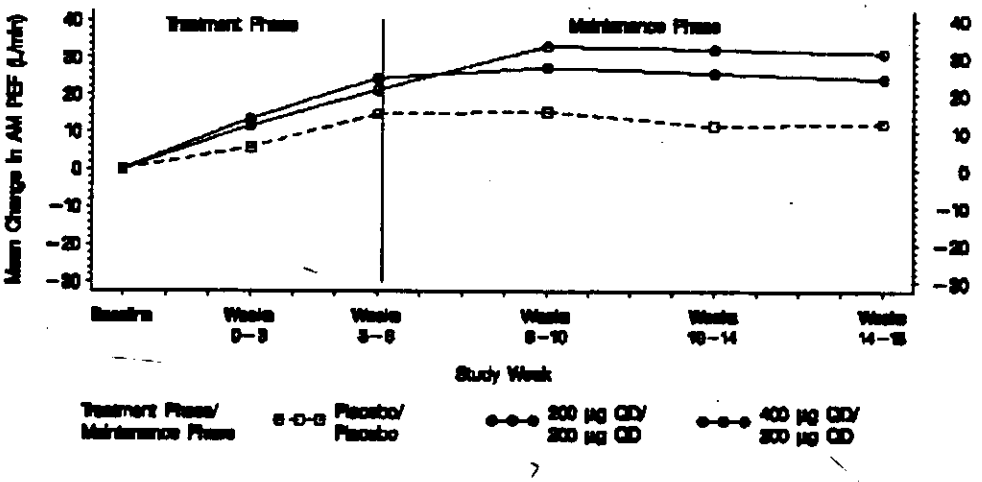


Figure 4: Mean Change in Morning PEF (L/min)
Inhaled GCS-Dependent Patients
(Last Observation Carried Forward)

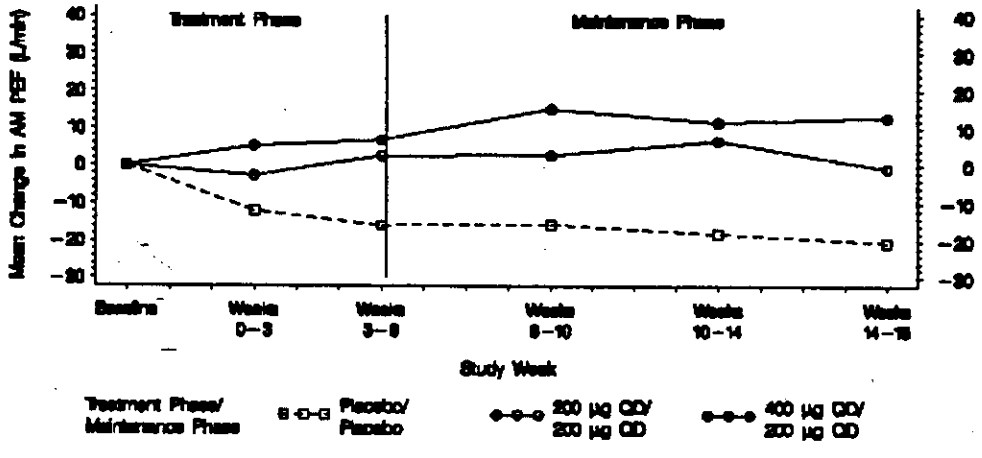


Table 8: Primary Analysis Results for FEV1 by Previous GCS Experience

FEV1 (L)		GCS-Free			GCS-Dependent		
		Placebo	200/200	400/200	Placebo	200/200	400/200
	N	55	57	60	43	44	41
Weeks	Baseline FEV1 (L)	2.72	2.36	2.52	2.90	2.72	2.87
0-6	Change from baseline	**0.08**	**0.20**	**0.19**	**-0.18**	**0.01**	**0.05**
	Mean difference		0.12	0.11		0.19	0.23
	p-value		0.054	0.072		0.007	0.002
6-18	Change from baseline	**0.02**	**0.19**	**0.17**	**-0.24**	**-0.03**	**0.02**
	Mean difference		0.17	0.15		0.21	0.26
	p-value		0.015	0.026		0.007	0.001

Figure 5: Mean Change in FEV_1 (L)
Inhaled GCS-Free Patients
(Last Observation Carried Forward)

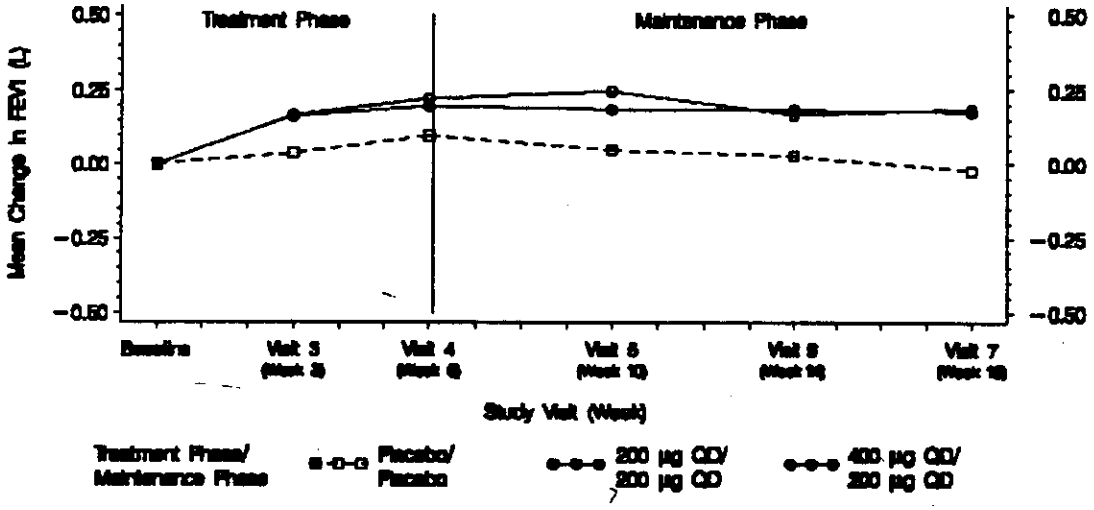
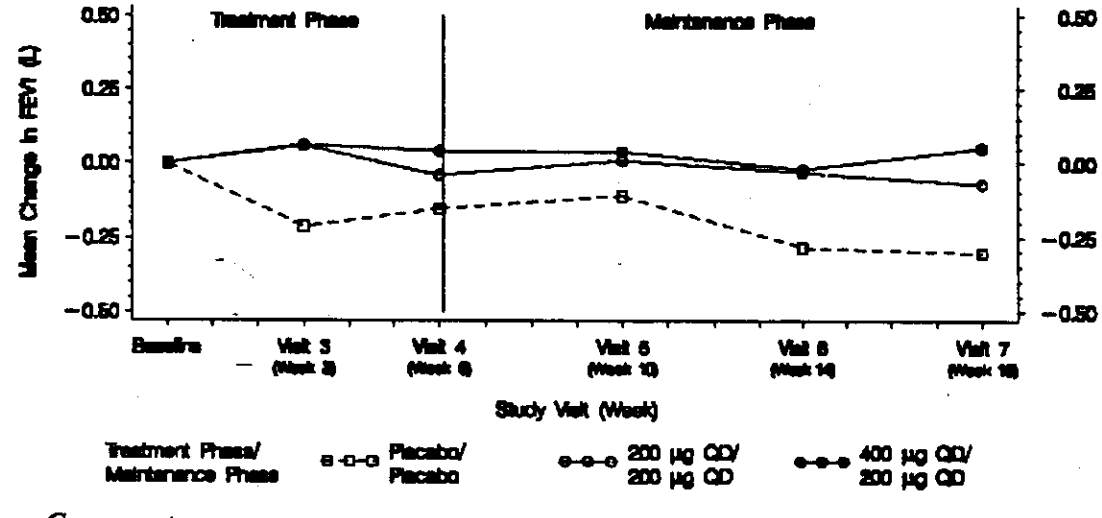


Figure 6: Mean Change in FEV_1 (L)
Inhaled GCS-Dependent Patients
(Last Observation Carried Forward)



Reviewer Comment

GCS-Free Patients

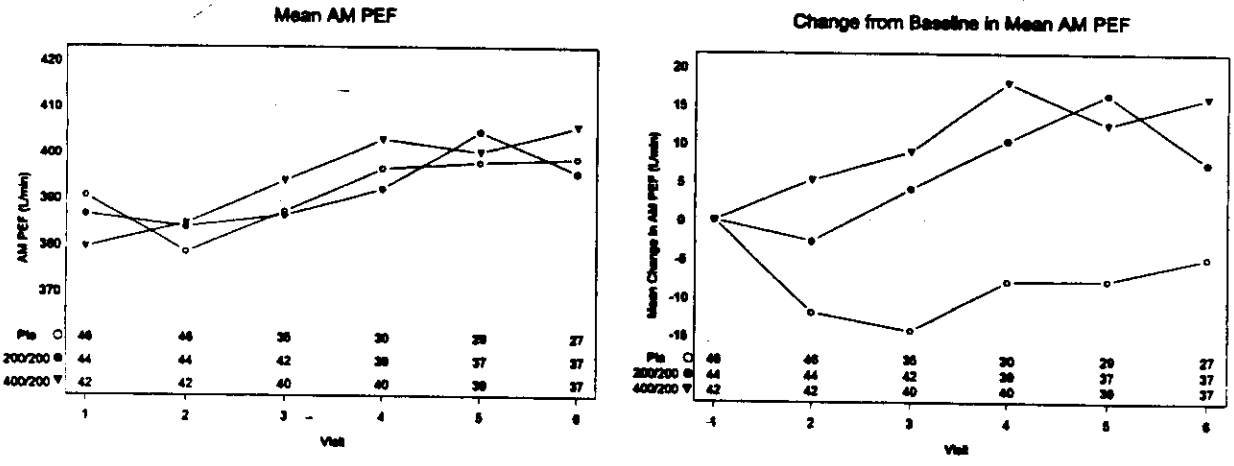
The study was not designed to detect differences within subgroups, therefore, the lack of consistent statistical significance of the differences between the placebo and active treatment groups among the GCS-free patients is not relevant. However, the differences between the placebo and the active treatment groups of the changes from baseline were small (Ranges, AM PEF: [redacted] L/min; FEV_1: [redacted] L) and are not clinically relevant, (according to the reviewing medical officer). The mean differences between the placebo and active treatment groups during the first six weeks were particularly small for one of the two primary variables (AM PEF: 6.0-7.9 L/min).

GCS-Dependent Patients

As discussed in Section 8.2, the comparisons between placebo and treatment groups among the GCS-dependent patients are compromised because of the large placebo dropout rate and differential dropout rates between placebo and treatment groups. From the graphs above, it appears as though the scores among the treated patients remained stable and similar to baseline during the treatment and maintenance phases of the study. Therefore, switching from twice daily glucocorticosteroid treatment to once daily treatment does not appear to have decreased the average scores among this patient population.

The graphs above include data carried forward for dropouts. It is informative to look at the profiles over time using only the observed data, in addition to means calculated using last observation carried forward for dropouts. The graphs below in Figure 7 are plots of the observed AM PEF means and change from baseline means of the GCS-dependent patients at each visit (no values carried forward for dropouts).

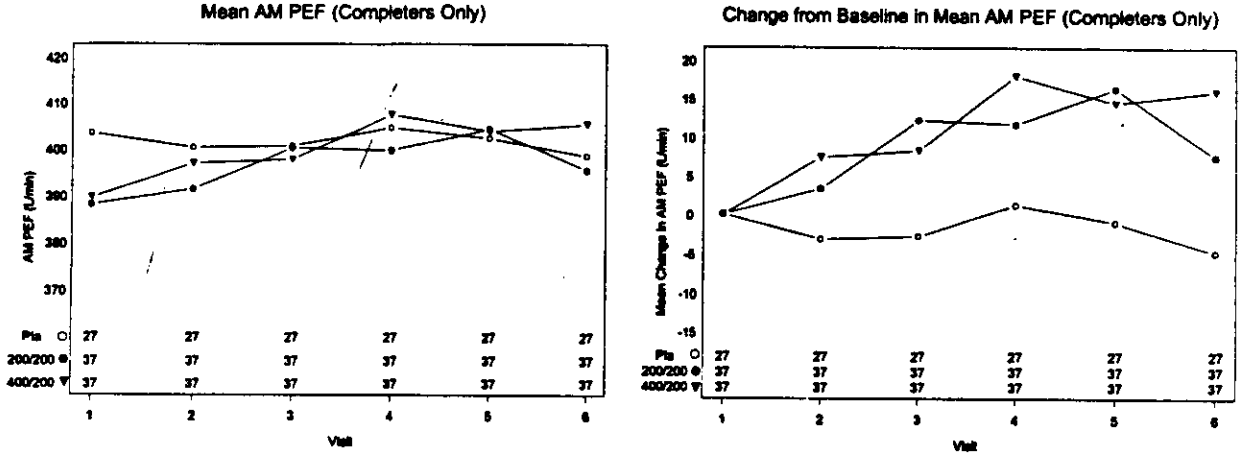
Figure 7: Observed Mean AM PEF scores and Change from Baseline in Mean AM PEF scores
All GCS-Dependent Patients
(no values carried forward for dropouts)



The number of patients remaining in the study at each time point is printed at the bottom of the graph. Nine placebo patients dropped out between visits 2 and 3. The AM PEF scores dropped at Visit 2, then increased at Visit 3 (probably due to the 9 placebo dropouts leaving the study). In the graph on the left it appears as though the active treatment patients who remained in the study had similar AM PEF scores to the placebo patients who remained in the study and that there is no mean difference in improvement of AM PEF scores between the treatment groups. This is in contrast to the graph on the right, which appears to demonstrate that the change from baseline scores were

different between the placebo and active treatment groups. The reason the graphs appear to show contrasting results is because the placebo patients who completed the study had higher baselines than the placebo patients who dropped out. This is depicted in Figure 8 below, in the graph on the left.

Figure 7: Observed Mean AM PEF scores and Change from Baseline in Mean AM PEF scores
GCS-Dependent Completers (Patients Who Completed All 18 Weeks)
(no values carried forward for dropouts)



The placebo patients who completed the study had a mean baseline score of 403 L/min whereas the placebo patients who dropped out had a mean baseline score of 372 L/min. The AM PEF scores of the placebo patients who completed the study deteriorated over time by about 5 L/min. The mean differences between active treatment and placebo were approximately 12 L/min for the 200/200 QD dose and 21 L/min for the 400/200 QD dose. The graphs in Figure 8 help to explain the apparent contrasting results in the graphs in Figure 7. Since the placebo completers began the study at such high values, even with the average decrease in scores over time, the mean AM PEF scores of the completers at the last visit was higher than the mean score of all patients at the first visit.

Therefore, the study demonstrates that Pulmicort Turbuhaler once daily keeps GCS-dependent patients stable longer than placebo, and improves the AM PEF scores more than placebo. The study is evidence of efficacy, but the dropouts make it difficult to definitively quantify the treatment effect in this subgroup of patients.

8.4.4 Time to Response

Time to response was computed across both phases of the study as the number of days required for the 5-day running mean in morning PEF to exceed the baseline value by ≥ 10%. Less than half the patients on placebo achieved the response (as defined above) before the end of the treatment phase (Day 42). Therefore, the median time to response for placebo during the treatment phase was not reached. The median time to response for the 200/200 and 400/200 Pulmicort doses and were 28 and 42 days, respectively. The log-rank test compares the survival curves (not the medians). The sponsor presented p-values of the log-rank tests comparing 200/200 and 400/200 Pulmicort to placebo using both the treatment and maintenance phase data (200/200 p=0.016; 400/200 p= 0.368).

Reviewer Comment

It appears that the sponsor performed the Kaplan-Meier analysis only for the treatment phase of the study, but then used the maintenance phase data to calculate the p-values of the log-rank tests. When including the data from the maintenance phase as well as the treatment phase, this reviewer calculated the median time to response for the placebo patients to be 57 days. The p-values of the log-rank tests corresponded to those the sponsor presented. When using only the treatment phase data, less than half the placebo group achieved the response (yielding no median time to response for the placebo group) and the p-values comparing the two treatment groups to placebo were 0.01 for the 200/200 dose and 0.2294 for the 400/200 group.

The results of this survival analysis are not consistent with those of the primary analysis, that is, the 400/200 dose group demonstrated a smaller effect for time to response than the 200/200 dose group whereas, in the primary analysis on mean change from baseline, the 400/200 dose group demonstrated a greater effect than the 200/200 dose group.

Table 9: Median Time to Response (in days) and Log Rank p-values

			Placebo	200/200	400/200
All Patients	Median Time to Response		57	28	42
	Treatment Phase	p-value		0.01	0.2294
		% Censored	60	39	50
	Treatment Phase and Maintenance Phase	p-value		0.0156	0.3683
		% Censored	48	30	39

The GCS-free and -dependent patients had different median times to response. The GCS-dependent patients responded much later than the -free patients. Less than half the GCS-dependent placebo group responded before the end of the study, therefore, no median time to response was achieved.

Table 10: Median Time to Response (in days) and Log Rank p-values by Previous GCS Experience

			Placebo	200/200	400/200
GCS-Free	Median Time to Response		36	18	32
	Treatment Phase	p-value		0.0476	0.7862
		% Censored	45	28	43
	Treatment Phase and Maintenance Phase	p-value		0.0267	0.7390
		% Censored	34	18	32
GCS-Dependent	Median Time to Response		N/A	41	128
	Treatment Phase	p-value		0.0470	0.1023
		% Censored	78	52	60
	Treatment Phase and Maintenance Phase	p-value		0.1573	0.3400
		% Censored	65	45	50

8.5 Secondary Efficacy Variable Analyses

The results of the secondary efficacy variables are summarized in the table below. The results of the diary card variables and the pulmonary function test variables were consistently statistically significant for both the treatment phase and the maintenance phase for both Pulmicort treatment groups as compared to placebo. For the Evening PEF, FVC and $FEF_{25-75\%}$ variables, the mean value of the placebo group decreased from baseline, whereas the mean values of the Pulmicort treatment groups all increased from baseline.

Table 11: Secondary Efficacy Variable Mean Changes from Baseline

		Placebo	200/200 mcg		400/200 mcg	
		n=102	n=101		n=102	
Variable	Weeks	Mean Change	Mean Change	p-value	Mean Change	p-value
Daytime	0-6	-.04	-0.27	[illegible]	-0.22	[illegible] 0.005
	6-18	-0.07	-0.23	[illegible]	-0.36	[illegible] <0.001
Nighttime	0-6	0.02	-0.15	[illegible]	-0.10	0.064
	6-18	0.02	-0.12	0.060	-0.17	[illegible]
Bronchodilat	0-6	-0.10	-0.98	[illegible]	-0.88	[illegible] 0.007
	6-18	-0.22	-1.11	[illegible]	-1.09	[illegible] 0.009
Evening PEF	0-6	-1.6	7.5	0.065	10.4	[illegible]
	6-18	-5.1	12.2	[illegible]	19.0	[illegible]
		n=98	n=101		n=101	
FVC	3-6	-0.05	0.10	[illegible]	0.12	[illegible]
	10-18	-0.13	0.06	[illegible]	0.11	[illegible]
$FEF_{25-75\%}$	3-6	-0.01	0.15	[illegible]	0.21	[illegible]
	10-18	-0.06	0.14	[illegible]	0.19	[illegible]

8.6 Adverse Events

The sponsor stated that the number and percent of patients reporting at least one adverse event was 67 (64%) in the placebo group, 63 (61%) in the 200/200 Turbuhaler group and 76 (75%) in the 400/200 Turbuhaler group.

Reviewer Comment

It appears that the 400/200 Turbuhaler group had a greater percentage of patients who experienced at least one adverse event; however, these patients were on the 200 ug dose for 12 of the 18 weeks of the trial. Table 12 was constructed to determine if there is a dose-effect.

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Table 12: Adverse Event Rates
(% of patients who experienced at least 1 adverse event)

	Randomized n	Trt Phase	Maintenance Phase	Total
Placebo	104	43 (41%)	28 (27%)	71 (68%)
200/200	103	35 (34%)	31 (30%)	66 (64%)
400/200	102	38 (37%)	39 (38%)	77 (75%)

Using this breakdown of the adverse events by phase, it appears as though when the 400/200 dose group patients were receiving the 400 ug dose they were not at a greater risk of experiencing an adverse event than when they were receiving the 200 ug dose.

9. Conclusions

The sponsor submitted one large (n=376) placebo-controlled study (Study CR-0009) to support the safety, efficacy and maintenance of efficacy of Pulmicort Turbuhaler once daily treatment in the morning with 200 μg or 400 μg of budesonide administered via Turbuhaler in patients with mild to moderate asthma. The study had 2 phases, a 6-week treatment phase followed by a 12-week maintenance phase.

The treatment effects ranged from 10.4-22.0 L/min difference between placebo and active treatment for AM PEF, one of the primary efficacy variables. The treatment effects of the other primary variable, FEV1, ranged from 0.10-0.13 L difference between placebo and active treatment groups.

The 400/200 dose was statistically significantly better than placebo even with a conservative post-hoc multiple-comparisons adjustment. The 200/200 dose was statistically significantly better than placebo for one of the 2 variables (FEV_1) in both phases and for the other (AM PEF) in the maintenance phase, but not the treatment phase.

The overall treatment effects in this study should be evaluated with caution because the treatment responses were markedly different between two subgroups of patients: the patients who were not taking glucocorticoid steroids before randomization (GCS-free) and the patients who were taking glucocorticoid steroids for at least 8 weeks before randomization (GCS-dependent). The pulmonary function test scores of the GCS-free patients increased slightly from baseline. The differences between the active treatment groups and placebo were not clinically relevant, according to the medical reviewer. The differences were particularly small during the first six weeks for one of the two primary variables (AM PEF [redacted] L/min). Among the GCS-dependent patients, the large placebo dropout rate (45%) makes the treatment effect difficult to quantify using the primary endpoints. The fact that 24% of the placebo GCS-dependent patients dropped out within the first three weeks as compared to only 5% of the active treatment groups is evidence of the drug's efficacy, however due to this large and differential dropout rate, the magnitude and confidence interval of the treatment effect within this subgroup of GCS-dependent patients cannot be accurately estimated.

/S/ /S/
Barbara Elashoff

concur: Steve Wilson /S/ 9/28/98

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cc:
Orig. NDA 20-441
HFD-570 / Division File
HFD-570 / JJenkins, RMeyer, MPurucker, DHilfiker
HFD-715 / Chron, division file
HFD-715 / BElashoff, SWilson

Appendix

Table A1: Demographic and Baseline Characteristics

Parameter	Placebo (n=104)	Pulmicort Turbuhaler 200/200 µg QD (n=103)	Pulmicort Turbuhaler 400/200 µg QD (n=102)
Sex: Male Female	44 (42%) 60 (58%)	33 (32%) 70 (68%)	30 (29%) 72 (71%)
Age, years (mean ± SD) Range	35.5 ± 11.8 18 to 69	38.8 ± 12.7 18 to 70	35.9 ± 11.7 18 to 68
Race: Caucasian Other Black Asian	94 (90%) 4 (4%) 6 (6%) ---	83 (81%) 13 (13%) 5 (5%) 2 (2%)	89 (87%) 5 (5%) 8 (8%) ---
Mean Morning PEF (L/min, ± SD)	381 ± 101	348 ± 101	369 ± 95
Mean FEV_1 (L, ± SD) Percent of predicted	2.87 ± 0.76 83%	2.50 ± 0.76 81%	2.71 ± 0.72 82%
Duration of asthma, years (mean ± SD)	17.2 ± 11.7	18.2 ± 12.7	19.0 ± 12.9
Prior Inhaled GCS Use No Yes	 57 (55%) 47 (45%)	 59 (57%) 44 (43%)	 60 (59%) 42 (41%)

Table A2: Demographics by Previous GCS Experience

Parameter	Inhaled GCS-Free (n =176)	Inhaled GCS-Dependent (n=133)
Age, years (mean ± SD) Range	35.7 ± 12 18-68	38.1 ± 12.3 18-70
Mean Morning PEF (L/min, ± SD)	351 ± 95	386 ± 103
Mean FEV_1 (L, ± SD) Mean Percent of predicted	2.6 ± 0.72 77%	2.8 ± 0.79 89%
Duration of asthma, years (mean ± SD)	17.5 ± 11.7	18.9 ± 13.3

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